Antithrombotic Therapy for Atrial Fibrillation

CHEST Guideline and Expert Panel Report

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Abbreviations:

ACS	acute coronary syndrome
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
b.i.d	bis in die (twice daily)
CABG	coronary artery bypass graft
CAP	Continued Access to PROTECT AF
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)
CI	confidence interval
CrCl	creatinine clearance
DOAC	direct oral anticoagulant drugs
ECG	electrocardiogram
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 (.65), drugs/alcohol concomitantly (1 point each)
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	hazard ratio
ICH	intracranial haemorrhage
INR	international normalized ratio
i.v.	intravenous
LAA	left atrial appendage
LAAO	left atrial appendage occlusion
o.d.	omni die (every day)
OAC	oral anticoagulant
NOAC	non-vitamin K antagonist oral anticoagulant drugs
NYHA	New York Heart Association
PCI	percutaneous cardiovascular intervention
PROTECT AF	System for Embolic PROTECTion in patients with Atrial Fibrillation
RE-LY	Randomized Evaluation of Long-term anticoagulant therapY with dabigatran etexilate
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
RRR	relative risk reduction
TIA	transient ischaemic attack
t.i.d.	ter in die (three times daily)
TE	thromboembolism

87	TEE	transesophageal echocardiogram
88	TTR	time in therapeutic range

Abstract

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 (e.g., CHA_2DS_2VASc 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_2VASc stroke risk factors. For patients with a single non-sex CHA_2DS_2VASc 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, $CHA_2DS_2VASc \geq 2$ 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 NOAC rather than adjusted-dose vitamin K antagonist therapy. With the latter, it is important to aim for good quality anticoagulation control with a TTR >70%.

Attention to modifiable bleeding risk factors (eg. uncontrolled blood pressure, labile INRs, concomitant use of aspirin or NSAIDs in an anticoagulated patient, alcohol excess) should be made at each patient contact, and HAS-BLED 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-gender CHA_2DS_2VASc stroke risk factor(s).

SUMMARY OF RECOMMENDATIONS

Note: Shaded text refers to recommendations that remain unchanged from the previous version of the guideline

1. **For patients with AF, including those with paroxysmal AF, stroke risk should be assessed using a risk factor based approach, rather than an categorisation into low, moderate/high risk strata. We recommend use of the CHA_2DS_2VASc as a simple clinical based stroke risk score to initially identify 'low stroke risk' patients that 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_2VASc 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 patients with one or more non-sex CHA_2DS_2VASc 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 (personalised 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 (e.g. treat gastric ulcer; optimise 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 (e.g. 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 110mg 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 (i.e, <65-70%) - implement additional measures (more regular INR tests; review medication adherence; address other factors known to influence INR control; education/counselling) to improve INR control or consider a 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_2score 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/counselling 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 hours or unknown duration undergoing elective electrical or pharmacological cardioversion, we recommend therapeutic anticoagulation with well-managed VKA (INR 2-3) or a 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 succesful 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 recommednations 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 endothelisation, 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 ≥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 one 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, 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 a NOAC at a dose licensed for stroke prevention in AF** (weak recommendation, low quality evidence).

    Remark: Only Dabigatran 150mg bid or (not licensed in USA) 110mg bid or Rivaroxaban 15mg qd are currently supported by clinical trial evidence. A 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 75-100mg 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 110mg 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 a 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 in 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 CHA2DS2-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 ischaemic stroke, we suggest that very early anticoagulation (<48h) 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 ischaemic stroke because they appear to increase the risk of symptomatic intracranial haemorrhage

without net benefit. The optimal timing of anticoagulation after acute ischaemic stroke is unknown.

35. **In AF patients with acute stroke without contraindications, we recommend that long term oral anticoagulation is indicate**d as secondary prevention (Strong recommendation, high quality evidence).
Remark: The optimal timing of anticoagulation early after acute ischaemic stroke is unknown. Early use of NOACs shows promise but requires testing in randomised controlled trials.

36. **In AF patients with acute ischaemic stroke, We suggest that oral anticoagulation should usually be started within 2 weeks of acute ischaemic 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 ischaemia, haemorrhagic 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 randomised trials, but shows promise in observational studies.

37. **In patients with AF and high ischaemic stroke risk, we suggest anticoagulation with a NOAC after acute spontaneous ICH (which includes subdural, subarachnoid and intracerebral haemorrhages) 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 favourable 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 ischaemic stroke
Remark: The optimal timing of anticoagulation after ICH is not known, but should be delayed beyond the acute phase (~48 hours) and probably for at least ~4 weeks. Randomised trials of NOACs and left atrial appendage occlusion are ongoing.

38. **In ICH survivors at high risk of recurrent ICH (e.g. 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 revascularisation 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 revascularisation, 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-revascularisation period (e.g. 1-3 months)

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 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_2VASc 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_2VASc) who present with AHREs, corresponding to atrial tachyarrhythmias/AF at electrograms assessment of less than 24 hours 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 hours, individual stroke risk (using CHA_2DS_2VASc), 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 hours,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 hours 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 >2mg/day). OAC should then be discontinued and replaced by adjusted-dose LMWH (target anti-Xa level 4-6 hours 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 a 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 breastfeed, 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 $CHA_2DS_2VASc \geq 2$ 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), we suggest using VKAs and selected NOACs (rivaroxaban 15mg QD, apixaban 2.5mg bid, edoxaban 30mg QD and (in USA only) dabigatran 75mg bid) with caution, based on pharmacokinetic data** (ungraded consensus-based statement).

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

54. **In end-stage renal disease (CrCl < 15 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 5mg 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 ischaemic 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 ischaemic 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 pre-operative 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 pre-operative management with bridging** (Weak recommendation, low quality evidence).

59. **In AF patients on antithrombotic prophylaxis with a NOAC, we suggest pre-operative 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 (see e-Table 25.

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 non-cardiovascular risk factors. AF without associated valvular heart disease (so-called 'non-valvular AF') is associated with a five-fold increase in stroke risk (approximately 5%/year), but this risk is dependent on the presence of various stoke 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 ACCP guidelines published in 2012[3], there have been substantial developments in AF thromboproprophylaxis, whether with regard to risk assessment, antithrombotic drugs or non-drug 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 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].

Aside from stroke prevention ('Avoid Stroke, use Anticoagulants), AF management requires patient centered and symptom directed decisions on rate or rhythm control ('Better symptom management') as well as 'Cardiovascular and other risk factor, and lifestyle management'[2]. The latter includes addressing risk factors (cardiac ischemia, heart failure, hypertension, sleep apnea, diabetes, etc.) and lifestyle (obesity, alcohol excess, stimulants etc.). This simple ABC approach (Atrial fibrillation Better Care approach) would simplify an integrated approach to AF management in a holistic manner. (Figure 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 [PAF])
- 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, ICH, ESUS, carotid disease
    - AHRE on devices
    - Chronic atrial flutter
    - Pregnancy
    - Chronic Kidney Disease
    - 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 (PSC). 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 (COI) by CHEST's PSC. 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.

Consistent with the 9th 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 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[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] Relative risk (RR) was used to report the results for dichotomous outcomes and mean difference (MD) for continuous outcomes with accompanying 95% confidence intervals (CI). Statistical heterogeneity of the pooled results was assessed using the Higgins' I^2 and the Chi-square tests. A Higgins'I^2 value of ≥50% or Chi-square $p<0.05$ 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 approach.[10] Evidence profiles were created using the Guideline Development Tool (GDT), which categorized the overall quality of the body of evidence into one of four 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 two patient advocates (MTH and DAL) 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 five-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 GOC, 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 ATRIAL FIBRILLATION

The extensive data on epidemiological burden of stroke associated with AF and well as the pathophysiology is detailed in the Online Supplement. It is beyond the scope of this document to consider the epidemiology of all comorbidities in AF.

In summary, healthcare 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 Caucasian populations[16]. However, reported prevalence varies substantially by world region (see e-Figure 1) and with more rigorous screening methods to detect AF.

Individuals with AF have increased risk of stroke (4-5 fold increase), heart failure (2-3 fold increase) and mortality (2-fold increase) (see web Supplement 1.1). Patients with AF also experience higher rates of morbidity, hospital admissions, as well as early dementia. The high AF-attributable risk of stroke, especially in the elderly, is evident since at least one in 3 to 4 individuals with an ischemic stroke, and over 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, 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 co-morbidities in AF patients have been reported.[20-36] Hypertension is the leading comorbid risk factor and is equally distributed in different races. Coronary heart disease (CHD) seems more common in Caucasians and the Middle East, than in Asians. The annual risk of AF-associated stroke in Asians is higher than that in Caucasians[37 28 29 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-Figure 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. In order 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 (15/16 studies positive, risk ratio [RR] 2.86), hypertension (11/20 studies positive, RR 2.27), aging (9/13 studies positive, RR 1.46 per decade increase), structural heart disease (9/13 studies positive, RR 2.0) and diabetes (9/14 studies positive, RR 1.62) were independent predictors of stroke. Supportive evidence was found for sex (8/22 studies positive, RR 1.67), vascular disease (6/17 studies positive, RR 2.61) and heart failure (7/18 studies positive, RR 1.85)[42]. Non-paroxysmal atrial fibrillation is associated with a highly significant increase in thromboembolism (multivariable adjusted hazard ratio 1.384, 95% CI 1.19-1.61, $P < 0.001$)[43].

In individuals with HF, AF is associated with worse prognosis than sinus rhythm[44,45]. HF is an independent predictor of stroke/TE, 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 HFrEF (HF with reduced ejection fraction) compared to HFpEF (HF with preserved ejection fraction) (RR 1.24, 95% CI 1.12-1.36, p<0.001), although stroke risk (RR 0.85, 0.70-1.03, p=0.094) and heart failure hospitalization (RR 1.21, 95% CI 0.96-1.53, p=0.115) are not significantly different[48].

Chronic kidney disease (CKD) is an independent predictor of risk of stroke/thromboembolism. AF patients with estimated glomerular filtration rate <60 mL/min compared with those with estimated glomerular filtration rate ≥60 mL/min have increased risk of stroke/thromboembolism (RR 1.62, 95% CI, 1.40-1.87; p<0.001), 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 to 2.14; p<0.001). There is also increased risk of bleeding in individuals with AF and CKD, compared with those without CKD.[50] Conversely, AF is associated with increased risk of chronic kidney disease (CKD) (RR 1.64, 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 Atrial Fibrillation and Chronic Kidney Disease section).

Over the last decade, rigorous detection strategies have shown that prevalence of AF in cryptogenic stroke is likely to be as high as 30%[55]. A systematic review and meta-analysis after transient ischemic attack (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 (LA) appendage 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 echocardiographic (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 OAC) would be changed[57].

Nevertheless, the most consistent independent predictor of ischemic stroke on TTE is the presence of moderate-severe LV systolic dysfunction. In patients undergoing transesophageal echocardiography (TEE), LA appendage thrombi[58] and LA spontaneous echo contrast[59] are both associated with increased thromboembolism, as well as the presence of low LA appendage 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 non-specific for a particular endpoint, and can be equally predictive not only of stroke but bleeding, death, hospitalization, heart failure etc., as well as non-cardiac conditions e.g., glaucoma.

The importance of biomarkers probably lies in the 'very low risk' strata of clinical scores (e.g., CHA_2DS_2VASc= 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 healthcare 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 (e.g., burden of AF), serum biomarkers (e.g., NT-proBNP), imaging (e.g., left atrial fibrosis on cardiac MRI) and echocardiography (e.g., 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/transient ischemic attack/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 TE events (all c-indexes approx. 0.60-0.65). Adding more and more clinical variables and complexity (i.e., simple versus more complex clinical risk scores) would only modestly increase the c-index to approximately 0.65-0.70. 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 or not.

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 non-adjudicated (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 this 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) healthcare plan.

Ethnic differences are also evident in stroke risk related to AF. In a Taiwanese cohort, the risk of stroke was 1.78%/year in patients aged 50-64 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 ($mCHA_2DS_2$-VASc) score has been proposed, assigning one point for patients aged 50 to 74 years.[65] The $mCHA_2DS_2$-VASc score performed better than CHA_2DS_2-VASc score in predicting ischemic stroke assessed by C indexes and net reclassification index. For patients having an $mCHA_2DS_2$-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 0.65-0.70. 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_2VASc score. The use of biomarkers have to balance the assay availability, lab 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_2VASc or $CHADS_2$ 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%/year or under, notwithstanding the possible need to re-categorize the age 65-74 criterion in Asians[65].

The majority of published studies and systematic reviews suggest that the CHA_2DS_2VASc score is generally better than $CHADS_2$, ATRIA and 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 (UK CPRD and Swedish cohorts vs Danish and Taiwan cohorts). Differences between the ATRIA and CHA_2DS_2VASc 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_2VASc scores in identifying low risk patients, but the CHA_2DS_2VASc 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 that 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_2VASc score to define a low risk group.

The 'C' in CHA_2DS_2-VASc refers to recent decompensated heart failure, irrespective of the ejection fraction (thus including heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF)) or the presence of moderate-severe LV systolic impairment on cardiac imaging, whether symptomatic or asymptomatic. The 'H' refers to history of hypertension or uncontrolled blood pressure, while 'S' refers to stroke, systemic embolism or a confirmed diagnosis of transient ischemic attack (TIA). 'V' refers to complicated vascular disease, including myocardial infarction or peripheral artery disease, 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 at 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 followup) was the best predictor for ischaemic stroke[67].

A stepwise approach to thromboprophylaxis would allow initial identification of low risk using CHA_2DS_2VASc (Step 1), following which stroke prevention can be offered to all others (Step 2)

irrespective of stroke point score or biomarkers used. This would 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 categorisation into low, moderate/high risk strata. We recommend use of the CHA_2DS_2VASc as a simple clinical based stroke risk score to initially identify 'low stroke risk' patients that 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_2VASc 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_2VASc 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 (personalised 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 ATRIAL FIBRILLATION

Observational studies

The rates of major bleeding on VKA among observational cohorts are shown in e-Table 8 and demonstrate highly variable rates, ranging from 1.4%/year[68,69] to 10.4%/year.[70] Nevertheless, there is significant heterogeneity between the study population characteristics, the inclusion of inception versus '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 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 NOACs trials where ISTH 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% to 4% (Table 2). 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 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 Bleeding Risk Score). 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 (see Figure 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, non-modifiable 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 to use of a formal bleeding risk score[78-80].

Blood pressure control

Good control of blood pressure 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 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 over-dose are also essential to minimize bleeding complications.

Concomitant medication pre-disposing to bleeding

Non-essential use of concomitant anti-platelet drugs and NSAIDs should be avoided since these medications increase the risk of bleeding in patients receiving OAC. Where concomitant anti-platelet therapy is necessary (i.e. post-coronary stent implantation), the duration of combination OAC and anti-platelet drugs should be kept to the minimum.[92] Since anti-platelet 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. OAC should not initiated among patients consuming alcohol in excess >14U/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 (e.g. 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 (e.g., pacemaker implantation or percutaneous coronary intervention) can be safely performed on OAC. Bridging (that is, 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 a 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 (i.e. walking aids, appropriate footwear, home review to remove trip hazards), whereas neurological assessment is warranted if falls are unexplained. The benefits of ischaemic 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 Hb or platelet count. Causes of renal impairment should be investigated and where possible reversed.

Patients with liver function abnormalities were generally excluded from the randomised 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, ischaemic 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[101] to 12[103] and the score or weighting associated with each risk factor also differs (see Table 2).

Age and prior bleeding are included as risk factors in all six bleeding risk scores but different age cut-offs are utilized, with three scores employing age 75 years or older[99,100,102] to indicate greater bleeding risk. Following age and prior bleeding, the most prevalent bleeding risk factors included in the scores are anemia,[99-103] renal disease,[98-100,102] hypertension[99,103] or uncontrolled systolic blood pressure,[98] concomitant anti-platelets,[98,102,103] and alcohol excess,[98,100,103] and prior stroke[98,100] or hepatic disease.[98,100] A variety of other risk factors including cancer,[103] labile INR,[98] genetic factors,[100] falls risks,[100] female sex,[103] diabetes mellitus,[103] and biomarkers[101] are included only in one bleeding risk score. For a comprehensive review of bleeding risk factors in AF patients see Zulkifly et al.[104]

The bleeding risk scores range in the simplicity of calculation and the cut-offs employed to indicate low, intermediate and high-risk of bleeding, and the prevalence of bleeding events reported in the validation cohorts (see Table 2).

Table 2: Risk factors, risk categories and bleeding events in the validation cohorts [partly reproduced with permission from Zukifly et al[104]]

		Risk categories			Bleeding events in validation cohort (per 100 patient years)		
Risk score	Risk factors (score for each factor)	Low	Intermediate	High	Low	Intermediate	High
ABC[101]	Age(†); Biomarkers (†) (GDF-15 or cystatin C/CKD-EPI, cTnT-hs, & Hb); Previous bleed (†)	<1%	1-2%	>3%	0.62	1.67	4.87
ORBIT[102]	Age ≥75 (1); ↓Hb/Hct/anemia (2); Bleeding history (2); ↓ renal function (1); APT (1)	0-2	3	≥4	2.4*	4.7	8.1
ATRIA[99]	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 (1); APT/NSAIDs (1); Alcohol excess (1)	0-1	2	≥3	1.02-1.13	1.88	≥3.74
$HEMORR_2HAGES$[100]	Hepatic/renal disease (1); Ethanol abuse (1); Malignancy; Age >75 (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[103]	Age ≥70 (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% [a]	2.0% [a]	5.4% [a]

APT = antiplatelet therapy; BP = blood pressure; cTnT-hs = Troponin T; DM = diabetes mellitus; GDF-15 = growth differentiation factor-15; Hb = hemoglobin; Hct = hematocrit; INR = international normalised ratio; Plt = platelet count or function; SBP = systolic blood pressure

* bleeding event in original derivation cohort; [a] at 3 months; ↓ reduced/decreased; ↑ elevated/increased; † score for each variable in ABC score is based on a nonogram (see reference[101])

Use of bleeding risk scores

As seen in Table 2 above, there are multiple bleeding risk scores that have been proposed for bleeding risk stratification, with the HEMORR$_2$HAGES, HAS-BLED, ATRIA, ORBIT and ABC-bleeding derived and validated in AF populations[104]. The risk factors included vary by scores [Table 2], and their derivation from selected clinical trial cohorts or 'real world' populations[104]. 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$_2$DS$_2$-VASc scores are also associated with greater bleeding risk, but the HAS-BLED score outperforms the CHADS$_2$ and CHA$_2$DS$_2$-VASc scores for predicting serious bleeding[105,106], which was also evident in the systematic review by Zhu et al[107]. Composite risk scores that include stroke and bleeding endpoints have also been proposed but have not been shown to perform incrementally better over the individual scores[108,109]. The bleeding risk scores in AF are also predictive of bleeding in non-AF populations, for example, in patients with ACS undergoing PCI-stenting[110].

Adding more clinical variables marginally improves the predictive value (at least statistically) but the c-indexes still remain approx. 0.6. The addition of biomarkers would all improve the c-indexes (to approx. 0.65) over scores based on clinical risk factors alone. Many of these risk scores have been derived from highly selected clinical trial cohorts, and biomarkers measured at baseline (or within a few months of study entry) then endpoints 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 (e.g. troponin, natriuretic peptides, inflammatory markers, coagulation markers, etc.) are also predictive of stroke, bleeding, death, heart failure, hospitalization [111]and even non-cardiovascular conditions such as (for example, as in the case of GDF-15 used in the ABC-bleed score) glaucoma progression[112]. The performance of biomarker-based scores in real world clinical practice (outside highly selected trial cohorts) has also been disappointing[113,114], 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 (e.g. in 4 weeks, rather than 4-6 months) – and depending on the outcome of interest, to address the associated modifiable risk factors accordingly [Figure 2]. 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[115], simply focusing on bleeding risk assessment using modifiable bleeding risk factors alone is an inferior strategy compared to 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 that sustain events (c-indexes approx. 0.6).

The systematic review by Caldera et al[116] reported that the sensitivity, specificity and diagnostic odds ratio (DOR) were respectively 0.53 (0.52–0.54), 0.65 (0.65–0.65) and 2.11 (1.91–2.35) for HAS-BLED, and 0.27 (0.26–0.27), 0.89 (0.89–0.89) and 2.90 (2.77–3.04) for HEMORR$_2$HAGES. When comparing HAS-BLED with ATRIA, sensitivity, specificity, and DOR were respectively 0.41 (0.35–0.48), 0.78 (0.76–0.79) and 2.22 (1.08–4.55) for HAS-BLED, and 0.23 (0.17–0.29), 0.91 (0.90–0.91) and 1.98 (1.29–3.03) for ATRIA. They concluded that HAS-BLED, due to its sensitivity (compared to other scores) and ease to apply, is recommended for the assessment of AF patients' major bleeding risk.

The systematic review by Zhu et al[107] (11 studies) found that discrimination analysis demonstrates that HAS-BLED has no significant C-statistic differences for predicting bleeding risk in the low (risk ratio [RR]: 1.16, 95% confidence interval [CI]: 0.63-2.13, *P* = 0.64) risk stratification but under predicts risk in the moderate (RR: 0.66, 95% CI: 0.51-0.86, *P* = 0.002) and high (RR: 0.88, 95% CI: 0.70-1.10, *P* = 0.27) risk strata (e-Table 11). Zhu et al[107] 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 [114].

Given that the patient pathway may include AF patients initially on no antithrombotic therapy, aspirin or anticoagulants, and the latter can include VKA 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 non-trial 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 [115,117,118]. It is also the only bleeding score predictive of intracranial bleeding[119].

The HAS-BLED score has also been shown to be similar or out-perform older bleeding scores, as well as more simple bleeding scores that include less clinical parameters. Amongst VKA-treated patients, the non-consideration of TTR would also mean that the HEMORR$_2$HAGES, ORBIT and ATRIA scores would all perform sub-optimally in VKA-treated patients[120,121]. 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 (e.g. treat gastric ulcer, optimise 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

ANTITHROMBOTIC 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 to therapies in the control arms, cardiovascular composite or survival outcomes presently do not reflect the primary rationale for therapy.

Randomized trials

Vitamin K antagonists compared to placebo or control

In a meta-analysis of 2900 subjects from six 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%/year (from 4.5%/year in controls) in primary prevention subjects and 8.4%/year (from 12%/year in controls) in secondary prevention subjects.[122]

Aspirin and antiplatelet therapy compared to placebo or control

In a meta-analysis of 8 trials of 4876 subjects, antiplatelet therapy compared to control or placebo was associated with a 22% (95% CI 6-35%) relative risk reduction in stroke (e-Table 13).[122] The Stroke Prevention in AF (SPAF-I) study demonstrated decrease in risk of stroke from 6.3%/year in placebo subjects to 3.6%/year (95% CI 9-63%)[123], but a meta-analysis of 7 trials of 3990 subjects found no significant benefit. SPAF-I was the only trial suggestive of a benefit for aspirin compared to 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 ACTIVE-A trial, which also predated the investigation of NOACs, compared aspirin plus clopidogrel versus aspirin monotherapy among patients in whom VKA was unsuitable.[124] The study found a decrease in risk of stroke with dual antiplatelet therapy, but the major bleeding rates with aspirin-clopidogrel were comparable to rates seen with warfarin (approx. 2%/year).

Vitamin K antagonists compared to antiplatelet therapy

Of 12 studies comparing warfarin to antiplatelet therapy, warfarin was associated with a 39% relative risk reduction (95% CI, 22%-52%) in strokes (e-Table 14).[122] In ACTIVE-W, the largest of these studies, warfarin was superior to dual antiplatelet therapy to warfarin for stroke and a cardiovascular composite outcome, with similar rates of major bleeding.[125]

Non-VKA oral anticoagulants (NOACs) compared to vitamin K antagonists

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 3), 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.[73,74,76,126]

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).[127] NOACs significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0.81; 95% CI 0.73-0.91; p<0.0001). The benefit was driven primarily by a 51% reduction in hemorrhagic stroke (RR 0.49; 95% CI 0.38-0.64; p<0.0001). Ischemic stroke was similar between NOACs and warfarin. (RR 0.92; 95% CI 0.83-1.02; p=0.10). NOACs were also associated with a significant 10% reduction in all-cause mortality (RR 0.90; 95% CI 0.85-0.95; p=0003). With regards to safety, NOACs were associated with a non-significant 14% reduction in major bleeding (RR 0.86; 95% CI 0.73-1.00; p=0.06) but a substantial 52% reduction in intracranial hemorrhage (RR 0.48; 95% CI 0.39-0.59; p<0.0001), NOACs were, however, associated with a significant increase in GI bleeding (RR 1.25; 95% CI 1.01-1.55; p=0.04). The relative efficacy and safety of NOACs was 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 time in therapeutic range <66% (RR 0.69, 95% CI 0.59-0.81; p-interaction=0.02).

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

1219 were associated with more ischemic strokes [the lower-dose regimen edoxaban 30/15 mg is not
1220 approved for the stroke prevention indication].
1221

1222 Table 3: Phase 3 AF trials of NOAC versus warfarin – Summary of key efficacy and safety results

	Trial									
	RE-LY			ROCKET-AF		ARISTOTLE		ENGAGE AF-TIMI 48		
Outcome	**Dabigatran 150 mg (n=6076)**	**Dabigatran 110 mg (n=6015)**	**Warfarin (n=6022)**	**Rivaroxaban 20/15 mg (n=7131)**	**Warfarin (n=7133)**	**Apixaban 5/2.5 mg (n=9120)**	**Warfarin (n=9081)**	**Edoxaban 60/30 mg (n=7035)**	**Edoxaban 30/15 mg (n=7034)**	**Warfarin (n=7036)**
Efficacy										
Stroke/SEE										
Event Rate (%/year)	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-value	0.004	0.29	NA	0.12	NA	0.01	NA	0.08	0.10	NA
Ischemic Stroke										
Event Rate (%/year)	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-value	0.03	0.35	NA	0.58	NA	0.42	NA	0.97	<0.001	NA
Hemorrhagic Stroke										
Event Rate (%/year)	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-value	<0.001	<0.001	NA	0.02	NA	<0.001	NA	<0.001	<0.001	NA
MI										
Event Rate (%/year)	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-value	0.12	0.09	NA	0.12	NA	0.37	NA	0.60	0.13	NA
All-Cause Death										
Event Rate (%/year)	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-value	0.05	0.13	NA	0.07	NA	0.047	NA	0.08	0.006	NA
Safety										
Major Bleeding										
Event Rate (%/year)	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-value	0.31	0.003	NA	0.58	NA	<0.001	NA	<0.001	<0.001	NA
ICH										
Event Rate (%/year)	0.32	0.23	0.76	0.5	0.7	0.33	0.80	0.39	0.26	0.85
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-value	<0.001	<0.001	NA	0.02	NA	<0.001	NA	<0.001	<0.001	NA
GI Bleeding										
Event Rate (%/year)	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-value	0.001	0.52	NA	<0.001	NA	0.37	NA	0.03	<0.001	NA

RE-LY: Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY); 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; 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.

