

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation

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1 About Healthcare Improvement Scotland

Healthcare Improvement Scotland was launched on 1 April 2011. This health body was created by the Public Services Reform (Scotland) Act 2010¹ and marks a change in the way the quality of healthcare across Scotland will be supported nationally.

Our vision

Our vision is to deliver excellence in improving the quality of the care and experience of every person in Scotland every time they access healthcare.

Our purpose

Our organisation has key responsibility to help NHSScotland and independent healthcare providers to:

- deliver high quality, evidence-based, safe, effective and person-centred care, and
- scrutinise services to provide public assurance about the quality and safety of that care.

What we do

We are building on work previously done by NHS Quality Improvement Scotland and the Care Commission, and our organisation includes:

- Healthcare Environment Inspectorate
- Scottish Health Council
- Scottish Health Technologies Group, and
- Scottish Intercollegiate Guidelines Network (SIGN).

Our work programme supports Scottish Government priorities, in particular those arising from the Healthcare Quality Strategy for NHSScotland. Our work encompasses all three areas of the integrated cycle of improvement with patient focus and public involvement at the heart of all that we do.

The integrated cycle of improvement involves:

- developing **evidence**-based advice, guidance and standards for effective clinical practice
- driving and supporting **improvement** of healthcare practice, and
- providing assurance about the quality and safety of healthcare through **scrutiny** and reporting on performance.

Integrated cycle of improvement



Visit our website: www.healthcareimprovementscotland.org for further information.

2 Introduction

The introduction of new oral anticoagulants, dabigatran etexilate (Pradaxa®) and rivaroxaban (Xarelto®) offers treatment options for non-valvular atrial fibrillation patients previously not suitable for warfarin and potential treatment options for some patients currently on warfarin.

In September 2011, the Scottish Medicines Consortium (SMC) approved the use of dabigatran in Scotland for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation². In February 2012, SMC approved the use of rivaroxaban in Scotland for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation patients who have poor INR control despite evidence that they are complying with a coumarin anticoagulant or are allergic to or unable to tolerate coumarin anticoagulants³.

In recognition that the benefits, risks and place of these new medicines in clinical practice needed to be further explored, Healthcare Improvement Scotland was tasked with facilitating the development of a statement to support their safe and effective use.

This issue is of significant importance to NHSScotland and closely aligns with the quality ambition “ensuring the most appropriate treatments, interventions, support and services will be provided at the right time to everyone who will benefit, and wasteful or harmful variation will be eradicated”⁴, which is high on the agenda of NHSScotland chief executives and chief professional officers.

Status of this advice

The status of Healthcare Improvement Scotland advice and guidance is defined as one of the following three categories; 'mandatory', 'required to consider', or 'for information only'.

This statement is being issued to NHS boards via area drug and therapeutic committees (ADTCs). It is issued as an evidence note to support clinical decision making in relation to the use of oral anticoagulants in the prevention of stroke and systemic embolism in adult non-valvular atrial fibrillation patients, and has the status 'required to consider.' Its recommendations should be taken into account when developing services, however it is a decision for NHS boards whether to adopt the statement as published or adapt it for local use.

3 Development of the statement for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation

Healthcare Improvement Scotland has been providing national leadership and support for the safe and effective use of this new anticoagulant through the development of a national statement.

Expert advisory group

In June 2011, Healthcare Improvement Scotland convened an expert advisory group of doctors, pharmacists and nurse specialists from across Scotland to develop a draft statement. The group considered the benefits and risks of dabigatran in relation to other oral anticoagulants, in particular warfarin. Membership of the expert advisory group is contained in Appendix 1.

The expert advisory group produced a draft statement for consideration by the wider clinical community in NHSScotland.

September 2011 meeting

A national meeting, hosted by Healthcare Improvement Scotland in Edinburgh on 21 September 2011, provided a forum for clinicians, managers and patients to discuss the safe and effective use of dabigatran. The meeting had good representation from NHS boards and included consultant cardiologists, haematologists, stroke physicians, GPs, pharmacists, specialist nurses, healthcare planners and patient representatives.

Participants were asked to comment on the statement before the meeting using an online survey, and were asked the same questions at the end of the meeting to further build consensus.

Issuing the statement

The expert advisory group used the input of NHSScotland colleagues obtained from the online survey and meeting to produce a statement. Healthcare Improvement Scotland issued the statement to NHS board chief executives and area drug and therapeutic committees (ADTCs) in October 2011.

