Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists

ASCEPT Submission to Review of Anticoagulation Therapies in Atrial Fibrillation

The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) thank you for the opportunity to provide comment to the Review of Anticoagulation Therapies in Atrial Fibrillation.

ASCEPT is the lead body in Australasia for clinical pharmacology policy and practice and its member expertise covers experimental and clinical pharmacology and toxicology including: clinical trial and regulatory issues, pharmacovigilance and quality use of medicines. Some of our members also have expertise in pharmacoeconomics.

ASCEPT has a number of comments on the use of anticoagulants in atrial fibrillation. We further note that these comments may be of relevance to anticoagulant use in other conditions. These comments cover sections A-D in the terms of reference, although not in that order. The drugs particularly considered in preparing this submission are warfarin, dabigatran, rivaroxiban and apixiban. Other anticoagulants considered include ximelgatran, the hirudin derivatives and the low molecular weight heparins.

In summary:

- Current trial data suggest most of the currently available anticoagulants are similarly effective.
- Warfarin is not always used optimally and the new anticoagulants are also unlikely to be always used optimally, or as well as they have been in clinical trials.
- The long-term safety of the new anticoagulants is not as well known as warfarin.
- Open label studies are vulnerable to bias and their results should be used with caution.
- The cost of the new anticoagulants is high and needs to be evaluated broadly with cost efficacy considering the above four points.
- Monitoring is likely to improve the optimal use of the new anticoagulants and this should be studied, although it will add to the cost of the use of the drugs.

Key points we wish the anticoagulant review to consider are:

1. Warfarin is cheap and effective and the limitations of warfarin are well known

It is important to state that anticoagulation with warfarin has been shown, over many years, to be cheap and effective. ***There have been many clinical trials and many years of patient experience, including in men and women, elderly, pregnant women and children. We are confident and comfortable about the safety and efficacy profile.*** This is not to neglect its many problems, including the requirement for monitoring, drug and food interactions, and the time lag to reach therapeutic efficacy. However these are well known and mostly manageable.

2. Newer anticoagulants are more expensive, probably similarly effective and their limitations (particularly long term safety) are unknown.

The newer oral anticoagulants are effective, most have demonstrated non-inferiority to warfarin in clinical

Website: www.ascept.org
Email: ascept@clems.com.au
ABN: 78 008 461 354

Secretariat: CLEMS
Address: Suite 5, 250 Gore Street, Fitzroy VIC 3065
Telephone: 61 03 9416 3833
Facsimile: 61 03 9416 0636

trials and in some situations (albeit with a population different to that exposed in clinical practice) there may be safety advantages in terms of bleeding events (1). As is often the case with new drugs, dabigatran patients studied in the trials on which registration is based are younger (for dabigatran mean age 71 years), larger (mean weight 82 kg) with better renal function (excluded if creatinine clearance <30 mL/min/1.73m2) and less comorbidity/comedication compared to those in whom it will be used in clinical practice (2). Interestingly, in these trials, the subgroup of patients aged over 75, dabigatran had no net benefit over warfarin and had a trend towards an increased rate of major bleeding (3). Thus the 'real world' adverse effect profiles remain unclear. This is particularly applicable to the patients likely to be treated including the frail, the elderly, people with cancer and people with multiple comorbidities.

Already there have been several case reports, a TGA warning and Australian publications (in press, written by members of ASCEPT) describing severe bleeding with dabigatran in special groups. Further there have been 'new' side effects reported, not seen with warfarin use. For example, in a meta-analysis published this year dabigatran was associated with an increased risk of myocardial infarction/acute coronary syndrome (OR 1.33; 95% CI, 1.03-1.71; P = .03) in a range of patients when tested against different controls (4). This is consistent with the small increase in MI seen in the RELY study. Lastly there is a lack of knowledge around potential drug interactions with the new anticoagulants, which has resulted in prescribers assuming the agents are 'safer' than warfarin. For example, with dabigatran these interacting drugs include verapamil, amiodarone and other PGP inhibitors. In the product information (PI) these increase AUC by 60%, yet it is stated that dabigatran dose adjustment is not needed in the AF setting with this coadministered agent, this is surprising. The difference being that with warfarin treating physicians are familiar with its clinical use, can measure the INR or pre-emptively adjust dosing.

