NICE Implementation Collaborative

Consensus

Supporting local implementation of NICE guidance on use of the novel (non-Vitamin K antagonist) oral anticoagulants in non-valvular atrial fibrillation

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Supporting local implementation of NICE guidance on use of the non-Vitamin K antagonist oral anticoagulants (NOACs) in non-valvular atrial fibrillation

This consensus report was developed following a workshop meeting at which health care professionals and patient group representatives discussed barriers to use of the non-Vitamin K antagonist oral anticoagulants (NOACs, previously called new or novel oral anticoagulants) for reducing stroke risk in non-valvular atrial fibrillation and how these barriers might be overcome locally to facilitate appropriate use of the drugs. The meeting was held on behalf of the NICE Implementation Collaborative, which provides support to the NHS to implement NICE technology appraisals.

Key Points

- The three currently licensed NOACs – dabigatran, rivaroxaban and apixaban – have been approved by NICE as options for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- The drugs must therefore be made available for prescribing within their licensed indications, and should be automatically included in local formularies
- Local arrangements for use of antithrombotic therapies in atrial fibrillation should be reviewed and policies developed for integration of NOACs into the care pathway
- The 2014 NICE clinical guideline on atrial fibrillation advises against use of aspirin for stroke prevention. Continued use of aspirin is a barrier to appropriate stroke prevention with oral anticoagulants
- Key groups in whom NOACs should especially be considered include patients who cannot take vitamin K antagonists (VKAs), those who cannot be stabilised on VKAs with poor time in therapeutic range (e.g., <65%) despite adequate adherence, and those taking aspirin for stroke prevention
- Patients must be actively involved with their clinician in decision making about their anticoagulant treatment options and agree the therapy that is best for them
- As there is no need for routine coagulation monitoring with the NOACs, concern has been expressed about patient adherence. Health care professionals should ensure that patients understand why they are taking an anticoagulant for their atrial fibrillation and the expected benefits. Pharmacists can reinforce the importance of treatment each time they dispense patients' prescriptions
- There are, as yet, no specific antidotes for the NOACs but there are steps that can be taken to reverse the drugs' effect in the event of a major bleed
- Primary care prescribing of NOACs needs local leadership. Not all GPs can be expected to be expert in the area of anticoagulation for atrial fibrillation. As the epidemic of atrial fibrillation continues to increase, local anticoagulant "champions" will be needed to take the lead

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THE NICE Implementation Collaborative was set up in 2012 to identify barriers to the implementation of NICE guidance, with the aim of ensuring that patients get quick and more consistent access to approved treatments. It is a partnership between the NHS, the life sciences industry, healthcare professional bodies, key health organisations and the public.

The use of NOACs – dabigatran, rivaroxaban and apixaban – for stroke prevention in non-valvular atrial fibrillation (AF) is one of the key areas that the Collaborative is currently working on.

Current guidance to the NHS in England on atrial fibrillation and the NOACs

An updated NICE clinical guideline on the management of AF is published this month (June 2014).[4] This replaces the 2006 clinical guideline, taking account of new evidence and the introduction of the NOACs. A related Quality Standard to define best practice is expected to be published in due course.

NICE technology appraisals have been issued for each of the currently licensed NOACs,[5–7] with all three drugs approved as options

The importance of stroke prevention in atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia: It affects about 1.6% of the population in England.[1] Men are more commonly affected than women and the prevalence of AF increases with age. AF is a major cause of ischaemic stroke, with the risk of stroke being five times higher than in a person with a normal heart rhythm.[2]

Anticoagulation to reduce the risk of stroke is an essential part of AF management but the Department of Health says that patients are not always appropriately anticoagulated. It suggests that 7,000 strokes could be avoided and 2,100 lives saved each year in England with appropriate AF management.[3]

for the prevention of stroke and systemic embolism in non-valvular AF, within their licensed indications. The recommendations made in the technology appraisals are incorporated into the new clinical guideline.

