West Yorkshire Cardiovascular Network

Recommendations for the Introduction of New Oral Anticoagulants

July 2012
New Oral Anticoagulant Agents for the Prevention of Stroke and Systemic Embolism in Atrial Fibrillation

The West Yorkshire Cardiovascular Network would like to acknowledge both the Bart’s and The London NHS Trust and the Cheshire & Merseyside Cardiac Network for sharing their work related to AF and Stroke Prevention which has contributed to this work.

A number of new novel agents have recently become available to prescribers. At this time, these include Dabigatran Etexilate (Pradaxa) and Rivaroxaban (Xarelto). This document focuses on these.

This guidance has been developed following the publication of NICE TA 249: Dabigatran Etexilate for the prevention of stroke and systemic embolism in atrial fibrillation, and NICE TA 256 Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation.

The West Yorkshire Cardiovascular Network Cardiac Clinical Advisory Group (WYCN CCAG) supports a consistent approach to the introduction of oral anticoagulant agents across the West Yorkshire catchment area.

The focus of AF management should be on identifying patients with AF, undertaking stroke risk assessment using either the CHADS2 or CHA2DS2VASc risk assessment tools and ensuring that appropriate patients at high risk (CHADS2 or CHA2DS2VASc > 1) are offered anticoagulation (please see attached example algorithm).

The WY CCAG recommends that high risk patients who are not currently anticoagulated should be reviewed and offered anticoagulation following a discussion about risks and benefits. This includes patients currently treated with aspirin for the prevention of stroke or systemic embolism in AF, who should have their treatment reviewed and switched to an oral anticoagulant if appropriate (CHADS2 or CHA2DS2VASc >1) and there are no contraindications to oral anticoagulant treatment.

The WY CCAG acknowledge that well controlled Warfarin is a well established, safe and effective treatment option for the prevention of stroke in atrial fibrillation and should be considered the treatment of choice for all current and new patients. It remains the first line treatment.

The WY CCAG are aware of the RCP Guidelines advocating that immediate anticoagulation is required for any patient presenting with confirmed TIA. Low Molecular Weight Heparin (LMWH) is recommended for these patients, followed by the introduction of Warfarin once discharged into primary care.

The WY CCAG recommend novel agents as a second line treatment option, following Warfarin failure, for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more of the following risk factors:

- Previous stroke, transient ischaemic attack or systemic embolism
- Left ventricular ejection fraction below 40%
- Symptomatic heart failure of New York Heart Association (NYHA) class 2 or above
- Age 75 years or older
- Age 65 years or older with one of the following: diabetes mellitus, coronary artery
disease or hypertension.

The decision about whether to start treatment with Warfarin or one of the novel agents should be made after a full and, informed discussion between the clinician and the patient about the relative risks and benefits of each agent.

The WY CCAG supports the careful introduction of novel agents into clinical practice. Priority patients include:

- Those currently taking Warfarin with poor INR control (defined below)
- Those with significant problems associated with the monitoring or taking of Warfarin (either actual in those currently taking Warfarin or likely in those considered appropriate for Warfarin)
- Those who clearly express the desire not to take Warfarin following an informed discussion of the clinical risks and benefits of each agent.

The WY CCAG recommends that individual patient’s TTR\(^1\) information should be documented in their anticoagulant record book by the anticoagulation service to allow assessment of their level of INR control and facilitate the discussion about the risks and benefits of novel agents as a treatment option, and patients with an unstable INR (TTR <65%)\(^1\) should be considered for switching to a novel agent. We are aware that there is no systematic monitoring of the new agents and therefore the recording of the drug (like the use of a “yellow book” with Warfarin) is not currently available, please see attached pre alert card.

*For people currently taking Warfarin, the potential risks and benefits of switching to Dabigatran, or another novel agent should be considered in light of their level of INR control. In people taking Warfarin with good INR control (Time in Therapeutic Range\(^1\) (TTR) >65%)\(^1\), there is little or no evidence of clinical benefit in terms of stroke reduction for switching to a novel agent.*

Reasons for poor control should be explored (in particular poor compliance, interacting co-prescribed medication and diet) before treatment is changed.

Where individual patient TTR\(^1\) information is not available, unstable Warfarin control may be indicated by 2 or more unexplained INR values above 5.0 or below 1.7 during a twelve month period.

Dabigatran and Rivaroxaban are both currently classed as a black triangle drug and experience of their use outside the clinical trial setting is limited and this includes the management of bleeding complications. There is currently no agreed and evidence based reversal strategy for a significant bleed. This is something currently being worked up.

