CATAG
Council of Australian Therapeutic Advisory Groups

Emeritus Professor Lloyd Sansom AO
Special Advisor
National Medicines Policy Framework
Department of Health and Ageing
MDP 900
GPO Box 9848
Canberra ACT 2601

Dear Professor Sansom,

Re: Review of Anticoagulation Therapies in Atrial Fibrillation

The Council of Australian Therapeutic Advisory Groups (CATAG) is an authoritative, expert, consensus-based collaboration of representatives from all Australian State and Territory Therapeutic Advisory Groups or their jurisdictional committee equivalents.

CATAG aims to standardise and improve medicines use primarily (but not exclusively) in the hospital sector across Australia through information sharing, advice and advocacy activities.

CATAG thanks DOHA for the opportunity to comment on the use of anticoagulation therapies in Atrial Fibrillation. CATAG has recently corresponded to the Drug Utilization Sub Committee (DUSC) of the Pharmaceutical Benefits Advisory Committee (PBAC) regarding a request for information on drug utilisation evaluations of the newer anticoagulants such as dabigatran, rivaroxaban and apixaban. CATAG's response to DUSC is attached (pages 3-4) .

As can be seen from the responses there is reasonable consistency nationally with regard to formulary listings. The responses have also identified a gap in DUE activity for the three identified medications, most likely due to their limited use. We hope this information is useful.

The consultation paper 'Review of Anticoagulation Therapies in Atrial Fibrillation' was sent to all CATAG members to give them the opportunity to comment. A collation of their comments is provided.

Reversal of agents
Unlike warfarin, there are no current effective antidotes for use in serious bleeding events for the reversal of the newer agents. The medications apixaban and rivaroxaban both act as direct factor Xa inhibitors and dabigatran acts a direct thrombin inhibitor. Prothrombin complex concentrate (PCC) and recombinant factor VIIa may be considered in the event of life threatening bleeding; however there are no published clinical data on the use of recombinant factor VIIa for reversal of the new oral anticoagulants and it is unclear whether it would be effective[i]. Prothrombin complex concentrate for the reversal of dabigatran is no longer recommended[ii]. An Effective antidote/s and serious bleeding event management guidelines are required, as the recommendations have changed and it is unclear which reversal agents are effective and in what circumstances they should be used[iii].

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Monitoring effectiveness

There are no currently available validated laboratory tests to monitor the effectiveness of the newer agents. In the presence of the newer agents the changes in the available tests such as aPPT and PT are subject to high variability. Although routine monitoring of coagulation with the newer agents is not indicated as per the manufacturers' product information, it would be of value to determine the extent of coagulation particularly in the event of overdose or serious bleeding. The development and wide availability of a laboratory test/s to monitor effectiveness of the agents is required.

National guidelines

The development of national guidelines addressing the following criteria are required:

a) Identifying the populations these new agents can be utilised in.
b) The process of switching a patient from one agent to another agent.
c) Clear guidance is required regarding the management of serious bleeding events and the action to be taken where immediate reversal is required for each agent.
d) Dosage and dose adjustments both in terms of monitoring the effectiveness of the agent and in relation to special populations for example the elderly, over and underweight individuals and in the presence of hepatic and renal impairment. To highlight the current difficulties arising without appropriate guidance;
    I. Rivaroxaban in elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance.
    II. The clinical trials using anti-thrombin agents excluded patients with common co morbidities and conjunctive antiplatelet treatments, therefore the risk of haemorrhage may be an underestimate of what is representative in practice.
    III. A recent meta analysis involving diabigatran in AF reported an increased incidence of acute coronary syndrome and myocardial infarction[iv]

Product Familiarisation Programs

Most public hospitals have strict guidelines regarding Product Familiarisation Programs (PFP) and the introduction of such a program is approved through a Drugs and Therapeutics committee after rigorous evaluation. The approved programs in public hospitals are highly monitored; essential to every program is the reporting of adverse events. It is less clear what occurs in community practice. As shown in the attached document there are a limited number of hospital formularies listing dabigatran throughout Australia. The experience with the Pradaxa® (dabigatran) PFP, which occurred mostly in the community resulted in many community based patients accessing public hospitals due to adverse events and therefore hospital clinicians were required to manage serious bleeding events with no available reversal agent. CATAG has developed Guiding Principles for Medication Access Programs (MAP) such as PFPs. Medicine Australia has been advised of the principles in the recent review of their Code of Conduct, it has been suggested to align their code with these principles[v]. CATAG would also support the adaptation of the MAP Guiding Principles for the community sector.

Kind regards,

Jane Donnelly
National Coordinator
On Behalf of CATAG
February 21, 2012

[i] Kazmi, R and Lwaleed, B. New anticoagulants: How to deal with treatment failure and bleeding complications. *Br J Clin Pharmacol 2011*; **72**: 593-603

[ii] Erenberg E, Kamphuisen P, Sijpkens M, Meijers J, Buller H, Levi M. Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate. A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects. *Circulation* 2011; **124**:1573-1579

[iii] Levi M, Eerenberg E, Kamphuisen PW. Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents. J Thromb Haemost 2011; 9: 1705–12.

[iv] Uchino K and Hernandez A. Dabigatran Association With Higher Risk of Acute Coronary Events; Meta-analysis of Noninferiority Randomized Controlled Trials. *Arch Intern Med.* Published online January 9, 2012

v Guiding Principles for Medicines Access Programs in Australian Public Hospitals: Council of Australian Therapeutic Advisory Groups, 2011. http://www.ciap.health.nsw.gov.au/nswtag/publications/otherdocs/CATAGPFPGuidingPrinciples291111.pdf