Current European guidance on AF is the European Society of Cardiology (ESC) guideline. This was published in 2010, with an update covering the new drugs in 2012.[8,9]

Funding arrangements for NICE-approved drugs

It is a statutory obligation for commissioners to make funding available within three months for drugs that have been recommended by a NICE technology appraisal. This point was highlighted in a recent NICE Good Practice Guidance on developing and updating local formularies[10] which says that drugs with a positive NICE technology appraisal should be automatically included within the local formulary. It emphasises that formularies should not duplicate NICE assessments or challenge an appraisal recommendation.

BARRIERS TO USE OF NOACS

Use of aspirin for stroke prevention

One of the barriers to appropriate use of anticoagulants in stroke prevention in AF is the myth about the superior safety of aspirin compared with vitamin K antagonists (VKAs).

Aspirin was included in the 2006 NICE AF clinical guideline for use in certain situations. However, the evidence base has moved on. For example, the 2007 Birmingham Atrial Fibrillation Treatment of the Aged study (BAFTA)[11] showed that for stroke prevention in AF patients aged ≥75 years there was no significant difference in major bleeding (or intracranial bleeding) risk between warfarin and aspirin.

There has been a move away from aspirin in this indication because of its poor efficacy in reducing risk of stroke compared with the oral anticoagulants. In the new NICE clinical guideline,[4] oral anticoagulants (a VKA or a NOAC) are recommended as first-line therapy for patients at increased stroke risk. NICE says that anticoagulation should be offered to people with a CHA_2DS_2VASc score of 2 or more, and considered for men with a CHA_2DS_2VASc score of 1, taking bleeding risk into account.

The guideline states that aspirin monotherapy should not be offered to patients for stroke prevention. National audit data for January – March 2013 from the Royal College of Physicians show that for patients with known AF admitted to hospital with stroke, only 36 per cent were taking an anticoagulant prior

to admission and 38 per cent were taking antiplatelet drugs which the RCP comments "are considered ineffective for patients in AF."[12]

Reversibility of effect

Lack of reversibility is a frequently raised clinician objection to the NOACs. However, although there are, as yet, no specific antidotes for these drugs, there are steps that can be taken to reverse the drugs' effect in the event of a major bleed.

British guidelines on management of bleeding[14] recommend cessation of treatment and general haemostatic measures. For minor bleeding, supportive measures, such as direct pressure, minor surgical intervention and fluid replacement, is recommended.In lifethreatening bleeding, pro-haemostatic agents such as Prothrombin Complex Concentrate (PCC) or activated Prothrombin Complex Concentrate (APCC) can be considered.

Local protocols should be available on management of bleeding in patients taking oral anticoagulants.

Cases of major bleeding are likely to increase as the drugs are used more widely. But it is important to note that in clinical trials all three NOACs were associated with reduced haemorrhagic stroke and intracerebral haemorrhage compared with warfarin.[9] NICE has noted that intracerebral bleeding is the most feared bleeding outcome for patients taking anticoagulants.[7] Recent reports of "real world" experience with dabigatran found that bleeding rates were consistent with the trial data.[15,16]

Cost issues

Although cost is a perceived barrier to the use of NOACs, NICE has concluded that the drugs are cost-effective and must be available to patients within their licensed indications.

Managed introduction of drugs can be useful, starting with the patient groups who are most likely to benefit. With NOACs, this would include patients who cannot take VKAs, those who cannot be stabilised on warfarin with

Current prescribing patterns in primary care

For stroke risk stratification, the 2014 NICE AF guideline, and the ESC guideline, recommend use of CHA_2DS_2VASc rather than the original $CHADS_2$ score. $CHADS_2$ is still included in the Quality and Outcomes Framework indicator sets, but this is under review.

One of the QOF indicators for atrial fibrillation is the percentage of patients with CHADS2 score >1 who are currently treated with anticoagulant. In 2012/13, 65% of patients in England received this intervention, but there is a high degree of exception reporting.[13]

Online data from 2,538 practices in England using the GRASP-AF audit tool show that, in October 2013, of patients with AF who had a $CHADS_2$ score of ≥1, 46% were taking an anticoagulant and 35% were taking an antiplatelet agent.

