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Submission to the Department of Health and Ageing
Review of anticoagulation therapies in Atrial Fibrillation

The Stroke Society of Australasia has a direct interest in the review of anticoagulation therapies for atrial fibrillation (AF). We represent a broad coalition of clinicians and researchers active in stroke care and research, as summarized by our society's slogan, 'many minds against stroke'.

In our submission to the panel, we will not provide a comprehensive literature review of this subject, as this information is already available. However, we would like to summarise current AF research and clinical management from the particular perspective of stroke specialists.

The following points are, we believe, well accepted, and will be addressed in turn:

- AF increases with age, and the Australian population is ageing
- AF is under-recognised and under-diagnosed in the community
- Cardioembolic stroke is linked to substantially higher rates of subsequent death and disability than other subtypes of ischaemic stroke
- Cardioembolism due to AF forms a significant proportion of stroke
- Anticoagulation is the stroke-prevention treatment of choice for the majority of patients with AF, but practical hurdles for both patient and practitioner in the use of warfarin mean that this treatment is under-utilised.
- Warfarin under-utilisation leads to a substantial burden of preventable stroke.

AF prevalence steadily increases with age; it is extremely rare in patients aged less than 50, has a prevalence of around 2% in patients aged 50-59, and roughly doubles each decade thereafter (to around 16% in patients aged over 80).[1] These figures obviously only include diagnosed cases. It is estimated that perhaps 20% of AF cases are undiagnosed; certainly there is little community knowledge of the importance of sinus rhythm (the normal heart rhythm) and the potential sequelae of having AF.

Stroke is the most feared and devastating consequence of AF. Strokes caused by atrial fibrillation are more severe than strokes of other common aetiologies. They are associated with higher mortality rates (28% vs. 12% in one recent large French study),[2] longer hospital stays and a greater need for rehabilitation.[3] Recent economic data presented to the government on ischaemic stroke cost did not stratify by stroke aetiology, and hence the cost of AF-related stroke was almost certainly an underestimate.[4]

Aspirin reduces the risk of stroke by around 22%, and dose-adjusted warfarin by 64%.[5] Compared with warfarin, the newer anticoagulants further reduce stroke/systemic embolism risk by 12%

(rivaroxaban),[6] 21% (apixaban)[7] and 34% (dabigatran)[8] respectively, the latter two statistically significantly. All reduce the risk of intracerebral haemorrhage, and apixaban additionally reduced the risk of extracranial major bleeding.

Not all people with AF have the same risk of thromboembolism and stroke. There are several commonly used risk-stratification tools for AF available to guide treatment. While it is generally accepted that patients with low risk AF (<1% stroke risk per year)[9] do not require anticoagulation, most guidelines recommend that the majority of patients with AF with moderate to high risk for thromboembolism (>2% per year)[9] should be anticoagulated. However, in reality, only a minority (44%) are treated.[10] This leads to a significant burden of preventable stroke.

According to the most recent Australian population-based epidemiological study, around 42% of stroke is now cardioembolic, and 35% cardioembolic stroke is due to atrial fibrillation.[11] This is significantly higher than in other populations.[2] The rising proportion of cardioembolic stroke in Australia is probably due to a number of factors, including better ascertainment (higher rates of heart rhythm monitoring), lower incidence rates of other subtypes due to better risk factor control, and longer survival of patients with ischaemic heart disease. Prevention of cardioembolism is an indispensible part of our fight against stroke.

In several recent Australian hospital-based stroke studies, under treatment of patients with atrial fibrillation has been shown to be a significant cause of preventable stroke, with perhaps 5-9% of all ischaemic stroke preventable through optimal anticoagulation.[12,13] There are a number of reasons for under-treatment and these include: a) physician perception that there is a low risk of thromboembolism; b) physician and/or patient perception that treatment is too risky (particularly the risk of bleeding); c) patient perception that the process of safe treatment (blood test monitoring, dietary restriction, difficulties with taking other tablets) is too onerous; d) complex medication interactions.