Dabigatran and Rivaroxaban are not suitable alternatives to Warfarin in patients with bleeding complications, contraindications to Warfarin therapy due to a high bleeding risk, poor compliance with Warfarin therapy, a history of alcohol abuse or drug overdose or trivial side effects related to Warfarin. Where compliance and concordance is thought to be an issue, Warfarin has an advantage that it is regularly monitored thus allowing the clinician some prior knowledge of bleed or stroke risk. Although the dose of Dabigatran is constant the tablets are not stable when used in compliance aids such as blister packs. It is also to be noted that Dabigatran cannot be used with dosette boxes which may introduce potential compliance issues for some patients.

Dabigatran is also contraindicated in moderate to severe renal impairment (creatinine clearance\(^2\) < 30ml/min). There is some evidence that in some sub groups, particularly elderly patients and or those with poor renal clearance the more effective dose of Dabigatran (150mg) is less safe than Warfarin. A number of Regulatory Authorities are scrutinising this medicine extensively.

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1. Creatinine clearance should be calculated using the Cockroft and Gault method
2. TTR should be calculated using the Rosendaal method
Comparison of New Oral Anticoagulants with Warfarin - Information for Prescribers

NB – Apixaban, as of June 2012 does not have a marketing authorisation, thus is not included. This will be amended later. This does not reproduce all the information in the SPC, the WY CCAG strongly recommend prescribers consult their BNF before making a prescribing decision.

<table>
<thead>
<tr>
<th>How does it work?</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
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<td></td>
<td>Warfarin has an effect on several steps of the clotting cascade using compounds made with vitamin K by the liver.</td>
<td>Acts as a direct thrombin (factor IIa) inhibitor. It is formulated as Dabigatran Etexilate, a prodrug converted to Dabigatran after administration.</td>
<td>Acts as a selective direct factor Xa inhibitor. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi.</td>
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<table>
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<tr>
<th>What is the evidence?</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
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<tr>
<td>In a meta-analysis, the RR reduction with Warfarin was highly significant and amounted to 64%, corresponding to an absolute annual risk reduction in all strokes of 2.7%. When only ischaemic strokes were considered, adjusted-dose VKA use was associated with a 67% RRR. This reduction was similar for both primary and secondary prevention and for both disabling and non disabling strokes.</td>
<td>The RE-LY study enrolled 18,113 patients with AF, who were at increased risk of stroke. 50% of patients were naive to oral anticoagulants. It was a prospective, open-label, blinded endpoint (PROBE) design. Dabigatran 150mg BD reduced the annual absolute risk of stroke or systemic embolism by 0.6% compared with Warfarin (35% RRR) and by 0.43% (10% RRR) compared with Dabigatran 110mg BD. Both haemorrhagic and ischaemic stroke occurred less often in the Dabigatran 150mg BD group than with Warfarin. Dabigatran was non-inferior to Warfarin. Compared with Warfarin, Dabigatran significantly reduced the incidence of haemorrhagic, but not ischaemic stroke.</td>
<td>ROCKET-AF was a double-blind, double dummy, randomised trial that enrolled 14,264 patients to either Rivaroxaban 20mg od or Warfarin with an INR 2. Patients were moderate to high risk of stroke (CHADS2 ≥3). Patients received 20mg od (15mg od if CrCl 30-49mls/min) or Warfarin. Rivaroxaban was found to be non-inferior to Warfarin for the prevention of stroke and systemic embolism in both the per-protocol and intention-to-treat (ITT) analysis. In the ITT analysis 2.1 events were recorded per 100 patient-years in the Rivaroxaban group compared to 2.4 events with Warfarin (HR 0.88, 95% CI 0.75 to 1.03, p&lt;0.001). A superiority test was pre-specified in the ITT population, but did not reach statistical significance. In the ITT population, 30% of outcome events in the Rivaroxaban arm occurred after discontinuation of treatment, compared with 22% of events in the Warfarin arm. This indicates a possible rebound effect, which may be related to the relatively short half life (5-13 hrs).</td>
