PostScRxipt
from the
NHSGGC Area Drug & Therapeutics Committee
Issue 66 November 2011

FOCUS ON . . . Use of dabigatran in atrial fibrillation

Dabigatran has received a significant amount of interest from both the medical and lay media. It is the first drug in its class to be licensed in the UK. Here, Dr David Murdoch, Consultant Cardiologist and Heart Disease Managed Clinical Network Lead, provides an update on the clinical issues.

This new medicine has recently been accepted by the Scottish Medicines Consortium for use in NHS Scotland for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (AF) with one or more of the following risk factors:
• previous stroke, transient ischaemic attack, or systemic embolism
• left ventricular ejection fraction <40%
• symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2
• age ≥75 years
• age ≥65 years associated with one of the following: diabetes mellitus, coronary artery disease or hypertension.

Its *Formulary* position is under review to allow consultation with the Heart Managed Clinical Network following publication of a national consensus statement. Dabigatran is currently non-*Formulary*. A decision on *Formulary* and guideline status is expected in December. Prescribers should not be considering review of patients with AF with respect to dabigatran use at this time.

Warfarin has been proven to reduce the risk of stroke in patients with AF but it can be a difficult drug to manage. Despite this, most patients in AF on warfarin in NHSGGC are well controlled. It has a narrow therapeutic range and multiple drug interactions so it is understandable that the advent of new anticoagulants has been keenly anticipated. Dabigatran, a direct thrombin inhibitor, is the first of these to be licensed for use in the UK.

Evidence for efficacy
This is based on one open-label clinical trial (RE-LY)[1] which compared two doses of dabigatran with warfarin in patients with nonvalvular AF at moderate-high risk of stroke. Net clinical benefit of dabigatran was seen in the composite end-point of stroke, systemic embolism, pulmonary embolism, MI, death and major bleeds. The difference reached statistical significance for dabigatran 150mg twice daily and warfarin (annual rate 7.11% *v* 7.91%).

A further analysis of the database (table below), however, demonstrated that in those centres with good INR control, the statistical and clinical benefits of dabigatran were diminished.[2]

Advantages of dabigatran over well-managed warfarin
• *Fewer intracranial bleeds:* Both doses of dabigatran were associated with a significantly smaller number of intracranial bleeds, even when compared to warfarin with good INR control.
• *Stable and rapid onset anticoagulant:* Unlike warfarin, there is no time lag before adequate anticoagulation is achieved.
• *Fewer interactions:* There are no food interactions and a shorter list of drug interactions.
• *No monitoring required:* This may suit patients who live in rural areas, who are housebound or spend a significant amount of time working away from home.

Disadvantages of dabigatran
• *More gastrointestinal bleeding:* A notable adverse effect of dabigatran when compared to warfarin was an increase in GI bleeding. This was statistically significant even for the lower dose in over 75-year-olds.
• *No specific antidote:* Unlike warfarin, dabigatran does not deplete clotting factors but is a direct clotting factor inhibitor.

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	Rate of stroke, systemic embolism, pulmonary embolism, MI, death and major bleeding per 100 person - years		
Time in therapeutic range of INR	**Dabigtran 110 mg**	**Dabigatran 150mg**	**Warfarin**
< 57.1%	7.65	6.83	10.13
57.1 - 65.5%	7.84	7.09	8.03
65.5 - 72.6%	6.88	7.41	7.13
> 72.6%	6.85	7.07	6.42

Website
http://www.ggcformulary.scot.nhs.uk

Latest ADTC decisions

Go to www.ggcformulary.scot.nhs.uk/Latest news/formulary update bulletin.pdf for full details of all ADTC decisions and links to SMC recommendations.

Added to the *Formulary*

Adrenaline pre-filled syringe (Jext®) Emergency treatment of severe acute allergic reactions (anaphylaxis). Preferred List. Jext® is the preferred brand of adrenaline injection for self-administration.

Ⓢ **Botulinum toxin type A (Xeomin®)** Treatment of post-stroke spasticity of the upper limbs (new indication). Total *Formulary*. Restricted to specialist use only.

Ⓢ **Cetuximab (Erbutux®)** EGFR-expressing KRAS wild-type metastatic colorectal cancer. Total *Formulary*. Restricted to specialist use in accordance with regional protocol.

Ⓢ **Denosumab (Prolia®)** Osteoporosis in postmenopausal women. Total *Formulary*. Restricted to specialist use in those patients for whom oral bisphosphonates and IV zoledronic acid are unsuitable, contraindicated or not tolerated in accordance with local protocol.

