Review Article

Use of Oral Anticoagulants in Atrial Fibrillation: Current Status

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting older people. AF increases risk of stroke, systemic embolism, heart failure and mortality. Stratifying risk of stroke and bleeding in AF patients by several risk scores have been effective in choosing the most appropriate anticoagulant treatment. Oral vitamin K antagonist (VKA) like warfarin has been the mainstay of thromboprophylaxis in AF patients. However, with the introduction of non-vitamin K antagonist novel oral anticoagulants (NOACs), these newer agents are being preferred now over VKA. Safer drug-drug interactions, predictable pharmacokinetics and lesser adverse effects are the main reasons for preference of NOACs in AF. This article summarizes the current evidence on use of VKA and NOACs in AF.

Key Words: Atrial fibrillation, Stroke prevention, Warfarin, Non–vitamin K antagonist oral anticoagulants

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting older people.[1] There is one in four lifetime risk of developing AF for patients aged above 40 years.1 It is being predicted that AF will affect 6 to 12 million people in USA by 2050 and 17.9 million people in Europe by 2060.[1] The United Kingdom -based West Birmingham atrial fibrillation project showed a prevalence of 0.6% in the Indian subset.[2]

AF is associated with an increased risk of ischemic stroke, systemic embolism, heart failure and mortality, overall reducing the quality of life.[3] It has also been seen that up to 30% of stroke may be attributed to AF.[4,5] Thus, AF poses as a major risk factor for thromboembolic stroke requiring management by anticoagulant therapy.

The cornerstone of thromboprophylaxis in AF patients has been vitamin K antagonist (VKA) over the last few decades. However, with the introduction of non-vitamin K antagonist novel oral anticoagulants (NOACs) and the existing therapeutic challenges faced because of VKA, there has been a paradigm shift in oral anticoagulant therapy in AF.

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The aim of this review is to provide a comprehensive summary of current evidence and guidelines on the use of NOACs and VKA in patients with AF.

RISK STRATIFICATION

Stratification of risk of stroke in AF

The first major step before providing stroke prophylaxis in AF patients is to stratify the risk of the patient requiring anticoagulant therapy. CHA2DS2-VASc thromboembolic score6 is being currently recommended to stratify AF patients at low risk (who do not require thromboprophylaxis) and those at high risk (who require thromboprophylaxis). The CHA2DS2-VASc risk stratification score is based on factors such as congestive heart failure, age, hypertension, etc (Table 1). The 2019 AHA/ACC guidelines[7] and 2018 ACCP CHEST guidelines8 have both approved the CHA2DS2-VASc scoring system.

In patients with lone AF, age < 65 years with CHA2DS2-VASc score = 0 (in males) or 1(in females) and without moderate-to-severe mitral stenosis or mechanical heart valve, oral anticoagulant therapy should not be considered.[7,8] In patients with AF (without moderate-to-severe mitral stenosis or mechanical heart valve) and a CHA2DS2-VASc score of ≥ 1 in men and ≥ 2 in females, oral anticoagulants to reduce thromboembolic stroke risk must be considered.[8] The only exclusion criterion of CHA2DS2-VASc score assessment is moderate-to-severe mitral stenosis or a mechanical heart valve.[7]

Table 1 CHA2DS2-VASc scoring system

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Prior Stroke/TIA/Systemic embolism	2
Vascular disease (prior MI, PAD or aortic plaque)	1
Age 65-74 years	1
Sex category(female)	1
Maximum score	**9**

TIA= transient ischaemic attack; MI=myocardial infarction; PAD=peripheral arterial disease

Stratification of bleeding risk in AF

Before prescribing an oral anticoagulant drug in patients with AF, bleeding risk assessment should be performed in all patients with AF at every patient contact, focusing especially on modifying the risk factors which includes uncontrolled BP, labile International Normalized Ratio INR (in patients already taking VKA), alcohol excess, concomitant use of NSAIDs or aspirin and bleeding tendency (eg. treating gastric ulcer, optimizing renal or hepatic function).