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<td><strong>Dose and Administration</strong></td>
<td>Variable dose taken once daily dependent on INR</td>
<td>Patients under 80 years - 150mg twice daily(^2) Patients ≥80 years - 110mg twice daily (due to the increased risk of bleeding in this population) Consider 110 mg twice daily when the thromboembolic risk is low and the bleeding risk is high(^2) or patients weigh &lt;50kg(^2)</td>
<td>20mg once daily(^{10}) 15mg once daily when CrCl is 15-49 ml/min (^{10})</td>
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<td><strong>Monitoring</strong></td>
<td>Needs to be adjusted to the individual needs of the patient and therefore requires regular monitoring using blood tests.</td>
<td>Available in two strengths which have predictable effects, meaning that the drug does not need the same level of monitoring as Warfarin. Renal function should be assessed in all patients before starting Dabigatran and at least once a year in patients &gt;75 years or those with a suspected decline in renal function(^5). A number of cases of serious and fatal haemorrhage have been reported in elderly patients with renal impairment who were receiving Dabigatran.</td>
<td>Available in two strengths which have predictable effects, meaning that the drug does not need the same level of monitoring as Warfarin.</td>
</tr>
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<td><strong>Safety</strong></td>
<td>Long-term safety based on 50 years’ use in clinical practice.</td>
<td>No information available on long-term safety. Cannot be used if CrCl &lt;30mls/min</td>
<td>No information available on long-term safety. CrCl 15-49mls/min a reduced dose is recommended(^{10}). Cannot be used if CrCl&lt;15ml/min</td>
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<td>Bleeding</td>
<td>See respective agent for comparison</td>
<td>RE-LY³ showed: Major bleeding rates were similar for Dabigatran 150mg bd and Warfarin; however major bleeding was lower with Dabigatran 110mg BD than with Warfarin. The incidence of GI bleeding was significantly higher with Dabigatran 150mg bd (p=0.0008), but similar with Dabigatran 110mg bd (p=0.52), than in patients treated with Warfarin. Intracranial bleeding was uncommon but higher with Warfarin. Dabigatran 150mg bd reduced the absolute risk of intracranial bleeding compared with Warfarin (0.32% vs 0.76% respectively) A recent audit of bleeding events with Dabigatran highlighted that frail, elderly patients particularly with renal impairment and low body weight are at risk of increased bleeds⁴.</td>
<td>ROCKET-AF¹¹ showed: No significant difference in the primary safety endpoint of major or non-major clinically relevant bleeding was seen in ROCKET-AF. GI bleeding was more common with Rivaroxaban than Warfarin (3.2% vs.2.2%, p=&lt;0.001), as were a decrease in Hb of &gt;2g/dl (4.3% vs. 3.6%, p=0.02), need for transfusion (2.6% vs. 2.1%, p=0.04), epistaxis (10.1% vs. 8.6%, p&lt;0.05), and haematuria (4.2% vs. 3.4%, p&lt;0.05). Intracranial haemorrhage was less common with Rivaroxaban than Warfarin (0.8% vs. 1.2%, p=0.02), as were critical bleeding (1.3% vs. 1.9%, p=0.007) and fatal bleeding (0.4% vs. 0.8%, p=0.003).</td>
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| Side effects | Other side effects can include hair loss | Dyspepsia occurred at a higher rate with both doses of Dabigatran, compared with Warfarin. These events may be due in part to the acidic core of the Dabigatran Etxilate capsule formulation (the tartaric acid core lowers pH and enhances Dabigatran Etxilate absorption). These GI adverse events frequently led to drug discontinuation (7%, 6.5% and 3.9% in the Dabigatran 150mg, 110mg and Warfarin groups respectively)\(^3\).

