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What do the guidelines suggest for non-vitamin K antagonist oral anticoagulant use for stroke prevention in atrial fibrillation?

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Vitamin K antagonists (VKAs, e.g. Warfarin) have been the cornerstone of stroke prevention in patients with non-valvular atrial fibrillation (AF) for well over 50 years, being highly efficacious in reducing stroke and mortality in this common arrhythmia. More recent data have shown the relative efficacy, safety, and convenience of the non-VKA oral anticoagulants (NOACs) over warfarin in patients with AF. Guidelines throughout Europe, America, and Canada acknowledge the value of NOACs and many recommend their use as first-line therapy, sometimes preferentially to warfarin. With the recent availability of reversal agents, there is little reason not to prescribe NOACs where appropriate. This article provides an overview of the current international guidelines with regard to NOAC use and highlights key areas by which emerging evidence may change the management of stroke prevention in patients with non-valvular AF.

Introduction

The vitamin K antagonists (VKAs, e.g. Warfarin) have been the cornerstone of stroke prevention in patients with non-valvular atrial fibrillation (AF) for well over 50 years, being highly efficacious in reducing stroke and mortality in this common arrhythmia.[1] In contrast, aspirin is largely ineffective nor safe, and is no longer recommended as monotherapy for stroke prevention in AF, given its neutral or negative net clinical benefit when balancing the lack of stroke prevention with an excess of serious bleeding.[2]

The landscape of anticoagulation for stroke prevention in patients with AF has been altered since 2009 with the availability of the non-VKA oral anticoagulants (NOACs). These drugs were initially referred to as new or novel OACs, or sometimes direct oral anticoagulants (DOACs), but the NOAC acronym has been preferentially retained to refer to non-VKA oral anticoagulants.[3,4] There are now four major outcome trials on the use of NOACs (dabigatran, apixaban, rivaroxaban, and edoxaban) compared with warfarin.[5–8] These drugs compare favourably with warfarin, showing at least non-inferiority in regards to stroke prevention, with a superior safety profile in relation to major bleeding.[9] Indeed, recent data from ancillary analyses from the major trials show that patients taking NOACs are at 30–50% lower risk of major bleeding than with warfarin.[10–12] The results are even more compelling amongst Asians compared with non-Asians.[13] The trial data are recently complemented by reassuring 'real-world' comparative effectiveness and safety data for the NOACs compared with warfarin.[14–17]

Concerns have been raised with regards to the risk of bleeding for patients taking NOACs despite encouraging trial data. Such apprehension is largely driven by the lack of a reversal agent in times of serious/life-threatening bleeding. However, with idarucizumab being recently licenced for use in patients taking the direct thrombin inhibitor, dabigatran, and allowing for rapid (and almost immediate) treatment reversal such concerns may no longer be warranted.[18,19] Other reversal agents are also in development.[20]

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Thus, NOACs provide a better, safer, and more convenient anticoagulation option with a greater net clinical benefit.[9] Accordingly, NOACs are now a well-established option (in addition warfarin) for the prevention of thrombo-embolic events in non-valvular AF and venous thrombo-embolism.

Guidelines regarding the use of NOACs have varied between countries and this largely reflects their current availability along with clinical experience of such forms of anti-coagulation in specific countries. This article provides an overview of the current international guidelines with regard to NOAC use and highlights key areas by which emerging evidence may change the management of stroke prevention in patients with non-valvular AF.

Initiating therapy with non-vitamin K oral anticoagulants

Prior to prescribing anticoagulation patients should be assessed with regards to the risk/benefit of starting such therapy. Stroke and bleeding risks in patients with AF are not homogeneous and risk stratification schemas such as the CHA_2DS_2VASc score (congestive heart failure, hypertension, age 65–74/>75, diabetes mellitus, stroke/transient ischaemic attack (TIA)/thrombo-embolism, vascular disease, female sex) and HAS BLED [hypertension systolic blood pressure (SBP) $>$ 160 mmHg, abnormal liver/renal function (with creatinine $\geq$200 μmol/L), stroke, bleeding history or predisposition, labile international normalised ratio (INR) (INR in range $<$60% of the time), elderly (>65), concomitant drugs/alcohol] are well validated and provide a simple yet concise methods of assessing a patient's suitability for anticoagulation, without the necessity of complex composite scores or multiple biomarkers.[21–23]

Currently four NOACs are recommended for anticoagulation in patients with non valvular atrial fibrillation (NVAF): dabigatran, rivaroxaban, apixaban, and edoxaban. However, their availability and indications for use can vary between countries and sometimes may reflect the financial costs of prescribing these agents long term.