HAS-BLED bleeding risk score is recommended at present to assess the bleeding risk.[9] The details have been shown in Table 2. HAS-BLED score predicts the one-year risk of major bleeding in patients with AF who are on antithrombotic therapy (anticoagulant drug or antiplatelet drug or both) or newly diagnosed AF who require an oral anticoagulant. Major bleeding in this context has been defined by the International Society on Thrombosis and Haemostasis[10] as

a) Fatal bleeding, and/or

b) Symptomatic bleeding in a critical area or organ, such as intracranial, intraocular, intraspinal, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome, and/or

c) Bleeding causing a fall in haemoglobin level of 2gm/dl or more, or leading to transfusion of two or more units of whole blood or red blood cells

If HAS-BLED score is ≥ 3, the potential harm caused by the oral anticoagulant offsets its beneficial effect on stroke risk reduction.[9]

Table 2 HAS-BLED scoring system

Risk factor	Score
Hypertension (uncontrolled BP)	1
Abnormal renal/liver dysfunction (1 point each)	1 or 2
Stroke	1
Bleeding history	1
Labile INR*	1
Elderly > 65 years	1
Drugs or alcohol (1 point each)	1 or 2
Maximum score	**9**

*INR= International Normalized Ratio

ORAL ANTICOAGULATION OPTIONS IN AF

Vitamin K antagonist (VKA)

Warfarin is the most commonly used VKA.

Mechanism of action

Warfarin blocks vitamin K epoxide reductase VKOR) enzyme which is encoded by the VKORC1 gene. Warfarin inhibits the conversion of oxidized vitamin K epoxide into its reduced form, vitamin K hydroquinone. This inhibits vitamin K–dependent γ-carboxylation of factors II, VII, IX and X because reduced vitamin K serves as a cofactor for γ-glutamyl carboxylase that catalyses the γ-carboxylation process whereby pro-zymogens are converted to zymogens capable of binding Ca2+ and interacting with anionic phospholipids.[11]

Clinical use of warfarin

Warfarin is used to prevent progression or recurrence of deep vein thrombosis (DVT) or pulmonary embolism (PE). It is also used to prevent stroke or systemic embolization in AF patients or patients with moderate-to-severe mitral stenosis or mechanical heart valve.[11]

Non-vitamin K antagonist novel oral anticoagulants (NOACs)

NOACs include the direct oral thrombin inhibitor dabigatran and direct oral factor Xa inhibitors rivaroxaban, apixaban and edoxaban.

Mechanism of action

Dabigatran is a thrombin inhibitor. It competitively and reversibly blocks the active-site of free and clot-bound thrombin, following which thrombin-mediated conversion of fibrinogen to fibrin is inhibited.[11]

Rivaroxaban, apixaban and edoxaban inhibit free and clot-associated factor Xa, which reduce thrombin generation and suppress platelet aggregation and fibrin formation.[11]

Clinical use of NOACs

Dabigatran is used for treatment of venous thromboembolism after initial treatment

with heparin or low molecular weight heparin. It is also used for stroke prevention in patients with AF. Rivaroxaban, apixaban and edoxaban are indicated for use in stroke prevention in AF patients, DVT and PE.[11] However, NOACs are contraindicated in AF patients with moderate-to-severe mitral stenosis or mechanical heart valve.[7]

Advantages of NOACs over VKA

Warfarin, the preferred VKA prior to approval of NOACs, has important limitations. It exhibits multiple drug–drug interactions, has a broad range of pharmacokinetic variability, requires dietary restrictions and frequent monitoring of INR to ensure adherence to a narrow therapeutic window of 2.0–3.0.[11] NOACs, on the other hand, have a rapid onset of action, short half-life, fewer drug and food interactions, and more predictable pharmacokinetics that allow fixed dosing.[11] The therapeutic window is wide and provides efficacy without the need for laboratory monitoring of anticoagulant effect. With these advantages in use, along with favourable effects compared to VKA in large clinical trials, NOACs are now preferred over VKA in atrial fibrillation.

Choosing Between VKA and NOACs

Time in therapeutic range (TTR) is a validated measure of anticoagulation control and predicts adverse events in patients already receiving VKA.[7] The risk of thromboembolism, major bleeding or death is lower when TTR ≥ 65%.[7] When TTR decreases, the risk of adverse outcomes increases with VKA and switching to NOACs is beneficial.[12] When patients with non-valvular AF are on VKA, target INR should be 2.0-3.0 with attention to individual TTR ≥ 65%.[7]

For patients with AF who are about to start an oral anticoagulant, the quality of anticoagulation can be ascertained by clinical risk score. SAMe-TT2R2 is a clinical risk score whose details have been summarized in Table 3. SAMe-TT2R2 scoring helps to identify AF patients likely to do well on VKA.[7]

a) **Score 0-2:** likely to achieve good TTR, so start with VKA

b) **Score > 2:** less likely to achieve good TTR with VKA, so start directly with NOACs

