



**PBS Post market
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Re: Review of Anticoagulation Therapies in Atrial Fibrillation

The NSW Therapeutic Advisory Group is an independent not for profit association that promotes the Quality Use of Medicines (QUM) within and across the continuum of acute care. Our members are clinical pharmacologists, pharmacists, and other clinicians from each of the Drug and Therapeutics Committees in NSW public hospitals and Local Health Districts. Our goal is to promote QUM by sharing unbiased, evidence based information about drug therapy. Our objectives are to investigate and evaluate new initiatives in therapeutics, to support Drug and Therapeutics Committees and to promote rational, high quality, safe prescription, dispensing and administration of medicines in public hospitals and the wider community and hence the relevance of our position in putting forward this submission.

The consultation paper was sent out to all NSW TAG members to give them the opportunity to comment. A collation of their comments together with the views of NSW TAG is provided below.

NSW TAG welcomes the review of strategies to improve the health outcomes of patients with atrial fibrillation (AF) treated with anticoagulation therapies. Although NSW TAG members are strong advocates for consumers to have access to innovative treatments, they have expressed concerns regarding safe and appropriate use of the newer anticoagulants such as dabigatran and the need to have a clear plan to safely introduce these agents and manage complications.

NSW TAG has a long association with strategies to ensure the judicious, appropriate, safe and effective dose of anticoagulants in the hospital setting and across the continuum of care. These strategies include:

- The development and implementation of policies and protocols in NSW public hospitals with regard to the safe use of anticoagulants including the various heparins and warfarin.
- The provision of advice to individual hospitals on the development of local protocols concerning anticoagulant use.
- The management of a repository for protocols and other resources regarding anticoagulant use that can be shared amongst members in order that individual members may be supported in the development and implementation of their organisation's policies and interventions.
- Input into safe warfarin prescribing in the design of the National Inpatient Medication Chart.
- The inclusion of various aspects of hospital-based oral anticoagulation therapy as Indicators of Quality Use of Medications in Hospitals¹. These indicators focussed on areas where knowledge gaps were known to exist and where practice change required facilitation such as measurements of the safe dosing of hospital-initiated warfarin; the

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- appropriate responses to abnormal INR results in hospital inpatients; and, the prescription of warfarin in atrial fibrillation patients discharged from hospital.
- The evaluation of hospital-managed antithrombotic therapy, including protocol development and implementation in the Medication Safety Self-Assessment survey, which seeks to ensure safe medication systems are in place in Australian hospitals for the management of anticoagulation therapiesⁱⁱ.

It is likely that many of the strategies described above will need to be applied when other anticoagulant therapies are introduced to ensure their safe and appropriate prescription, dispensing, administration and monitoring in hospitals and in patients leaving hospital. Unfortunately it remains a sad fact that those patients who are most at risk of stroke from atrial fibrillation are also likely to be most at risk of adverse bleeding events. Hence careful patient selection, dosing and on-going monitoring will remain critical to the use of these drugs to achieve optimal outcomes in AF patients.

At this time, to our knowledge, no public hospitals in NSW have introduced dabigatran or other new anticoagulants to their formulary for use in atrial fibrillation patients. The disconnect between the community and acute health care sectors in access to dabigatran meant that hospitalised patients, who were taking dabigatran (admitted to hospital for events other than dabigatran adverse effects), were advised to bring their own supply to hospital. Many hospitals' experiences of the new oral anticoagulants (OACs) have been limited to treating patients suffering from the adverse effects of these medications. Since the introduction of dabigatran to community AF patients, hospital clinicians have frequently been faced with managing emergency bleeding events for which there is no reversal agent. Moreover, since the results of the RELY trial were published and the PBAC conducted its review process, further analysis has noted increased rates of myocardial infarction in dabigatran-treated patients^{iii,iv}. These events have raised serious questions about the methods by which new drugs and, in particular, a new class of drugs, should be introduced to the Australian population.

