Review of Anticoagulation Therapies in Atrial Fibrillation

A private submission

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January 2012

Submission to the Department of Health & Ageing on Anticoagulant Therapies in Atrial Fibrillation

This is a private submission, offered on the basis of the author's background:

1. I was trained in laboratory and clinical haematology and practised in both of those specialties exclusively from 1982 to 1999;

2. For the last 12 years I have been working as a general physician in Broken Hill, where the population is a lot older than almost any other part of the country. My academic duties include education of medical students and junior medical staff in pathology;

3. I have a significant medico-legal practice, and note that thrombosis and anti-thrombotic therapy is forming an increasing proportion of referrals for medico-legal opinion.

Introduction

The terms of reference of the review of anticoagulant therapies in atrial fibrillation (AF) are as follows:

> a. To report on current and future options for improving the health outcomes of patients with atrial fibrillation treated with oral anticoagulants.
>
> b. To report on modes of health system delivery which may be used to optimise the use of currently available anticoagulants.
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> c. To report to what extent optimisation of the use of currently available anticoagulant treatments used in patients with atrial fibrillation would improve health outcomes and at what cost.
>
> d. To examine the future role of newer anticoagulant therapies for atrial fibrillation.
>
> e. To report on any other matter relevant to items a to d above and on any other matters referred to it by the Minister.

I also understand that an external evaluator has been engaged to conduct a literature review, so I will not spend a lot of time on the obvious literature regarding anticoagulant therapy in AF.

The numbers of elderly patients with AF will be increasing in coming years. With that comes an increase in a risk of embolic stroke which can be prevented by a range of anticoagulant therapies. Anticoagulation is used in patients with AF at a variable standard across the country. This is guided by either clinician opinion or, ideally, individualised evaluation of the patient using such clinical tools as the $CHADS_2$

score[1].

Before considerable resources are allocated to this issue, the Australian taxpayer is entitled to be sure that anticoagulants are used in a safe and effective manner for AF, giving value for money.

"Blood Thinners"

People who simplistically call all anticoagulants "blood thinners" do our profession and the patients it serves is done a great disservice. Anticoagulants had no effect on the blood viscosity; they work in many different ways at various levels of the coagulation system.

Aspirin and other anti-platelet therapies are very effective in preventing thrombosis in high velocity, high shear flows. They are the mainstay of treatment in coronary artery, cerebrovascular and peripheral vascular disease. They are useless in prevention or treatment of venous thrombosis, and almost useless in prevention of thrombotic stroke in atrial fibrillation. For example, a meta-analysis published in 2007[2] demonstrated that:

- With a trial population of 3990 participants in seven trials;
- The reduction of stroke risk using aspirin did not reach statistical significance, as;
- The confidence intervals did not cross the origin – the overall risk reduction was 19%, but the confidence intervals were -1 to 35%.

Heparin, both in its unfractionated (UFH) and highly purified low molecular weight (LMWH) forms, works differently to warfarin, which again works differently to the novel anticoagulants dabigatran, rivaroxaban and apixaban. All have proven benefit in treatment of venous thrombosis and prevention of venous thrombosis. Warfarin is of proven value in prevention of embolic stroke in AF.

'Landmark' studies establishing the value of all three of the novel anticoagulants for reduction of embolic stroke in AF have been published in the last two years. All three studies used different comparators and have been subject to various criticisms, but have satisfactorily established that dabigatran, rivaroxaban and apixaban are effective for this purpose.

It is thus clear to this author that the main focus of this Review should be on warfarin and what I have called the novel anticoagulants. The Commonwealth Department of Ageing and Health will need to act with appropriate, measured pace to introduce the novel anticoagulants into clinical usage.

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[1] Olesen JB Lip GYH Hansen ML *et al.* Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342:d124 doi:10.1136/bmj.d124.

[2] Robert G. Hart, MD; Lesly A. Pearce, MS; and Maria I. Aguilar, MD Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation. *Ann Intern Med.* 2007;**146**:857-867.

The Problems with Warfarin

Warfarin has been in clinical use for a long time, having originally been discovered as the cause of haemorrhagic disease in cattle in the 1920s. Its mechanism of action is well understood.

Diet and lifestyle effects

Warfarin works by inhibiting the conversion of Vitamin K to a number of coagulation factors. The Vitamin K itself in turn is produced by microflora in the small intestine during digestion of precursors found in leafy green vegetables, particularly of the *Brassicaceae* group. This leads to another problem. Well intentioned but ill-informed advice is often proffered to patients on warfarin that they should restrict their intake of cabbages, broccoli and the like. This of course is absolute nonsense of the "a little knowledge is a dangerous thing" variety. Much of this misinformation is perpetuated by pharmacists.

The result of this misinformation is that the very patients who need to maintain an intake of anti-oxidant rich vegetables often restrict their intake of these foods, for no good reason. The correct advice should be simply to ensure that the diet does not change radically from day to day or week to week.

Warfarin also interacts with alcohol and a number of drugs. This, with the inappropriate dietary advice they receive, often means that patients feel that they are forced to choose between an ill-defined risk of stroke and significant changes in their lifestyle. Many choose not to take warfarin because of this.

Monitoring of warfarin

Although this is able to be done easily for many patients and competently by many doctors, practice is by no means uniform.

In the landmark studies of dabigatran, rivaroxaban and apixaban, the time in the therapeutic range (TTR) for the warfarin control groups were quite low – 55-62%. If this is the result of warfarin used in highly controlled clinical trials, the rates of good or excellent control of warfarin therapy in the general community must surely be lower still.