Public and Primary-Care education programs may improve awareness and detection of AF – encouraging patients to check their own pulse for regularity and performing yearly ECGs in patients aged over 65. Dissemination of the simple $CHADS_2$ or CHA_2DS_2-VASc risk stratification scores may assist GPs.

Comprehensive intervention programs incorporating regular patient monitoring can both increase the frequency of warfarin prescribing and the quality of control of anti-coagulation (level of anti-coagulation and consistency of anti-coagulation).[14,15] These programs have not been widely adopted in Australia, however. Pharmacogenomics-guided prescribing may improve control of anti-coagulation and is currently under assessment. These initiatives (especially aimed at community-living citizens aged 65 and older) may therefore reduce the burden of stroke and the SSA would be supportive of additional government funding directed to these initiatives.

It is likely, however, that a significant evidence-practice gap will remain. In this context it is worth considering the newer anticoagulants, which, due to ease of use (fixed doses, depending on age and kidney function), lack of need for monitoring with blood tests, reduced dietary and medication interactions and net clinical benefit for stroke prevention are attractive to both doctors and patients. As clinicians, we all have patients who bemoan the burden associated with taking warfarin, particularly the need for regular blood testing that may be quite unpleasant for some patients. The newer drugs, dabigatran being the first, offer the possibility of improved quality of life for patients at risk of stroke and requiring anti-coagulation.

Compared with warfarin, dabigatran (at a dose of 150mg) offers a significant risk reduction for stroke/systemic embolism (annualised absolute risk-reduction (ARR) 0.56%), intracranial haemorrhage (0.28%) and vascular death (0.41%), despite increasing risks of myocardial infarction (0.21%) and gastrointestinal haemorrhage (0.49%). It has been noted that average time in the therapeutic range (TTR) influences interpretation of the RELY trial,[16] but it is almost certain that the

level of INR control achieved by Australian patients in the trial (74%) is not achieved in routine Australian practice (it may be around 60% or perhaps even lower[17]). Although it seems probable that anticoagulation and compliance with this drug would be less optimal in routine care than in a trial setting, the advantages of such an easy-to-use drug with similar or improved efficacy for stroke prevention appear clear.

Health economic analyses have generally shown cost-effectiveness of dabigatran 150mg (but not 110mg) versus warfarin,[18-21] even though it may be marginal where a high TTR can be routinely achieved (this is possible in centres with comprehensive intervention programmes for patients taking warfarin, as described above). Additionally, as the PBAC recognized,[22] it is likely (though difficult to prove) that many moderate-high risk AF patients who refuse warfarin because of the perceived burden of therapy or risks of bleeding will be willing to take dabigatran or an alternative newer agent with similar efficacy and safety profile. Anecdotally, many Society members have patients with AF who pay for non-subsidised dabigatran.

The SSA notes that in addition to dabigatran, two other medications mentioned above have either been approved by the FDA in the USA (rivaroxaban) or are awaiting probable FDA approval (the apixaban decision is due by March 28th) and thus likely to be submitted for approval in Australia in the near future. The Society recognises that all three of these new anti-coagulant medications offer an attractive alternative to warfarin from both a patient and physician perspective (as a consequence of increased efficacy, reduced bleeding risk and ease of use). Wide public availability of these medications will most likely reduce the current evidence-practice gap in use of anticoagulation treatment in AF, reducing stroke, stroke death and stroke-related disability. We are confident that these views reflect the opinions of our membership having discussed these data in several national meetings in the last 12 months. For these reasons, we support the recent PBAC recommendation for a listing for dabigatran in moderate-high risk atrial fibrillation.

Yours Sincerely on behalf of the Stroke Society of Australasia,

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Conflicts of interest:

A/Professor Dewey, Dr Kleinig and Dr Wijeratne have all attended Annual Stroke Unit Heads meetings, which are supported by Boehringer Ingelheim. In addition, A/Professor Dewey has previously been a member of an Australian Stroke Advisory Board for Boehringer Ingelheim.

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