CHEST

Antithrombotic Therapy for Atrial Fibrillation

CHEST Guideline and Expert Panel Report

Gregory Y. H. Lip, MD; Amitava Banerjee, MD, DPhil; Giuseppe Boriani, MD, PhD; Chern en Chiang, MD, PhD; Ramiz Fargo, MD, FCCP; Ben Freedman, MD, PhD; Deirdre A. Lane, PhD; Christian T. Ruff, MD, MPH; Mintu Turakhia, MD; David Werring, PhD; Sheena Patel, MPH; and Lisa Moores, MD, FCCP

BACKGROUND: The risk of stroke is heterogeneous across different groups of patients with atrial fibrillation (AF), being dependent on the presence of various stroke risk factors. We provide recommendations for antithrombotic treatment based on net clinical benefit for patients with AF at varying levels of stroke risk and in a number of common clinical scenarios.

METHODS: Systematic literature reviews were conducted to identify relevant articles published from the last formal search perfomed for the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). The overall quality of the evidence was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach. Graded recommendations and ungraded consensus-based statements were drafted, voted on, and revised until consensus was reached.

RESULTS: For patients with AF without valvular heart disease, including those with paroxysmal AF, who are at low risk of stroke (eg, CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65-74 and sex category

ABBREVIATIONS: ABC = Atrial fibrillation Better Care; ACS = acute coronary syndrome; ACTIVE W = Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events; ACUTE = Assessment of Cardioversion Using Transesophageal Echocardiography; AFFIRM = Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management; AHRE = atrial high-rate episode; aPTT = activated partial thromboplastin time; ARISTOTLE = Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; AVERROES = Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; BRIDGE = Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery; CAA = cerebral amyloid angiopathy; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65-74 and sex category (female); $CHADS_2$ = congestive heart failure; hypertension = age; diabetes = stroke (doubled); CIED = cardiac implanted electrical device; CKD = chronic kidney disease; CMB = cerebral microbleed; COI = conflicts of interest; CrCl = creatinine clearance; DAPT = dual antiplatelet therapy; ESUS = embolic stroke of undetermined source; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; HAS-BLED = hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (0.65), drugs/alcohol concomitantly (1 point each); $HEMORR_2HAGES$ = hepatic or renal disease, ethanol abuse, malignancy, older, reduced platelet count/function, hypertension, anemia, genetic factors, excessive fall risk, and stroke; HF = heart failure; HR = hazard ratio; ICH = intracranial hemorrhage; INR = international normalized ratio; LAA = left atrial appendage; LAAO = left atrial appendage occlusion; LMWH = low-molecular-weight heparin; MI = myocardial infarction; MOST = Atrial Diagnostics Ancillary Study of the Mode Selection Trial; NOAC = non-vitamin K antagonist oral anticoagulant drug; OAC = oral anticoagulant; o.d. = omni die (every day); PAD = peripheral arterial disease; PCC = prothrombin complex concentrate; PCI = percutaneous coronary intervention; PREVAIL = Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy trial; PROTECT AF = Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation; RCT = randomized controlled trial; RE-ALIGN = Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement; RE-LY = Randomized Evaluation of Long-term Anticoagulant Therapy with Dabigatran Etexilate; RE-VERSE AD = Reversal Effects of Idarucizumab on Active Dabigatran; ROCKET AF = Rivaroxaban Once daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RR = risk ratio; SPAF-I = Stroke Prevention in AF; TEE = transesophageal echocardiography; TIA = transient ischemic attack; t.i.d. = ter in die (three times daily); TT = thrombin time; TTE = transthoracic echocardiography; TTR = time in therapeutic range; UFH = unfractionated heparin; VKA = vitamin K antagonist

AFFILIATIONS: From the Institute of Cardiovascular Sciences, University of Birmingham, United Kingdom; Liverpool Centre for Cardiovascular Science, University of Liverpool, and Liverpool Heart and Chest Hospital, Liverpool, United Kingdom; and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark (Dr Lip); Institute of Health Informatics,

(female)] score of 0 in males or 1 in females), we suggest no antithrombotic therapy. The next step is to consider stroke prevention (ie, oral anticoagulation therapy) for patients with 1 or more non-sex CHA_2DS_2-VASc stroke risk factors. For patients with a single non-sex CHA_2DS_2-VASc stroke risk factor, we suggest oral anticoagulation rather than no therapy, aspirin, or combination therapy with aspirin and clopidogrel; and for those at high risk of stroke (eg, CHA_2DS_2-VASc ≥ 2 in males or ≥ 3 in females), we recommend oral anticoagulation rather than no therapy, aspirin, or combination therapy with aspirin and clopidogrel. Where we recommend or suggest in favor of oral anticoagulation, we suggest using a non-vitamin K antagonist oral anticoagulant drug rather than adjusted-dose vitamin K antagonist therapy. With the latter, it is important to aim for good quality anticoagulation control with a time in therapeutic range $> 70\%$. Attention to modifiable bleeding risk factors (eg, uncontrolled BP, labile international normalized ratios, concomitant use of aspirin or nonsteroidal antiinflammatory drugs in an anticoagulated patient, alcohol excess) should be made at each patient contact, and HAS-BLED (hypertension, abnormal renal/liver function [1 point each], stroke, bleeding history or predisposition, labile international normalized ratio, elderly (0.65), drugs/alcohol concomitantly [1 point each]) score used to assess the risk of bleeding where high risk patients (≥ 3) should be reviewed and followed up more frequently.

CONCLUSIONS: Oral anticoagulation is the optimal choice of antithrombotic therapy for patients with AF with ≥ 1 non-sex CHA_2DS_2-VASc stroke risk factor(s).

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KEY WORDS: antithrombotic therapy; atrial fibrillation; evidence-based medicine; guidelines

Note on Shaded Text: *In this guideline, shaded text with an asterisk (shading appears in PDF file only) refers to recommendations that remain unchanged from the previous version of the guideline.*

Summary of Recommendations

1. For patients with AF, including those with paroxysmal AF, stroke risk should be assessed using a risk factor based approach, rather than an categorization into low, moderate/high risk strata. We recommend use of the CHA_2DS_2-VASc as a simple clinical based stroke risk score to initially identify 'low stroke risk' patients who should not be offered antithrombotic therapy to prevent stroke and reduce mortality (Strong recommendation, moderate quality evidence).

Remark: Low risk patients are generally those age < 65 and 'lone AF' irrespective of sex (this includes those with a CHA_2DS_2-VASc score $= 0$ in males, or 1 in females).

2. Subsequent to this initial step, for patients with AF, including those with paroxysmal AF, we recommend stroke prevention should be offered to those AF

University College London (Dr Banerjee), London, United Kingdom; Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena & Reggio Emilia, Modena University Hospital (Dr Boriani), Modena, Italy; General Clinical Research Center and Division of Cardiology, Taipei Veterans General Hospital and National Yang-Ming University (Dr Chiang), Taipei, Taiwan; Division of Pulmonary and Critical Care, Department of Internal Medicine, Riverside University Medical Center, Moreno Valley, CA, and Division of Pulmonary, Critical Care, Hyperbaric, and Sleep Medicine, Department of Internal Medicine, Loma Linda University Medical Center (Dr Fargo), Loma Linda, CA; Heart Research Institute/Charles Perkins Centre, University of Sydney and Department of Cardiology Concord Hospital, University of Sydney (Dr Freedman), Sydney, Australia; Institute of Cardiovascular Sciences, University of Birmingham, United Kingdom, and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University (Dr Lane), Aalborg, Denmark; Cardiovascular Medicine Division, Brigham and Women's Hospital, Harvard Medical School (Dr Ruff), Boston, MA; Department of Medicine, Stanford University School of Medicine (Dr Turakhia), Stanford, CA; Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, University College Hospitals NHS Foundation Trust (Dr Werring), London, United Kingdom; CHEST (Ms Patel), Glenview, IL; and Uniformed Services University of the Health Sciences, F. Edward Hebert School of Medicine (Dr Moores) Bethesda, MD.

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CORRESPONDENCE TO: Gregory Y.H. Lip, MD, Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, United Kingdom; e-mail: gregory.lip@liverpool.ac.uk

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patients with one or more non-sex CHA_2DS_2-VASc stroke risk factors (score of ≥ 1 in a male or ≥ 2 in a female) (Strong recommendation, moderate quality evidence).

Remark: Consideration of other less established clinical stroke risk factors, imaging (cardiac or cerebral), or biomarkers (urine, blood, or genetics) may refine risk stratification based on simple clinical factors. A complex risk schema using a variety of such data that could accurately place more patients in the low risk stratum not requiring anticoagulants than current simple clinically based scores (personalized medicine) should be the goal of future research, but it will be very difficult to find non-anticoagulated patient cohorts for prospective validation.

3. For patients with AF, we recommend bleeding risk assessment should be performed for all patients with AF at every patient contact and should initially focus on potentially modifiable bleeding risk factors (Strong recommendation, low quality evidence).

Remark: Modifiable risk factors may include: Uncontrolled blood pressure; Labile INRs (in a patient taking VKA); Alcohol excess; Concomitant use of NSAIDs or aspirin in an anticoagulated patient; bleeding tendency or predisposition (eg, treat gastric ulcer, optimize renal or liver function, etc).

4. For patients with AF, we recommend use of the HAS-BLED score to address modifiable bleeding risk factors in all AF patients. Those potentially at high risk (HAS-BLED score ≥ 3) warrant more frequent and regular reviews or follow-up (Strong recommendation, moderate quality evidence).

Remark: Given that bleeding risk is highly dynamic, attention to modifiable bleeding risk factors should be prioritized during every patient contact and review.

5. In VKA-treated patients, we suggest the use of the HAS-BLED score for bleeding risk assessment (Weak recommendation, low quality evidence).

Remark: A high HAS-BLED score (≥ 3) is rarely a reason to avoid anticoagulation. The individual modifiable components of the score, when reviewed with the patient, can serve to ameliorate bleed risk.

6. For patients with AF, we recommend against antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) for stroke prevention alone, regardless of stroke risk (Strong recommendation, moderate quality evidence).

Remark: Patients with AF might have other indications for antiplatelet drugs (eg, acute coronary syndrome, stents).

7. In patients with AF who are eligible for OAC, we recommend NOACs over VKA (Strong recommendation, moderate quality evidence).

Remark: Patient and caregiver preferences, cost, formulary considerations, anticipated medication adherence or compliance with INR testing and dose adjustment should be incorporated into clinical decision-making.

8. In patients on VKAs with consistently low time in INR therapeutic range (eg, TTR < 65%), we recommend considering interventions to improve TTR or switching to NOACs (Strong recommendation, moderate quality evidence).

Remark: Action required if TTR < 65% - implement additional measures (more regular INR tests; review medication adherence; address other factors known to influence INR control; education/counselling) to improve INR control.

9. In patients with prior unprovoked bleeding, warfarin-associated bleeding, or at high risk of bleeding, we suggest using apixaban, edoxaban, or dabigatran 110 mg (where available) as all demonstrate significantly less major bleeding compared with warfarin (Weak recommendation, very low quality evidence).

Remark: In patients with prior gastrointestinal bleeding apixaban or dabigatran 110 mg bid may be preferable as they are the only NOACs associated without an increased risk of gastrointestinal bleeding compared with warfarin.

Remark: Dabigatran 150 mg twice daily recommended in patients at high risk of ischemic stroke as only agent/dose with superior efficacy compared with warfarin. However, bleeding risk would need to be assessed and patients monitored.

10. For patients with non-valvular AF, when VKAs are used, we suggest the target should be INR 2.0-3.0, with attention to individual TTR, ideally ≥ 70% (Ungraded consensus-based statement).

Remark: Action required if TTR sub-optimal (ie, <65-70%) - implement additional measures (more regular INR tests; review medication adherence; address other factors known to influence INR control;

education/counseling) to improve INR control or consider an NOAC.

Remark: When possible, experienced specialized anticoagulation clinics should be utilized for VKA and INR management.

11. For patients with AF, we suggest the SAMe-TT_2R_2 score to aid decision-making to help identify patients likely to do well on VKA (Ungraded consensus-based statement).

Remark: Those with score 0-2 are likely to achieve a good TTR. Those with score $>$ 2 are less likely to achieve a good TTR and would require more regular INR checks, education/counseling and frequent follow-up, or alternatively, NOAC should be considered as a better management option if high medication adherence can be expected.

12. For patients with AF of greater than 48 h or unknown duration undergoing elective electrical or pharmacologic cardioversion, we recommend therapeutic anticoagulation with well-managed VKA (INR 2-3) or an NOAC using dabigatran, rivaroxaban, edoxaban, or apixaban for at least 3 weeks before cardioversion or a transesophageal echocardiography (TEE)-guided approach with abbreviated anticoagulation before cardioversion rather than no anticoagulation (Strong recommendation, moderate quality evidence).

Remark: With NOACs adherence and persistence should be strongly emphasized.

13. For patients with AF of greater than 48 hours or unknown duration undergoing elective electrical or pharmacologic cardioversion, we recommend therapeutic anticoagulation (with VKA or NOAC) for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of the baseline risk of stroke (Strong recommendation, moderate quality evidence).

Remark: Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in recommendations 1 and 2, and not on the basis of successful cardioversion.

14. In patients in which LAA thrombus is detected on TEE, cardioversion postponed, and OAC continued for another 4-12 weeks, to allow thrombus resolution or endothelization, we suggest that a decision on whether a repeat TEE is performed should be individualized (Ungraded consensus-based statement).

***15. For patients with AF of documented duration of 48 hours or less undergoing elective cardioversion (electrical or pharmacologic), we suggest starting anticoagulation at presentation (low-molecular-weight heparin or unfractionated heparin at full venous thromboembolism treatment doses) and proceeding to cardioversion rather than delaying cardioversion for 3 weeks of therapeutic anticoagulation or a TEE-guided approach** (Weak recommendation, low quality evidence).

***16. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic), after successful cardioversion to sinus rhythm, we suggest therapeutic anticoagulation (with VKA or full adherence to NOAC therapy) for at least 4 weeks rather than no anticoagulation, regardless of baseline stroke risk** (Weak recommendation, low quality evidence).

Remark: Decisions about long-term anticoagulation after cardioversion should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in recommendations 1 and 2.

***17. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic), we suggest that therapeutic-dose parenteral anticoagulation be started before cardioversion, if possible, but that initiation of anticoagulation must not delay any emergency intervention** (Weak recommendation, low quality evidence).

***18. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic), after successful cardioversion to sinus rhythm, we suggest therapeutic anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of baseline stroke risk** (Weak recommendation, low quality evidence).

Remark: Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in recommendations 1 and 2.

***19. For patients with atrial flutter undergoing elective or urgent pharmacologic or electrical cardioversion, we suggest that the same approach to thromboprophylaxis be used as for patients with atrial fibrillation undergoing cardioversion** (Ungraded consensus-based statement).

20. In AF patients presenting with an ACS and/or undergoing PCI/stenting, we recommend assessment of stroke risk using the CHA_2DS_2-VASc score (Strong recommendation, moderate quality evidence).

Remark: All such patients are not 'low risk' and should be considered for concomitant OAC.

21. In AF patients presenting with an ACS and/or undergoing PCI/stenting, we suggest attention to modifiable bleeding risk factors at every patient contact, and assessment of bleeding risk using the HAS-BLED score (Weak recommendation, low quality evidence).

Remark: Where bleeding risk is high (HAS-BLED $\geq$ 3), there should be more regular review and follow-up.

22. In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is low (HAS-BLED 0-2) relative to risk for recurrent ACS and/or stent thrombosis, we suggest triple therapy for 1-3 months, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) until 12 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).

23. In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is high (HAS-BLED ≥ 3), we suggest triple therapy for 1 month, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) for 6 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).

24. In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is unusually high and thrombotic risk relatively low, we suggest use of OAC plus single antiplatelet (preferably clopidogrel) for 6 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).

Remark: Patients at unusually high bleeding risk may include patients with HAS-BLED $\geq$ 3 and recent acute bleeding event. High thrombotic risk may include those with left main stent, multivessel PCI/stenting, etc.

25. In AF patients requiring OAC presenting with an ACS, undergoing PCI/stenting, where bleeding risk is low (HAS-BLED 0-2) relative to risk for ACS or stent thrombosis, we suggest triple therapy for 6 months, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) until 12 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).

26. In AF patients requiring OAC presenting with an ACS, undergoing PCI/stenting, where bleeding risk is high (HAS-BLED ≥ 3), we suggest triple therapy for 1-3 months, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) up to 12 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).

27. In AF patients requiring OAC presenting with an ACS, undergoing PCI/stenting where bleeding risk is unusually high and thrombotic risk low, we suggest OAC plus single antiplatelet (preferably clopidogrel) for 6-9 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).

Remark: Patients at unusually high bleeding risk may include patients with HAS-BLED $\geq$ 3 and recent acute bleeding event. High thrombotic risk may include those with left main stent, multivessel PCI/stenting, etc.

28. In AF patients with ACS or undergoing PCI in whom OAC is recommended, we suggest using VKA with TTR > 65-70% (INR range 2.0-3.0), or to use an NOAC at a dose licensed for stroke prevention in AF (Weak recommendation, low quality evidence).

Remark: Only dabigatran 150 mg bid or (not licensed in USA) 110 mg bid or rivaroxaban 15 mg qd are currently supported by clinical trial evidence. An NOAC based strategy has lower bleeding risk compared to a VKA-based strategy.

29. In AF patients in which aspirin is concomitantly used with OAC, we suggest a dose of 75-100 mg qd with concomitant use of PPI to minimize gastrointestinal bleeding (Weak recommendation, low quality evidence).

30. In AF patients in which a P2Y12 inhibitor is concomitantly used with OAC, we suggest the use of clopidogrel (Weak recommendation, low quality evidence).

Remark: Newer agents (eg, ticagrelor) can be considered where bleeding risk is low. Data on the combination of ticagrelor with either dabigatran 110 mg bid or 150 bid (without concomitant aspirin use) are available from the RE-DUAL PCI trial.

***31. For patients with AF and stable coronary artery disease (eg, no acute coronary syndrome within the previous year) and who choose oral anticoagulation, we suggest OAC with either an NOAC or adjusted-dose VKA therapy alone (target international normalized ratio [INR] range, 2.0-3.0) rather than the combination of OAC and aspirin** (Weak recommendation, low quality evidence).

32. In patients with AF in whom catheter ablation of AF or implantation of cardiac electronic implantable devices is planned, we suggest performing the procedure on uninterrupted VKA (within the INR therapeutic range), dabigatran or rivaroxaban (Weak recommendation, low quality evidence).

33. In patients in whom sinus rhythm has been restored, we suggest that long-term anticoagulation should be based on the patient's CHA_2DS_2-VASc thromboembolic risk profile, regardless of whether sinus rhythm has been restored via ablation, cardioversion (even spontaneous), or other means (Weak recommendation, low quality evidence).

34. In AF patients with acute ischemic stroke, we suggest that very early anticoagulation (< 48 h) using heparinoids or VKA should not be used (Ungraded consensus-based statement).

Remark: Heparinoids should not be used as bridging therapy in the acute phase of ischemic stroke because they appear to increase the risk of symptomatic intracranial hemorrhage without net benefit. The optimal timing of anticoagulation after acute ischemic stroke is unknown.

35. In AF patients with acute stroke without contraindications, we recommend that long-term oral anticoagulation is indicated as secondary prevention (Strong recommendation, high quality evidence).

Remark: The optimal timing of anticoagulation early after acute ischemic stroke is unknown. Early use of NOACs shows promise but requires testing in randomized controlled trials.

36. In AF patients with acute ischemic stroke, we suggest that oral anticoagulation should usually be started within 2 weeks of acute ischemic stroke, but the optimal timing within this period is not known (Ungraded consensus-based statement).

Remark: Although infarct size is clinically used to guide timing of anticoagulation, it is predictive of a higher risk of early recurrent ischemia, hemorrhagic transformation of the infarct, and poor outcome, so might not be helpful in determining the net benefit of early treatment.

Remark: Anticoagulation with NOACs soon after stroke (earlier than 1 week) has not been tested in randomized trials, but shows promise in observational studies.

37. In patients with AF and high ischemic stroke risk, we suggest anticoagulation with an NOAC after acute spontaneous ICH (which includes subdural, subarachnoid, and intracerebral hemorrhages) after careful consideration of the risks and benefits (Ungraded consensus-based statement).

Remark: The balance of net benefit from long-term oral anticoagulation might be more favorable in those with deep ICH or without neuroimaging evidence of cerebral amyloid angiopathy.

Remark: In ICH survivors with AF, clinicians should aim to estimate the risk of recurrent ICH (using ICH location and, where available, MRI biomarkers including cerebral microbleeds) and the risk of ischemic stroke.

Remark: The optimal timing of anticoagulation after ICH is not known, but should be delayed beyond the acute phase (approximately 48 h) and probably for at least approximately 4 weeks. Randomized trials of NOACs and left atrial appendage occlusion are ongoing.

38. In ICH survivors at high risk of recurrent ICH (eg, those with probable cerebral amyloid angiopathy), we suggest left atrial appendage occlusion (Ungraded consensus-based statement).

Remark: Cerebral amyloid angiopathy should be diagnosed using validated clinico-radiological criteria.

39. In patients with AF and symptomatic carotid stenosis (> 50%), we suggest carotid revascularization with endarterectomy or stenting in addition to OAC as indicated (Weak recommendation, moderate quality evidence).

40. In patients with AF and carotid stenosis treated with revascularization, we suggest OAC therapy, without long-term antiplatelet therapy (Ungraded consensus-based statement).

Remark: There is limited evidence to guide the optimal treatment of patients with AF and carotid stenosis not requiring revascularization.

Remark: Short-term concomitant antiplatelet therapy (dual or mono) is generally used in the immediate post-revascularization period (eg, 1-3 months).

41. For patients who present with a clinically documented episode of AF (12-lead ECG or other means, eg, external devices with validated rhythm detection), we suggest that the presence or absence of symptoms must not influence the process of decision-making with regard to the need for anticoagulation based on risk stratification (Ungraded consensus-based statement).

42. In cases of AHRE (atrial high-rate episodes) detected by a CIED of at least 5 min duration, we suggest that direct analysis of electrograms corresponding to AHRE is clinically indicated to exclude artifacts or other causes of inappropriate detection of atrial tachyarrhythmias or AF (Ungraded consensus-based statement).

Remark: In patients with CIED-detected AHRE, a complete cardiological evaluation is indicated, with 12-lead ECG, general assessment of clinical conditions and clinical risk stratification for stroke using CHA_2DS_2-VASc score.

Remark: There is no evidence in support or against prescription of oral anticoagulants in patients at risk of stroke (intermediate to high risk according to CHA_2DS_2-VASc) who present with AHREs, corresponding to atrial tachyarrhythmias/AF at electrograms assessment of less than 24 h duration.

43. In patients with AF, we suggest prescription of oral anticoagulants could be considered as a result of an individualized clinical assessment taking into account overall AHRE burden (in the range of hours rather than minutes) and specifically, the presence of AHRE > 24 h, individual stroke risk (using CHA_2DS_2-VASc), predicted risk benefit of oral anticoagulation and informed patient preferences (Ungraded consensus-based statement).

Remark: In patients with CIED-detected AHRE, continued patient follow-up is recommended, preferentially combining clinical follow-up with remote monitoring of the CIED or else more frequent device interrogation than standard for CIED follow-up, to detect the development of clinical AF (symptomatic or asymptomatic), to monitor the evolution of AHRE or AF burden and specifically the transition to AHRE lasting more than 24 h, onset or worsening of heart failure, or any clinical change that might suggest a change in clinical profile or clinical conditions.

44. For patients with atrial flutter, we suggest that antithrombotic therapy decisions follow the same risk-based recommendations as for AF (Ungraded consensus-based statement).

45. For women receiving OAC for prevention of stroke/TE in AF who become pregnant, we suggest discontinuation of OAC with a VKA between weeks 6 and 12 and replacement by LMWH twice daily (with dose adjustment according to weight and target anti-Xa level 4-6 h post-dose 0.8-1.2 U/mL), especially in patients with a warfarin dose required of > 5 mg/day (or phenprocoumon > 3 mg/day or acenocoumarol > 2 mg/day). OAC should then be discontinued and replaced by adjusted-dose LMWH (target anti-Xa level 4-6 h post-dose 0.8-1.2 U/mL) in the 36th week of gestation (Ungraded consensus-based statement).

46. For women on treatment with long-term vitamin K antagonists who are attempting pregnancy and are candidates for LMWH substitution, we suggest performing frequent pregnancy tests and use LMWH instead of VKA when pregnancy is achieved rather than switching to LMWH while attempting pregnancy (Ungraded consensus-based statement).

47. For pregnant women, we suggest avoiding the use of NOACs (Ungraded consensus-based statement).

Remark: For women on treatment with an NOAC we suggest switching to vitamin K antagonists, rather than switching to LMWH while attempting pregnancy.

48. For lactating women using warfarin, acenocoumarol, or UFH who wish to breast-feed, we suggest continuing the use of warfarin, acenocoumarol, LMWH, or UFH (Ungraded consensus-based statement)

49. For breast-feeding women, we suggest alternative anticoagulants rather than NOACs (Ungraded consensus-based statement).

50. For mild CKD (Stage II, CrCl 60-89 mL/min), we suggest that oral anticoagulation clinical decision-making and treatment recommendations match that of patients without CKD (Weak recommendation, very low quality evidence).

51. For moderate CKD (Stage III, CrCl 30-59 mL/min), we suggest oral anticoagulation in patients with a CHA_2DS_2-VASc ≥ 2 with label-adjusted NOACs or dose-adjusted vitamin K antagonists (Weak recommendation, very low quality evidence).

Remark: With VKA, good quality anticoagulation control (TTR > 65-70%) is recommended.

52. In severe non-dialysis CKD (Stage IV CrCl 15-30 mL/min), we suggest using VKAs and selected NOACs (rivaroxaban 15 mg QD, apixaban 2.5 mg bid, edoxaban 30 mg QD and [in USA only] dabigatran 75 mg bid) with caution, based on pharmacokinetic data (Ungraded consensus-based statement).

53. In end-stage renal disease (CrCl < 15 mL/min or dialysis-dependent), we suggest that individualized decision-making is appropriate (Ungraded consensus-based statement).

54. In end-stage renal disease (CrCl < 15 mL/min or dialysis-dependent, we suggest using well-managed VKA with TTR > 65-70% (Ungraded consensus-based statement).

Remark: NOACs should generally not be used, although in USA, apixaban 5 mg bid is approved for use in AF patients receiving hemodialysis.

Remark: In patients with CKD who initiate OAC, concomitant antiplatelet therapy including low-dose aspirin is likely to substantially elevate bleeding risk and should be used very judiciously.

55. In patients with AF at high risk of ischemic stroke who have absolute contraindications for OAC, we suggest using LAA occlusion (Weak recommendation, low quality evidence).

Remark: When taking into account LAAO as a potential option, the risk of bleeding related to antiplatelet agents that need to be prescribed in the first months has to be considered and the possibility to use NOACs.

56. In AF patients at risk of ischemic stroke undergoing cardiac surgery, we suggest surgical exclusion of the LAA for stroke prevention, but the need for long-term OAC is unchanged (Weak recommendation, low quality evidence).

57. In AF patients taking warfarin without high risk of thromboembolism or who do not have a mechanical valve, we suggest preoperative management without bridging (Weak recommendation, low quality evidence).

58. In AF patients on antithrombotic prophylaxis with warfarin with a high risk of thromboembolism or with a mechanical valve, we suggest preoperative management with bridging (Weak recommendation, low quality evidence).

59. In AF patients on antithrombotic prophylaxis with an NOAC, we suggest preoperative management without bridging (Weak recommendation, low quality evidence).

60. In AF patients who have previously refused OAC, we suggest reinforcing educational messages at each contact with the patient and revisit OAC treatment decisions (Ungraded consensus-based statement).

Remark: Patient and physician treatment objectives often differ significantly and it is important to elicit from the patient what outcomes of OAC treatment are important to them.

Remark: Explain the risk of stroke and benefit/risks of treatment in terms the patient can understand and signpost the patient to appropriate educational resources.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with an increasing prevalence and incidence with age. In adults aged > 40 years, there is a 1 in 4 lifetime risk of developing AF, with incident AF commonly related to various associated cardiovascular and noncardiovascular risk factors. AF without associated valvular heart disease (so-called "nonvalvular AF") is associated with a fivefold increase in stroke risk (approximately 5% per year), but this risk is dependent on the presence of various stroke risk factors.[1] Many of the risk factors leading to incident AF are also risk factors for ischemic stroke, and the promotion of an integrated or holistic approach to AF management is needed, incorporating stroke prevention, addressing symptoms and risk factor management.[2]

Stroke prevention is the principal priority in the holistic approach to AF management.[1] Even since the last edition of the CHEST guidelines published in 2012,[3] there have been substantial developments in AF thromboprophylaxis, whether with regard to risk assessment, antithrombotic drugs, or nondrug approaches.