In addition to the clinical decision making when initiating NOAC treatment, the importance of patient education when initiating NOAC therapy should be emphasized.[24,25] The patient must be made aware that missing a dose of NOAC potentially removes the stroke protection due to the markedly shorter half-life of these agents vs. VKAs. In line with this, guidelines also emphasize the need for patient education and involvement in decision making when deciding the most appropriate anticoagulation.

The 2012 American College of Chest Physicians (ACCP) guidelines recommend using the older $CHADS_2$ score for stroke risk stratification, with consideration of non-$CHADS_2$ risk factors (age 65–74, vascular disease and female sex) when deciding on stroke prevention with oral anticoagulants, whether with warfarin or dabigatran.[26] At the time of publication, only dabigatran was licensed. The ACCP guidelines are currently being updated.

Subsequent guidelines have used the CHA_2DS_2VASc score for risk stratification.[27]

The most recent 2016 European Society of Cardiology guidelines on AF management recommend that low-risk patients (CHA_2DS_2VASc score 0 in males, 1 in females) are for no antithrombotic therapy; those with one CHA_2DS_2VASc risk factor (i.e. score 1 in males or 2 in females) be considered for OAC (Class IIa recommendation); and those with $\geq$2 CHA_2DS_2VASc risk factors (i.e. males with score $\geq$2 or females with score $\geq$3) are recommended OAC (Class I recommendation).[28] This categorical approach takes into account that for a Class I recommendation, randomized trial evidence is needed and currently there are no specific randomized trials of patients with one CHA_2DS_2VASc risk factor. The 2016 ESC guidelines give a strong recommendation for using NOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) over VKAs (Class I recommendation).

The 2014 ACC/AHA/HRS guidelines recommend that $CHA_2DS_2VASc \geq 2$ are recommended OAC (Class I recommendation), whereas the low-risk patients (CHA_2DS_2VASc score 0) are for no antithrombotic therapy; for those with CHA_2DS_2VASc 1 OAC, aspirin or no antithrombotic therapy can be considered (Class IIb recommendation).[29] NOACs are considered 'alternatives' to the VKAs.

The Canadian Cardiovascular Society (CCS) guidelines recommend the use of NOACs in preference to warfarin in AF patients suitable for anticoagulation. The most recent update of guidelines continues to propose the 'CCS algorithm' which incorporates some, but not all the CHA_2DS_2VASc criteria.[30] Patients $\geq$65 or with a $CHADS_2$ score of $\geq$1 are recommended for OAC. Those $<$65 with a $CHADS_2$ 0 but with vascular disease are recommended for aspirin.

The evidence-based National Institute for Health and Care Excellence (NICE) recommends using the CHA_2DS_2VASc score to initially identify low-risk patients (CHA_2DS_2VASc score 0 in males, 1 in females) who do not need antithrombotic therapy; following this step, stroke prevention (i.e. warfarin or a NOAC) can be considered for patients with one or more additional stroke risk factors.[31] At the time of NICE guidelines publication, edoxaban was not licenced and thus recommendations are made for apixaban, rivaroxaban, and dabigatran. Of note, NICE highlights the importance regarding INR control in patients taking warfarin and emphasizes patient preferences in the inconvenience of repeated blood tests and fear of bleeding from 'high INRs'. Despite there being individual guidance for three of the NOACs, individual preference for one NOAC over another is not given as no direct head-to-head trials comparing NOACs have yet been completed and indirect comparison studies have not provided reliable means by which to make such recommendations, although they are clearly superior to antiplatelet therapy.[32–34]

The 2013 Asia Pacific Heart Rhythm Society guidelines recommend low-risk patients (CHA_2DS_2VASc score 0) for no antithrombotic therapy, CHA_2DS_2VASc score 1 for dabigatran or apixaban preferentially due to the trials including such patients, and for CHA_2DS_2VASc score $\geq$2, any of the NOACs.[35] In addition, warfarin is recommended, but in elderly patients. They highlight that an INR of 1.6–2.6 may be considered, reflecting the guidelines in Japan. In the Asia-Pacific region, however, there is differential uptake on implementation of NOACs due to different approval status for

each of the four drugs, with countries such as Pakistan having no approval for the use of NOACs. Aspirin is generally not recommended.[35]

Asian patients on warfarin had not only a higher incidence of stroke, major bleeding, and intracranial bleeding compared with non-Asians[36] but also poorer quality of anticoagulation control, with a time in therapeutic range (TTR) of only 55% in the Asian subgroup of the RELY trial.[36] For those receiving NOACs in the randomized trials, the rates of ICH were appreciable lower with Asians, although still having a greater incidence than non-Asians.[13]