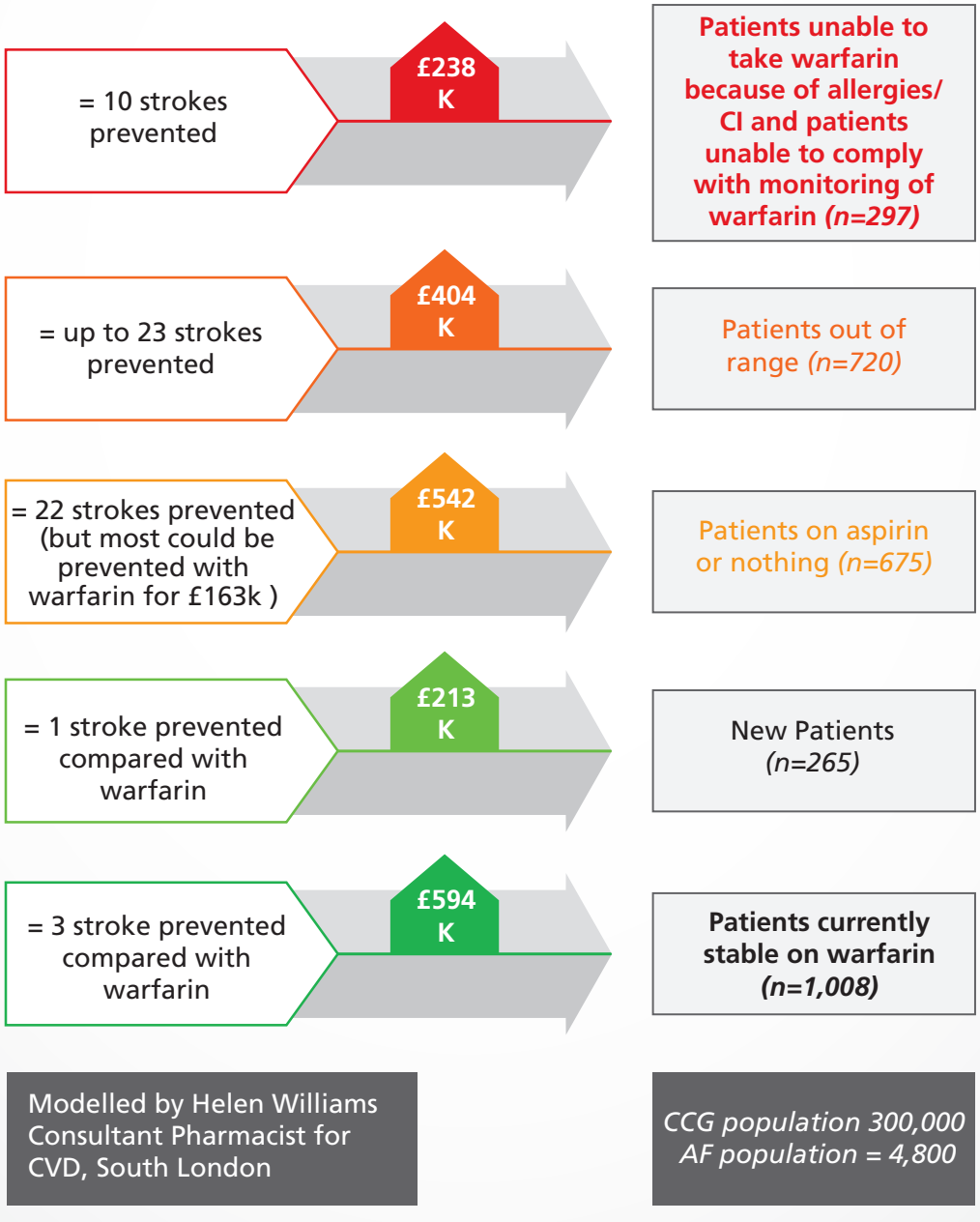
poor time in therapeutic range (e.g., <65%[4]) and those taking aspirin for stroke prevention for whom a NOAC may be an option.

Medical, societal and personal savings from avoiding stroke have to be taken into account.

The budgetary impact of NOAC introduction is demonstrated in the costing model shown in the Panel, which highlights the costs and benefits for specificpatient groups.