It is clear that AF should not be considered in isolation, at the stage of detection, prevention, or treatment. For example, the majority of deaths in individuals with AF are from cardiac causes, including heart failure (HF), whereas stroke and bleeding represent a small subset of deaths, yet most interventions focus on stroke prevention.[4] Thus, a more holistic approach is needed to take comorbidities and cross-disease sequelae of AF, bridging primary and secondary care.[2]

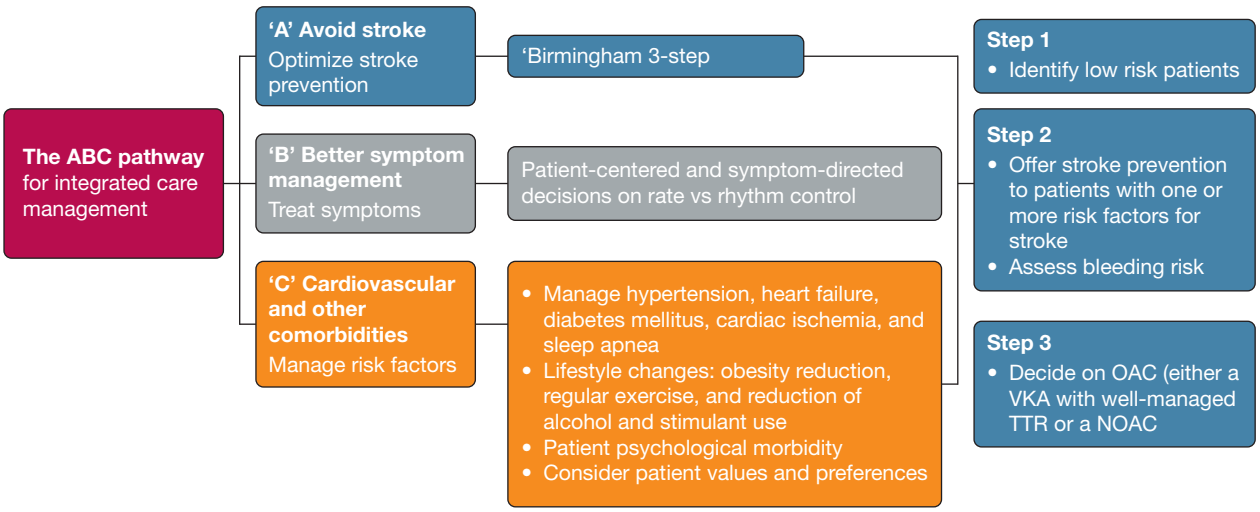

Figure 1 – *The ABC pathway of integrated care management. ABC = Atrial fibrillation Better Care; NOAC = non-vitamin K antagonist oral anticoagulant drug; OAC = oral anticoagulant; VKA = vitamin K antagonist; TTR = time in therapeutic range. (Adapted from Lip.[2])*

Apart from stroke prevention ('A' Avoid Stroke, use Anticoagulants), AF management requires patient-centered and symptom-directed decisions on rate or rhythm control ('B' Better symptom management) as well as 'C' Cardiovascular and other risk factor, and lifestyle management.[2] The latter includes addressing risk factors (eg, cardiac ischemia, HF, hypertension, sleep apnea, diabetes) and lifestyle (eg, obesity, alcohol excess, stimulants). This simple ABC (Atrial fibrillation Better Care) approach would simplify an integrated approach to AF management in a holistic manner (Fig 1).[2]

This guideline focuses on stroke prevention and begins with a brief discussion of the methods used to develop these guidelines and the recommendations for antithrombotic therapy in patients with AF. Next, we provide our treatment recommendations, divided into the following sections:

- Stroke and bleeding risk assessment
- Antithrombotic therapy in patients with AF in general (includes patients with permanent, persistent, or paroxysmal AF)
- Antithrombotic therapy in patients with AF in special situations:
  - Managing bleeding
  - Antithrombotic therapy for patients with AF undergoing cardioversion
  - Acute coronary syndrome (ACS) and stenting
  - Stable coronary artery disease
  - Rhythm control and electrophysiological procedures
  - Acute ischemic stroke, intracranial hemorrhage (ICH), embolic stroke of undetermined source (ESUS), carotid disease
  - Atrial high-rate episodes (AHREs) on devices
  - Chronic atrial flutter
  - Pregnancy
  - Chronic kidney disease (CKD)
  - Valvular heart disease

The article ends with a discussion of practical and patient-centered issues as well as suggestions for future research.

Methods

Expert Panel Composition

The chair of the panel (G.Y.H.L.) was appointed and subsequently reviewed and approved by CHEST's Professional Standards Committee. Panelists were nominated by the chair based on their expertise relative to potential guideline questions.

Conflicts of Interest

All panel nominees were reviewed for their potential conflicts of interest (COIs) by CHEST's Professional Standards Committee. After review, nominees who were found to have no substantial COIs were approved, whereas nominees with potential intellectual and financial COIs that were manageable were "approved with management." Panelists approved with management were prohibited from participating in discussions or voting on recommendations in which they had substantial COIs. A grid was created listing panelists' COIs for each recommendation for use during voting. Of note, the chair (G.Y.H.L.) recused himself from any voting on recommendations. The COI grid can be found in e-Table 1.

Formulation of Key Questions

Table 1 specifies the clinical questions being addressed in this article (in PICO [population, intervention, comparator, outcomes] format) and the types of studies included.

TABLE 1] PICO Questions

	Section	Question	Patients	Intervention	Control	Outcomes	Methodology
	Burden of stroke in AF						
1.2	• Established clinical risk factors for ischemic stroke in AF (including AF burden) • Echocardiographic risk factors for ischemic stroke in AF • Potential novel risk factors for ischemic stroke in AF	What are the risk factors for ischemic stroke and TE?	Patients with AF - Established clinical risk factors - Risk factors on echocardiography - Novel risk factors Patients with chronic atrial flutter	NA	NA	Ischemic stroke Systemic TE Mortality	Cohort studies Non-warfarin arms of RCTs
1.3	Risk stratification for ischemic stroke and TE	What risk stratification schemes most accurately predict ischemic stroke and TE, and mortality?	Patients with AF	NA	NA	C-statistic NRI, IDI, DCA Absolute rates of ischemic stroke and TE	Cohort studies Clinical prediction rules
	Antithrombotic Therapy						
2.1	Patients with nonvalvular AF	What are the benefits and risks of different stroke prevention strategies?	Patients with nonrheumatic AF - Low risk - Intermediate risk - High risk (including prior stroke)	VKA	No VKA	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs

(Continued)

TABLE 1] *(Continued)*

	Section	Question	Patients	Intervention	Control	Outcomes	Methodology
2.1	Patients with nonrheumatic AF		As above	Antiplatelet drug (aspirin or other)	No antiplatelet drug	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs
			As above	VKA	Antiplatelet drug (aspirin or other)	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs
			As above	Adjusted dose VKA	Fixed minidose or low-intensity VKA ± aspirin	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	

(Continued)

TABLE 1] *(Continued)*

	Section	Question	Patients	Intervention	Control	Outcomes	Methodology
			As above	Clopidogrel + aspirin	Aspirin	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs
			As above	NOACs	VKA	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
			As above	NOAC	Aspirin	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies

(Continued)

TABLE 1] *(Continued)*

	Section	Question	Patients	Intervention	Control	Outcomes	Methodology
			As above	Device therapy (WATCHMAN, PLAATO)	VKA	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death - cardiac tamponade	SR RCTs Cohort studies
			As above	Nonpharmacologic therapies - Removal or ligation of left atrial appendage - Surgical or catheter ablation - Maze procedure	VKA	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death - procedural / surgical complications	SR RCTs Cohort studies
2.2	Patients with valvular AF	What are the benefits and risks of different stroke prevention strategies?	Patients with AF and rheumatic heart disease (ie, mitral stenosis)	VKA	No VKA	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies

(Continued)

TABLE 1] *(Continued)*

	Section	Question	Patients	Intervention	Control	Outcomes	Methodology
2.3	Patients with prosthetic valves	What are the benefits and risks of different stroke prevention strategies?	Patients with AF and prosthetic valves	VKA	No VKA	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
4	Antithrombotic therapy for AF (or atrial flutter) patients undergoing cardioversion						
3.1	Urgent cardioversion	What are the benefits and risks of antithrombotic therapy for AF patients undergoing urgent cardioversion?	Patients with AF undergoing urgent cardioversion	Anticoagulation	No anticoagulation	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
3.2	Elective cardioversion	What are the benefits and risks of antithrombotic therapy for AF patients undergoing elective cardioversion?	Patients with AF undergoing elective cardioversion	Anticoagulation	No anticoagulation	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage	SR RCTs Cohort studies

(Continued)

TABLE 1] *(Continued)*

	Section	Question	Patients	Intervention	Control	Outcomes	Methodology
						- MI - Vascular death	
3.3	TEE-guided cardioversion	What are the benefits and risks of antithrombotic therapy when using TEE-guided cardioversion?	Patients with AF undergoing TEE-guided cardioversion	TEE-guided cardioversion	Conventional anticoagulation	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
5	Practical issues in the use of adjusted-dose VKA therapy						
5.1	Optimal target INR	What target INR provides the optimal balance between stroke prevention and bleeding in AF?	Patients with AF	INR, 2-3	Other	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
			Patients with AF and valvular heart disease/ prosthetic valves	INR, 2-3	Other	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies

(Continued)

TABLE 1] *(Continued)*

	Section	Question	Patients	Intervention	Control	Outcomes	Methodology
5.1	TTR	What is the association between TTR and outcomes in AF?	Patients with AF	Good TTR	Poor TTR	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
5.1	Monitoring of VKA therapy	What is the most effective way to monitor VKA therapy?	Patients with AF on VKA therapy	Point-of-care testing, patient self-monitoring	Usual care	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
5.2	NOACs						
	Special situations						
5.3a	Patients with AF with stable coronary artery disease or peripheral arterial disease	What are the benefits and risks of adding aspirin therapy to VKA therapy?	Patients with coronary artery disease or peripheral arterial disease	OAC + aspirin	OAC	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies

(Continued)

TABLE 1] *(Continued)*

	Section	Question	Patients	Intervention	Control	Outcomes	Methodology
5.3b	Patients with AF presenting with ACS?	As above	Patients with ACS	OAC + aspirin + clopidogrel	Aspirin + clopidogrel	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
5.3c	Patients with AF undergoing percutaneous coronary intervention with stenting	As above	Patients undergoing percutaneous coronary intervention + stenting	OAC + aspirin + clopidogrel	Aspirin + clopidogrel	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
5.4	Patients with AF being treated in a rhythm control strategy	What are the benefits and risks of OAC therapy in patients treated with a rhythm control strategy?	Patients being treated with a rhythm control strategy (eg, maze procedure, catheter ablation, electrophysiology procedure, pharmacologic)	VKA, NOAC	No OAC	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies

(Continued)

TABLE 1] *(Continued)*

	Section	Question	Patients	Intervention	Control	Outcomes	Methodology
5.5	Perioperative management of OACs (including devices) Atrial high rate episodes on devices or monitors	How should VKA therapy be managed for AF patients undergoing surgery/invasive procedure?	Patients with AF on OAC therapy	"Bridging" therapy with LMWH or IV heparin	No bridging therapy	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	Cohort studies
5.6	Patients with AF presenting with an acute stroke AF patients with an ICH	What is the optimal timing for initiation of anticoagulation?	Patients with acute stroke	Anticoagulation immediately	Anticoagulation delayed	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
5.7a	Patients with AF who are pregnant	What are the benefits and risks of VKA therapy in pregnancy?	Patients with AF who are pregnant	VKA	No VKA	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies

(Continued)

TABLE 1] *(Continued)*

	Section	Question	Patients	Intervention	Control	Outcomes	Methodology
5.7b	Patients with chronic atrial flutter	What are the benefits and risks of different stroke prevention strategies?	Patients with atrial flutter	As in 2.1	As in 2.1	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
6	Bleeding						
6.1	Risk factors for bleeding on OAC therapy	What are the risk factors for bleeding while on VKA therapy?	Patients with AF on VKA therapy	NA	NA	- Fatal hemorrhage - Intracranial hemorrhage (subdural, subarachnoid, intracerebral) - Major extracranial hemorrhage - Minor bleeding	Epidemiologic studies Cohort studies RCTs
6.2	Bleeding risk assessment	What risk stratification schemes most accurately predict the risk of bleeding?	Patients with AF on OAC therapy	NA	NA	C-statistic NRI, IDI, DCA Absolute rates of bleeding outcomes (as listed above)	Clinical prediction rules
7	The patient						
		What are the values and preferences of patients with AF regarding VKA therapy, risk of stroke, and risk of bleeding?	Patients with AF	NA	NA	Patient preferences Factors which affect patient preferences Quality of life	RCTs Observational studies

ACS = acute coronary syndrome; AF = atrial fibrillation; DCA = decision curve analysis; ICH = intracranial hemorrhage; IDI = integrated discrimination index; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NA = not available; NOAC = non-vitamin K antagonist oral anticoagulant drug; NRI = net reclassification index; OAC = oral anticoagulant; RCT = randomized controlled trial; SR = systematic reviews; TE = thromboembolism; TEE = transesophageal echocardiography; TTR = time within therapeutic range; VKA = vitamine K antagonist.

TABLE 2] CHEST Grading System

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, High quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	We are very confident that the true effect lies close to that of the estimate of the effect	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect
Strong recommendation, Moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Strong recommendation, Low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.	Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Strong recommendation, very low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak (conditional) recommendation, High quality evidence	Benefits closely balanced with risks and burden	We are very confident that the true effect lies close to that of the estimate of the effect	The best action may differ depending on circumstances or patients' or societal values. Further research is very unlikely to change our confidence in the estimate of effect
Weak (conditional) recommendation, Moderate-quality evidence	Benefits closely balanced with risks and burden	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Best action may differ depending on circumstances or patients' or societal values. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Weak (conditional) recommendation, Low quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk and burden may be closely balanced	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate

(Continued)

TABLE 2] (Continued)

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Weak (conditional) recommendation, very-low quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk and burden may be closely balanced	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Ungraded consensus-based suggestions			
Ungraded Consensus-Based Statement	Uncertainty due to lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa	Insufficient evidence for a graded recommendation	Future research may well have an important impact on our confidence in the estimate of effect and may change the estimate

Consistent with the ninth edition of the guideline, the outcomes most relevant to patients with AF include death, nonfatal stroke, systemic embolism, nonfatal major extracranial bleeding, and the burden and lifestyle limitations associated with outpatient antithrombotic therapy.[3] To facilitate decision-making, the term "stroke" in this guideline includes both ischemic stroke and hemorrhagic stroke, which together with systemic embolism was the principal outcome in most stroke prevention trials. Additional considerations were all-cause and cardiovascular mortality. For bleeding outcomes, we focused on major bleeding, which was the principal safety outcome in most stroke prevention trials. Major bleeding included intracranial bleeding, the most severe and disabling form of anticoagulant-related bleeding.

Literature Searches and Study Selection

To inform our guideline development, we searched for relevant articles published since the last formal literature search performed for the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition), which were published in 2012.[3] Searches were also conducted specifically for existing guidelines and systematic reviews. In cases in which existing, good quality systematic review(s) were retrieved, the results of the review informed our recommendations.

Specifically, for literature regarding the assessment of stroke risk in patients with AF, we searched MEDLINE via PubMed and the Cochrane Library for articles published from October 2009 to October 2017 using the search terms "atrial fibrillation," "atrial flutter," "risk assessment," "risk factors," "risk stratification," "stroke," and "thromboembolism."

For literature regarding prevention of stroke and thromboembolism in patients with AF, we searched MEDLINE via PubMed and the Cochrane Library for articles published from January 1, 2007, to October 2017 using the search terms "coumarins," "warfarin," "dicumarol," "phenprocoumon," "acenocoumarol," "fondaparinux," "idraparinux," "aspirin," "triflusal," "indobufen," "dabigatran," "ximelagatran," "rivaroxaban," "apixaban," "ticlopidine," "clopidogrel," "catheter ablation," "watchman," "PLAATO," "cardioversion," "atrial fibrillation," and "atrial flutter."

Titles and abstracts of the search results were reviewed independently and in parallel to identify potentially relevant articles based on the inclusion and exclusion criteria from the PICO elements. Discrepancies were resolved by discussion. Studies deemed eligible then underwent a second round of full-text screening following the same methodology used during title/abstract review. Important data from each included study were then extracted into structured evidence tables.

Risk of Bias Assessment

The methodologist assessed the risk of bias in all included studies. The Cochrane Risk of Bias tool was used to assess the risk of bias for randomized controlled trials (RCTs)[5] and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool to evaluate risk of bias for observational studies.[6] In cases in which existing systematic reviews were available, we used the Documentation and Appraisal Review Tool to assess methodological quality.[7]

Meta-analysis

When individual studies were available or an existing meta-analysis needed to be updated, we used the Cochrane Collaboration Review Manager, version 5.2,[8] to pool the results across individual studies. We used a random-effects model and the method of DerSimonian and Laird to pool the individual estimates.[9] Risk ratio (RR) was used to report the results for dichotomous outcomes and mean difference for continuous outcomes with accompanying 95% CIs. Statistical

heterogeneity of the pooled results was assessed using the Higgins' I^2 and the χ^2 tests. A Higgins'I^2 value of $\geq$ 50% or χ^2 $P < .05$ was considered to represent significant heterogeneity.

Assessing the Overall Quality of the Evidence

The overall certainty (quality) of the evidence was assessed for each critical or important outcome of interest using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach.[10] Evidence profiles were created using the Guideline Development Tool, which categorized the overall quality of the body of evidence into 1 of 4 levels: high, moderate, low, or very low.

Drafting Recommendations

The panel drafted and graded recommendations based on the results of the meta-analyses and evidence profiles. Recommendations were graded according to CHEST's grading system, which uses the GRADE approach (Table 2).[11,12] The recommendations were either "strong" or "weak" according to this approach. Strong recommendations use the wording "we recommend" and weak recommendations use the wording "we suggest." The implications of the strength of recommendation are summarized in e-Table 2.

In instances in which there was insufficient evidence, but a clinically relevant area was felt to require a guiding comment, a weak suggestion was developed and "Ungraded Consensus-Based Statement" replaced the grade.[13]

In developing our treatment recommendations, we attempted to account for patient values and preferences regarding these outcomes, and had 2 patient advocates (Mellanie True Hills and D. A. L.) who participated in the panel discussion, and specifically addressed patient-centered issues.

Consensus Development

All drafted recommendations and suggestions were presented to the panel in an anonymous online voting survey to reach consensus and gather feedback. Panelists were requested to indicate their level of agreement on each statement based on a 5-point Likert scale derived from the GRADE grid.[14] Panelists with COIs related to the individual recommendations recused themselves from voting on those statements. Of note, the chair (G. Y. H. L.) recused himself from any voting on recommendations. According to CHEST policy, each recommendation and statement required a 75% voting participation rate and at least 80% consensus to "pass." Any recommendation or suggestion that did not meet these criteria was revised by the panel based on the feedback, and a new survey that incorporated those revisions was completed.

Peer Review Process

Reviewers from the Guideline Oversight Committee, the CHEST Board of Regents, and the *CHEST* journal reviewed the methods used and the content of the manuscript for consistency, accuracy, and completeness. The manuscript was revised according to feedback from the reviewers.

Stroke Risk in AF

The extensive data on epidemiologic burden of stroke associated with AF and well as the pathophysiology is detailed in e-Appendix 1. It is beyond the scope of this document to consider the epidemiology of all comorbidities in AF.

In summary, health-care systems face increasing prevalence, incidence, and lifetime risk of AF, which is as high as 1 in 4 in contemporary studies in high-income settings.[15] Epidemiologic studies largely represent Western countries and white populations.[16] However, reported prevalence varies substantially by world region (e-Fig 1) and with more rigorous screening methods to detect AF.

Individuals with AF have increased risk of stroke (fourfold to fivefold increase), HF (twofold to threefold fold increase), and mortality (twofold increase) (see e-Appendix 1). Patients with AF also experience higher rates of morbidity and hospital admissions, as well as early dementia. The high AF-attributable risk of stroke, especially in the elderly, is evident since at least 1 in 3 to 4 individuals with an ischemic stroke, and > 80% of those with ischemic stroke of cardioembolic subtype, also have AF.[17] Overall, non-white ethnicity shows evidence of association with lower risk of incident AF.

Several of the risk factors for incident AF are also risk factors for stroke in AF.[18] Primary prevention strategies for AF have not been conclusively proven in randomized trials, and opportunistic screening is the recommended strategy to detect AF at the population-level.[19] A systematic review of the associations of 23 cardiovascular risk factors and incident AF including 20,420,175 participants and 576,602 AF events, respectively, found hypertension, obesity, taller height, and coronary heart disease showed consistent, direct associations with incident AF.[18] Ethnic differences in comorbidities in AF patients have been reported (e-Table 3).[20-36] Hypertension is the leading comorbid risk factor and is equally distributed in different races. Coronary heart disease seems more common in whites and the Middle East, than in Asians. The annual risk of AF-associated stroke in Asians is higher than that in whites,[28,29,37,38] and the risk of stroke may start to increase at a younger age in Asians.[37]

Classification of AF

AF is classified as paroxysmal (self-terminating within 7 days), persistent (continuous for > 7 days), long-standing persistent (continuous for > 1 year), or permanent (chronic). AF becomes increasingly persistent and resistant to therapy over time, perhaps due to the development of atrial fibrosis, as well as other pathophysiological processes (e-Fig 2). AF and atrial flutter frequently co-exist, and share similar risk factors for arrhythmia development and stroke risk.[39] Lone AF

is a low risk patient group that is a diagnosis of exclusion, after ensuring no comorbidity risk factors are evident.[40] "Lone" atrial flutter (without any recognizable underlying disease), like lone AF, is also rare: only 2% of atrial flutter patients.[41] The role of anticoagulation in atrial flutter has not been assessed in clinical trials, but since individuals with atrial flutter often have concomitant AF or are at increased risk of developing AF, the risk of stroke and thromboembolism is assumed to be the same, and the same risk stratification approaches are recommended.

Risk Factors for Ischemic Stroke: Clinical Risk Factors for Ischemic Stroke in AF: Although AF is an independent risk factor for stroke, not all patients with AF have equal stroke risk. To correctly assess the risk of stroke in order to inform anticoagulation, risk prediction or stratification tools have been developed, based on the risk factors most strongly and consistently associated with stroke.

A systematic review of stroke risk factors found that prior stroke or transient ischemic attack (TIA) (15 of 16 studies positive; RR, 2.86), hypertension (11 of 20 studies positive; RR, 2.27), aging (9 of 13 studies positive; RR, 1.46 per decade increase), structural heart disease (9 of 13 studies positive; RR, 2.0), and diabetes (9 of 14 studies positive; RR, 1.62) were independent predictors of stroke. Supportive evidence was found for sex (8 of 22 studies positive; RR, 1.67), vascular disease (6 of 17 studies positive; RR, 2.61), and HF (7 of 18 studies positive; RR, 1.85).[42] Nonparoxysmal AF is associated with a highly significant increase in thromboembolism (multivariable adjusted hazard ratio [HR], 1.384; 95% CI, 1.19-1.61; $P < .001$).[43]

In individuals with HF, AF is associated with worse prognosis than sinus rhythm.[44,45] HF is an independent predictor of stroke/thromboembolism, mortality, and other clinical outcomes in individuals with AF, compared with no HF.[46] Moreover, HF is a predictor of development of AF and has been incorporated in tools for risk prediction of incident AF.[47] All-cause mortality is higher in AF patients with HF with reduced ejection fraction compared with HF with preserved ejection fraction (RR, 1.24; 95% CI, 1.12-1.36; $P < .001$), although stroke risk (RR, 0.85; 95% CI, 0.70-1.03; $P = .094$) and HF hospitalization (RR, 1.21; 95% CI, 0.96-1.53; $P = .115$) are not significantly different.[48]

CKD is an independent predictor of risk of stroke/thromboembolism. AF patients with an estimated glomerular filtration rate < 60 mL/min compared with those with an estimated glomerular filtration rate ≥ 60 mL/min have increased risk of stroke/thromboembolism (RR, 1.62; 95% CI, 1.40-1.87; $P < .001$), with a 0.41% (0.17%-0.65%) annual increase in rate for a 10 mL/min decrease in renal function.[49] The risk is higher in individuals requiring renal replacement therapy (HR, 1.83; 95% CI, 1.57-2.14; $P < .001$). There is also an increased risk of bleeding in individuals with AF and CKD, compared with those without CKD.[50] Conversely, AF is associated with an increased risk of CKD (RR, 1.64; 95% CI, 1.41-1.91).[51] The clinical relevance of renal function is not only for risk prediction but also for choice of anticoagulation and other therapies[52-54] (see *AF and CKD* section).

Over the last decade, rigorous detection strategies have shown that the prevalence of AF in cryptogenic stroke is likely to be as high as 30%.[55] A systematic review and meta-analysis after TIA has shown a pooled AF detection rate for all methods of 4% (95% CI, 2-7).[56]

Echocardiographic Risk Factors: The role of echocardiography in evaluation before cardioversion or ablation, and in predicting the presence of left atrial appendage (LAA) thrombus is dealt with in sections *Cardioversion* and *Catheter or Surgical Ablation, Electrophysiological Procedures*. There may also be a role in evaluating thromboembolic risk stratification to select appropriate antithrombotic therapy. e-Table 4 summarizes major studies which have shown an association between transthoracic echocardiography (TTE) parameters and ischemic stroke. However, there are very limited data to suggest that there would be any incremental clinical benefit in risk prediction, and moreover there is no evidence that management (in terms of oral anticoagulant [OAC]) would be changed.[57]

Nevertheless, the most consistent independent predictor of ischemic stroke on TTE is the presence of moderate-severe left ventricular systolic dysfunction. In patients undergoing transesophageal echocardiography (TEE), LAA thrombi[58] and left atrial spontaneous echo contrast[59] are both associated with increased thromboembolism, as well as the presence of low LAA velocities and complex aortic plaque; however, the same limitations as for TTE parameters apply.[57]

Biomarkers: e-Table 5 summarizes important studies involving currently available biomarkers ("biological markers") that have shown associations with stroke and thrombosis in AF, but both study design and scale of the studies limit possible conclusions. Caveats with the use

of these biomarkers include the inter- and intra-patient and assay variability; some have a diurnal variation and can be highly influenced by associated comorbidities and drug therapies. Many biomarkers are nonspecific for a particular end point and can be equally predictive not only of stroke but bleeding, death, hospitalization, HF, etc, as well as noncardiac conditions (eg, glaucoma).

The importance of biomarkers probably lies in the "very low risk" strata of clinical scores (eg, CHA_2DS_2-VASc = 0-1 group) where they may influence the decision to anticoagulate, yet there are limited data available in these patients. There are several other hurdles, including variations in availability in health-care systems, biomarker assays, access to laboratories, biomarkers diurnally, by comorbidities and by anticoagulation and other therapies. For these reasons, the clinical application of biomarkers in management of AF is unlikely to be significant.

Other Potential Novel Risk Factors for Ischemic Stroke in AF: As with established risk factors, novel risk factors may improve prediction of thromboembolic risk in AF patients, where current risk scores are suboptimal.[60] These novel factors include clinical risk factors (eg, burden of AF), serum biomarkers (eg, N-terminal pro–B-type natriuretic peptide), imaging (eg, left atrial fibrosis on cardiac MRI), and echocardiography (eg, left atrial volume index and longitudinal strain). However, these factors are currently neither proven to significantly add to risk prediction, nor likely to influence the decision to anticoagulate.

Risk Stratification for Stroke and Thromboembolism in AF: A comparison of features included in various published stroke risk stratification schemes in AF is shown in e-Table 6. A summary of studies comparing the various stroke risk stratification schema is available in e-Table 7. The risk stratification scheme commonly used in many guidelines is the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥ 75 years [doubled], diabetes, stroke/TIA/thromboembolism [doubled], vascular disease [prior myocardial infarction (MI), peripheral arterial disease (PAD), or aortic plaque], age 65-74 years, sex category [female]) score.[1]

All risk schemes based on clinical risk factors have broadly similar predictive value for "high risk" patients who sustain stroke and thromboembolism events (all c-indexes approximately 0.60-0.65). Adding more and more clinical variables and complexity (ie, simple vs more complex clinical risk scores) would only modestly increase the c-index to approximately 0.65 to 0.70. Many score comparisons focus on identification of "high risk" and do not focus on "low risk end of the spectrum" and so are not helpful for decision-making on whether to anticoagulate.

Event rates per score point varies according to study setting, ethnicity, cohort, and community vs hospitalized population, etc (as might be expected).[61] Also, reported events depends on use of highly selected clinical trial cohort vs "real-world" unselected, and anticoagulated vs non-anticoagulated patients.[62] Mortality rates from observational cohorts may also include fatal strokes as postmortems are not mandated, outcomes are nonadjudicated (as in clinical trials), and cerebral imaging is not performed. Analytical methodology matters and outcomes depend on thresholds for treatment, varying risk profile during the study (which does not remain static), and statistical analysis methods.[63] Some analyses which exclude patients on anticoagulants are flawed by "conditioning on the future" methodology, and follow-up can be dependent on continuation in a (US) health-care plan.

Ethnic differences are also evident in stroke risk related to AF. In a Taiwanese cohort, the risk of stroke was 1.78% per year in patients aged 50 to 64 years and a CHA_2DS_2-VASc 0.[64] The risk exceeds the threshold for OAC use for stroke prevention. A modified CHA_2DS_2-VASc score has been proposed, assigning one point for patients aged 50 to 74 years.[65] The modified CHA_2DS_2-VASc score performed better than the CHA_2DS_2-VASc score in predicting ischemic stroke assessed by c-indexes and net reclassification index. For patients having a modified CHA_2DS_2-VASc score of 1 (males) or 2 (females) because of the resetting of the age threshold, use of warfarin was associated with a 30% lower risk of ischemic stroke and a similar risk of ICH compared with no treatment. Net clinical benefit analyses also favored the use of warfarin in different weighted models. These findings suggest that the age-based treatment threshold for stroke prevention may need to be reset in East Asians.[65]

Adding biomarkers would (statistically) improve prediction, but c-indexes are still approximately 0.65 to 0.70. Recent studies in real-world cohorts do not support the clinical usefulness of biomarker-based scores over clinical risk scores such as the CHA_2DS_2-VASc score. The use of biomarkers has to balance the assay availability, laboratory variability, costs, and added complexity and lower practicality for everyday use. Also, many biomarker studies are based on anticoagulated

highly selected clinical trial cohorts, with all included subjects already in the high risk group (CHA_2DS_2-VASc or $CHADS_2$ [congestive heart failure, hypertension, age, diabetes, stroke (doubled)] score of 2 or greater). There are few/no studies on non-anticoagulated AF patients, to ascertain the true impact of biomarkers on (non-anticoagulation treated) stroke rates. Current studies do not inform whether the biomarkers will discriminate/identify low risk in lower/intermediate risk patients who are not anticoagulated.

Rather than focus on identifying "high risk," the focus should be on initially identifying "low risk" patients. A "low risk" categorization by the CHA_2DS_2-VASc (0 in males and 1 in females) consistently identifies low risk patients, with event rates around 1% per year or under, notwithstanding the possible need to re-categorize the age 65 to 74 years criterion in Asians.[65]

The majority of published studies and systematic reviews suggest that the CHA_2DS_2-VASc score is generally better than $CHADS_2$, Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA), and $CHADS_2$ score plus age 65-74 years, used in Canadian guidelines (CHADS65) in identifying "low risk" patients, although the proportion of the population assigned as low risk is small. However, there are conflicting data in different cohorts for performance of the ATRIA score (United Kingdom Clinical Practice Research Datalink [UK CPRD] and Swedish cohorts vs Danish and Taiwan cohorts). Differences between the ATRIA and CHA_2DS_2-VASc disappear when cut-points are optimized for stroke risk of the cohort. There are discrepancies between individual studies on the relative performance of ATRIA and CHA_2DS_2-VASc scores in identifying low risk patients, but the CHA_2DS_2-VASc score is easier to calculate.