Revising the statement

Following the restricted approval of rivaroxaban by SMC in February 2012 the expert advisory group was reconvened to revise the statement to apply to both dabigatran and rivaroxaban. Healthcare Improvement Scotland will issue the updated statement to NHS board chief executives and area drug and therapeutic committees (ADTCs).

4 Statement for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation

The aim of the statement is to support the safe and effective use of dabigatran and rivaroxaban in NHSScotland.

Through the process outlined above it was agreed that, for the majority of non-valvular atrial fibrillation patients who are well controlled on warfarin, then warfarin should remain the treatment of clinical choice. Particular patient groups were identified where dabigatran or rivaroxaban should be considered as a treatment option.

The statement advises that:

- **on balance of risks and benefits, warfarin remains the anticoagulant of clinical choice for moderate or high risk atrial fibrillation patients (CHA₂DS₂-VASc \geq 2) with good INR control, and**
- **clinicians should consider prescribing dabigatran or rivaroxaban in patients with:**
 - **poor INR control despite evidence that they are complying, or**
 - **allergy to or intolerable side effects from coumarin anticoagulants.**

This statement was agreed with recognition of the fact that dabigatran and rivaroxaban are two new oral anticoagulants and there is little experience of their use in treating non-valvular atrial fibrillation in the UK outwith clinical trial settings.

Draft frequently asked questions for dabigatran

Upon publication of the statement in October 2011 it was agreed that there was a need to support prescribers to ensure patients are aware of the issues contributing to clinical decisions for individuals with non-valvular atrial fibrillation. As such the statement was supported by draft frequently asked questions (FAQs) on the introduction of dabigatran.

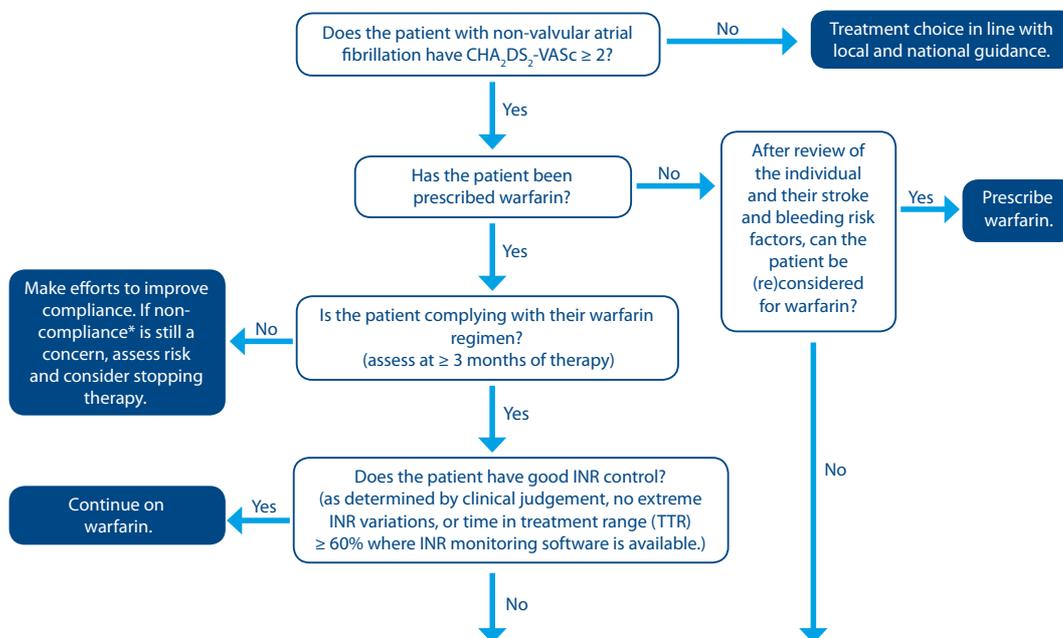
The expert advisory group and a virtual network of GPs identified the key questions and responses for the draft FAQs, which were then shaped by an FAQ subgroup of the expert advisory group and published alongside the statement (see Appendix 2 for membership of the FAQ subgroup).

Healthcare Improvement Scotland has reviewed the draft FAQs and a final version has been published alongside this revised statement.

The dabigatran FAQs are available on the Healthcare Improvement Scotland website www.healthcareimprovementscotland.org.