The 2013 Japanese Cardiology Society (JCS) guidelines recommend the $CHADS_2$ score for risk stratification of patients with non-valvular AF. JCS recommends low-risk patients ($CHADS_2$ score 0) for no antithrombotic therapy; $CHADS_2$ score 1 for dabigatran or apixaban preferentially due to the trials including such patients, with consideration of rivaroxaban or warfarin as 'alternatives'; and for $CHADS_2 \geq 2$, any of the NOACs or warfarin. For cardiomyopathy, age 65–74 and vascular disease, NOACs or warfarin 'may be considered'.

In summary, current guidelines generally state that NOACs should be considered wherever possible as the first-line therapy for patients suitable for OAC in non-valvular AF, either as alternative or in preference to VKA.

How should we follow up patients started on non-vitamin K oral anticoagulants therapy?

Despite patients being alleviated from the burden of repeated INR testing to ensure TTR is adequate, the use of NOACs still requires particular vigilance. NOACs (like warfarin) are prescribed to an ever ageing and generally frailer population. With this comes heightened risk of bleeding along with the accumulation of comorbidities and concomitant medication.

Current European consensus is that patients initiated on NOAC therapy should have a 1 month follow-up in the first instance in order to check the following: compliance, change in concomitant medication, bleeding events, other side effects along with blood sampling.[37,38] Subsequent follow-ups are dependent upon individual patient profiles along with the NOAC prescribed. For example, patients taking dabigatran should undergo more regular renal function testing, as should the frail, elderly population as all NOACs require dose reduction upon reduced renal function.[37]

Particular attention to renal function is needed, as all the NOACs do have a degree of renal excretion. In order to assess renal function, the Cockcroft Gault method for calculating creatinine clearance (CrCl) is recommended in European guidelines, as this was the method used in the NOAC trials. Of the available NOACs, dabigatran has the highest renal dependency (80% excretion), although the RELY trial did not specify dose reduction in patients with a CrCl below 30–50 mL/min.[39] In the USA, the Food and Drug Agency have approved dabigatran 75 mg b.i.d. for patients with severe renal insufficiency (CrCl 15–30 mL/min); however, outcome data for patient with CrCl <30 mL/min are lacking and thus European licensing (and guidelines) does not recommend

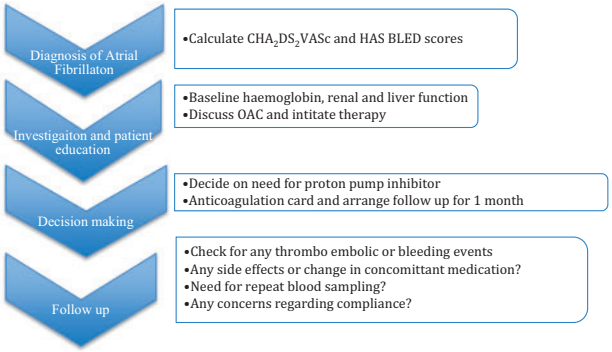

Figure 1 Flow diagram representing approach to initiation and subsequent management of patients prescribed non-vitamin K antagonist oral anticoagulant therapy.

prescribing dabigatran in this population. Rivaroxaban is approved for chronic kidney disease stage IV (i.e. CrCl 15–30 mL/min) provided the lower dose of 15 mg o.d. is used.[40] Apixaban dose reduction to 2.5 mg b.i.d. is recommended in patients >80 years of age, weight <60 kg, or with a serum creatinine >1.5 mg/dL. Studies comparing reduced dose of rivaroxaban and apixaban have shown reduced incidences of major bleeding when compared with warfarin.[41,42] The ENGAGE AF-TIMI (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction) 48 trial shows that the safety and net clinical benefit of Edoxaban are preserved across mild–moderate renal dysfunction.[43]

Despite evidence to suggest a higher risk of stroke and bleeding in Asian population, current guidelines within APHRS, Japan and Taiwan do not specify any follow-up timescale for NOAC-treated patients.[35,40] Guidelines from Japan do make reference to the need to pay vigilance to changes in patient risk profile, namely blood pressure monitoring and use of medication that may (in parallel with NOAC) increase bleeding risk.

Flow diagram representing a suggested approach to initiation and subsequent management of patients prescribed NOAC therapy is shown in *Figure 1*.

Does evidence from clinical trials match 'real-world data'?

