SUBMISSION

REVIEW OF ANTICOAGULATION THERAPIES IN ATRIAL FIBRILLATION

Peter A. Blombery M.B.,B.S.,B.Sc(Med), Ph.D.,F.R.A.C.P., D.D.U.
Honorary Cardiovascular Physician, Heart Centre, Alfred Hospital, Prahran. Victoria
Director, Avenue Cardiovascular Centre, 42 The Avenue, Windsor. Victoria

I have prepared this short submission to the Australian Government "Review of Anticoagulation Therapies in Atrial Fibrillation" as a practising vascular physician with many years experience managing patients with atrial fibrillation and its multiple complications. As a consequence, I am acutely aware of the efficacy and limitations of currently available anticoagulation therapies at the treating doctor/patient level.

There is an extensive literature about the role and optimal requirements for anticoagulation therapy in the management of atrial fibrillation (AF). The external evaluator and reference group of this Review will also be familiar with this literature, which I will not review in detail, but summarise the salient data that is relevant.

In this submission, I will confine my comments to those that I consider pertinent to clinical management of the patient with chronic AF.

BACKGROUND:

Atrial fibrillation is a common disorder in industrialised countries such as Australia, affecting approximately 0.95% population over age 20.[1] Its prevalence increases with age such that it is present in nearly 10% of people over age 80.

The major complications of AF are stroke and systemic embolism due to formation of intracardiac thrombi, portions of which may then embolise to the brain or other organs. It is estimated that 15 – 20% of all strokes are due to AF, increasing to 25% strokes in people older than 85.[2] Strokes secondary to AF tend to be more severe with excess death and disability compared to other strokes. Peripheral embolism requiring treatment accounts for only 6 - 7% of embolic events in patients with AF, the remainder presenting as stroke 7,9

In Sweden, the total annual direct and indirect cost of AF was calculated as € 708 million in 2011.[3] This is more than the annual cost of heart failure, diabetes, breast cancer, depression or osteoporosis. Assuming a similar cost structure in Australia and allowing for the difference in population suggests that the cost of management of chronic AF in Australia is about $A 2 billion per annum. Atrial fibrillation and its complications is therefore a major economic healthcare factor.

ORAL VITAMIN K ANTAGONISTS:

Prior to 1989, patients presenting with stroke or peripheral embolism in the setting of AF were usually initiated on anticoagulant therapy after acute management of the thromboembolic presentation. At The Alfred Hospital in the 1980's, I recollect seeing 40 to 50 patients each year present with peripheral embolism threatening limb viability requiring surgical embolectomy. Virtually all these patients were in chronic AF but on no prophylactic anticoagulant therapy and were commenced on the oral anticoagulant, warfarin, after the event.

In 1989, the AFASAK study was published, which compared treatment with placebo, aspirin or warfarin in patients with chronic AF who had not sustained embolic events.[4] Warfarin therapy was associated with a significant reduction in stroke and systemic embolism compared to aspirin or placebo, albeit at a moderate cost in terms of increased bleeding events. There have been many trials since then confirming these findings. Warfarin and other vitamin K antagonists (VKA) are now established as evidence-based therapy for patients with chronic AF at significant risk of thromboembolism..

Overall, VKA reduces the risk of stroke and systemic embolism in patients with AF by 62% compared to no prophylactic anticoagulant treatment.[5] This is associated with the development of major bleeding in approximately 2.5 to 3.5% patients on VKA per annum.[6,7]

Because of the significant bleeding complications associated with the use of VKA, oral anticoagulation is not appropriate or necessary in all patients with AF. The risk of thromboembolic events, in particular stroke, in patients with AF can be stratified by the use of a variety of risk profiling tools such as the $CHADS_2$ score.[8] Using this score, the individual patient presenting with AF can be stratified into different risk groups, ranging from a 2% annual stroke rate at a $CHADS_2$ score of 0 to 18% annual stroke rate at a $CHADS_2$ score of 6. It is generally accepted that oral anticoagulation with VKA is appropriate at a $CHADS_2$ score of 2 or more (annual stroke rate of 4% or more). At lower $CHADS_2$ scores, the risks of bleeding outweigh the small absolute reduction in stroke obtained with VKA.