NSW TAG members believe important lessons need to be noted:

- There is a lack of understanding by clinicians of what TGA approval means. TGA approval indicates efficacy based on company-supplied data not effectiveness. TGA approval does not imply superiority, cost savings or improved safety to existing therapies.
- Randomised controlled trials (RCTs) investigate efficacy but not effectiveness. Patients in trials are often carefully selected and do not represent real world patients. Further studies are required to investigate new drugs in real world populations and help prescribers become knowledgeable about the appropriate and safe use of new drugs and their utilisation in the health care sector. This point seems particularly relevant to the case of dabigatran where adverse effects have occurred primarily in frail elderly patients or patients with renal impairment, who were often not included in RCTs.
- Medications, which belong to a new drug class, require particular care as safety data is often not adequate. There is usually little international experience by which we can be guided. Examples of drug classes for which later evidence led to their withdrawal and caveats on their use include the COX-2 inhibitors such as rofecoxib and lumericoxib and the glitazones, rosiglitazone and pioglitazone. A rethink of the best methods to implement translational research is required.
- Warfarin, the comparator for dabigatran, while problematic, is an extremely well-known drug. It is approximately a tenth of the price of dabigatran, its effect is measurable, it has a reversal agent, has a long half life and is a once-daily medication. In comparison, dabigatran represents a significant cost, lacks markers of effect, has a short half-life and requires twice daily administration with possible non-adherence issues. While many of these issues are the remit of the PBAC, who endorsed the cost-effectiveness of the product, at the time of its consideration the PBAC did not have the complete

- information. The cost and effect equation is substantially different if the drug causes major adverse cardiovascular and bleeding events in real world patients. The under-reporting of adverse effects occurring in clinical trials is of concern.
- There is insufficient information available regarding switching between oral anticoagulants.
 - TAG members report that they were aware of the product familiarisation program (PFP) for dabigatran conducted in the community, with primary participation by general practitioners. A significant number of adverse events were reported to NSW TAG by our members indicating that the factors that influenced its quality use were not well understood. The Pradaxa® PFP contrasted with other PFPs, which are usually conducted in hospitals. In order for PFPs to be conducted in hospitals, they require Drug and Therapeutic Committee review with appropriate monitoring of safety as part of the program. A commitment to report adverse events must be an essential measure of any PFP. The Council of Australian Therapeutic Advisory Groups (CATAG), of which NSW TAG is a member, has developed Guiding Principles for Medication Access Programs such as PFPs and alerted Medicine Australia to these principles in order that their Code of Conduct be aligned with CATAG recommendations^v.
 - To truly understand the role of the warfarin comparators, we require information about INR control in patients in the Australian community and hospitals
 - An area of great concern to NSW TAG members is the limited resources to support patients and clinicians managing ever-increasing complex medication regimens. Interventions involving clinical pharmacists have shown improved patients outcomes in acute and community health care sectors. For example, Stafford et al demonstrated that a Home Medicines Review after discharge reduced the risk of bleeding or rehospitalisation^{vi}. The Australian Commission on Safety and Quality in Health Care and the NPS: Better Choices, Better Health have recognised the significant safety gap in medicines particularly around transitions of care and highlighted the importance of medication reconciliation^{vii,viii}. The introduction of such interventions, including building workforce capacity, can assist in improved patient outcomes and requires support from government, administrators and policymakers.
 - Given the role of the media in conveying information about medicines, particularly with the advent of new drug therapies, and the prevalence of poor health literacy, there is a need to ensure that balanced information in an easily understood format is readily available for patients, their carers and their health care professional.

In summary, NSW TAG members wish to highlight the need for a cautious approach in the introduction of new agents, particularly those from new drug classes, such as the thrombin inhibitors and Factor Xa inhibitors. Given the recent experience with dabigatran use in vulnerable patients, an approach ensuring judicious, appropriate, safe and effective use of these medicines is recommended so that patient outcomes are optimised and adverse events minimised.

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