Evidence from clinical trials does not always reliably predict outcomes in daily clinical practice. NOACs however have proved that the net clinical benefit seen in clinical trials does indeed translate into 'real-world' clinical practice.

Given that dabigatran has been licensed and available the longest, this NOAC has been compared with warfarin in various 'real-world' studies.[44] Reassuringly, results have broadly echoed clinical trial findings.[45] For example, large US database compromising of 12 793 patients with a mean age of 74 was used to compare dabigatran and warfarin, showing that dabigatran was shown to be superior to warfarin with regards to stroke prevention [adjusted hazard ratio (95% confidence interval) 0.73 (0.55–0.97)] with a lower incidence of major bleeding [adjusted hazard ratio for

intracranial bleeding 0.49 (0.3–0.79)].[15] Broadly consistent findings have been reported by other registries.[16,46] A recent meta-analysis of these observational data (over 20 studies, totalling 711 298 patients) found a lower risk of ischaemic stroke compared with warfarin (hazard ratio 0.86, confidence interval 0.74–0.99) with a lower incidence of intracranial bleeding (0.45, confidence interval 0.38–0.52), but higher risk of gastrointestinal bleeding (1.13, confidence interval 1.00–1.28).[47]

Real-world data regarding rivaroxaban and apixaban are also gathering momentum. The XANTUS observational study is a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in AF, including 6784 patients initiated on rivaroxaban across 311 centres in Europe, Israel, and Canada. Rates of stroke were found to be low in these cohorts of patients with 43 patients suffering a stroke and 43 a major bleed (0.7 events per 100 patient-years and 2.1 events per 100 patient-years).[48] More recently, Coleman *et al.*[49] compared data for AF patients newly started on rivaroxaban, apixaban, or warfarin. When compared with warfarin, rivaroxaban was associated with a reduction in intracranial haemorrhage (0.49% vs. 0.96% per year, hazard ratio 0.53, confidence interval 0.35–0.79), with a non-significant reduction in ischaemic stroke (0.54% vs. 0.83% per year, hazard ratio 0.71, confidence interval 0.47–1.07).[49] The ongoing industry-funded GARFIELD AF registry aims to recruit between 55 and 60 000 patients with AF, investigating trends of anticoagulation use in patients with AF. In the fourth cohort of GARFIELD AF more than 70% of AF patients are anticoagulated, with a growing proportion being initiated on NOAC therapy over warfarin (37%); additionally, anticoagulation is associated with a 35% lower risk of death.[50] Other registry data have since been published for various comparative effectiveness and safety data for dabigatran, rivaroxaban, apixaban, and warfarin.[51–53]

Major limitations of observational studies should be recognized, and include the likelihood of confounding variables, inability to fully control concomitant medication, and difficulty in assessing quality of TTR for patients taking warfarin.[45] Despite this real-world data regarding NOACs are consistent with (and complementary to) randomized control trial results showing a positive net clinical benefit over warfarin in patient with non-valvular AF.

Conclusion

There is little doubt that NOACs provide patients with NVAF a superior net clinical benefit over VKA, with equivalent if not superior stroke protection alongside reduced major bleeding risk. A summary of current recommendations from various guidelines, for the initiation and subsequent management of NOAC therapy is provided in *Table 1*.

Within Europe, the USA, and Canada, the use of NOACs is well established and arguments against its preferential use are few and far between. With the approval of reversal agents on the horizon, upcoming guidance revisions will point to the need to consider NOACs as first-line therapy with warfarin being a suitable alternative, only in those patients that either decline NOAC use or are deemed

Table 1 Summary of current recommendations for the initiation and management of NOAC therapy