Statement for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation

On balance of risks and benefits, warfarin remains the anticoagulant of clinical choice for moderate or high risk atrial fibrillation patients (CHA₂DS₂-VASc ≥ 2) with good INR control



Consider prescribing dabigatran or rivaroxaban in patients with:

- poor INR control despite evidence that they are complying
- allergy to or intolerable side effects from coumarin anticoagulants†

Check the licensed indications of dabigatran and rivaroxaban before prescribing – refer to the Summary of Product Characteristics (SPC) available at www.medicines.org.uk for this and other prescribing information.

Many contraindications to warfarin therapy will also apply to dabigatran and rivaroxaban, eg high bleeding risk, severe renal impairment, coagulation disorders and liver failure.

†If patient has allergy to or intolerable side effects from warfarin, consider trying alternative coumarin anticoagulants before decision to prescribe dabigatran or rivaroxaban.

Individual NHS boards may wish to consider prescribing dabigatran or rivaroxaban in those patient groups when the use of warfarin is logistically more challenging, eg patients with inability to access services, difficult venepuncture, poor understanding of the process.

***Non-compliance**

Non-compliance alone is not an indication for initiating therapy with dabigatran or rivaroxaban as many of the causes of non-compliance with warfarin may also result in non-compliance with dabigatran or rivaroxaban, eg alcoholism, chaotic lifestyle, wilful non-compliance.

Monitored dosage systems

The entire unopened blister containing dabigatran must be added to the monitored dosage system (MDS). The practicality of this approach is limited by the blister size and the need for the patient to extract the capsule from the MDS and the blister by peeling off the backing foil. No special storage conditions are required for rivaroxaban.

CHA₂DS₂-VASc scoring

Congestive heart failure (inc LVD)	1
Hypertension	1
Aged 75 or more	2
Diabetes	1
Stroke/TIA/thromboembolism	2
Vascular disease (prior MI, PAD or aortic plaque)	1
Aged 65–74	1
Sex category: female	1

Potential advantages of warfarin over dabigatran and rivaroxaban

- Patients with good INR control using warfarin may achieve slightly better health benefits than those using dabigatran, ie benefits of dabigatran versus warfarin diminish with improving INR control.
- It is easier to manage major bleeding with patients on warfarin. The anticoagulant effect of warfarin is easier to measure and rapid reversal can be achieved with vitamin K and prothrombin complex concentrates. There is currently no licensed product available to rapidly reverse dabigatran and rivaroxaban.
- INR monitoring enables assessment of compliance with warfarin. Dabigatran and rivaroxaban are not monitored routinely but do affect coagulation tests and their interpretation. However, this does not lend easily to assessment of compliance.
- Patients with poor compliance may be at greater risk of thromboembolic complications with dabigatran and rivaroxaban as the shorter half lives will potentially result in more time with insufficient levels of anticoagulation.
- Rates of major GI bleeding and GI symptoms are greater with dabigatran and rivaroxaban.
- The safety profiles of dabigatran and rivaroxaban are still not fully understood and there are no long-term safety data.
- Warfarin has been in clinical use for almost 60 years.

Potential advantages of dabigatran and rivaroxaban over warfarin

- In the RE-LY clinical trial, high dose dabigatran (150mg twice daily) has been shown to reduce risk of stroke compared with warfarin with similar rates of major bleeding. Low dose dabigatran (110mg twice daily) has been shown to reduce risk of major bleeding compared with warfarin but there was no difference in risk of stroke. However, it is important to note that the relative risk of major bleeding with dabigatran, compared to warfarin, increases with age. Relative risk was highest in patients ≥ 75 years.
- In the ROCKET clinical trial, rivaroxaban was non-inferior to warfarin for the prevention of stroke, whilst the rates of major bleeding compared with warfarin were similar.
- There is no need for anticoagulant monitoring.
- The dosing regimens are uncomplicated.
- A more stable level of anticoagulation is achieved.
- There are fewer potential interactions with other medication, alcohol and diet. However, in patients concomitantly receiving verapamil, the dose of dabigatran should be reduced to 110mg twice daily (refer to SPCs for full prescribing information). There is no need to reduce the dose of rivaroxaban when used with verapamil.
- There is a rapid onset of action (2–4 hours after first dose). Use with caution post surgery.
- There is a rapid offset of action. Therapeutic effect lost within 24–48 hours post dose.