A Costing Model for NOACs

The drug acquisition cost (minus the cost of warfarin/INR monitoring) is highlighted for different patient groups together with the expected number of strokes that will be prevented for a CCG of population 300,000



Assumptions and References

Based on CCG population of 300,000; AF prevalence 1.6%[1]; AF population 4,800; assuming 75% require anticoagulation using CHA_2DS_2VASc score (n=3,600) and 75% uptake of anticoagulation in this cohort (n=2,700)

- 11% patients unable to take warfarin because of allergies or contraindications or unable to comply with monitoring[17]
- 41.7% of patients fail to achieve ≥ 65% time within therapeutic range (TTR)[18]
- 25% patients on aspirin or nothing, assuming 75% uptake of warfarin
- Annual new AF incidence rate 0.0886%[19]
- Cost of warfarin = £241 per annum; cost of novel oral anticoagulant = £803 per annum[5]
- Annual stroke event rate in untreated population = 5%[20]
- Warfarin reduces event rates by 64%[21]

Adherence

Because the NOACs have predictable pharmacokinetics, coagulation control does not need to be monitored. This is convenient for both patients and health care professionals. However, with warfarin and the other VKAs the requirement for regular monitoring does have the benefit of re-inforcing to patients the importance of treatment and there is some concern that the lack of monitoring with the NOACs might lead to poor adherence.

There is need for ongoing patient education and support. Health care professionals should ensure that patients understand why they are taking an anticoagulant and the expected benefits. Pharmacists can reinforce the importance of treatment and the need to take every prescribed dose each time they dispense patients' prescriptions.

Good adherence is even more important with the NOACs than with VKAs because of the drugs' relatively short half-lives. With warfarin, patients retain some benefit for 48–72 hours after missing a dose while with NOACs the anticoagulant effect fades rapidly after 12–24 hours.[22]

Programmes for patients to help support adherence may be available from the NOAC manufacturers.

LOCAL CARE PATHWAYS FOR USING NOACs

NICE-approved treatments have to be made available for prescribing, but CCGs have flexibility in how to make this happen and different models will be used to suit local needs.

Arrangements for use of antithrombotic therapies in atrial fibrillation should be reviewed and policies developed for integration of NOACs in the local care pathway. NICE guidance on introducing new medicines to a local formulary[10] emphasises the importance of stakeholder engagement, communication and dissemination.

There should be agreed protocols across primary and secondary care for initiation of NOAC therapy. There have been reports of patients being told they have to try a VKA first, before a NOAC can be considered. There should be no such restrictions and a NOAC can be considered for newly-diagnosed patients, for certain patients who are currently taking a VKA, and for patients currently taking aspirin.

In some cases CCGs might choose to commission a service from the hospital anticoagulant clinics. In primary care, not all

GPs will want to take responsibility for the first prescription of a NOAC (although they should be familiar with the prescribing information). One approach could be for each practice to have a designated health care professional (GP, nurse or pharmacist) with expertise in the area of anticoagulation in AF to take the lead in this.

Local leadership

In Bradford, Yorkshire, an AF Quality Improvement Programme demonstrates what can be achieved with local clinical leadership. The programme was set up to support practices wanting to increase their anticoagulant prescribing. Over 18 months, anticoagulant prescribing for patients with $CHADS_2$ score ≥1 increased from 49% to 65% in practices taking part in the programme. Over 1,000 new patients were started on an anticoagulant, including high-risk patients who have in the past often only been given aspirin. In the lead GP's practice, use of NOACs in patients with $CHADS_2$ score ≥2 increased from 0% to 8.6% in the 18 months to October 2013. Patients taking warfarin who are compliant but have poor INR control are targeted for switching to a NOAC.

NOAC hospital clinic

In Buckinghamshire Healthcare NHS Trust, a pharmacist-led clinic in secondary care was set up to manage the entry of the NOACs, with active review and informed discussion and consideration of the anticoagulant options with patients.[23] Except in an emergency, all NOACs are initiated in this clinic, with agreed criteria for use. Two weeks after the first prescription, patients have a follow-up telephone consultation to check on side effects and any anxieties. In most cases, patients are then discharged to the GP for continuation of prescribing. Preliminary feedback from patients and GPs has been positive. This model is seen as a successful collaboration between primary and secondary care for safe and cost-effective managed entry of the new drugs.