A Scandinavian group recently published a study using a rigorously controlled method demonstrating that the TTR could be maintained at 75%[3]. That leaves 25% of warfarin patients at any time either unprotected or at risk of bleeding, in the best of circumstances.

We are seeing the 'grey nomad' phenomenon increasingly in ageing Australians. In Broken Hill there are large influxes of people beyond retirement age through the winter months. If 1% or 2% of these people were on warfarin for AF, they would have a lot of trouble locating a general

[3] Wieloch M, Själander A, Frykman V, *et al.* Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. *Eur Heart J* 2011;**32**:2282-9.

practitioner to organise their warfarin monitoring.

Self-monitoring of warfarin using point-of-care (POC) devices is used in some countries. A paper published last year[4] demonstrated that self-monitoring of INR using POC devices on a weekly basis was equivalent to monthly clinic testing in terms of stroke rates, major bleeding episodes and overall deaths. It was not superior, and the report did not suggest that there was any cost benefit in home testing.

In Australia POC testing is not directly subsidised by the Medicare Benefits Scheme, although there are various ways for general practitioners to recoup the cost of test strips. POC devices used under the supervision of an Approved Pathology Provider can qualify for Medicare benefits. Neither of these, of course, are true "home monitoring". This author's impression is that if home monitoring were underwritten in Australia, the cost of monitoring of warfarin would increase, as patients would be inclined to do more tests than necessary for ideal control.

Risk assessment

Before starting elderly patients on warfarin, (or for that matter on any of the novel anticoagulants either) the clinician should make a careful assessment of the falls risk of the elderly patient. A patient with a relatively low risk of embolic stroke (for example a $CHADS_2$ score of 2) may have a demonstrably high risk of falls resulting in major bleeding and thus not be best treated with anticoagulation at all. The patient and/or carer should participate in this decision.

Reversal of warfarin

Warfarin can be effectively reversed with oral or intravenous Vitamin K, taking 6 to 12 hours to have its full effect. If immediate reversal is needed, Australian manufactured, heat-treated prothrombin complexes are effective[5].

This is an important observation, because a lot of clinicians still use whole fresh frozen plasma (FFP) for warfarin reversal. This causes inappropriate blood transfusion exposure and potential volume overload in these elderly patients. Among the educational challenges in the treatment of AF with anticoagulants will be promoting the proper way to reverse warfarin (and for that matter the novel anticoagulants – see below).

[4] David B. Matchar, Alan Jacobson, Rowena Dolor, *et al.* Effect of Home Testing of International Normalized Ratio on Clinical Events *N Engl J Med* 2010;**363**:1608-20.

[5] H. Tran, M. Collecutt, S. Whitehead and H. H. Salem. Prothrombin complex concentrates used alone in urgent reversal of warfarin anticoagulation. *Int Med J* pp 337-343 July 2011. doi:10.1111/j.1445- 994.2010.02237.x

Issues with Novel Anticoagulants

The first and obvious issue is the potential costs of these drugs. Cost effectiveness data have been published for dabigatran, and the PBAC recommended dabigatran's listing. There is no doubt that the cost implications of PBS listing of novel anticoagulants will be considerable. A lot of the perceived barriers to anticoagulant therapy will be overcome in both the patient's and the clinician's mind. We must not underestimate the effect of eager and legitimate promotion of the drugs by its licenced patent holders.

The non-reversibility of novel anticoagulants has been used as an argument against their use. The same resistance is commonplace amongst surgeons and cardiologists when considering the relative merits of UFH versus LMWH. In both the UFH versus LMWH question and the warfarin versus novel anticoagulants question, the clinical studies clearly show bleeding rates that are comparable in both groups. So non-reversibility does not make bleeding more likely in clinical practice.

A recent publication[6] showed that the effect of rivaroxaban, a Factor Xa antagonist, is reversed by the prothrombin complex, whereas dabigatran, a direct thrombin antagonist, is not. Apixaban, also a Factor Xa inhibitor, is probably also reversible with prothrombin complexes.

This is only a consideration in the event of a patient on novel anticoagulants presenting with major bleeding or in need of urgent surgery.

Quality Use of Medicines

I am not aware of any objective assessment of current Quality Use of Medicines programs.

The NSW Clinical Excellence Commission's *Blood Watch* program uses Academic Detailing quite effectively. I am involved in this program. The program has reduced blood usage in NSW by 11% over the last four years. No other jurisdiction in the world has equalled that achievement: most are still using more blood year by year.

The PBAC identified the challenges in ensuring that the people likely to benefit from anticoagulation for AF receive it in a safe, effective manner. Neither the funder (DOHA) nor the seller (the pharmaceutical companies) will be seen as independent in this exercise. Credible, independent bodies like the Clinical Excellence Commission will be of high value.

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[6]Eerenberg ES Kamphuisen PK Sijpkens MK *et al.* Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate: A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects. *Circulation*. 2011;**124**:1573-1579.)

Conclusion

Despite the cost implications, this author believes that the novel anticoagulants could and should replace warfarin in patients who have difficulty with control of their warfarin dose or for any of the objections to warfarin mentioned above, including convenience when travelling.

As rivaroxaban (and probably apixaban) may be reversed by prothrombin complexes, these two are preferred over dabigatran. Because of its 12-hour duration of action, the compliance issues with rivaroxaban will need to be measured against the safety issues of a drug that is out of the system fairly quickly, compared with apixaban.

The challenge of ensuring the safe and appropriate use of anticoagulants is daunting, but achievable with a multi-faceted approach.