There was a non-significant increase in the number of myocardial infarctions (MI) in patients taking Dabigatran compared to Warfarin (0.82% for 110mg and 0.81% for 150mg vs. 0.64% \(p=0.12\))\(^3,6,7\).

A meta-analysis\(^8\) combining 7 studies showed Dabigatran was significantly associated with a higher risk of MI or ACS than that seen with agents used in the control group. The control group varied and included enoxoparin, Warfarin and placebo\(^8\).

| Reversibility | Effective and well known antidote, should a severe bleed occur whilst being treated | No antidotes currently known. Patients with bleeding risk factors were excluded from RE-LY. Haemodialysis will clear Dabigatran\(^9\).

The serious consequences of the lack of an effective reversal agent should not be underestimated. Prolonged bleeding has increased morbidity and possibly contributed to deaths \(^4\).

|  |  | There were no significant differences in the incidence of any other adverse event other than bleeding in ROCKET-AF\(^10\) (81% with Rivaroxaban vs 82% of Warfarin patients). The most frequently reported adverse events in the Rivaroxaban group were epistaxis (10%), peripheral oedema (6.1%) and dizziness (6.1%), and in the Warfarin group were epistaxis (8.6%), nasopharyngitis (6.4%) and dizziness (6.3%).

The rate of MI was numerically, but not statistically, significantly lower in the Rivaroxaban arm compared with the Warfarin group\(^11\). |
<table>
<thead>
<tr>
<th>Interactions</th>
<th>Drug-food interactions</th>
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<td></td>
<td>Cranberry juice and alcohol interact with Warfarin. Some foods interact with Warfarin (e.g., foods containing high amounts of Vitamin K).</td>
<td>Currently there are no known food interactions.</td>
<td>Currently there are no known food interactions.</td>
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<td>Many interactions requiring additional INR monitoring.</td>
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<td>Drug-drug interactions</td>
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<td>No effect on cytochrome P450, so the potential for cytochrome P450 drug interactions is low. There is a potential for P-gp interactions. Concomitant treatment with systemic and P-gp inhibitors. These active substances are strong inhibitors or both CYP3A4 and P-gp. Rivaroxaban has no effect on any major CYP isoforms like CYP3A4.</td>
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<td>Drug-drug interactions</td>
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<td>Not recommended with concomitant systemic treatment with azole-antimycotics e.g., ketoconazole, itraconazole, voriconazole or HIV protease inhibitors. These active substances are strong inhibitors or both CYP3A4 and P-gp. Rivaroxaban has no effect on any major CYP isoforms like CYP3A4.</td>
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| Contraindications | Haemorrhagic stroke | Severe renal impairment (CrCL < 30 ml/min) | Hypersensitivity to the active substance or to any of the excipients. Clinically significant active bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C. Pregnancy and breast feeding. CrCl <15 mls/min is contraindicated.

| When should it be avoided? | Intolerance to Warfarin including allergy, rash, side effects likely to result in discontinuation of therapy (other than bleeding complications) e.g., severe alopecia (although acenocoumarol may be a suitable alternative in these patients). Demonstrated unmanageable Warfarin control due to long term interacting drug therapy (INR persistently and significantly above or below range that does not respond to dose titration) | AVOID Dabigatran in patients with a history of poor medication adherence. Dabigatran is not stable in compliance aids such as blister packs. | AVOID Rivaroxaban in patients with a history of poor medication adherence. |
| | | AVOID in patients with severe renal impairment and patients with liver disease or severe hepatic impairment. | AVOID in patients with severe renal impairment and patients with liver disease or severe hepatic impairment. Rivaroxaban is not a suitable alternative to Warfarin in patients with bleeding complications associated with Warfarin treatment, contraindications to Warfarin therapy due to a high bleeding risk or trivial side effects related to Warfarin. |
References
WHAT SHOULD I KNOW ABOUT XARELTO?

- Xarelto, an anticoagulant, acts to prevent you from suffering dangerous blood clots.
- Xarelto must be taken exactly as prescribed by your doctor. To ensure optimal protection from blood clots, never skip a dose.
- You must not stop taking Xarelto without first talking to your doctor as your risk of blood clots may increase.
- Speak to your health care provider before taking any other medication.
- Inform your health care providers that you are taking Xarelto prior to any surgery or invasive procedure.

WHEN SHOULD I SEEK ADVICE FROM MY HEALTH CARE PROVIDER?

When taking an anticoagulant such as Xarelto, it is important to be aware of its possible side effects. Bleeding is the most common side effect. Do not start taking Xarelto if you are at risk of abnormal bleeding, without first discussing this with your doctor.

Tell your health care provider straight away if you have any signs or symptoms of bleeding such as the following:

- unexplained dizziness or weakness
- swelling and discomfort
- sudden, severe headache
- unusual bruising, nosebleeds, bleeding of gums, cuts that take a long time to stop bleeding
- menstrual flow or vaginal bleeding that is heavier than normal
- pink or brown urine, red or black stools
- coughing up blood, or vomiting blood or material that looks like coffee grounds.

Please read the Patient Information Leaflet for further information on Xarelto and its side effects.

HOW DO I TAKE XARELTO

- To ensure optimal protection, Xarelto must be taken with food.

PATIENT ALERT CARD

Xarelto® 15mg
Xarelto® 20mg

- KEEP THIS CARD WITH YOU AT ALL TIMES
- PRESENT THIS CARD TO EVERY PHYSICIAN OR DENTIST PRIOR TO TREATMENT

Date of preparation: May 2012
UK.PH.GM.XAR.2012.223
I AM UNDER ANTICOAGULATION TREATMENT WITH XARELTO (RIVAROXaban)

<table>
<thead>
<tr>
<th>Name</th>
<th>Other medications/conditions</th>
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I AM USING XARELTO 15MG □
XARELTO 20MG □

Doctor’s name
Doctor’s phone
Doctor’s stamp

IN CASE OF EMERGENCY
PLEASE NOTIFY

NAME

Phone
Relationship

INFORMATION FOR HEALTH CARE PROVIDERS

- INR values should not be used as they are not a dependable measure of the anticoagulant activity of Xarelto
- Please refer to the SmPC as this gives further information on testing

PLEASE ALSO NOTIFY

Name
Contraindications to the Initiation of Oral Anticoagulants & Anti-platelet Agents in Patients with Atrial Fibrillation in Primary Care

As a patient's relative stroke & bleeding risk can change, it is essential that all AF patients are reviewed at LEAST annually for a re-assessment of their stroke versus bleeding risk & the anti-thrombotic treatment option of choice.