AF clinics in secondary care: The Birmingham experience

When stroke prevention is discussed with newly diagnosed VKA-naïve patients, patients are counselled on the need for oral anticoagulation and the pros and cons of antithrombotic therapy. Clinic staff routinely calculate the CHA_2DS_2-VASc and HAS-BLED scores to assess stroke and bleeding risk, respectively (as recommended in the NICE guideline[4]) and renal function (based on creatinine clearance).

After seeing the doctor, the oral anticoagulant options are then discussed in an extra counselling session in the clinic conducted by a specialist nurse or psychologist. Indications, benefits and risks of oral anticoagulants are explained to patients, as well as the need for compliance. A checklist proforma is signed by the patient and counsellor.

If the patient opts for warfarin, good quality anticoagulation control with TTR>70% is strongly emphasised. The availability of NOACs as an option is also discussed. In patients who are warfarin-naïve, a "trial of warfarin" is not undertaken, as such patients would be at risk of stroke during the initiation phase, while trying to achieve INR stability. The $SAMeTT_2R_2$* $_{24}$ score is used to help identify warfarin-naïve patients who are likely to do well on warfarin ($SAMeTT_2R_2$ score 0–1). Those who are predicted to do less well ($SAMeTT_2R_2$ score >2) are preferentially offered a NOAC.

For patients already on warfarin, their TTR is assessed from their INRs on the computerised records or their anticoagulation booklet.

In patients scheduled for cardioversion, a NOAC is the preferred option to enable early cardioversion, approximately three weeks after initiation of the NOAC. Extra counselling is performed to ensure that the patient fully understands the necessity for compliance as poor compliance would leave the patient unprotected against thromboembolism. A proforma is signed by the patient and counsellor, with emphasis on drug compliance pre- and post-cardioversion.

**$SAMeTT_2R_2$: Sex female, Age <60 years, Medical history (at least 2 of the following – hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease), Treatment (interacting drugs (e.g., amiodarone for rhythm control): All 1 point. Plus current Tobacco use (2 points) and Race (non-Caucasian, 2 points)[24]*

Shared decision making

An essential part of appropriate prescribing of NOACs is to ensure that patients are fully informed and actively involved in decision making about their anticoagulant treatment.

The NICE technology appraisals[5–7] say: "The decision about whether to start treatment [with NOAC] should be made after an informed discussion between the clinician and the person about the risks and benefits [of NOAC] compared with warfarin [and the other NOACs]. For people who are taking warfarin, the potential risks and benefits of switching [to NOAC] should be considered in light of their level of International Normalised Ratio (INR) control."

NICE has emphasised[25] that health care professionals have a duty to help patients make decisions about their treatment "based on an understanding of the likely benefits and risks rather than on misconceptions" and must "accept that patients may have different views from healthcare professionals about the balance of risks, benefits and side effects of medicines." NICE has produced a patient decision aid to support patients and clinicians in choosing between the recommended options for stroke prevention in AF.

For patients, key factors in favour of NOACs include quality of life benefits from removing the lifestyle restrictions and monitoring requirements associated with VKAs. But some patients will be reassured to have regular INR monitoring (and so may prefer warfarin), some might be concerned about the lack of a specific reversal agent and some might choose to have no anticoagulant therapy.

Questions you may wish to ask your doctor about medicines[26,27]

- What are the benefits of this medicine?
- What are the risks in using this medicine?
- What effect might the medicine have on my symptoms and everyday life?
- How long will it take to have an effect?
- Are there any side effects associated with this medicine?
- What other treatments are available?
- Will the medication I am taking be affected by other medication?
- Will food or drink affect my AF or medication?
- What if I miss a dose?
- How often will I need blood tests to check my blood thinning levels (INR)? *[VKA only]*
- Does the GP's surgery offer INR testing, or where will I need to go for this? *[VKA only]*
- How often will I need to have a "check-up"?
- Who can I call if I feel more unwell than usual?
- How can I find out further information?
- Is there a local patient support group?
- What support can you offer me if I decide not to take any medicines?