However, there are significant barriers to widespread acceptance and utilization of oral anticoagulation therapy with VKA in patients with $CHADS_2$ score of 2 or more, where significant patient benefit is obtained. These include bleeding complications, the need for regular monitoring and the narrow therapeutic range of VKA. Outside an INR range of 2.0 to 3.0, the risk of bleeding and embolic events increases markedly.[9] The best measure of control of VKA therapy is time in the therapeutic range (TTR) in a group of patients. TTR varies from country to country, with Sweden generally accepted as having the best control of INR with a TTR of 76%.[10] Australia fares moderately well in control of VKA dose with estimates for TTR ranging between 50.4% and 68% (PBAC). TTR in clinical trials of oral anticoagulants is typically about 10% higher than in real-life situations.[9]

As a consequence of these barriers to VKA use, a recent review found that in the majority of surveys of patients with chronic AF, <60% of patients who are appropriate candidates for oral anticoagulation are actually offered the treatment.[11] In Australia, there are no figures available about the extent of VKA use in these patients but there is no data to suggest that Australia is different in this regard. A study in Australia looking into the reasons family physicians did not prescribe VKA to appropriate patients found that fear of bleeding and experience of bleeding events were major drivers in this inappropriate decision making.[12] Another study found that underuse of VKA is particularly the case in the elderly and those subject to falls.[2] Underprescribing of VKA is therefore widespread. It appears that overall, about twice as many patients with chronic AF require treatment with VKA than is currently the case.

When one combines this extensive underprescribing of VKA with the average 60% TTR in Australia, it is likely that only 30% at-risk patients with AF and a significant risk of stroke currently receive adequate oral anticoagulation with VKA.

This is grossly inadequate management of these high-risk patients with AF, exposing many of the population unnecessarily to the devastating risk of stroke.

Another way of assessing efficacy of oral anticoagulant treatment is net clinical benefit. This may be defined as the estimated reduction in stroke and systemic embolism attributable to anticoagulant therapy minus 1.5 times the estimated increase in the rate of intracranial haemorrhage attributable to anticoagulant therapy. The net clinical benefit is the net number of events prevented per 100 patient years with the treatment. Using such an analysis in a cohort of almost 14,000 patients with AF, Singer et al concluded that net clinical benefit was imperceptible at $CHADS_2$ score <2 in these patients but increased from 0.97% to 2.22% per annum from $CHADS_2$ score of 2 to 6.[13]

NEW ORAL ANTICOAGULANTS:

In the last 5 years, a number of new oral anticoagulants have become available and so far three - dabigatran, apixaban and rivaroxaban - have been compared to warfarin in large clinical trials in high –risk patients with AF.[6,7,14] None of these agents requires regular monitoring with blood tests or variable dosing as VKA do.

These clinical trials have demonstrated that none of the new drugs is inferior to warfarin in preventing stroke and embolic events. Moreover, all are associated with a markedly lower rate of intracranial haemorrhage and haemorrhagic stroke than warfarin (Table 1), although the extent of this reduction varies from drug to drug. In addition, in the RELY trial, the dabigatran 150 mg bd group had a lower rate of ischaemic stroke (HR 0.76) than those on warfarin [6] and in the ARISTOTLE trial, the apixaban group had a lower mortality (HR 0.89) than the matching warfarin group.[7]

A study of net clinical benefit of these three new anticoagulants compared to warfarin in patients with AF found that all three new anticoagulants had a positive net clinical benefit for patients with $CHADS_2$ score of 2 or more compared to warfarin. Net clinical benefit (events prevented p.a.) compared to warfarin was 1.08% with dabigatran 110mg bd, 0.94% with apixaban, 0.79% with dabigatran 150 mg bd and 0.42% with rivaroxaban.[15]

The new anticoagulants are not without limitations. We do not have data on the frequency of adverse reactions in long-term use, as dabigatran, the first of these drugs to be approved by the TGA and FDA, has only been used for up to 3 years in individual patients as far as I am aware.

There are no direct antidotes currently available for these agents in the presence of major bleeding. However, it is possible that prothrombin complex concentrate will be useful in reversing the effects of rivaroxaban and possibly apixaban [16] and an antibody is currently being evaluated to reverse the anticoagulant effect of dabigatran [17]. In practice, the relatively short half lives of the new drugs means that cessation of the drug is usually sufficient to control bleeding, except in the most severe cases.