NOACs vs. Aspirin

Apixaban is the only NOAC that has been compared with aspirin in AF patients. The Apixaban vs. Acetylsalicyclic Acid to Prevent Strokes (AVERROES) trial compared apixaban 5 mg twice daily with aspirin in AF patients who were not candidates for VKA therapy.[128] The trial was stopped early for benefit as apixaban significantly reduced the risk of stroke or systemic embolism compared with aspirin (hazard ratio 0.45, 95% CI 0.32-0.62; p<0.001) (e-Table 16). There was no significant difference in major bleeding (hazard ratio 1.13, 95% CI 0.74-1.75; p=0.57) 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 post-marketing 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-analysess 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 in concordance with clinical trial efficacy, based on both quality of care and generalizability.[129 2016]

A meta-analysis of real-world observational studies of dabigatran was consistent with findings from RE-LY. Compared to VKA, risk of stroke with dabigatran versus warfarin was 1.65 vs. 2.85 per 100 patients-years (HR 0.86, 95% CI 0.74-0.99).[130] 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[131]. Overall, the risk of stroke/systemic thromboembolism (TE) with rivaroxaban were similar compared with dabigatran, but were significantly reduced when compared to warfarin (HR 0.75, 0.64-0.85). Major bleeding risk was significantly higher with rivaroxaban vs. dabigatran (HR 1.38, 1.27-1.49), but similar to warfarin (HR 0.99, 0.91-1.07). Rivaroxaban was associated with increased all-cause mortality and gastrointestinal bleeding (GIB), but similar risk of acute myocardial infarction (AMI) and intracranial hemorrhage (ICH) compared with dabigatran. When compared with warfarin, rivaroxaban was associated with similar risk of any bleeding, mortality and AMI, but a higher risk of GIB and lower risk of ICH.

Another large analysis of three 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.[132] However, a new-user FDA Medicare analysis of 118,891 patients found that rivaroxaban compared to dabigatran had a statistical trend towards 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 bleeding (HR 1.48, 95% CI 1.32-1.67).[133] Absolute risk differences were small (2.0-2.1 per 1000 person-years) and well within a range vulnerable to confounding.

Different Ethnic Groups

Asian AF patients have a higher risk of intracranial hemorrhage compared with Caucasians when VKAs are used.[134] The higher risk of bleeding on VKA in Asians vs. non-Asians has also been observed in major clinical trials of NOACs,[135] even though Asians received a lower intensity of anticoagulation with VKA.[136]

In a recent meta-analysis comprising 5 NOAC trials (RE-LY, ROCKET AF, J-ROCKET AF, ARISTOTLE, and ENGAGE AF), the effects of NOACs versus warfarin in Asians vs non-Asians were compared.[137] For standard-dose NOACs (dabigatran 150 mg, rivaroxaban 20 mg, apixaban 5 mg, and edoxaban 60 mg), the effect sizes of the primary efficacy endpoint (stroke and SE) and the primary safety endpoint (major bleeding) were greater in Asians versus non-Asians. The risk reduction in hemorrhagic stroke and GI 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, appears similar among Asians and non-Asians.

There are several real-world studies from Asia comparing NOACs with warfarin[138,139]. 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 were 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.[140-142] Strategies to target FXII or FXI 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 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 non-inferior and the 300 mg IONIS-416858 regimen was superior compared with enoxaparin in preventing the composite endpoint of asymptomatic deep venous thrombosis (DVT), symptomatic DVT or pulmonary embolism, or venous thromboembolism related mortality.[143] The rates of major or clinically relevant non-major 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 (phase 2 study ongoing https://clinicaltrials.gov/ct2/show/NCT02553889. Another area of interest is in patients with mechanical heart valves. Data from a phase II trial of dabigatran in patients with mechanical heart valves (RE-ALIGN) demonstrated inferior efficacy and more bleeding, compared to warfarin.[144] FXI-directed strategies may be very effective in this setting because FXI depletion abolished mechanical valve induced thrombin generation in vitro.[143]

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 (e.g. 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 110mg 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 VITAMIN K ANTAGONIST THERAPY

The vitamin K antagonists (VKA) are a class of oral anticoagulants; the most commonly used are the 4-hydroxycoumarins, and include warfarin, phenprocoumon and acenocoumarol.[145] 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,[146] 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[81,83,85,147-149] whereas INR levels >3.0 are associated with a greater incidence of major bleeding, especially intracranial hemorrhage when the INR rises above 3.5.[81-86] All the phase III NOAC trials employed an INR target of 2.0-3.0 among patients receiving warfarin;[73,76,126,128] J-ROCKET employed a lower INR target of 1.6-2.6 for the Japanese population.[150]

In some Asian countries, there is the perception that a lower target INR range e.g., 1.6-2.6 should be used, especially in the elderly. Only one small prospective randomized trial allocated 115 secondary prevention AF patients to conventional-intensity group (INR 2.2 to 3.5) or a low-intensity group (INR 1.5 to 2.1).[151] Major hemorrhagic complications occurred in 6 patients in the conventional-intensity group (6.6% per year) compared to the low-intensity group (0% per year, P=0.01). 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 1.6-2.6, and therefore the conventional, evidence-based INR target of 2.0-3.0 should be employed globally.

Importance of time in therapeutic 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 two consecutive INR values,[152] known as the time in therapeutic range (TTR) or by the percentage of INRs within therapeutic range (PINRR).[153] However, a limitation of the Rosendaal method of interpolation is that INRs more than 42 days apart

have generally not been interpolated in studies due to large uncertainties in fluctuation. Although TTR and PINRR are highly correlated[154,155] 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[155-157] 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%. [127,155-157] Indeed, random 'one off' INR values give little insight into the degree of anticoagulation control, and many adverse outcomes (e.g., bleeding) occur even within the therapeutic INR range of 2.0-3.0.[158] 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%[159,160] to maximize efficacy and safety and this should be the treatment target, although in clinical practice this may be more difficult to achieve.[155-158,161] An analysis of anticoagulation control in the GARFIELD-AF registry (n=9934), 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 sub-therapeutic.[157] After adjustment, the risk of stroke/systemic embolism (HR 2.55. 95% 1.61 to 4.03), all-cause mortality (HR 2.39, 95% CI 1.87 to 3.06) and major bleeding (1.54, 95% CI 1.04 to 2.26) was greater with TTR <65%, when compared to TTR ≥65%.[157]

TTR varies widely by geographical region (TTR≥65% Asia 16.7%, North America 45.9%, Europe 49.4%).[157] An analysis of individual TTR from Swedish registries (n=40,449) revealed an overall mean individual TTR (iTTR) 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 iTTR was ≥70% compared to iTTR<70%, respectively.[156]

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/counselling) to improve INR control or consider a 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 (such as age, sex, socioeconomic status, diet, ethnicity, hospitalization, length of time on VKA, medical and psychiatric co-morbidities, non-adherence, polypharmacy, genetic factors, etc.)[145,158,162] and healthcare system-related factors, particularly how VKA is managed (by country, setting of OAC management eg. anticoagulation clinic

vs. physician/community-based practices),[90,163,164] distant to OAC clinic,[163,164] self-monitoring/self-management,[91] frequency of INR monitoring etc.[158] It is also important to note that site level variation in VKA management has also been demonstrated in RCTs[165-169] and for NOACs.[170] 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[171]. Amongst patients initiating VKA, the 'Time to achieve Therapeutic Range' (TtTR) has also been related to the likelihood of achieving a subsequently good Time in Therapeutic Range (TTR)[172,173].

The more common clinical factors influencing TTR have been used to formulate the SAMe-TT_2R_2 score[174,175] (**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 (e.g. TTR≥65%) with a VKA and those who probably will not, where a NOAC may be preferred or where other interventions (eg. more frequent INR monitoring, patient education/counselling 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 is not clear if these patients would do substantially better on a NOAC or if they would do poorly anyway.

Table 5: The SAMe-TT_2R_2 score[174,175]

Acronym	Risk factors	Points
S	Sex (female)	1
A	Age (<60 years)	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, e.g., amiodarone)	1
T	Tobacco use (within 2 years)	2
R	Race (non-Caucasian)	2
	Maximum score	**8**

The SAMe-TT_2R_2 score has been assessed in 15 exclusively AF cohorts,[176-187] with six[177,179,181,182,185,188] reporting its predictive ability to forecast good or poor anticoagulation control, with c-statistics ranging from 0.56[182] to 0.72.[174] However, these cohorts were predominantly elderly, Western (white) populations and its predictive ability in non-Western populations has relatively limited data as only three studies have assessed it,[176,177], with only one reporting c-statistics (c-statistic 0.54, 95% CI 0.52 to 0.57).[177] In the multi-ethnic non-Caucasian Singaporean population by Bernaitis et al[176] the SAMe-TT_2R_2 score was able to dichotomize the patients likely to do well on VKA, compared to 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 non-predictive in non-VKA users[189]. The score has also been tested in some VTE populations, where it similarly identifies patients likely to achieve a good TTR.[190,191]

Patients with AF who require OAC should not have to fail with a VKA before they are offered a NOAC; the most appropriate OAC based on the patient's *individual* risk profile and patient preference, should be offered from the beginning of OAC therapy. However, in some healthcare systems where the patient has to have a period on VKA and their TTR determined, before a decision to use a NOAC is approved, the SAMe-TT_2R_2 score could be used to aid decision-making[175].

Recommendation

11. For patients with AF, we suggest the SAMe-TT_2R_2score 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/counselling and frequent follow-up, or alternatively, a 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[192] and not all patients are suitable for NOACs, therefore a large proportion requires VKA which necessitates INR monitoring. Point-of-care (POC) 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 POC monitoring is an increasingly standard method of INR monitoring associated with an appropriate degree of precision and accuracy for clinical practice,[193] however routine calibration is warranted and quality control systems should adhere with the FDA Medical devices regulation guidance[194].

Patient self-monitoring and self-management

A recent Cochrane review[91] evaluating the effect of self-monitoring or self-management of OAC therapy compared to 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 to 0.75; 7594 participants in 18 studies) and with both self-monitoring (RR 0.69, 95% CI 0.49 to 0.97; 4097 participants in 7 studies) and self-management (RR 0.47, 95% CI 0.31 to 0.70; 3497 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 to 1.01, 6358 participants in 11 studies), however self-management did reduce all-cause mortality (0.55, 95% CI 0.36 to 0.84; 3058 participants in 8 studies). Neither self-monitoring nor self-management reduced the risk of major bleeding compared to standard OAC monitoring (RR 0.95, 95% CI 0.80 to 1.12; 8018 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 healthcare system infrastructure and patient support which may not be feasible globally. For many AF patients, a 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 (Figure 4). The initial step is to determine the risk of stroke. As noted in the Stroke Risk section, risk scores for stroke in patients with AF lack specificity, and are therefore not clinically useful in identifying and categorizing high-risk patients. As noted in the stroke risk 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 that 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 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 flagged up for this reason.

The final decision point is to decide which oral anticoagulant to use for stroke prevention. As noted in AT 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 co-morbidities might be considerations in choosing an agent (see Table 6) for comparative information. The vitamin K antagonists 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.

1570 **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/SE/TIA despite good anticoagulation control (TTR≥70%). Consider agent with superior efficacy for preventing both ischemic and hemorrhagic stroke	D150	[127]	[130]	In general, any NOAC would be recommended, esp. where warfarin control suboptimal (TTR<65%). Ensure good adherence and avoid under-dosing
• Moderate-severe renal impairment CrCl 15-49 ml/min	A* D† E30 R15	[127]	[195]	All RCTs excluded patients with Cockroft-Gault CrCl <30ml/min (<25mls/min, for apixaban)
• High risk of GI bleeding	A D110	[127]	[130,196]	
• Major GI symptoms or dyspepsia. Also consider increased risk of bleeding	A R E	[197]	[198,199]	
• High risk of bleeding (HAS-BLED ≥3). Consider agent with the lowest bleeding risk	A D110 E	[127]	[130,131,196,200,201]	
• Once daily dosing or preference to have lower pill burden	E R VKA	#	[202,203]	
• Asian patients. Consider agents with reduced risk of ICH and major bleed in Asian populations	A D E	[137]	[138,139,204]	
• Less likely to do well on VKA (SAMe-TT_2R_2 score >2). Avoid <u>any</u> potential 'trial' of VKA if possible	NOAC preferred (A D E R)	…	[176,185,189]	VKA with additional education, more regular follow-up and frequent INR checks

1571
1572 A= apixaban. BID=twice daily. CrCl=creatinine clearance. D= dabigatran. E=edoxaban. GI=gastro-intestinal. ICH= intracranial hemorrhage. INR= international normalised
1573 ratio. NOAC=non-vitamin K antagonist oral anticoagulant. R=rivaroxaban. SE= systemic embolism. TIA= transient ischemic attack. TTR=time in therapeutic range.

VKA=vitamin K antagonist. *Reduced to 2·5 mg BID with two of three criteria from age ≥80 years, bodyweight ≤60 kg, or serum creatinine concentration ≥133 μmol/L. †110 mg BID for patients with a CrCl 30–49 mL/min (most countries, but not in the USA); in the USA only, 75 mg BID (available in the USA only) for patients with CrCl 15–29 mL/min (and only 150 mg BID dose available in the USA for CrCl >30 mL/min). ‡30 mg with CrCl 15–49 mL/min, P-glycoprotein inhibitors, or weight <60 kg. §110 mg BID dose not available in the USA for atrial fibrillation. ¶Reduced to 15 mg if CrCl 15–49 mL/min.
‖Dose to be halved if the patient has any of the following: CrCl 15–49 mL/min, bodyweight ≤60 kg, or concomitant use of P-glycoprotein inhibitors. # not available

MANAGING BLEEDING ON OAC

Bleeding on VKA

Management of active bleeding on a VKA depends on the severity (Figure 6). For all bleed 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 (blood pressure, pulse etc.). Assessment of INR, prothrombin time and activated partial thromboplastin time 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 should be considered to restore coagulation. PCCs are preferred over FFP for reversal due to a higher concentration of clotting factors and less volume.

Bleeding on NOAC

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.[205] A helpful framework to consider when managing NOAC related bleeding includes: (1) prevention of bleeding, (2) general principles and supportive measures, (3) non-specific hemostatic agents, and (4) NOAC-specific reversal agents.[206]

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 non-steroidal anti-inflammatory drugs should be avoided when possible as concomitant administration substantially increases bleeding risk. Blood pressure 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 red blood cell and platelet transfusion, if appropriate.[207-209] In cases of overdose or in

patients who took their last NOAC dose within 2 to 4 hours, oral activated charcoal may attenuate absorption of drug.[210-213]

Laboratory Measurements

With respect to common coagulation tests, a prolonged activated partial thromboplastin time (aPTT) indicates an anticoagulant effect of dabigatran, and a prolonged prothromin time (PT) indicates an anticoagulant effect of the FXa inhibitors.[208] 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 FXa 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 thrombin time (dTT) can be used to quantify dabigatran drug levels as it has good correlation across a wide range of dabigatran concentrations.[214] Chromogenic anti-FXa assays are recommended for rivaroxaban, apixaban, and edoxaban with calibration for the specific agent.[208] However, validation of these specialized coagulation tests is required, they are not universally available, and often have delayed turn-around 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.

Non-Specific Hemostatic Agents

Hemostatic factors that have been studied as potential non-specific NOAC reversal agents including prothrombic complex concentrates (PCC), activated PCC (aPCC), recombinant activated factor VII (rFVIIa), and fresh-frozen plasma (FFP). PCCs are the preferred non-specific 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 PCC have variable ability to normalize anticoagulation parameters and prevent or attenuate bleeding across the NOACs.[209,215-221] The limited data in humans are restricted to healthy volunteers. In three small (12-93 patients) randomized, placebo-controlled studies, PCC reversed the anticoagulant effect of rivaroxaban and edoxaban but not dabigatran.[210,222-224] 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.[225-227]

Specific Reversal Agents

Idarucizumab

Idarucizumab is a humanized monoclonal antibody fragment developed as a specific reversal agent for dabigatran (Table 7). It binds with high affinity (350 times higher than thrombin) to free and thrombin-bound dabigatran[228] and binding is effectively irreversible.[229] 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 5g idarucizumab (administered as two rapid 2.5g intravenous 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).[230] Idarucizumab resulted in immediate, complete, and sustained reversal of dabigatran. Median time to cessation of bleeding in Group A was between 2.5 hours after reversal and in Group B, median time to surgery after reversal was 1.6 hours 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 and fondaparinux) FXa inhibitors that act through antithrombin. It is a modified human recombinant FXa 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 FXa inhibitors within the vascular space, endogenous FXa activity is restored.[231] Due to its pharmacodynamic half-life of 1-hour, andexanet is administered as a bolus followed by an infusion.

The ongoing ANNEXA-4 phase 3b–4 study (http://www.clinicaltrials.gov, NCT02329327) is evaluating the efficacy and safety of andexanet in patients taking FXa 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-hour infusion of andexanet substantially reduced anti-factor Xa activity with clinically adjudicated effective hemostasis occuring in 79% of patients.[232] 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, low molecular weight heparins, fondaparinux, and the oral direct Xa and IIa inhibitors. It binds to targets through non-covalent hydrogen bonding and charge-charge interactions thereby preventing the anticoagulants from binding to their endogenous targets.[233] Ciraparantag is earlier in it development program as 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, intracranial hemorrhage, 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 (e.g., 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 non-specific 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 a NOAC.

Table 7: Comparison of specific NOAC reversal agents [adapted from Ruff CT, Giugliano RP, Antman EM. Circulation. 2016; 134(3)248-61]

	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 two 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	~350x greater affinity for dabigatran than factor IIa	Affinity for direct factor Xa inhibitors similar to that of native factor Xa	Not reported
Onset	<5 minutes	2 minutes	5-10 minutes
Half-life	Initial: 47 minutes Terminal: 10.3 hours	Terminal: ~6 hours	Duration of action 24 hours
Elimination	Kidney (protein catabolism)	Not reported	Not reported
Anticoagulant(s) reversed	Dabigatran	Direct and indirect factor Xa inhibitors*	- 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 minutes, 15 minutes apart (repeat dosing can be considered if recurrent bleeding or require second emergent procedure if elevated coagulation parameters)	400-800 mg intravenous bolus (30 mg/min) followed by infusion of 4-8 mg/min[#]	100-300 mg intravenous bolus
Storage	Refrigerated	Refrigerated	Room temperature

* 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.

[#]Lower dose to reverse apixaban, higher dose to reverse rivaroxaban

PRACTICAL ISSUES WITH VKA AND NOAC

CARDIOVERSION

Antithrombotic therapy for patients with AF undergoing cardioversion

In AF of documented short duration (i.e.≤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 more than 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 (TE) with peri-cardioversion anticoagulation (with VKA) versus no anticoagulation (0.3% vs 2.0%; relative risk, RR, 0.16, 95% CI, 0.05-0.48), but did not report major bleeding events[234].

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 pathophysiologic 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 1.5-2.4 before cardioversion than INR of 2.5 (0.93% vs 0%, P 0.012)[235]. Retrospective observational studies suggest that, after cardioversion, the highest risk of stroke and thromboembolism is in the first 72 hours. In addition, most thromboembolic complications are within 10 days of cardioversion[236]. However, even if sinus rhythm is restored on ECG, transoesophageal echocardiography (TEE) studies have shown that atrial mechanical dysfunction can persist for several weeks following cardioversion[237]. Recent Finnish registry data suggest that most post-cardioversion strokes are associated with not using anticoagulation[238]. 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 history of ischemic stroke[239]. It is also worth noting that although the risk of ischemic stroke/TE is higher with non-paroxysmal vs. paroxysmal AF (multivariable adjusted hazard ratio 1.38, 95% CI: 1.19-1.61, p<0.001), pattern of AF does not affect the decision regarding long-term OAC.

NOACs

Evidence is available for all four currently available NOACs: dabigatran, apixaban, rivaroxaban and edoxaban. An existing systematic review from Renda et al. compared the use of NOAC versus VKA in the setting of cardioversion in six studies.[240] Reported pooled risk ratios (RRR) 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 under-powered 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 [241,242]. Available data support use of rivaroxaban[243 244], dabigatran[245], apixaban[246] and edoxaban[247] in patients to be continued on these NOACs if scheduled for cardioversion. Similar observations were found in a randomized trial of apixaban vs. warfarin (EMANATE) [248].

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[249]. 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 is from the Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) RCT, which compared a TEE-guided strategy of abbreviated therapeutic anticoagulation with IV unfractionated heparin (started 24 h before cardioversion) or warfarin (INR 2.0-3.0) (started 5 days before cardioversion) to a strategy of therapeutic anticoagulation for at least 3 weeks before cardioversion[250].

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 versus 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.[251] An updated search of this systematic review identified one additional study. Pooled results found the relative risk ratio for stroke/TE was 0.33 (0.06-1.68) for NOACs versus warfarin (e-Figure 3, e-table 18). Although these data indicate safety and probable equivalence of NOACs in the TEE-guided approach versus VKA, the trials were under-powered 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, low-molecular-weight heparin at full VTE treatment doses or IV unfractionated heparin (to maintain an activated partial thromboplastin time prolongation that corresponds to plasma heparin levels of 0.3-0.7 International Units/mL anti-factor Xa activity) should be started at the time of TEE and cardioversion performed within 24 hours of the TEE if no thrombus is seen. Observational data and one RCT show that low-molecular-weight heparin has similar efficacy compared with heparin or warfarin for immediate anticoagulation before TEE[252-256]. 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 left atrial appendage thrombus with a 3.5-fold increased risk of stroke/TE[257], 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 TE, 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[258].

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, but 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[259-262]. Second, the 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[263]. Thirdly, patients with paroxysmal AF are often asymptomatic during episodes of AF recurrence, with one series suggesting that only one in every 12 paroxysms are symptomatic[264].

Recommendation

12. For patients with AF of greater than 48 hours or unknown duration undergoing elective electrical or pharmacologic cardioversion, we recommend therapeutic anticoagulation with well-managed VKA (INR 2-3) or a 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 succesful 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 recommednations 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 endothelisation, 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 hours). 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[265,266]. In addition, the high prevalence of asymptomatic AF makes determining the exact duration of AF difficult[267]. If there is uncertainty about precise time of AF onset, then such patients should be managed as if AF >48 hours.

A recent Finnish observational study of 5,116 successful cardioversions in 2,481 patients with acute (<48 h) AF showed low incidence of stroke/TE during the 30 days following cardioversion, even without perioperative anticoagulation (0.7%)[268]. These results concur with low rates of stroke/TE in observational studies (Table 8). However, there is lower incidence of stroke/TE with cardioversions performed during anticoagulation (0.1% vs 0.7%, p=0.001), and with anticoagulation versus no anticoagulation in patients with a CHA_2DS_2VASc score of ≥2 (0.2% vs 1.1%, p=0.001). 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[269]. 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/TE[268], even if an individual is presenting for the first time with AF.

Table 8. Thromboembolic Complications in Patients With No Anticoagulation After Cardioversion of Acute (<48 h) Atrial Fibrillation in Previous Studies (from Airaksinen et al. 2013[268])

First Author (Ref. #)	n	Mean Age, yrs	Male	Success Rate	Thromboembolism

Weigner et al.[270]	224	68	NA	95%	0.9%*
Michael et al. [271]	217	64	54	86%	0.5%*
Burton et al. [272]	314	61	55	86%	0†
Gallagher et al. [235]	198	63	68	100%	0.5%‡
Stiell et al. [273]	414	65	56	92%	0†
Xavier Scheuermeyer et al. [274]	104	57	92	96%	0

∗All 3 thromboembolic events after spontaneous cardioversion and in elderly (>75 years) women.
†Follow-up of 7 days.
‡Plus 1 probable thromboembolic event. NA, not available

Recommendations

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 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

Patients undergoing urgent cardioversion for hemodynamically unstable AF

Our systematic review of anticoagulation versus no anticoagulation in patients with AF undergoing urgent 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 (e.g., with IV unfractionated heparin or low-molecular weight heparin) would be expected to reduce the risk of stroke/TE based on studies of elective cardioversion. Initiation of anticoagulation therapy should not delay any emergency interventions required in order to stabilize the patient.

Recommendation

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 TE 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 TE in patients after cardioversion for atrial flutter and AF[235,275,276], 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 peripheral artery disease[277,278]. Some AF patients with coronary disease may present with an acute coronary syndrome (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.

There are 4 considerations when managing these patients, as follows[277,279]:

- Stroke prevention, necessitating OAC, whether with VKA or NOAC
- Prevention of stent thrombosis, necessitating antiplatelet therapy (APT). There is evidence for using 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 PEGASUS

trials, to reduce non-stent related ischemic and stroke events, but at the risk of more bleeding events[280].

- Serious bleeding risks (e.g., 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[110]. Coronary stent technology has also evolved, with small strut sizes necessitating shorter duration of dual APT (DAPT, i.e. aspirin plus P2Y12 inhibitor such as clopidogrel). We are also in the era of NOACs, which may offer a better safety profile compared to VKA based therapy. Nonetheless the latter may be relatively safe in the presence of well managed anticoagulation control with high TTR[281].

AF patients undergoing percutaneous coronary intervention

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 HRS and APHRS, which provides consensus recommendations on optimal management of such patients[277,279]. A similar North American expert consensus document has been published[282].

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-S) Chaudhary et al[283], showed that DAPT and VKA was 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[284] 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 (i.e., acute coronary syndrome, 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[285] reported a meta-analysis restricted to the subgroups of patients on aspirin therapy (n=21,722) from the four 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 [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 intracranial hemorrhage (HR: 0.38 [0.26-0.56]). Thus, it may be both safer and more effective to use NOACs as compared with VKA to treat patients with non-valvular AF and concomitant aspirin therapy.