Contraindications listed below apply to BOTH anti-platelet agents (e.g. aspirin, clopidogrel, dipyridamole) & ALL oral anticoagulants (e.g. warfarin, phenindione, dabigatran, rivaroxaban) except where indicated.

Absolute Contraindications
- Known large oesophageal varices.
- Significant thrombocytopenia (platelet count < 50 x 10^9/L) - refer to haematologist.
- Within 72 hours of major surgery with risk of severe bleeding - defer & reassess risk postoperatively.
- Previously documented hypersensitivity to either the drug or excipients – consider cardiology opinion.
- Acute clinically significant bleed - defer & re-assess stroke versus bleeding risk within 3 months.
- Decompensated liver disease or deranged baseline clotting screen (INR>1.5) – refer to Gastroenterology /Hepatology. Contraindication applies to oral anticoagulants only
- Pregnancy or within 48 hours post partum - seek urgent haematological/obstetric/cardiology advice. Contraindication applies to oral anticoagulants only.
- Severe renal impairment (GFR < 30 mL/min/1.73 m2 or on dialysis). Contraindication applies to dabigatran only.

Relative Contraindications
- Previous history intracranial haemorrhage - as some AF patients especially those considered at higher stroke risk (i.e. CHADS2 score ≥3) may benefit from anti-coagulant and anti-platelet therapy, seek the opinion of a stroke specialist.
- Recent major extracranial bleed within the last 6 months where the cause has not been identified or treated – decision for oral anti-thrombotic therapy should be deferred.
- Recent documented peptic ulcer (PU) within last 3 months – decision for oral anti-thrombotic therapy should be deferred until treatment for PU completed. In all cases with history PU give PPI cover whilst on anti-thrombotic.
- Recent history recurrent iatrogenic falls in patient at higher bleeding risk.

A patient at higher bleeding risk is assessed by having 3 or more of the following risk factors:-
- age > 65 years
- previous history bleed or predisposition to bleeding (e.g. diverticulitis)
- uncontrolled hypertension
- severe renal impairment (i.e. serum creatinine > 200umol/L, GFR < 30 mL/min/1.73 m2 or on dialysis)
- acute hepatic impairment (e.g. bilirubin > 2xULN + LFTS > 3x ULN), chronic liver disease (eg cirrhosis)
- low platelet count < 80 x 10^9/L or a thrombocytopenia or anaemia of undiagnosed cause
- on concomitant drugs associated with an increased bleeding risk eg SSRIs, oral steroids, NSAIDs, methotrexate or other immune-suppressant agents.

NB: A risk of falls is not a contraindication to initiating oral anticoagulation (e.g. a patient with an annual stroke risk of 5% (CHADS2 score 2-3) would need to fall 295 times for fall risk to outweigh stroke reduction benefit of warfarin).

- Dementia or marked cognitive impairment with poor medicines compliance & no access to carer support.
- Chronic alcohol abuse – especially if associated with binge drinking.

N.B. Poor compliance with any oral anticoagulant agent will reduce benefits but may increase risks associated with treatment.
Contraindications to the Initiation of Oral Anticoagulant & Anti-Platelet Therapy for Atrial Fibrillation in Primary Care - Supporting Information & Acknowledgements.

Summary
The aim of this document is to give GPs a pragmatic decision guide on the absolute and relative contraindications to oral anticoagulants and anti-platelet agents in AF management in primary care. The information given has been drawn from “expert clinical opinion” together with established documented clinical evidence where available.

The key message is that although aspirin or aspirin/clopidogrel combinations may be chosen in preference to oral anticoagulants to reduce stroke risk in AF, the contraindications to using anti-platelet agents almost mirror those of oral anticoagulants. In addition the reduction in stroke risk in AF conferred by antplatelets has never been shown to be as effective as oral anticoagulants.