It is also important that the new anticoagulants are used according to the prescribing guidelines for each. Since dabigatran was approved by the TGA for use in high risk patients with AF in April 2011, anecdotal reports suggest that it is being prescribed for patients who have poor renal function and GFR<30 ml/min by general practitioners, perhaps because the eGFR as stated on pathology reports is mistakenly assumed to accurately reflect GFR, which is not the case in underweight patients. This may have resulted in significant bleeding complications with dabigatran in Australia and it is vital that prescriber education is focused on this area.

IMPLICATIONS FOR MANAGEMENT OF ANTICOAGULATION IN ATRIAL FIBRILLATION:

There is clearly a large unmet need in treatment of high risk patients with AF as outlined above due to the combination of underprescribing and inadequate treatment with VKA. How may this be improved?

There are two options available to make available effective anticoagulation to the 70% patients who are not currently receiving it.

These are:

(i) to improve compliance with and utilisation of VKA, and/or

(ii) to utilise new anticoagulants.

I will discuss each in turn.

(1) Improving compliance and utilisation of VKA:

The major impediment to increasing usage of VKA in patients with AF is lack of education and understanding of the issues by treating doctors, particularly in patients perceived to be at high risk of bleeding or who are very elderly. At the moment, general practitioners are involved in programs on appropriate use of anticoagulants as part of their Continuing Professional Development but these appear to have been largely unsuccessful in translating the available evidence into clinical practice. Such education would clearly require further improvement but it is difficult to know how effective this would be.

Improving compliance with VKA, ie improving TTR, is feasible and has been modeled in terms of cost saving by Rose et al.[18] Using a quality improvement program (mainly using dedicated anticoagulation clinics rather than management by individual clinicians), it was estimated that a minimal improvement in TTR of 3% was required to be cost saving in AF patients. The authors are now looking at the impact of such a program compared to use of dabigatran.

TTR can also be improved with use of point of care devices and home monitoring with an estimated improvement of 3.8% in TTR.[19] However, this did not translate into a change in clinical outcomes in this study. In addition, point of care devices are expensive and may not be cost effective.

The use of pharmacogenetic data to guide VKA dose selection and adjustment has the potential to improve efficacy and safety of this drug but whether this improves TTR and thromboembolic endpoints remains to be shown.[20] There would also be a significant incremental cost involved in this testing.

It is unlikely that TTR would ever improve in the real world beyond the 76% observed in Sweden, limiting the extent of possible improvement in efficacy.

(2) Use of new anticoagulants:

The new anticoagulants mentioned above offer an attractive alternative to VKA in the management of patients with AF. They avoid the requirement for regular blood testing and are associated with a lower rate of the feared complication of intracranial bleeding.

In the clinical trial setting, they offer a significant net clinical benefit over VKA. Because of these benefits, they are almost certain to be offered to many of the patients who currently are not offered VKA therapy and therefore will save considerable money in the long term by preventing events, both thrombotic and haemorrhagic. There is however a significant opportunity cost as the PBAC has noted.

There have been questions raised about the cost-effectiveness of the new agents compared to VKA when VKA are used with a high TTR. In an analysis comparing dabigatran to warfarin, it was determined that with a TTR of more than 65%, dabigatran 150 mg bd was no longer cost effective.[21] This contrasts with other cost effectiveness studies comparing dabigatran to warfarin [22,23,24] although Kamel et al [23] reported that TTR had a significant effect on incremental cost effectiveness of dabigatran compared to warfarin. Much of the variation in these studies is a function of where the willingness-to-pay threshold per QALY is set.

Such comparisons would require that the TTR for use of warfarin in Australia improved significantly for it to be a potentially effective alternative. This is challenging as outlined above. It is relevant to note that none of the cost-effectiveness studies above included the cost of transportation and lost work productivity associated with INR measurement in the warfarin group. This raises serious questions about the applicability of the conclusions of these cost-effectiveness studies.

Furthermore, in an analysis of the RELY trial looking at outcomes with dabigatran compared to warfarin at differing TTR,[25] there was no relationship between TTR in the warfarin group and the rate of intracranial bleeding. Although stroke and systemic embolism overall event rates decreased with higher TTR in the warfarin group, it was concluded that stroke was reduced with dabigatran, irrespective of INR control.