The largest observational cohort was reported by Lamberts et al[286], 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, i.e. aspirin plus clopidogrel), no increased risk of recurrent coronary events was seen for OAC plus clopidogrel (hazard ratio [HR]: 0.69, 95% CI: 0.48 to 1.00), OAC plus

aspirin (HR: 0.96, 95% CI: 0.77 to 1.19), or aspirin plus clopidogrel (HR: 1.17, 95% CI: 0.96 to 1.42), but aspirin plus clopidogrel was associated with a higher risk of ischemic stroke (HR: 1.50, 95% CI: 1.03 to 2.20). OAC plus aspirin and aspirin plus clopidogrel were associated with a significant increased risk of all-cause death (HR: 1.52, 95% CI: 1.17 to 1.99 and HR: 1.60, 95% CI: 1.25 to 2.05, respectively). When compared to triple therapy, bleeding risk was non-significantly lower for OAC plus clopidogrel (HR: 0.78, 95% CI: 0.55 to 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 to 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 WOEST trial[287], which randomized 573 adults receiving oral anticoagulants (65% with AF) and undergoing PCI to clopidogrel alone (double therapy) or clopidogrel plus aspirin (triple therapy). The primary endpoint 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<0·0001). Of the secondary endpoints, 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 endpoints, and the primary endpoint 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 ISAR-TRIPLE trial[288], a 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 endpoint (composite of death, myocardial infarction (MI), definite stent thrombosis, stroke, or Thrombolysis In Myocardial Infarction (TIMI) 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 to 1.91; p=0.63). There were no significant differences for the secondary combined ischemic endpoint of cardiac death, MI, definite stent thrombosis, and ischemic stroke (12 [4.0%] vs. 13 [4.3%]; HR: 0.93; 95% CI: 0.43 to 2.05; p=0.87) or the secondary bleeding endpoint of TIMI major bleeding (16 [5.3%] vs. 12 [4.0%]; HR: 1.35; 95% CI: 0.64 to 2.84; p=0.44). 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 the PIONEER AF-PCI trial[289], 2,124 patients with AF undergoing PCI with stenting were randomized to low-dose rivaroxaban (15 mg once daily, reduced to 10mg with moderate renal impairment) plus a P2Y12 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 two groups receiving rivaroxaban than in the VKA group (16.8% in group 1, 18.0% in group 2, and 26.7% in group 3; hazard ratio for group 1 vs. group 3, 0.59; 95% CI 0.47 to 0.76; P<0.001; hazard ratio for group 2 vs. group 3, 0.63; 95% CI, 0.50 to 0.80; P<0.001). The rates of death from cardiovascular causes, myocardial infarction, or stroke were similar in the three groups but the trial was underpowered for efficacy endpoints. There was only a minority of newer P2Y12 inhibitors used

as APT. There was an associated reduction in hospitalizations in the 2 rivaroxaban arms, compared to VKA[290].

In the RE-DUAL PCI trial[291], 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 to 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 (≥80 years of age; ≥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 non-major 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<0.001 for non-inferiority; P<0.001 for superiority) and 20.2% in the 150-mg dual-therapy group as 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 to 0.88; P<0.001 for non-inferiority). The incidence of the composite efficacy end point of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization was 13.7% in the two dual-therapy groups combined as compared with 13.4% in the triple-therapy group (hazard ratio, 1.04; 95% CI, 0.84 to 1.29; P=0.005 for non-inferiority). Thus, the risk of bleeding was lower among those who received dual therapy with dabigatran and a P2Y12 inhibitor than among those who received triple therapy with warfarin, a P2Y12 inhibitor, and aspirin. Dual therapy was non-inferior to triple therapy with respect to the risk of thromboembolic events. In contrast to the PIONEER-AF trial, the REDUAL PCI trial tested dabigatran doses (110mg and 150mg bid) which are licensed for stroke prevention in AF.

There are limited data on use of the newer P2Y12 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 regime, compared to when clopidogrel is used as part of the triple therapy regime[292]. Only a minority of patients in PIONEER AF-PCI had newer P2Y12 agents, whereas the largest experience in AF patients was in the RE-DUAL PCI trial, which allowed ticagrelor in combination with dabigatran 110mg or 150mg bid.

In the GEMINI-ACS-1 trial[293], 3037 patients with ACS (i.e. essentially a non-AF population) were randomly assigned to either aspirin 100mg or rivaroxaban 2.5mg bid, and the subsequent choice of clopidogrel (44%) or ticagrelor (in 56%) during trial conduct was non-randomized. Low-dose rivaroxaban with a P2Y12 inhibitor for the treatment of ACS patients had similar risks of clinically significant bleeding (5%) as aspirin and a P2Y12 inhibitor [HR 1·09 [95% CI 0·80-1·50]; p=0·5840)].

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 myocardial infarction, prior peripheral artery disease, or aortic plaque) as a single risk factor have a high stroke rate of 4.85 per 100 person-years[294]. This corresponds to CHA_2DS_2-VASc=1 for males and a CHA_2DS_2-VASc=2 for females, with rates of 4.53 and 5.69, respectively. Contrasting low risk CHA_2DS_2-VASc (that is, score 0 (male) or 1 (female)) as a reference population vs. those with ≥1 additional stroke risk factors (i.e. CHA_2DS_2-VASc score =1 (male) 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[295], PAD may confer an ischemic stroke risk that is much higher than that seen in Western populations[296].

In AF patients with stable CAD there is no evidence that adding APT to OAC reduces stroke/SE, 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[297] where 8700 AF patients (mean age, 74.2 years; 38% women) with stable CAD (defined as 12 months from an acute coronary event) followed-up for a mean 3.3 years, found the risk of myocardial infarction/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 to warfarin, aspirin at <100mg 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 was maintained irrespective of aspirin use[298]. Only the RELY 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[299].

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 CAD would be generally applicable to PAD or carotid disease. One post-hoc ancillary analysis[300] 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 = 0.34). However, there was a higher risk of major bleeding or NMCR 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 = 0.037).

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 one 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 one 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 a NOAC at a dose licensed for stroke prevention in AF (weak recommendation, low quality evidence).**
Remark: Only Dabigatran 150mg bid or (not licensed in USA) 110mg bid or Rivaroxaban 15mg qd are currently supported by clinical trial evidence. A 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 75-100mg 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 110mg 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 a 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[301]. In a randomized trial of 1584 patients, uninterrupted warfarin, compared to interruption with heparin bridging, has been shown to have a lower risk of periprocedural stroke and bleeding[302]. A randomized trial of uninterrupted rivaroxaban vs. uninterrupted VKA in AF ablation demonstrated similar event rates in both arms[303]. A similar randomized trial of uninterrupted dabigatran found that dabigatran was associated with fewer bleeding complications than uninterrupted warfarin[304]. Although these studies were open-label, they strongly support the use of uninterrupted anticoagulation for electrophysiology procedures **(Table 9)**. Two recent systematic reviews with meta-analyses that include these studies found consistent with results[305,306].

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[307,308].

After catheter ablation, discontinuation of OAC is associated with an increased risk of stroke[301]. Similarly, post-operative AF may confer a long-term risk of stroke. In a U.S. claims analysis of 1.7 million patients hospitalized for surgery, perioperative atrial fibrillation was associated with an increased long-term risk of ischemic stroke, especially following non-cardiac surgery[309]. 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 in 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 CHA2DS2-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).

Table 9: Summary of Studies of Periprocedural Anticoagulation for Catheter Ablation of Atrial Fibrillation and Implantation of Cardiac Electronic Implantable Devices:

Trial	Population	Interventions	Results
COMPARE[302]	Catheter ablation of AF N=1584	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[303]	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[304].	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[310]	Pacemaker or defibrillator	Uninterrupted warfarin vs.	Significant reduction in pocket hematoma

	implantation N = 343	interrupted warfarin with heparin bridging	(3.5% vs. 16%)

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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[311], while other studies suggest a recurrence risk of between 0.4% and 1.3% per day in the first 7-14 days [311-315]. AF-related ischemic strokes are more often disabling or fatal than other types, with longer hospital stays and higher costs[316], so preventing early recurrence is a key clinical challenge.

The safety and benefit of OAC in acute stroke have not been established. Early anticoagulation (i.e. in the first few days) might increase the risk of symptomatic intracranial hemorrhage, including hemorrhagic transformation of the infarct (estimated at ~1% per day[317]), leading to clinical uncertainty about when to start anticoagulation. Recent studies reported an 8-10% risk of recurrent ischemic stroke and a 2-4% risk of symptomatic intracranial hemorrhage within 90 days of AF-related ischemic stroke[318,319].

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 [320] while recent European Society of Cardiology guidelines recommend starting anticoagulation - according to infarct size – at 1, 3, 6, or 12 days[321] 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=1029) suggested that anticoagulation at 4-14 days after cardioembolic stroke had the best outcome, but did not have statistical power to determine benefit of earlier anticoagulation [322]. Increasing cerebral infarct size is associated with increased risk of both symptomatic hemorrhagic transformation and early recurrent ischemia [317]

A systematic review and meta-analysis of 7 randomized trials of unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) or heparinoids (n=4624) started <48 hours, vs. aspirin or placebo, found that early anticoagulation was associated with non-significantly reduced recurrent ischemic stroke, but with increased intracranial bleeding, and no reduction in death or disability (e-Table 19).[314] 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 vitamin K antagonists (to achieve therapeutic levels by day 7) [319,323-325]. Observational data suggest that the use of low molecular weight heparin (as a "bridging" strategy) together with oral anticoagulation is associated with a higher risk of symptomatic hemorrhage.[318,326-328]

Observational studies suggest early (<14 days) anticoagulation with NOACs might be safe [318 319,322 329]. One study reported improved outcomes and no early ICH with NOAC started at a median of 4

days post-stroke (n=1192)[330,331]. The Pre-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% [332]. There are no large trials of NOACs including patients within 7-14 days of a stroke, but one small study (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 (~30%) or intracranial bleeding (~30%) at 4 weeks, with reduced hospital stay for rivaroxaban[333].

Recommendations

34. In AF patients with acute ischaemic stroke, we suggest that very early anticoagulation (<48h) 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 ischaemic stroke because they appear to increase the risk of symptomatic intracranial haemorrhage without net benefit. The optimal timing of anticoagulation after acute ischaemic 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 ischaemic stroke is unknown. Early use of NOACs shows promise but requires testing in randomised controlled trials.

36. In AF patients with acute ischaemic stroke, We suggest that oral anticoagulation should usually be started within 2 weeks of acute ischaemic 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 ischaemia, haemorrhagic 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 randomised trials, but shows promise in observational studies.

AF patients with intracerebral hemorrhage (ICH)

Spontaneous (non-traumatic) intracerebral 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. 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.[334] In a recent hospital ICH cohort study, 25% of patients had AF[335]

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_2VASC score and it seems reasonable to use this score in populations of ICH survivors[336].

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[337]. Computed tomography 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).[338] The risk of recurrence has been reported to be higher for lobar ICH than after deep ICH,[337] 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. Magnetic resonance imaging (MRI) can identify biomarkers of small vessel disease including cerebral microbleeds (CMBs), whose distribution can be used to diagnose cerebral amyloid angiopathy (CAA) with high specificity in ICH cohorts[339]. In a recent pooled analysis of observational studies, patients with ICH classified using CMBs as due to CAA had a ~7% annual recurrence risk, compared with ~1% for those not fulfilling criteria for CAA[340].

Since oral anticoagulants 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.[341] In ICH survivors the number of CMBs is also associated with the risk of recurrent ICH.[342]

Balancing the risks of ischemic stroke and recurrent ICH

A decision analysis which modelled warfarin for AF in an ICH survivor suggested that in lobar ICH avoiding warfarin increased quality-adjusted life (QOL) 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)[343]. 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=0.28) with no increased risk of recurrent ICH (pooled RR 1.01; 95% CI 0.58–1.77; Q=24.68, P for heterogeneity <0.001).[344] 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.[345,346] 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 hours).

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.[347] There are no large scale randomized controlled trials to answer the question of whether long-term anticoagulation has net benefit in ICH survivors with AF. NOACs have a ~50% lower ICH risk than VKA[127], and are therefore preferred in most ICH survivors, except where warfarin is indicated (e.g. 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.[348]

There are two 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 (www.restarttrial.org –antiplatlets vs, no antiplatelets in patients with ICH with an indication for antiplatelets).

Left atrial appendage occlusion in ICH survivors

Randomized trials indicate that left atrial appendage 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.[349] Observational data from 1025 patients suggest that LAAO might be safe and effective in patients with a contra-indication to long term oral anticoagulation, but only a minority of patients (15%) in this study had suffered ICH.[350] 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 [351,352] 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 ischaemic stroke risk, we suggest anticoagulation with a NOAC after acute spontaneous ICH (which includes subdural, subarachnoid and intracerebral haemorrhages) 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 favourable 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 ischaemic stroke

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

38. In ICH survivors at high risk of recurrent ICH (e.g. 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.[353] 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.[354] Thus in patients with both carotid stenosis and AF there are indications for both anticoagulation and antiplatelet therapy, 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.[355] 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 revascularisation 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 revascularisation, 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-revascularisation period (e.g. 1-3 months)

Patients presenting with Embolic Stroke of Undetermined Source (ESUS)

In North America and Europe, about 1 in 4 ischemic strokes remain of uncertain etiology (i.e. not attributable to definite cardiac embolism, large artery atherosclerosis, or small artery disease), despite adequate investigation, and are termed “cryptogenic”.[320,356]

Because most cryptogenic strokes are embolic, a more recent concept of embolic stroke of undetermined source (ESUS) has been developed, 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 hours, and imaging of the intracranial and extracranial arteries supplying the affected brain area: is not lacunar (subcortical, less than 15mm diameter); where there is absence of extracranial or intracranial atherosclerosis causing ≥50%

luminal stenosis in the arteries supplying the area of ischemia; no major-risk cardioembolic source of embolism (permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intra-cardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumours, mitral stenosis, recent (<4 weeks) myocardial infarction, left ventricular ejection fraction less than 30%, valvular vegetations, or infective endocarditis); and no other specific cause of stroke identified (e.g. arteritis, dissection, migraine/vasospasm, drug misuse)[357].

Thus, ESUS is a sub-category of cryptogenic stroke, accounting for about 1 in 6 ischemic strokes.[358] A careful and systematic diagnostic work up 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). 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[359].

Two randomized controlled trials 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 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); [360] while in EMBRACE, 572 patients randomly assigned to additional ambulatory monitoring with a 30-day external loop recorder (intervention group) or a 24-hour 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).[361]

In a systematic review and meta-analysis, Sposato et al[362] 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 post-stroke leading to underdiagnosis.[363]

Table 10: Phases of screening for AF in cryptogenic stroke patients, methods and incidence of AF diagnosed [362]

4 sequential phases of screening	Cardiac monitoring methods	% (95% CI) diagnosed with
Phase 1 (emergency room)-	admission electrocardiogram (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)

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[364,365]. In a retrospective analysis, newly detected atrial tachycardia (AT) or AF (NDAF; AT/AF >5 minutes on any day) was identified in 30% patients with implantable cardiac rhythm devices and ≥1 stroke risk factors during a follow-up of 1.1 years[366]. The presence of AT/AF >6 hours on ≥1 day increased significantly with increased $CHADS_2$ scores. Similarly, the ASSERT-II study reported that subclinical AF lasting ≥5 minutes was present in 34.4% per year, in a prospective cohort of elderly patients with risk factors but no prior stroke[367].

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 3-fold and 15-fold higher compared with that in patients with a score of 0, respectively[368]. If ESUS is phenotypically different from AF-associated stroke, we should see differences in stroke severity and outcomes; however, no difference in NIHSS score was evident in ESUS where AF was detected on follow-up, compared to where no AF was evident[369]. 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[370].

Current guidelines recommend use of antiplatelet agents including aspirin in ESUS patients[320] unless AF is detected (often requiring prolonged work up, 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 (more than 4% per year) despite the frequent use of antiplatelet agents in clinical practice.[358] 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 to 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 (e.g. prolonged rhythm monitoring) after discussion and consideration of patient preference.

ATRIAL HIGH-RATE EPISODES DETECTED BY CARDIAC IMPLANTED ELECTRONIC DEVICES

Cardiac implanted electrical devices (CIEDs) with an atrial lead or with capability of rhythm discrimination (i.e. implantable cardiac monitors) allow continuous monitoring of the cardiac rhythm and appropriate detection of atrial tachyarrhythmias, including AF, as atrial high-rate episodes (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 bpm, 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) [371-377].

Although temporal cut-offs for detection and storage of AHRE data as short as 30-60 seconds have been used, the diagnostic accuracy is reliable when episodes ≥5 minutes in duration are considered, since, using this cut-off, the appropriateness in AF detection is 95%, minimizing the risk of over-sensing due to detection of artefacts caused by myopotentials or other sources of electrical interference [378,379]. 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 be easily made through analysis of tracings recorded in the device's memory [159]. After detection of AHREs by CIEDs, conventional Holter or other ECG long-term recordings (i.e., patient operated devices) can be considered in specific cases (e.g. 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 [372,380 381 382]), 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 [371,375,376,383,384].

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 around 10% of patients implanted with a CIED [375]. 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[375]. Considering these findings, as well as data from the literature reported in e-Table 20, there is evidence that AHREs with a duration >5-6 min are common in patients implanted with CIEDs.

In patients implanted with CIEDs for conventional indications, AHREs, with a short duration, ranging from three atrial premature complexes to 15–20 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 [385]. For this reason most of the interest is patient with CIEDs is focused on AHRE with a duration ≥5–6 min, a finding associated with a substantial risk of subsequently presenting clinical AF (HR 5.5–6.0), initially reported by the ancillary MOST analysis [386] and then by the ASSERT study [375], where a 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 (that is, the maximum time spent in adjudicated AF in one day of the follow-up

period)[375,385-393]. The studies show that AHRE burden with a duration ≥5–6 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 [394], 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 analysed in the SOS AF project, with a pooling of three prospective studies (PANORAMA, Italian Clinical Services Project, and TRENDS) resulting in 10,016 patients [391]. 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 a hazard ratio for ischemic stroke of 2.11 (95% CI 1.22–3.64, *P* = 0.008), 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 [389] found that an AHRE burden of 5.5 h in a day, in a 30-day period, was associated with a two-fold increase in the adjusted risk of stroke (absolute risk of thromboembolism around 1.8% per year)[389]. 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 [395].

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 to patients with AHRE detected by continuous monitoring via a CIED [374,376]. 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 oral anticoagulants 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[372,376].

Two randomized controlled trials are ongoing evaluating the efficacy and risk-benefit ratio of oral anticoagulation to no oral anticoagulation (aspirin only) in patients with CIED-detected AHRE (ARTESiA (NCT01938248)[396] and NOAH – AFNET 6 (NCT02618577).[397]

In the absence of the results of these on-going trials, management of patients with CIEDs-detected AHREs requires cardiological clinical evaluation, clinical decision making and follow up (Figure 7). Oral anticoagulants 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 hours, 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 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_2VASc 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_2VASc) who present with AHREs, corresponding to atrial tachyarrhythmias/AF at electrograms assessment of less than 24 hours duration.

43. In patients with AF, we suggest that 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 hours, individual stroke risk (using CHA_2DS_2VASc), 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 hours,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 to AF. However, patients with atrial flutter frequently present phases of AF alternated with phases of classical flutter or regular atrial rhythm [398-400]. 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.[235,273,275,276,401-411] Echocardiographic studies reported prevalence of intra-atrial thrombi from 0% to 38% and a prevalence of spontaneous echo contrast up to 28%. [398,399,409,412-421] One ablation study in non-anticoagulated patients with atrial flutter reported thromboembolic events in 13.9% of cases. [422] The differences in patient selection, type of study and, importantly, use of oral anticoagulation explain the heterogeneity of reported data with regard to echo findings and thromboembolic complications. Observational studies demonstrated an increased risk of stroke (risk ratio 1.4, 95% CI 1.35 to 1.46) and death (HR 1.9, 95% CI 1.2 to 3.1)[401] compared to controls 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 2000–2013, found that the rate of thromboembolic events for atrial flutter patients was 0.46 per 100 persons-years, not significantly different from that of patients

presenting with AF (HR adjusted for several variables including anticoagulation = 1.22 [0.62–2.41]).[401]

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. [423]

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

Atrial fibrillation (AF) and atrial flutter are very rare during pregnancy, unless when there is an underlying structural heart disease or hyperthyroidism. [424] Lone AF is uncommon in pregnancy and is associated with older age and late pregnancy. [425] 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. [425] Peri-partum cardiomyopathy AF is common, with a prevalence that may reach 10%, and may severely impair hemodynamic status. [426]

In a registry of >250, 000 pregnancies in Southern California [427] AF was evident in 0.6 per 1000, more frequently in white women (1,1 per 1000 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.[428]

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 women with AF at risk of stroke/thromboembolism in the non-pregnant state, pregnancy will increase this risk 3- to 4- fold.[428,429]

Vitamin K antagonists 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 vitamin K antagonists during the first trimester of pregnancy [428]. Vitamin K antagonists have also been associated with central nervous system abnormalities after exposure during any trimester, but these complications are uncommon. [428] 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. [424]

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

Unfractionated heparin (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 [428]. 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 hours 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. [430] 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 a 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).

With regard to breast-feeding, warfarin, in view of its characteristics (polar, non-lipophilic, and highly protein bound) can be considered safe since two reports showed that warfarin is not detected in breast milk and does not induce an anticoagulant effect in the breast-fed infant when nursing mothers consume the drug. [431,432] Acenocoumarol, which is commonly used in Europe, has similar properties. [433,434] 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 hours 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 >2mg/day). OAC should then be discontinued and replaced by adjusted-dose LMWH (target anti-Xa level 4-6 hours 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 a 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 breastfeed, 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).

ATRIAL FIBRILLATION AND CHRONIC KIDNEY DISEASE

Chronic kidney disease (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 16-21% in non-dialysis dependent CKD and 15-40% in patients on dialysis[435].

Among patients with AF, CKD is present in one-third of patients at the time of AF diagnosis[51 436] 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 chronic kidney disease (1.64, 1.41 to 1.91), as well as all-cause mortality (relative risk 1.46, 95% CI 1.39 to 1.54), cardiovascular mortality (2.03, 1.79 to 2.30), major cardiovascular events (1.96, 1.53 to 2.51), stroke (2.42, 2.17 to 2.71), ischemic stroke (2.33, 1.84 to 2.94), ischemic heart disease (1.61, 1.38 to 1.87), sudden cardiac death (1.88, 1.36 to 2.60), heart failure (4.99, 3.04 to 8.22), and peripheral arterial disease (1.31, 1.19 to 1.45).

AF, CKD and stroke

CKD increases the baseline risk of ischemic stroke in patients with AF[435]. 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, heart failure, 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 seven 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[437]. One study from Taiwan showed that the CHA_2DS_2-VASc score could adequately risk stratify for ischemic stroke amongst a haemodialysis population (c-index 0.682, superior to $CHADS_2$) [438].

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 antiplatelet therapy. The clinical bleeding risk scores (e.g., HAS-BLED, ORBIT, ATRIA) all include CKD measures as part of their score calculation[104]. 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 [439].

Fourth, there are virtually no randomized trial data of oral anticoagulation in severe CKD (creatinine clearance < 25-30 ml/min). Some observational data suggest that warfarin may be harmful in end stage renal disease (ESRD) patients on haemodialysis, 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 time in therapeutic range (TTR)[440-442].. 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%[440-442].

The latest systematic review and meta-analysis by Harel et al[443] 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 intracranial hemorrhage (hemorrhagic stroke; 4 studies; 15,726 participants; aHR, 1.93; 95% CI, 0.93-4.00) (e-Table 23). 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 to aspirin or no antithrombotic therapy, with no excess in serious bleeds (ICH) [247].

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[444]. Fortunately, the pivotal NOAC randomized trials have demonstrated non-inferiority of NOACs to warfarin among patients with creatinine clearance of 30-50 ml/min (and for apixaban 25-50 ml/min)[246].

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 creatine-clearance according to licensed indications [see Figure 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 CHA2DS2-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), we suggest using VKAs and selected NOACs (rivaroxaban 15mg QD, apixaban 2.5mg bid, edoxaban 30mg QD and (in USA only) dabigatran 75mg bid) with caution, based on pharmacokinetic data (ungraded consensus-based statement).**

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

54. **In end-stage renal disease (CrCl < 15 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 5mg 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.

AF WITH ASSOCIATED VALVULAR HEART DISEASE

A recent physician survey[445] reported marked heterogeneity in the definition of valvular and non-valvular AF and variable management strategies, including NOACs in patients with valvular heart disease (VHD) other than prosthetic heart valves or hemodynamically significant mitral stenosis. Whilst 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[446].

The use of the term non-valvular 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 VHD 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 VHD at higher risk compared with those without valvular disease, the efficacy and safety of NOACs versus warfarin is consistent in regardless of the presence or absence of VHD[240].

AF patients with mechanical heart valves should only be prescribed VKAs. Data from the only phase II trial of a NOAC, dabigatran, in patients with mechanical heart valves (RE-ALIGN trial) demonstrated inferior efficacy and more bleeding[447]. However,patients with bioprosthetic valves were included in the ARISTOTLE trial[448] (apixban) the ENGAGE AF-TIMI 48 trial[449] (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 (**E**valuated **H**eart valves, **R**heumatic or **A**rtificial) categorization in relation to the type of oral anticoagulation (OAC) use in patients with AF [see Summary Box]. 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 (TMVI, e.g., to include both MitraClip and Mitral valve replacement) are emerging as a possible therapeutic options[450], but more data are awaited especially in relation to OAC use. Also, EHRA Type I is broadly similar to the previously described MARM-AF[451].

Table 11. Summary box: *Evaluated Heart valves, Rheumatic or Artificial) categorization in relation to the type of oral anticoagulation (OAC) use 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 a NOAC', also taking into consideration CHA_2DS_2VASc 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 (TAVI)

EHRA, Evaluated Heart valves, Rheumatic or Artificial; NOAC, non-vitamin K antagonist oral anticoagulant; VHD, Valvular heart disease; VKA, vitamin K antagonist

Non-drug alternatives and perioperative considerations

Occlusion of the left atrial appendage 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 [452].

Left atrial appendage occlusion 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 an high risk of bleeding or in the presence of contraindications to OACs.

Two randomized studies evaluated the WATCHMAN (Atritech, Inc) device versus warfarin, the PROTECT-AF and the PREVAIL AF trials [453-459]. 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 [460]. The serious complication rate of around 7%, has been reported also for first or second generation Amplatzer occluders [461,462]. A recent systematic review network meta-analysis on the use of oral anticoagulants and 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 to placebo/control (Watchman Device OR, 95% CI: 0.35, 0.16-0.80).[463] 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, [460].

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 [464]. No randomized controlled study comparing this device with oral anticoagulation is currently available.

In addition, the role of LAAO devices in AF patients has also 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%/year) and are associated with a risk of ischemic stroke during follow-up[465,466].

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 [467,468]. These observations and the lack of a clear benefit on stroke prevention evident from a 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 [469,470].

Recommendations

55. **In patients with AF at high risk of ischaemic 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 ischaemic 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 oral anticoagulants 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 [471-473].

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 [474-476]. 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 post-operative 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 patients is receiving and creatinine clearance. Important differences exist between the management of patients treated with VKA or NOACs[476,477]. 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 ≤1.4 -1.5 the day before surgery or the same day of surgery[475]. 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 [476,477].

- **Evaluation of the need for bridging.** Pre-operative bridging can be considered in patients receiving VKA who are particularly high risk of TE (e.g., recent stroke, mechanical heart valve)[475]. In these cases, LMWH at therapeutic doses is usually prescribed starting 3 days before the procedure/intervention. Post-operative bridging includes administration of a LMWH when VKA is resumed in the post-operative period, with administration of both agents until achievement of a therapeutic INR.

  The role of bridging has been tested in a randomized trial, the BRIDGE trial (Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery) performed in patients on warfarin who were candidate to an invasive procedure (patients with mechanical valves were excluded)[478]. The risk of TE 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 post-operative 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 pre-operative 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 pre-operative management with bridging (Weak recommendation, low quality evidence).