Table 3 SAMe-TT2R2 scoring system

Risk factor	Score
Sex(female)	1
Age < 60 years	1
Medical history*	1
Treatment (interacting drugs)	1
Tobacco use (within 2 years)	2
Race(non-Caucasian)	2
Maximum score	**8**

*Defined as ≥ 2 from the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral artery disease, congestive heart failure, prior stroke, hepatic or renal disease

In patients with AF who are eligible for oral anticoagulation, NOACs are recommended over VKA if not contraindicated.[6,7] Switching between VKA and NOACs is of paramount importance in patients with AF who are receiving oral anticoagulation therapy. Switching is required as patients may experience complications during oral anticoagulation therapy or worsening of clinical condition (hepatic or kidney dysfunction).

Identifying Proper Clinical Situations for VKA or NOACs

Contraindications to both VKA and NOACs should be identified beforehand. Absolute contraindications to oral anticoagulants like active bleeding or severe anaemia are applicable to both VKA and NOACs.[12] The 2019 AHA/ACC guidelines[7] and 2018 ACCP CHEST guidelines8 suggest that NOACs are not to be used in patients of AF with moderate-to-severe mitral stenosis and mechanical heart valve. The guidelines also introduced categorization known as EHRA (Evaluated Heart Valves; Rheumatic or Artificial) in relation to type of oral anticoagulant use in patients with AF.

AF patients with valvular heart disease (VHD) needing therapy with VKA (EHRA type 1 VHD) include moderate-to-severe mitral stenosis of rheumatic origin and mechanical prosthetic valve replacement. AF patients with VHD needing therapy with VKA or NOACs taking into consideration CHA2DS2-VASc score risk factor components (EHRA type 2 VHD) include mitral regurgitation, mitral valve repair, aortic stenosis, aortic regurgitation, tricuspid stenosis, tricuspid regurgitation, pulmonary stenosis, bioprosthetic valve replacement and trans-aortic valve intervention.[8]

Renal function is a major determinant of choice of oral anticoagulant and dosing in patients with AF. Chronic kidney disease (CKD) is frequently present in AF patients and has significant implications on the trajectory of AF, stroke risk and bleeding risk of anticoagulation. Dabigatran is 80% renally excreted while apixaban has 27% renal excretion and the remaining NOACs have various degrees of renal excretion.[11] Therefore, dose reduction is required with NOACs in AF patients with CKD.

The following four situations in CKD with AF require separate approach in choice of oral anticoagulant and its dosing[7]:

a) **Mild CKD (Stage II, Creatinine clearance 60-89ml/min) :** oral anticoagulant recommendation same as AF patients without CKD

b) **Moderate CKD (Stage III, Creatinine clearance 30-59/min) :** oral anticoagulation with VKA or NOACs in patients with CHA2DS2-VASc ≥ 2 ; if VKA used, TTR > 65-70% is recommended

c) **Severe non-dialysis CKD (Stage IV, Creatinine clearance 15-29/min):** VKA or NOACs should be used with caution based on pharmacokinetic data and reduced doses since all the NOACs have some degree of renal elimination

d) **End stage renal disease (Creatinine clearance <15ml/min or dialysis dependent):** VKA should be used with TTR > 65-70%. NOACs are not recommended in end stage CKD

Edoxaban is the only NOAC which is contraindicated at both creatinine clearance < 15ml/min and > 95 ml/min because of risk of ischemic stroke compared with VKA at higher creatinine clearance.[11]

SPECIAL SITUATIONS

AF + ISCHAEMIC STROKE: If AF patients on anticoagulation with VKA suffer an ischaemic stroke, switching to NOACs is recommended. Conversely, if ischaemic stroke occurs while patient is already on a NOAC, there is no firm evidence regarding

switching to another NOAC. If NOACs are considered, start at ≥ 3 days in patients with mild, ≥ 6-8 days with moderate and ≥ 12-14 days with severe stroke.[13]