Fluorouracil 0.5% and salicylic acid (Actikerall®) Topical treatment of hyperkeratotic actinic keratosis (gradeI/II) in adults. Total *Formulary*.

Ⓢ **Golimumab (Simponi®)** Severe active ankylosing spondylitis in adults. Total *Formulary*. Restricted to specialist use in accordance with the British Society of Rheumatology guidelines. Use of the 100mg dose has not been accepted by SMC and remains non-*Formulary*.

Pravastatin ADTC appeal. Prevention of cardiovascular events. Total *Formulary*. Restricted to use only in patients in whom drug interactions might pose a problem or for patients who are intolerant of simvastatin and atorvastatin.

Ⓢ **Tapentadol (Palexia® SR)** Management of severe chronic pain in adults. Total *Formulary*. Restricted to initiation by, or on the advice of, pain specialists only in patients who have failed to respond to, or tolerate, both morphine and oxycodone.

Ⓢ **Tenofovir disoproxil (Vread®)** Chronic hepatitis B in adults with decompensated liver disease (new indication). Total *Formulary*. Restricted to initiation on the advice of specialists.

New medicines, indications and formulations not added to the *Formulary*

- **Abatacept (Orencia®)** for rheumatoid arthritis in combination with methotrexate after failure of one or more DMARD.
- **Bromfenac (Yellox®)** for the treatment of post-operative ocular inflammation following cataract surgery.
- **Conestat alfa (Ruconest®)** for treatment of angioedema attacks in adults with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency.
- **Eribulin (Halaven®)** for third line treatment of locally advanced or metastatic breast cancer.
- **Infliximab (Remicade®)** for moderately active Crohn's disease.
- **Olmesartan/amlodipine/hydrochlorothiazide (Sevikar HCT®)** for hypertension in patients controlled on these constituents.
- **Quetiapine (Seroquel XL®)** as add-on treatment of major depressive episodes.
- **Rosuvastatin (Crestor®)** for primary prevention of cardiovascular events.
- **Vardenafil orodispersible tablet (Levitra®)** for erectile dysfunction.

Other *Formulary* decisions

- **Buprenorphine and naloxone sublingual tablets (Suboxone®)** for the treatment of opioid dependency had its restriction reviewed via a *Formulary* appeal. It is now restricted to initiation by addiction services or GPs who have received appropriate training and authorisation from Addiction Services, for those patients in whom methadone is not suitable and for whom the use of buprenorphine is considered appropriate.
- **Rosuvastatin (Crestor®)** had its restriction reviewed following SMC advice and a *Formulary* appeal. It is now restricted to use in patients who fail to reach target lipid levels in accordance with NHSGGC Lipid Lowering Guidelines. Doses in excess of 40mg should only be initiated by, or on the advice of a specialist. The use for primary prevention is not recommended by SMC and is non- *Formulary*.

Formulary decisions still to be made

The following new medicines, indications or formulations have had a decision on *Formulary* status deferred to allow further consultation, protocol development or implementation plans. Until a decision is made, these medicines, indications or formulations are non-*Formulary*.

- **Azacitidine (Vidaza®)** for the treatment of adults with intermediate-2 and high-risk myelodysplastic syndrome (MDS), chronic myelomonocytic leukaemia (CMML) or acute myeloid leukaemia (AML) who are not eligible for haematopoietic stem cell transplantation (Regional Cancer Advisory Group).
- **Boceprevir (Victrelis®)** for the treatment of chronic hepatitis C genotype 1 infection in combination with peg interferon alfa and ribavirin in treatment experienced and treatment naïve patients (Hepatitis MCN).
- **Bortezomib and thalidomide** for the first line treatment of multiple myeloma as outlined in NICE MTA 228 (Regional Cancer Advisory Group).
- **Dabigatran (Pradaxa®)** for the prevention of stroke and systemic embolism in adults with atrial fibrillation (Heart MCN).

Use of statins

The current recommendations for statins in NHSGGC are:

1 **Simvastatin:** first choice simvastatin 40mg daily
2 **Atorvastatin:** restricted to patients who fail to meet goals for cholesterol reduction on simvastatin 40mg.
3 **Pravastatin:** restricted to use only in patients in whom drug interactions might pose a problem, or for patients who are intolerant of simvastatin and atorvastatin.
4 **Rosuvastatin:** restricted to use in patients who fail to reach target lipid levels in accordance with NHSGGC Lipid Lowering Guidelines.