59. In AF patients on antithrombotic prophylaxis with a NOAC, we suggest pre-operative 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 is 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,[479-484] medications used to treat AF, particularly OAC, and do not clearly comprehend the benefit/risk associated with stroke prevention regimens.[480-483,485-491] Although there is increasing advocacy from clinical guidelines[159,160] and expert consensus[488,492,493] 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[494] or Jessa Atrial Fibrillation Knowledge questionnaire[495]), 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 or not they wish to take OAC, and if they do, which OAC they would prefer.[488,489,496] 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 US found that most (87%) desired more information about AF and how to reduce their risk of AF-related stroke.[485] 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 healthcare providers,[479,485,497] and updated over time. Full details on shared decision-making, patient preferences and patient education/counseling are provided in the Online Supplement (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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4560 Table 1. PICO Questions
4561

	Section	Question	Patients	Intervention	Control	Outcomes	Methodology
	Burden of stroke in atrial fibrillation (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	N/A	N/A	Ischemic stroke Systemic thromboembolism (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	N/A	N/A	c-statistic NRI. IDI, DCA Absolute rates of ischemic stroke and TE	Cohort studies Clinical prediction rules
	Antithrombotic therapy						
2.1	**Patients with non-valvular AF**	What are the benefits and risks of different stroke prevention strategies?	Patients with non-rheumatic AF - low risk - intermediate risk - high risk (including prior stroke)	Vitamin K antagonist (VKA)	No VKA	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage	SR RCTs

						(subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	
2.1	**Patients with non-rheumatic AF (cont'd)**		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	
			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	SR RCTs Cohort studies

						intracerebral) - Major extracranial hemorrhage - MI - Vascular death	
			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
			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	Non-pharmacologic	VKA	- Death - All stroke	SR RCTs

				therapies - removal or ligation of left atrial appendage - surgical or catheter ablation - maze procedure		- Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death - procedural / surgical complications	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 (i.e., mitral stenosis)	Vitamin K antagonist (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
2.3	**Patients with prosthetic valves**	What are the benefits and risks of different stroke prevention strategies?	Patients with AF and prosthetic valves	Vitamin K antagonist (VKA)	No VKA	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral)	SR RCTs Cohort studies

						- Major extracranial hemorrhage - MI - Vascular death	
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 - MI - Vascular death	SR RCTs Cohort studies

3.3	**Transesophageal echocardiography (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	SR RCTs Cohort studies

						intracerebral) - Major extracranial hemorrhage - MI - Vascular death	
5.1	**Time within therapeutic range (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**	What are the	Patients with coronary	OAC + aspirin	OAC	- Death	

	coronary artery disease or peripheral arterial disease	benefits and risks of adding aspirin therapy to VKA therapy?	artery disease or peripheral arterial disease			- All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
5.3b	**Patients with AF presenting with acute coronary syndrome?**	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 PCI + stenting	OAC + aspirin + clopidogrel	Aspirin + clopidogrel	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage	SR RCTs Cohort studies

						- MI - Vascular death	
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 (e.g. maze procedure, catheter ablation, electrophysiology procedure, pharmacological)	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
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	SR RCTs Cohort studies

						intracerebral) - Major extracranial hemorrhage - MI - Vascular death	
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
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	Patients with AF on VKA therapy	N/A	N/A	-Fatal hemorrhage -Intracranial hemorrhage	Epidemiologic studies

		therapy?				(subdural, subarachnoid, intracerebral) -Major extracranial hemorrhage -Minor bleeding	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	N/A	N/A	c-statistic NRU, 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	N/A	N/A	Patient preferences Factors which affect patient preferences Quality of life	RCTs Observational studies

4562 Table 2. CHEST Grading System

4563

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.
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.

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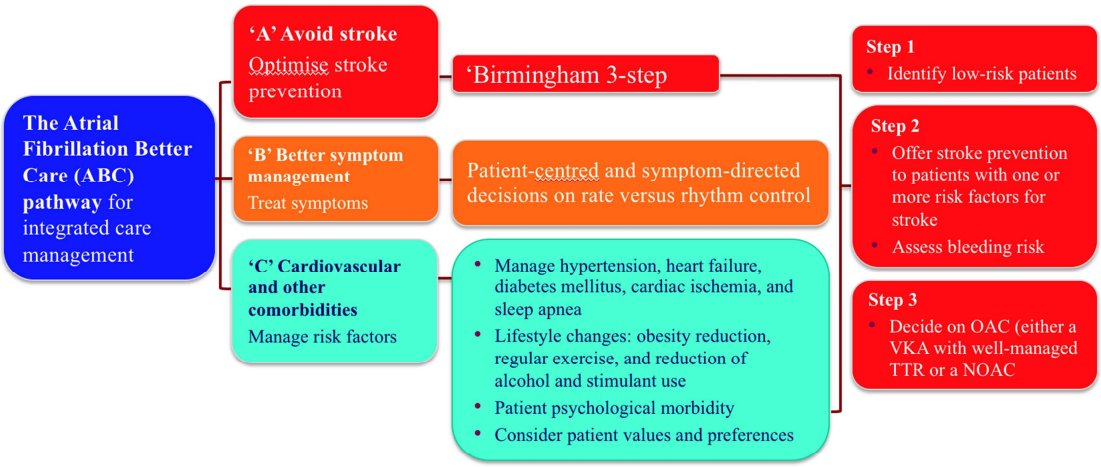
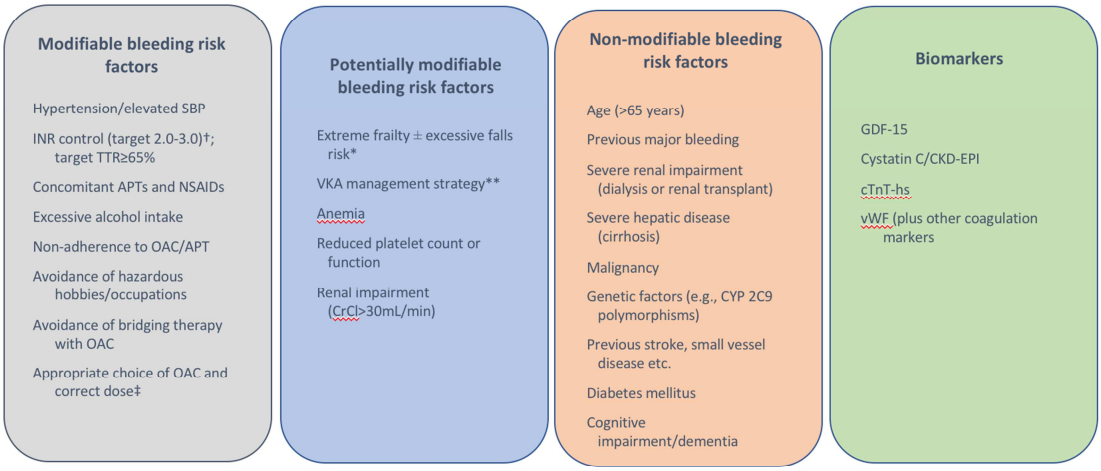


Figure 1 The Atrial fibrillation Better Care (ABC) Pathway of Integrated Care Management (from Lip et al 2017)[2].

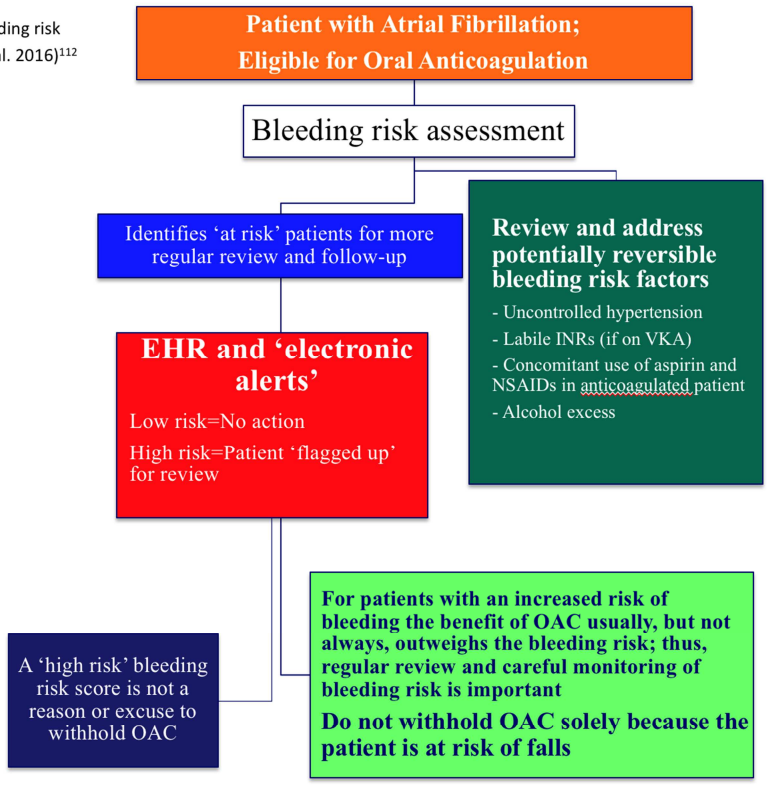
Figure 2: Risk factors for bleeding with oral anticoagulation (NOAC and VKA) and antiplatelet therapy

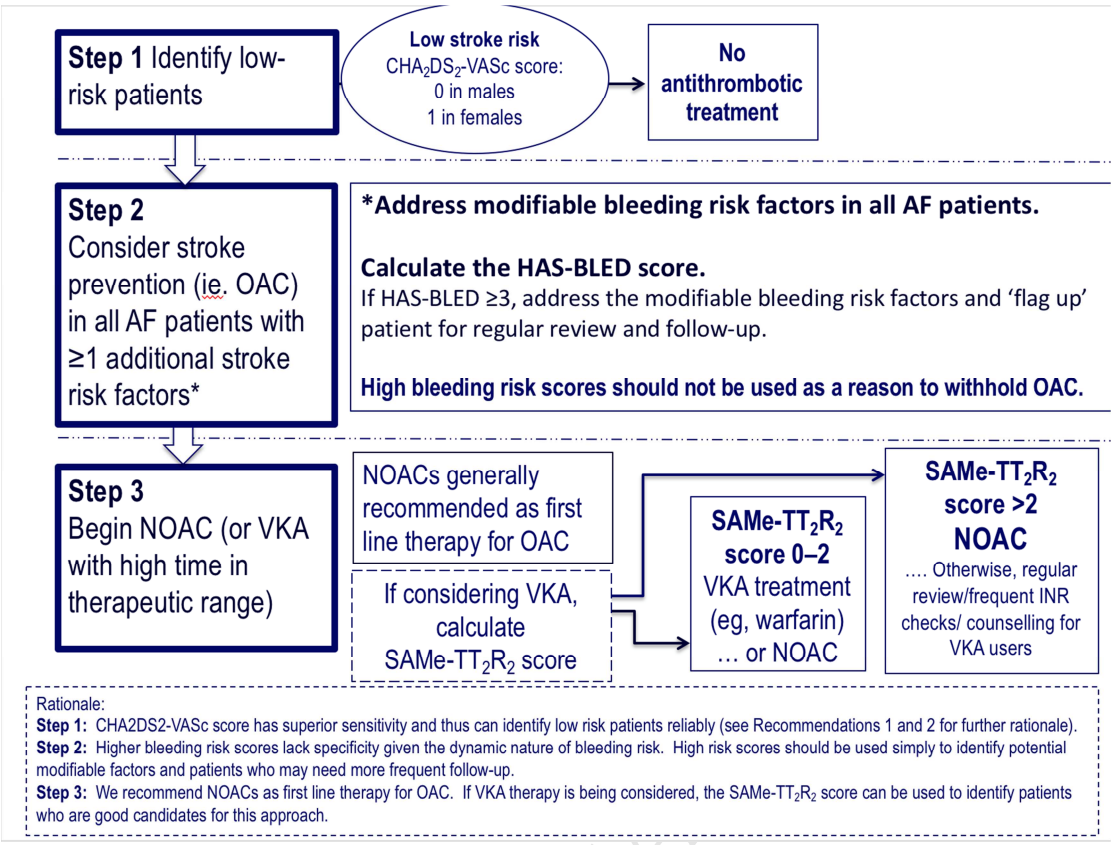


APT = anti-platelets; CrCl = creatinine clearance; cTnT-hs = high sensitivity Troponin T; GDF-15 = growth differentiation factor-15; INR = international normalised ratio; NSAIDs = non-steroidal anti-inflammatory drugs; OAC = oral anticoagulation; SBP = systolic blood pressure; TTR = time in the therapeutic range; vWF = von Willebrand Factor

†for patients receiving VKA treatment; ‡dose adaptation based on patient's age, body weight and serum creatinine; *walking aids; appropriate footwear; home review to remove trip hazards; neurological assessment where appropriate); ** increased INR monitoring, dedicated OAC clinics, self-monitoring/self-management, educational/behavioural interventions

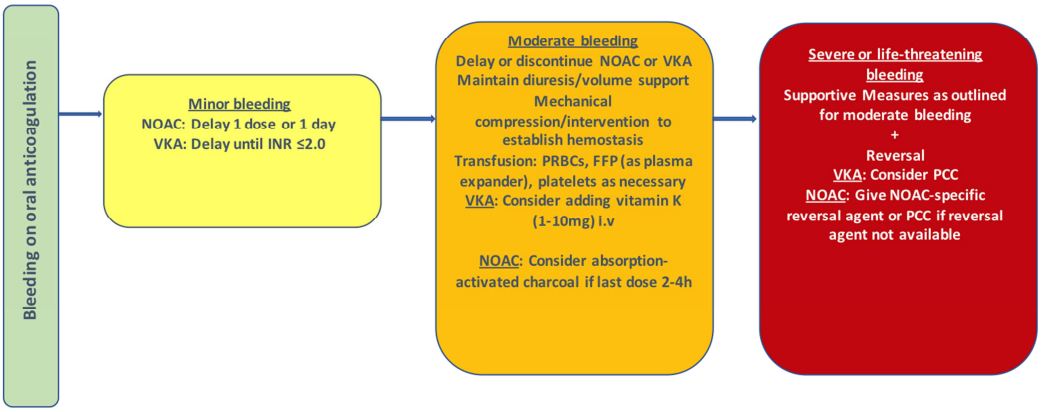
Figure 3: Practical application of bleeding risk assessment in AF patients (from Lip et al. 2016)[112]





Rationale:
Step 1: CHA2DS2-VASc score has superior sensitivity and thus can identify low risk patients reliably (see Recommendations 1 and 2 for further rationale).
Step 2: Higher bleeding risk scores lack specificity given the dynamic nature of bleeding risk. High risk scores should be used simply to identify potential modifiable factors and patients who may need more frequent follow-up.
Step 3: We recommend NOACs as first line therapy for OAC. If VKA therapy is being considered, the SAMe-TT_2R_2 score can be used to identify patients who are good candidates for this approach.

Figure 5: Management of patients with active bleeding on oral anticoagulation (NOAC and VKA)



FFP, fresh frozen plasma; h, hours; i.v., intravenous; NOAC, non-vitamin K antagonist oral anticoagulant; PCC, prothrombin complex concentrate; PRBC, packed red blood cells; VKA, vitamin K antagonist

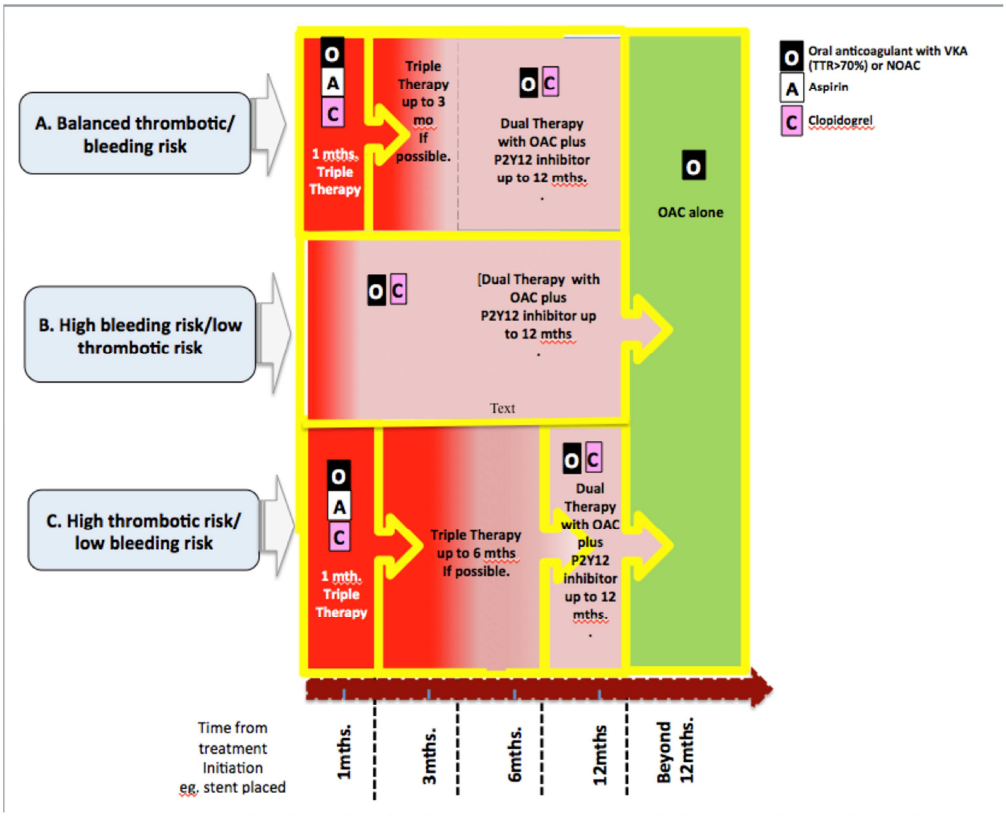
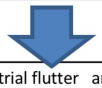


Figure 6. Management of oral antiplatelet therapy in patients with (A) balanced thrombotic bleeding risk, (B) low thrombotic–high bleeding risk, and (C) high thrombotic–low bleeding risk (adapted from Angiolillo et al. 2016)[282]

FLOW CHART for patient management in case of CIED detected AHRE	
Detection of AHRE	Patient with a CIED, no previous AF and detection of AHRE (≥5-6 min and >180 bpm)
	
Clinical evaluation of device data and evaluation of patient cardiac status and profile	Analysis of device electrograms (AF/atrial tachyarrhythmias confirmed? Artifacts excluded?)
	Clinical cardiological evaluation + 12-lead ECG
	Consideration for ECG recordings (Holter, patient operated devices) in specific cases (e.g. unavailable electrograms or unclear diagnosis at device electrograms analysis)
	Clinical risk stratification for stroke (CHA_2DS_2VASc score?
	
Clinical decision making and follow up	If diagnosis of AF or atrial flutter and intermediate (CHA_2DS_2VASc score =1 in males and =2 in females) or high risk (CHA_2DS_2VASc score ≥2 in males and ≥3 in females): -Monitoring of AHRE evolution (remote monitoring is advised) -Clinical follow up for evaluating if AHRE > 24 hours and/or clinical AF develops, as well as changes in patient status/clinical profile (e.g. heart failure) -Individual considerations for prescription of OAC considering overall AHRE burden and AHRE > 24 hours, individual CHA_2DS_2VASc, predicted risk benefit of OAC (specifically risk of major bleeding) and patient preferences

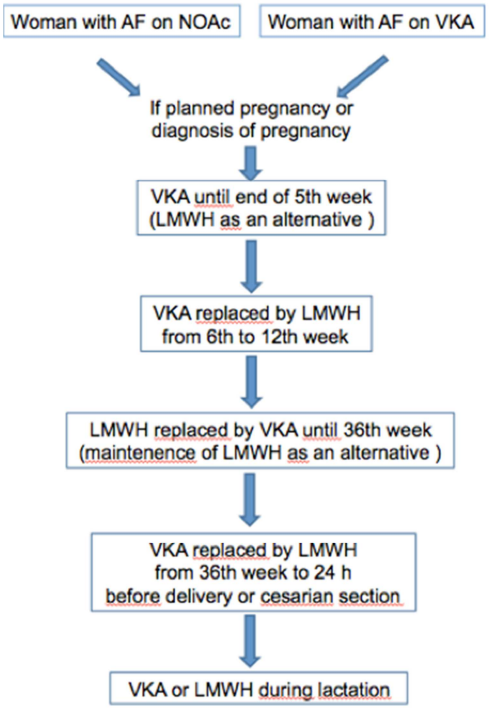


Figure 8. Suggested algorithm for the decision-making process in prescribing oral anticoagulant therapy in patients with various degrees of renal function impairment (from Lau et al 2016).[436]

Drug	CrCl ≥50 mL/min	CrCl 30-49 mL/min	CrCl 15-29 mL/min	CrCl <15 mL/min or ESRD on RRT
VKA	If TTR ≥70%	If TTR ≥70%	If TTR ≥70%	If TTR ≥70%
Dabigatran	150mg bid § (or 110mg bid)	150 mg bid (or non-US, 110mg bid) §	✖ (Outside US) 75mg bid in US§	✖
Rivaroxaban	20 mg qd	15mg qd	15 mg qd	✖
Apixaban	5mg bid*	5mg bid*	2.5mg bid	✖ (Outside US) 5mg bid in US only*
Edoxaban	60 mg q#	30mg qd	30mg qd	✖

- **Closely monitor renal function, especially in NOAC users.**
- **Schedule for frequent clinical follow-up, look for development of new cardiovascular risk factors, comorbidities.**
- **Reassess and address bleeding risk factors.**

*Use 2.5 mg BID if 2 of 3 of the following criteria are present: age >80 years old, weight <60 kg, serum creatinine >133 mmol/l.
§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.
#In the United States only, caution is advised where CrCl is >95 ml/min.

ANTITHROMBOTIC THERAPY FOR ATRIAL FIBRILLATION

Recommendations or Suggestions
1. For patients with AF, including those with paroxysmal AF, stroke risk should be assessed using a risk factor based approach, rather than an categorisation into low, moderate/high risk strata. We recommend use of the CHA2DS2VASc as a simple clinical based stroke risk score to initially identify 'low stroke risk' patients that 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 CHA2DS2VASc 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 CHA2DS2VASc 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 (personalised 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, 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 AF patient, bleeding tendency or predisposition (e.g. treat gastric ulcer, optimise 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 and 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 encounter.
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
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 (e.g. 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)
9. In patients with prior unprovoked bleeding, warfarin-associated bleeding, or at high risk of bleeding, we suggest apixaban, edoxaban, or dabigatran 110 mg (if available) may be considered as they demonstrated significantly less major bleeding compared with warfarin (Weak recommendation, very low quality evidence). Remark: In patients with prior gastrointestinal bleeding apixaban or dabigatran 110mg 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.
10.In patients with prior unprovoked bleeding, warfarin-associated bleeding, or at high risk of bleeding, we suggest apixaban, edoxaban, or dabigatran 110 mg (if available) may be considered 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 110mg 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.
11. 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 <65% - implement additional measures (more regular INR tests; review medication adherence/other factors known to influence INR control; education/counselling) to improve INR control or consider a NOAC. Remark: When possible, experienced specialized anticoagulation clinics should be utilized for VKA and INR management.
12. For patients with AF of greater than 48 hours or unknown duration undergoing elective electrical or pharmacologic cardioversion, we recommend therapeutic anticoagulation with well-managed VKA (INR 2-3) or a 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. 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 endothelisation, we suggest that a decision on whether a repeat TEE is performed should be individualized (ungraded consensus-based statement)
14. In AF patients presenting with an ACS and/or undergoing PCI/stenting, we recommend assessment of stroke risk using the CHA2DS2-VASc score (Strong recommendation, moderate quality evidence) Remark: All such patients are not 'low risk' and should be considered for concomitant OAC.
15. In AF patients presenting with an ACS and/or undergoing PCI/stenting, we recommend attention to modifiable bleeding risk factors, and assessment of bleeding risk using the HAS-BLED score is recommended (weak recommendation, low quality evidence).Remark: Where bleeding risk is high (HAS-BLED ,â•3), there should be regular review and follow-up.
16. 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 is recommended (weak recommendation, low quality evidence). Remark: Where bleeding risk is high (HAS-BLED ≥3), there should be more regular review and follow-up.
17. In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is high (HAS-BLED ≥3), we suggest triple therapy for one 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)
18. In AF patients requiring OAC undergoing elective PCI/stenting , where bleeding risk is unusually high and thrombotic risk low, we suggest considering OAC plus single antiplatelet (preferably clopidogrel) for 6 months, following which OAC monotherapy can be used (weak recommendation, low quality evidence)
19. 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)
20. 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).
21. 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).
22. 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 a NOAC at a dose licensed for stroke prevention in AF (weak recommendation, low quality evidence). Remark: Only Dabigatran 150mg bid or (not licensed in USA) 110mg bid or Rivaroxaban 15mg od are currently supported by clinical trial evidence. A NOAC based strategy has lower bleeding risk compared to a VKA-based strategy.
23. In AF patients in which aspirin is concomitantly used with OAC, we suggest a dose of 75-100mg od with concomitant use of PPI to minimize gastrointestinal bleeding (Weak recommendation, low quality evidence)
24. 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 110mg bid or 150 bid (without concomitant aspirin use) are available from the RE-DUAL PCI trial.
25. In patients in whom sinus rhythm has been restored, we suggest that long-term anticoagulation should be based on the patient's CHA2DS2-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).
26. In AF patients with acute ischaemic stroke, we suggest that very early anticoagulation (<48h) 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 ischaemic stroke because they appear to increase the risk of symptomatic intracranial haemorrhage without net benefit. The optimal timing of anticoagulation after acute ischaemic stroke is unknown.
27. In AF patients with acute stroke without contraindications, we suggest that long term oral anticoagulation is indicated (Strong recommendation, high quality evidence). Remark: The optimal timing of anticoagulation early after acute ischaemic stroke is unknown. Early use of NOACs shows promise but requires testing in randomised controlled trials.
28. In AF patients with acute ischaemic stroke, We suggest that anticoagulation should usually be started within 2 weeks of acute ischaemic 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 ischaemia, haemorrhagic 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 randomised trials, but shows promise in observational studies.
29. In patients with AF and high ischaemic stroke risk, we suggest considering anticoagulation with a NOAC after acute spontaneous ICH (which includes subdural, subarachnoid and intracerebral haemorrhages) 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 favourable 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, if available, MRI biomarkers including cerebral microbleeds) and the risk of ischaemic stroke Remark: The optimal timing of anticoagulation after ICH is not known, but should be delayed beyond the acute phase (~48 hours) and probably for at least ~4 weeks. Randomised trials of NOACs and left atrial appendage occlusion are ongoing.
30. In ICH survivors at high risk of recurrent ICH (e.g. those with probable cerebral amyloid angiopathy), we suggest considering left atrial appendage occlusion (ungraded consensus-based statement). Remark: Cerebral amyloid angiopathy should be diagnosed using validated clinico-radiological criteria.