NOAC vs. VKA	ESC[54]/EHRA[38] NOAC	ACC/AHA/HRS[27] No preference	CCS[30] NOAC	APHRS[35] NOAC	JCS[43] NOAC
Dose reduction in CKD	Dabigatran not recommended if CrCl<30 mL/min 15 mg o.d. Rivaroxaban if CrCl 30–49 mL/min. 2.5 mg b.i.d. Apixaban if serum creatinine ≥ 1.5 mg/dL. 30 mg (or 15 mg) o.d. Edoxaban if CrCl<50 mL/min	75 mg b.i.d. Dabigatran if CrCl 15–30 mL/min 15 mg o.d. Rivaroxaban if CrCl 15–50 mL/min 2.5 or 5 mg b.i.d. Apixaban if CrCl 30–50 mL/min	In all patients taking NOAC dose reduction to lower dose recommended irrespective of NOAC if eGFR is 30–50 mL/min/1.73 m^2	110 mg b.i.d. Dabigatran if CrCl 30–50 mL/min 15 mg o.d. Rivaroxaban if CrCl 30–50mL/min 2.5 mg b.i.d. Apixiban if serum creatinine ≥ 1.5 mg/dL	Statement advising dose adjustment to lower doses in patients with 'moderate' renal dysfunction
Management of acute severe bleeding/emergency surgery	Consider specific antidote or PCC if antidote unavailable	Not specified	Not specified	Not specified	Administration of VII, IX, FFP Consider dialysis for dabigatran Gastric lavage with activated charcoal
Duration of cessation of NOAC therapy for elective procedures	24 h if low bleeding risk 48 h if high bleeding risk	24 h if low bleeding risk 48 h if high bleeding risk	24 h if low bleeding risk 48 h if high bleeding risk	Up to 5 days for major surgery	Up to 4 days with possible heparin bridging
Follow-up timeline	First follow-up at 1 month	Not specified	Not formally specified but recommendation of annual renal function monitoring	Not specified	Not specified

ESC, European Society of Cardiology; EHRA, European Heart Rhythm Association; ACC, American College Cardiology; ACCP, American College of Chest Physicians; CCS, Canadian Cardiology Society; APHRS, Asian Pacific Heart Rhythm Society; JCS, Japan Cardiology Society; NOAC, non-vitamin K oral anticoagulants; VKA, vitamin K antagonists; CKD, chronic kidney disease; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; PCC, plasma cell concentrate; FFP, fresh frozen plasma.

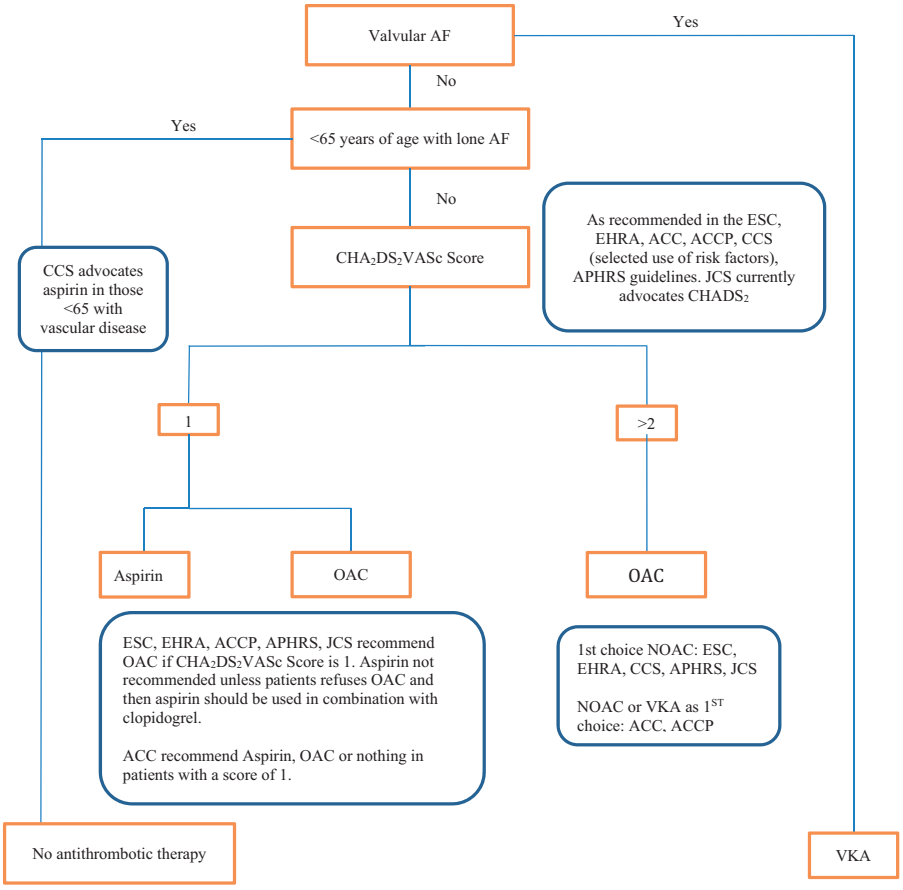

Figure 2 Decision tree for antithrombotic therapy in patients with non-valvular atrial fibrillation: a summary of recent guidelines.

unsuitable. *Figure 2* provides a summary of what recent guidelines state with regard to use of antithrombotic therapy in patients with non-valvular AF.

Conflict of interest: G.Y.H.L. is a consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo and is a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. The other authors declared no conflict of interest.

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