Rather than using risk scores in a categorical manner—recognizing the various limitations of scores to predict "high risk" patients who sustain events—and given that for each risk strata or given risk score point, we recognized there is wide variation in reported event rates based on reported study clinical setting, patient population, ethnicity, etc. Notwithstanding that the default should be stroke prevention for all AF patients unless deemed to be "low risk," the focus should be to use scores to initially identify "low risk" patients who do not need antithrombotic therapy, rather than focus on identification of "high risk" patients. Prior guidelines have also opted for the CHA_2DS_2-VASc score to define a low risk group.

The 'C' in CHA_2DS_2-VASc refers to recent decompensated HF, irrespective of the ejection fraction (thus including HF with reduced ejection fraction or HF with preserved ejection fraction) or the presence of moderate-severe left ventricular systolic impairment on cardiac imaging, whether symptomatic or asymptomatic. The 'H' refers to history of hypertension or uncontrolled BP, while 'S' refers to stroke, systemic embolism, or a confirmed diagnosis of TIA. 'V' refers to complicated vascular disease, including MI or PAD, or if performed, the presence of complex aortic plaque on TEE. Female sex (Sc criterion) is only relevant as a risk modifier if age > 65 or additional associated risk factors are present, given that females age < 65 with no other risk factors are not at excess stroke risk.[66] Stroke risk is also dynamic, and risk should be re-assessed at every patient contact. This was seen in a study where the "delta CHA_2DS_2VASc score," representing the change in stroke risk between between baseline and follow-up), was the best predictor for ischemic stroke.[67]

A stepwise approach to thromboprophylaxis would allow initial identification of low risk using CHA_2DS_2-VASc (Step 1), following which stroke prevention can be offered to all others (Step 2) irrespective of stroke point score or biomarkers used. This approach uses stroke risk scores in a reductionist manner to aid decision-making, and balances simplicity and practicality (and costs).

Recommendations

1. For patients with AF, including those with paroxysmal AF, stroke risk should be assessed using a risk factor based approach, rather than an categorization into low, moderate/high risk strata. We recommend use of the CHA_2DS_2-VASc as a simple clinical based stroke risk score to initially identify 'low stroke risk' patients who should not be offered antithrombotic therapy to prevent stroke and reduce mortality (Strong recommendation, moderate quality evidence).

Remark: Low risk patients are generally those age < 65 and 'lone AF' irrespective of sex (this includes those with a CHA_2DS_2-VASc score $= 0$ in males, or 1 in females).

2. Subsequent to this initial step, for patients with AF, including those with paroxysmal AF, stroke prevention should be offered to those AF patients with one or more non-sex CHA_2DS_2-VASc stroke risk factors (score of ≥ 1 in a male or ≥ 2 in a female) (Strong recommendation, moderate quality evidence).

Remark: Consideration of other less established clinical stroke risk factors, imaging (cardiac or cerebral), or biomarkers (urine, blood, or genetics) may refine risk

stratification based on simple clinical factors. A complex risk schema using a variety of such data that could accurately place more patients in the low risk stratum not requiring anticoagulants than current simple clinically based scores (personalized medicine) should be the goal of future research, but it will be very difficult to find non-anticoagulated patient cohorts for prospective validation.

Bleeding Risk in AF

Observational Studies

The rates of major bleeding on vitamin K antagonists (VKAs) among observational cohorts are shown in e-Table 8 and demonstrate highly variable rates, ranging from 1.4% per year[68,69] to 10.4% per year.[70] Nevertheless, there is significant heterogeneity between the study population characteristics, the inclusion of inception vs "experienced" OAC cohorts, significant disparity in the exposure period (follow-up) and differences in the definitions of major bleeding employed. In addition, information on the specific risks of bleeding of the individual cohorts, using a validated bleeding risk score, are lacking, the definitions of major bleeding were often not provided, and the quality of anticoagulation, such as time in therapeutic range (TTR), is generally lacking. Therefore, direct comparison of the rates of major bleeding on VKA between observational cohorts and with RCTs is problematic.

Clinical Trials

The definitions of major bleeding are available in most clinical trials, especially in the non-vitamin K antagonist oral anticoagulant drug (NOAC) trials where International Society on Thrombosis and Haemostasis definitions were used.[71] Before the NOAC era, the rates of major bleeding due to VKA were generally in the range of 1% to 3% per year (e-Table 9). In the 5 NOAC trials,[72-76] the annual rates of major bleeding of warfarin were between 3% and 4% (Table 3). Data from NOACs trials are more reliable, because patients were randomized to treatment, the majority were double-blinded, and the quality of anticoagulation (such as TTR) was generally better than observational studies. The risk of major bleeding on NOACs, especially the low-dose regimen (dabigatran 110 mg and edoxaban 30 mg), was generally lower than that on warfarin, except 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) trial.[73]

Risk Factors for Bleeding With NOAC, VKA, and Antiplatelet Therapy: Numerous risk factors for bleeding among AF patients receiving antithrombotic therapy have been identified and incorporated into bleeding risk scores (see section on *Use of Bleeding Risk Scores*). Bleeding risk varies from person to person depending on their pre-existing comorbidities, current antithrombotic regimen and adherence, concomitant medication, and lifestyle choices. Many of these factors cannot be altered but some are modifiable or potentially modifiable (Fig 2). In order to reduce antithrombotic treatment-associated bleeding, it is important to recognize that bleeding risk is also dynamic and should be reassessed at every patient review. While modifiable bleeding risk factors that can be changed or managed should clearly be addressed as part of a holistic approach to AF patient assessment and management, nonmodifiable bleeding risks are important drivers of bleeding events when occurring synergistically with modifiable ones.[77] An approach to bleeding risk assessment soley based only on modifiable bleeding risk factors is an inferior assessment strategy compared with use of a formal bleeding risk score.[78-80]

BP Control: Good control of BP is vital to reduce the risk of stroke and is essential to decrease the risk of bleeding on antithrombotic therapy; adherence to current guidelines on the management of hypertension should be followed.

Anticoagulation Control: Among patients receiving VKA, maintenance of an international normalized ratio (INR) in the therapeutic range (2.0-3.0) is essential. The proportion of time spent in this range (TTR) should be at least 65% but the ultimate aim/target should be 100% (see *Optimal INR Target Range* section). The risk of bleeding increases when the INR exceeds 3.0, particularly for ICH risk when INR $>$ 3.5.[81-86]

INR control can potentially be improved by more frequent monitoring and review of factors influencing INR control (diet-, alcohol-, and drug-interactions). There is evidence that improving patient education about INR control,[87] INR management by dedicated anticoagulation clinics with experienced personnel,[88-90] and self-monitoring/self-management in selected patients[91] can increase TTR. Increasing patient's awareness of the importance of OAC medication adherence and the potential bleeding risks associated with overdose are also essential to minimize bleeding complications.

TABLE 3] Risk Factors, Risk Categories and Bleeding Events in the Validation Cohorts

Risk Score	Risk Factors (Score for Each Factor)	Risk Categories			Bleeding Events in Validation Cohort (per 100 patient-years)		
		Low	Intermediate	High	Low	Intermediate	High
ABC[100]	Age[a]; biomarkers[a] (GDF-15 or cystatin C/CKD-EPI, cTnT-hs, and Hb); previous bleed[a]	< 1%	1%-2%	> 3%	0.62	1.67	4.87
ORBIT[101]	Age ≥ 75 (1); ↓Hb/Hct/anemia (2); bleeding history (2); ↓ renal function (1); APT (1)	0-2	3	≥4	2.4[b]	4.7	8.1
ATRIA[69]	Anemia (3); severe renal disease (3); age ≥ 75 (2); prior bleed (1); hypertension (1)	0-3	4	5-10	0.83	2.41	5.32
HAS-BLED[98]	↑SBP (1); severe renal/hepatic disease (1 each); stroke (1); bleeding (1); labile INR (1); age > 65 y (1); APT/NSAIDs (1); alcohol excess (1)	0-1	2	≥ 3	1.02-1.13	1.88	≥ 3.74
HEMORR$_2$HAGES[99]	Hepatic/renal disease (1); ethanol abuse (1); malignancy; age > 75 y (1); ↓Plt (1); re-bleeding risk (2); ↑BP (1); anemia (1); genetic factors (1); ↑ falls risk (1); stroke (1)	0-1	2-3	≥ 4	1.9-2.5	5.3-8.4	10.4-12.3
Shireman et al[102]	Age ≥ 70 y (0.49); female (0.31); previous bleed (0.58); recent bleed (0.62); alcohol/drug abuse (0.71); DM (0.27); anemia (0.86); APT (0.32)	≤ 1.07	> 1.07/< 2.19	≥ 2.19	0.9%[c]	2.0%[c]	5.4%[c]

↓ = reduced/decreased; ↑ = elevated/increased; ABC = Atrial fibrillation Better Care; APT = antiplatelet therapy; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; cTnT-hs = high-sensitivity troponin T; DM = diabetes mellitus; GDF-15 = growth differentiation factor-15; HAS-BLED = hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (.65), drugs/alcohol concomitantly (1 point each); Hb = hemoglobin; Hct = hematocrit; HEMORR$_2$HAGES = hepatic or renal disease, ethanol abuse, malignancy, older, reduced platelet count/function, hypertension, anemia, genetic factors, excessive fall risk, and stroke; INR = international normalized ratio; NSAIDs = nonsteroidal antiinflammatory drugs; ORBIT = Outcomes Registry for Better Informed Treatment of Atrial Fibrillation Registry; Plt = platelet count or function; SBP = systolic BP. See Table 1 legend for expansion of other abbreviation. (Partly reproduced with permission from Zulkifly et al.[103])

[a]Score for each variable in ABC score is based on a nonogram (see reference[100]).

[b]Bleeding event in original derivation cohort.

[c]At 3 months.

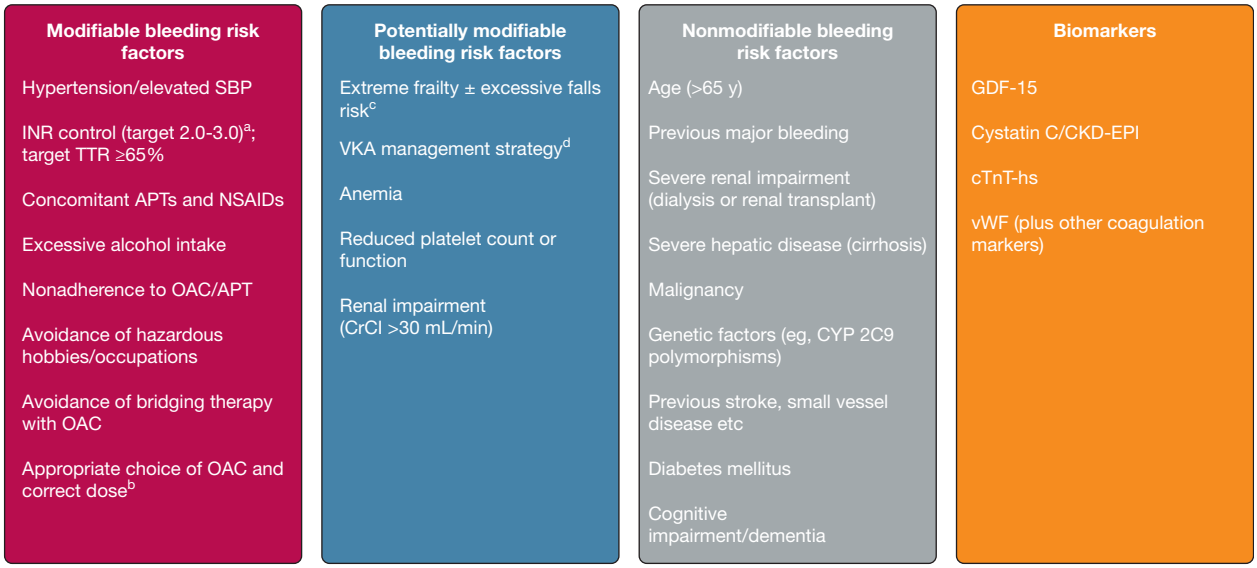

Figure 2 – *Risk factors for bleeding with oral anticoagulation and antiplatelet therapy.* [a]*For patients receiving VKA treatment.* [b]*Dose adaptation based on patient's age, body weight, and serum creatinine level.* [c]*Walking aids; appropriate footwear; home review to remove trip hazards; neurologic assessment where appropriate.* [d]*Increased INR monitoring, dedicated OAC clinicals, self-monitoring/self-management, educational/behavioral interventions. APTs = antiplatelets; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CrCl = creatinine clearance; cTnT-hs = high-sensitivity troponin T; CYP = cytochrome P450; GDF-15 = growth differentiation factor-15; INR = international normalized ratio; NSAIDs = nonsteroidal antiinflammatory drugs; SBP = systolic blood pressure; vWF = von Willebrand factor. See Figure 1 legend for expansion of other abbreviations.*

Concomitant Medication Predisposing to Bleeding: Nonessential use of concomitant antiplatelet drugs and NSAIDs should be avoided since these medications increase the risk of bleeding in patients receiving OACs. Where concomitant antiplatelet therapy (APT) is necessary (ie, postcoronary stent implantation), the duration of combination OAC and antiplatelet drugs should be kept to the minimum.[92] Since antiplatelet drugs/NSAIDs are widely available over-the-counter, patients need to be made aware of the bleeding risk associated with their use in combination with OAC.

Alcohol Intake: Excessive alcohol intake (chronic or binge-drinking) increases the risk of bleeding predominantly due to the risk of trauma, but in chronic alcohol abuse through poor medication adherence, hepatic and variceal disease. OACs should not initiated among patients consuming alcohol in excess > 14 U/week. There is no clear definite threshold where bleeding risk is increased. Patients also need to be made aware of the potential dangers associated with excessive alcohol consumption in combination with OAC/antithrombotic therapy.

Lifestyle Factors: Avoidance of work and/or leisure activities that have the potential to cause serious trauma (eg, contact sports, rock-climbing, occupations working at height or operating heavy machinery) should be advised.

Bridging Periods Off Anticoagulation: Interruption of OAC should be avoided to reduce stroke risk since the majority of cardiovascular procedures (eg, pacemaker implantation or percutaneous coronary intervention [PCI]) can be safely performed on OAC. Bridging (ie, stopping OAC and providing anticoagulation cover with heparin) should be used in patients with mechanical heart valves but does not appear to be otherwise advantageous.[93,94]

Appropriate Choice of OAC: Choice of OAC should be made on an individual basis after stroke and bleeding risk assessment and discussion with the patient. Before an NOAC is initiated, the patient's age, body weight, and renal function should be considered to allow for appropriate dose adaptation where necessary.

Falls Risk and Cognitive Impairment: In frail patients and those at high risk of falls, an individual risk assessment needs to be undertaken prior to OAC initiation. In cases where the risk is that of mechanical falls, strategies to improve walking/reduce risk of tripping should be explored (ie, walking aids, appropriate footwear, home review to remove trip hazards), whereas neurological assessment is warranted if falls are unexplained. The benefits of ischemic stroke reduction generally outweigh the risk of harm from serious bleeding with OAC use; one estimate was that

the patient would need to fall 295 times per year for the risk from falls to outweigh the benefits of stroke reduction.[95] In patients with cognitive impairment or dementia, OAC should only be withheld if there is no available caregiver who can guarantee medication adherence.

Reversal of Biochemical Anomalies: Patients with anemia or reduced platelet count or function should be treated where possible to improve their hemoglobin or platelet count. Causes of renal impairment should be investigated and where possible reversed.

Patients with liver function abnormalities were generally excluded from the randomized trials, and especially where there is abnormal clotting tests, such patients may be at higher risk of bleeding on VKA, possibly less so on NOACs; in cirrhotic patients, ischemic stroke reduction may outweigh bleeding risk.[96,97]

Bleeding Risk Assessment: Since 2006, six risk scores have been developed and validated for the assessment of bleeding risk in AF populations.[98-103] The number of risk factors included in the bleeding risk schemas varies considerably, from three[100] to 12,[102] and the score or weighting associated with each risk factor also differs (Table 3).[69,98-103]

Age and prior bleeding are included as risk factors in all 6 bleeding risk scores but different age cutoffs are utilized, with 3 scores employing age 75 years or older[69,99,101] to indicate greater bleeding risk. Following age and prior bleeding, the most prevalent bleeding risk factors included in the scores are anemia,[69,99-102] renal disease,[69,98,99,101] hypertension[69,102] or uncontrolled systolic BP,[98] concomitant antiplatelets,[98,101,102] and alcohol excess,[98,99,102] and prior stroke[98,99] or hepatic disease.[98,99] A variety of other risk factors, including cancer,[102] labile INR,[98] genetic factors,[99] falls risks,[99] female sex,[102] diabetes mellitus,[102] and biomarkers,[100] are included only in one bleeding risk score. For a comprehensive review of bleeding risk factors in AF patients see Zulkifly et al.[103]

The bleeding risk scores range in the simplicity of calculation and the cutoffs employed to indicate low, intermediate, and high risk of bleeding, and the prevalence of bleeding events reported in the validation cohorts (Table 3).

Use of Bleeding Risk Scores: As seen in Table 3, there are multiple bleeding risk scores that have been proposed for bleeding risk stratification, with the $HEMORR_2HAGES$ (hepatic or renal disease, ethanol abuse, malignancy, older, reduced platelet count/function, hypertension, anemia, genetic factors, excessive fall risk, and stroke), HAS-BLED (hypertension, abnormal renal/liver function [1 point each], stroke, bleeding history or predisposition, labile INR, elderly (0.65), drugs/alcohol concomitantly [1 point each]), ATRIA, ORBIT, and ABC-bleeding derived and validated in AF populations.[103] The risk factors included vary by scores (Table 3), and their derivation from selected clinical trial cohorts or "real-world" populations.[103] Various validation studies have been summarized in e-Table 10.

Unsurprisingly, stroke risk scores are also associated with bleeding, as stroke and bleeding risks correlate with each other. For example, higher $CHADS_2$ and CHA_2DS_2-VASc scores are also associated with greater bleeding risk, but the HAS-BLED score outperforms the $CHADS_2$ and CHA_2DS_2-VASc scores for predicting serious bleeding,[104,105] which was also evident in the systematic review by Zhu et al.[106] Composite risk scores that include stroke and bleeding end points have also been proposed but have not been shown to perform incrementally better over the individual scores.[107,108] The bleeding risk scores in AF are also predictive of bleeding in non-AF populations; for example, in patients with ACS undergoing PCI-stenting.[109]

Adding more clinical variables marginally improves the predictive value (at least statistically), but the c-indexes still remain approximately 0.6. The addition of biomarkers would all improve the c-indexes (to approximately 0.65) over scores based on clinical risk factors alone. Many of these risk scores have been derived from highly selected clinical trial cohorts (often anticoagulated), with the biomarkers measured at baseline (or within a few months of study entry) then end points determined many years later. Biomarkers are also expensive, and may be subject to laboratory variability, inter-assay differences, diurnal variation and may change in individual patients depending on how risk factors and drug treatments change over time. Many biomarkers (**eg**, troponin, natriuretic peptides, inflammatory markers, coagulation markers, etc) are also predictive of stroke, bleeding, death, HF, hospitalization,[110] and even noncardiovascular conditions such as glaucoma progression (eg, as in the case of growth differentiation factor-15 used in the ABC-bleed score).[111] The performance of biomarker-based scores in real-world clinical practice (outside highly selected trial cohorts) has also been disappointing,[112,113] given that baseline (or near-baseline) determination of biomarkers to predict

bleeding risks after many years is bedeviled by the changing clinical risk profile of patient's risks as well as modification of risk factors.

Given that modifiable bleeding risk factors should be addressed in all patients, the appropriate and responsible way to use a clinical risk score is to identify those patients at particularly high risk, for appropriate early review and follow-up (eg, in 4 weeks, rather than 4-6 months) and depending on the outcome of interest, to address the associated modifiable risk factors accordingly (Figs 2, 3). A high bleeding risk score is not a reason to withhold OAC, as the net clinical benefit is even greater in those patients with high bleeding risk.

While bleeding risk is highly dynamic and depends on many potentially modifiable bleeding risk factors,[114] simply focusing on bleeding risk assessment using modifiable bleeding risk factors alone is an inferior strategy compared with using a validated bleeding risk score which has been designed to formally assess bleeding score.[78-80]

A comparison of the different bleeding risk scores has been addressed in 2 systematic reviews, and the studies are summarized in e-Table 10. As with stroke risk scores, most bleeding risk scores based on simple clinical risk factors only have modest predictive value for identifying the high risk patients who sustain events (c-indexes approximately 0.6).

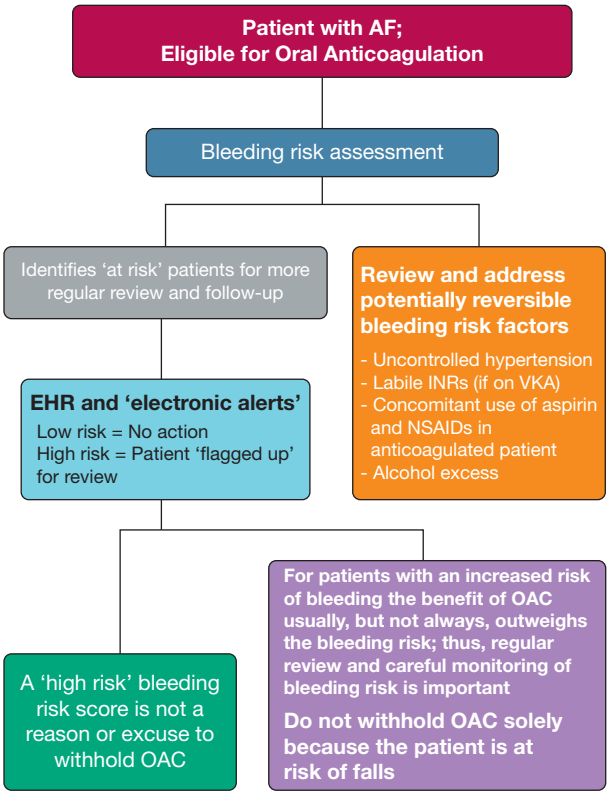

Figure 3 – *Practical application of bleeding risk assessment in patients with AF. AF = atrial fibrillation; EHR = electronic health record. See Figure 1 and 2 legends for expansion of other abbreviations.*

The systematic review by Caldeira et al[115] reported that the sensitivity, specificity and diagnostic ORs were, respectively, 0.53 (95% CI, 0.52-0.54), 0.65 (95% CI, 0.65-0.65), and 2.11 (95% CI, 1.91-2.35) for HAS-BLED, and 0.27 (95% CI, 0.26-0.27), 0.89 (95% CI, 0.89-0.89), and 2.90 (95% CI, 2.77-3.04) for HEMORR$_2$HAGES. When comparing HAS-BLED with ATRIA, sensitivity, specificity, and diagnostic ORs were, respectively, 0.41 (95% CI, 0.35-0.48), 0.78 (95% CI, 0.76-0.79), and 2.22 (95% CI, 1.08-4.55) for HAS-BLED, and 0.23 (95% CI, 0.17-0.29), 0.91 (95% CI, 0.90-0.91), and 1.98 (95% CI, 1.29-3.03) for ATRIA. They concluded that HAS-BLED, due to its sensitivity (compared with other scores) and ease to apply, is recommended for the assessment of AF patients' major bleeding risk.

The systematic review by Zhu et al[106] (11 studies) found that discrimination analysis demonstrates that HAS-BLED has no significant C-statistic differences for predicting bleeding risk in the low (RR, 1.16; 95% CI, 0.63-2.13; $P = .64$) risk stratification but underpredicts risk in the moderate (RR, 0.66; 95% CI, 0.51-0.86; $P = .002$) and high (RR, 0.88; 95% CI, 0.70-1.10; $P = .27$) risk strata (e-Table 11). Zhu et al[106] concluded that the HAS-BLED score performed better than the HEMORR$_2$HAGES and ATRIA bleeding scores but was superior to the CHADS$_2$ and CHA$_2$DS$_2$-VASc stroke scores for bleeding prediction. In a real-world AF cohort, there was no long-term advantage of the ABC-bleeding score over the HAS-BLED score, for predicting bleeding; in contrast, HAS-BLED was better in identifying those patients at low risk of bleeding.[113]

Given that the patient pathway may include AF patients initially on no antithrombotic therapy, aspirin, or anticoagulants, and the latter can include VKAs or NOACs, a bleeding risk score needs to be applicable throughout the patient pathway. The HAS-BLED score has been validated in AF patients from clinical trial and nontrial cohorts, whether on no antithrombotic therapy, aspirin or anticoagulants, VKA or non-VKA anticoagulants, and is predictive of bleeding in AF and non-AF cohorts, and in different ethnic groups.[98,114,116] It is also the only bleeding score predictive of intracranial bleeding.[117]

The HAS-BLED score has also been shown to be similar or outperform older bleeding scores, as well as more

simple bleeding scores that include fewer clinical parameters. Among VKA-treated patients, the nonconsideration of TTR would also mean that the $HEMORR_2HAGES$, ORBIT, and ATRIA scores would all perform suboptimally in VKA-treated patients.[118,119] Finally, bleeding risk assessment is dynamic, and should be formally reassessed and recorded at every patient contact. Indeed, follow-up HAS-BLED or "delta HAS-BLED score" was more predictive of major bleeding compared with baseline HAS-BLED or the simple determination of modifiable bleeding risk factors.[77]

Recommendations

3. For patients with AF, bleeding risk assessment should be performed in all patients with AF at every patient contact and should initially focus on potentially modifiable bleeding risk factors (Strong recommendation, low quality evidence).

Remark: Modifiable risk factors may include: Uncontrolled blood pressure, Labile INRs (in a patient taking VKA), Alcohol excess; Concomitant use of NSAIDs or aspirin, in an anticoagulated patient, bleeding tendency or predisposition (eg, treat gastric ulcer, optimize renal or liver function, etc).

4. For patients with AF, we recommend use of the HAS-BLED score to address modifiable bleeding risk factors in all AF patients. Those potentially at high risk (HAS-BLED score ≥ 3) warrant more frequent and regular reviews or follow-up (Strong recommendation, moderate quality evidence).

Remark: Given that bleeding risk is highly dynamic, attention to modifiable bleeding risk factors should be prioritized during every patient contact or review.

5. In VKA-treated patients, we recommend use of the HAS-BLED score for bleeding risk assessment (Weak recommendation, low quality evidence).

Remark: A high HAS-BLED score (≥ 3) is rarely a reason to avoid anticoagulation. The individual modifiable components of the score, when reviewed with the patient, can serve to ameliorate bleed risk

Anti-Thrombotic Therapy and Other Approaches for Stroke Prevention

The principal goal of OAC in AF is to reduce the risk of stroke and systemic embolism, while minimizing the incremental bleeding risk associated with OAC. Although these outcomes may be in part mechanistically related to lower risk of bleeding and ischemic stroke compared with therapies in the control arms, cardiovascular composite or survival outcomes presently do not reflect the primary rationale for therapy.

Randomized Trials: VKAs Compared With Placebo or Control: In a meta-analysis of 2,900 subjects from 6 randomized trials, adjusted-dose warfarin was associated with a 64% relative risk reduction in stroke (95% CI, 49-74) (e-Table 12). The absolute risk reduction was 2.7% per year (from 4.5% per year in control subjects) in primary prevention subjects and 8.4% per year (from 12% per year in control subjects) in secondary prevention subjects.[120]

Aspirin and APT Compared With Placebo or Control: In a meta-analysis of 8 trials of 4,876 subjects, APT compared with control or placebo was associated with a 22% (95% CI, 6-35) relative risk reduction in stroke (e-Table 13).[120] The Stroke Prevention in AF (SPAF-I) study demonstrated decrease in risk of stroke from 6.3% per year in placebo subjects to 3.6% per year (95% CI, 9-63),[121] but a meta-analysis of 7 trials of 3,990 subjects found no significant benefit. SPAF-I was the only trial suggestive of a benefit for aspirin compared with placebo, but there was internal heterogeneity between the anticoagulation-eligible and anticoagulation-ineligible subgroups, and given the trial was stopped early, the effect size could have been exaggerated. Aspirin also showed no benefit in the elderly, or in preventing severe strokes. All these trials had significant heterogeneity in study design, variability in aspirin dose tested, short follow-up, and predated contemporary use of oral anticoagulation in AF.

The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-A) trial, which also predated the investigation of NOACs, compared aspirin plus clopidogrel vs aspirin monotherapy among patients in whom VKA was unsuitable.[122] The study found a decrease in risk of stroke with dual antiplatelet therapy (DAPT), but the major bleeding rates with aspirin-clopidogrel were comparable to rates seen with warfarin (approximately 2% per year).

