The Australasian Society of Thrombosis and Haemostasis (ASTH) represents over 270 clinicians and scientists committed to promoting and fostering the acquisition, exchange and diffusion of knowledge and ideas relating to normal and abnormal haemostasis. The Society serves as a forum for bringing together a broad array of disciplines which relate to bleeding, thrombosis and cognate fields. The ASTH aims to promote, foster, develop and assist the study of research in and the acquisition, dissemination and application of knowledge and information concerning thrombosis and haemostasis, and to promote and improve standards of knowledge, diagnosis and management of thrombotic and bleeding disorders and allied subjects.

The Haematology Society of Australia and New Zealand (HSANZ) aims to promote, foster, develop and assist the study and application of information concerning haematology in all its aspects; promote improved standards, interest and research in all aspects of haematology; encourage, stimulate and foster interest in haematology amongst other interested persons including regional and international bodies; provide opportunities for meeting others in related fields of interest and discussing matters of common interest; encourage, assist and arrange for scientists, practitioners and others to visit Australia in order to promote scientific communication in the field of haematology and encourage, assist and arrange for scientists, practitioners and others to travel abroad and promote scientific communication in the field of haematology.

The Australian and New Zealand Society of Blood Transfusion's (ANZSBT) broad aims are the advancement of knowledge in blood transfusion and transfusion medicine; the promotion of improved standards in the practice of blood transfusion; the collaboration with international and other regional societies interested in blood; the promotion of interest in research into blood transfusion and allied subjects and the formulation of guidelines in key areas of transfusion practice

Together the ASTH, HSANZ and ANZSBT thank the Department of Health and Ageing for the opportunity to provide a written submission to the Review of Anticoagulation Therapies in Atrial Fibrillation.

New Oral anticoagulants (NOACs) and Atrial Fibrillation

We consider the development of new oral anticoagulant agents (NOACs) a breakthrough in anticoagulant management of patients at risk of thromboembolism and support their use in appropriate patients. It is likely they will offer improved protection against thromboembolic complications with greater convenience in specific at-risk populations, in particular atrial fibrillation (AF). Dabigatran, in particular has already been deemed to be cost-effective for the prevention of stroke in patients with high-risk atrial fibrillation by the Pharmaceutical Benefits Advisory Committee in 2011. Warfarin has a difficult pharmacological profile and many at-risk patients are reluctant to receive it despite its known clinical benefit in preventing thromboembolism. The practical advantage of NOACs (namely not requiring routine monitoring and few interactions with foods and medications) will contribute to overcome the under-treatment of many at-risk AF patients and reduce the number of devastating consequential strokes.

However, as is the case when other new classes of therapy have been introduced, we are concerned about a number of issues relating to the introduction of NOACs in Australia.

There appears to be a limited appreciation of the care required for patient selection. Elderly patients, those with impaired renal function or low body weight are at particularly high risk of bleeding complications. We suggest the following criteria be considered prior to initiating NOACs:

- At-risk atrial fibrillation patients ($CHADS_2$ score ≥2):
- Adequate renal function (when dabigatran is considered in patients with calculated [1] GFR 30-50ml/min, review co-morbidities and concomitant medications and careful dose selection; for oral direct factor Xa inhibitor calculated[1] GFR>30ml/min)
- Body weight greater than 50kg (for dabigatran)
- For patients aged greater than 75 years, careful case-by-case evaluation for net benefit (and careful dose selection in the case of dabigatran)

In addition, it should be noted that subgroup analyses have shown no proven benefit for efficacy of stroke prevention in the patient group already well

[1]Cockcroft-Gault

controlled on warfarin (warfarin time in therapeutic range >65% over a three month period). Provided they meet the safety criteria above, patients who are established on warfarin, may however benefit for additional reasons such as:

- Poor venous access
- Patients living in remote areas where INR monitoring cannot be readily accessed
- Patients requiring concomitant medications that are likely to make warfarin control (INR) difficult (e.g., anticonvulsants or azoles)
- Patients with unpredictable dietary intake of vitamin K (e.g., malabsorption syndromes, long-term parenteral nutrition)

It is imperative that a comprehensive education program be readily available to prescribers to ensure appropriate and safe prescribing of NOACs with particular emphasis on patient selection. In addition, the following important safety issues should be highlighted:

- At present, there is no reversal agent for patients who develop bleeding or require urgent surgery while taking NOACs
- The net benefit of the NOACs over warfarin in patients older than 75 years of age is not as great as those under 75 years
- Interactions of commonly used cardiovascular medications, such as verapamil and amiodarone, can significantly increase the anticoagulant effect of some NOACs
- Transition from warfarin to NOACs requires care, ensuring that the INR is less than 2 prior to starting NOACs
- There is currently no widely available, routine diagnostic laboratory test that can determine accurately and reproducibly the level of anticoagulant effect of these drugs in patients
- Increased adherence is needed for those NOACs requiring twice daily dosing (e.g., dabigatran and apixiban)
- There is a rapid offset of action compared to warfarin
- NOACs have a rapid onset and offset of action compared with warfarin
- Patients taking dabigatran who develop renal failure will, as a consequence, have delayed dabigatran elimination and their bleeding risk may increase
- Regular monitoring of renal function is advisable in at risk patients (e.g., concomitant neprophrotoxic drugs)

The lack of a specific antidote for NOACs makes the management of bleeding complications associated with these agents difficult when it occurs. Prothrombin complex concentrate appears to reverse the anticoagulant effect of rivaroxaban but failed to reverse the anticoagulant effect of dabigatran in healthy volunteers. Similarly, recombinant factor VIIa (NovoSeven™) did not reverse the melagatran-induced effects on thrombin generation, and platelet activation in healthy volunteers. Charcoal and haemodialysis are possible methods to reverse the anticoagulant effect of dabigatran but can be impractical. Therefore, the management of haemorrhagic complications is mainly supportive.

It is not known how participants in phase III clinical trials that evaluated the efficacy and safety of dabigatran in patients with atrial fibrillation or venous thrombosis, who developed major bleeding, were managed to normalise haemostasis. The provision of this information by sponsors of the study is vital in the development of guidelines to manage dabigatran-related major bleeding.

The management of patients receiving NOACs who develop recurrent thromboembolism or require clearance for urgent surgery is problematic as there is no currently available coagulation test that can accurately and reproducibly determine their anticoagulant effects. We, the specialist haematology professional societies of Australia and New Zealand (Australasian Society of Thrombosis and Haemostasis, Australian and New Zealand Society of Blood Transfusion, Haematology Society of Australia and New Zealand) would welcome support from pharmaceutical industries to work collaboratively to set up the most appropriate laboratory testing for use in specific clinical scenarios, in particular by making available NOAC drug solutions.

Anticoagulant-related major bleeding is an important public health issue and increased vigilance and adverse events capture is critical for ongoing drug safety. We will be implementing the Anticoagulant Reversal and Events Study (ARES) Study, the aim of which is to document and monitor outcomes of patients in Australia and New Zealand who are receiving warfarin or NOACs and present to emergency departments with bleeding or thromboembolic

events. We have also begun working to formulate practical protocols and recommendations for patients receiving NOACs including:

- Appropriate laboratory testing
- Effective management of major haemorrhage
- Guidelines for peri-procedural management
- Management for patients incurring thromboembolism

We would like to see that these promising NOACs are introduced into clinical practice as safely as possible.