‘New’ Anticoagulants
Dr Eric Watts

DAWN AC 2012
New Drugs, New Information

• Reviews
• Expert guidance
• Case reports
• Adverse incident reports
• Round table discussions
• Local practice
Reviews 1

- Little difference from available studies – a head to head comparison is needed
- but 150 mg dabigatran appears most effective in preventing SE and Apixaban lowest rate of bleeding
• **Drugs.** 2012 Sep 10;72(13):1739-53

• New oral anticoagulants: a review of the literature with particular emphasis on patients with impaired renal function.

• All are effective but dabigatran and rivoroxaban have renal excretion and should be used with caution in renal impairment

• Risk for apixaban is lower

Comparative Effectiveness of Warfarin and New Oral Anticoagulants for the Management of Atrial Fibrillation and Venous Thromboembolism: A Systematic Review.

Six good-quality RCTs compared NOACs
(2 DTI studies, 4 FXa inhibitor studies) with warfarin. In AF, NOACs decreased all-cause mortality (risk ratio [RR], 0.88 [95% CI, 0.82 to 0.96])

in VTE, NOACs did not differ for mortality or VTE outcomes

Across indications, adverse effects of NOACs compared with warfarin were -

fatal bleeding (RR, 0.60 [CI, 0.46 to 0.77])

major bleeding (RR, 0.80 [CI, 0.63 to 1.01]),
gastrointestinal bleeding (RR, 1.30 [CI, 0.97 to 1.73])
Reviews - 3.1

- Discontinuation due to adverse events (RR, 1.23 [CI, 1.05 to 1.44])
- Higher risk for myocardial infarction with DTIs than with FXa inhibitors.
- Bleeding risk for NOACs may be increased in persons older than 75 years or those receiving warfarin who have good control.

**CONCLUSION:**

- New oral anticoagulants are a viable option for patients receiving long-term anticoagulation. Treatment benefits compared with warfarin are small and vary depending on the control achieved by warfarin treatment.
VTE – Are we focussing on the right targets?
Post Thrombotic Syndrome
• Baglin letter on preventing Post Thrombotic Syndrome (PTS) - JTH 2012 10 1702-3
• A possible role for Oral Direct Inhibitors (ODIs) of thrombin & Xa
• PTS is common – 30 % and is associated with poor TTR in first 4/52 - factor of 2.7
• 1/12 of clexane –PTS reduced 23%
• IF ODIs as effective as clexane......
• Trials to include PTS as an end point are needed
The following recommendations have been made:

- Dabigatran etexilate is recommended as an option 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 dabigatran etexilate should be made after an informed discussion between the clinician and the person about the risks and benefits of dabigatran etexilate compared with warfarin.

- For people who are taking warfarin, the potential risks and benefits of switching to dabigatran etexilate should be considered in light of their level of international normalised ratio (INR) control.
NICE Rivoroxaban Af 23/5/2012

• Rivaroxaban is recommended as an option for the prevention of stroke
• The decision about whether to start treatment with rivaroxaban should be made after an informed discussion between the clinician and the person about the risks and benefits of rivaroxaban compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to rivaroxaban should be considered in light of their level of international normalised ratio (INR) control.
Novel antithrombotics in AF

Dabigatran etexilate or rivaroxaban can be considered as an alternative to warfarin in the management of patients with atrial fibrillation with one or more risk factors for stroke.

In selecting dabigatran etexilate consideration should be given to:

- the relative lack of experience of long term use compared with a VKA or aspirin
- the lack of a licensed product for rapid reversal of the anticoagulant effect of dabigatran etexilate (although the half-life is relatively short)
- the higher rates of gastrointestinal bleeding, especially with the higher dose regimen and in the elderly
- the limited data on use in patients at the extremes of body weight and those with renal and hepatic impairment.
In selecting rivaroxaban consideration should be given to:

- the relative lack of experience of long term use compared with a VKA or aspirin
- the lack of experience with rapid reversal of the anticoagulant effect with PCC, in patients
- the higher rates of gastrointestinal bleeding, especially with the higher dose regimen and in the elderly
- the limited data on use in patients at the extremes of body weight and those with renal and hepatic impairment.
At the June network board the following was agreed:

- initial recommendation for dabigatran (NICE TAG 249)
- that the approach will be one of gradual implementation recognising that these are new drugs with emerging safety concerns
- that the approach will be reviewed at September network board to include rivaroxaban TAG and further in Spring 2013 to include apixaban

The Essex Cardiac Network recommendation for prioritisation of groups of patients to be treated with dabigatran, in preference to warfarin, which is still the established treatment of choice, is summarised below drawing on the licensed indications and NICE TAG 249:

Secondary prevention:
1. Patients who have had a stroke/TIA whilst maintained on warfarin if 150mg twice daily (bd) dosage indicated (see note 1 below)
2. New patients who have a stroke/TIA where the 150mg bd dosage is indicated (see note 1 below)
Primary prevention for patients with a CHADS2 score of 3 or more and one of the following:

3. Patients who are allergic to warfarin (and not stabilised on phenindione) or have an adverse drug reaction necessitating stopping treatment or for whom there is a contraindication for warfarin but not for dabigatran.

4. Patients with unstable anticoagulation who are outside the INR range for more than 35% of the time i.e. the aim is to be within range for 65% (as measured over the previous 12 months by sequential INR measurements outside range of 2-3 plus or minus 10%). Concordance reasons should be excluded as a reason for unstable anticoagulation.

5. Where access to INR monitoring is a significant clinical issue e.g. housebound patient and near patient testing is not available. This may be a consideration in some localities in Essex.
Safety:

Warfarin is an effective drug in use for 40 years and its benefits and its profile is known whereas these new drugs may have some benefits eg dabigatran has superiority at 150mg dose and in prevention of intracerebral haemorrhage, widescale use outside clinical trials has yet to demonstrate full safety profile (all are black triangle drugs). As well as the customary concerns re use of a new drug in considering whether dabigatran is appropriate for an individual patient factors include:

- Lack of reversibility of dabigatran
- Renal function
- Bleeding risk especially GI bleeding risk
- Drug interactions (similar to warfarin)
- Concordance
Expert guidance – commissioning support

Expert guidance – commissioning support

The annual risk of stroke associated with AF increases steeply from 1.5% at age 50, to 23.5% at age 80 to 90 years. The most effective treatment to prevent stroke in patients with AF is anticoagulation. The 2008 NICE guidance for the management of AF recommended thromboprophylaxis according to individual risk, with either aspirin 75 to 300 mg daily in patients at low risk of a stroke, or warfarin (target INR 2.5, range 2.0 to 3.0) in those at high risk of stroke.

Clinical evidence for efficacy and safety

One phase 3 randomised controlled trial, the RE-LY trial, compared oral dabigatran etexilate (150 or 110 mg twice daily) with oral warfarin in 18,113 patients with AF who were at increased risk of stroke. Eligible patients had at least one of the following risk factors: previous stroke or TIA, LVEF ≤ 40%, NYHA class II or higher heart failure symptoms within six months of screening, age 75 years, or 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease. Patients receiving dabigatran etexilate were blinded to dose assignment; warfarin administration was open-label. The primary efficacy outcome was the incidence of stroke or systemic embolism, and the primary safety outcome was major haemorrhage. Secondary outcomes included the incidences of myocardial infarction (MI) and all-cause mortality.

Incidence of stroke or systemic embolism: Both doses of dabigatran etexilate were non-inferior to warfarin. During a median of two years' follow-up, significantly fewer patients receiving the high dose (150 mg twice daily) of dabigatran etexilate had a stroke or systemic embolism than warfarin-treated patients (0.9% with dabigatran versus 1.3% with warfarin, p = 0.001, 2-year NNT = 39). There was no significant difference in stroke incidence between warfarin and the low dose (110 mg twice daily) of dabigatran etexilate.

Incidence of major haemorrhage: There was no significant difference between high-dose dabigatran etexilate and warfarin. Significantly fewer patients on low-dose dabigatran etexilate had a major bleed than those receiving warfarin treatment (5.6% vs. 6.8%, p = 0.003, 2-year NNT = 77).

Incidence of MI: After a median of two years' follow-up, a significantly higher incidence of MI was seen in patients receiving high-dose dabigatran etexilate than in those receiving warfarin; 1.4% of dabigatran-treated patients were affected compared with 0.95% of warfarin-treated patients (relative risk 1.53 [95% CI 1.03 to 2.21]; p = 0.024; 2-year NNT = 244). There was no significant difference between the low-dose dabigatran group and warfarin.