VKAs Compared With APT: Of 12 studies comparing warfarin vs APT, warfarin was associated with a 39% relative risk reduction (95% CI, 22-52) in strokes (e-Table 14).[120] In the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W), the largest of these studies, warfarin was superior to DAPT to warfarin for stroke and a

TABLE 4] Phase 3 AF Trials of NOAC vs Warfarin: Summary of Key Efficacy and Safety Results

	Trial									
	RE-LY[72]			ROCKET-AF[73]		ARISTOTLE[74]		ENGAGE AF-TIMI 48[76]		
Outcome	Dabigatran 150 mg (n = 6,076)	Dabigatran 110 mg (n = 6,015)	Warfarin (n = 6,022)	Rivaroxaban 20/15 mg (n = 7,131)	Warfarin (n = 7,133)	Apixaban 5/2.5 mg (n = 9,120)	Warfarin (n = 9,081)	Edoxaban 60/30 mg (n = 7,035)	Edoxaban 30/15 mg (n = 7,034)	Warfarin (n = 7,036)
Efficacy										
Stroke/SEE										
Event rate (%/y)	1.11	1.54	1.71	2.1	2.4	1.27	1.60	1.57	2.04	1.80
HR (95% CI)	0.72 (0.58-0.90)	0.90 (0.74-1.10)	NA	0.88 (0.75-1.03)	NA	0.79 (0.65-0.95)	NA	0.87 (0.73-1.04)	1.13 (0.96-1.34)	NA
P	.004	.29	NA	.12	NA	.01	NA	.08	.10	NA
Ischemic stroke										
Event rate (%/y)	0.92	1.34	1.22	1.34	1.42	0.97	1.05	1.25	1.77	1.25
HR (95% CI)	0.76 (0.59-0.97)	1.11 (0.88-1.39)	NA	0.94 (0.75-1.17)	NA	0.92 (0.74-1.13)	NA	1.00 (0.83-1.19)	1.41 (1.19-1.67)	NA
P	.03	.35	NA	.58	NA	.42	NA	.97	< .001	NA
Hemorrhagic stroke										
Event rate (%/y)	0.10	0.12	0.38	0.26	0.44	0.24	0.47	0.26	0.16	0.47
HR (95% CI)	0.26 (0.14-0.49)	0.31 (0.17-0.56)	NA	0.59 (0.37-0.93)	NA	0.51 (0.35-0.75)	NA	0.54 (0.38-0.77)	0.33 (0.22-0.50)	NA
P	< .001	< .001	NA	.02	NA	< .001	NA	< .001	< .001	NA
MI										
Event rate (%/y)	0.81	0.82	0.64	0.91	1.12	0.53	0.61	0.70	0.89	0.75
HR (95% CI)	1.27 (0.94-1.71)	1.29 (0.96-1.75)	NA	0.81 (0.63-1.06)	NA	0.88 (0.66-1.17)	NA	0.94 (0.74-1.19)	1.19 (0.95-1.49)	NA
P	.12	.09	NA	.12	NA	.37	NA	.60	.13	NA
All-cause death										
Event rate (%/y)	3.64	3.75	4.13	1.87	2.21	3.52	3.94	3.99	3.80	4.35
HR (95% CI)	0.88 (0.77-1.00)	0.91 (0.80-1.03)	NA	0.85 (0.70-1.02)	NA	0.89 (0.80-1.0)	NA	0.92 (0.83-1.01)	0.87 (0.79-0.96)	NA
P	.05	.13	NA	.07	NA	.047	NA	.08	.006	NA
Safety										
Major bleeding										
Event rate (%/y)	3.32	2.87	3.57	3.6	3.4	2.13	3.09	2.75	1.61	3.43
HR (95% CI)	0.93 (0.81-1.07)	0.80 (0.70-0.93)	NA	1.04 (0.90-1.20)	NA	0.69 (0.60-0.80)	NA	0.80 (0.71-0.91)	0.47 (0.41-0.55)	NA
P	.31	.003	NA	.58	NA	< .001	NA	< .001	< .001	NA
ICH										
Event rate (%/y)	0.32	0.23	0.76	0.5	0.7	0.33	0.80	0.39	0.26	0.85

(Continued)

TABLE 4 (*Continued*)

Outcome	Trial									
	RE-LY[72]			ROCKET-AF[73]		ARISTOTLE[74]		ENGAGE AF-TIMI 48[76]		
	Dabigatran 150 mg (n = 6,076)	Dabigatran 110 mg (n = 6,015)	Warfarin (n = 6,022)	Rivaroxaban 20/15 mg (n = 7,131)	Warfarin (n = 7,133)	Apixaban 5/2.5 mg (n = 9,120)	Warfarin (n = 9,081)	Edoxaban 60/30 mg (n = 7,035)	Edoxaban 30/15 mg (n = 7,034)	Warfarin (n = 7,036)
HR (95% CI)	0.41 (0.28-0.60)	0.30 (0.19-0.45)	NA	0.67 (0.47-0.93)	NA	0.42 (0.30-0.58)	NA	0.47 (0.34-0.63)	0.30 (0.21-0.43)	NA
P	< .001	< .001	NA	.02	NA	< .001	NA	< .001	< .001	NA
GI bleeding										
Event rate (%/y)	1.56	1.15	1.07	2.0	1.24	0.76	0.86	1.51	0.82	1.23
HR (95% CI)	1.48 (1.18-1.85)	1.08 (0.85-1.38)	NA	1.66 (1.34-2.05)	NA	0.89 (0.70-1.15)	NA	1.23 (1.02-1.50)	0.67 (0.53-0.83)	NA
P	.001	.52	NA	< .001	NA	.37	NA	.03	< .001	NA

ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ENGAGE AF-TIMI 48 = Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48; HR = hazard ratio; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SEE = systemic embolic events. See Table 1 legend for expansion of other abbreviations.

cardiovascular composite outcome, with similar rates of major bleeding.[123]

NOACs Compared With VKAs: Several NOACs that directly inhibit thrombin (factor IIa) or activated factor X (factor Xa) have been approved as alternatives to VKAs for stroke prevention in AF. They differ from VKAs in that they have a rapid onset/offset of action, absence of an effect of dietary vitamin K intake on their activity, and fewer drug interactions. The predictable anticoagulant effects of the NOACs enable their administration in fixed doses without the need for routine coagulation monitoring, thereby simplifying therapy.

Individually in their respective phase 3 trials (Table 4), dabigatran, rivaroxaban, apixaban, and edoxaban have been shown to be at least as safe and effective as warfarin for preventing stroke and systemic embolism in patients with AF.[72-74,76]

A meta-analysis of the four phase 3 trials compared patients taking NOACs (higher dose) (n = 42,411) with warfarin (n = 29,272) (e-Table 15).[124] NOACs significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR, 0.81; 95% CI, 0.73-0.91; $P < .0001$). The benefit was driven primarily by a 51% reduction in hemorrhagic stroke (RR, 0.49; 95% CI, 0.38-0.64; $P < .0001$). Ischemic stroke was similar between NOACs and warfarin (RR, 0.92; 95% CI, 0.83-1.02; $P = .10$). NOACs were also associated with a significant 10% reduction in all-cause mortality (RR, 0.90; 95% CI, 0.85-0.95; $P = .0003$). Regarding safety, NOACs were associated with a nonsignificant 14% reduction in major bleeding (RR, 0.86; 95% CI, 0.73-1.00; $P = .06$) but a substantial 52% reduction in ICH (RR, 0.48; 95% CI, 0.39-0.59; $P < .0001$). NOACs were, however, associated with a significant increase in gastrointestinal bleeding (RR, 1.25; 95% CI, 1.01-1.55; $P = .04$). The relative efficacy and safety of NOACs were consistent across all patient subgroups with the exception that the relative reduction in major bleeding with NOACs was greater at centers with poor INR control as defined as a center-based TTR < 66% (RR, 0.69; 95% CI, 0.59-0.81; P interaction = .02).

Lower dose NOAC regimens (dabigatran 110 mg and edoxaban 30/15 mg) showed similar overall reductions in stroke or systemic embolism but a more favorable bleeding profile than warfarin but were associated with more ischemic strokes (the lower dose regimen edoxaban 30/15 mg is not approved for the stroke prevention indication).

NOACs vs Aspirin: Apixaban is the only NOAC that has been compared with aspirin in AF patients. The Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial compared apixaban 5 mg bid with aspirin in AF patients who were not candidates for VKA therapy.[125] The trial was stopped early for benefit as apixaban significantly reduced the risk of stroke or systemic embolism compared with aspirin (HR, 0.45; 95% CI, 0.32-0.62; $P < .001$) (e-Table 16). There was no significant difference in major bleeding (HR, 1.13; 95% CI, 0.74-1.75; $P = .57$) between apixaban and aspirin.

Real-World Observational Data: With the availability of large health-care system administrative data and the advent of quality improvement and postmarketing anticoagulation registries, the number of observational outcome studies on OAC in AF far outnumber randomized trials. Although these data have helped to successfully identify treatment variation and gaps in care, the use of these data for comparative effectiveness and safety studies of OACs must be interpreted with prudence. Despite the use of sophisticated, high quality methods to minimize confounding and bias and improve causal inference, even very small amounts of residual confounding by treatment selection or measurement error can attenuate or amplify the small absolute risk differences observed in the randomized trials.

Similarly, definitive conclusions cannot be drawn from indirect comparisons such as network meta-analyses of NOACs to each other due to small absolute risk differences. Real-world or observational data are generally insufficient to guide selection of individual anticoagulant drugs. Therefore, observational data are best used to reaffirm that real-world effectiveness is concordant with clinical trial efficacy, based on both quality of care and generalizability.[126]

A meta-analysis of real-world observational studies of dabigatran was consistent with findings from Randomized Evaluation of Long-term Anticoagulant Therapy with Dabigatran Etexilate (RE-LY). Compared with VKA, risk of stroke with dabigatran vs warfarin was 1.65 vs 2.85 per 100 patient-years (HR, 0.86; 95% CI, 0.74-0.99).[127] Dabigatran was also associated with a lower risk of intracranial bleeding (HR, 0.45; 95% CI, 0.38-0.52) and lower risk of death (HR, 0.73; 95% CI, 0.61-0.87). Risk of gastrointestinal bleeding was higher.

One systematic review and meta-analysis provided comparative effectiveness and safety data for rivaroxaban vs dabigatran (n = 3 trials), rivaroxaban vs warfarin (n = 11 trials), or both (n = 3 trials) for stroke prevention in AF.[128] Overall, the risks of stroke/systemic thromboembolism with rivaroxaban were similar compared with dabigatran but were significantly reduced when compared with warfarin (HR, 0.75; 95% CI, 0.64-0.85). Major bleeding risk was significantly higher with rivaroxaban vs dabigatran (HR, 1.38; 95% CI, 1.27-1.49) but similar to warfarin (HR, 0.99; 95% CI, 0.91-1.07). Rivaroxaban was associated with increased all-cause mortality and gastrointestinal bleeding but similar risk of acute MI and ICH compared with dabigatran. When compared with warfarin, rivaroxaban was associated with similar risk of any bleeding, mortality, and acute MI but a higher risk of gastrointestinal bleeding and lower risk of ICH.

Another large analysis of 3 Danish nationwide databases of 61,678 patients found that NOACs were at least as safe and effective as warfarin, with small but significant differences in risk of stroke, death, and bleeding across rivaroxaban, apixaban, and dabigatran.[129] However, a new-user Food and Drug Administration Medicare analysis of 118,891 patients found that rivaroxaban compared with dabigatran had a statistical trend toward a decreased risk of stroke (HR, 0.81; 95% CI, 0.65-1.01) and significantly increased risk of intracranial (HR, 1.47; 95% CI, 1.32-1.67) and major non-intracranial (HR, 1.48; 95% CI, 1.32-1.67) bleeding.[130] Absolute risk differences were small (2.0-2.1 per 1,000 person-years) and well within a range vulnerable to confounding.

Different Ethnic Groups: Asian AF patients have a higher risk of ICH compared with whites when VKAs are used.[131] The higher risk of bleeding on VKA in Asians vs non-Asians has also been observed in major clinical trials of NOACs,[132] even though Asians received a lower intensity of anticoagulation with VKA.[133]

In a recent meta-analysis comprising 5 NOAC trials (RE-LY, ROCKET AF, Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [J-ROCKET AF], Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation [ARISTOTLE], and Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 [ENGAGE AF-TIMI 48]), the effects of NOACs vs warfarin in

Asians vs non-Asians were compared.[134] For standard-dose NOACs (dabigatran 150 mg, rivaroxaban 20 mg, apixaban 5 mg, and edoxaban 60 mg), the effect sizes of the primary efficacy end point (stroke and systemic embolism) and the primary safety end point (major bleeding) were greater in Asians vs non-Asians. The risk reduction in hemorrhagic stroke and gastrointestinal bleeding was also greater in Asians vs non-Asians. These data suggest that standard-dose NOACs, when compared with warfarin, were more effective and safer in Asians than in non-Asians. The efficacy and safety of low-dose NOACs (dabigatran 110 mg, rivaroxaban 15 mg, and edoxaban 30 mg), when compared with warfarin, appear similar among Asians and non-Asians.

There are several real-world studies from Asia comparing NOACs with warfarin.[135,136] Despite low-dose NOACs, such as dabigatran 110 mg or rivaroxaban 15 mg/10 mg, being more commonly used than standard-dose NOACs (dabigatran 150 mg or rivaroxaban 20 mg), the use of NOACs was associated with reduced risk of ischemic stroke or systemic embolization, major bleeding, ICH, and total mortality compared with warfarin. Published data suggest that NOACs are preferentially indicated for stroke prevention in Asians.[37]

Other Investigational Drugs: Although NOACs are safer than VKAs, serious bleeding still occurs. The potential for bleeding often discourages initiation of anticoagulant therapy in patients deemed to be at high risk of bleeding, and patients who experience a bleed frequently have permanent or prolonged discontinuation of their anticoagulant. Therefore, continued interest remains in developing even safer anticoagulants than thrombin and factor Xa inhibitors. Current investigation has focused on the upstream targets factor XI and factor XII in the contact pathway, as emerging research has elucidated their critical role in thrombosis with minimal or no role in hemostasis.[137-139] Strategies to target factor XII or factor XI include antisense oligonucleotides that reduce hepatic synthesis of the clotting proteins, monoclonal antibodies that block activation or activity, aptamers, small molecules that block the active site or induce allosteric modulation, and polyanion antagonists that attenuate contact activation by nullifying stimulators of the pathway.[7]

Human data are limited. The factor XI-directed antisense oligonucleotide IONIS-416858 was compared with enoxaparin in 300 patients undergoing elective knee arthroplasty. Patients were randomized to receive IONIS-416858 at doses of 200 or 300 mg starting 35 days prior to surgery, or enoxaparin at a dose of 40 mg starting after the surgery. The 200 mg IONIS-416858 regimen was noninferior and the 300 mg IONIS-416858 regimen was superior compared with enoxaparin in preventing the composite end point of asymptomatic DVT, symptomatic DVT or pulmonary embolism, or VTE-related mortality.[140] The rates of major or clinically relevant nonmajor bleeding were 3% in both IONIS-416858 groups and 8% in the enoxaparin group. With respect to patients with AF, potential unmet needs addressed by these agents include patients at high risk for bleeding, such as those with end-stage renal disease who are on hemodialysis (ongoing phase 2 study).[141] Another area of interest is in patients with mechanical heart valves. Data from a phase 2 trial of dabigatran in patients with mechanical heart valves (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement [RE-ALIGN]) demonstrated inferior efficacy and more bleeding, compared with warfarin.[142] Factor XI-directed strategies may be very effective in this setting because factor XI depletion abolished mechanical valve-induced thrombin generation in vitro.[140]

Recommendations

6. For patients with AF, we recommend against antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) for stroke prevention alone, regardless of stroke risk (Strong recommendation, moderate quality evidence).

Remark: Patients with AF might have other indications for antiplatelet drugs (eg, acute coronary syndrome, stents).

7. In patients with AF who are eligible for OAC, we recommend NOACs over VKA (Strong recommendation, moderate quality evidence).

Remark: Patient and caregiver preferences, cost, formulary considerations, anticipated medication adherence or compliance with INR testing and dose adjustment should be incorporated into clinical decision-making.

8. In patients on VKAs with consistently low time in INR therapeutic range (eg, TTR < 65%), we recommend considering interventions to improve TTR or switching to NOACs (Strong recommendation, moderate quality evidence).

Remark: Action required if TTR < 65% - implement additional measures (more regular INR tests; review medication adherence; address other factors known to influence INR control; education/counseling) to improve INR control.

9. In patients with prior unprovoked bleeding, warfarin-associated bleeding, or at high risk of bleeding, we suggest using apixaban, edoxaban, or dabigatran 110 mg (where available) as all demonstrate significantly less major bleeding compared with warfarin (Weak recommendation, very low quality evidence).

Remark: In patients with prior gastrointestinal bleeding apixaban or dabigatran 110 mg bid may be preferable as they are the only NOACs not associated with an increased risk of gastrointestinal bleeding compared with warfarin.

Remark: Dabigatran 150 mg twice daily recommended in patients at high risk of ischemic stroke as only agent/dose with superior efficacy compared with warfarin. However, bleeding risk would need to be assessed and patients monitored.

Adjusted-Dose Oral VKA Therapy

The VKAs are a class of OACs; the most commonly used are the 4-hydroxycoumarins and include warfarin, phenprocoumon, and acenocoumarol.[143] Less commonly used VKAs are phenindione and fluindione, which are 1,3-indandione derivatives. Geographical variation in VKA popularity is evident, with warfarin commonly used worldwide but acenocoumarol being popular in Spain and phenprocoumon in Germany. In randomized clinical trials, most have used warfarin.

Optimal INR Target Range in AF: For stroke prevention in patients with AF receiving a VKA, the optimal INR target range is 2.0 to 3.0,[144] aiming for an INR value of 2.5 to maximize the proportion of time spent in the therapeutic INR range. Numerous observational studies of AF patients have demonstrated that the risk of thromboembolism/ischemic stroke is greater when INR is < 2.0,[81,83,85,145-147] whereas INR levels > 3.0 are associated with a greater incidence of major bleeding, especially ICH when the INR rises above 3.5.[81-86] All the phase 3 NOAC trials employed an INR target of 2.0 to 3.0 among patients receiving warfarin[72,73,76,125]; J-ROCKET employed a lower INR target of 1.6 to 2.6 for the Japanese population.[148]

In some Asian countries, there is the perception that a lower target INR range (eg, 1.6-2.6) should be used, especially in the elderly. Only 1 small prospective randomized trial allocated 115 secondary prevention AF patients to a conventional-intensity group (INR, 2.2 to 3.5) or a low-intensity group (INR, 1.5 to 2.1).[149] Major hemorrhagic complications occurred in 6 patients in the conventional-intensity group (6.6% per year) compared with the low-intensity group (0% per year; $P = .01$). Other Asian registries have suggested that low intensity (INR, 1.5-2.5) was associated with less bleeding, but no information on quality of INR control was reported. There is currently no robust evidence for implementing a target INR range of 1.6 to 2.6, and therefore the conventional, evidence-based INR target of 2.0 to 3.0 should be employed globally.

Importance of TTR INR Range: The proportion of time spent within the therapeutic INR range (INR, 2.0 to 3.0) is intrinsically linked to the risk of adverse events. The temporal pattern of INR control is most commonly calculated using the Rosendaal method of linear interpolation between 2 consecutive INR values,[150] known as the TTR or by the percentage of INRs within therapeutic range.[151] However, a limitation of the Rosendaal method of interpolation is that INRs > 42 days apart have generally not been interpolated in studies due to large uncertainties in fluctuation. Although TTR and percentage of INRs within therapeutic range are highly correlated,[152,153] they are not equivalent and should not be used interchangeably. TTR is a widely accepted and validated measure of anticoagulation control and predicts adverse events in patients receiving VKA,[153-155] and is the quality and performance measure of choice for specialized anticoagulation clinics.

Numerous studies have demonstrated that the risk of thromboembolism, major bleeding, and death is lower when the proportion of TTR is higher, at least ≥ 65%.[124,153-155] Indeed, random "one off" INR values give little insight into the degree of anticoagulation control, and many adverse outcomes (eg, bleeding) occur even within the therapeutic INR range of 2.0 to 3.0.[156] Thus, when VKAs are used, attention should be focused on the average *individual* TTR as a measure of the quality of anticoagulation control.

Clinical guidelines on the management of AF advocate an *individual* TTR of at least ≥ 65%[157,158] to maximize efficacy and safety, and this should be the treatment target, although in clinical practice this may be more difficult to achieve.[153-156,159] An analysis of anticoagulation control in the Global Anticoagulation Registry in the Field [GARFIELD-AF] registry (n = 9,934), a global observational study, revealed that only

41.1% had TTR ≥ 65% and of all the INR values, only 51.4% were in the therapeutic range (INR, 2.0 to 3.0), with one-third being subtherapeutic.[155] After adjustment, the risk of stroke/systemic embolism (HR, 2.55; 95% CI, 1.61-4.03), all-cause mortality (HR, 2.39; 95% CI, 1.87-3.06), and major bleeding (HR, 1.54; 95% CI, 1.04-2.26) was greater with TTR < 65%, when compared with TTR ≥ 65%.[155]

TTR varies widely by geographical region (TTR ≥ 65%, Asia 16.7%, North America 45.9%, Europe 49.4%).[155] An analysis of individual TTR from Swedish registries (n = 40,449) revealed an overall mean individual TTR of 68.6% and significantly lower annual rates of thromboembolism (2.37% vs 4.41%), all-cause mortality (1.29% vs 4.35%), and major bleeding (1.61% vs 3.81%) when individual TTR was ≥ 70% compared with individual TTR < 70%, respectively.[154]

Recommendation

10. For patients with non-valvular AF, when VKAs are used, we suggest the target should be INR 2.0-3.0, with attention to individual TTR, ideally ≥ 70% (Ungraded consensus-based statement).

Remark: Action required if TTR sub-optimal (< 65-70%) - implement additional measures (more regular INR tests; review medication adherence; address other factors known to influence INR control; education/counseling) to improve INR control or consider an NOAC.

Remark: When possible, experienced specialized anticoagulation clinics should be utilized for VKA and INR management.

Factors Affecting INR Control: Many factors affect TTR, including patient-related aspects (eg, age, sex, socioeconomic status, diet, ethnicity, hospitalization, length of time on VKA, medical and psychiatric comorbidities, nonadherence, polypharmacy, genetic factors, etc)[143,156,160] and health-care system-related factors, particularly how VKA is managed (by country, setting of OAC management [eg, anticoagulation clinic vs physician/community-based practices]),[90,161,162] distance to OAC clinic,[161,162] self-monitoring/self-management,[91] frequency of INR monitoring, etc.[156] It is also important to note that site-level variation in VKA management has also been demonstrated in RCTs[163-167] and for NOACs.[168] The value of dietary measures to improve anticoagulation control is debatable, and it is perhaps more relevant to maintain a stable dietary habit, avoiding wide changes in the intake of vitamin K.[169]

Among patients initiating VKA, the time to achieve therapeutic range has also been related to the likelihood of achieving a subsequently good TTR.[170,171]

The more common clinical factors influencing TTR have been used to formulate the SAMe-TT_2R_2 (awarding 1 point for each of the following: sex [female]; age <60 years; medical history [≥3 comorbidities: hypertension, diabetes, coronary heart disease/myocardial infarction, peripheral artery disease, heart failure, prior stroke, lung disease, liver disease or renal failure]; treatments [such as amiodarone]; smoking status [double]; and race [non-Caucasian, double]) score[172,173] (Table 5). This clinical score is based on routine clinical parameters, which can be used to identify patients who may be able to attain good anticoagulation control (eg, TTR ≥ 65%) with a VKA and those who probably will not, where an NOAC may be preferred or where other interventions (eg, more frequent INR monitoring, patient education/counseling, etc) may need to be implemented to ensure good INR control. Many of the factors included in the SAMe-TT_2R_2 score have been associated with decreased adherence with NOACs and in the absence of trial data it is not clear if these patients would do substantially better on an NOAC or if they would do poorly anyway.

The SAMe-TT_2R_2 score has been assessed in 15 exclusively AF cohorts,[174-185] with six[175,177,179,180,183,186] reporting its predictive ability to forecast good or poor anticoagulation control, with c-statistics ranging from 0.56[180] to 0.72.[172] However, these cohorts were predominantly elderly, Western (white) populations, and its predictive ability in non-Western populations has relatively limited data as only 3 studies have assessed it,[174,175] with only 1 reporting c-statistics (c-statistic, 0.54; 95% CI, 0.52-0.57).[175] In the multi-ethnic non-white Singaporean population by Bernaitis et al,[174] the SAMe-TT_2R_2 score was able to dichotomize the patients likely to do well on VKA, compared with those (score > 2) more likely to achieve poor TTR. In the Loire Valley AF project, the SAMe-TT_2R_2 score was predictive of labile INR in AF patients who were VKA users, and was significantly associated with the adverse consequences of labile INR, including stroke, serious bleeding, and death; the score was nonpredictive in non-VKA users.[179] The score has also been tested in some VTE populations, where it similarly identifies patients likely to achieve a good TTR.[187,188]

Patients with AF who require OAC should not have to fail with a VKA before they are offered an NOAC; the most appropriate OAC based on the patient's *individual* risk profile and patient preference should be offered

TABLE 5] The SAMe-TT_2R_2 Score[172,173]

Acronym	Risk Factors	Points
S	Sex (female)	1
A	Age (< 60 y)	1
Me	Medical history (≥ 2 from: hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease)	1
T	Treatment (interacting drugs [eg, amiodarone])	1
T	Tobacco use (within 2 y)	2
R	Race (non-white)	2
Maximum score		8

from the beginning of OAC therapy. However, in some health-care systems where the patient has to have a period on VKA and their TTR determined, before a decision to use an NOAC is approved, the SAMe-TT_2R_2 score could be used to aid decision-making.[173]

Recommendation

11. For patients with AF, we suggest the SAMe-TT_2R_2 score to aid decision-making to help identify patients likely to do well on VKA (Ungraded consensus-based statement).

Remark: Those with score 0-2 are likely to achieve a good TTR. Those with score > 2 are less likely to achieve a good TTR and would require more regular INR checks, education/counseling and frequent follow-up, or alternatively, an NOAC should be considered as a better management option if high medication adherence can be expected.

Monitoring Anticoagulant Therapy: Point-of-Care Testing: There is an increasing demand for oral anticoagulation among AF patients[189] and not all patients are suitable for NOACs; therefore, a large proportion requires VKA which necessitates INR monitoring. Point-of-care testing using a coagulometer (INR monitor) is more convenient and time-efficient, particularly where patient's self-monitor and/or self-manage. Home or clinic point-of-care monitoring is an increasingly standard method of INR monitoring associated with an appropriate degree of precision and accuracy for clinical practice[190]; however, routine calibration is warranted, and quality control systems should adhere with the Food and Drug Administration medical devices regulation guidance.[191]

Patient Self-Monitoring and Self-Management: A recent Cochrane review[91] evaluating the effect of self-monitoring or self-management of OAC therapy compared with standard OAC monitoring on thromboembolic events, major bleeding, and death revealed a significant decrease in thromboembolic events overall (RR, 0.58; 95% CI, 0.45-0.75; 7,594 participants in 18 studies) and with both self-monitoring (RR, 0.69; 95% CI, 0.49-0.97; 4,097 participants in 7 studies) and self-management (RR, 0.47; 95% CI, 0.31-0.70; 3,497 participants in 11 studies), although not all patients were AF. There was no overall reduction in the risk of death (RR, 0.85; 95% CI, 0.71-1.01; 6,358 participants in 11 studies); however, self-management did reduce all-cause mortality (RR, 0.55; 95% CI, 0.36-0.84; 3,058 participants in 8 studies). Neither self-monitoring nor self-management reduced the risk of major bleeding compared with standard OAC monitoring (RR, 0.95; 95% CI, 0.80-1.12; 8,018 participants in 20 studies). Rating of the quality of evidence was low to moderate, and the findings should be interpreted accordingly.

The advantages of self-monitoring and self-management include convenience and freedom for the patient, patient empowerment/control over their condition and treatment, increased patient satisfaction, all of which may improve quality of life. However, this approach may not be a viable option for all patients requiring VKA therapy as it is initially expensive, requires mastery of the point-of-care device, and for those self-managing, the knowledge and ability to dose-adjust, plus the appropriate health-care system infrastructure and patient support which may not be feasible globally. For many AF patients, an NOAC might be a more suitable alternative.

Practical Patient Management Algorithm

The approach to stroke prevention in patients with AF can be simplified into a simple 3-step algorithm (Fig 4). The initial step is to determine the risk of stroke. As noted in the *Stroke Risk in AF* section, risk scores for stroke in patients with AF lack specificity, and are therefore not

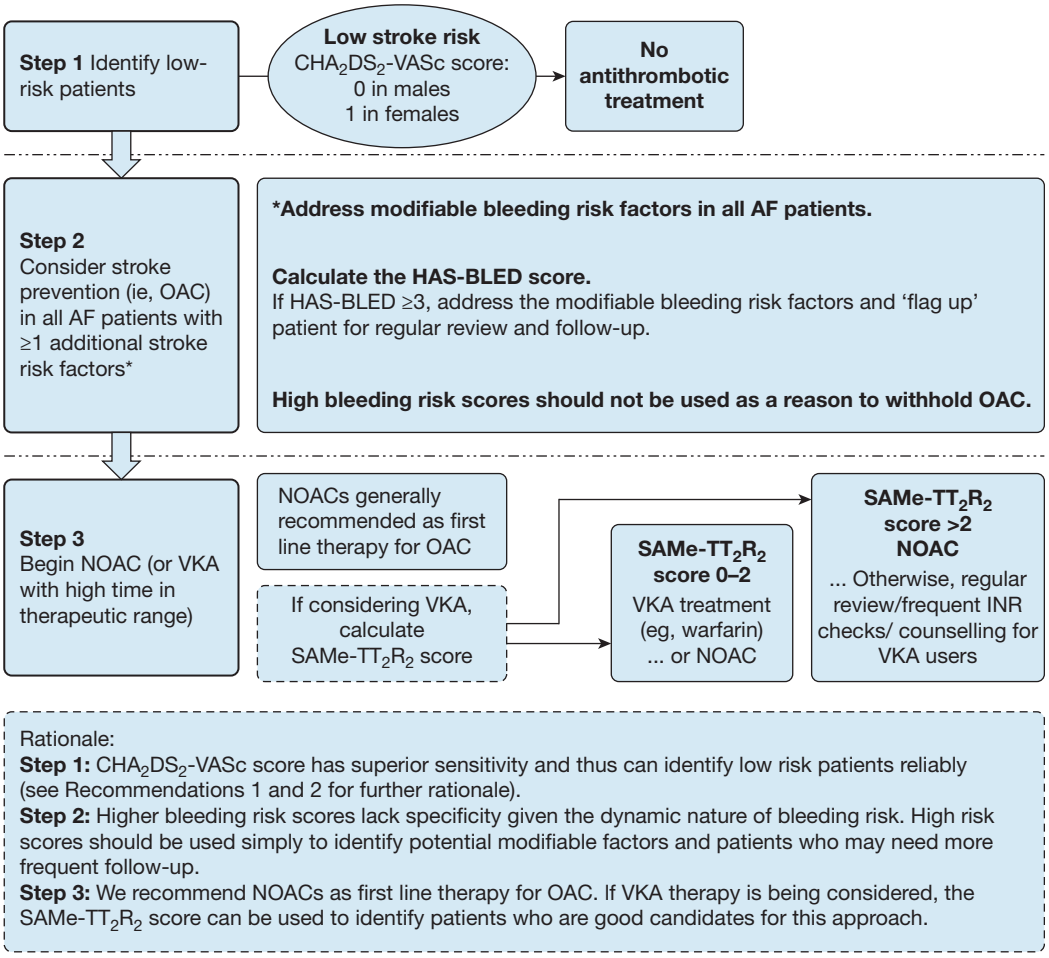

Figure 4 – *Practical management algorithm. CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65-74 and sex category (female); HAS-BLED = hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (0.65), drugs/alcohol concomitantly (1 point each); SAMe-TT2R2 score = awarding 1 point for each of the following: sex (female); age <60 y; medical history (≥3 comorbidities: hypertension, diabetes, coronary heart disease/myocardial infarction, peripheral artery disease, heart failure, prior stroke, lung disease, liver disease or renal failure); treatments (such as amiodarone); smoking status (double); and race (non-Caucasian, double). See Figure 1, 2, and 3 legends for expansion of other abbreviations.*

clinically useful in identifying and categorizing high-risk patients. As noted in the *Stroke Risk in AF* section, we recommend the use of the CHA_2DS_2-VASc score given its superior sensitivity and ability to accurately and safely identify patients at low risk of stroke. Patients who are low risk (a score of 0 in males, 1 in females) do not require antithrombotic treatment.