Ⓢ specialist use only Ⓢ specialist initiation only

Recent safety issues

1 Dronedarone

Dronedarone was added to the Total *Formulary* in February 2011 to prevent recurrence of atrial fibrillation (AF) or to lower ventricular rate in adult clinically stable patients with a history of, or current, non-permanent AF. Following new evidence of cardiovascular, hepatic and pulmonary risk, the MHRA has advised that dronedarone should only be prescribed after other treatment options have been considered (this is the context of NHSGGC *Formulary* inclusion). Patients should have their treatment reviewed at the next routine appointment to ensure that they remain eligible for dronedarone treatment. Regular monitoring of cardiac, liver and renal function during treatment is recommended. See **www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON131928** for more detail.

Dronedarone is now **contraindicated** in patients with:
- unstable haemodynamic conditions.
- a history of, or current, heart failure or left ventricular systolic dysfunction.
- permanent AF (ie duration ≥6 months or unknown, and attempts to restore sinus rhythm no longer considered by physician).
- liver and lung toxicity related to previous use of amiodarone.

Monitoring requirements
- Patients should receive regular cardiac examinations, including an ECG at least every six months, to identify those who revert to AF.
- Liver-function tests should be done before starting treatment; after one week; after one month; then every month for six months; at month nine; at month 12 and periodically thereafter.
- Plasma creatinine values should be measured before and seven days after initiation. Renal function should be monitored periodically afterwards.
- If pulmonary toxicity is suspected during treatment, relevant lung examinations should be considered and treatment discontinued if confirmed.

2 Systemic fusidic acid

Systemic fusidic acid (Fucidin®) should not be given with statins because of a risk of serious and potentially fatal rhabdomyolysis. See **www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON128951** for details.

- In patients for whom the use of systemic fusidic acid is essential, statin treatment should be temporarily discontinued throughout the duration of fusidic acid treatment.
- To ensure clearance, statin therapy may be reintroduced seven days after the last dose of systemic fusidic acid.
- In exceptional cases, where prolonged treatment is necessary, the need for co-administration of a statin should be considered on an individual basis and only under close medical supervision.
- Patients should be clearly advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

Tapentadol: A new drug for severe chronic pain

Tapentadol has been added to the Total Formulary *for the treatment of severe chronic pain in adults. It is restricted to initiation by, or on the advice of, pain specialists only in patients who have failed to respond to, or tolerate, both morphine and oxycodone. It was as effective as oxycodone and better tolerated, with less constipation, nausea and vomiting. There are no direct cost issues, as tapentadol is priced at the same level as oxycodone. It is a slow-release formulation given on a twice-daily basis. As a Schedule 2 Controlled Drug, it is subject to the same prescription writing and storage requirements as morphine or oxycodone. Dr Mick Serpell, Consultant Anaesthetist at Gartnavel, discusses some of the clinical issues with this new drug.*

Tapentadol is a novel analgesic drug with two modes of action; it is a mu opioid agonist and a noradrenaline re-uptake inhibitor (MOR-NRI). Some other analgesics block the re-uptake of serotonin as well as noradrenaline. Serotonin can both inhibit and facilitate pain mechanisms and may, therefore, impair analgesic efficacy. Tapentadol, a Step 3 analgesic, has demonstrated equivalent efficacy to oxycodone in several studies looking at acute post-operative and chronic non-cancer pain such as low back pain and osteoarthritis.

Tapentadol is available as a prolonged release formulation. The dose is initiated at 50mg twice daily, titrating up to a maximum of 250mg twice daily (equivalent to oxycodone 100mg daily or morphine 200mg daily). The consensus in non-cancer pain is that short acting opioids are best avoided and the daily opioid dose should not exceed the equivalent of 200mg morphine unless specialist input is involved.

The ADTC decided that tapentadol prolonged release should be added to the *Formulary* for third line use in chronic pain (after morphine and oxycodone), restricted to initiation by, or on the advice of, a pain specialist. The use of tapentadol will be carefully monitored. If the experience in clinical practice indicates there is a wider place in the treatment pathway, this restriction could be reviewed. For example, the noradrenaline effect is a major mechanism involved in analgesia for neuropathic pain, and so this type of pain may be more responsive to tapentadol than to other opioids. There may be indirect savings if the use of tapentadol reduces co-prescription of tramadol or some of the analgesic antidepressants.

Tapentadol should be considered, prescribed and monitored under the same principles as any other strong opioid. The current guidelines on 'Opioids for non-cancer pain' within the *NHSGGC Primary Care Guidelines for the Management of Chronic Pain*, explains this process (**www.staffnet.ggc.scot.nhs.uk/Clinical%20Info/Clinical%20Guidelines/Clinical%20Guidelines%20By%20Clinical%20Topic/Pages/PainManagement.aspx**). The opioid guidelines will be reviewed and changes incorporated as further evidence becomes available and experience with this new drug develops.