The Panel shows examples of questions that patients might wish to ask when discussing anticoagulation.

Selecting appropriate patients for NOACs

New patients

NOACs might be prescribed for newly-diagnosed patients if this is the preferred option after discussion of the alternatives.

Patients currently taking warfarin

There will be some patients currently taking warfarin or other VKA for whom a switch to a NOAC is appropriate. These will include:

- Patients who, despite adequate adherence, spend less than 65% of time in therapeutic range,[4] indicating suboptimal anticoagulant control.
- Patients with allergic reactions or intolerance to warfarin
- Patients who have genuine difficulty in attending for INR monitoring

Practical details on making the switch from warfarin are included in product SmPCs and in the EHRA guide.[22]

Patients currently taking aspirin

Patients taking aspirin for stroke prevention are another priority group to consider. These patients can be directly switched from aspirin to a NOAC the next day.

Good practice points for patients taking a NOAC

- After patients start on a NOAC, it is good practice for clinicians to see them for regular review, preferably every three months[22]
- Information on what to do when a dose is missed and on drug interactions (which are currently much fewer than with warfarin) is given in the product SmPCs
- Rivaroxaban (at the dosage used for AF) should be taken with food as this increases its bioavailability. Absorption of dabigatran and apixaban is not affected by food
- Patients should be encouraged to seek advice before taking over-the-counter medicines, including herbal remedies
- Patients should be encouraged to carry an anticoagulant card for use in emergency situations. Several different cards are available, including the traditional "yellow card" but also a "green card" from the AF Association (www.atrialfibrillation.org.uk) or a NOAC card from the European Heart Rhythm Association (www.NOACforAF.eu). There is also a "medication passport" (www.clahrc-northwestlondon.nihr.ac.uk/research-projects/bespoke-projects/my-medication-passport)
- If a patient has a bleed and the NOAC is stopped, it is important to consider restarting the anticoagulant, after discussion with the patient, once the bleeding issue is resolved

Renal function

As the NOACs are at least partially cleared by the kidney, there may be need for dose reduction in renal impairment. Patients with chronic kidney disease will need careful monitoring of renal function, with details of dose modifications in the product SmPCs and in the EHRA guide.[22]

Patients undergoing surgery

There should be local protocols on when to stop a NOAC before elective surgery and invasive procedures, and when to restart the drug. "Bridging anticoagulation" is not generally necessary for planned surgery[22] because of the drugs' predictable decline in effect and rapid onset of action on restarting after surgery.

Practical guide

The European Heart Rhythm Association (EHRA) has produced a practical guide to use of the NOACs in AF, covering a range of common clinical scenarios[22]

Non-valvular AF

The NOACs are licensed for use in non-valvular AF. They must **not** be used in AF patients with rheumatic heart disease (including mitral stenosis) or metal heart valves.

Useful resources

AF Association http://www.atrialfibrillation.org.uk

Anticoagulation Europe http://www.anticoagulationeurope.org

Website developed by the European Heart Rhythm Association of the European Society of Cardiology http://www.afibmatters.org

NICE. You and your prescribed medicines: Enabling and supporting patients to make informed decisions http://publications.nice.org.uk/ifp76

Making the most of your medicines: http://www.rpharms.com/promoting-pharmacy-pdfs/patients---making-the-most-of-medicines.pdf

More technical

Practical guide for NOAC prescribing: www.NOACforAF.eu

NICE. Medicines adherence: Involving patients in decisions about prescribed medicines and supporting adherence. Clinical Guideline 76; 2009. http://guidance.nice.org.uk/CG76

Centre for Pharmacy Postgraduate Education. Essential skills for medicines optimisation. http://www.cppe.ac.uk/learning/Details.asp?TemplateID=EssMedsOpt-E-01&Format=E&ID=115&EventID=43157

Guide on medicines optimisation http://www.rpharms.com/promoting-pharmacy-pdfs/helping-patients-make-the-most-of-their-medicines.pdf

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