In fact the whole area of potential for drug interactions has been under-researched for these newer anticoagulants, and is a particular problem for people taking many medications, a group not included in the clinical trials. Alarmingly, in the marketing of these drugs, this lack of data on interactions is promoted to our prescribers as a benefit.

3. Therapeutic index, dosing and monitoring

All anticoagulants have a narrow therapeutic index with risks of lack of efficacy with thromboembolism if underdosed and toxicity with bleeding if overdosed. One of the purported benefits of the newer anticoagulants is that unlike warfarin there is no need for monitoring. Further, the manufacturers of these newer anticoagulants typically recommend a one-dose-fits-all approach with exceptions, whereas their own published pharmacokinetic data support a more continuous adjustment of dosing dependent upon individualised estimates of drug clearance.

Ideally all drugs are dosed to clinical effects. In the case of anticoagulants, these include thrombosis and haemorrhage, which can be severe. Therefore, it is preferable to 1) begin with doses adjusted for each individual's elimination of the anticoagulant and 2) use surrogate markers with good predictive performance of these effects. These surrogate markers may include biomarkers or drug concentrations.

We have fundamental concerns regarding the manufacturers' guidance on dosing, and that monitoring is

not required for the newer anticoagulants, beyond the clinical endpoints of thrombosis and haemorrhage. Clinical trial populations are likely to poorly represent usual practice in matters such as patient adherence and clinical adherence to patient selection and dosing. For example in the treatment of hypertension 50% of patients are non-adherent after one year. We note that the inclusion/exclusion criteria for the clinical trials contributed selection biases favoring the new agent.

We further note that the new anticoagulants could be monitored using coagulation biomarkers or drug concentrations. We would like to see formal analysis of the utility and costs of monitoring as part of evaluation of new anticoagulants when being compared to warfarin. There should also be a scientifically robust discussion on the dosing of these newer drugs.

There are places in clinical practice where monitoring is important. For example, when patients undergo surgery it is important to quantitate their bleeding risk. Furthermore, the pharmacokinetics and pharmacodynamics of newer drugs will differ between individuals, as is the case for all drugs. Therefore, patients will need to be monitored to ensure that they are not under or over anticoagulated. This is particularly important for patients with significant renal impairment, drug-drug interactions, or at the extremes of size, in whom there is little clinical trial data and there are likely to be significant differences in pharmacokinetics and pharmacodynamics.

4. Reversibility of anticoagulation

Life-threatening bleeding is a rare but severe side effect of anticoagulation. For warfarin the fact that this bleeding can be very easily or partially reversed in several ways within a few hours is helpful in clinical practice. We are concerned about ***the lack of reversibility*** with the new anticoagulants. This problem is largely ignored in clinical trial outcomes because a major bleeding event is a major bleeding event whether or not it is treatable. Specifically for dabigatran, this non-reversibility is considered clinically problematic.

5. Applicability to the Australian Population

Relative to atrial fibrillation patients in Australia, the populations studied in the major trials are healthier, have better adherence, have interactions closely managed and exclude patients with known contraindications.

Dabigatran example

Dabigatran was the first of the new oral anticoagulants to be considered by the PBAC. The most important study of dabigatran is the RELY trial (op cit.). We have three substantive concerns about the validity of the RELY trial.

1. *It was open label and thus vulnerable to investigator and subject biases.*
   A similar drug (ximelgatran), when studied in a double blind double dummy trial, was found to have similar efficacy to warfarin.
2. *Most of the events driving the RELY trial results were in countries/centres with poor use of warfarin. In Australia, and other "western countries", event rates were similar in both groups.*

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3. *Emerging real world Australian data suggests higher bleeding rates and the emergence of possible additional harms* (5,6).