All AF patients with ≥ 1 stroke risk factors are candidates for stroke prevention with oral anticoagulation. At this point, it is important to assess the bleeding risk. Although the benefit of stroke prevention outweighs the risk of bleeding in almost all patients, calculation of the bleeding risk allows the practitioner to identify potentially modifiable factors that elevate the bleeding risk (uncontrolled hypertension, concomitant use of antiplatelet or nonsteroidal agents, excessive alcohol intake; poor INR control [TTR < 65%] in VKA patients). In addition, patients identified as high risk for bleeding should be scheduled for more frequent follow-up and monitoring. As noted in the *Bleeding Risk in AF* section, we make a consensus suggestion that the HAS-BLED score be used for this purpose, so those with a HAS-BLED score ≥ 3 can be identified as 'high risk' for this reason.

The final decision point is to decide which OAC to use for stroke prevention. As noted in atrial tachycardia therapy and other approaches to stroke prevention, we recommend one of the NOACs (dabigatran, apixaban, edoxaban, or rivaroxaban) as first line in patients with AF. These agents have not been compared head-to-head, and we therefore do not recommend one over the other. Local availability, cost, and patient comorbidities might

be considerations in choosing an agent (Table 6)[124,127,128,134-136,174,181,183,192-201] for comparative information. The VKAs are still widely used and are an acceptable alternative with target TTR ≥ 70%. As outlined in the section *Factors Affecting INR Control*, we recommend that the SAMe-TT_2R_2 score be used to help identify patients likely to do well on VKA therapy.

Managing Bleeding on OAC

Bleeding on VKA: Management of active bleeding on a VKA depends on the severity (Fig 5).[202] For all bleeding events, the site of bleeding should be assessed, with mechanical compression where appropriate, the time-point of the last dose of VKA should be obtained, with factors affecting bleeding risk documented (other medications, kidney function, alcohol abuse, other comorbidities) and hemodynamic status assessed (BP, pulse, etc). Assessment of INR, prothrombin time (PT), and activated partial thromboplastin time (aPTT) is essential; other laboratory tests should include renal function, hemoglobin, hematocrit, and platelet count. For minor bleeding, VKA administration should be withheld until INR < 2.0. Management of moderate bleeding requires prompt identification and intervention to treat the cause and may also necessitate fluid replacement and/or blood transfusion. Where bleeding is severe or life-threatening, immediate reversal of the anticoagulant effect is required and administration of IV vitamin K, fresh frozen plasma, and prothrombin complex concentrates (PCCs) should be considered to restore coagulation. PCCs are preferred over fresh-frozen plasma for reversal due to a higher concentration of clotting factors and less volume.

Bleeding on NOAC (Fig 5): Many physicians and patients have been reluctant to embrace NOACs due to their perception that they are not able to effectively manage patients who present with bleeding, particularly without a specific reversal agent or antidote.[203] A helpful framework to consider when managing NOAC-related bleeding includes: (1) prevention of bleeding, (2) general principles and supportive measures, (3) nonspecific hemostatic agents, and (4) NOAC-specific reversal agents.[204]

Minimize the Risk of Bleeding: Selecting the right dose of the NOAC is the most important step to minimize bleeding risk. Prescribing information for all NOACs includes dose reduction criteria to avoid increased drug exposure (primarily due to impaired renal function). Concomitant administration of antiplatelet drugs and nonsteroidal antiinflammatory drugs should be avoided when possible as concomitant administration substantially increases bleeding risk. BP should be well controlled.

General Supportive Measures: Given the short half-lives of these medications, minor bleeds may only require temporary discontinuation of anticoagulation for several doses. More significant bleeds may require additional supportive measures that include: local management (mechanical/surgical); volume resuscitation; and consideration of RBC and platelet transfusion, if appropriate.[205-207] In cases of overdose or in patients who took their last NOAC dose within 2 to 4 h, oral activated charcoal may attenuate absorption of drug.[208-211]

Laboratory Measurements: With respect to common coagulation tests, a prolonged aPTT indicates an anticoagulant effect of dabigatran, and a prolonged PT indicates an anticoagulant effect of the factor Xa inhibitors.[206] However, the clinical utility of these common tests is limited due to the fact that a normal aPTT or PT does not exclude clinically relevant plasma levels of dabigatran and factor Xa inhibitors, respectively. The thrombin time (TT) is the most sensitive test for dabigatran; even low levels of dabigatran will prolong the TT so a normal TT excludes clinically relevant dabigatran concentrations. The dilute TT can be used to quantify dabigatran drug levels as it has good correlation across a wide range of dabigatran concentrations.[212] Chromogenic anti-factor Xa assays are recommended for rivaroxaban, apixaban, and edoxaban with calibration for the specific agent.[206] However, validation of these specialized coagulation tests is required, they are not universally available, and often have delayed turnaround time, which diminishes their usefulness in emergent situations. Asking patients when they took their last dose of NOAC is often the most practical method for quickly assessing residual anticoagulant activity.

Nonspecific Hemostatic Agents: Hemostatic factors that have been studied as potential nonspecific NOAC reversal agents including PCCs, activated PCC, recombinant activated factor VII, and fresh-frozen plasma. PCCs are the preferred nonspecific hemostatic agent for NOAC reversal. PCCs are plasma-derived products that contain 3 (factors II, IX, and X) or 4 (addition of factor VII) clotting factors in addition to variable amounts of heparin and the natural coagulation inhibitors protein C and protein S. Animal studies have demonstrated that PCCs have variable ability to normalize anticoagulation parameters and prevent or

TABLE 6] A Simplified Schema to Assist Physician Choice of Anticoagulant (VKA or Individual NOAC) According to Patient Characteristics

Patient Characteristic	Possible OAC Choice	References to RCT Subgroup Data	References to Real-World Data or Indirect Evidence	Comments
• Recurrent ischemic stroke/systemic embolism/TIA despite good anticoagulation control (TTR ≥ 70%). Consider agent with superior efficacy for preventing both ischemic and hemorrhagic stroke	D150	124	127	In general, any NOAC would be recommended, especially where warfarin control suboptimal (TTR < 65%). Ensure good adherence and avoid underdosing
• Moderate-severe renal impairment CrCl 15-49 mL/min	A[a] D[b] E30[d] R15	124	192	All RCTs excluded patients with Cockroft-Gault CrCl < 30 mL/min (< 25 mL/min, for apixaban)
• High risk of GI bleeding	A D110	124	127, 193	
• Major GI symptoms or dyspepsia. Also consider increased risk of bleeding	A R E	194	195, 196	
• High risk of bleeding (HAS-BLED ≥ 3). Consider agent with the lowest bleeding risk	A D110 E	124	127, 128, 193, 197, 198	
• Once-daily dosing or preference to have lower pill burden	E R VKA	[c]	199, 200	
• Asian patients. Consider agents with reduced risk of ICH and major bleed in Asian populations	A D E	134	135, 136, 201	
• Less likely to do well on VKA (SAMe-TT_2R_2 score > 2). Avoid *any* potential "trial" of VKA if possible	NOAC preferred (A D E R)	…	146, 179, 183	VKA with additional education, more regular follow-up, and frequent INR checks

A = apixaban; CrCl = creatinine clearance; D = dabigatran; E = edoxaban; R = rivaroxaban; TIA = transient ischemic attack. See Table 1 and 2 legends for expansion of other abbreviations.

[a]Reduced to 2.5 mg bid with two of three criteria from age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine concentration ≥ 133 μmol/L.

[b]110 mg bid for patients with a CrCl 30 to 49 mL/min (most countries, but not in the United States); in the United States only, 75 mg bid (available in the United States only) for patients with CrCl 15 to 29 mL/min (and only 150 mg bid dose available in the United States for CrCl > 30 mL/min).

[c]Not available.

[d]Dose to be halved if the patient has any of the following: CrCl 15 to 49 mL/min, body weight ≤ 60 kg, or concomitant use of P-glycoprotein inhibitors.

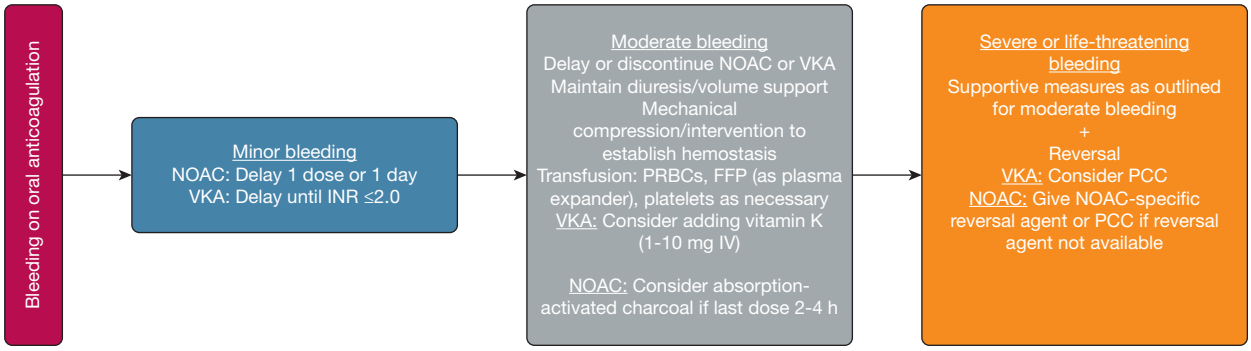

Figure 5 – *Management of patients with active bleeding on oral anticoagulation (NOAC and VKA). FFP = fresh frozen plasma; PCC = prothrombin complex concentrate; PRBC = packed RBCs. See Figure 1 legend for expansion of other abbreviations.*

attenuate bleeding across the NOACs.[207,213-219] The limited data in humans are restricted to healthy volunteers. In 3 small (12-93 patients) randomized, placebo-controlled studies, PCC reversed the anticoagulant effect of rivaroxaban and edoxaban but not dabigatran.[208,220-222] There was a dose-dependent relationship with complete reversal with 50 U/kg and partial reversal with 25 U/kg.

It is unclear whether normalizing coagulation parameters in healthy volunteers translates to improved outcomes in patients who are actively bleeding. Furthermore, the use of these agents in managing bleeding caused by VKA or in hemophiliac patients has been associated with an increased risk of thrombotic complications, especially when activated factors are used.[223-225]

Specific Reversal Agents: *Idarucizumab:* Idarucizumab is a humanized monoclonal antibody fragment developed as a specific reversal agent for dabigatran (Table 7).[204] It binds with high affinity (350 times higher than thrombin) to free and thrombin-bound dabigatran,[226] and binding is effectively irreversible.[227] The Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study was a phase 3, global, prospective, cohort study investigating the safety and efficacy of 5 g idarucizumab (administered as two rapid 2.5 g IV boluses) in dabigatran-treated patients who present with uncontrolled or life-threatening bleeding (Group A) or non-bleeding patients who require emergent surgery or intervention (Group B).[228] Idarucizumab resulted in immediate, complete, and sustained reversal of dabigatran. Median time to cessation of bleeding in Group A was between 2.5 h after reversal and in Group B, median time to surgery after reversal was 1.6 h with intraoperative hemostasis deemed "normal" by investigators in 93.4% of patients. Idarucizumab has worldwide approval and availability.

Andexanet Alfa: Andexanet alfa (andexanet) is a specific reversal agent for direct (apixaban, rivaroxaban, and edoxaban) and indirect (low-molecular-weight heparins [LMWHs] and fondaparinux) factor Xa inhibitors that act through antithrombin. It is a modified human recombinant factor Xa decoy protein that is catalytically inactive due to replacement of an active-site serine with alanine and with deletion of the membrane binding domain, which eliminates the ability to assemble the prothrombinase complex. Andexanet retains the ability to bind to NOACs with high affinity and a 1:1 stoichiometric ratio and by sequestering factor Xa inhibitors within the vascular space, endogenous factor Xa activity is restored.[229] Due to its pharmacodynamic half-life of 1 h, andexanet is administered as a bolus followed by an infusion.

The ongoing ANNEXA-4 phase 3b–4 study[230] is evaluating the efficacy and safety of andexanet in patients taking factor Xa inhibitors with acute major bleeding. Unlike RE-VERSE AD, this study does not include patients without bleeding but who require emergency or urgent procedures. A preliminary interim analysis of 67 patients demonstrated that an initial bolus and subsequent 2-h infusion of andexanet substantially reduced anti-factor Xa activity with clinically adjudicated effective hemostasis occuring in 79% of patients.[231] Andexanet is in late-stage review by regulatory authorities.

Ciraparantag (PER977): Ciraparantag is a small synthetic water-soluble molecule developed as a reversal agent for unfractionated heparin (UFH), LMWHs, fondaparinux, and the oral direct Xa and IIa inhibitors. It binds to targets through noncovalent hydrogen bonding

TABLE 7] Comparison of Specific NOAC Reversal Agents

	Idaracizumab	Andexanet alfa	Ciraparantag
Company	Boehringer Ingelheim	Portola Pharmaceuticals	Perosphere Inc.
Chemical structure	Humanized monoclonal antibody fragment	Recombinant truncated human factor Xa variant (decoy)	Synthetic water-soluble cationic small molecule consisting of 2 L-arginine units connected with a piperazine containing linker chain
Binding	Noncompetitive binding to dabigatran	Competitive binding to direct factor Xa inhibitors or to indirect factor Xa inhibitor-activated antithrombin	Covalent hydrogen bonding
Target affinity	Approximately 350× greater affinity for dabigatran than factor IIa	Affinity for direct factor Xa inhibitors similar to that of native factor Xa	Not reported
Onset	< 5 min	2 min	5-10 min
Half-life	Initial: 47 min Terminal: 10.3 h	Terminal: approximately 6 h	Duration of action 24 h
Elimination	Kidney (protein catabolism)	Not reported	Not reported
Anticoagulant(s) reversed	Dabigatran	Direct and indirect factor Xa inhibitors[a]	- Dabigatran - Argatroban - Low-molecular-weight heparins - Unfractionated heparin - Oral and parenteral factor Xa inhibitors
Route and dose in clinical studies	5 g administered as 2 doses of 2.5 g IV over 5-10 min, 15 min apart (repeat dosing can be considered if recurrent bleeding or require second emergent procedure if elevated coagulation parameters)	400-800 mg IV bolus (30 mg/min) followed by infusion of 4-8 mg/min[b]	100-300 mg IV bolus
Storage	Refrigerated	Refrigerated	Room temperature

(Adapted from Ruff et al.[204])

[a]For the indirect factor Xa inhibitors, andexanet alfa likely to completely reverse fondaparinux which only inhibits factor Xa but not low-molecular weight heparins which also inhibit factor IIa.

[b]Lower dose to reverse apixaban, higher dose to reverse rivaroxaban.

and charge-charge interactions thereby preventing the anticoagulants from binding to their endogenous targets.[232] Ciraparantag is earlier in its development program compared with other specific reversal agents.

Management Approach to Bleeding on NOACs: The vast majority of bleeds can be managed conservatively with temporary discontinuation of NOACs and supportive measures. Reversal agents should be used sparingly in the cases of severe and life-threatening bleeding, which includes bleeding causing hemodynamic compromise, ICH, bleeding into a critical organ or closed space, persistent bleeding despite general supportive measures and local hemostatic support, or risk of recurrent bleeding due to excess NOAC drug exposure due to delayed clearance of NOAC (eg, acute renal failure) or overdose. In a patient with serious bleeding, a specific reversal agent (where available) should be used instead. General hemostatic agents as nonspecific agents are less effective in reversing coagulation abnormalities, have not been shown to improve outcomes, and are potentially prothrombotic.

Although coagulation testing will identify those patients with therapeutic levels of anticoagulation who will likely benefit from specific reversal agents, and helps physicians to monitor the response to reversal, it is reasonable to administer specific reversal agents immediately without waiting for a laboratory test confirming therapeutic levels of anticoagulation in patients who present with life-threatening bleeding presumed to be on an NOAC.

Practical Issues With VKA and NOAC Cardioversion

Antithrombotic Therapy for Patients With AF Undergoing Cardioversion: In AF of documented short duration (ie, ≤ 48 h), urgent cardioversion commonly occurs without prolonged pre-cardioversion anticoagulation. In the context of elective cardioversion, whether electrical or chemical, therapeutic anticoagulation either with adjusted-dose VKAs, or NOACs is currently recommended for a minimum of 3 weeks before, and for a minimum of 4 weeks after, the procedure. In AF of > 48 h duration or unknown duration, a TEE-guided approach provides an alternative strategy to guide anticoagulation management before cardioversion. In this section, we appraise and summarize the evidence and give recommendations for the use of antithrombotic therapy in patients undergoing electrical or pharmacologic cardioversion for AF (or atrial flutter). In particular, the option of NOACs in the setting of cardioversion is reviewed.

Cardioversion of AF of > 48 h or Unknown Duration

VKA: Observational data support the use of VKA in the context of elective cardioversion, whether electrical or pharmacologic. A systematic review of 18 observational studies provides moderate-quality evidence for a lower risk of stroke or thromboembolism with peri-cardioversion anticoagulation (with VKA) vs no anticoagulation (0.3% vs 2.0%; RR, 0.16; 95% CI, 0.05-0.48), but did not report major bleeding events.[233]

The recommended duration of a minimum of 3 weeks' therapeutic anticoagulation with VKA before cardioversion and a minimum 4 weeks subsequently is arbitrary and has no trial basis, being based on indirect pathophysiological and observational data. The rationale for maintenance of a therapeutic INR in the peri-cardioversion period is from observational data, showing that thromboembolism is significantly more common at INR of 1.5 to 2.4 before cardioversion than INR of 2.5 (0.93% vs 0%; $P = .012$).[234] Retrospective observational studies suggest that, after cardioversion, the highest risk of stroke and thromboembolism is in the first 72 h. In addition, most thromboembolic complications are within 10 days of cardioversion.[235] However, even if sinus rhythm is restored on ECG, TEE studies have shown that atrial mechanical dysfunction can persist for several weeks following cardioversion.[236] Recent Finnish registry data suggest that most post-cardioversion strokes are associated with not using anticoagulation.[237] Although data relating to the impact of long-term anticoagulation post-cardioversion are lacking, relevant Swedish observational data suggest that discontinuation of warfarin after catheter ablation is not safe in high-risk patients, especially those individuals with a history of ischemic stroke.[238] It is also worth noting that although the risk of ischemic stroke/thromboembolism is higher with non-paroxysmal vs paroxysmal AF (multivariable adjusted HR, 1.38; 95% CI, 1.19-1.61; $P < .001$), the pattern of AF does not affect the decision regarding long-term OAC.

NOACs: Evidence is available for all 4 currently available NOACs: dabigatran, apixaban, rivaroxaban, and edoxaban. An existing systematic review from Renda et al[239] compared the use of NOAC vs VKA in the setting of cardioversion in 6 studies. Reported pooled RRs (relative risk reductions) were 0.82 (0.38-1.75) for stroke/systemic embolism, 0.72 (0.27-1.90) for mortality, and 0.72 (0.19-2.71) for MI, respectively, suggesting at least comparable efficacy of NOACs with VKA in the setting of cardioversion (e-Table 17). It should be noted that despite these reassuring data, the included trials were underpowered for safety and efficacy, and judged to be of poor quality.

The need for consensus guidance is illustrated by the current wide variation in VKA and NOAC use in the setting of elective cardioversion.[240,241] Available data support the use of rivaroxaban,[242,243] dabigatran,[244] apixaban,[245] and edoxaban[246] in patients to be continued on these NOACs if scheduled for cardioversion. Similar observations were found in a randomized trial of apixaban vs warfarin (Eliquis Evaluated in Acute Cardioversion Compared to Usual Treatments for Anticoagulation in Subjects With Atrial Fibrillation [EMANATE]).[247]

A TEE-guided approach with abbreviated anticoagulation before cardioversion has been recommended as an alternative to the conventional approach of using a minimum of 3 weeks' therapeutic pre-cardioversion anticoagulation as outlined above.[248] In the TEE-guided strategy, patients receive VKA and once therapeutic, undergo a screening TEE. If the TEE identifies thrombus in either the atrial appendage or atrium, cardioversion is postponed, given the presumed high risk of thromboembolism. In the absence of thrombus, cardioversion is immediately performed. Given the need for accurate visualization of thrombus, the TEE-guided strategy requires an experienced

echocardiographer. The best data for the use of VKA in the TEE-guided approach are from the Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) RCT, which compared a TEE-guided strategy of abbreviated therapeutic anticoagulation with IV UFH (started 24 h before cardioversion) or warfarin (INR, 2.0-3.0) (started 5 days before cardioversion) vs a strategy of therapeutic anticoagulation for at least 3 weeks before cardioversion.[249]

Overall, the evidence is of low quality, and therefore the results are not conclusive with respect to either a benefit or harm with the TEE-guided strategy vs the conventional approach of 3 weeks of anticoagulation pre-cardioversion.

For NOACs vs warfarin in the TEE-guided approach, our review found an existing systematic review and meta-analysis.[250] An updated search of this systematic review identified 1 additional study. Pooled results found that the relative RR for stroke/thromboembolism was 0.33 (95% CI, 0.06-1.68) for NOACs vs warfarin (e-Fig 3, e-Table 18). Although these data indicate safety and probable equivalence of NOACs in the TEE-guided approach vs VKA, the trials were underpowered to show efficacy, and therefore the evidence is of low quality (e-Table 18). The advantage of NOACs is that their mode of action is quicker than VKA, and therefore there is no delay in waiting for a therapeutic INR. However, the need for strict adherence to the NOAC therapy must be emphasized to patients, particularly in the post-cardioversion period.

Individuals who are very symptomatic due to AF may gain greatest benefit from the TEE-guided approach since cardioversion can be expedited by a thrombus-negative TEE. In addition, a TEE-guided approach can be used to avoid prolonged VKA before cardioversion, which is a particular consideration in patients at increased risk for bleeding. The NOACs now offer an alternative to prolonged anticoagulation before cardioversion. However, a "risk-based approach" to anticoagulation should be used, and avoiding anticoagulation with a TEE-guided strategy should only be considered in the absence of stroke risk factors and a low risk of recurrent AF.

For patients undergoing a TEE-guided approach, LMWH at full VTE treatment doses or IV UFH (to maintain an aPTT prolongation that corresponds to plasma heparin levels of 0.3-0.7 IU/mL anti-factor Xa activity) should be started at the time of TEE and cardioversion performed within 24 h of the TEE if no thrombus is seen. Observational data and 1 RCT show that LMWH has similar efficacy compared with heparin or warfarin for immediate anticoagulation before TEE.[251-255] In the outpatient setting, a TEE-guided approach should involve initiation of VKA (INR, 2.5; range, 2.0-3.0) followed by the TEE and subsequent cardioversion scheduled 5 days later (if the INR is in therapeutic range at that time). The NOACs again offer an alternative in outpatient treatment before TEE-guided cardioversion, with no bridging therapy necessary.

Among AF patients undergoing TEE, 10% have LAA thrombus with a 3.5-fold increased risk of stroke/thromboembolism,[256] but no specific data are available in the context of cardioversion. If atrial thrombus is seen on TEE, then there is heterogeneity in current clinical practice regarding both when or whether to perform the TEE again, as well as subsequent management of anticoagulation. There is no evidence to support re-imaging, although it is a reasonable strategy. Although current practice favors not performing cardioversion if re-imaging shows thrombus due to the presumed high risk of thromboembolism, there is a lack of direct data about the safety of cardioversion in the presence of thrombus. Taken together, a risk-based approach to anticoagulation can be recommended and with respect to TEE, individualization of therapy on a case-by-case basis is proposed. It should be noted that in a multicenter registry of AF patients undergoing catheter ablation, TEE-guided cardioversion did not show a benefit compared with uninterrupted NOAC therapy.[257]

Although there is no direct evidence to guide decision-making about long-term management of anticoagulation in patients who appear to be in sinus rhythm at 4 weeks after cardioversion, indirect evidence suggests strongly that long-term anticoagulation should be based on the risk of stroke rather than the apparent success of the cardioversion procedure. First, recurrence of AF at 1 year after cardioversion occurs in approximately one-half of patients, and therefore long-term stroke risk is significant.[258-261] Second, the Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (AFFIRM) study, in which many patients stopped anticoagulation after initial (apparently) successful restoration of sinus rhythm, demonstrated similar rates of thromboembolism with a rhythm control strategy compared with a rate control strategy.[262] Third, patients with paroxysmal AF are often asymptomatic during

episodes of AF recurrence, with 1 series suggesting that only 1 in every 12 paroxysms are symptomatic.[263]

Recommendation

12. For patients with AF of greater than 48 h or unknown duration undergoing elective electrical or pharmacologic cardioversion, we recommend therapeutic anticoagulation with well-managed VKA (INR 2-3) or an NOAC using dabigatran, rivaroxaban, edoxaban, or apixaban for at least 3 weeks before cardioversion or a transesophageal echocardiography (TEE)-guided approach with abbreviated anticoagulation before cardioversion rather than no anticoagulation (Strong recommendation, moderate quality evidence).

Remark: With NOACs adherence and persistence should be strongly emphasized.

13. For patients with AF of greater than 48 h or unknown duration undergoing elective electrical or pharmacologic cardioversion, we recommend therapeutic anticoagulation (with VKA or NOAC) for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of the baseline risk of stroke (Strong recommendation, moderate quality evidence).

Remark: Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in recommendations 1 and 2, and not on the basis of successful cardioversion.

14. In patients in which LAA thrombus is detected on TEE, cardioversion postponed, and OAC continued for another 4-12 weeks, to allow thrombus resolution or endothelization, we suggest that a decision on whether a repeat TEE is performed should be individualized (Ungraded consensus-based statement).

Cardioversion of AF of 48 h Duration or Less: The duration of AF necessary for development of thrombus is not clear. Therefore, the threshold of AF duration below which pre-cardioversion anticoagulation can be safely avoided is not known. It is common practice to cardiovert without TEE or prolonged pre-cardioversion anticoagulation if AF is of short duration (< 48 h). The problem with this approach is the presence of left atrial thrombus on TEE in up to 14% of patients with AF of short duration in observational studies.[264,265] In addition, the high prevalence of asymptomatic AF makes determining the exact duration of AF difficult.[266] If there is uncertainty about precise time of AF onset, then such patients should be managed as if AF > 48 h.

A recent Finnish observational study of 5,116 successful cardioversions in 2,481 patients with acute (< 48 h) AF showed low incidence of stroke/thromboembolism during the 30 days following cardioversion, even without perioperative anticoagulation (0.7%).[267] These results concur with low rates of stroke/thromboembolism in observational studies (Table 8).[234,267-272] However, there is lower incidence of stroke/thromboembolism with cardioversions performed during anticoagulation (0.1% vs 0.7%; $P = .001$), and with anticoagulation vs no anticoagulation in patients with a CHA_2DS_2-VASc score of ≥ 2 (0.2% vs 1.1%; $P = .001$). It should also be noted that there is a high risk of recurrence of the composite of cardioversion failure and recurrence of AF within 30 days (40%) in acute AF.[273]

Overall, the evidence suggests that peri-cardioversion anticoagulation is beneficial and that the decision regarding peri- and post-cardioversion anticoagulation should be based on risk of stroke/thromboembolism,[267] even if an individual is presenting for the first time with AF.

Recommendations

***15. For patients with AF of documented duration of 48 h or less undergoing elective cardioversion (electrical or pharmacologic), we suggest starting anticoagulation at presentation (low-molecular-weight heparin or unfractionated heparin at full venous thromboembolism treatment doses) and proceeding to cardioversion rather than delaying cardioversion for 3 weeks of therapeutic anticoagulation or a TEE-guided approach** (Weak recommendation, low quality evidence).

***16. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic), after successful cardioversion to sinus rhythm, we recommend therapeutic anticoagulation (with VKA or full adherence to NOAC therapy) for at least 4 weeks rather than no anticoagulation, regardless of baseline stroke risk** (Weak recommendation, low quality evidence).

Remark: Decisions about long-term anticoagulation after cardioversion should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in recommendations 1 and 2.

TABLE 8] Thromboembolic Complications in Patients With No Anticoagulation After Cardioversion of Acute (< 48 h) AF in Previous Studies

Study	No.	Mean Age, y	Male	Success Rate	TE
Weigner et al[268]	224	68	NA	95%	0.9%[a]
Michael et al[269]	217	64	54	86%	0.5%[a]
Burton et al[270]	314	61	55	86%	0[b]
Gallagher et al[234]	198	63	68	100%	0.5%[c]
Stiell et al[271]	414	65	56	92%	0[b]
Xavier Scheuermeyer et al[272]	104	57	92	96%	0

NA = not available. See Table 1 legend for expansion of other abbreviations. (From Airaksinen et al.[267])
[a]All 3 thromboembolic events after spontaneous cardioversion and in elderly (>75 years) women.
[b]Follow-up of 7 days.
[c]Plus 1 probable thromboembolic event.