Mortality: The incidence of death from any cause was not significantly different between groups; 7.4% of the patients receiving low-dose dabigatran etexilate died compared with 8.0% of warfarin-treated patients (RR 0.91, 95% CI 0.8 to 1.03, p = 0.13 vs. warfarin) and 7.2% of patients in the high-dose dabigatran etxile group died (RR 0.90, 95% CI 0.77 to 1.00, p = 0.001 vs. warfarin).
Considerations for cost impact

There were 82,156 patients recorded on the atrial fibrillation register in the West Midlands (2009/10 QOF data\(^6\)), of which about 46,000 should be receiving warfarin treatment.\(^7\)

Cost estimates for a year’s treatment with warfarin 7.5 mg daily, including monitoring, range widely depending on local arrangements, e.g. from about £220 to £480. Per patient, the cost of a year’s treatment with dabigatran etexilate 150 mg or 110 twice daily is currently £801.80.
Case Reports

• New Zealand – 38 major bleeds, ½ fatal - mostly > 80yrs, low BMI, often poor renal function, sometimes U&E not checked until patient admitted with bleeding

• NB this group of patients included many for whom NAC were deemed to be an advantage including prior CVA, housebound or mobility problems and forgetful with poor TTR
Dabigatran Interactions, from Drugs.com - 295 interacting medications reported

• Common medications checked in combination with dabigatran
  • Aspirin Low Strength (aspirin)
  • Celebrex (celecoxib)
  • Centrum (multivitamin with minerals)
  • Centrum Silver (multivitamin with minerals)
  • Coenzyme Q10 (ubiquinone)
  • Coumadin (warfarin)
  • Crestor (rosuvastatin)
  • Cymbalta (duloxetine)
  • Fish Oil (omega-3 polyunsaturated fatty acids)
  • Humalog (insulin lispro)
Dabigatran – common interactions

- L Thyroxine Roche (levothyroxine)
- Lantus (insulin glargine)
- Levaquin (levofloxacin)
- Lipitor (atorvastatin)
- Milk of Magnesia (magnesium hydroxide)
- Paracetamol (acetaminophen)
- Toprol-XL (metoprolol)
- Vitamin B6 (pyridoxine)
- Vitamin D3 (cholecalciferol)
- Xarelto (rivaroxaban)
Medicines.org.uk – Black Triangle

<table>
<thead>
<tr>
<th>SOC / Preferred Term.</th>
<th>Primary VTE prevention after hip or knee replacement surgery</th>
<th>Stroke and SEE prevention in patients with atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC / Preferred Term.</td>
<td>Dabigatran etexilate 150 mg once daily</td>
<td>Dabigatran etexilate 220 mg once daily</td>
</tr>
<tr>
<td>Number of patients treated</td>
<td>2,737</td>
<td>2,682</td>
</tr>
</tbody>
</table>

Blood and lymphatic system disorders

<table>
<thead>
<tr>
<th>Anaemia</th>
<th>Common</th>
<th>Common</th>
<th>Common</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin decreased</td>
<td>Common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Gastrointestinal haemorrhage</th>
<th>Common</th>
<th>Common</th>
<th>Common</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Nausea</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
</tbody>
</table>
### Drug Analysis Print

#### Drug name: DABIGATRAN

<table>
<thead>
<tr>
<th>Drug name:</th>
<th>DABIGATRAN</th>
<th>Report type:</th>
<th>Spontaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report run date:</td>
<td>27-Jul-2012</td>
<td>Report origin:</td>
<td>UNITED KINGDOM</td>
</tr>
<tr>
<td>Data lock date:</td>
<td>26-Jul-2012 22:16:24</td>
<td>Route of admin:</td>
<td>ALL</td>
</tr>
<tr>
<td>Period covered:</td>
<td>01-Jul-1963 to 26-Jul-2012</td>
<td>Reporter type:</td>
<td>ALL</td>
</tr>
<tr>
<td>Earliest reaction date:</td>
<td>02-Jan-2009</td>
<td>Reaction:</td>
<td>ALL</td>
</tr>
<tr>
<td>MedDRA version:</td>
<td>MedDRA 15.0</td>
<td>Age group:</td>
<td>ALL</td>
</tr>
</tbody>
</table>