Until now, there has been insufficient evidence to suggest that one opioid is more effective or better tolerated than another. Morphine is generally accepted as first line. It is the golden standard because there is greatest experience in use and it is the least expensive. If the initial choice of opioid does not work, then one or two alternative opioids should be tried in sequence before concluding that the pain is either not opioid responsive or that the patient is opioid intolerant.

Webwatch

New NHSGGC prescribing website
A dedicated website aiming at supporting all prescribers in NHS Greater Glasgow & Clyde (**www.ggcprescribing.org.uk**) goes live in November 2011. This replaces the previous ADTC website and can be accessed from any device with an internet connection. When viewed on a mobile phone or similar portable device, the *Formulary* database page is automatically resized to allow optimal viewing and searching of *Formulary* information.

The core focus of the site is the NHS Greater Glasgow & Clyde Medicines *Formulary* (the NHSGGC *Formulary*), which is updated as soon as *Formulary* changes are agreed by the Area Drug & Therapeutics Committee. This replaces the previous printed editions of the GGC *Formulary*. One of the benefits of this is that many of the medicines have links to the *British National Formulary* if the site is accessed from the NHSGGC network

From the GGC Prescribing website you can read and subscribe electronically to any of the *PostScript* bulletins via email or a RSS feed. Examples of other publications in the family include:
• *PostScript Primary Care*: A monthly newsletter aimed at distributing key messages to GPs and non-medical prescribers working in practices
• *PostScript Safety*: Important information aimed at reducing risk associated with prescribing and the use of medicines
• *PostScript Extra*: A summary of the evidence base for medicines and therapies. It gives a ready reference for busy health professionals

The site also contains a wealth of other information on prescribing and preferred products including an electronic version of *Therapeutics: A Handbook for Prescribing in Adults*. There are policies and procedures relating to the management of medicines and links to the Clinical Guidelines portal on StaffNet.

A designated patient information area allows members of the public to obtain information about the access to new medicines on the NHS and includes a specific e-mail address to allow further advice to be sought.

The website features a discussion forum for prescribers from within NHSGGC to share best practice on a range of issues. Registration to the forum is required before the discussion boards can be viewed, new discussions started or comments made.

Focus on use of dabigatran in atrial fibrillation
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This means that administration of clotting factors, such as recombinant activated Factor VII or prothrombin complex concentrate, may not be wholly effective in reversing dabigatran's effects. Dabigatran is predominantly renally excreted so haemodialysis may be effective.

• *Lack of monitoring:* This could be a disadvantage in some patients. For example, in those who suffer an ischaemic stroke while on dabigatran, it would be clinically important to determine whether this was as a result of poor compliance or under-anticoagulation. It is also important in the elderly since the effect of dabigatran increases as renal function declines. Ironically, work is under way to produce a routinely available assay.
• *Twice daily dosing:* Dabigatran has a short half-life (around 13 hours in patients without renal impairment) so good compliance is important.
• *Cost:* Dabigatran is very expensive (£900-£1000 per annum) compared to warfarin (£35-£50 per annum). There are up to 15,000 patients in NHSGGC with AF at moderate to high risk of stroke so the additional cost would be in excess of £12 million each year if all patients received this drug. This cost pressure is one of the items being considered in the development of the 2012-13 financial plan.

Local and national guidance
Patients who are stable on warfarin and spend more than 60% of their time in the target range are least likely to benefit from switching to dabigatran. This group constitutes the majority of patients in AF in NHSGGC. New local and national guidelines are in development which will consider a balance of efficacy and affordability for anticoagulant products and varying levels of stroke risk in patients with AF. Dabigatran is likely to be positioned only for those patients who, despite good compliance, have poor INR control.

The Health Improvement Scotland National Consensus group will publish a 'frequently asked questions' sheet with the national consensus statement to help prescribers deal with patient enquiries. Further details are expected with the final *Formulary* and guideline announcements in the next edition.

There are several other new anticoagulants awaiting licensing and approval (rivaroxaban, apixaban, edoxaban). Each will be considered in due course and the recommendations reviewed if necessary.

For all article references, check our website www.ggcformulary.scot.nhs.uk

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Published by the Communications Sub-group to reflect the views of the Area Drug & Therapeutics Committee but not necessarily those of NHS Greater Glasgow and Clyde.

PostScRxipt

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© NHSGGC Area Drug & Therapeutics Committee November 2011
Design and layout:
Strathcashel Publications Project Management (01505 850 344)