CONCLUSION:

Treatment of chronic AF in 2012 in Australia with oral anticoagulation with VKA is suboptimal.

There is a major unmet clinical need in this patient group due to difficulties in INR control and nontreatment of almost half the patients for the reasons outlined above.

This shortfall in evidence-based therapy could best be addressed by making available the new anticoagulant drugs to Australians as Authority Required items on the Pharmaceutical Benefits Scheme. This would fulfil the objective of the National Medicines Policy to provide timely access to the medicines that Australians need, at a cost individuals and the community can afford.

The new agents are more convenient for the patients, safer and result in better clinical outcomes than VKA. They have the potential to be significantly cost-saving in the long-term management of AF.

The VKA have more marked limitations than the new anticoagulants. Improving TTR and increasing the chronic underuse of VKA would be very challenging and even if successful would still result in an excess of intracranial bleeding compared to the new agents. Compared to optimal use of VKA, the new drug dabigatran is associated with a lower risk of stroke and systemic embolism which would be denied to many Australian patients if subsidised prescribing was not available.

The American College of Chest Physicians in their latest evidence-based clinical practice guidelines,[26] published this month have come to the same conclusion. They recommend the new anticoagulant dabigatran over warfarin for stroke prevention in AF. Their statement reads “Where we recommend or suggest in favour of oral anticoagulation, we suggest dabigatran 150 mg bd rather than adjusted-dose vitamin K antagonist therapy.”

I submit that the new anticoagulants, prescribed properly, are the most appropriate way to improve the currently inadequate management of Australian patients with chronic atrial fibrillation.

P.A. Blombery

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Table 1 - COMPARISON OF RELY, ROCKET AND ARISTOTLE STUDIES

RESULTS Expressed as % events p.a. unless otherwise stated	**RELY[6]** ITT					**ROCKET[14]** ITT		**ROCKET[14]** AS TREATED SAFETY POPULATION			**ARISTOTLE[7]** ITT		
	Warf	**Dab 110**	*HR vs warf*	**Dab 150**	*HR vs warf*	**Warf**	**Riva**	**Warf**	**Riva**	*HR vs warf*	**Warf**	**Apix**	*HR vs warf*
Stroke or systemic embolism	**1.71**	**1.54**	*0.90*	**1.11**	***0.65†***	**2.4**	**2.1**	**2.2**	**1.7**	***0.79†***	**1.6**	**1.27**	***0.79†***
Ischaemic/other stroke	**1.20**	**1.34**	***1.11***	**0.92**	***0.76†***			**1.52**	**1.40**	*0.92*	**1.05**	**0.97**	*0.92*
Haemorrhagic stroke	**0.38**	**0.12**	***0.31†***	**0.10**	***0.26†***			**0.44**	**0.26**	***0.59†***	**0.47**	**0.24**	***0.51†***
Intracranial haemex	**074#**	**0.23 #**	***0.31†***	**0.30 #**	***0.41†***			**0.7**	**0.5**	***0.67†***	**0.80**	**0.33**	***0.42†***
Total mortality	**4.13**	**3.75**	*0.91*	**3.64**	*0.88*	**4.9**	**4.5**	**2.21**	**1.87**	*0.85*	**3.94**	**3.52**	***0.89†***
Vasc. mortality	**2.69**	**2.43**	*0.90*	**2.28**	***0.85†***			**1.71**	**1.53**	*0.89*	**2.02**	**1.8**	*0.89*
Major bleed ISTH	**3.57**	**2.87**	*0.80*	**3.32**	***0.93***			**3.4**	**3.6**	*1.06*	**3.09**	**2.13**	***0.69 †***
TIMI											**1.69**	**0.96**	
GUSTO											**1.13**	**0.52**	
Major GI bleed	**1.02**	**1.12**	*1.10*	**1.51**	***1.48†***			**2.16#**	**3.15#**	*1.46*	**0.86**	**0.76**	*0.89*
AMI	**0.64**	**0.82**	*1.29*	**0.81**	*1.27*			**1.12**	**0.91**	*0.81*	**0.61**	**0.53**	*0.88*

HR is hazard ratio for new drug vs warfarin.
Hazard ratios marked with † and green background indicate statistical superiority compared to warfarin.
Overall % event rate in study, not annual %.

RELY figures are from revised event rate.

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