Key Supporting References
  - Recommendation that selection of anti-thrombotic therapy should be based upon the absolute risks of stroke/thrombo-embolism and bleeding and the relative risk and benefit for a given patient. Highlights the use of the ‘HAS-BLED’ bleeding risk score as a tool to assess bleeding risk in AF patients.
  - Latest updated BCSH guidance- includes statement re concomitant use of anticoagulants & anti-platelets
  - BAFTA study showed clear superiority of warfarin over aspirin with no increase in risk of major haemorrhage. Mean age of population was 81.5 years.
  - Recurrent stroke among survivors of primary intracranial haemorrhage (ICH) occurs at a rate of about 4% per patient year and most are recurrent ICH. Survivors of ICH likely to have a higher risk of recurrent ICH than of ischaemic stroke with CHADS 2 score < 3. (Adjusted annual stroke rate with CHADS 2 score 2.3 is 5.9%)
  - Showed a calculated risk of a subdural haemorrhage from falling in patients with annual stroke risk 5% would require a patient to fall 295 times for falls risk to outweigh stroke reduction benefit of warfarin.

2. The ACTIVE Writing Group on behalf of the ACTIVE investigators. Lancet 2006; 367: 1903–

12
- Study found incidence of bleeding was significantly greater with aspirin + clopidogrel compared with warfarin (19.3% vs. 16.5%; NNH 35; RR=1.21, 95% CI 1.08–1.35, P=0.001).
  - Study found significant difference in bleeding complications between those patients prescribed at least three additional medicines & those prescribed less than three.
  - Found history of bleeding to be a significant independent predictor of future bleeding events.
- PROGRESS Collaborative Group. RCT of a perindopril-based BP-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001 Sep 29;358(9287):1033-41
  - Study showed importance of BP control in patients with cerebrovascular disease in significantly lowering risk of first ICH.
  - Study found both systolic and diastolic BP to be significantly higher in those patients with bleeding complications than in those without bleeding complications.
  - Oesophageal varices develop in patients with cirrhosis at an annual rate of 5–8%, but varices large enough to pose a risk of bleeding occur in only 1–2% of cases. Approx 4–30% of pts with small varices will develop large varices each year & therefore be at risk of bleeding. Mortality resulting from bleeding depends on the severity of the underlying liver disease.
- Summary Product Characteristics for Marevan (warfarin) Pradaxa (Dabigatran); Plavix (Clopidogrel). Electronic Medicines Compendium @ http://www.medicines.org.uk

Acknowledgements
This document was written in collaboration with Dr Matthew Fay, GP & NHS Heart Improvement Clinical Lead and Dr Paul Guyler, Lead Stroke Consultant Southend University Hospital NHS Foundation Trust and Stroke Improvement Programme Associate, with contributions received from various clinical healthcare professionals/ specialists in cardiology, neurology, haematology and gastroenterology. Thanks to NHS Buckinghamshire for sharing the document
Dabigatran (Praxada®), Rivaroxaban (Xarelto®)
GP Information and Patient Frequently asked Questions

Atrial fibrillation (AF for short) is a condition that affects the heart, causing it to beat irregularly. AF is also associated with an increased risk of stroke. Patients with additional risk factors such as coronary heart disease, age >70 years or previous stroke are deemed to be at high risk of stroke.

The anticoagulant drug warfarin is highly effective at reducing risk of strokes, and is therefore prescribed for patients at high risk. Warfarin therapy requires regular blood tests in order to ensure that the dose prescribed ‘thins’ the blood down to the required level.

The new oral agents including dabigatran etexilate (Pradaxa®) and rivaroxaban (Xarelto®) have recently been licensed as an alternative to warfarin for patients with atrial fibrillation who are at high risk of stroke. This has been shown to be most beneficial for people in whom it is difficult to achieve blood results within the recommended range with warfarin. There is much less evidence that the benefit for those that are stable and well controlled on warfarin, the novel agents also have a number of disadvantages such as:

- Dabigatran needs to be taken twice daily (warfarin is once daily), conceivably this might exacerbate compliance problems if they are there.
- Dabigatran has a higher incidence of indigestion than warfarin
- Studies show that slightly more patients give up dabigatran and rivaroxaban, compared with warfarin
- Whilst regular INR monitoring might be inconvenient, it does give some advantages in that it allows adjustments to be made and the clinician can actively discuss the therapy and compliance with their patients.
- In the event of an overdose or bleeding with dabigatran or rivaroxaban there is not yet an evidence based or proven way of reversing, unlike warfarin
- New agents are significantly more expensive than warfarin