Patients Undergoing Urgent Cardioversion for Hemodynamically Unstable AF: Our systematic review of anticoagulation vs no anticoagulation in patients with AF undergoing urgent cardioversion found no published data regarding the optimal anticoagulation strategy to use before or during urgent cardioversion for patients with AF and hemodynamic instability. On the basis of the above evidence for anticoagulation in elective cardioversion, initiation of anticoagulation immediately before urgent cardioversion (eg, with UFH or LMWH) would be expected to reduce the risk of stroke/thromboembolism based on studies of elective cardioversion. Initiation of anticoagulation therapy should not delay any emergency interventions required in order to stabilize the patient.

Recommendations

***17. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic), we suggest that therapeutic-dose parenteral anticoagulation be started before cardioversion, if possible, but that initiation of anticoagulation must not delay any emergency intervention** (Weak recommendation, low quality evidence).

***18. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic), after successful cardioversion to sinus rhythm, we suggest therapeutic anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of baseline stroke risk** (Weak recommendation, low quality evidence).

Remark: Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in recommendations 1 and 2.

Patients Undergoing Elective or Urgent Cardioversion for Atrial Flutter

There are no specific trials which have considered electrical cardioversion in the context of atrial flutter and associated anticoagulation. Despite the low risk of thromboembolism after cardioversion for atrial flutter, which has been suggested by some observational studies, even in absence of anticoagulation, other studies have shown a similar risk of thromboembolism in patients after cardioversion for atrial flutter and AF,[234,274,275] perhaps due to co-existence of AF and atrial flutter. Adults with congenital heart disease represent a growing, important population with atrial flutter where long-term studies of outcomes with anticoagulation are required.

Recommendation

***19. For patients with atrial flutter undergoing elective or urgent pharmacologic or electrical cardioversion, we suggest that the same approach to thromboprophylaxis be used as for patients with atrial fibrillation undergoing cardioversion** (Ungraded consensus-based statement).

Patients With AF With Coronary Artery Disease

ACS and/or PCI: AF commonly coexists with vascular disease, whether coronary, carotid, or PAD.[92,276] Some AF patients with coronary disease may present with an ACS. Whether stable or acute, such patients may undergo percutaneous intervention with stent deployment. This section deals with the antithrombotic therapy management of this group of patients (Fig 6).

There are 4 considerations when managing these patients, as follows[92,277]:

- Stroke prevention, necessitating OAC, whether with VKA or NOAC.
- Prevention of stent thrombosis, necessitating APT. There is evidence for using dual antiplatelet therapy (DAPT) for up to 12 months in non-AF patients.
- Prevention of recurrent cardiac ischemia in an ACS patient, necessitating APT. There is some evidence for using DAPT for beyond 12 months in non-AF patients from the DAPT and Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trials, to reduce nonstent-related ischemic and stroke events, but at the risk of more bleeding events.[278]
- Serious bleeding risks (eg, ICH) with the combination of OAC and one or more antiplatelet drug.

Additional considerations are the duration of treatment, acute or stable setting, type of APT, stent type, OAC type, bleeding risks, etc. Bleeding risk can be assessed by various bleeding risk scores, with the focus on modifiable bleeding risk factors; however, the HAS-BLED score is predictive of bleeding in the setting of ACS and/or PCI-stenting.[109] Coronary stent technology has also evolved, with small strut sizes necessitating shorter duration of DAPT (ie, aspirin plus a $P2Y_{12}$ inhibitor such as clopidogrel). We are also in the era of NOACs, which may offer a better safety profile compared with VKA-based therapy. Nonetheless, the latter may be relatively safe in the presence of well-managed anticoagulation control with high TTR.[279]

AF Patients Undergoing PCI: Various case series and cohort studies of AF patients undergoing PCI/stenting have been reported. These have been systematically reviewed as part of the 2014 and 2018 joint European consensus documents, endorsed by the Heart Rhythm Society and the Asia-Pacific Heart Rhythm Society, which provides consensus recommendations on optimal management of such patients.[92,277] A similar North American expert consensus document has been published.[202]

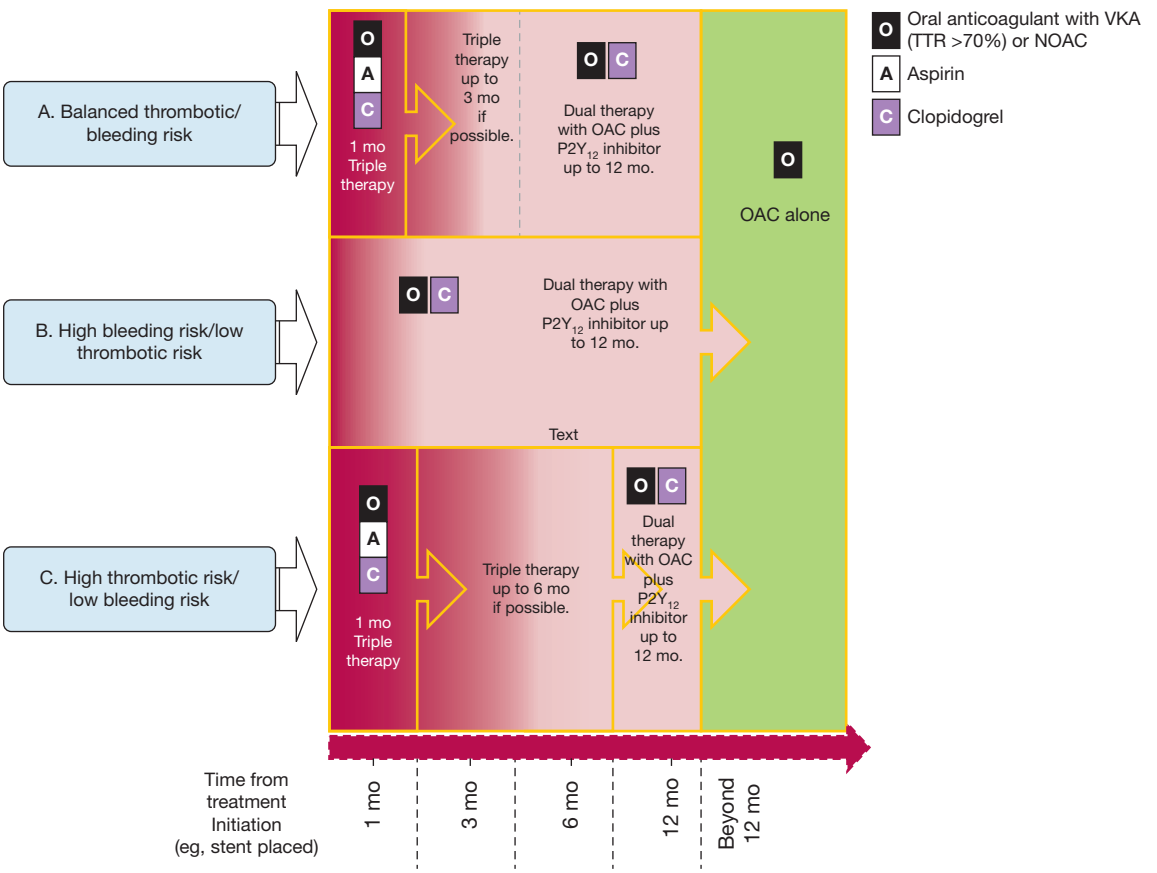

Figure 6 – *A-C, Management of oral antiplatelet therapy in patients with (A) balanced thrombotic/bleeding risk, (B) low thrombotic/high bleeding risk, and (C) high thrombotic/low bleeding risk. See Figure 1 legend for expansion of abbreviations. (Adapted from Angiolillo et al.[202])*

In a systematic review and meta-analysis (18 studies with 20,456 patients with AF; 7,203 patients received DAPT + VKA and 13,253 patients received DAPT after PCI/stenting), Chaudhary et al[280] showed that DAPT and VKA were associated with significantly lower risk of stroke, stent thrombosis, and all-cause mortality, but the risk of major bleeding was significantly higher in the DAPT and VKA group.

Broadly similar conclusions were drawn from the systematic review and meta-analysis (17 studies, 104,639 patients) by Zhu et al[281] where triple therapy (DAPT + OAC) was associated with an increased risk of bleeding compared with DAPT alone, with no differences observed between triple therapy and the dual therapy for all-cause death, cardiovascular death, or thrombotic complications (ie, ACS, stent thrombosis, thromboembolism/stroke, and major adverse cardiac and cerebrovascular events). In both systematic reviews, there was marked heterogeneity in study size, patient population, intervention types, stent use, etc.

Bennaghmouch et al[282] reported a meta-analysis restricted to the subgroups of patients on aspirin therapy (n = 21,722) from the 4 RCTs comparing VKA and NOACs (N = 71,681) in AF patients. NOACs were more effective (outcome stroke or systemic embolism HR, 0.78 [95% CI, 0.67-0.91] and vascular death HR, 0.85 [95% CI, 0.76-0.93]) and as safe as VKA with respect to major bleeding (HR, 0.83 [95% CI, 0.69-1.01]). NOACs were safer with respect to the reduction of ICH (HR, 0.38 [95% CI, 0.26-0.56]). Thus, it may be both safer and more effective to use NOACs compared with VKAs to treat patients with nonvalvular AF and concomitant aspirin therapy.

The largest observational cohort was reported by Lamberts et al,[283] which included a total of 12,165 AF patients (60.7% male; mean age, 75.6 years) hospitalized with MI and/or undergoing PCI between 2001 and 2009. Relative to triple therapy (OAC plus DAPT; ie, aspirin plus clopidogrel), no increased risk of recurrent coronary events was seen for OAC plus clopidogrel (HR, 0.69; 95% CI, 0.48-1.00), OAC plus aspirin (HR, 0.96; 95% CI, 0.77-1.19), or aspirin plus clopidogrel (HR, 1.17; 95% CI, 0.96-1.42), but aspirin plus clopidogrel was associated with a higher risk of ischemic stroke (HR, 1.50; 95% CI, 1.03-2.20). OAC plus aspirin and aspirin plus clopidogrel were associated with a significant increased risk of all-cause death (HR of 1.52 [95% CI, 1.17-1.99] and HR of 1.60 [95% CI, 1.25-2.05], respectively). When compared with triple therapy, bleeding risk was nonsignificantly lower for OAC plus clopidogrel (HR, 0.78; 95% CI, 0.55-1.12) and significantly lower for OAC plus aspirin and aspirin plus clopidogrel. Thus, OAC and clopidogrel was equal or better for both benefit and safety outcomes compared with triple therapy. However, this analysis provides limited information on the duration of therapies, quality of INR control, stent type, underlying bleeding risk profile, etc.

Randomized Trials: Prospective RCTs in AF patients presenting with ACS and/or undergoing PCI/stenting are limited. The first trial was the What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (WOEST) trial,[284] which randomized 573 adults receiving OACs (65% with AF) and undergoing PCI to clopidogrel alone (double therapy) or clopidogrel plus aspirin (triple therapy). The primary end point of "any bleeding" was seen in 19.4% receiving double therapy and 44.4% receiving triple therapy (HR, 0.36; 95% CI, 0.26-0.50; $P < .0001$). Of the secondary end points, there was no increase in the rate of thrombotic events, but all-cause mortality was higher in the triple-therapy arm. This trial was underpowered for efficacy and safety end points, and the primary end point of "any bleeding" was driven by minor bleeds given that triple therapy was mandated for 12 months.

The duration of triple therapy was also addressed by the Intracoronary Stenting and Antithrombotic Regimen-Testing of a Six-Week Versus a Six-Month Clopidogrel Treatment Regimen In Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting (ISAR-TRIPLE) study,[285] an RCT in 614 patients receiving OAC plus aspirin, randomized to either 6 weeks of clopidogrel therapy (n = 307) or 6 months of clopidogrel therapy (n = 307). The primary end point (composite of death, MI, definite stent thrombosis, stroke, or Thrombolysis In Myocardial Infarction major bleeding at 9 months) occurred in 30 patients (9.8%) in the 6-week group compared with 27 patients (8.8%) in the 6-month group (HR, 1.14; 95% CI, 0.68-1.91; $P = .63$). There were no significant differences for the secondary combined ischemic end point of cardiac death, MI, definite stent thrombosis, and ischemic stroke (12 [4.0%] vs 13 [4.3%]; HR, 0.93; 95% CI, 0.43-2.05; $P = .87$) or the secondary bleeding end point of Thrombolysis In Myocardial Infarction major bleeding (16 [5.3%] vs 12 [4.0%]; HR, 1.35; 95% CI, 0.64-2.84; $P = .44$). Thus, 6 weeks of triple therapy was not superior to 6 months of therapy with

respect to net clinical outcomes, suggesting that physicians should weigh the trade-off between ischemic and bleeding risk when choosing a shorter or longer duration of triple therapy.

In an open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI) trial,[286] 2,124 patients with AF undergoing PCI with stenting were randomized to low-dose rivaroxaban (15 mg once daily, reduced to 10 mg with moderate renal impairment) plus a $P2Y_{12}$ inhibitor for 12 months (group 1), very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months (group 2), or standard VKA (once daily) plus DAPT for 1, 6, or 12 months (group 3). The rates of clinically significant bleeding were lower in the 2 groups receiving rivaroxaban than in the VKA group (16.8% in group 1, 18.0% in group 2, and 26.7% in group 3; HR for group 1 vs group 3, 0.59; 95% CI, 0.47-0.76; $P < .001$; HR for group 2 vs group 3, 0.63; 95% CI, 0.50-0.80; $P < .001$). The rates of death from cardiovascular causes, MI, or stroke were similar in the 3 groups, but the trial was underpowered for efficacy end points. There was only a minority of newer $P2Y_{12}$ inhibitors used as APT. There was an associated reduction in hospitalizations in the 2 rivaroxaban arms, compared with VKA.[287]

The RE-DUAL PCI (A Prospective, Randomized, Phase 3b Study Comparing the Safety and Efficacy of Dual Antithrombotic Therapy With Dabigatran Etexilate Versus Warfarin Triple Therapy in Patients With Nonvalvular Atrial Fibrillation Who Have Undergone Percutaneous Coronary Intervention With Stenting) trial[288] randomized 2,725 patients with AF who had undergone PCI to triple therapy with warfarin plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and aspirin (for 1-3 months) (triple-therapy group) or dual therapy with dabigatran (110 mg or 150 mg twice daily) plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and no aspirin (110-mg and 150-mg dual-therapy groups). Outside the United States, elderly patients ($\geq$ 80 years of age; $\geq$ 70 years of age in Japan) were randomly assigned to the 110-mg dual-therapy group or the triple-therapy group. The incidence of the primary end point (major or clinically relevant nonmajor bleeding) was 15.4% in the 110-mg dual-therapy group compared with 26.9% in the triple-therapy group (HR, 0.52; 95% CI, 0.42 to 0.63; $P <$ .001 for noninferiority; $P < .001$ for superiority) and 20.2% in the 150-mg dual-therapy group compared with 25.7% in the corresponding triple-therapy group, which did not include elderly patients outside the United States (HR, 0.72; 95% CI, 0.58-0.88; $P < .001$ for noninferiority). The incidence of the composite efficacy end point of thromboembolic events (MI, stroke, or systemic embolism), death, or unplanned revascularization was 13.7% in the 2 dual-therapy groups combined compared with 13.4% in the triple-therapy group (HR, 1.04; 95% CI, 0.84-1.29; $P = .005$ for noninferiority). Thus, the risk of bleeding was lower among those who received dual therapy with dabigatran and a $P2Y_{12}$ inhibitor than among those who received triple therapy with warfarin, a $P2Y_{12}$ inhibitor, and aspirin. Dual therapy was noninferior to triple therapy with respect to the risk of thromboembolic events. In contrast to the PIONEER-AF trial, the RE-DUAL PCI trial tested dabigatran doses (110 mg and 150 mg bid) which are licensed for stroke prevention in AF.

There are limited data on the use of the newer $P2Y_{12}$ inhibitors (ticagrelor, prasugrel) with OAC. Observational cohorts in AF patients report a higher bleeding rate where these newer APT agents are used as part of a triple-therapy regimen, compared with when clopidogrel is used as part of the triple-therapy regimen.[289] Only a minority of patients in PIONEER AF-PCI had newer $P2Y_{12}$ agents, whereas the largest experience in AF patients was in the RE-DUAL PCI trial, which allowed ticagrelor in combination with dabigatran 110 mg or 150 mg bid.

In the GEMINI-ACS-1 trial (A randomized trial to compare the safety of rivaroxaban vs aspirin in addition to either clopidogrel or ticagrelor in acute coronary syndrome),[290] 3,037 patients with ACS (ie, essentially a non-AF population) were randomly assigned to either aspirin 100 mg or rivaroxaban 2.5 mg bid, and the subsequent choice of clopidogrel (44%) or ticagrelor (in 56%) during trial conduct was nonrandomized. Low-dose rivaroxaban with a $P2Y_{12}$ inhibitor for the treatment of ACS patients had similar risks of clinically significant bleeding (5%) as aspirin and a $P2Y_{12}$ inhibitor (HR, 1.09; 95% CI, 0.80-1.50; $P = .5840$).

Stable Vascular Disease: The presence of vascular disease adds to stroke risk in patients with AF. In the Danish registries, AF patients with vascular disease (prior MI, prior PAD, or aortic plaque) as a single risk factor have a high stroke rate of 4.85 per 100 person-years.[291] This corresponds to CHA_2DS_2-VASc = 1 for males and CHA_2DS_2-VASc = 2 for females, with rates of 4.53 and

5.69, respectively. Contrasting low risk CHA_2DS_2-VASc (ie, score 0 [male] or 1 [female]) as a reference population vs those with ≥1 additional stroke risk factors (ie, CHA_2DS_2-VASc score = 1 [males] or = 2 [females]), the risk attributable to vascular disease had a crude HR of 2.7 (95% CI, 1.7-4.2). In Asian countries,[292] PAD may confer an ischemic stroke risk that is much higher than that seen in Western populations.[38]

In AF patients with stable coronary artery disease, there is no evidence that adding APT to OAC reduces stroke/systemic embolism, death, or MI. However, the risk of major bleeding and ICH is substantially increased with the addition of APT to OAC. The largest cohort was reported by Lamberts et al[293] where 8,700 AF patients (mean age, 74.2 years; 38% women) with stable coronary artery disease (defined as 12 months from an acute coronary event) followed up for a mean 3.3 years, found the risk of MI/coronary death was similar for VKA plus aspirin (HR, 1.12; 95% CI, 0.94-1.34) and VKA plus clopidogrel (HR, 1.53; 95% CI, 0.93-2.52), relative to VKA monotherapy. However, the risk of bleeding increased > 50% when aspirin (HR, 1.50; 95% CI, 1.23-1.82) or clopidogrel (HR, 1.84; 95% CI, 1.11-3.06) was added to VKA.

In the RCTs of NOACs compared with warfarin, aspirin at < 100 mg daily was allowed. Ancillary analyses show no added benefit of adding aspirin on stroke or mortality rates; however, absolute bleeding rates were higher with combination therapy, but the relative efficacy and safety with NOAC vs warfarin use were maintained irrespective of aspirin use.[294] Only the RE-LY trial showed data for combination of dabigatran with aspirin and/or clopidogrel, and as expected, major bleeding risks were increased with a single APT and further increased where 2 APTs were used.[295]

Less data are evident for OAC use in AF patients with stable isolated **PAD** or carotid disease, in relation to OAC use. However, it is reasonable to assume that data for coronary artery disease would be generally applicable to PAD or carotid disease. One post hoc ancillary analysis[296] from the ROCKET-AF trial reported that the efficacy of rivaroxaban when compared with warfarin for the prevention of stroke or systemic embolism was similar in patients with PAD (HR, 1.19; 95% CI, 0.63-2.22) and without PAD (HR, 0.86; 95% CI, 0.73-1.02; interaction $P = .34$). However, there was a higher risk of major bleeding or non-major, clinically relevant bleeding with rivaroxaban when compared with warfarin in AF patients with PAD (HR, 1.40; 95% CI, 1.06-1.86) compared with those without PAD (HR, 1.03; 95% CI, 0.95-1.11; interaction $P = .037$).

Recommendations

20. In AF patients presenting with an ACS and/or undergoing PCI/stenting, we recommend assessment of stroke risk using the CHA_2DS_2-VASc score (Strong recommendation, moderate quality evidence).

Remark: All such patients are not 'low risk' and should be considered for concomitant OAC.

21. In AF patients presenting with an ACS and/or undergoing PCI/stenting, we suggest attention to modifiable bleeding risk factors at every patient contact, and assessment of bleeding risk using the HAS-BLED score (Weak recommendation, low quality evidence).

Remark: Where bleeding risk is high (HAS-BLED ≥ 3), there should be more regular review and follow-up.

22. In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is low (HAS-BLED 0-2) relative to risk for recurrent ACS and/or stent thrombosis, we suggest triple therapy for 1 month, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) until 12 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).

23. In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is high (HAS-BLED ≥ 3), we suggest triple therapy for 1 month, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) for 6 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).

24. In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is unusually high and thrombotic risk relatively low, we suggest use of OAC plus single antiplatelet (preferably clopidogrel) for 6 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).

Remark: Patients at unusually high bleeding risk may include patients with HAS-BLED ≥ 3 and recent acute bleeding event. High thrombotic risk may include those with left main stent, multivessel PCI/stenting, etc.

25. In AF patients requiring OAC presenting with an ACS, undergoing PCI/stenting, where bleeding risk is low (HAS-BLED 0-2) relative to risk for ACS or stent thrombosis, we suggest triple therapy for 6 months,

followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) until 12 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).

26. In AF patients requiring OAC presenting with an ACS, undergoing PCI/stenting, where bleeding risk is high (HAS-BLED ≥ 3), we suggest triple therapy for 1-3 months, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) up to 12 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).

27. In AF patients requiring OAC presenting with an ACS, undergoing PCI/stenting where bleeding risk is unusually high and thrombotic risk low, we suggest OAC plus single antiplatelet (preferably clopidogrel) for 6-9 months may be considered, following which OAC monotherapy can be used. (Weak recommendation, low quality evidence).

Remark: Patients at unusually high bleeding risk may include patients with HAS-BLED ≥ 3 and recent acute bleeding event. High thrombotic risk may include those with left main stent, multivessel PCI/stenting, etc.

28. In AF patients with ACS or undergoing PCI in whom OAC is recommended, we suggest using VKA with TTR > 65-70% (INR range 2.0-3.0), or to use an NOAC at a dose licensed for stroke prevention in AF (Weak recommendation, low quality evidence).

Remark: Only dabigatran 150 mg bid or (not licensed in USA) 110 mg bid or rivaroxaban 15mg qd are currently supported by clinical trial evidence. An NOAC based strategy has lower bleeding risk compared to a VKA-based strategy.

29. In AF patients in which aspirin is concomitantly used with OAC, we suggest a dose of 75-100 mg qd with concomitant use of PPI to minimize gastrointestinal bleeding (Weak recommendation, low quality evidence).

30. In AF patients in which a $P2Y_{12}$ inhibitor is concomitantly used with OAC, we suggest the use of clopidogrel (Weak recommendation, low quality evidence).

Remark: Newer agents (eg, ticagrelor) can be considered where bleeding risk is low. Data on the combination of ticagrelor with either dabigatran 110 mg bid or 150 bid (without concomitant aspirin use) are available from the RE-DUAL PCI trial.

***31. For patients with AF and stable coronary artery disease (eg, no acute coronary syndrome within the previous year) and who choose oral anticoagulation, we suggest OAC with either an NOAC or adjusted-dose VKA therapy alone (target international normalized ratio [INR] range, 2.0-3.0) rather than the combination of OAC and aspirin** (Weak recommendation, low quality evidence).

Catheter or Surgical Ablation, Electrophysiological Procedures

Periprocedural Anticoagulation for Catheter Ablation and Implantable Devices: Randomized trials have shown that uninterrupted warfarin is safe and superior to warfarin interruption for implantation of cardiac implantable electronic devices.[7]

For catheter ablation, anticoagulation guidelines pertinent to cardioversion generally apply to periprocedural anticoagulation and are detailed in a recent professional society expert consensus statement.[297] In a randomized trial of 1,584 patients, uninterrupted warfarin, compared with interruption with heparin bridging, has been shown to have a lower risk of periprocedural stroke and bleeding.[298] A randomized trial of uninterrupted rivaroxaban vs uninterrupted VKA in AF ablation demonstrated similar event rates in both arms.[299] A similar randomized trial of uninterrupted dabigatran found that dabigatran was associated with fewer bleeding complications than uninterrupted warfarin.[300] Although these studies were open-label, they strongly support the use of uninterrupted anticoagulation for electrophysiology procedures (Table 9).[298-301] Two recent systematic reviews with meta-analyses that include studies with such patients consistent with results.[302,303]

Long-term Anticoagulation After Restoration of Sinus Rhythm

Clinical observations indicate that AF and stroke are often temporally discordant, with stroke occurring during periods of sinus rhythm in the majority of patients with paroxysmal AF.[304,305]

After catheter ablation, discontinuation of OAC is associated with an increased risk of stroke.[297] Similarly, postoperative AF may confer a long-term risk of stroke. In a US claims analysis of 1.7 million patients hospitalized for surgery, perioperative AF was associated with an increased long-term risk of ischemic stroke,

TABLE 9] Summary of Studies of Periprocedural Anticoagulation for Catheter Ablation of AF and Implantation of Cardiac Electronic Implantable Devices

Trial	Population	Interventions	Results
COMPARE[298]	Catheter ablation of AF N = 1,584	Uninterrupted warfarin vs interrupted warfarin with low-molecular weight bridging	Significant reduction in stroke (0.25% vs 3.7%), TIA (0% vs 1.3%), and minor bleeding with uninterrupted warfarin
VENTURE-AF[299]	Catheter ablation of AF N = 248	Uninterrupted rivaroxaban vs uninterrupted VKA	No difference in overall low incidence of major bleeding (0.4%) or thromboembolic events (0.8%)
RE-CIRCUIT[300]	Catheter ablation of AF N = 704	Uninterrupted dabigatran vs uninterrupted warfarin	Significant reduction in major bleeding events with dabigatran (1.6% vs 6.9%)
BRUISE-CONTROL[301]	Pacemaker or defibrillator implantation N = 343	Uninterrupted warfarin vs interrupted warfarin with heparin bridging	Significant reduction in pocket hematoma (3.5% vs 16%)

BRUISE-CONTROL = Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial; COMPARE = Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation; RE-CIRCUIT = Randomized Evaluation of Dabigatran Etexilate Compared to Warfarin in Pulmonary Vein Ablation: Assessment of an Uninterrupted Periprocedural Anticoagulation Strategy trial; VENTURE-AF = a randomized, open-label, active-controlled multicenter study to evaluate the safety of rivaroxaban and vitamin K antagonists in subjects undergoing catheter ablation for atrial fibrillation. See Table 1 and 6 legends for expansion of abbreviations.

especially following noncardiac surgery.[306] It is not known to what extent the risk was mediated by AF recurrence (often asymptomatic) or was independent of rhythm. Thus, patients should be anticoagulated according to their thromboembolic risk profile based on CHA_2DS_2-VASc, regardless of whether sinus rhythm has been restored via ablation, cardioversion, or other means.

Recommendations

32. In patients with AF in whom catheter ablation of AF or implantation of cardiac electronic implantable devices is planned, we suggest performing the procedure on uninterrupted VKA (within the INR therapeutic range), dabigatran or rivaroxaban (Weak recommendation, low quality evidence).

33. In patients in whom sinus rhythm has been restored, we suggest that long-term anticoagulation should be based on the patient's CHA_2DS_2-VASc thromboembolic risk profile, regardless of whether sinus rhythm has been restored via ablation, cardioversion (even spontaneous), or other means (Weak recommendation, low quality evidence).

Cerebrovascular Disease

AF Patients Presenting With an Acute Ischemic Stroke or TIA: In AF-associated acute ischemic stroke, the risk of early recurrence is high: for example, the International Stroke Trial reported a 4.8% risk of recurrent stroke in those with AF within the first 2 days,[307] while other studies suggest a recurrence risk of between 0.4% and 1.3% per day in the first 7 to 14 days.[307-311] AF-related ischemic strokes are more often disabling or fatal than other types, with longer hospital stays and higher costs,[312] so preventing early recurrence is a key clinical challenge.

The safety and benefit of OAC in acute stroke have not been established. Early anticoagulation (ie, in the first few days) might increase the risk of symptomatic ICH, including hemorrhagic transformation of the infarct (estimated at approximately 1% per day[313]), leading to clinical uncertainty about when to start anticoagulation. Studies reported an 8% to 10% risk of recurrent ischemic stroke and a 2% to 4% risk of symptomatic ICH within 90 days of AF-related ischemic stroke.[314,315]

Current Uncertainty Regarding Optimal Timing of Anticoagulation: Current guidelines do not provide clear recommendations on the timing of OAC after acute AF-related stroke. US guidelines suggest that

commencing OAC within 14 days is reasonable,[316] while recent European Society of Cardiology guidelines recommend starting anticoagulation—according to infarct size—at 1, 3, 6, or 12 days[317] based only on expert consensus. Current UK guidelines recommend delaying anticoagulation for 14 days for "disabling" stroke (Intercollegiate Stroke Working Party, National Clinical Guideline for Stroke 2016; https://www.strokeaudit.org).

A recent observational study (n = 1,029) suggested that anticoagulation at 4 to 14 days after cardioembolic stroke had the best outcome but did not have statistical power to determine benefit of earlier anticoagulation.[318] Increasing cerebral infarct size is associated with increased risk of both symptomatic hemorrhagic transformation and early recurrent ischemia.[313]

A systematic review and meta-analysis of 7 randomized trials of UFH, LMWH, or heparinoids (n = 4,624) started < 48 h vs aspirin or placebo, found that early anticoagulation was associated with nonsignificantly reduced recurrent ischemic stroke but with increased intracranial bleeding, and no reduction in death or disability (e-Table 19).[310] In contrast, other small studies suggested fewer ischemic strokes without an increase in intracranial bleeding, as well as reduced mortality and disability with early initiation of VKAs (to achieve therapeutic levels by day 7).[315,319-321] Observational data suggest that the use of LMWH (as a "bridging" strategy) together with oral anticoagulation is associated with a higher risk of symptomatic hemorrhage.[314,322-324]

Observational studies suggest that early (< 14 days) anticoagulation with NOACs might be safe.[314,315,318,325] One study reported improved outcomes and no early ICH with NOAC started at a median of 4 days' poststroke (n = 1,192).[326,327] The Pre-Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation: a Prospective Multicenter Registry-based Non-inferiority Randomized Controlled Clinical Trial (TIMING) observational study of 249 patients with AF-associated acute ischemic stroke treated with OAC (< 5 days) reported in-hospital recurrent ischemic stroke in 4.4%, and symptomatic ICH in 3.1%.[328] There are no large trials of NOACs including patients within 7 to14 days of a stroke, but 1 small study (Phase 2 Exploratory Clinical Study to Assess the Effects of Xarelto (Rivaroxaban) Versus Warfarin on Ischemia, Bleeding, and Hospital Stay in Acute Cerebral Infarction Patients With Non-valvular Atrial Fibrillation [Triple AXEL]) randomized 195 patients with AF-related acute ischemic stroke to rivaroxaban or warfarin < 5 days and found similar rates of symptomatic/asymptomatic MRI-defined recurrent ischemia (approximately 30%) or intracranial bleeding (approximately 30%) at 4 weeks, with reduced hospital stay for rivaroxaban.[329]

Recommendations

34. In AF patients with acute ischemic stroke, we suggest that very early anticoagulation (< 48 h) using heparinoids or VKA should not be used (Ungraded consensus-based statement).