Total number of reactions*: 958  
Total number of ADR reports: 497  
Total number of fatal ADR reports: 20

Products included in this print - Single active constituent products (PBGs):
PRADAXA

### Drug Analysis Print

#### Drug name: WARFARIN

<table>
<thead>
<tr>
<th>Drug name:</th>
<th>WARFARIN</th>
<th>Report type:</th>
<th>Spontaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report run date:</td>
<td>26-Jul-2012</td>
<td>Report origin:</td>
<td>UNITED KINGDOM</td>
</tr>
<tr>
<td>Data lock date:</td>
<td>25-Jul-2012 22:24:03</td>
<td>Route of admin:</td>
<td>ALL</td>
</tr>
<tr>
<td>Period covered:</td>
<td>01-Jul-1963 to 25-Jul-2012</td>
<td>Reporter type:</td>
<td>ALL</td>
</tr>
<tr>
<td>Earliest reaction date:</td>
<td>29 Jun-1964</td>
<td>Reaction:</td>
<td>ALL</td>
</tr>
<tr>
<td>MedDRA version:</td>
<td>MedDRA 15.0</td>
<td>Age group:</td>
<td>ALL</td>
</tr>
</tbody>
</table>

Total number of reactions*: 5898  
Total number of ADR reports: 2733  
Total number of fatal ADR reports: 360

Products included in this print - Single active constituent products (PBGs):
MAREVAN  
NORTON PHARMS WARFARIN  
SANDOZ LTD WARFARIN  
TARO PHARMS UK WARFARIN  
TEVA UK WARFARIN  
WB WARFARIN
Round Table Discussion ISHT

- Rivoroxaban – INR *usually* prolonged to 1.5 measured at peak effect, 2-3 hrs post ingestion; TTR not determined by INR
- INR reduced by PCC but this does not correspond with clinical bleeding
- Dabigatran – APTT *usually* prolonged to 1.5 measured at peak effect, 2-3 hrs post ingestion; TTR not determined by APTT
- No correction with PCC
Evidence based protocols for bleeding of Mice, Men & Medics

• 12 Dutch medical students given dabigatran and rivoroxaban with coagulation profiles monitored – before & after Prothrombin Complex Concentrate (PCC)
  • Rivoroxaban – improved INR
  • Dabigatran – no change in APTT
  • Rat tail bleeding time improved but not normalised by PCCs
• ? Relevance of mutilated/ tormented rodents
ISHT advice on problem areas - Major Bleeding

- Stop the drug
- Give rbc
- Consider FFP, platelets
- Base treatment on clinical observation - Clotting tests do not help
- Use local haemostatic measures
- Consider PCC, DDAVP, FEIBA, FVIIr
ISHT advice planned Invasive procedures - dabigatran

- Half life is 15hrs with normal renal function
- Low risk procedures – stop drug for 24 hrs, high risk 48hrs
- Creatinine clearance < 50 double these times
- PTT is ‘reasonable’ in reflecting the reduction in drug effect
- Restarting - ½ dose next day (if not bleeding)
- No case for bridging (unknown reduction off effect, rapid onset)
Obese patients

- Obesity Statistics UK - Weight Loss, FREE Diet ...
- Obesity Statistics & Trends in the UK ... Trends in Overweight Obesity. About 46% of men in England and 32% of women are overweight (a body ...)
- BBC - Health: Obesity
- What is obesity? In the UK an estimated 60.8 per cent of adults and 31.1 per cent of children are overweight. According to figures from 2009
- ODI's not as effective in obese patients
- No weight adjusted protocols available
Patient’s Choice & responsibility

- All new A/Cs cause bleeding
- Good compliance essential
- No reliable antidote *i.e.* Managing bleeding could be problematic.
- Info sheet & consent form
NEQAS meeting Dr Harry Bouler

• Best way to gain experience – start as a group
• Have a patient info booklet – main value to present to A&E – info “don’t do tests – call the haematologist”
• Carry out an evaluation after every 50 patients
• Advise the lab to comment on the limited value of coag screen
• NZ experience – the problem of putting novel drugs straight into the hands of generalists
NEQAS – Dr Michelle Samana