Following extensive discussion and consideration of all the available evidence, the West Yorkshire Cardiac Clinical Advisory Group (WY CCAG) have produced a guideline for the safe and effective introduction of the new agents as well as considered the risks and benefits of them compared to warfarin. Based on this, Prescribers have been advised that they should only consider prescribing the novel agents when:

- Warfarin has been prescribed for a period of at least 6 months and most of the blood tests have been out of the target range, despite good compliance with treatment
- A patient is allergic to or intolerant of warfarin (see CI information sheet)
- Those who clearly express the desire not to take warfarin following a full and informed discussion of the risks and benefits of each agent
- Warfarin is also prescribed for conditions other than atrial fibrillation, such as deep vein thrombosis. At this stage there is little experience of using dabigatran for these other conditions, therefore it is not recommended.
Patient frequently asked questions

Q: **What is Atrial Fibrillation?**

A: Atrial Fibrillation (known as AF) is a condition that affects the heart, causing it to beat irregularly. People with AF may be at an increased risk of blood clots because their heart does not pump blood round the body as efficiently as usual. This means they may be more likely to have a stroke, which can happen if a clot blocks an artery in the brain.

Q: **What are dabigatran and rivaroxaban and what are they used for?**

A: Both these drugs are new types of oral anticoagulants. They are used to lower the risk of blood clots in people with AF and other factors for stroke. Dabigatran does this by interfering with a substance in the body (Thrombin) that is involved in the development of blood clots and rivaroxaban helps by stopping a substance called Factor Xa from working which aids in the binding together of a clot. Whereas these agents work by only stopping one blood clotting formation warfarin works by interfering with a wide range of substances.

Q: **Which of the new agents is better?**

A: As the trials for both of these new agents have not been directly compared with each other in a clinical trail it is not possible to say if one is better than the other. They share some of the same advantages and disadvantages compared to warfarin, but because they work slightly differently, they also have some unique characteristics that make them better suited for different types of patients. Your doctor will consider individual patient needs when deciding on which medication to prescribe.

Q: **For patients with AF, is it worth changing from warfarin?**

A: Warfarin has been prescribed for more than 50 years and therefore there is plenty of experience of its clinical use. Trials have shown that when warfarin is used well, it is probably as effective as any of the newer agents currently available and, if anticoagulant control is very good (as measured by blood tests), warfarin may be better overall.

Q: **Do the new agents cause less bleeding than warfarin?**

A: As dabigatran, rivaroxaban and warfarin all affect blood clotting, patients may experience side effects such as bruising and bleeding. Rivaroxaban also caused more nose-bleeds and haematuria (blood in urine) than warfarin in a clinical trial. Intracranial bleeding (bleeding into the brain) is worrying because it is usually very serious. In clinical trials, dabigatran and rivaroxaban both caused less intracranial bleeding than warfarin. Gastrointestinal (stomach and bowel) bleeding is also a concern as it varies widely in terms of severity and is more common. Sever gastrointestinal bleeds occurred more often in the new agents that warfarin in clinical trials.

Q: **If bleeding occurs with the new agents can it be reversed?**

A: There is currently no antidote for dabigatran and rivaroxaban. However, if urgent treatment is required the drugs will be discontinued and supportive measures will be started. It is more difficult to manage major bleeding in patients on a new agent.

Q: **Are the new agents associated with any side effects?**

A: All anticoagulants are associated with side effects. In the clinical trials, more patients stopped taking dabigatran and rivaroxaban than warfarin because of side effects. Dabigatran caused more gastrointestinal symptoms than warfarin (e.g. indigestion and stomach ache) and rivaroxaban caused more nose-bleeds and haematuria (blood in urine) than warfarin.
Q: What happens if I miss a dose of dabigatran or rivaroxaban?

A: Your doctor will tell you what to do if you miss a dose, but do not take a double dose to make up for a missed dose.

It is important to take your regular dose as agreed with your doctor, if you find it difficult to take your regular dose; the new agents may not be the right solution for you. This is because the protective effect against strokes wears off quicker after take dabigatran and rivaroxaban than it does warfarin, warfarin stays in our system for longer so that even if you miss a dose you will have some protection against the risk of stroke.

Q: Do the new agents interact with other medicines, food or alcohol?

A: Dabigatran and rivaroxaban have fewer potential interactions with other medicines compared with warfarin, and at present there are no known interactions with specific foods or alcohol. There are some medicines that dabigatran and rivaroxaban do interact with, so patients should inform their prescriber and pharmacists if the names if all medicines they are taking (including over the counter medicines), vitamins and herbal supplements such as St Johns Wort.

Q: Are regular blood tests needed to monitor the new agents?