Authors	COIs Relevant to Recommendation/Suggestion
Amitava Banerjee, MD	no relevant COIs
Giuseppe Boriani, MD, PhD	Received compensation for the following: Speaking Activities for Boehringer Ingelheim, Boston Scientific, Medtronic, St. Jude Medical; Advisory Committee for Biotronik.
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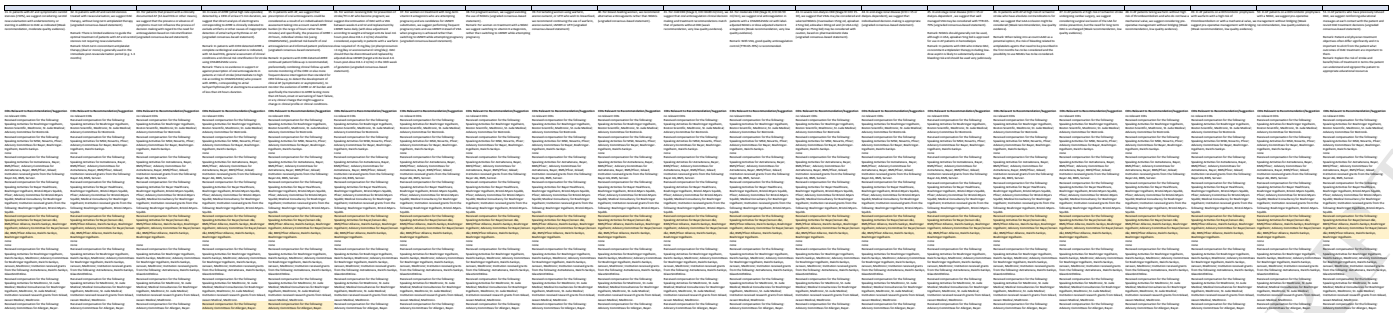
David Werring, PhD	Received compensation for the following: Advisory Committees for Allergan, Bayer.

Highlighted cell reflects panelist recused themselves from voting on specific recommendation



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e-Table 2. Implications of Strength of Recommendations for different users of guidelines

	Strong Recommendation	**Conditional (weak) Recommendation**
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but some would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

e-Appendix 1. Burden of Stroke in Atrial Fibrillation

Epidemiology and contemporary burden of ischemic stroke in AF

Atrial fibrillation (AF) is the commonest arrhythmia worldwide[1]. Health 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[2]. Age is an important risk factor for both AF and stroke and increasing age and demographic change are projected to drive future increases in AF and stroke[3]. Epidemiologic studies largely represent Western countries and Caucasian populations[4]. However, reported prevalence varies substantially by world region: India (0.1%)[5], Europe[6] and North America (1–2%)[7] and Australia (4%)[8], with pooled age- and sex-adjusted prevalence estimated as 2.8% (95% CI: 2.3–3.4%)[9]. Figure 1 illustrates the prevalence of AF in reported studies outside North America and Europe[4]. Recent data from rural India using the approved single-lead electrocardiography device, Alivecor, for 2 minutes on 5 consecutive days found a higher prevalence of AF (~5%) than prior studies[10]. As well as regional variation, reported prevalence is therefore higher with more rigorous screening methods to detect AF, and the low prevalence reported in certain world regions may well be an underestimate of true AF burden.

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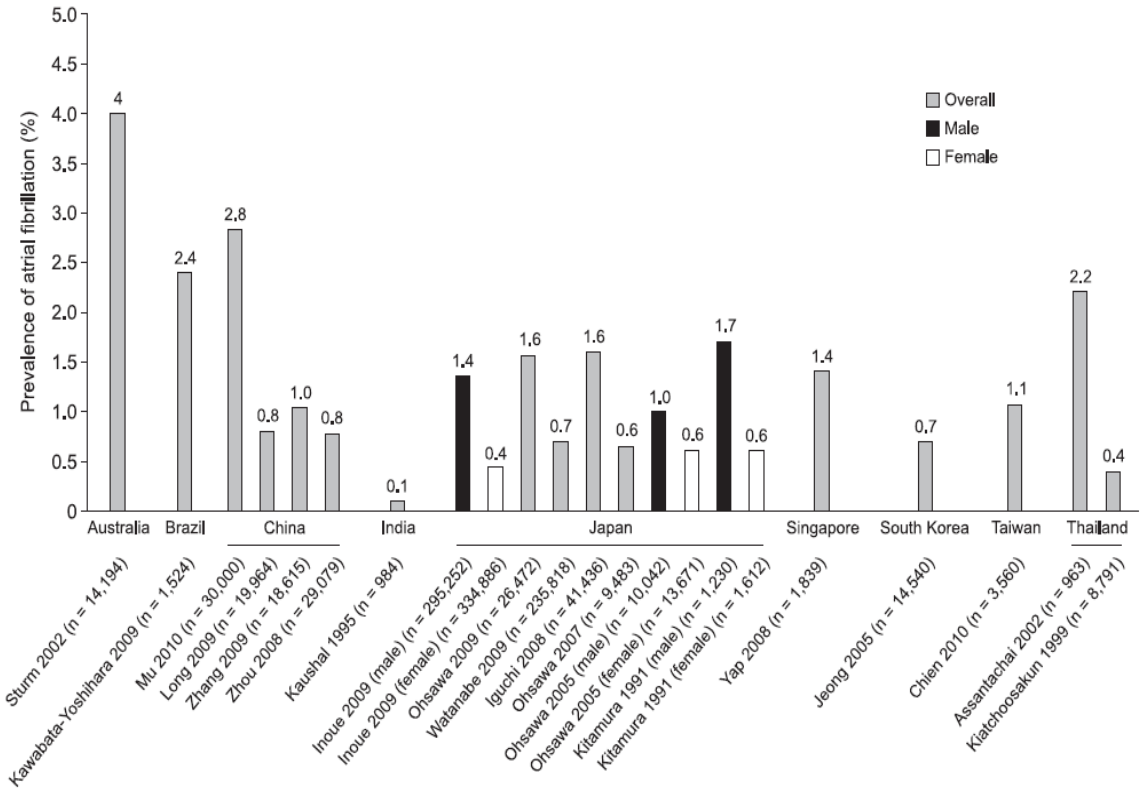

e-Figure 1. Prevalence of atrial fibrillation reported in community-based studies from countries outside North America and Europe. The overall prevalence is presented where available; otherwise, the prevalence in men and women is presented separately. (from Lip et al 2012)[4]

Individuals with AF have increased risk of serious complications, including stroke (4-5 fold increase)[11], heart failure (2-3 fold increase)[12] and mortality (2-fold increase)[12,13]. The Global Burden of Disease Study has shown that burden of disease in terms of age-adjusted disability-adjusted life years has increased by 19% between 1990 and 2010[1]. Patients with AF also experience higher rates of morbidity, hospital admissions, as well as 'premature' dementia[2,14]. Recent data from population-based studies and stroke registries demonstrate a high AF-attributable risk of stroke, especially in the elderly. At least one in 3 to 4 individuals with an ischemic stroke and over 80% of those with ischemic stroke of cardioembolic subtype, also has AF[15].

Mechanism of development of AF

A systematic review of the associations of 23 cardiovascular risk factors and incident AF was recently conducted, including both consented and electronic health record cohorts of 20,420,175 participants and 576,602 AF events respectively. It showed significant heterogeneity in AF definition, quality of reporting, and adjustment for other risk factors[16]. Hypertension, obesity, taller height and coronary heart disease showed consistent, direct associations with incident AF. Higher cholesterol (0.76 [0.59-0.98] to 0.94 [0.90-0.97]) and higher diastolic blood pressure (0.87 [0.78-0.96] to 0.92 [0.85-0.99]) showed some evidence of being associated with lower risk of incident AF. Evidence for the widely-held clinical opinion that alcohol use is associated with incident AF in the primary preventative setting was minimal. Several of the risk factors for incident AF are also risk factors for stroke in AF[16].

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Ethnic differences

Overall, non-white ethnicity shows evidence of association with lower risk of incident AF in a recent systematic review of electronic health record studies of AF. For African American, Asian, Chinese, Hispanic and Non-Hispanic Black (compared to White) ethnicities, significant inverse associations (from 0.35 [NR–NR] to 0.84 [0.82–0.85]). Only 1 country (USA) reported estimates for the association of ethnicity and incidence of AF[17]. There is likely to be considerable variation in prevalence, incidence and outcome by ethnicity and geographic region, but the number of studies to-date is limited. For example, incidence and long-term mortality following hospitalised AF is higher in Aboriginal versus non-Aboriginal individuals in Australia[18]. Variations which have been observed need to be validated. For example, the low reported prevalence rates of AF in India may represent under-diagnosis rather than true low rates[10].

The racial differences in co-morbidities in AF patients have been reported recently.[19,20] The mean age, sex, and prevalence of several stroke-related cardiovascular co-morbidities among different races in major surveys and cohorts are shown in e-Table 3.[21-37] The mean ages were 60 to mid-70, except in the Middle East (mean age 57 years). Males were generally predominant. Hypertension (52-85.2%) leads other risk factors and is equally distributed in different races. The prevalence rates of heart failure (18.9-47.5%) and diabetes (16-36.8%) show no major differences among races. With one exception in China,[26] coronary heart disease (CHD) seems more common in Caucasians and Middle East (16.0-36.4%) than in Asians (7.4-25.4%). Only 1 of the remaining 9 Asian cohorts has a prevalence rate of CHD more than 20%, while 7 of the 10 cohorts in Caucasians and the Middle East have CHD prevalence rate above 20%. A higher prevalence rate of previous history of stroke/transient ischemic attack (TIA) was found in Asians (10.2-23.1%) than in Caucasians and Middle East (9-19%). Eight out of the 10 Asian cohorts have a history of stroke/TIA above 15%, but only 1 of the 10 cohorts of Caucasians and the Middle East has a prevalence rate over 15%.

The annual risk of AF-associated stroke in Asians is higher than that in Caucasians.[20] In the recent AF cohorts from Taiwan[29], Hong Kong,[30] and Sweden[38], the annual stroke risk in antithrombotic-naïve patients who had a CHA_2DS_2-VASc score 0 was 1.1%, 2.4% and 0.2%, respectively. The similar trends were shown for CHA_2DS_2-VASc 1 (1.7%, 6.6%, and 0.6% respectively), CHA_2DS_2-VASc 2 (3.2%, 7.8%, and 2.2% respectively), CHA_2DS_2-VASc 3 (4.2%, 9.6%, and 3.2% respectively), and CHA_2DS_2-VASc 4 (5.8%, 11.6%, and 4.8% respectively). It has been suggested that the risk of stroke starts to increases at a younger age in Asians.[20] In a Taiwanese cohort, the risk of stroke was 1.78%/year in patients who had an age of 50-64 years and a CHA_2DS_2-VASc 0.[39] The risk exceeds the threshold for OAC use for stroke prevention. A modified CHA_2DS_2-VASc ($mCHA_2DS_2$-VASc) score has been proposed assigning one point for patients aged 50 to 74 years.[40] The $mCHA_2DS_2$-VASc score performed better than CHA_2DS_2-VASc score in predicting ischemic stroke assessed by C indexes and net reclassification index. For patients having an $mCHA_2DS_2$-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 non-treatment. Net clinical benefit analyses also favored the use of warfarin in different weighted models. These findings suggest that the age threshold may need to be reset in East Asians.[40]

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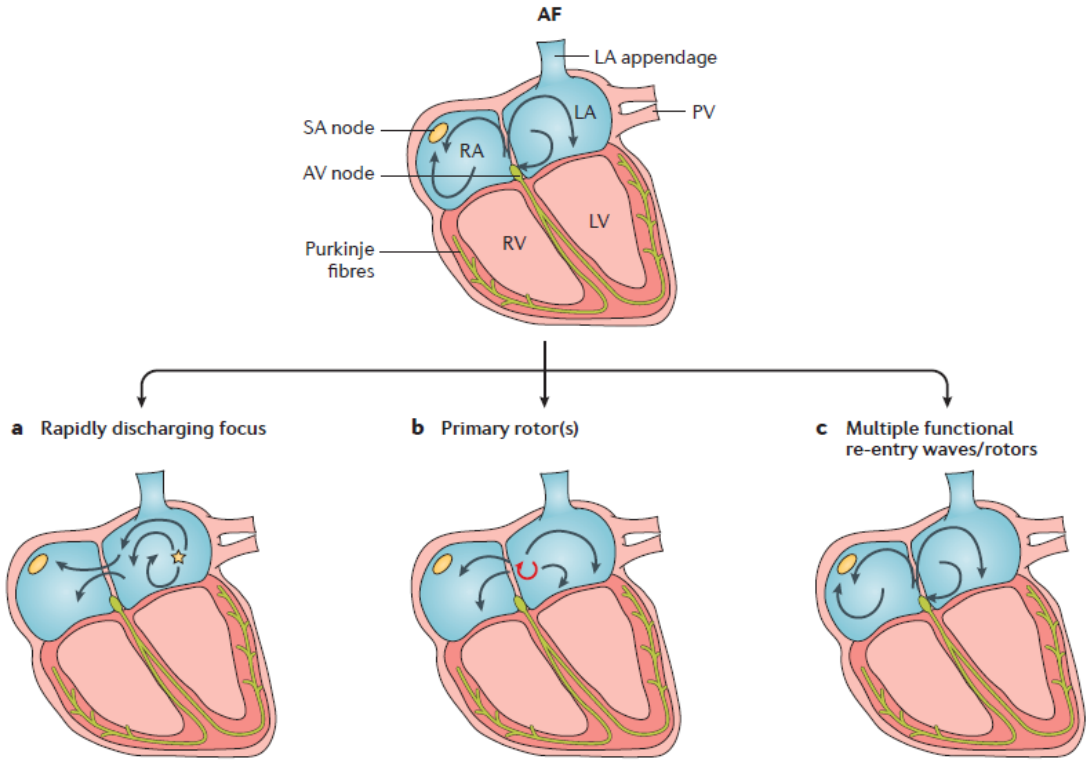
e-Table 3. Co-morbidities of AF in different races in major surveys and cohorts

	Asians										**Caucasians**									**Middle East**
Survey/ cohorts	RECORD AF AP [21]	RELY AF Southeast Asia [22]	GARFIELD East and Southeast Asia [23]	J-Rhythm [24]	Fushimi [25]	China [26]	CAFR [27]	GLORIA 1 Chinese [28]	Taiwan [29]	HK [30]	Euro Heart Survey [31]	RECORD AF [32]	ORBIT AF [33]	RELY AF West Europe [22]	EORP AF [34]	PREFER [35]	GARFIELD, other region excluding East and South East Asia [23]	GLORIA I Europe [28]	SPRINT [36]	GULF SAFE [37]
Age (mean)	64	69.5	67.1	69.7	74.2	75	65.8	69	72.0	76.9	66	66	75	69.4	68.8	71.5	71.3	71	75.7	57
Female(%)	40	44.6	39.8	31.1	40.7	27.1	40.4	42.8	46.0	52.1	43	43	42	38.8	40.4	39.9	44.5	50.5	44.7	48
CHD(%)	19	10.9	7.4	11.6	15.0	59.4	7.8	25.4	15.3	18.2	32	18	32	18.2	36.4	23.4	16.0	20.3	25.1	28
Diabetes(%)	18	29.2	23.5	22.1	23.2	36.8	24.5	19.5	26.9	22.0	18	16	29	17.1	20.6	22.4	23.7	27.1	29.7	30
HF(%)	25	26.3	26.6	34.4	27.9	21.2	18.9	24.7	38.7	22.8	33	26	32	21.2	47.5	21.3	20.8	22.3	18.8	27
HT(%)	58	64.1	73.1	71.1	60.6	72.5	66.1	70.1	62.9	54.7	63	68	83	59.9	70.9	72.0	82.0	85.2	73.6	52
Stroke/ TIA(%)	13	22.1	15.3	17.3	21.8	20.2	17.0	10.2	20.5	23.1	9	10	16	12	10.5	8.4	13.7	10.7	15.0	13

Pathophysiology – a brief overview
AF is characterised by rapid, uncoordinated atrial activity, caused by: (a) a rapidly discharging atrial focus, (b) a primary re-entrant rotor, or (c) multiple functional re-entry circuits[4] (figure w3). The initiation and perpetuation of AF needs both "triggers" for its onset and a "vulnerable substrate" for its maintenance. "Triggers" of focal spontaneous firing typically arise from the pulmonary veins[41], but can also emanate from other foci[42]. The 'vulnerable substrate' maintains the arrhythmia, dependent on cardiac and non-cardiac risk factors, including genetic pre-disposition, cardiac remodelling due to underlying heart disease, autonomic imbalance and thyroid dysfunction.



e-Figure 2. Mechanisms that can maintain atrial fibrillation (from Lip et al 2016[4]).
AF, atrial fibrillation; AV, atrioventricular; LA, left atrium; LV, left ventricle; PV, pulmonary vein; RA, right atrium; RV, right ventricle; SA, sinoatrial.

Although the micro-pathophysiology has been relatively well-established, the epidemiology of how risk factors individually or in combination, create the "vulnerable substrate", is relatively unknown. Until the interplay of these risk factors is better understood, primary prevention strategies for AF are likely to be restricted, despite development of risk prediction tools for AF. Although currently primary prevention strategies for AF have not been conclusively proven in randomized trials, opportunistic screening is the recommended strategy to detect AF at population-level[43].

Echocardiographic risk factors for ischemic stroke in AF
Underlying heart disease, whether as a result of hypertension, coronary artery disease or heart failure, is important in the aetiology and prognosis of AF. Therefore, it is not surprising that echocardiographic characteristics have been associated with risk of ischemic stroke in AF. 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 association between transthoracic echocardiographic (TTE) parameters and ischemic stroke.

In summary, there are small-scale studies to suggest a role for various measures (LA and LV size, volume and strain) on TTE. However, there are very limited data to suggest that there would be any incremental benefit in risk prediction, and moreover there is no evidence that management (in terms of OAC) would be changed[44]. In the recent ENGAGE AF-TIMI trial, larger LV size and higher filling pressures (measured by E/e' ratio) were significantly associated with increased risk for death, but neither left atrial nor LV measures were associated with thromboembolic risk[45]. In patients undergoing transesophageal echocardiography (TEE), LA appendage thrombi[46] and LA spontaneous echo contrast[47] are both associated with increased thromboembolism, but the same limitations as for TTE parameters apply[44]. In terms of risk stratification, the role of echocardiography is currently restricted to the inclusion of heart failure (left ventricular systolic dysfunction) in the CHA_2DS_2-VASc score[48].

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e-Table 4. Key evidence concerning transthoracic echocardiographic parameters and prediction of stroke and thromboembolism in patients with non-valvar AF. Adapted from Providencia et al 2013[44]

Study	Study design and setting	Main findings
The Stroke Prevention in Atrial Fibrillation Investigators (1992)[49]	Cohort n=568 Non-rheumatic AF Mean follow-up, 1.3 years	14 transthoracic echocardiographic variables were assessed for predicting ischemic stroke or systemic embolism. Only LA size (measured on M-mode echocardiography) and depressed LVEF were independent predictors of thromboembolism on multivariate analysis and improved risk stratification when combined with three clinical risk factors: history of hypertension, recent congestive heart failure, and previous thromboembolism
Osranek *et al.* (2005)[50]	Cohort n=45 Lone AF Mean follow-up, 27 years	Individuals with indexed LA volume ≥ 32 mL/m^2 had worse event-free survival (HR, 4.46; P = 0.005) Cerebral infarction occurred in 7 patients, all with indexed LA volumes ≥ 32 mL/m^2
Lee *et al.* (2008)[51]	Cross-sectional n=330 Persistent AF and preserved LVEF	E/E' ratio was independently associated with ischemic stroke on multivariate analysis
Shin *et al.* (2010)[52]	Cohort n=148 AF and heart failure with preserved LVEF Median follow-up, 27 months	S' and E', particularly when combined, were independent predictors of a composite of cardiovascular death, recurrent heart failure, and ischemic stroke
Azemi *et al.* (2012)[53]	Case-control n=57 in each group Nonvalvular AF $CHADS_2$ score ≤ 1 before index event	Patients with stroke presented reduced peak negative and peak positive LA strain values, when compared with controls
Su et al. (2013)[54]	Cohort 196 patients with persistent AF Mean follow-up, 21 months	Global left ventricular longitudinal systolic strain (GLS) was independently associated with adverse CV events including stroke in multivariate models.

LVEF, Left ventricular ejection fraction.

Biomarkers

The role of biomarkers in stroke/thromboembolism in AF has been extensively investigated. e-Table 5 summarizes important studies involving biomarkers. Although several biomarkers of prothrombotic state and of endothelial dysfunction have shown associations with stroke and thrombosis, both study design and scale of the studies limit possible conclusions.

Caveats with the use of biomarkers include 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 non-specific for a particular endpoint, and can be equally predictive not only of stroke but bleeding, death, hospitalization, heart failure etc., as well as non-cardiac conditions e.g., glaucoma.

The importance of biomarkers probably lies in the CHA_2DS_2VASc=0-2 group (currently without anticoagulation) where they may influence the decision to anticoagulate, yet there is a paucity of data available in these patients. There are several other hurdles including variations in availability in healthcare systems, biomarker assays, access to laboratories, biomarker 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.

The disease burden-oriented school of thought states, "Research resources should not be allocated disproportionately to emerging novel risk factors that may account for up to only 20% of all strokes at the expense of researching the determinants of the relatively few established causal factors that account for up to 80% of all strokes." [55] Any biomarker, whether blood, urine or imaging (cardiac, cerebral or otherwise) will always improve on risk prediction based on clinical factors, but this needs to be balanced against the practical usefulness, cost and daily applicability for everyday clinical practice.

e-Table 5. Biomarkers in prediction of various thromboembolic events in patients with atrial fibrillation.

Study, Year	***Participants***	***Biomarker***	***Investigation***
Heppell et al.[56] 1997	*109 (19 with left atrial thrombosis)*	*BTG, vWF*	*Association with presence of left atrial thrombosis (BTG: p=0.002; vWF: p=0.04; LAA velocity: p=0.001)*
Mondillo et al.[57] 2000	*45 chronic AF, 35 control*	*vWF, thrombomodulin*	*Higher levels in chronic AF; association with a prothrombotic state and endothelial dysfunction, coagulation factors and left atrial dimension. (Plasma fibrinogen: p<0. 005; platelet factor 4: p<0.001; thromboglobulin: p<0.001; D-dimer: p<0.03, tPA: p<0.006, plasminogen activator inhibitor: p<0.04; vWF: p<0.0001 and soluble thrombomodulin: p<0.03)*
Conway et al.[58] 2003	*994 AF patients taking aspirin*	*vWF, P-selectin*	*Rise in vWF was predictive of stroke and vascular events. After adjustment for covariates, vWf was an independent predictor of vascular events (RR 1.2 [95% CI, 1.0-1.4] per 20 IU/dL increase in vWf; p=0.02), but not stroke.*
Conway et al.[59] 2004	*106 AF; 41 control*	*IL-6, CRP, TF*	*Higher levels in AF patients; TF associated with stroke risk (p = 0.003)*
Heeringa et al.[60] 2006	*162 AF, 324 control*	*P-selectin*	*Association with cardiac mortality in AF (RR 1.27; 1.08-1.50, per 5-unit increase)*
Nozawa et al.[61] 2006	*509*	*D-dimer*	*Thromboembolic risk in patients without the clinical risk factors was quite low (0.7%/year) when D-dimer was < 150*

Study, Year	Participants	Biomarker	Investigation
			ng/ml, but not low (3.8%/year) when D-dimer was >or==150 ng/ml. Association with thromboembolic events even in AF patients on anticoagulation.
Ferro et al.[62] 2007	285	CD-40 ligand	Predictor of vascular events (stroke and myocardial infarct): HR 4.63, 1.91–11.1; p=0.001
Lip et al.[63] 2007	880	hsCRP	Correlation with stroke risk factors and prognosis (mortality: 0.001, cardiovascular events: p=0.05)
Kurl et al.[64] 2009	958 men	NT-proBNP, NT-proANP	Predictor for stroke (RR 1.35; 95% CI 1.01-1.84, p=0.049) and AF in The multivariable adjusted risk was for any stroke and 1.30-fold (95% CI 0.90 to 1.91, p = 0.0150) for ischemic stroke for each log-transformed SD (0.240 pmol/l) increment in NT-proBNP.
Pinto et al.[65] 2009	373	TNF-a, IL-6, vWF	Predictor for new-onset stroke in persistent AF
Yuce et al.[66] 2010	205 chronic AF	MPV	MPV is not related with left atrial thrombus in patients with chronic AF
Sadanaga et al.[67] 2011	261	BNP	Association with thromboembolic events in patients with AF during oral anticoagulant therapy
Hijazi et al.[68] 2012	6 189	NT-proBNP, Troponin I	Association with risk for stroke and mortality

AF = atrial fibrillation; BTG = β-thromboglobulin; CHF = chronic heart failure; CRP = C-reactive protein; HF = heart failure; hsCRP = highly sensitive C-reactive protein; IL = interleukin; LAA = left atrial appendage; MMP = metallopeptidase; MPV = mean platelet volume; NT-proANP = N-terminal prohormone of ANP; NT-proBNP = N-terminal prohormone of BNP; OAC = oral anticoagulants; RR = relative risk; SPAF III = Stroke Prevention in Atrial Fibrillation III; TF = tissue factor; TNF = tumor necrosis factor; von Willebrand factor(vWF). (From Szymanski et al 2015[69])

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e-Table 6. Comparison of features included in risk stratification schemes

Study	Age (yrs)	HTN	DM	Prior Stroke or TIA	Female Sex	Heart Failure	Coronary Artery Disease	Systolic BP	Abnormal LV Function	Other
Atrial Fibrillation Investigators (1994)[70]	≥65	+	+	+						
Stroke Prevention in Atrial Fibrillation Investigators (1995) [71]	>75*	+		++	++*	++		>160	++	
European Atrial Fibrillation Trial Investigators (1995)**[72]				+				>160		
Atrial Fibrillation Investigators (1998)[73]	>65	+	+	+					+	
Stroke Prevention in Atrial Fibrillation Investigators (1998)[73]	>75#	+	+	++	++#			>160		
$CHADS_2$ (2001)[74]	≥75	+	+	++		+				
American College of Chest Physicians (2001)[75]	≥65 >75	++	+	++		++	+		++	
Framingham Heart Study (2003)[76]	+		+	+	+			+		
van Walraven et al. (2003)[77]		+	+	+			+	+		
American College of Chest Physicians (2004)[78]	≥65 >75	++	++	++		++			++	
Birmingham/NICE (UK)(2006)[79]	≥65	+	+	++		++	+		++	
ACC/AHA/ESC Guidelines (2006)^[80]	≥75	+	+	++	^	+	^		+	
American College of Chest Physicians (2008)[81]	≥75	+	+	++		+				
CHA_2DS_2-VASc 2010[82]	>65	+	+	++	+	+	∞	+	+	
American College of Chest Physicians (2012)[83]	≥75 (±65-74)	+	+	++	±	+	±Vascular disease			
ESC 2012[84]	>65	+	+	++	+	+	∞	+	+	Stepwise, to initially identify low risk