- Dilute thrombin time could be used for monitoring Boehringer are developing it as ‘Haemoclot’
- Coag testing not monitoring but measuring – could be helpful in some circumstances - renal, or hepatic impairment – a ‘snapshot’
- Emergency surgery, thrombotic or bleeding events, suspected OD or interaction (many interactions being reported)
- ? Gauging reversal, ?? Detecting drug accumulation
Dresden Clinical Experience

- Thromboprophylaxis fewer VTE with rivoroxaban cf clexane (7.5% vs 12 %) and fewer bleeds (8 vs 11)
- Patients switched from warfarin – 50% because of low TTR
  20% because of bleeding
  18% because of falls
- “The patients prefer it” but any real advantage? Is there less bleeding? Falls safer?
Compliance & safety

• Low TTR may indicate poor compliance – should they be on *any* potent anticoagulant?

• Dabigatran has BD dosing missing a dose means more rapid loss of A/C effect.
Local Practice

• “Best drug ever!”
• who would say this? - “he does n’t understand”
• (I don’t have a budget) – I don’t treat bleeding complications
• “best” at preventing strokes – worse for pts with hepatorenal impairment – especially if coronary prone
Local Experience

• Very few patients on dabigatran
• Most were changed from warfarin because of poor TTR one ‘exceptional’ epistaxis
• Some have complained of indigestion
• Concern re reversibility
• Awaiting recommendation from cardiologists
INFORMATION SHEET FOR PATIENTS ON DABIGATRAN

• **Dabigatran** is one of the new types of anti-clotting drug. It has some advantages over Warfarin:
  • It is predictable in the way it works, unlike Warfarin, and thus:
    – It is taken as the same, fixed dose every day.
    – No regular blood tests are required, unlike with Warfarin.
  • It has limited interactions with other drugs and no interaction with diet or alcohol.
  • It has some drawbacks:
    • There is no obvious antidote for bleeding. This may not be so serious as, unlike Warfarin, its effects wear off very quickly in a matter of hours.
    • There is no easy blood test for it, unlike the INR for Warfarin
    • **As no regular blood tests are necessary it is most important that you take the prescribed dose every day without fail, usually twice daily.** Unlike Warfarin, because the effect wears off quickly, missing doses can lead to a greater risk of getting another blood clot.
Info on Dabigatran - 2

- In trials other side-effects seen that were commoner than with Warfarin.
- Indigestion – occurred in 5-10% of patients compared to less than 1% with Warfarin.
- Diarrhoea – occurred in 4-5% compared to 3% on Warfarin.
- Other side-effects noted were headache, nausea, breathlessness, back, joint or limb pain and ankle swelling, but these side effects were also seen equally with Warfarin.

Follow up
- This will be undertaken by your anticoagulant clinic who will also prescribe the Dabigatran for you. You may be seen monthly initially and then at less frequent intervals.
- At each visit a blood sample will be taken to check for anaemia and to check your kidney and liver tests. This is a routine thing to do.
- Each clinic visit will also give a chance to see how you are getting on with the new drug and to check that you are not getting any significant side effects.
DABIGATRAN - PATIENT AGREEMENT

- I confirm that I have fully discussed treatment with Dabigatran with ......................................................
  and that the reasons for using it and the potential benefits, side-effects and risks have been fully explained to my satisfaction.

- I can confirm that I have read the information leaflet provided.

- I understand the need to comply very strictly with the dosing requirements in order for the drug to be most effective, especially as no regular blood tests as regards its effects are either necessary or possible. Failure to comply may be associated with an increased risk of getting blood clots or serious bleeding.

- I understand the need to attend for regular clinic follow up.

- I confirm that I am willing to start taking Dabigatran as prescribed instead of other available anti-clotting drugs.

Signed.........................................................................................................................

Print name........................................................................................................... Date..................................................
Conclusion

• ODIs are at least as effective as warfarin for Prevention of embolisation in Af.
• Increasing side effects and drug interactions are being reported.
• Their use is largely limited to patients who are poorly controlled on warfarin or who have specific indications
• The increased cost is the major deterrent
Thanks for Listening