A: There is no need for regular blood tests to measure either dabigatran or rivaroxaban. However, a blood test is needed to measure how well the kidneys are working before starting treatment with dabigatran and then at least once a year whilst on dabigatran treatment.

Q: Should patients stop taking dabigatran or rivaroxaban if they are going to have a dental or medical procedure?

A: Patients should always tell their healthcare professional (doctor, dentist, nurse or pharmacist) that they are taking anticoagulants. Patients should NOT stop taking dabigatran or rivaroxaban without first talking to their doctor or dentist. The new agents may need to be stopped for one or more days before any planned surgery, dental or medical procedure.

Thanks to Kent, Surrey and Sussex Health Policy Support Unit for the sharing of their developed frequently asked questions
Patient Information – Dabigatran (Pradaxa®) & Rivoroxaban

Atrial fibrillation is a disorder of heart rhythm which is associated with an increased risk of stroke. Patients with additional risk factors, such as coronary heart disease, age >70 years or previous stroke are deemed to be at high risk of stroke.

The anticoagulant drug warfarin is highly effective at reducing risk of strokes and is therefore prescribed for patients at high risk. Warfarin therapy requires regular blood tests in order to ensure that the dose prescribed ‘thins’ the blood down to the required level.

The drugs Dabigatran (Pradaxa®) and Rivoroxaban are recently licensed alternatives to warfarin for patients with atrial fibrillation who are at high risk of stroke. This has been shown to benefit people in whom it is difficult to achieve blood results within the recommended range with warfarin. The benefits to patients treated with warfarin who are stable and well controlled are less. The new agents also have a number of disadvantages such as:

- Dabigatran needs to be taken twice daily (warfarin is once daily).
- Dabigatran has a higher incidence of indigestion than warfarin.
- Studies show that more patients give up Dabigatran, compared with warfarin.
- There is an increase in heart attacks on Dabigatran compared with warfarin.
- Both Dabigatran and warfarin are associated with an increased risk of bleeding. Whilst regular INR monitoring might be inconvenient, it does provide an advantage in that it allows adjustments to be made.
- In the event of an overdose or bleeding, with Dabigatran there is no way of reversing the drug effect, unlike warfarin.
- Dabigatran is significantly more expensive than warfarin.

The West Yorkshire Cardiovascular Network Clinical Advisory Group (WYCCAG), whose members span the whole district in the specialty of cardiovascular medicine (this includes Cardiologists, Care of the Elderly Physicians, Stroke Physicians and Haematologists) have considered the risks and benefits of the new agents compared to warfarin. An agreement and Network wide recommendations have been published so that both primary and secondary care organisations can begin planning the use and appropriate introduction of the new agents; points to consider for prescribing are:

- Warfarin has been prescribed for a period of at least six months and most of the blood tests have been out of the target range, despite good compliance with treatment;
- A patient is allergic to, or intolerant of, warfarin.

Warfarin is also prescribed for conditions other than atrial fibrillation, such as deep vein thrombosis. At this stage there is little experience of using Dabigatran for these other conditions, therefore it is not recommended.

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Patient confirmed to have Atrial Fibrillation on ECG recording.
All forms of Atrial Fibrillation (Paroxysmal, Persistent, Long Term Persistent & Permanent) require Stroke Risk Assessment

Is the patient less than 65 years old with no cardiovascular risk factors?
Such as diabetes, hypertension, PVD, IHD, LVSD, CCF

Undertake a CHA₂DS₂-VASc score to define low risk patients

No thromboprophylaxis required
Aspirin only prescribed if required for previously diagnosed vascular disease

Discuss anticoagulation with the patient with AF, this should include attention to bleeding risk.
Remember that published evidence suggests that patients are generally accepting of higher risk of bleeding than clinicians to prevent stroke

Can the patient take Warfarin therapy (no previous allergic response or side effects)?

Consideration of a Novel Oral Anticoagulant (NOAC) should be made.
There are two currently licensed medication Dabigatran and Rivaroxaban.
Dose adjustments are required for Age, Renal Function and body mass
I suggest that the renal function and FBC is checked every 3 months
I would not suggest this form of medication in the frail or if poor compliance is an issue
These medications currently cannot be monitored or reversed

After 3 months consider a switch to a NOAC if the INR >5, OR 2 consecutive INRs <1.8, OR frequent INR testing required

After 3 months is the Warfarin well controlled with an Individual Time in Therapeutic Range (iTTR) of >65%

Continue oral anticoagulation indefinitely with annual reassessment of FBC, U&E, LFTs, and consideration of iTTR and bleeding risk