RE-LY clinical trial

Connolly SJ, Ezekowitz MD, Yusuf et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139-1151

ROCKET clinical trial

Patel MR, Mahaffey KW, Garg J et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91

Appendix 1: Membership of the expert advisory group

Name	Title	NHS board area/ organisation
Julia Anderson	Consultant Haematologist	NHS Lothian
Moray Baylis	Project Officer	Healthcare Improvement Scotland
Allan Bridges	Consultant Cardiologist	NHS Forth Valley
Alison Campbell	Public Health Pharmacist	NHS Greater Glasgow and Clyde
Andrew Coull	Consultant Physician Medicine of the Elderly	NHS Lothian
Anne Marie Etherington	Nurse Consultant	NHS Greater Glasgow and Clyde
Simon Hart	Consultant Physician Stroke Medicine	NHS Lothian
Christopher Lush	Consultant Haematologist	NHS Highland
David MacDougall	Cath Lab Director & Consultant Cardiologist	NHS Lanarkshire
Stephen McGlynn	Specialist Principal Pharmacist (Cardiology)	NHS Greater Glasgow and Clyde
Laura McIver	Chief Pharmacist	Healthcare Improvement Scotland
Paul Micallef-Eyraud	Lead Clinician Anticoagulant Services	NHS Ayrshire & Arran
Andrew Moore	General Practitioner	NHS Highland
David Murdoch	Consultant Physician and Cardiologist	NHS Greater Glasgow and Clyde
Sandra Nash	Senior Pharmacist Medicine of the Elderly	NHS Lothian
Marjory Neill	Cardiology Pharmacist	NHS Lothian
Joy Nicholson	Consultant Pharmacist	Healthcare Improvement Scotland
David Northridge (Chair to October 2011)	Consultant Cardiologist	NHS Lothian

Appendix 2: Membership of the FAQ subgroup

Name	Title	NHS board area/ organisation
Mary Ballantyne	Chair	Angus Cardiac Group
Moray Baylis	Project Officer	Healthcare Improvement Scotland
Robert Bell	Public Partner	Healthcare Improvement Scotland
Helen Cadden	Public Partner	Healthcare Improvement Scotland
David Clark	Chief Executive	Chest, Heart & Stroke Scotland
Susan Downie	Medical Writer	Healthcare Improvement Scotland
Hirek Kwiatkowski	Patient Representative	NHS Forth Valley
Stella Macpherson	Public Partner	Healthcare Improvement Scotland
Karen McGeary	Communication and Publications Co-ordinator	Healthcare Improvement Scotland
Stephen McGlynn	Specialist Principal Pharmacist (Cardiology)	NHS Greater Glasgow and Clyde
Lorna McTernan	Health Information Manager	Chest, Heart & Stroke Scotland
Isobel Miller	Patient Representative	NHS Lothian
Joyce Mouriki	Senior Public Partnership Officer	Healthcare Improvement Scotland
David Murdoch	Consultant Physician and Cardiologist	NHS Greater Glasgow and Clyde
Joy Nicholson	Consultant Pharmacist	Healthcare Improvement Scotland
Emma Riches	Medical Writer	Healthcare Improvement Scotland

Appendix 3: Glossary

anticoagulants	See coumarin anticoagulants.
arrhythmias	Any variation from the normal, regular heartbeat.
atrial fibrillation	A type of arrhythmia, in which the top chambers of the heart (the atria) beat very rapidly and irregularly, causing the heart to beat in an irregular way.
coumarin anticoagulants	Medications that thin the blood and reduce the risk of blood clots.
CHA₂DS₂-VASc	A clinical scoring system for predicting the future risk of stroke in patients with non-rheumatic, or non-valvular atrial fibrillation. The higher the CHA ₂ DS ₂ -VASc score the greater the risk of stroke.
INR	International Normalised Ratio. A measure of the clotting ability of blood, usually following use of anticoagulant drugs. It is calculated as a ratio of the length of time it takes blood to clot over the time it would take the blood of a normal subject to clot.
monitored dosage systems (MDS)	Medication storage devices designed to simplify taking oral medications for patients.
non-valvular atrial fibrillation	Atrial fibrillation where the heart rhythm is abnormal, but the heart valves are healthy.
systemic embolism	A blood clot causing a blockage in the circulatory system.
TTR	Time in treatment range. A measure of the percentage of time a patient's INR remains within the optimum therapeutic range.

Appendix 4: References

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