AF + ISCHAEMIC HEART DISEASE : The risk of myocardial infarction(MI) is lower in AF patients treated with NOACs than with patients treated with VKA.[14] A major trial (REDUAL-PCI trial) comparing dabigatran + P2Y12 inhibitor versus warfarin + P2Y12 inhibitor + aspirin showed a lower rate of major bleeding without increasing risk of MI and stent thrombosis in dabigatran group.[15] In PIONEER AF-PCI trial rivaroxaban + antiplatelet therapy showed lower rate of significant bleeding but similar efficacy compared to warfarin + antiplatelet therapy in AF patients undergoing percutaneous coronary intervention.[16] In a recent trial conducted in Japan (AFIRE trial), rivaroxaban monotherapy was non-inferior to combination therapy with rivaroxaban + antiplatelet therapy with respect to major adverse cardiovascular events and superior with respect to major bleeding in AF patients with stable coronary artery disease over one year duration.[17]

The 2018 EHRA guidelines[13] and 2019 AHA/ACC guidelines[7] suggest that NOACs are safer than VKA in AF patients with ischaemic heart disease on antiplatelet therapy and should be used regularly.

SPECIFIC ANTIDOTES TO NOACs

Andexanet alpha is a recombinant factor Xa which was approved by USFDA in 2018 as a specific antidote against factor Xa inhibitors for management of life threatening or uncontrollable bleeding. It has markedly reduced anti-factor Xa activity and showed excellent haemostatic efficacy.[18] Idarucizumab is a monoclonal antibody which was approved in 2015 by USFDA as a specific antidote against dabigatran.[19] With the introduction of these antidotes, NOACs have emerged as a better and safer option than VKA.

CONCLUSION

Clinicians are empowered now with various scoring systems to stratify risk of stroke and bleeding in patients with AF. The risk stratification scoring must be accompanied by careful evaluation of individual patient prior to getting VKA or NOACs. NOACs are presently being preferred over VKA as they have significantly reduced risk of major bleeding in patients with AF requiring long term anticoagulation. However, in special situations like end stage renal disease and in patients requiring additional antiplatelet therapy, the advantage of NOACs is yet to be clearly understood. Future large-scale trials are required to fulfil this unmet need.

REFERENCES

1. Morillo CA, Banerjee A, Perel P, Wood D, Jouven X. Atrial fibrillation: the current epidemic. J Geriatr Cardiol 2017; 14:195–203
2. Lip GY, Bawden L, Hodson R. Atrial fibrillation amongst the Indo-Asian general practice population. The West Birmingham Atrial Fibrillation Project. Int J Cardiol 1998; 65:187–92
3. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 2002; 113:359–64.
4. Perera KS, Vanassche T, Bosch J, Swaminathan B, Mundl H, Giruparajah M, et al. Global survey of the frequency of atrial fibrillation-associated stroke: embolic stroke of undetermined source global registry. Stroke 2016; 47:2197–202

5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991; 22:983–8
6. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010; 137:263-72
7. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019; 74:104-32
8. Lip GYH, Banerjee A, Boriani G, Chiang Ce, Fargo R, Freedman B, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest 2018; 154:1121-201
9. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. Chest 2010; 138:1093–100
10. Schulman S, Kearon C on behalf of the subcommittee on control of anticoagulation of the Scientific and Standardization committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Scientific and Standardization Committee Communication. J Thromb Haemost 2005; 3:692–4
11. Hogg K, Weltz JI. Blood coagulation and anticoagulant, fibrinolytic, and antiplatelet drugs. In: Brunton L, Hilal-Dandan R, Knollmann B, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th ed. New York: McGraw Hill Education; 2018: p585-603
12. Pastori D, Menichelli D, Gingis R, Pignatelli P, Violi F. Tailored practical management of patients with atrial fibrillation: a risk factor-based approach. Front Cardiovasc Med 2019; 6:17
13. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eu Heart J 2018; 39:1330–93
14. Lee CJ, Gerds TA, Carlson N, Bonde AN, Gislason GH, Lamberts M, et al. Risk of myocardial infarction in anticoagulated patients with atrial fibrillation. J Am Coll Cardiol 2018; 72:17–26
15. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. New Engl J Med 2017; 377:1513–24
16. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. New Engl J Med 2016; 375:2423–34
17. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, et al. Antithrombotic therapy for atrial fibrillation with stable coronary artery disease. New Engl J Med 2019; 381:1103-13
18. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. N Engl J Med 2019; 380:1326-35
19. Pollack CV Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA. Idarucizumab for dabigatran reversal - full cohort analysis. N Engl J Med 2017; 377:431-41