Remark: Heparinoids should not be used as bridging therapy in the acute phase of ischemic stroke because they appear to increase the risk of symptomatic intracranial hemorrhage without net benefit. The optimal timing of anticoagulation after acute ischemic stroke is unknown.

35. In AF patients with acute stroke without contraindications, we recommend that long-term oral anticoagulation is indicated as secondary prevention (Strong recommendation, high quality evidence).

Remark: The optimal timing of anticoagulation early after acute ischemic stroke is unknown. Early use of NOACs shows promise but requires testing in randomized controlled trials.

36. In AF patients with acute ischemic stroke, we suggest that oral anticoagulation should usually be started within 2 weeks of acute ischemic stroke, but the optimal timing within this period is not known (Ungraded consensus-based statement).

Remark: Although infarct size is clinically used to guide timing of anticoagulation, it is predictive of a higher risk of early recurrent ischemia, hemorrhagic transformation of the infarct, and poor outcome, so might not be helpful in determining the net benefit of early treatment.

Remark: Anticoagulation with NOACs soon after stroke (earlier than 1 week) has not been tested in randomized trials, but shows promise in observational studies.

AF Patients With Intracranial Hemorrhage (ICH): Spontaneous (nontraumatic) intracranial hemorrhage (ICH) causes about 1 in 10 strokes, and is caused by the rupture of a cerebral artery or arteriole, most often a small vessel affected by either hypertensive arteriopathy or cerebral amyloid angiopathy (CAA). ICH is the most feared, often lethal, complication of antithrombotic (anticoagulant and antiplatelet) therapy. Recent data indicate that about 50% of people with ICH are taking an

antithrombotic agent at the time of ICH.[330] In a recent hospital ICH cohort study, 25% of patients had AF.[331]

Risk of Ischemic Stroke: Survivors of ICH with AF are at risk of further brain ischemia but also recurrent ICH. The use of antithrombotic therapy (antiplatelet agents and anticoagulants) following ICH thus presents a major clinical dilemma. The risk of ischemic stroke with and without antithrombotic treatment must be weighed carefully against the possible increase in ICH risk associated with antithrombotic therapy. The risk of ischemic stroke in people with AF is typically estimated using instruments such as the CHA_2DS_2-VASC score, and it seems reasonable to use this score in populations of ICH survivors.[332]

Risk of Recurrent ICH: The future risk of ICH is highly variable; the annual recurrence risk was between 1.8% and 7.4% in one recent systematic review of observational studies.[333] CT is a highly sensitive test for ICH and can classify the location as "lobar" (originating in the lobes of the brain) or "deep" (originating in the basal ganglia or brainstem).[334] The risk of recurrence has been reported to be higher for lobar ICH than after deep ICH,[333] a finding which is probably related to different underlying small vessel diseases that cause ICH in the different locations. Although CT can define ICH location, it cannot reliably identify the underlying type of causal small vessel disease. MRI can identify biomarkers of small vessel disease, including cerebral microbleeds (CMBs), whose distribution can be used to diagnose CAA with high specificity in ICH cohorts.[335] In a recent pooled analysis of observational studies, patients with ICH classified using CMBs as due to CAA had an approximately 7% annual recurrence risk, compared with about 1% for those not fulfilling criteria for CAA.[336]

Since OACs increase the risk of ICH, some experts have recommended avoiding them in patients with ICH attributed to CAA. In survivors of ischemic stroke and TIA, CMBs are also associated with increased risk of ischemic stroke, although as the number of CMBs increases, the risk of future ICH increases more steeply than that of ischemic stroke.[337] In ICH survivors, the number of CMBs is also associated with the risk of recurrent ICH.[338]

Balancing the Risks of Ischemic Stroke and Recurrent ICH: A decision analysis which modeled warfarin for AF in an ICH survivor suggested that in lobar ICH, avoiding warfarin increased quality-adjusted life years by 1.9, compared with 0.3 for deep ICH; the authors concluded that anticoagulation for AF should not be offered to patients with lobar ICH and only to survivors of deep ICH if the risk of ischemic events was high (> 7% per year).[339] However, CMBs were not considered in this analysis. In contrast, recent "real-world" observational studies (including some very large registry datasets) from ICH survivors with AF suggest that anticoagulation might reduce mortality and ischemic complications, without an unacceptable increase in ICH.

A recent systematic review and meta-analysis of observational studies suggested that restarting anticoagulation was associated with a significantly lower risk of thromboembolic complications (pooled RR, 0.34; 95% CI, 0.25-0.45; Q = 5.12; *P* for heterogeneity = .28) with no increased risk of recurrent ICH (pooled RR, 1.01; 95% CI, 0.58-1.77; Q = 24.68; *P* for heterogeneity < .001).[340] However, none of the real-world studies stratified ICH by location, nor by CMB burden or distribution. Two small randomized studies of early anticoagulation after ICH were not able to confirm benefit or harm.[341,342] There are no reliable randomized trial data to guide the timing of anticoagulation after ICH. In acute ICH, hematoma expansion is common and is aggravated by anticoagulation. Anticoagulants should therefore be reversed and avoided in acute ICH (< 24-48 h).

A survival model based on observational data indicated that the total stroke risk (both ischemic and ICH) was lowest when anticoagulation was restarted after about 10 weeks, and a delay of at least 4 weeks after ICH was suggested.[343] There are no large-scale RCTs to answer the question of whether long-term anticoagulation has net benefit in ICH survivors with AF. NOACs have an approximately 50% lower ICH risk than VKA[124] and are therefore preferred in most ICH survivors, except where warfarin is indicated (eg, in those with metallic mechanical heart valves). Observational data suggest that ICH occurring on OAC are of similar size and with similar clinical outcome in patients taking VKA or NOACs.[344]

There are 2 ongoing randomized trials of antithrombotic use after ICH: APACHE-AF (http://apache-af.nl, aspirin vs apixaban vs no antithrombotics for the treatment of AF in patients after ICH) and Restart or Stop Antithrombotics Randomised Trial (RESTART) (www.restarttrial.org, antiplatelets vs no antiplatelets in patients with ICH with an indication for antiplatelets).

LAA Occlusion in ICH Survivors: Randomized trials indicate that LAA occlusion (LAAO) has similar efficacy to oral anticoagulation in patients with AF; thus, in ICH survivors with AF and high ischemic stroke risk, LAAO

is a potentially attractive option to reduce ischemic stroke and systemic embolism from AF without the need to expose patients to a long-term risk of oral anticoagulation.[345] Observational data from 1,025 patients suggest that LAAO might be safe and effective in patients with a contraindication to long-term oral anticoagulation, but only a minority of patients (15%) in this study had suffered ICH.[346] Small studies of ICH survivors suggest that LAAO, using antiplatelet treatment as periprocedural antithrombotic treatment, is safe and effective in this population, including those with CAA.[347,348] Randomized trials of LAAO, ideally in comparison to NOACs, are needed to definitively determine the safety and efficacy of each approach in ICH survivors.

Recommendations

37. In patients with AF and high ischemic stroke risk, we suggest anticoagulation with an NOAC after acute spontaneous ICH (which includes subdural, subarachnoid, and intracerebral hemorrhages) after careful consideration of the risks and benefits (Ungraded consensus-based statement).

Remark: The balance of net benefit from long-term oral anticoagulation might be more favorable in those with deep ICH or without neuroimaging evidence of cerebral amyloid angiopathy.

Remark: In ICH survivors with AF, clinicians should aim to estimate the risk of recurrent ICH (using ICH location and, where available, MRI biomarkers including cerebral microbleeds) and the risk of ischemic stroke

Remark: The optimal timing of anticoagulation after ICH is not known, but should be delayed beyond the acute phase (approximately 48 h) and probably for at least approximately 4 weeks. Randomized trials of NOACs and left atrial appendage occlusion are ongoing.

38. In ICH survivors at high risk of recurrent ICH (eg, those with probable cerebral amyloid angiopathy), we suggest left atrial appendage occlusion (Ungraded consensus-based statement).

Remark: Cerebral amyloid angiopathy should be diagnosed using validated clinico-radiological criteria.

AF Patients With Carotid Disease: Carotid stenosis is present in about 8% of people over the age of 60.[349] A recent multicenter retrospective study found > 50% carotid stenosis in 18.3% of patients with AF, which was associated with a doubling of stroke risk.[350] Thus, in patients with both carotid stenosis and AF, there are indications for both anticoagulation and APT, yet this combination, at least in the long term, is associated with high bleeding risk and is thus generally not recommended.

Randomized trials show superiority for carotid endarterectomy over stenting in patients with symptomatic stenosis (> 50%) of the internal carotid artery.[351] This could reduce the need for combination therapy with OAC and antiplatelet drugs in those with AF. Current practice is to treat all potential stroke risk factors including AF and carotid stenosis. Those who have had successful carotid revascularization are typically managed with OAC alone. In patients with carotid stenosis not treated by revascularization (including those with asymptomatic disease) as well as AF, the optimal management is not known and requires further randomized data; meanwhile, decisions need to be tailored to the individual patient.

Recommendations

39. In patients with AF and symptomatic carotid stenosis (> 50%), we suggest carotid revascularization with endarterectomy or stenting in addition to OAC as indicated (Weak recommendation, moderate quality evidence).

TABLE 10] Phases of Screening for AF in Cryptogenic Stroke Patients, Methods and Incidence of AF Diagnosed[355]

4 Sequential Phases of Screening	Cardiac Monitoring Methods	% (95% CI) Diagnosed With Poststroke AF
Phase 1 (emergency room)	Admission ECG	7.7% (5.0–10.8)
Phase 2 (in hospital)	Serial ECG, continuous inpatient ECG monitoring, continuous inpatient cardiac telemetry, and in-hospital Holter monitoring	5.1% (3.8–6.5)
Phase 3 (first ambulatory period)	Ambulatory Holter	10.7% (5.6–17.2)
Phase 4 (second ambulatory period)	Mobile cardiac outpatient telemetry, external loop recording, and implantable loop recording	16.9% (13.0–21.2)

See Table 1 legend for expansion of abbreviation.

40. In patients with AF and carotid stenosis treated with revascularization, we suggest OAC therapy, without long-term antiplatelet therapy (Ungraded consensus-based statement).

Remark: There is limited evidence to guide the optimal treatment of patients with AF and carotid stenosis not requiring revascularisation**.**

Remark: Short-term concomitant antiplatelet therapy (dual or mono) is generally used in the immediate post-revascularization period (eg, 1-3 months).

Patients Presenting With ESUS: In North America and Europe, about 1 in 4 ischemic strokes remain of uncertain etiology (ie, not attributable to definite cardiac embolism, large artery atherosclerosis, or small artery disease), despite adequate investigation, and are termed "cryptogenic."[316,352]

Because most cryptogenic strokes are embolic, a more recent concept of ESUS has been developed. ESUS has been defined as ischemic stroke detected by CT or MRI that, after a standardized and adequate diagnostic pathway including brain imaging, echocardiography, cardiac rhythm monitoring for at least 24 h, and imaging of the intracranial and extracranial arteries supplying the affected brain area: is not lacunar (subcortical, $<$ 15 mm diameter); where there is absence of extracranial or intracranial atherosclerosis causing $\geq$ 50% luminal stenosis in the arteries supplying the area of ischemia; no major-risk cardioembolic source of embolism (permanent or paroxysmal AF, sustained atrial flutter, intra-cardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumours, mitral stenosis, recent [$<$ 4 weeks] MI, left ventricular ejection fraction $<$ 30%, valvular vegetations, or infective endocarditis); and no other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm, drug misuse).[353]

Thus, ESUS is a subcategory of cryptogenic stroke, accounting for about 1 in 6 ischemic strokes.[357] A careful and systematic diagnostic workup in patients with ESUS is needed as there might be important management differences between underlying embolic sources if detected, such as aortic arch atheroma, patent foramen ovale, and paroxysmal AF. This brief section only refers to the latter.

As a general principle, AF can be detected in a high proportion of ESUS patients, if we "look harder, look longer and look with more sophisticated monitoring" (Table 10).[355] Screening consecutive patients with ischemic stroke with routine Holter or event loop recorder monitoring will identify new AF/atrial flutter in approximately 1 in 20 patients.[356]

Two RCTs clearly showed that prolonged cardiac monitoring increases the detection of occult AF in patients with TIA or acute ischemic stroke presenting in sinus rhythm. In Cryptogenic Stroke and Underlying Atrial Fibrillation [CRYSTAL AF], 441 patients randomly assigned to prolonged ambulatory cardiac monitoring with a subcutaneous implantable loop recorder or to a control group with conventional follow-up, detected more AF in the monitored group (8.9% vs 1.4% in the control group; HR, 6.4; 95% CI, 1.9-21.7),[357] while in a 30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event: A Randomized Controlled Trial [EMBRACE], 572 patients randomly assigned to additional ambulatory monitoring with a 30-day external loop recorder (intervention group) or a 24-h Holter monitor (control group) found more AF in the intervention group (16.1% vs 3.2% in the control group; absolute difference, 12.9%; 95% CI, 8.0-17.6).[358]

In a systematic review and meta-analysis, Sposato et al[355] described a much higher rate of AF detection after multi-phase sequential cardiac monitoring, at 23.7% (Table 10). Despite this, one recent analysis only found that 2.6% and 9.7% of stroke patients had ambulatory ECG monitoring in the 7 days and 12 months' poststroke, leading to underdiagnosis.[359]

Unsurprisingly, AF is more likely to be detected in elderly patients with more prolonged monitoring, especially if there is evidence of prior embolic cortical or cerebellar infarction.[360,361] In a retrospective analysis, newly detected atrial tachycardia or AF (atrial tachycardia/AF $>$ 5 min on any day) was identified in 30% patients with implantable cardiac rhythm devices and $\geq$ 1 stroke risk factors during a follow-up of 1.1 years.[362] The presence of atrial tachycardia/AF $>$ 6 h on $\geq$ 1 day increased significantly with increased $CHADS_2$ scores. Similarly, the Prevalence of Sub-Clinical Atrial Fibrillation Using an Implantable Cardiac Monitor in Patient With Cardiovascular Risk Factors [ASSERT-II] study reported that subclinical AF lasting $\geq$ 5 min was present in 34.4% per year, in a prospective cohort of elderly patients with risk factors but no prior stroke.[363]

Of note, data from the Athens Stroke Registry show that the $CHADS_2$ and CHA_2DS_2-VASc scores are independently associated with the risk of ischemic stroke/TIA recurrence and death in ESUS patients, with

the risk of stroke recurrence and death in patients with a CHA_2DS_2-VASc score ≥ 2 being approximately threefold and 15-fold higher compared with that in patients with a score of 0, respectively.[364] If ESUS is phenotypically different from AF-associated stroke, we should see differences in stroke severity and outcomes; however, no difference in National Institutes of Health Stroke Scale score was evident in ESUS where AF was detected on follow-up, compared with where no AF was evident.[365] Nevertheless, it remains possible that within ESUS there is a spectrum of underlying proximal embolic sources, suggested by the strong effect of age on recurrence risk and mortality.[366]

Current guidelines recommend use of antiplatelet agents including aspirin in ESUS patients[316] unless AF is detected (often requiring prolonged workup, as above), when such patients would be managed with oral anticoagulation. The available data (mainly from retrospective observational studies) suggest a sizeable rate of stroke recurrence (> 4% per year) despite the frequent use of antiplatelet agents in clinical practice.[354] Thus, there is an important clinical need for more effective antithrombotic therapy for ESUS. Since a large proportion of ESUS are likely to be due to undetected AF, oral anticoagulation is a theoretically attractive option.

Ongoing randomized trials comparing NOACs with aspirin in ESUS patients are in progress. Prior to data from these trials, physicians might, in the meantime, consider the use of anticoagulation in parallel with continued cardiac evaluation (eg, prolonged rhythm monitoring) after discussion and consideration of patient preference.

AHREs Detected by Cardiac Implanted Electronic Devices

Cardiac implanted electrical devices (CIEDs) with an atrial lead or with capability of rhythm discrimination (ie, implantable cardiac monitors) allow continuous monitoring of the cardiac rhythm and appropriate detection of atrial tachyarrhythmias, including AF, as AHREs as well as storing arrhythmia electrograms in the device's memory for review and specific diagnosis. AHREs, currently defined as episodes of at least 5 min of atrial tachyarrhythmias/AF with an atrial rate >180 beats/min, are usually asymptomatic, discovered during routine device follow-up, and classified in terms of duration of the single episode or time spent in atrial tachyarrhythmias during a day (from minutes to hours).[367-373]

Although temporal cutoffs for detection and storage of AHRE data as short as 30 to 60 s have been used, the diagnostic accuracy is reliable when episodes ≥ 5 min in duration are considered, since, using this cutoff, the appropriateness in AF detection is 95%, minimizing the risk of over-sensing due to detection of artifacts caused by myopotentials or other sources of electrical interference.[374,375] Individual patient analysis of electrograms corresponding to AHREs is clinically indicated to exclude artifacts or other causes of inappropriate detection of atrial tachyarrhythmias or AF. Electrograms of AHREs correspond to intracardiac electrograms recorded from right atrial appendage or right atrium so a diagnosis of tachyarrhythmias can easily be made through analysis of tracings recorded in the device's memory.[157] After detection of AHREs by CIEDs, conventional Holter or other ECG long-term recordings (ie, patient-operated devices) can be considered in specific cases (eg, unavailable electrograms or unclear diagnosis at device electrograms analysis).

The possibility of continuous monitoring of AF through implanted devices has led to new terms, such as "AF burden," defined as the overall time spent in AF during a specified period of time,[368,376-378] and "subclinical AF," corresponding to episodes of atrial tachyarrhythmias with duration between 5 min and 24 h, detected by a CIED in patients without clinical history or clinical symptoms of AF.[367,370-372]

The prevalence of AHRE, often reported as AF burden, among patients implanted with CIEDs varies, depending on underlying heart disease, periods of observation, and above all previous history of clinically overt atrial tachyarrhythmias, including AF. In the ASSERT study, subclinical atrial tachyarrhythmias with at least 6 min duration were detected within 3 months in approximately 10% of patients implanted with a CIED.[371] During a follow-up period of 2.5 years, additional subclinical atrial tachyarrhythmias occurred in approximately 25% of patients, and around 16% of those who had subclinical atrial tachyarrhythmias developed symptomatic AF.[371] Considering these findings, as well as data from the literature reported in e-Table 20, there is evidence that AHREs with a duration > 5 to 6 min are common in patients implanted with CIEDs.

In patients implanted with CIEDs for conventional indications, AHREs, with a short duration, ranging from 3 atrial premature complexes to 15 to 20 s, are currently considered of no specific clinical significance since this type of AHRE was found not to be significantly

associated with episodes of longer duration, or with an increased risk of stroke or systemic thromboembolism.[379] For this reason, most of the interest in patients with CIEDs is focused on AHRE with a duration ≥ 5 to 6 min, a finding associated with a substantial risk of subsequently presenting clinical AF (HR, 5.5-6.0), initially reported by the ancillary Atrial Diagnostics Ancillary Study of the Mode Selection Trial (MOST) analysis[380] and then by the ASSERT study,[371] where CIED-detected AHREs > 6 min were followed by clinical AF detected by a surface ECG in approximately 16% of patients at 2.5 years of follow-up (e-Table 21).

The association between CIED-detected atrial tachyarrhythmias of variable durations and stroke or systemic thromboembolism has been evaluated by several studies that overall collected data on > 22,000 patients, taking into account the maximum duration of AHRE episode, or the maximum daily AF burden (ie, the maximum time spent in adjudicated AF in 1 day of the follow-up period).[371,379-387] The studies show that AHRE burden with a duration ≥ 5 to 6 min are significantly associated with an increase in the risk of stroke or systemic thromboembolism (HR, 2-9). In a re-analysis of the ASSERT study,[388] the increase in the risk of stroke occurred only when the longest duration of the various episodes of detected AHREs was > 24 h. The largest dataset of patients with CIED-detected AHREs was analyzed in the Stroke Prevention Strategies Based on Atrial Fibrillation Information From Implanted Devices [SOS AF] project, with a pooling of 3 prospective studies (Phase IV Long Term Observational Study of Patients Implanted With Medtronic CRDM Implantable Cardiac Devices [PANORAMA], Italian Clinical Services Project, and A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics [TRENDS]) resulting in 10,016 patients.[385] During a median follow-up of 24 months, 43% of an unselected cohort of patients with implanted devices experienced ≥ 1 day with ≥ 5 min of AHRE burden, and a 1-h threshold of AHRE burden was associated with an HR for ischemic stroke of 2.11 (95% CI, 1.22-3.64; $P = .008$), although the absolute risk of ischemic stroke in patients with AHREs was low (0.39% annual rate in the whole cohort). Similarly, the TRENDS study[383] found that an AHRE burden of 5.5 h in a day, in a 30-day period, was associated with a twofold increase in the adjusted risk of stroke (absolute risk of thromboembolism around 1.8% per year).[383] Integration of AHRE presence, duration, or burden (≥ 5 min or ≥ 24 h) into risk scores for thromboembolism may modestly improve c-statistics of both the $CHADS_2$ and CHA_2DS_2-VASc scores for predicting stroke.[389]

The clinical significance of AHRE is presumably different from that of clinically identified AF since the latter, detected using conventional surface ECG methods, corresponds to a much higher AF burden as compared with patients with AHRE detected by continuous monitoring via a CIED.[370,372] The actual rates of stroke or systemic embolic events reported in studies evaluating CIED-detected AHREs are often lower than what would be predicted by $CHADS_2$ and CHA_2DS_2-VASc scores, and this may be related to concurrent treatment with OACs in each study, risk of under-reporting, and confounding. Also, the temporal relationship between ischemic stroke and AF is less strict than expected, since stroke may occur without the concurrent presence of atrial tachyarrhythmias or AF at the time of stroke or in the days before. These findings suggest that the relationship between AF and stroke can be complex, with AF involved but not always in a causative role (mediated by a left atrial thrombus), but also simply representing a marker of increased vascular risk.[368,372]

Two RCTs are ongoing evaluating the efficacy and risk/benefit ratio of oral anticoagulation to no oral anticoagulation (aspirin only) in patients with CIED-detected AHRE (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation [ARTESiA; NCT01938248])[390] and Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes [NOAH-AFNET 6; NCT02618577).[391]

In the absence of the results of these ongoing trials, management of patients with CIEDs-detected AHREs requires cardiological clinical evaluation, clinical decision-making, and follow up (Fig 7). OACs could be considered as a result of an individualized clinical assessment taking into account overall AHRE burden (in the range of multiple hours rather than few minutes) and specifically presence of AHRE > 24 h, individual stroke risk (CHA_2DS_2-VASc), predicted risk/benefit of oral anticoagulation (specifically risk of major bleeding), and informed patient preferences.

Recommendations

41. For patients that present with a clinically documented episode of AF (12-lead ECG or other means, eg, external devices with validated rhythm detection), we suggest that the presence or absence of symptoms must not influence the process of decision-

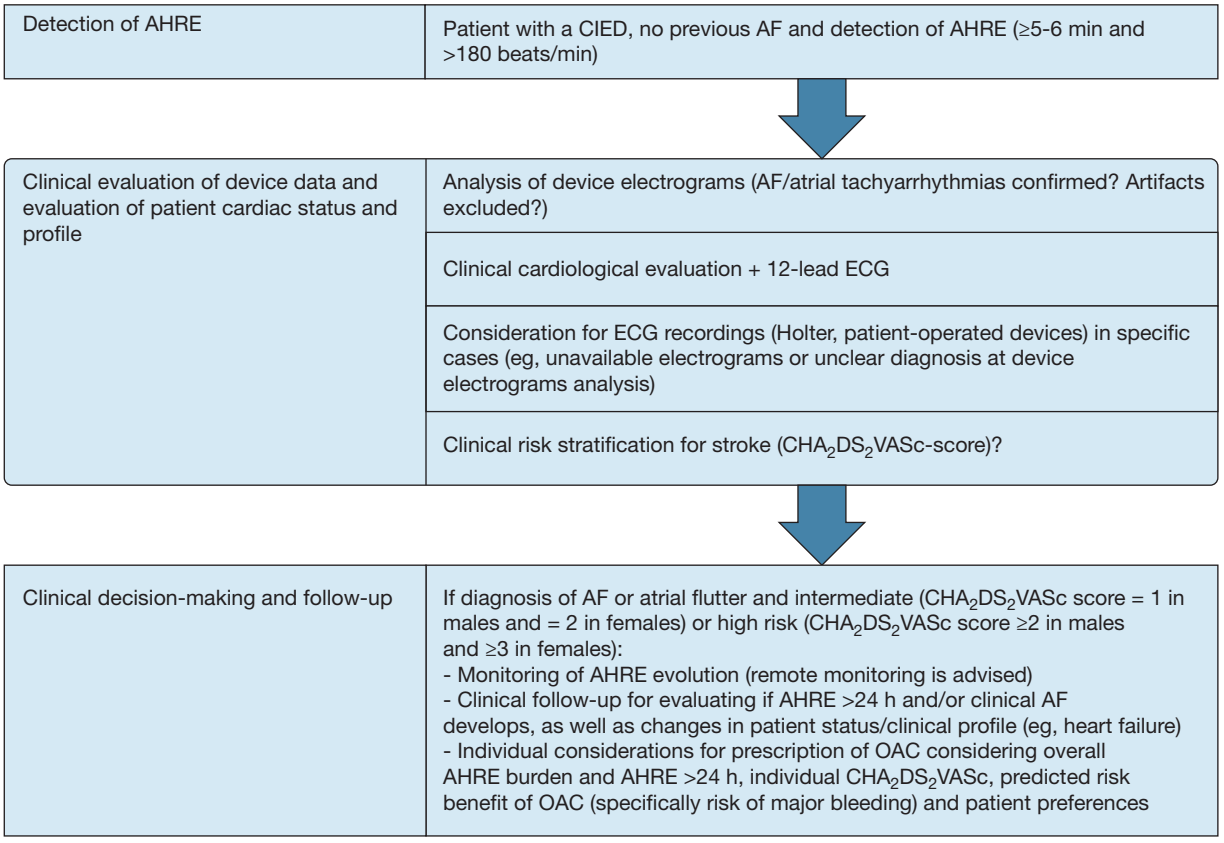

Figure 7 – *Flowchart for clinical management and decision-making in patients with CIEDs-detected AHRE. AHRE = atrial high-rate episode; CIED = cardiac implanted electrical device. See Figure 1, 3, and 4 legends for expansion of other abbreviations.*

making with regard to the need for anticoagulation based on risk stratification (Ungraded consensus-based statement).

42. In cases of AHRE (atrial high-rate episodes) detected by a CIED of at least 5 min duration, we suggest that direct analysis of electrograms corresponding to AHRE is clinically indicated to exclude artifacts or other causes of inappropriate detection of atrial tachyarrhythmias or AF (Ungraded consensus-based statement).

Remark: In patients with CIED-detected AHRE, a complete cardiological evaluation is indicated, with 12-lead ECG, general assessment of clinical conditions, and clinical risk stratification for stroke using CHA_2DS_2-VASc score.

Remark: There is no evidence in support or against prescription of oral anticoagulants in patients at risk of stroke (intermediate to high risk according to CHA_2DS_2-VASc) who present with AHREs, corresponding to atrial tachyarrhythmias/AF at electrograms assessment of less than 24 h duration.

43. In patients with AF, we suggest prescription of oral anticoagulants as a result of an individualized clinical assessment taking into account overall AHRE burden (in the range of hours rather than minutes) and specifically, the presence of AHRE > 24 h, individual stroke risk (using CHA_2DS_2-VASc), predicted risk/benefit of oral anticoagulation and informed patient preferences (Ungraded consensus-based statement).

Remark: In patients with CIED-detected AHRE, continued patient follow-up is recommended, preferentially combining clinical follow-up with remote monitoring of the CIED or else more frequent device interrogation than standard for CIED follow-up, to detect the development of clinical AF (symptomatic or asymptomatic), to monitor the evolution of AHRE or AF burden and specifically the transition to AHRE lasting more than 24 h, onset or worsening of heart failure, or any clinical change that might suggest a change in clinical profile or clinical conditions.

Atrial Flutter

The risk of thromboembolism and stroke in patients with atrial flutter has been evaluated in relatively few studies compared with AF. However, patients with atrial flutter frequently present phases of AF alternated with phases of classical flutter or regular atrial rhythm.[392-394] A systematic review on the thromboembolic risk associated with atrial flutter, including 52 articles, found that thromboembolic event rates after cardioversion varied from 0% to 6% with a follow-up from 1 week to 6 years.[234,271,274,275,395-405] Echocardiographic studies reported prevalence of intra-atrial thrombi from 0% to 38% and a prevalence of spontaneous echo contrast up to 28%.[392,393,403,406-415] One ablation study in non-anticoagulated patients with atrial flutter reported thromboembolic events in 13.9% of cases.[416] The differences in patient selection, type of study, and, importantly, use of oral anticoagulation explain the heterogeneity of reported data regarding echo findings and thromboembolic complications. Observational studies demonstrated an increased risk of stroke (RR, 1.4; 95% CI, 1.35-1.46) and death (HR, 1.9; 95% CI, 1.2-3.1)[395] compared with control subjects at long-term follow-up.