The comparative cost-efficacy of increased resources into supporting and improving warfarin use has not been evaluated to our knowledge. This should be done.

While we note that the review is specific to anticoagulants for atrial fibrillation. We note that anticoagulants are also used for other indications and the same issues are likely to arise with other chronic conditions notably venous thromboembolism.

Although these are some of the major problems with the newer anticoagulants, we do believe there are some potential solutions:

1. **More caution – development of national pharmacovigilance system.**

There needs to be more caution in rolling out the newer anticoagulants prior to real world evidence being available in the special groups. An obvious way to obtain information on safety and effectiveness in the 'real world' is through linkage of routine health-service databases. Over the years, there have been repeated calls for this to occur from pharmacologists in this country, although little progress has been made at a national level. For example, Professor David Henry and the 'Newcastle Group' have suggested many times that by linking routine prescription data with routinely-collected health outcome data would provide a powerful capacity to evaluate the effects of drugs in real-world situations. This has been discussed at national meetings and was published in the Medical Journal of Australia in 2007 (7). However, Australia still does not have a national system of data linkage and as demonstrated by the issues with the newer anticoagulants, this is now an urgent priority (5). We also encourage the development of a new TGA-requirement to broaden inclusion criteria with new medications. This includes people of different body sizes, the elderly, ethic subgroups (including Australian Aborigines) and those with comorbidity in Sponsor studies.

2. **Restriction of these medications** to Hospital Specialists for use in those patients where warfarin has been problematic or not tolerated. We recognise that this may be difficult given the likely number of patients.

3. **Individualisation of therapy.** Australia's national medicines policy calls for the right dose of the right drug for the right patient. It is essential that these factors are considered for each patient with AF. There is a need for more research to inform dosing of the newer anticoagulants, and selection of the best anticoagulant for each patient will depend on a number of patient factors including comorbidities, co-medication, physical and cognitive function and access to health care services. There has been extensive research to define these factors for warfarin, and this information is required to define the place of the newer drugs in therapy.

4. **Education to occur with the marketing.**

Given the likely extent of use and the substantial risks of poor prescribing substantial clinician education is indicated.

If funded the cost of the medication should consider the cost of appropriate clinician education. An independent clinician education programme should be mandated and occur concurrently with the marketing

The need for informed academic leadership in clinical practice and clinical education is apparent in many areas of therapeutics. The current health system favours the training and appointment of front line "organ based" specialists and Clinical Pharmacology expertise is a very limited resource in Australia. We note that Clinical Pharmacology is the medical specialty concerned with the safe, effective and rational use of medications. **We recommend that specific resources are allocated to the training and employment of specialists in Clinical Pharmacology**.

5. Cost containment is essential

Standard measures to reduce drug expenditure, such as already occurs under PBPA processes and QH Medication Services such as competitive tender between drugs, could lead to substantial cost savings. The obvious question is ***are we potentially prepared to spend a large amount on new anticoagulants for relatively unknown benefit - when work on improved use of warfarin could well achieve the same outcomes for less cost***? We cite recent evidence such as routine low-dose vitamin K supplementation with warfarin (9) (analogous to folic acid and methotrexate), algorithms for home monitoring of INR (10) and correction of excessive anticoagulation to support an injection of funding into research and education in clinical pharmacology. Although the cost of low-dose Vitamin K supplementation has not been estimated, it could be, and in any case it will be relatively inexpensive and has no substantial risks. However local research would be needed to ensure this is as effective in our clinical practice as the studies suggest.

Conclusion:

We thank you for the opportunity to comment on options for improving the health outcomes of patients treated with anticoagulation therapies in Australia. We would be very pleased to discuss any of the issues raised.

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