R_2CHADS_2 (2013)[85]	≥75	+	+	++		+				Renal dysfunction Ie. CrCl<60
QStroke (2013)[86]	Range 25-84	+	+		Separate models for M and F		CHD	+	CHF	Ethnicity; Deprivation score; Smoking; TC:HDL; BMI; FH; RA; CKD; Valvular HD
ATRIA (2013)[87]	Range <65 to ≥85	+	+	Separate models for 1° and 2° prevention	+	+				Proteinuria; eGFR<45ml/min
NICE2014[88]	>65	+	+	++	+	+	∞	+	+	Stepwise, to initially identify low risk
AHA/ACC/HRS 2014[87]	>65	+	+	++	+	+	∞	+	+	Categorised, based on CHA_2DS_2-VASc
CHADS65 (2014 CCS algorithm)[89]	≥65	+	+	+		+				
ABC-Stroke (2016)[90]	44-90			+						Biomarkers (NT-ProBNP, hs Troponin)
ESC 2016[91]	>65	+	+	++	+	+	∞	+	+	Categorised, based on CHA_2DS_2-VASc risk factors (not score)

e-Table 7. Comparison of Stroke Risk Schema – additional information

Author/Study	Cohort	Schemes compared	Events	Findings	Comments
ABC-stroke Hijazi et al 2016[90]	Trial cohorts (ARISTOTLE and STABILITY)	ABC-Stroke, CHA_2DS_2-VASc	Stroke/SE	The ABC-stroke score yielded higher c-indices than CHA_2DS_2-VASc in both the derivation cohort (0.68(95%CI 0.65, 0.71) vs. 0.62 (0.60, 0.65), P< 0.001) and external validation cohort (0.66 (0.58, 0.74) vs. 0.58 (0.49,0.60), P < 0.001).	Developed and internally validated in 14 701 anticoagulated trial patients with biomarkers levels determined at baseline, median follow-up of 1.9 years. External validation in 1400 AF patients (mixed OAC/non-OAC), median follow-up 3.4 years. NB all patients in the derivation cohort had elevated risk to get into the ARISTOTLE trial, and similar elevated risk scores in the STABILITY CAD trial
Aakre [92]	longitudinal community-based cohort study from Olmsted County	8 Schemes compared ((AF investigators, SPAF, NICE guidelines, ACC/AHA/ESC guideline, ACCP Guideline	Ischemic stroke/SE	**High risk:** The Stroke Prevention in Atrial Fibrillation (SPAF; hazard ratio, 2.75; *c*=0.659), $CHADS_2$-revised (hazard ratio, 3.48; *c*=0.654), and $CHADS_2$-classical (hazard ratio, 2.90; *c*=0.653) risk schemes were most accurate in risk stratification. **Low-risk cohort** within the CHA_2DS_2-VASc scheme had the lowest event rate among all low-risk cohorts (0.11 per 100 person-years), but only 5% of the population were classified as low risk,	A direct comparison of 9 risk schemes reveals no profound differences in risk stratification accuracy for high-risk patients. Accurate prediction of low-risk patients is perhaps more valuable in determining those unlikely to benefit from OAC therapy. CHA_2DS_2-VASc performed best, but only small proportion were classified as low risk
Abraham[93]	longitudinal cohort of 5981 women with AF not on warfarin at baseline (mean age 65.9 years) enrolled in the Women's Health Initiative and followed for a median of 11.8 years.	CHADS2 CHA_2DS_2-VASc	Ischemic stroke/TIA	CHA_2DS_2-VASc had a higher c statistic than $CHADS_2$: 0.67 (95% CI, 0.65-0.69) versus 0.65 (95% CI, 0.62-0.67), P <.01. For $CHADS_2$ scores <2, stroke risk almost doubled with every additional CHA_2DS_2-VASc point. Possible that some women were started later on warfarin. As all cohort were women, CHA_2DS_2-VASc =1 was solely female sex	Both CHADS2, and CHA_2DS_2-VASc are predictive of stroke risk in postmenopausal women with AF. CHA_2DS_2-VASc further risk-stratifies patients with a $CHADS_2$ score <2.
Abu-Assi [94]	186 patients with non-valvular AF and off anticoagulant therapy	4 risk schemes: The Framingham, the 8th ACCP, the ACC/AHA/ESC 2006, and the CHA2DS2-VASc.	Ischemic stroke/SE	c-statistic ranged from 0.59 [for CHA_2DS_2-VASc] to 0.73 [for Framingham]. CHA_2DS_2-VASc categorized the fewest patients into low and intermediate-risk categories, whereas the Framingham schema assigned the highest patients into low-risk strata. No TE events in the low and intermediate-risk categories using CHA_2DS_2-VASc , whereas the most schemes assigned patients into intermediate-risk category had an event rate ranging from 2.5 (ACC/AHA/ESC and 8th ACCP schemes) to 6% (Framingham). The negative predictive value of TE events was of 100% for the no high-risk patients using CHA_2DS_2-VASc .	Small study, with few events, and only 6 patients with CHA_2DS_2-VASc score of 0 or 1. Therefore caveat on conclusion that CHA_2DS_2-VASc risk stratification schema may be better in discriminating between patients at a low and intermediate risk of TE complications.

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Abumuaileq[95]	non-anticoagulated cohort of 154 patients; 911 patients formed the cohort of patients on VKA	CHA_2DS_2-VASc , R2CHADS2 and ATRIA (used the conventional ATRIA cut-off of 0-5, and did not explore lower cut points)	Ischemic stroke/SE	During 11 ± 2.7 months. CHA_2DS_2-VASc showed significant association with TE: hazard ratio (HR) = 1.58 [95%CI 1.01–2.46), but R_2CHADS_2 and ATRIA did not (HR = 1.23 (95 % CI 0.86–1.77) and 1.20 (95 % CI 0.93–1.56), respectively. In the anticoagulated cohort, after 10 ± 3 months of follow up, the three scores showed similar association with TE risk: HR = 1.49 (95 % CI 1.13–1.97), 1.41 (95 % CI 1.13–1.77) and 1.37 (95 % CI 1.12–1.66) for CHA_2DS_2-VASc , R_2CHADS_2 and ATRIA, respectively.	Small study with only 9 TE events in total and only 23 patients in CHA_2DS_2-VASc low risk group. CHA_2DS_2-VASc better association with TE events than R_2CHADS_2 and ATRIA scores in the non-anticoagulated cohort. CHA_2DS_2-VASc and R_2CHADS_2 can identify patients at truly low risk regardless of the anticoagulation status.
Chao [29]	186,570 AF patients without antithrombotic therapy Taiwan Health Insurance database	CHA2DS2VASc, ATRIA (used the conventional ATRIA cut-off of 0-5, and did not fully explore lower cut points. There was a pointwise gradation of risk from ATRIA score 0 to 5)	Ischemic stroke	**High risk:** CHA2DS2-VASc score performed better than ATRIA score in predicting ischemic stroke as assessed by c-indexes (0.698 vs. 0.627, respectively; p < 0.0001). CHA2DS2-VASc score improved the net reclassification index by 11.7% compared with ATRIA score (p < 0.0001). **Low risk:** Among 73,242 patients categorized as low-risk on the basis of an ATRIA score of 0 to 5, the CHA2DS2-VASc scores ranged from 0 to 7, and annual stroke rates ranged from 1.06% to 13.33% at 1-year follow-up. c-index of CHA2DS2-VASc score (0.629) was significantly higher than that of the ATRIA score (0.593) in this "low-risk" category (p < 0.0001).	Patients categorized as low-risk by use of the ATRIA score were not necessarily low-risk, and the annual stroke rates can be as high as 2.95% at 1-year follow-up. ATRIA score may perform better if a lower cut point is chosen CHA2DS2-VASc score of 0 had a truly low risk of ischemic stroke, with an annual rate of approximately 1%
Chao [96]	186,570 AF patients without antithrombotic therapy Taiwan Health Insurance database	CHA2DS2VASc, CHADS2	Ischemic stroke	CHA2DS2VASc, score performed better than CHADS2 score in predicting ischemic stroke assessed by c-indexes (0.698 vs 0.659, P o.0001). Among 25,286 patients with a CHADS2 score of 0, the CHA2DS2VASc, score ranged from 0 to 3, and the annual stroke rate ranged from 1.15% to 4.47%.	Very large study with high numbers of events. CHADS2 score of 0 were not necessarily "low risk," and the annual stroke rate can be as high as 4.47% when further stratified by CHA2DS2VASc. CHA2DS2VASc score of 0 had a truly low risk of ischemic stroke, with an annual rate around 1.15%.

Chen [97]	Systematic review and meta-analysis of the predictive abilities of CHADS2 and CHA2DS2VASc	CHA2DS2VASc, CHADS2		Unsuitable to perform a direct meta-analysis because of high heterogeneity. When analyzed as a continuous variable, the C-statistic ranged from 0.60 to 0.80 (median 0.683) for CHADS2 and 0.64–0.79 (median 0.673) for CHA2DS2VASc (no significant difference). The average ratio of endpoint events in the low-risk group of CHA2DS2VASc was less than CHADS2 (0.41% *vs*. 0.94%, $P < 0.05$). The average proportion of the moderate-risk group of CHA2DS2VASc was lower than CHADS2 (11.12% *vs*. 30.75%, $P < 0.05$).	The C-statistic suggests a similar clinical utility of the CHADS2 and CHA2DS2VASc scores in predicting stroke and thromboem- bolism, but CHA2DS2VASc has the important advantage of identifying extremely low-risk patients with AF, as well as classi- fying a lower proportion of patients as moderate risk.
Coppens[98]	Trial cohort from AVERROES and ACTIVE all treated with aspirin and some with concomitant clopidogrel	CHA2DS2VASc, CHADS2		Of 4670 patients with a baseline CHADS2 score of 1, 26% had a CHA2DS2VASc score of 1 and 74% had a score of ≥2. After 11414 patient-years of follow-up, the annual incidence of SSE was 0.9% (95% CI: 0.6–1.3) and 2.1% (95% CI: 1.8–2.5) for patients with a CHA2DS2VASc score of 1 and ≥2, respectively. The c-statistic of the CHA2DS2VASc score was 0.587 (95% CI: 0.550–0.624). Age 65 to <75 years was the strongest of the three new risk factors in the CHA2DS2VASc score	The CHA2DS2VASc score reclassifies 26% of patients with a CHADS2 score of 1 to a low annual risk of SSE of 1% and age 65-74 is the major contributor.
Guo et al [26]	1034 AF patients (27.1% female, median age 75; 85.6% non-anticoagulated) with mean follow-up of 1.9 years. PLA General Hospital electronic medical database 2007-2010	CHA2DS2VASc, CHADS2	Stroke/TE	In patients with a CHADS2 or CHA2DS2-VASc score=1, the rate of stroke/TE was 2.9% and 0.9% respectively. In patients at "high risk" (scores≥2), this rate was 4.6% and 4.5%, respectively. The c-statistics for predicting stroke/TE with CHADS2 and CHA2DS2-VASc were 0.58 (p = 0.109) and 0.72 (p <0.001), respectively. Compared to CHADS2, the use of CHA2DS2-VASc would result in a Net Reclassification Improvement (NRI) of 16.6% (p=0.009) and an Integrated Discrimination Improvement (IDI) of 1.1% (p = 0.002). Cumulative survival of the patients with a CHA2DS2-VASc score ≥ 2 was decreased com- pared to those with a CHA2DS2-VASc score 0–1 (p < 0.001), but the CHADS2 was not predictive of mortality.	Vascular disease was a strong independent predictor of stroke/TE in Chinese patients with AF, and CHA2DS2-VASc. superior to CHADS2 at low scores.

Hippisley-Cox [86]	1 897 168 eligible patients from 451 general practices in England and Wales contributing to the national QResearch database. Excluded patients with prior stroke or TIA, and those on anticoagulant	QStroke CHA2DS2VASc, CHADS2	Stroke or TIA	AF patients at baseline: C statistic in men was 0.71 (0.69-0.73) for QStroke, 0.67 (0.65, 0.69) for CHA2DS2VASc, and 0.63 for CHADS2(0.61-0.66) C statistics in women was 0.65 (0.62-0.67) for QStroke, 0.62 (0.59, 0.65) for CHA2DS2VASc, and 0.61 for CHADS2(0.59-0.64)	4% of patients were low risk on CHA2DS2VASc but high risk on Qstroke and had a 10 year observed stroke rate of 7.6%, compared to 2.6% for those low risk on both scores and 21.2% for those at high risk on both scores. A high risk on CHA2DS2VASc but low on Qstroke (4% of patients) had a10 year stroke rate of 2.8%. These results pertain only to patients without a prior stroke or TIA
Kornej [85]	N=2069; 66% men; 60±10 years; 62% paroxysmal AF Referred for ablation	CHADS2, CHA2DS2-VASc, and R2CHADS2	Stroke, transient ischemic attack, or systemic embolism	C-indexes: CHADS2 0.72(0.70-0.739); CHA2DS2-VASc 0.736(0.716-0.755) and R2CHADS2 0.736 (0.716-0.755) CHA2DS2-VASc score further differentiated TE risk in patients with CHADS2 and R2CHADS2 0 to 1 (0.13% if CHA2DS2- VASc was 0–1 and 0.71% if CHA2DS2-VASc was >2) and had the best predictive value in patients with AF recurrences (c-index 0.894, *P*=0.022 versus CHADS2, *P*=0.031 versus R2CHADS2).	CHA2DS2-VASc score differentiated TE risk in the low-risk strata based on CHADS2 and R2CHADS2 scores in a post-ablation cohort, with half of the TE events occurring in the 30 days post ablation
Lip[99]	207,543 incident hospital discharge patients with AF from 1999 to 2012 Danish registry linked data	CHA2DS2VASc, ATRIA	Ischemic stroke/TE	Patients categorized as low risk using the ATRIA score, the 1-year stroke/thromboembolic event rate ranged from 1.13 to 36.94 per 100 person-years, when subdivided by CHA2DS2VASc scores. In patients with an ATRIA score 0 to 5 (i.e. low risk), C statistics at 1 year follow-up in the Cox regression model were significantly improved from 0.626 (95% CI, 0.612-0.640) to 0.665 (95% CI, 0.651-0.679) when the CHA2DS2VASc score was used for categorizing stroke risk instead of the ATRIA score (*P* <.001). Low-risk category (i.e., CHA2DS2VASc score 0 for men or a score 1 for women) would identify a truly low-risk cohort, with annual event rates at 1- year of 1.13 per 100 person-years.	Patients categorized as low risk using an ATRIA score 0 to 5 are not necessarily low risk, with 1-year event rates as high as 36.94 per 100 person-years. However, no exploration on risk at ATRIA scores between 0-5, and whether a lower ATRIA cut point would perform differently **CHA2DS2VASc score best at identifying the "truly low risk" subjects with AF compared to ATRIA 0-5 low risk definition**
Lip[100]	22,582 non-anticoagulated hospital discharged patients age < 65 years with a CHADS2 score of 0 who were stratified according to the CHA2DS2-VASc score, except female sex, which would be an indication for OAC according to the ESC guidelines.	CHA2DS2VASc, CHADS65	Ischemic stroke/TE/ TIA	Overall rate of the combined end point of ischemic stroke/systemic embolism/transient ischemic attack was 4.32 per 100 person-years (95% CI 3.26-5.74) at 1 year, among the patients who would have had an indication for OAC therapy according to 2012 ESC guidelines (based on CHA2DS2VASc score) and "OAC not recommended" according to CCS algorithm. Subgroup of patients with previous vascular disease and CHADS2 score of 0 (i.e., recommended only aspirin treatment according to the CCS algorithm) had an event rate of 4.84 (95% CI, 3.53-6.62) per 100 person-years	Based on the 2014 CCS algorithm, the "OAC not recommended" subgroup can have a high 1-year stroke rate overall, showing that such patients are not "low risk." Use of CHA2DS2-VASc offers refinement of stroke risk stratification in such patients.

	Danish Registry linked data			at 1-year follow-up. Sensitivity analysis yielded similar result with events restricted to stroke/systemic embolism	
Nielsen et al[101]	Supplemental information to Can J Cardiol 2015 31; 24-28 responding to Cairns et al editorial on the original Lip et al article	CHA2DS2VASc, CHADS65		Contrasting low risk CHA2DS2-VASc (that is, score 0 (male) or 1 (female)) as a reference population vs those with ≥1 additional non-sex stroke risk factors (i.e. CHA2DS2- VASc score =1 (male) or =2 (females)) to express the hazard attributable to vascular disease resulted in a crude HR of 2.7 (95%CI 1.7-4.2). **'Vascular disease' Event rates per 100 person-years: MI 2.5 (1.4-4.3); PAD 3.0 (1.3-6.7); Both 15.0 (4.8-46.4)**	Any stroke RF other than sex (including vascular disease) in CHA2DS2-VASc provides a high enough risk of adverse events to warrant a recommendation for anticoagulation
Nielsen [102]	198697 hospital discharged AF patients, of which 15% truly low risk Danish registry linked data (NB Lip and Nielsen papers from the same cohorts)	CHA2DS2-VASc, but compares guideline approaches and addresses the varying event rates reported for different guideline cut-offs and different analysis approaches	Ischemic stroke, and composite of ischemic stroke and systemic embolism	Rate of composite endpoint using censoring of observation at time of OAC commencement was 0.54/100 person-years for truly low risk (CHA2DS2-VASc 0 males, 1 females), 1.53 for CHA2DS2-VASc =1 in males, 2.33 for CHA2DS2-VASc =2, and 5.49 for CHA2DS2-VASc >2. The analysis using conditioning on the future revealed an event rate of only 1.17/100 patient-years for CHA2DS2-VASc =1 (males)	Stroke and TE event rates vary according to method of analysis. Some evidence that formal approach, and conditioning on the future (exclusion of patients who commence OAC) will underestimate the event rate, and this is most important for CHA2DS2-VASc =1 (males)

Okumura [103]	6,387 patients taking warfarin and the other 997 not taking warfarin were prospectively examined for 2 years. J-Rhythm registry	CHADS2; modified CHA2DS2-VASc (*m*CHA2DS2-VASc) using coronary disease only	Thrombo-embolism (combined ischemic stroke, TIA and systemic embolism)	*m*CHA2DS2-VASc score 0, 1, and ≥2, thromboembolism occurred in 2/141 (0.7%/year), 4/233 (0.9%/year), and 24/623 (1.9%/year), respectively, in the non-warfarin group, and in 1/346 (0.1%/year, P=0.19 vs. non-warfarin), 4/912 (0.2%/year, P=0.05), and 92/5,129 (0.9%/year, P=0.0005), respectively, in the warfarin group. When female sex was excluded from the score, thromboembolism occurred in 2/180 patients (0.6%/year), 5/245 (1.0%/year), and 23/572 (1.6%/year), respectively, in the non-warfarin group, and in 1/422 (0.1%/year, P=0.20 vs. non-warfarin), 5/1,096 (0.2%/year, P=0.02), and 91/4,869 (0.9%/year, P=0.0005), respectively, in the warfarin group.	Small numbers and no information on OAC use at follow-up in the non-warfarin group. In Japanese NVAF patients, the *m*CHA2DS2-VASc score is useful for identifying patients at truly low risk. Concluded that 'Female sex may be excluded as a risk from the score.' But numbers are too small to substantiate that conclusion.

Palm[104]	Ludwigshafen Stroke Study (LuSSt), prospective ongoing population-based stroke register, 187 patients with a first-ever ischemic stroke (FEIS) owing to AF in 2006 and 2007.	CHA2DS2VASc, CHADS2	First ischemic stroke	Retrospective pre- stroke risk stratification according to CHADS2 score indicated low/intermediate risk in 34 patients (18%) and high risk (CHADS2 ≥2) in 153 patients (82%). Application of CHA2DS2-VASc score reduced number of patients at low/intermediate risk (CHA2DS2-VASc score 0–1) to five patients (2.7%).	Small, retrospective study of people with ischemic stroke. CHA2DS2-VASc score appears to be a more valuable risk stratification tool than CHADS2 score.
Philippart[105]	Loire Valley AF project: Among 8053 patients seen in Cardiology Dept with non-valvular AF (ESC guidelines definition), patients were categorized into Group 1 (no valve disease, n=6851; 85%) and Group 2 (valve disease with neither rheumatic mitral stenosis nor valve prothesis, n = 1202; 15%).	CHA2DS2VASc in 'non-valvular' and (non-rheumatic or prosthetic 'valvular' AF	Stroke/TE	For Group 1, the rate of events was 0.87%/year when CHA2DS2VASc score was 0–1, rising to 9.67%/year when score was ≥6. For patients in Group 2, similar finding were evident with a rate of stroke/TE events increasing from 0.90%/year with a CHA2- DS2VASc score 0–1 to 11.07%/year when CHA2DS2VASc score was ≥6. Main purpose of the study was to compare stroke/TE rates, and prediction of these by CHA2DS2VASc in patients with AF with and with "valvular" AF other than rheumatic mitral or prosthetic	CHA2DS2VASc performs similar in both groups If low risk (score 0-1), event rates low, approx. 0.9%/year, but 56-60% were on OAC, so rate is underestimated.

Potpara.[106]	Cohort of 345 "lone" AF patients with a 12-year follow-up.	CHA(2)DS(2)-VASc, CHADS(2), and van Walraven risk stratification schemes	Ischemic stroke (absence of) i.e. Prediction of LOW RISK	In the multivariable analysis, only the CHA(2)DS(2)-VASc score of 0 was significantly related to the absence of stroke (odds ratio 5.1, 95% CI: 1.5-16.8, P=0.008). Only the CHA(2)DS(2)-VASc score had a significant prediction ability for absence of ischemic stroke (c-statistic 0.72 [0.61-0.84], P=0.031).	Small study of lone AF with 12 year follow-up CHA(2)DS(2)-VASc score reliably identified the "lone" AF patients who were at "truly low risk" for TE
Ruff[107]	Biomarker sub-study of ENGAGE-AF, using cardiac troponin I, N-terminal pro-B-type natriuretic peptide, and d-dimer in 4880 patients with all 3 biomarkers available	CHA(2)DS(2)-VASc ± biomarkers	Stroke or systemic embolism	When added to the CHA2DS2-VASc score, the biomarker score significantly enhanced prognostic accuracy by improving the C statistic from 0.586 (95% CI, 0.565-0.607) to 0.708 (95% CI, 0.688-0.728) (P < .001) and reclassification with a net reclassification improvement of 59.4% (P < .001).	All patients were anticoagulated, and all patients were CHADS2 =2 or greater, so cannot comment on discrimination of low risk patients without anticoagulant

Singer [108]	Derivation ATRIA cohort consisted of 10 927 patients with non-valvular AF contributing 32 609 person-years off warfarin and 685 thromboembolic events (TEs). The external validation ATRIA-CVRN cohort included 25 306 AF patients contributing 26 263 person-years off warfarin and 496 TEs.	ATRIA, CHA(2)DS(2)-VASc, CHADS(2),	Ischemic stroke/TE	c-index in the ATRIA cohort was 0.73 (95% CI, 0.71 to 0.75), increasing to 0.76 (95% CI, 0.74 to 0.79) when only severe events were considered. The C-index was greater and net reclassification improvement positive comparing the ATRIA score with CHA(2)DS(2)-VASc, or CHADS(2) The NRI improvement was primarily seen for predicting severe strokes. No analysis was done to determine the relative performance of scores to detect a truly low risk group who should not be treated rather than a low intermediate and high risk group	Follow-up was censored at the date of the outcome event, death or health plan disenrollment. Analysis based on all person-time off warfarin. Results comparing risk scores were very similar when restricted the analysis to the 4342 patients who did not take warfarin at any point during follow-up (… but 'conditioning on the future').
Siu[30]	9727 hospitalized AF patients, follow-up for 3.19 years	CHA(2)DS(2)-VASc, CHADS(2),	Ischemic stroke	c-statistics revealed that CHA(2)DS(2)-VASc scores (0.525, 95% CI 0.509–0.541, P = .017) was better than CHADS(2) scores (0.506, 95% CI 0.490–0.522, P = .584) in predicting ischemic stroke. Net clinical benefit favors warfarin over aspirin and no therapy for stroke prevention in a broad range of Chinese AF patients.	CHA(2)DS(2)-VASc and HAS-BLED scores appear to be the appropriate risk stratification tools for stroke risk and ICH, respectively, for Chinese. C-Statistics relatively low for prediction of ischemic stroke compared to other cohorts. Annual risk of stroke relatively higher in low risk groups (CHA(2)DS(2)-VASc score =0 or 1) in Chinese than that in Europeans
Tomita[109]	997 AF patients in JRHYTHM registry with no warfarin at baseline Same cohort as Okamura without the cohort taking warfarin as comparison	mCHA2DS2-VASc and mCHA2DS2-VA scores (i.e. excluding female sex) Modified as based on coronary artery disease (no information on PAD)	Thrombo-embolic events including symptomatic cerebral infarction, transient ischemic attack (TIA), and systemic embolism	No sex difference was found in patient groups stratified by CHA2DS2-VASc and CHA2DS2-VA scores. Significant c-statistic difference (0.029, Z=2.3, P=0.02) and NRI (0.11, 95% CI 0.01–0.20, P=0.02), with the CHA2DS2-VA score being superior to the CHA2DS2-VASc score. In patients with CHA2DS2-VASc scores 0 and 1 (n=374), there were significant c-statistic difference (0.053, Z=6.6, P<0.0001) and NRI (0.11, 95% CI 0.07–0.14, P<0.0001), again supporting superiority of CHA2DS2-VA to CHA2DS2-VASc score.	Small numbers and no information on OAC use at follow-up in the non-warfarin group (may explain low absolute event rates even at high scores). Very few females in study and only 90 with CHA2DS2-VASc =1 or 2. NB CHA2DS2-VASc score of 1 in a woman is excluded in ESC guidelines

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Van den Ham. [110]	60,594 patients with AF CPRD UK cohort (primary care based but incident AF could be hospital discharge) in incident AF, censored at warfarin prescription or outcome event)	CHADS2, CHA2DS2-VASc and ATRIA	Ischemic stroke	C statistics for the full point scores were 0.70 (95% confidence interval [CI]: 0.69 to 0.71) for the ATRIA risk score, 0.68 (95% CI: 0.67 to 0.69) for CHADS2, and 0.68 (95% CI: 0.67 to 0.69) for CHA2DS2-VASc risk score. The net reclassification improvement was 0.23 (95% CI: 0.22 to 0.25) for ATRIA compared with CHA2DS2-VASc. Median follow-up was only 0.74 years over a 15-year study period; though mean follow-up was 2.8 years, indicating distribution of follow-up is skewed. Using ATRIA, 40% were categorized as low-risk (that is, ATRIA score of ≤5, with annualized stroke rates of 0.40% to 1.99%),	ATRIA score performed better than either CHADS2, CHA2DS2-VASc for predicting events. ATRIA identified 40% as low-risk patients vs CHA2DS2-VASc score, which identified only 6.6% as low risk, and assigned these patients to higher-risk categories.
Aspberg[111]	152 153 AF patients not receiving warfarin in Swedish AF cohort – hospitalized or visiting hospital OPD. future analysis	CHADS2, CHA2DS2-VASc and ATRIA	Ischemic stroke	ATRIA had a good C of 0.708 (0.704–0.713), significantly better than CHADS2 0.690 (0.685–0.695) or CHA2DS2-VASc 0.694 (0.690–0.700). Net reclassification improvement favored ATRIA 0.16 (0.14–0.17) vs. CHADS2 and 0.21 (0.20–0.23) vs. CHA2DS2-VASc (with a reclassification down for the comparison with CHA2DS2-VASc, and a reclassification up for the comparison with CHADS2.	Analyses restricted to patients who did not use any anticoagulant therapy during the follow-up period – thus *'conditioning on the future'.* When categorical cut-points were optimized to the stroke rate of the population, the differences between scores in NRI and C statistic disappeared
Xiong[112]	Systematic review and meta-analysis, East Asian patients. Included 6 cohort studies with 31,539 patients	CHA(2)DS(2)-VASc, CHADS(2),	Predomin-antly ischemic stroke, 2 with thrombo-embolism	Meta-analysis revealed that when compared with the CHA2DS2-VASc score, there was a 1.71-fold elevated risk of stroke when patients were stratified as 'low risk' using a CHADS2 score = 0, or a 1.40-fold increase with a CHADS2 score = 1.	CHA2DS2-VASc score is superior to the CHADS2 score in identifying 'low risk' East Asian AF patients.
Zhu[113]	Systematic review and meta-analysis Included 12 cohort studies with 205,939 patients	CHA2DS2-VASc, CHADS2,	Stroke, Thrombo-embolism	CHA2DS2-VASc scores ≥2 have a greater risk of stroke (risk ratio [RR]=5.15; 95% confidence interval [CI], 3.85–6.88; P <0.00001) and thromboembolism (RR=5.96; 95% CI, 5.50–6.45; P <0.00001) (Pdiff=0.34) than do patients with CHA2DS2-VASc scores <2, independent of anticoagulation therapy (RR=5.76; 95% CI, 5.23–6.35; P <0.00001 in anticoagulated patients; and RR=6.12; 95% CI, 5.40–6.93; P <0.00001 in patients not taking anticoagulants; P =0.45). In the comparison of the rates of endpoint events among low-risk patients (1.67% vs 0.75%; P <0.001), the findings imply that some CHADS(2) low- risk patients might still benefit from anticoagulation	Superior diagnostic performance of CHA2DS2-VASc over CHADS2 for identifying genuinely low-risk patients with AF.