A report from the Danish nationwide registry on patients undergoing an atrial flutter ablation or an AF ablation procedure between 2000 and 2013 found that the rate of thromboembolic events for atrial flutter patients was 0.46 per 100 person-years, not significantly different from that of patients presenting with AF (HR adjusted for several variables including anticoagulation = 1.22 [95% CI, 0.62-2.41]).[395]

The role of anticoagulant therapy for patients with atrial flutter has not been evaluated in large randomized clinical trials, but because these patients often have concomitant AF or are at increased risk of developing AF, it is reasonable to base decisions regarding antithrombotic therapy on the same risk stratification schemes and scores used for AF.[3]

Recommendation

44. For patients with atrial flutter, we suggest that antithrombotic therapy decisions follow the same risk-based recommendations as for AF. (Ungraded consensus-based statement).

Pregnancy

AF and atrial flutter are very rare during pregnancy, unless when there is an underlying structural heart disease or hyperthyroidism.[417] Lone AF is uncommon in pregnancy and is associated with older age and late pregnancy.[418] In countries where the prevalence of rheumatic heart disease is still high or among immigrants from these areas to Western countries, the prevalence of AF in pregnancy may be commonly related to rheumatic heart disease.[418] Peri-partum cardiomyopathy AF is common, with a prevalence that may reach 10%, and may severely impair hemodynamic status.[419]

In a registry of > 250,000 pregnancies in Southern California,[420] AF was evident in 0.6 per 1,000, more frequently in white women (1.1 per 1,000 pregnancies), and was associated with more advanced age, higher BMI, hypertension, hyperlipidemia, and diabetes. Decision-making on antithrombotic therapy during pregnancy has been reviewed in detail in the 9th Edition of the Antithrombotic Therapy and Prevention Guidelines; here we provide an update with recommendations focused on AF.[421]

The use of anticoagulant therapy during pregnancy is challenging because of the potential for both fetal and maternal complications. Pregnancy-induced changes in hemostasis lead to a state of hypercoagulability, so in a woman with AF at risk of stroke/thromboembolism in the non-pregnant state, pregnancy will increase this risk threefold to fourfold.[421,422]

VKAs cross the placenta and have the potential to cause fetal wastage, bleeding in the fetus, and teratogenicity. The most common fetal anomaly developing as a consequence of fetal exposure to warfarin consists of midfacial hypoplasia and stippled epiphyses and typically occurs after in utero exposure to VKAs during the first trimester of pregnancy.[421] VKAs have also been associated with CNS abnormalities after exposure during any trimester, but these complications are uncommon.[421] There is general consensus that in order to minimize the risk of warfarin embryopathy, it is reasonable to avoid warfarin between weeks 6 and 12 of gestation because of the high risk of fetal defects, especially if the dose of warfarin is higher than 5 mg per day.[417]

LMWH does not cross the placenta, and there is no evidence that LMWH causes teratogenicity or increases fetal bleeding. Because of accelerated clearance, LMWH has a shorter half-life and lower peak plasma concentration during pregnancy, thus potentially requiring higher doses. For this reason, use of LMWH (such as between weeks 6 and 12) has to be managed

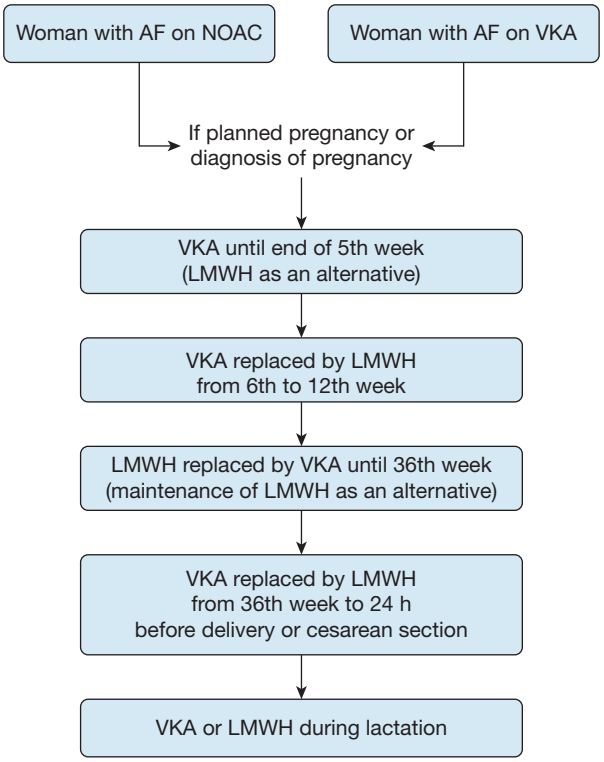

Figure 8 – *Management of women with AF during pregnancy is shown. LMWH = low-molecular-weight heparin. See Figure 1 and 3 legends for expansion of other abbreviations.*

with dose adjustment according to weight and target anti-Xa level (4-6 h post-dose 0.8-1.2 U/mL).

UFH does not cross the placenta and therefore can be safely used in pregnancy. However, it carries some risk of heparin-induced thrombocytopenia and osteopenia, which may lead to symptomatic vertebral fracture in approximately 2% of women.[419] Moreover, the pharmacokinetic changes of pregnancy result in a shorter half-life and lower peak plasma concentration of heparin compounds, with the need to titrate doses in order to keep the mid-interval aPTT (6 h post dose ≥ twice control values). Since both the risk of heparin-induced thrombocytopenia and the risk of osteoporosis are lower with LMWH than with UFH, the former is preferred as subcutaneous treatment during pregnancy.

Pregnant women were excluded from participating in clinical trials evaluating NOACs. Given the rather low molecular weight of NOACs and data on placental transfer in rats, all NOACs are expected to cross the placenta.[423] Hence, use of NOACs in pregnancy should be avoided. Limited data are available on the consequences of exposure to NOACs, but women inadvertently exposed to an NOAC in early pregnancy before diagnosis of pregnancy) can be reassured, since the risk of embryopathy seems low. In case of planned pregnancy, avoidance of NOACs should be considered (with switching to LMWH).

Regarding breast-feeding, warfarin, in view of its characteristics (polar, non-lipophilic, and highly protein bound), can be considered safe since 2 reports showed that warfarin is not detected in breast milk and does not induce an anticoagulant effect in the breast-fed infant when breast-feeding mothers consume the drug.[424,425] Acenocoumarol, which is commonly used in Europe, has similar properties.[426,427] Use of UFH and LMWH in breast-feeding women appears safe. No clinical data on the effect of NOACs on breast-fed infants are available, and therefore the recommendation is against use these medications in breast-feeding women.

A flow chart on how to manage women with AF during pregnancy is shown in Figure 8.

Recommendations

45. For women receiving OAC for prevention of stroke/TE in AF who become pregnant, we suggest discontinuation of OAC with a VKA between weeks 6 and 12 and replacement by LMWH twice daily (with dose adjustment according to weight and target anti-Xa level 4-6 h post-dose 0.8-1.2 U/mL), especially in patients with a warfarin dose required of > 5 mg/day (or phenprocoumon > 3 mg/day or acenocoumarol > 2 mg/day). OAC should then be discontinued and replaced by adjusted-dose LMWH (target anti-Xa level 4-6 h post-dose 0.8-1.2 U/mL) in the 36th week of gestation (Ungraded consensus-based statement).

46. For women on treatment with long-term vitamin K antagonists who are attempting pregnancy and are candidates for LMWH substitution, we suggest performing frequent pregnancy tests and use LMWH instead of VKA when pregnancy is achieved rather than switching to LMWH while attempting pregnancy (Ungraded consensus-based statement).

47. For pregnant women, we suggest avoiding the use of NOACs (Ungraded consensus-based statement).

Remark: For women on treatment with an NOAC we suggest switching to vitamin K antagonists, rather than switching to LMWH while attempting pregnancy.

48. For lactating women using warfarin, acenocoumarol, or UFH who wish to breast-feed, we suggest continuing the use of warfarin,

acenocoumarol, LMWH or UFH (Ungraded consensus-based statement).

49. For breast-feeding women, we suggest alternative anticoagulants rather than NOACs (Ungraded consensus-based statement).

AF and CKD

CKD is frequently present in patients with AF and has significant implications on the trajectory of AF, risk of stroke, and bleeding risk of anticoagulation. The presence of CKD or AF bi-directionally affects the incident risk of the other. Among patients with CKD, the prevalence of AF is substantially higher than in the general population, ranging from 16% to 21% in nondialysis dependent CKD and 15% to 40% in patients on dialysis.[428]

Among patients with AF, CKD is present in one-third of patients at the time of AF diagnosis[51,429] although this may be substantially higher among cohorts of prevalent AF subjects. The impact of AF is illustrated in the systematic review by Odutayo et al,[51] whereby the presence of AF increased CKD (HR, 1.64; 95% CI, 1.41 to 1.91), as well as all-cause mortality (RR, 1.46; 95% CI, 1.39-1.54), cardiovascular mortality (HR, 2.03; 95% CI, 1.79-2.30), major cardiovascular events (RR, 1.96; 95% CI, 1.53-2.51), stroke (RR, 2.42; 2.17-2.71), ischemic stroke (RR, 2.33; 1.84-2.94), ischemic heart disease (RR, 1.61; 95% CI, 1.38-1.87), sudden cardiac death (RR, 1.88; 1.36-2.60), HF (RR, 4.99; 95% CI, 3.04-8.22), and PAD (RR, 1.31; 95% CI, 1.19-1.45).

AF, CKD, and Stroke: CKD increases the baseline risk of ischemic stroke in patients with AF.[428] The pathophysiological mechanisms responsible for stroke and systemic embolism in these patients are multifactorial. The precise attributable risk of AF as a causal agent of cardioembolic stroke is therefore unclear, particularly where patients have substantially higher risk of atherothrombotic ischemic stroke due to hypertension, intracranial and carotid atherosclerosis, HF, and CAD.

Second, CKD increases the competing risk of death from causes unrelated to AF-associated stroke and may attenuate expected benefit of stroke prevention therapy. In a recent analysis of 7 risk stratification scores, all had substantially poorer discrimination in CKD patients than those without CKD (c-statistics, 0.50-59 vs 0.69-0.70, respectively), and inclusion of CKD stage did not improve calibration or discrimination.[430] One study from Taiwan showed that the CHA_2DS_2-VASc score could adequately risk stratify for ischemic stroke among a hemodialysis population (c-index, 0.682; superior to $CHADS_2$).[431]

Third, moderate to severe CKD increases the risk of major and intracranial bleeding through a number of mechanisms, and the risk may be further increased by the use of oral anticoagulation or APT. The clinical bleeding risk scores (eg, HAS-BLED, ORBIT, RIA) all include CKD measures as part of their score calculation.[103] Therefore, CKD is both a marker of risk of disease and of its therapy, and there is significant controversy as to the net clinical benefit of oral anticoagulation in severe CKD despite encouraging observational studies.[432]

Fourth, there are virtually no randomized trial data of oral anticoagulation in severe CKD (creatinine clearance [CrCl] < 25-30 mL/min). Some observational data suggest that warfarin may be harmful in end-stage renal disease patients on hemodialysis, with no reduction (or an increase) in stroke and an excess of major bleeding; however, many of these studies (largely from North America) do not report quality of anticoagulation control, as reflected by TTR.[433-435] In contrast, European data suggest that there is a beneficial reduction in ischemic stroke which outweighs the increase in severe bleeding, where TTR is good (> 65%-70%).[433-435]

The latest systematic review and meta-analysis by Harel et al[436] of 14 observational studies (20,398 participants) among hemodialysis with AF, found that the use of warfarin was not associated with ischemic stroke (14 studies; 20,398 participants; HR, 0.85; 95% CI, 0.55-1.07), or ICH (hemorrhagic stroke; 4 studies; 15,726 participants; adjusted HR, 1.93; 95% CI, 0.93-4.00) (e-Table 22). They concluded that warfarin was not associated with a clear benefit or harm among patients who have AF and receive dialysis. However, there was marked study heterogeneity including the inability to account for major confounders such as the quality of anticoagulation control (TTR). One study reported that in AF patients on peritoneal dialysis, warfarin reduced stroke and thromboembolism compared with aspirin or no antithrombotic therapy, with no excess in serious bleeds (ICH).[246]

The lack of clinical trial data in severe CKD is a major evidence gap with the NOACs, even though some regulatory agencies such as the Food and Drug Administration have approved reduced-dosed NOACs for severe CKD and dialysis on the basis of pharmacokinetic data.[437] Fortunately, the pivotal NOAC randomized trials have demonstrated noninferiority of NOACs to warfarin among patients with CrCl of 30 to 50 mL/min (and for apixaban 25-50 mL/min).[245]

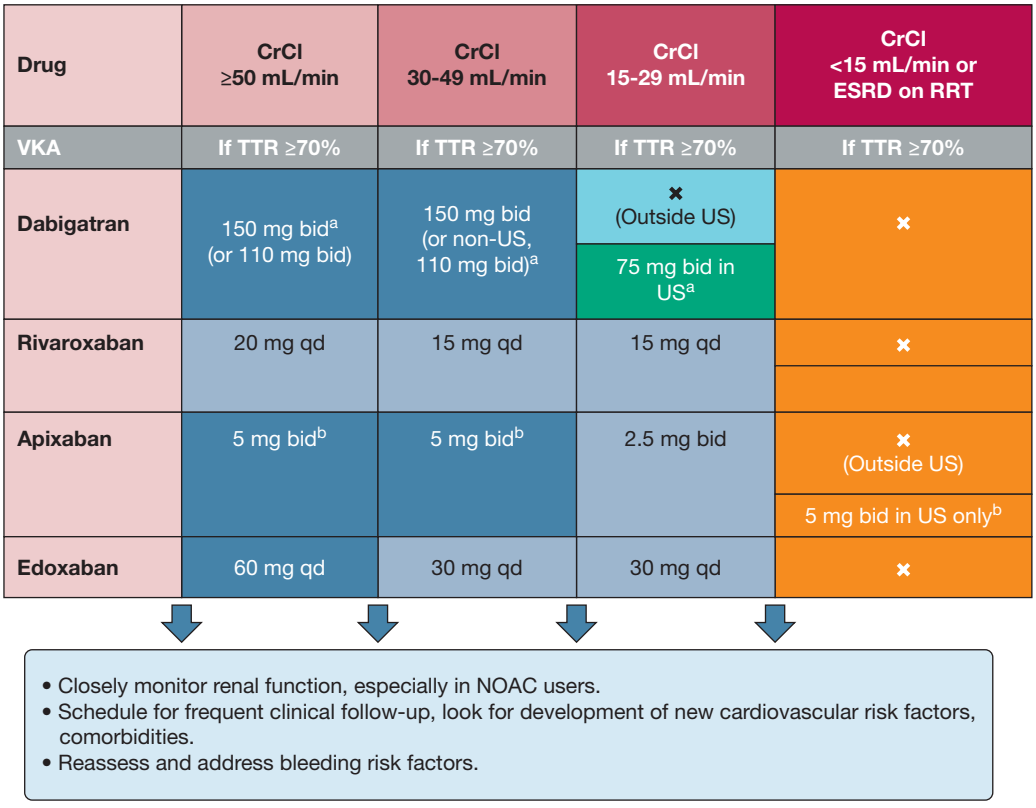

Figure 9 – *Suggested algorithm for the decision-making process in prescribing OAC therapy in patients with various degrees of renal function impairment.* [a]*The 110-mg dose is not available in the United States. Unless the patient is elderly or has high bleeding risk or is taking p-glycoprotein inhibitors, where dabigatran 110 mg bid is preferred, except in the United States, where the 110-mg dose is not available.* [b]*Use 2.5 mg bid if 2 of 3 of the following criteria are present: age > 80 years, weight < 60 kg, or serum creatinine > 133 mmol/L.* [c]*In the United States, caution is advised when CrCl is > 95 mL/min. ESRD = end-stage renal disease; RRT = renal replacement therapy. (Adapted from Lau et al.*[437]*) See Figure 1 and 2 legends for expansion of other abbreviations.*

All the NOACs have some degree of renal elimination, Cmax, and half-life, 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 trials and therefore insufficient evidence to recommend one agent over another. Given these limitations, treatment should be individualized, and the dose adapted on the basis of CrCl according to licensed indications[437] (Fig 9).

Recommendations

50. For mild CKD (Stage II, CrCl 60-89 mL/min), we suggest that oral anticoagulation clinical decision-making and treatment recommendations match that of patients without CKD (Weak recommendation, very low quality evidence).

51. For moderate CKD (Stage III, CrCl 30-59 mL/min), we suggest oral anticoagulation in patients with a CHA_2DS_2-VASc ≥ 2 with label-adjusted NOACs or dose-adjusted vitamin K antagonists (Weak recommendation, very low quality evidence).

Remark: With VKA, good quality anticoagulation control (TTR > 65-70%) is recommended.

52. In severe non-dialysis CKD (Stage IV, CrCl 15-30 mL/min), we suggest using VKAs and selected NOACs (rivaroxaban 15 mg QD, apixaban 2.5 mg bid, edoxaban 30 mg QD and [in USA only] dabigatran 75 mg bid) with caution, based on pharmacokinetic data (Ungraded consensus-based statement).

53. In end-stage renal disease (CrCl < 15 mL/min or dialysis-dependent), we suggest that individualized decision-making is appropriate (Ungraded consensus-based statement).

54. In end-stage renal disease (CrCl < 15 mL/min or dialysis-dependent, we suggest using well- managed VKA with TTR > 65-70% (Ungraded consensus-based statement).

Remark: NOACs should generally not be used, although in USA, apixaban 5 mg bid is approved for use in AF patients receiving hemodialysis.

TABLE 11] Summary Box: EHRA Categorization in Relation to the Type of OAC Used in Patients With AF

Definition	
EHRA type 1 VHD AF patients with "VHD needing therapy with a vitamin K antagonist (VKA)"	• Mitral stenosis (moderate-severe, of rheumatic origin) • Mechanical prosthetic valve replacement
EHRA type 2 VHD AF patients with "VHD needing therapy with a VKA or an NOAC," also taking into consideration CHA_2DS_2-VASc score risk factor components	• Mitral regurgitation • Mitral valve repair • Aortic stenosis • Aortic regurgitation • Tricuspid regurgitation • Tricuspid stenosis • Pulmonary regurgitation • Pulmonic stenosis • Bioprosthetic valve replacements • Trans-aortic valve intervention

CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65-74 and sex category (female); EHRA = Evaluated Heart Valves, Rheumatic or Artificial; VHD = valvular heart disease. See Table 1 legend for expansion of other abbreviations.

Remark: In patients with CKD who initiate OAC, concomitant antiplatelet therapy including low-dose aspirin is likely to substantially elevate bleeding risk and should be used very judiciously.

AF With Associated Valvular Heart Disease

A recent physician survey[438] reported marked heterogeneity in the definition of valvular and nonvalvular AF and variable management strategies, including NOACs in patients with valvular heart disease other than prosthetic heart valves or hemodynamically significant mitral stenosis. While hypertrophic cardiomyopathy is sometimes discussed in association with valvular AF, this will not be addressed in this section; specific guidelines on this condition are available.[439]

The use of the term nonvalvular AF is unfortunate and misleading as patients with a wide range of valvular pathology and severity were enrolled in all of the phase 3 NOAC trials. The only valvular heart disease uniformly excluded from all the NOAC trials were significant (moderate or severe) mitral stenosis and mechanical heart valves.

A meta-analysis of the four phase 3 AF trials comparing NOAC with warfarin found that although patients with valvular heart disease are at higher risk compared with those without valvular disease, the efficacy and safety of NOACs vs warfarin are consistent regardless of the presence or absence of valvular heart disease.[239]

AF patients with mechanical heart valves should only be prescribed VKAs. Data from the only phase II trial of an NOAC, dabigatran, in patients with mechanical heart valves (RE-ALIGN trial) demonstrated inferior efficacy and more bleeding.[440] However, patients with bioprosthetic valves were included in the ARISTOTLE trial[441] (apixban), the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48) trial[442] (edoxaban), and the relative efficacy and safety of NOACs compared with warfarin was consistent in these patients, although the number of patients with bioprosthetic valves was limited (< 300).

In keeping with a recent European consensus document, with endorsement by international learned societies, we propose that the term "valvular AF" is outdated. Given that any definition ultimately relates to the evaluated practical use of oral anticoagulation (OAC) type, we propose a functional EHRA (Evaluated Heart valves, Rheumatic or Artificial) categorization in relation to the type of oral anticoagulation (OAC) use in patients with AF (Table 11). This classification would have the advantage that it may easily evolve or be updated (type 1 may become type 2 or vice versa) when there are new results. For example, transcatheter mitral valve interventions (eg, to include both MitraClip and Mitral valve replacement) are emerging as a possible therapeutic options,[443] but more data are awaited, especially in relation to OAC use. Also, EHRA type 1 is broadly similar to the previously described mechanical and rheumatic mitral valvular AF (MARM-AF).[444]

Nondrug Alternatives and Perioperative Considerations

Occlusion of the LAA With Devices or Surgical Techniques: Approximately 90% of the thrombi found in patients with non-valvular AF and 57% of the thrombi found in valvular AF are located in the LAA.[445]

LAAO using specific percutaneous devices (WATCHMAN, Amplatzer Cardiac Plug, or WaveCrest device or the Lariat endocardial and epicardial ligation technique) or occlusion during a cardiac surgery procedure with either LAA amputation and closure or a stapler device have been proposed and tested for patients with AF at high risk of stroke in the presence of a high risk of bleeding or in the presence of contraindications to OACs.

Two randomized studies evaluated the WATCHMAN (Atritech, Inc) device vs warfarin: the Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT AF) and the Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL AF).[446-452] In the PROTECT AF trial, the efficacy of LAA closure with the device met the pre-specified criteria for non-inferiority vs warfarin, but the rate of adverse safety events in the intervention group was 4.4% with evidence of harmful periprocedural complications (pericardial effusion and procedure-related ischemic stroke). For acute complications, a "learning curve" appeared to be present, with serious pericardial effusions (requiring drainage) in 7.1% of the first 3 implant patients at each site compared with 4.4% of subsequent patients.[453] The serious complication rate of about 7% has been reported also for first- or second-generation Amplatzer occluders.[454,455] A recent systematic review network meta-analysis on the use of OACs and the Watchman device showed that the use of VKA, NOAC, and the Watchman device significantly reduce the risk of any stroke and systemic embolism as compared with placebo/control (Watchman device OR, 0.35; 95% CI, 0.16-0.80).[456] Data on the use of the WATCHMAN device in patients with contraindications to anticoagulation are very limited, and DAPT is needed for at least 6 weeks after the procedure, potentially exposing the patient to increased risk of bleeding.[453]

The Lariat device is based on an epicardial snare that requires positioning using a percutaneous approach to the epicardium through a pericardial access and in combination a percutaneous endocardial approach. In inexperienced operators, incomplete occlusion of the LAA after LARIAT ligation was relatively common (20% of cases) and was associated with risk of thromboembolic events.[457] No randomized controlled study comparing this device with oral anticoagulation is currently available.

In addition, the role of LAAO devices in AF patients also has to consider that no trials are available comparing these devices with NOACs. Thrombus formation on LAAO devices is also not uncommon (as high as 7.2% per year) and is associated with a risk of ischemic stroke during follow-up.[458,459]

Different surgical techniques have been applied for surgical exclusion of LAA (simple suture ligation, over-sewing of the LAA base without excision, appendage excision or amputation, surgical stapling), but data on TEE during follow-up suggest incomplete occlusion in up to 60% of subjects.[460,461] These observations and the lack of a clear benefit on stroke prevention evident from an RCT indicate that in patients with AF, these surgical techniques do not currently allow avoidance or interruption of oral anticoagulation in patients at risk of stroke.[462,463]

Recommendations

55. In patients with AF at high risk of ischemic stroke who have absolute contraindications for OAC, we suggest using LAA occlusion (Weak recommendation, low quality evidence).

Remark: When taking into account LAAO as a potential option, the risk of bleeding related to antiplatelets agents that need to be prescribed in the first months has to be considered and the possibility to use NOACs.

56. In AF patients at risk of ischemic stroke undergoing cardiac surgery, we suggest considering surgical exclusion of the LAA for stroke prevention, but the need for long-term OAC is unchanged (Weak recommendation, low quality evidence).

Surgical Procedures and Interventions: Patients with AF on long-term prophylaxis with OACs may need surgical or interventional procedures that require appropriate management. Since bleeding risk may obviously be increased by the anticoagulant effect, interrupting anticoagulation for an intervention or a procedure transiently exposes the patient to increased risk of thromboembolism. Appropriate management requires balancing reducing the risk of thromboembolism and preventing excessive procedure-related bleeding.

In the NOAC RCTs, surgical or other invasive procedures were required during a follow up of around 2 years in one-quarter of patients in RE-LY and one-third of patients in ROCKET AF and ARISTOTLE.[72-74]

General principles of management can be considered, to be combined with individual clinical judgment, but they are derived from consensus of experts, since no data from RCTs are available to guide clinical decision-making.

The following steps are important for appropriate management:

- **Estimation of the bleeding risk associated with a specific intervention/procedure.** The risk of bleeding can be predicted by the type of intervention and by its need, urgent or elective. e-Table 23 classifies surgical and interventional procedures according to bleeding risk as well as thromboembolic risk.[205,464,465] The direct consequence of this evaluation is that interventions or procedure at very low bleeding risk, such as simple dental extractions or minor skin excision, can be planned and performed without interruption of oral anticoagulation.
  If the bleeding risk is substantial, then interruption of anticoagulation prior to the procedure intervention is needed to minimize the hemorrhagic risk, both in the intra-operative and immediate postoperative phase.
- **Estimation of patient thromboembolic risk.** Calculate the CHA_2DS_2-VASc score (low risk if 0 or 1) but an additional transient increase in risk has to be considered in case of recent stroke or recent pulmonary embolism.
- **Planning of the timing of anticoagulation interruption.** The timing of interruption is strictly dependent on the specific anticoagulant the patient is receiving and CrCl. Important differences exist between the management of patients treated with VKA or NOACs.[205,466] The effect of warfarin can be monitored through INR; however, no standard laboratory test exists to measure the effect of NOACs. Discontinuation of warfarin is usually instituted 5 days before an elective surgical intervention, with INR checked the day before surgery, with the usual indication that surgery can be regularly planned if the INR is $\leq$ 1.4 to 1.5 the day before surgery or the same day of surgery.[465] For NOACs, the planning of interruption and resumption of therapy for surgical interventions/procedures is dependent on the type of procedure/intervention, the specific agent used, and renal function, estimated by creatine clearance (using the Cockroft-Gault equation). In case of urgent surgery, reversal of anticoagulation or specific measures may be required.[205,466]
- **Evaluation of the need for bridging.** Pre-operative bridging can be considered in patients receiving VKA who are at particularly high risk of thromboembolism (eg, recent stroke, mechanical heart valve).[465] In these cases, LMWH at therapeutic doses is usually prescribed starting 3 days before the procedure/intervention. Postoperative bridging includes administration of an LMWH when VKA is resumed in the postoperative period, with administration of both agents until achievement of a therapeutic INR. The role of bridging has been tested in a randomized trial, Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE), performed in patients on warfarin who were candidates for an invasive procedure (patients with mechanical valves were excluded).[94] The risk of thromboembolism after the procedure was similar in patients with and without bridging, but the risk of major bleeding was higher in those who were bridged. Thus, we suggest that preoperative bridging is not required in AF patients treated with warfarin who do not have a particularly high risk of thromboembolism and who do not have a mechanical valve.
- In patients receiving NOACs, bridging is not required, but bridging could be considered in the postoperative phase if the patient cannot take oral medications for a prolonged period.

Recommendations

57. In AF patients taking warfarin without high risk of thromboembolism or do not have a mechanical valve, we suggest preoperative management without bridging (Weak recommendation, low quality evidence).

58. In AF patients on antithrombotic prophylaxis with warfarin with a high risk of thromboembolism or with a mechanical valve, we suggest preoperative management with bridging (Weak recommendation, low quality evidence).

59. In AF patients on antithrombotic prophylaxis with an NOAC, we suggest preoperative management without bridging (Weak recommendation, low quality evidence).

The Patient

Patient knowledge and understanding of the stroke risk associated with AF and the benefit of OAC to prevent stroke are crucial to patient acceptance of anticoagulants, as well as adherence, and life-long persistence (in most cases), to OAC. However, research

demonstrates that AF patients generally have poor awareness and knowledge about their condition,[467-472] medications used to treat AF, particularly OAC, and do not clearly comprehend the benefit/risk associated with stroke prevention regimens.[203,468-471,473-478] Although there is increasing advocacy from clinical guidelines[157,158] and expert consensus[2,203,479] to incorporate patient preferences for treatment into the decision-making process, a patient's ability to make an informed decision may be hindered by their lack of understanding about the relationship between AF and stroke and the efficacy/safety of OAC for stroke prevention, particularly at diagnosis, when these decisions are invariably addressed. Assessment of patient's knowledge (using the AF Knowledge questionnaire[480] or Jessa Atrial Fibrillation Knowledge questionnaire[481]), as well as their values and preferences, could be undertaken to ascertain gaps to be filled; this may lead to better decision-making and improved adherence and persistence.

Patient education is essential to provide patients with sufficient information to enable them to make an informed decision about whether they wish to take OAC, and if they do, which OAC they would prefer.[203,476,482] Education needs to be tailored to the person's desire for information and their level of health literacy to promote patient understanding. Recently, a prospective survey of 499 AF patients (with and without previous stroke) in the United States found that most (87%) desired more information about AF and how to reduce their risk of AF-related stroke.[473] AF patients perceive greater satisfaction with treatment if they are engaged in treatment decisions and provided with relevant information (verbal, visual, written, electronic/on-line resources, as appropriate, chosen by the patient), which is well communicated by their health-care providers,[467,473,483] and updated over time. Full details on shared decision-making, patient preferences, and patient education/counseling are provided in e-Tables 24-26.

Recommendations

60. In AF patients who have previously refused OAC, we suggest reinforcing educational messages at each contact with the patient and revisit OAC treatment decisions (Ungraded consensus-based statement).

Remark: Patient and physician treatment objectives often differ significantly and it is important to elicit from the patient what outcomes of OAC treatment are important to them.

Remark: Explain the risk of stroke and benefit/risks of treatment in terms the patient can understand and signpost the patient to appropriate educational resources

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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