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Kim[114]	5855 oral anticoagulant naive NVAF patients enrolled from Korea National Health Insurance Service-Sample Cohort	CHA_2DS_2-VASc, $CHADS_2$ and ATRIA	Ischaemic stroke	CHA_2DS_2-VASc had the best sensitivity (98.8% versus 85.7% in $CHADS_2$ and 74.8% in ATRIA) and negative predictive value (98.8% versus 95.3% for $CHADS_2$ and 93.7% for ATRIA) for the prediction of stroke incidence and was best for the prediction of the absence of ischemic stroke during 5 years of follow-up (odds ratio, 16.4 [95% confidence interval, 8.8-30.8]).	CHA_2DS_2-VASc score shows good performance in defining truly low-risk Asian patients with atrial fibrillation for stroke compared with $CHADS_2$ and ATRIA
Rivera-Caravaca[115]	1125 NVAF patients	Compared long-term predictive performances of the ABC-stroke and CHA2DS2-VASc	Ischaemic stroke	114 ischemic strokes (1.55% per year) at 6.5 years. ABC-stroke c-index at 3.5 years (0.663) was higher than CHA2DS2-VASc (0.600, P=0.046), but nonsignificantly different at 6.5 years. For ABC-stroke, net reclassification improvement was nonsignificantly different at 3.5 years, and a negative reclassification at 6.5 years, vs CHA2DS2-VASc. Decision curve analyses did not show marked improvement in clinical usefulness of the ABC-stroke score over the CHA2DS2-VASc score.	ABC-stroke score did not offer better 'real world' predictive performance compared with the CHA2DS2-VASc score over long term

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e-Table 8. Major bleeding rates with VKAs in observational studies

Study	Patients on VKA, n	Age, years	Mean follow-up	Major bleeding, per year
EURO HEART SURVEY (2010)[116]	2115	66.8	1 y	1.5%
ATRIA (2011)[117]	9186	71	3.5 y	1.4%
Olesen et al. (2011)[118]	37425	70.6	10 y	4.62%
Gallego et al. (2012)[119]	965	76	861 d	3.6%
Donze et al. (2012)[120]	515	71.2	1 y	6.8%
Friberg et al. (2012)[38]	48599	76.2	1.5 y	1.9%
Burgess et al. (2013)[121]	321	69.2	2.5 y	3.8%
ORBIT-AF (2013)[122]	4804	76	6 m	1.8%
Seet et al. (2013)[123]	100	79.3	19 m	9.79%
Guo et al. (2013)[26]	149	63	1.9 y	2.7%
Deitelzweig et al. (2013)[124]	48260	67.3	802 d	10.4%
MAQI2 (2014)[125]	2600	70.1	1 y	4.5%
Wang et al. (2016)[126]	15418	65	4.6 m	5.5%

d=day; m= month; VKA=vitamin-K antagonist; y=year

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e-Table 9. Major bleeding rates on oral anticoagulants in randomized clinical trials

Trial	Patients on anticoagulants, n	Age, year	Mean follow-up	Major bleeding, per year
BAATAF (1990)[127]	212 (VKA)	68.5	2.2 y	2 patients in 2.2 y (VKA)
CAFA (1991)[128]	187 (VKA)	68	15.2 m	2.5% (VKA)
SPAF I (1991)[129]	1330 (VKA)	67	1.3 y	1.5% (VKA)
SPINAF (1992)[130]	260 (VKA)	67	1.8 y	1.3% (VKA)
EAFT (1993)[131]	1007, 225(VKA)	77	2.3 y	2.8% (VKA)
SPAF II (1994)[132]	1100 (VKA)	64 (age≤75) 80 (age>75)	2.3 y	1.7% (age≤75) (VKA) 4.2% (age>75) (VKA)
SPAF III, (1996)[133]	523 (VKA)	71	1.1 y	2.1% (VKA)
AFASAK2, (1998)[134]	170 (VKA)	73.2	1	2.4% (VKA)
Pengo et al. (1998)[135]	153 (VKA)	73.6	14.5 m	2.6% (VKA)
Hellemons et al. (1999)[136]	131 (VKA)	70	2.7 y	0.5% (VKA)
Yamaguchi et al. (2000)[137]	55 (VKA)	65.7	658 d	6.6% (VKA)
SPORTIFF III (2003)[138]	1703 (VKA) 1704 (Ximelagatran)	70.1 (VKA) 70.3 (Ximelagatran)	17.4 m	1.8% (VKA) 1.3% (Ximelagatran)
NASPEAF, (2004)[139]	496 (VKA)	69.6 (Intermediate) 66.6 (High intensity)	965 d (Intermediate) 1075 d (High intensity)	1.8% (Intermediate) (VKA) 2.13% (High intensity) (VKA)
SPORTIFF V (2005)[140]	1962 (VKA) 1960 (Ximelagatran)	71.6 (VKA) 71.6 (Ximelagatran)	20 m	3.1% (VKA)* 2.4% (Ximelagatran)*
ACTIVE W (2006)[141]	3371 (VKA)	70.2	1.28 y	2.21% (VKA)
Chinese ATAFS (2006)[142]	704 (VKA)	63.3	19 m	1.5% (VKA)
AMADEUS (2008)[143]	2293	70.2	10.7 m	1.4%
RE-LY (2009)[144]	6022 (VKA) 6076 (D, 110 mg) 6015 (D, 150 mg)	71.6 (VKA) 71.5 (D, 110 mg) 71.4 (D, 150 mg)	2 y	3.36% (VKA) 2.71% (D, 110 mg) 3.11% (D, 150 mg)
ROCKET AF (2011)[145]	7133 (VKA) 7131 (R, 20 mg)	73 (VKA) 73 (R, 20 mg)	2 y	3.4% (VKA) 3.6% (R, 20 mg)
ARISTOTLE (2011)[146]	9120 (VKA) 9081 (A, 5 mg)	70 (VKA) 70 (A, 5 mg)	1.8 y	3.09% (VKA) 2.13% (A, 5 mg)
J-ROCKET (2012)[147]	639 (VKA) 639 (R, 15 mg)	71.2 (VKA) 71 (R, 15 mg)		3.59% (VKA) 3.00 (R, 15 mg)
ENGAGE AF (2013)[148]	7036 (VKA) 7035 (E, 30 mg) 6015 (E, 60 mg)	72 (VKA) 72 (E, 30 mg) 72 (E, 60 mg)	907 d	3.43% (VKA) 1.61% (E, 30 mg) 2.75% (E, 60 mg)

*= major extra-cerebral bleeding
A=apixaban; D=dabigatran; d=day; E=edoxaban; m=month; R=rivaroxaban; VKA= vitamin-K antagonist; y=year

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e-Table 10. Studies comparing bleeding risk schemas

Study	Cohort	Schemes compared	Events	Findings	Comments
Barnes et al[149]	2,600 patients in 7 anticoagulation clinics, 2009-2013. Only warfarin used. Warfarin initiators followed with retrospective scores. First major bleed only included	$CHADS_2$, CHA_2DS_2-VASc, $HEMORR_2HAGES$, HAS-BLED, ATRIA	116 major bleeds (ISTH definition)	NB mean follow up only 1.0 years. AUC under ROC compared with C statistic and NRI. Used low mod and high cutoffs from scores. C stat similar for 3 bleeding risk scores (0.66.to 0.69), and all bleeding scores performed better than $CHADS_2$ or CHA_2DS_2-VASc (C stat 0.53 to 0.56). For NRI, HAS_BLED better than ATRIA or HEMORRHAGES, and ATRIA better than $HEMORR_2HAGES$, while all 3 better than $CHADS_2$ or CHA_2DS_2-VASc	NRI differences for HAS-BLED vs other bleeding risk scores only significant for low vs mod/high. Diff of NRI in bleeding risk scores not significant for low/mod vs High risk. All bleeding risk scores had only moderate prediction i.e. C statistic is only 0.66-0.69
Caldeira et al[150]	Systematic review of $HEMORR_2HAGES$, HAS-BLED, ATRIA scores	$HEMORR_2HAGES$, HAS-BLED, ATRIA. Compared high risk category only	Major bleeds in studies reviewed from search	6 studies found 5 studies compared $HEMORR_2HAGES$ and HAS-BLED, 4 studies compared HAS-BLED vs ATRIA. HAS-BLED had significantly higher sensitivity (but therefore also lower specificity for major bleeding. Conclusion was a preference for HAS-BLED because of higher sensitivity coupled with ease of use	Systematic review
Christersson et al [151]	Aristotle trial in 14,878 out of 18,201 pts randomized to warfarin or apixaban. Follow-up in trial	HAS-BLED alone vs adding D-Dimer	647 Major bleeds (2.6%), and 1276 with clinically relevant non-major bleeds (5.1%) (admission to hospital but without drop in Hb of 2g or 2 unit transfusion)	C statistic was 0.61 and 0.618 in the no-VKA and on VKA groups respectively and adding D-Dimer increased the C statistic to 0.641, and 0.635 resp. NRI was 23 to 28%	Modest increase in C statistic only. D-Dimer predictive in its own right with similar C-statistic

Suzuki et al..[152]	231 patients starting warfarin. Prospective study	HAS-BLED exploring various cut points of renal function (3 groups) in Japanese population (eGFR) using Japanese MDRD formula	44 ISTH major bleeds	Moderate kidney disease (eGFR 30-59) also associated with increased major hemorrhage. C statistic including moderate renal disease in HAS-BLED increased from 0.64 to 0.67 (p, NS) but NRI improved significantly	Small trial, so hard to draw solid conclusions, but perhaps even moderate renal disease will be important and therefore may need to include in the HAS-BLED definition
O'Brien et al. [153]	ORBIT AF registry, 7411 pts taking OAC. Median 2 year follow-up. External validation in 14,264 pts in ROCKET-AF study warfarin and Rivaroxaban pts (not all elements of all scores available)	ORBIT score (full score, and 5 factor score) vs HAS-BLED and ATRIA bleeding scores	581 (7.8%) ISTH major bleeding events in ORBIT registry	See table 4 for topline results. C indices of 0.69 and 0.67 for the full and 5 factor ORBIT score in ORBIT registry, compared to 0.64 and 0.66 for HAS-BLED and ATRIA resp. In ROCKET-AF, Full and 5 factor ORBIT model C stat 0.63 and 0.62 respectively, vs 0.59 and 0.60 for HAS-BLED and ATRIA respectively. Model calibration better for ORBIT score in ROCKET-AF, followed by HAS-BLED then ATRIA	All scores showed only moderate predictive ability and discrimination
Zhu et al. [154]	Systematic review and meta-analysis of HAS-BLED score vs other scores, in 11 studies identified	HAS_BLED vs CHADS2, CHADSVASc, HEMORR2HAGES and ATRIA	Variable events in the 11 studies	C statistic not significantly different between HAS-BLED and other 2 bleeding risk scores (0.65 vs 0.63 and 0.63 synthesized result), but better than CHADS2 and CHADSVASc. HAS-BLED superior to all other scores for NRI (NB not in all studies). Calibration analysis shows HAS-BLEC over predicts in the low and under-predicts in the mod and high risk categories.	All scores perform better than the stroke risk scores, and HAS-BLED has a marginal advantage over HEMORR2HAGES and ATRIA
Esteve-Pastor et al. [155]	FANTSIIA registry, 571 pts undergoing cardioversion, 1276 pts with persistent AF. Most VKA, some NOAC	ORBIT vs HAS-BLED	21 ISTH major bleeds in the 571 cardioversion pts, and 46 in the persistent AF population	C statistic in cardioversion group 0.77 vs 0.82 HAS-BLED vs ORBIT (ns), and in persistent AF group 0.63 vs 0.70 (ns)	Relatively small number of major bleeding events in both arms of the study, so not much weight can be put on the study. Prediction only modest for both scores

Hijazi et al. ABC-Bleeding score.[156]	ARISTOTLE study 14,537 pts apixaban vs warfarin) for development and RELY study (8468 pts on warfarin or Dabigatran) for validation.	ABC-bleeding score (Age; Biomarker GDF-15, CTnT hs, Hb; Clinical history of bleeding) vs HAS-BLED and ORBIT bleeding risk scores	ISTH major bleeds: 662 in ARISTOTLE, and 463 in RELY.	ABC score discriminated in all risk groups of HAS-BLED and ORBIT in both derivation and validation cohorts. C statistic significantly higher 0.68 for ABC bleeding vs 0.61 and 0.68 HAS-BLED and ORBIT in ARISTOTLE, and also in RELY 0.71, vs 0.62 and 0.68 for HAS-BLED and ORBIT resp. Similar results when hematocrit, CTnIhs and Cystatin C or Creatinine clearance substituted.	Simplicity and bedside use favor the simpler scores, though substitution of more readily available biomarkers would be an option. Even with Biomarkers, performance still only moderate
Nielsen et al. [157]	Danish national registry 210,299 pats with AF	Recalibration of HAS-BLED using an extra point for hemorrhagic stroke (S in HAS-BLED)	ISTH major bleeding 4.3/100 patient/years	No significant difference for C statistic for the 2 scores, and modest for both (0.613 original and 0.616 for the additional point HAS-BLED). NRI was 10% and relative IDI 23.6%	Minor gain by adding an extra point for ICH to the one point for stroke. It is reasonably intuitive that someone with a prior ICH is really at high danger of a major bleed
Proietti et al. [158]	SPORTIF III and V trials. 3,551/3,665 pts assigned to warfarin. Only 20% VKA naïve at baseline	HAS-BLED vs HEMORR2HAGES , ATRIA, and ORBIT scores plus additional analysis for latter 3 scores plus a term for TTR	127 adjudicated major bleeds. 1.6 years median F/U. 162 investigator level major bleeds	Rather complex analysis quoting similar AUC, without C statistics quoted. Analyzed both adjudicated and investigator level major bleeds (latter not usually included in other studies), then added TTR to the 3 scores that do not contain it, again against both endpoints. These scores improved prediction, indicating TTR is likely to be an important issue that is not included in scores other than HAS-BLED	All scores showed only moderate prediction, but HAS-BLED performed best in 1 respect of having no investigator level major bleeds ion the low risk stratum. While low TTR may be useful to assess risk, it has no role in the VKA naïve patient. Relatively low risk of major bleeds in this stud
Senoo et al. [159]	2293 patients receiving VKA in AMADEUS trial (idraparinux vs VKA in AF).	HAS-BLED vs ATRIA and ORBIT	39 Major bleeds and 251 clinically relevant bleeds (these are not usually counted in prior analyses of scores)	No difference in AUC between 3 scores in major bleeds. Some difference in clinically relevant bleeds, with HAS-BLED having greater AUC. Modest improvement for ATRIA and ORBIT by adding TTR	All scores showed modest at best prediction of bleeding. While low TTR may be useful to assess risk, and is only included in HAS-BLED, it has no role in the VKA naïve patient. Low risk group as patients with major bleeds excluded from study

Steinberg et al. [160]	9715 patients in ORBIT registry. Probably some overlap with the O'Brien study above	HAS-BLED, ATRIA, and physician assessment	Major bleeds (not defined), and no numbers given, just incidence rate /100 patient/years in each stratum	C statistic 0.63 ATRIA and 0.60 HAS-BLED not significantly different. Both better than physician assessment (C Stat 0.55), which did not add anything to the bleeding risk scores	Physician assessment overall poor and worse that scores
Wang et al..[161]	USA United Health OAC initiator (VKA and Dabigatran. 21,934 patients included	CHADS2, CHADSVASc, and HAS-BLED	Approx. 1000 major bleed (4.6%). Used ISTH, TIMI or GUSTO major bleed definition	C statistic of 0.60 for major bleeding. No difference according to major bleed definition. Calibration of rates of major bleeding using model data from RELY trial showed great underestimation of major bleeding, especially for warfarin initiators in high risk HAS-BLED category	Trial data based models (RCT) giving rates of major bleeding taken from bleeding risk models underestimate the true rate of major bleeds in real world practice for that risk stratum, esp. in warfarin initiators
Poli et al.[162]	4,579 patients in a prospective registry (START) of NVAF	HAS-BED (omit the L for labile INR) as all are inception patients, vs CHADS2 and CHADSVASc	115 ISTH major bleeds (1.6 per 100 pt. years	C statistic 0.58 and 0.61 for HAS-BED and HAS-BLED. Similar to CHADS2 and CHADSVASc (0.58, 0.56 respectively)	Cannot understand how a HAS-BLED score was calculated in the study, as all were initiators (77% VKA), and why it should be different to HAS-BED, unless they used TTR after registry commenced in the 77% on VKA. Low bleeding risk cohort overall in this registry
Esteve-Pastor et al[163]	1120 "real-world" anticoagulated NVAF patients with long-term follow-up.	HAS-BLED vs ABC-bleeding score	After 6.5 years of follow-up, 207 (2.84 %/year major bleeding events, of which 65 (0.89 %/year) were intracranial haemorrhage (ICH) and 85 (1.17 %/year) gastrointestinal bleeding (GIB).	c-index of HAS-BLED was significantly higher than ABC-Bleeding for major bleeding (0.583 vs 0.518; p=0.025), GIB (0.596 vs 0.519; p=0.017) and for the composite of ICH-GIB (0.593 vs 0.527; p=0.030). NRI showed negative reclassification for major bleeding and for the composite of ICH-GIB with the ABC-Bleeding score. Using DCAs, the use of HAS-BLED score gave an approximate net benefit of 4 % over the ABC-Bleeding score.	HAS-BLED performed significantly better than the ABC-Bleeding score in predicting major bleeding, GIB and the composite of GIB and ICH

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Guo et al[164]	Hospital based cohort	HEMORR2HAGES, HAS-BLED, ATRIA, and ORBIT, vs 'European score' based on modifiable bleeding risk factors		European score c-index for major bleeding 0.63, 95% CI 0.56-0.69) and intracranial hemorrhage (0.72, 0.65-0.79) HAS-BLED score was superior to European score (Delong test, all P < .05), net reclassification improvement values of 13.0%-34.5% (all P < .05), and integrated discrimination improvement values of 0.7%-1.4% (all P < .05). European score performed worst compared to HEMORR2HAGES, HAS-BLED, ATRIA, and ORBIT	Relying on bleeding risk assessment using modifiable bleeding risk factors alone is an inferior strategy
Esteve-Pastor et al[165]	AMADEUS trial cohort	HAS-BLED vs modifiable bleeding risk factors based on ESC guidelines	597 (13.0%) experienced any clinically relevant bleeding event and 113 (2.5%) major bleeding	Only the HAS-BLED score was significantly associated with the risk of any clinically relevant bleeding (hazard ratio 1.38; 95%CI 1.10–1.72; p = 0.005). The HAS-BLED score performed best in predicting any clinically relevant bleeding (c-indexes for HAS-BLED, 0.545 vs. 'modifiable bleeding risk factors score', 0.530; c-index difference 0.015, z-score = 2.063, p = 0.04).	While modifiable bleeding risk factors should be addressed in all AF patients, the use of a formal bleeding risk score (HAS-BLED) has better predictive value for bleeding risks
Chao et al[166]	Nationwide cohort study of 40,450 NVAF patients who received warfarin	HAS-BLED, $HEMORR_2HAGES$, ATRIA, ORBIT, Modifiable bleeding risk (MBR) approach (based on ESC guidelines)	581 (3.91%) patients sustained ICH and 6889 (17.03%) patients sustained major bleeding events	When HAS-BLED was compared to other bleeding scores, c-indexes were significantly higher compared to MBR factors (p<0.001) and ORBIT (p=0.05) scores for major bleeding. C-indexes for the MBR factors score significantly lower vs. all other scores (De long test, all p<0.001).	All contemporary bleeding risk scores had modest predictive value for predicting major bleeding but the best predictive value and NRI was found for the HAS-BLED score. Simply depending on modifiable bleeding risk factors had suboptimal predictive value for the prediction of major bleeding

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e-Table 11. GRADE Evidence Profile on Bleeding Risk Scores

Question: Bleeding Risk tools for patients with Atrial Fibrillation
Bibliography: W. Zhu et al. The HAS-BLED Score for predicting major bleeding risk in anticoagulated patients with atrial fibrillation: A systematic review and meta-analysis. Clin Cardiol. 2015. 38:55-561

Quality assessment							Impact	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
HAS-BLED									
7	observational studies	not serious	not serious	not serious	not serious	none	C-statistic range: 0.60–0.69 (median, 0.66); pooled c-statistic: 0.65 (0.61-0.69)	⊕⊕ LOW	CRITICAL
HEMORR2HAGES									
5	observational studies	not serious	not serious	not serious	not serious	none	C-statistic range: 0.60–0.67 (median, 0.63); pooled c-statistic: 0.63 (0.61-0.66)	⊕⊕ LOW	CRITICAL
ATRIA									
3	observational studies	not serious	not serious	not serious	not serious	none	C-statistic range: 0.59–0.69 (median, 0.61); pooled c-statistic: 0.63 (0.56-0.72)	⊕⊕ LOW	CRITICAL
CHADS2									
3	observational studies	not serious	not serious	not serious	not serious	none	C-statistic range: 0.51–0.59 (median, 0.53); pooled c-statistic: 0.55 (0.49-0.61)	⊕⊕ LOW	CRITICAL
CHA2DS2-VASc									
3	observational studies	not serious	not serious	not serious	not serious	none	C-statistic range: 0.53–0.58 (median, 0.56); pooled c-statistic: 0.56 (0.53-0.59)	⊕⊕ LOW	CRITICAL

CI: Confidence interval

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e-Table 12. GRADE Evidence Profile of VKA compared to Placebo or control

Question: VKA compared to Placebo or control
Bibliography: Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Annals of internal medicine. 2007;146(12):857-867.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VKA	Placebo	Relative (95% CI)	Absolute (95% CI)		
All Stroke												
6	randomised trials	serious [a]	not serious	not serious	not serious	none	54/1450 (3.7%)	133/1450 (9.2%)	**RR 0.36** (0.26 to 0.51)	**56 fewer per 1,000** (from 42 fewer to 66 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

a. One study did not report appropriate randomization methods; Partial blinding reported in 3 trials

e-Table 13. GRADE Evidence Profile of Aspirin compared to placebo or control

Question: Aspriin compared to placebo or control
Bibliography: Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Annals of internal medicine. 2007;146(12):857-867.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin + Antiplatelets	Control	Relative (95% CI)	Absolute (95% CI)		
All Stroke												
8	randomised trials	serious [a]	not serious	not serious	not serious	none	245/2602 (9.4%)	296/2594 (11.4%)	**RR 0.78** (0.94 to 0.65)	**25 fewer per 1,000** (from 7 fewer to 40 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

a. Unclear randomization and blinding methods in several studies

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e-Table 14. GRADE Evidence Profile of VKA compared to antiplatelet therapy

Question: VKA compared to Antiplatelet therapy
Bibliography: Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Annals of internal medicine. 2007;146(12):857-867.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VKA	AP	Relative (95% CI)	Absolute (95% CI)		
All Stroke												
12	randomised trials	serious [a]	not serious	not serious	not serious	none	205/6558 (3.1%)	341/6575 (5.2%)	**RR 0.61** (0.78 to 0.48)	**20 fewer per 1,000** (from 11 fewer to 27 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

a. Unclear randomization and blinding methods in several studies

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e-Table 15. GRADE Evidence Profile of VKA compared to NOAC (not stratified by specific agent)

Question: VKA compared to Antiplatelet therapy
Bibliography: Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955-962.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VKA	NOAC	Relative (95% CI)	Absolute (95% CI)		
Stroke or SE events												
4	randomised trials	serious [a]	not serious	not serious	not serious	none	1107/29229 (3.8%)	911/29312 (3.1%)	**RR 0.81** (0.73 to 0.91)	**6 fewer per 1,000** (from 3 fewer to 8 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Major Bleeding												
4	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	1802/29211 (6.2%)	1541/29287 (5.3%)	**RR 0.86** (0.73 to 1.00)	**7 fewer per 1,000** (from 0 fewer to 14 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

a. Issues with allocation concealment and blinding of participants and personnel
b. I-squared value of 83% indicating substantial heterogeneity
c. 95% CI includes no effect

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e-Table 16. GRADE Evidence Profile of NOAC vs. Aspirin

Bibliography: Connolly SJ, et al. Apixaban in patients with atrial fibrillation. The New England journal of medicine. 2011;364(9):806-817.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NOAC	Aspirin	Relative (95% CI)	Absolute (95% CI)		
Stroke or SE												
1	randomised trials	not serious	not serious	not serious	not serious	none	51/2802 (1.8%)	113/2791 (4.0%)	**HR 0.45** (0.32 to 0.62)	**22 fewer per 1,000** (from 15 fewer to 27 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Major Bleeding												
1	randomised trials	not serious	not serious	not serious	not serious	none	44/2802 (1.6%)	39/2791 (1.4%)	**HR 1.13** (0.74 to 1.75)	**2 more per 1,000** (from 4 fewer to 10 more)	⊕⊕⊕⊕ HIGH	CRITICAL

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e-Table 17. GRADE Evidence Profile of NOAC vs. VKA for electric cardioversion

Question: NOAC compared to VKA for Patients with Atrial Fibrillation undergoing elective-cardioversion
Bibliography: Cappato 2014, Flaker 2014, Goette 2016, Nagarakanti 2011, Piccini 2013, Plitt 2016

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studie	Study desig	Risk of	Inconsistency	Indirectness	Imprecision	Other consideration	NOAC	VKA	Relative (95% CI)	Absolute (95% CI)		
Stroke/SE												
6	randomised trials	serious [a]	not serious	not serious	serious [b]	none	16/4136 (0.4%)	12/2928 (0.4%)	RR 0.82 (0.38 to 1.75)	1 fewer per 1,000 (from 3 fewer to 3 more)	⊕⊕◯◯ LOW	CRITICAL
Mortality - all cause (follow up: range 30 to 60; assessed with: all cause)												
4	randomised trials	serious [a]	not serious	not serious	serious [b]	none	9/2679 (0.3%)	10/2132 (0.5%)	RR 0.72 (0.27 to 1.90)	1 fewer per 1,000 (from 3 fewer to 4 more)	⊕⊕◯◯ LOW	CRITICAL
MI												
3	randomised trials	serious [a]	not serious	not serious	serious [b]	none	4/2428 (0.2%)	5/2018 (0.2%)	RR 0.72 (0.19 to 2.71)	1 fewer per 1,000 (from 2 fewer to 4 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; RR: Riskratio

a. Issues with allocation concealment and blinding of participants and personnel; studies underpowered to detect a difference
b. Low number of events; Fairly wide confidence intervals around estimate of effect

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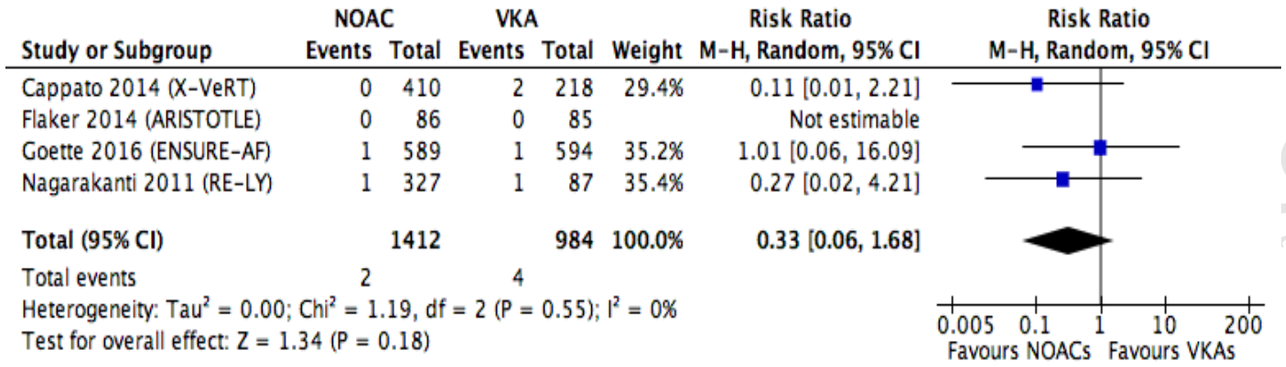
e-Figure 3. NOACs versus warfarin in the TEE-guided approach to cardioversion



e-Table 18. GRADE Evidence Profile of NOAC vs. VKA for TEE-guided cardioversion

Question: NOACs compared to VKA for AF patients undergoing TEE-guided CV
Setting:
Bibliography: Cappato 2014, Flaker 2014, Goette 2016, Nagarakanti 2011

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NOACs	VKA	Relative (95% CI)	Absolute (95% CI)		
Stroke/SE												
4	randomised trials	serious [a]	not serious	not serious	serious [b]	none	2/1412 (0.1%)	4/984 (0.4%)	**RR 0.33** (0.06 to 1.68)	**3 fewer per 1,000** (from 3 more to 4 fewer)	⨁◯◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

a. Issues with allocation concealment and blinding of participants and personnel; studies not powered enough to detect a difference
b. Small number of events; Fairly wide confidence intervals around estimate of effect

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e-Table 19. GRADE Evidence Profile of Heparinoids compared to Aspirin/placebo for patients with acute ischemic stroke or TIA

Question: Heparinoids compared to Aspirin/placebo for patients with acute ischemic stroke or TIA
Bibliography: Paciarno 2007

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Ris of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Heparinoids	Aspirin/placebo	Relative (95% CI)	Absolute (95% CI)		
Recurrent ischemic stroke												
5	randomised trials	serious [a]	not serious	not serious	serious [b]	none			OR 0.68 (0.44 to 1.06)	1 fewer per 1,000 (from 0 fewer to 1 fewer)	⨁⨁◯◯ LOW	CRITICAL
Death												
6	randomised trials	serious [a]	not serious	not serious	not serious	none	1729/2351 (73.5%)	1637/2217 (73.8%)	OR 1.01 (0.82 to 1.24)	2 more per 1,000 (from 39 more to 40 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; OR: Odds ratio

Explanations

a. issues with allocation concealment and blinding of participants and personnel
b. wide 95% CI that crosses no effect

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e-Table 20. Relationship between CIED-detected AHREs > 5-6 min and thromboembolic events/stroke

Trial	No. of patients	Duration of follow-up	AHRE or AF burden threshold	Atrial rate cut-off (bpm)	Risk of clinical AF	Clinical AF during follow-up	Risk of thromboembolic event	Thromboembolic event rate (below vs above AF burden threshold; %)
Ancillary MOST (2003)[167]	312	27 months (median)	>5 min in a day	>220	HR 5.93, 95% CI 2.88–12.2, *P* = 0.0001	25% in patients with AHREs	HR 6.7, 95% CI 1.4–33.2, *P* = 0.020 for stroke or SEE	3.2 overall (1.3 vs 5.0)
Italian AT500 Registry (2005)[168]	725	22 months (median)	> 24 h	>174	NA	NA	HR 3.1, 95% CI 1.1–10.5, *P* = 0.044 for stroke or SEE	1.2 annual rate
Botto *et al.* (2009)[169]	568	1 year (mean)	$CHADS_2$ and AF burden (≥5 min in a day or >24 h)	>174	NA	NA	NA	2.5 overall (5.0 vs 0.8, *P* = 0.03 comparing high vs low risk on th basis of $CHADS_2$ and AF burden
TRENDS (2009)[170]	2,486	1.4 years (mean)	≥5.5 h in a day occurring in a 30-day window	>175	NA	NA	HR 2.2, 95% CI 0.96–5.05, *P* = 0.06 for stroke, TIA, or SEE, by comparing AF burden ≥5.5 h vs zero burden	1.2 annual rate overall (1.1 for z burden or AF burden <5.5 h vs 2 for AF burden ≥5.5 h)
Home Monitor CRT (2012)[171]	560	370 days (median)	≥3.8 h in a day	>180	NA	NA	HR 9.4, 95% CI 1.8–47.0, *P* = 0.006 for stroke or SEE, by comparing daily AF burden ≥3.8 h vs zero burden	2.0 overall
ASSERT (2012)[172]	2,580	2.5 years (mean)	>6 min in a day	>190	HR 5.56, 95% CI 3.78–8.17, *P* <0.001	15.7% in patients with AHREs	HR 2.49, 95% CI 1.28–4.85, *P* = 0.007 for ischemic stroke or systemic embolism	1.69 vs 0.69 annual rate in patie with vs without device-detected tachyarrhythmias
SOS (2014)[173]	10,016	2 years (median)	≥5 min and ≥1 h	>175	NA	NA	HR 1.76, 95% CI 1.02–3.02, *P* = 0.041 for ischemic stroke with AF burden ≥5 min vs <5 min. HR 2.11, 95% CI 1.22–3.64, *P* = 0.008 for ischemic stroke with AF burden ≥1 h vs <1 h	0.39 annual rate in the whole co

AF, atrial fibrillation; AHRE, atrial high-rate episode; ICD, implantable cardioverter–defibrillator; NA, not available; SEE, stroke or systemic embolism; TIA, transient ischemic attack.

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e-Table 21. Time relationships between device-detected atrial tachyarrhythmias and ischemic stroke, transient ischemic attacks or systemic embolism in patients with CIEDs under continuous monitoring of the atrial rhythm

	N. of TE events (Ischemic Stroke /TIA/SE)	Minimum device detected AF/AT duration/burden	Device detected AF/AT at any time before TE event	Device detected AF/AT in the 30 days before TE event	Device detected AF/AT at the time of TE event	Device detected AF/AT only after TE event
Daoud et al., 2011 [174]	40 Ischemic Stroke/TIA/SE	≥ 20 sec	50%	28%	15%	15%.
Boriani et al., 2012 [175]	33 Ischemic Stroke/TIA/SE	≥5 min	64%	33%	15%	NA
Shanmugam et al., 2012 [171]	11 Ischemic Stroke/TIA/SE	Around 6-10 s	64%	NA	27%	NA
Brambatti et al., 2014 [176]	51 Ischemic Stroke/SE	>6 min	35%	8%	2%	16%
Martin et al., 2015 [177]	69 Ischemic Stroke/SE	Around 6-10 s	13%	6%	NA	7%

AF: atrial fibrillation; AT: atrial tachyarrhythmias; CIED: cardiac implantable electronic device; SE: systemic embolism; TE: thromboembolic; TIA: transient ischemic attack; NA: not available

e-Table 22. GRADE Evidence Profile of Warfarin compared to no treatment/placebo for CKD

Question: Warfarin compared to No anticoagulation/placebo for CKD
Bibliography: Harel 2017

Certainty assessment							Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	Absolute (95% CI)		
Ischemic Stroke										
14	observational studies	not serious	serious [a]	not serious	not serious [a]	none	**HR 0.85** (0.62 to 1.15)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Intracranial Hemorrhage										
4	observational studies	not serious	not serious	not serious	serious [b]	none	**HR 1.93** (0.93 to 4.00)	**2 fewer per 1,000** (from 1 fewer to 4 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio

Explanations
a. I-squared value of 69% represents serious heterogeneity
b. wide 95% CI

e-Table 23. Factors to be considered in estimating the bleeding and thromboembolic risk associated with a surgical procedure or intervention in a patient on oral anticoagulants for AF or previous venous thromboembolism. Modified from Boriani G et al. [178]

Hemorrhagic risk related to surgical or interventional procedures	Thromboembolic risk related to oral anticoagulation interruption
Low hemorrhagic risk (2-day risk of major bleeding between 0 and 2%)	***Low thromboembolic risk (annual risk of arterial thromboembolism < 5% or 1-month risk of venous thromboembolism < 2%)***
Cataract and other ophthalmic surgery , with the exception of vitro-retinal surgery	Nonvalvular atrial fibrillation with $CHADS_2$ score 0 or 1
Simple dental extractions	Single previous remote venous thromboembolism (> 12 months) with no other risk factors
Skin excision	
Carpal tunnel repair	
Central venous catheter removal	
Non-coronary angiography	
Pacemaker and cardiac defibrillator implant	
Bronchoscopy with biopsy	
Cutaneous and lymph node biopsies (for bladder, prostate, thyroid, breast masses)	
Abdominal hysterectomy	
Hemorrhoidal surgery	
Abdominal hernia repair	
Hydrocele repair	
Knee or hip replacement and shoulder, hand or foot surgery and arthroscopy	
Cholecystectomy	
Gastrointestinal endoscopy or biopsy, enteroscopy, biliary or pancreatic stent without sphincterotomy	
	Intermediate thromboembolic risk (annual risk of arterial thromboembolism between 5 and 10% or 1-month risk of venous thromboembolism between 2 and 10%)
	Previous venous thromboembolism within 3 and 12 months
	Valvular prosthesis in aortic position without risk factors
	Nonvalvular atrial fibrillation with $CHADS_2$ score 2 or 3
	Recurrent stroke or transient ischemic attack without risk factors for cardiac embolism
High hemorrhagic risk (2-day risk of major bleeding between 2 and 4%)	***High thromboembolic risk (annual risk of arterial thromboembolism >10% or 1-month risk of venous thromboembolism >10%)***
Heart valve replacement	Recent venous thromboembolism (<3 months)
Coronary artery bypass	Recent stroke or transient ischemic attack, (< 3 months)
Surgery for aortic diseases	Previous thromboembolic event with known hypercoagulability due to genetic factors (Protein S or C deficiency, anti-thrombin deficiency, homozygous factor V Leiden mutation, antiphospholipid syndrome) or paraneoplastic thromboembolism or recurrent idiopathic thromboembolism
Vascular and general surgery	Non valvular atrial fibrillation with $CHADS_2$ score ≥ 4
Neurosurgery	Atrial fibrillation with rheumatic heart disease, mechanical valvular prosthesis or previous stroke
Surgery for urologic, thoracic, abdominal or breast cancer	Any valvular prosthesis in mitral position or older valvular prosthesis (caged-ball; tilting-disc) in aortic position
Transurethral prostate resection	Prosthetic heart valve with other risk factors (prior thromboembolism, severe left ventricular dysfunction) or recently placed (<3 months) or associated with hypercoagulable state
Bilateral knee replacement	Intra-cardiac thrombus detected by echocardiography or other imaging techniques
Laminectomy	
Kidney biopsy	
Polypectomy, variceal treatment, biliary sphincterectomy, pneumatic dilatation	
Placement of a percutaneous endoscopic gastrostomy (PEG)	
Endoscopically guided fine-needle aspiration	
Multiple tooth extractions	
Any major operation with a procedure duration > 45 minutes	

e-Table 24. Decision-making and management of a patient under treatment with a NOAC in the phases before and after a procedure/intervention.

Interruption before the procedure/intervention				
	CrCl	**Minor procedure/ intervention without an important risk of bleeding and with possible adequate local haemostasis**	**Procedure/ intervention at low risk of bleeding**	**Procedure/ intervention at high risk of bleeding**
Apixaban,	CrCl > 30 mL/min	Plan to perform the procedure/intervention at trough level (i.e. 12 h after last intake)	Give last dose 2 days before procedure/intervention (i.e., skip 2 doses on the day before the procedure/intervention and skip the dose the day of the procedure/ intervention)	Give last dose 3 days before procedure/intervention (i.e., skip 4 doses on the 2 days before the procedure/intervention and skip the dose the day of the procedure/ intervention)
	CrCl 15-30 mL/min	Plan to perform the procedure/intervention at trough level (i.e. 12 h after last intake) or at 24 hours from last intake	Give last dose 2 days before procedure/intervention (i.e., skip 2 doses on the day before the procedure/intervention and skip the dose the day of the procedure/ intervention)	Give last dose 3 days before procedure/intervention (i.e., skip 4 doses on the 2 days before the procedure/intervention and skip the dose the day of the procedure/ intervention)
Edoxaban, Rivaroxaban	CrCl > 30 mL/min	Plan to perform the procedure/intervention at trough level (i.e. 24 h after last intake)	Give last dose 2 days before procedure/intervention (i.e., skip 1 dose on the day before the procedure/intervention and skip the dose the day of the procedure/ intervention)	Give last dose 3 days before procedure/intervention (i.e., skip 2 doses on the 2 days before the procedure/intervention and skip the dose the day of the procedure/ intervention)
	CrCl 15-30 mL/min	Plan to perform the procedure/intervention at trough level (i.e. 24 h after last intake) or at 36 hours from last intake	Give last dose 2 days before procedure/intervention (i.e., skip 1 dose on the day before the procedure/intervention and skip the dose the day of the procedure/ intervention)	Give last dose 3 days before procedure/intervention (i.e., skip 2 doses on the 2 days before the procedure/intervention and skip the dose the day of the procedure/ intervention)
Dabigatran	CrCl > 50 mL/min	Plan to perform the procedure/intervention at trough level (i.e. 12 h after last intake)	Give last dose 2 days before procedure/intervention (i.e., skip 2 doses on the day before the procedure/intervention and skip the dose the day of the procedure/ intervention)	Give last dose 3 days before procedure/intervention (i.e., skip 4 doses on the 2 days before the procedure/intervention and skip the dose the day of the procedure/ intervention)
	CrCl 30–50 mL/min	Plan to perform the procedure/intervention at trough level (i.e. 12 h after last intake) or at 24 hours from last intake	Give last dose 3 days before procedure/intervention (i.e., skip 4 doses on the 2 days before the procedure and skip the dose the day of the procedure/ intervention)	Give last dose 5 days before procedure/intervention (i.e., skip 8 doses on the 4 days before the procedure and skip the dose the day of the procedure/ intervention)
Resumption after the procedure/intervention				
Apixaban, Dabigatran, Edoxaban, Rivaroxaban		The drug can be resumed without skipping expected doses	The drug can be resumed 24 hours after the procedure/ intervention	The drug can be resumed 48-72 hours after the procedure/ intervention

For all the DOACs usually there is no need for bridging with LMWH/UFH

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Section 19 The Patient

Shared decision-making

More recently there have been calls for a more co-ordinated approach to the management of AF, 'integrated AF care'.[179-183] Physicians are encouraged to adopt a shared-decision making approach[184-186] to empower the patient to contribute to treatment decisions and participate in the management of their AF.

It is imperative to elicit from each patient what outcomes of treatment are important for them rather than assume that all patients have the same treatment goals,[184] and to be aware that patients and physicians treatment objectives often differ significantly. Research has overwhelmingly demonstrated that patients with AF wish to avoid a stroke and are often willing to accept major bleeding to achieve this,[187-190] as many patients view a major disabling stroke as a consequence worse than death.[189] Bleeds, although feared, are considered by many patients to be preferable to a stroke. In contrast, some physicians are more concerned with reducing the risk of death[187] and decreasing the chance of bleeding rather than the prevention of stroke.[188,191] Physicians should note that in addition to reducing the risk of stroke, OAC also significantly reduces the risk of death.[192] However, it is important to note that preferences for avoidance of stroke do not always translate into actions/decisions to take OAC; in a study of elderly AF patients, 12% would not take OAC even if was 100% effective for stroke prevention.[189] External factors, such as negative media coverage (TV adverts, particularly in the US) can create fear among patients on OAC about severe or fatal bleeding, which may translate into patients stopping OAC or failing to initiate.

Patient preferences for OAC

Since the introduction of NOACs, 7 studies[193-199] have investigated which factor patients perceive as the important attribute when choosing OAC. In 4 studies[195-198] patients rated stroke prevention as the most important characteristic for OAC, while in others, the lack of interactions with food/drugs,[193] availability of an antidote,[199] or ease of administration[194] were of greatest importance. However, methodological differences between studies may explain the inconsistency in outcomes, particularly where efficacy and safety were not included in the attributes presented.[194] None of the studies asked patients to actively generate the attributes they felt were most important; all used pre-defined lists generated by researchers for patients to rank, which might have led to exclusion of certain responses of importance to patients. Further, most of these studies[193-199] did not examine patient perceptions of AF and stroke, or knowledge about stroke, which may determine these preferences.

Only a few studies have compared patient preferences for vitamin K antagonists (VKAs) and NOACs.[193,194,197-201] Generally NOACs were preferred to VKAs due to convenience factors mainly related to absence of INR monitoring[194,198-201] and a lower risk of bleeding.[201] Cost of OAC, particularly NOACs, is problematic in countries where healthcare is not free or fully reimbursed, particularly in the US, and consequently affordability can drive patient (and physician) OAC preferences. Only three OAC preference studies in AF patients[195-197] have examined the impact of cost/affordability on factors that were important in choosing an OAC; all reported stroke prevention to be the most important factor. One[197] found that NOACs were preferred over warfarin as their cost decreased. In two North American studies, one found that cost was the fifth most important attribute of OAC,[195] while in a larger US study of AF patients with and without stroke,[196] cost was the least important attribute. Consequently, patient preferences are likely to vary considerably based on the healthcare system in which they operate as well as their health expectations and previous experiences.

Patient education and counselling

Communication with patients is crucial as physicians may deliberately or inadvertently persuade patients to concur with their treatment decision by creating fear (either fear of stroke or fear of bleeding to death). Therefore, explaining risk of stroke and benefit/risks of treatment in terms the

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patient can understand is paramount in enabling the patient to choose whether or not they wish to take OAC. Many patient decision aids have been created to assist physicians in these discussions with patients (see e-Table 26). Eliciting the barriers patients perceive they may have with NOACs/OAC allows HCPs to give clear explanations/offer strategies to overcome these barriers and improve OAC uptake, adherence, and persistence. In addition, it is important to dispel myths patients may hold about alternatives to OAC for stroke prevention.

Adherence and persistence with OAC is paramount to treatment efficacy and safety.[202] Educating patients on why adherence and persistence is so important, discussions on how to be adherent (timing of medication, frequency, with/without food, interacting medications to avoid, what to do if dose missed/overdose etc.) requires specific instructions from the HCP prescribing the medication; this could be facilitated by the use of patient education checklist (e-Table 26) and enhanced by devising and sharing strategies to increase adherence and persistence (reminders, medication tracking etc.). Understanding the necessity of OAC therapy and the potential adverse complications of non-adherence (stroke or bleeding) increases patient adherence and persistence.[203]

Physician education is also important to ensure that they are familiar with the latest guidelines and current preferred AF management strategies, implementing them in order to prevent under-treatment (choice of drug and dose should be decided on the basis of patient characteristics, and to use their knowledge to inform patients about the specifics of the OAC to improve shared-decision making and adherence and persistence. Comprehensive reviews of 'best practice' for patient education for AF and OAC are available.[204-207]

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e-Table 25. Patient and healthcare provider decision aids and apps, patient resources, and patient and patient and professional organisations*†

Patient decision aids	Reference/URL
AFGuST	208
Keele University Decision support	http://www.anticoagulation-dst.co.uk/
NICE 2014 PDA	https://www.nice.org.uk/guidance/cg180/resources/endorsed-resource-decision-support-tool-552601405
'Patient pages' for AF and OAC	
Causes, symptoms and treatment of AF	209,210
Living with AF	211
Prevention of stroke in AF	212,213
Management of vitamin K antagonists	214,215
Non-vitamin K antagonists oral anticoagulants (NOACs)	216
Left atrial appendage occlusion devices	217
Patient apps	
European Society of Cardiology Patient app (My AF)	218 Free to download to all smartphones- search for 'My AF'
mAFA	219
Health Buddies app	220
CardioVisual app	http://cardiovisual.com
Afib Companion app	http://afibcompanion.com
Medication tracker apps	
Medisafe	https://www.medisafe.com
Mango Health	https://www.mangohealth.com
HCP apps	
European Society of Cardiology Healthcare Professional app (AF manager)	218 Free to download to all smartphones- search for 'AF manager'
Patient advocacy groups and foundations	
Anticoagulation Europe	http://www.anticoagulationeurope.org/
Arrhythmia Alliance International	www.aa-international.org
Atrial Fibrillation Association International	www.afa-international.org
Heart and Stroke Foundation-Canada	http://www.world-heart-federation.org/what-we-do/awareness/atrial-fibrillation/
My AFib Experience	http://myafibexperience.org/
Sign Against Stroke in Atrial Fibrillation	https://www.signagainststroke.com/en
Stop Afib.org	http://www.stopafib.org/
World Heart Federation:	http://www.world-heart-federation.org/what-we-do/awareness/atrial-fibrillation/
Professional societies or organizations	
American College of Cardiology:	https://www.cardiosmart.org/Heart-Conditions/Atrial-Fibrillation
American Heart Association	http://www.heart.org/HEARTORG/Conditions/Arrhythmia/AboutArrhythmia/AFib-Resources-and-FAQ_UCM_423786_Article.jsp#
European Heart Rhythm Association	http://www.afibmatters.org/
Heart Rhythm Society	http://www.hrsonline.org/Patient-Resources/Heart-Diseases-Disorders/Atrial-Fibrillation-AFib#axzz3L30TnuiT

***Taken in part from[205]; †not an exhaustive list**

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e-Table 26. Patient education checklist for atrial fibrillation patients initiating oral anticoagulation

Patient education checklist for oral anticoagulation for stroke prevention in atrial fibrillation	Tick when completed
The condition - Atrial fibrillation	
What is atrial fibrillation?	
What is the link between AF and stroke?	
Discuss patient's risk of stroke (CHA_2DS_2-VASc score & associated co-morbidities)	
Why is OAC recommended for stroke prevention?	
Duration of treatment (usually lifelong)	
Treatment options	
What are the treatment options? VKA or NOAC?	
Patient values/preferences for treatment (stroke prevention; lowest risk of bleeding; no routine monitoring; fewest side effects; once/twice daily dosing; cost etc.)	
Mode of action of chosen OAC (VKA or NOAC)	
Benefits/risks of specific OAC (stroke risk reduction vs. bleeding risk)	
For VKA patients, need for INR monitoring & explanation of INR tests; importance of TTR	
Why INR monitoring is not necessary (for VKA-experienced patients)	
Dosing	
How often the drug needs to be taken (once or twice daily)?	
What time(s) of day the OAC must be taken?	
Take with/without food	
If twice daily drug, **NEVER** take both doses together	
What to do if a dose is missed/overdose	
Highlight importance of medication adherence/ potential consequences of non-adherence	
Discuss how medication will be incorporated into daily routine	
Tools to assist patient to remember (if necessary)	
Bleeding	
Discuss patient's risk of bleeding on OAC treatment	
Distinction between minor and major bleeding	
Signs and symptoms of bleeding	
When to seek medical care or attend emergency room	
What do to in the case of head injury	
Presence/absence of antidote	
Lifestyle	
Concomitant medication (interactions; avoid antiplatelets/other OAC; minimize NSAID use; discuss permissible pain medication)	
Diet (for VKA patients)	
Alcohol intake (particularly for VKA patients)	
Natural remedies/health-food supplements	
For women: menstruation, pregnancy, breastfeeding	
Holidays and travel	
Exercise and potentially dangerous hobbies	
Occupational hazards	
Surgical or dental procedures	
Before discharge	
Confirm patient understands dosing regimen, bleeding signs/symptoms and management of bleeding, when to seek medical attention and from whom	
Provide written education materials and Patient Alert card (if available)	
Arrange follow-up and provide contact details of prescribing physician	
Patient aware of laboratory tests needed – why, how and when	

AF, atrial fibrillation; NSAIDs, non-steroidal anti-inflammatory drugs; OAC, oral anticoagulation; VKA, vitamin K antagonist

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