The Royal Australian College of General Practitioners

RACGP Submission to the Department of Health and Ageing

Review of Anticoagulation Therapies in Atrial Fibrillation

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Stakeholder details

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1. Introduction

The Royal Australian College of General Practitioners (RACGP) thanks the Department of Health and Ageing for the opportunity to contribute to the Review of Anticoagulation Therapies in Atrial Fibrillation.

The RACGP is the specialty medical college for general practice in Australia, responsible for defining the nature of the discipline, setting the standards and curriculum for education and training, maintaining the standards for quality clinical practice, and supporting general practitioners in their pursuit of excellence in patient care and community service.

The RACGP supports safe and effective prescribing, and wise use of medicines in Australian health care. We acknowledge the worthy intention of this review to appraise Anticoagulation Therapies in Atrial Fibrillation. The College felt this issue warranted a response because of concerns about medication safety in primary care.

The RACGP believes General Practitioners (GPs) have the training and skills to prescribe these medications. General Practitioners are the largest group prescribing, monitoring and evaluating anticoagulants in Australia.

The review is timely given the introduction of new anticoagulant options. The RACGP believes this has been associated with significant marketing processes which have the capacity to reduce both quality prescribing and patient safety.

The introduction of these therapies also highlights an ongoing concern for the RACGP; the migration of moderate risk medications (serious adverse event rate 2.7%) into primary care in the absence of suitable infrastructure to monitor drug efficacy, drug interaction, and post-marketing surveillance in general.

The RACGP believes that the current quality of “time in therapeutic range” for warfarin therapy in Australian primary care may negate the perceived benefits of the new drug.

This submission will highlight the need for drug safety infrastructure in General Practice, as well as details our concerns regarding oral anticoagulant therapies from a General Practice perspective.

2. Medication Safety in Primary Care

The decision to initiate therapies is often a static decision based on variables of the day. Patient lives however are dynamic, and those variables constantly change. Whilst GPs are well trained, and have some data checks built into their prescribing systems, as healthcare becomes increasingly complex we believe there needs to be further infrastructure provided in the general practice setting to support drug safety.

Medication safety and audit systems are common in secondary and tertiary care systems. The same levels of safety and support have not migrated to primary care despite more complex drugs and therapeutic regimes transferred to General Practice for management.

The Australian Commission for Safety and Quality in Health Care has deemed medication safety a core national goal for Australia's Healthcare. This goal is supported by the RACGP. Our *Standards for general practices (4th edition)* already support clinical governance in general practice and the need to demonstrate drug safety. Whilst there is some medication safety audit occurring in general practice we believe it is still in its infancy and there is a need of major infrastructural support. Only in general practice can years of accumulated history, co-morbidity and pathology be combined to produce a comprehensive medication monitoring system.

Unless medication safety infrastructure is strengthened in general practice, the PBS will continue to be in a similar position as it is now with Dabigatran – uncertain as to the prescribing quality and efficacy processes to ensure safe and optimal prescribing (other examples include antibiotic stewardship and narcotics management).

Recommendation

- The RACGP recommends to the review, that to meet current and future demands for medication audit and safety, improved medication auditing processes be introduced into general practice. This can range from simple computerised auditing processes in small practices, to dedicated staff in larger environs to implement and monitor drug utilisation and safety patterns[i].

3. General Practice Population with Atrial Fibrillation

Management of Atrial fibrillation (AF) in general practice is commonplace. AF is estimated to affect approximately 10% of the population aged over 65 years in Australia. As our population ages, this cohort is also far more likely to be suffering from multi-morbidities and as a result, be taking several prescription drugs for multiple conditions.

To inform this submission we undertook a quick audit of the characteristics of patients with atrial fibrillation in general practice. The primary intent was to examine renal comorbidities and current INR control issues. The audit involved approximately 800 patients with AF in 4 city and 1 rural general practice. The audit was performed in patients aged 65 years and older as non-valvular AF increases the risk of stroke in this age group.

In patients with atrial fibrillation

- Approximately 10% of patients over the age of 65 have AF. Renal impairment is common with CKD 3 at 42% and CKD 4 or greater at 5-6%. In addition, significant multi-morbidity is reflected in the high percentage of patients taking 8 or more medications (68%).
- A very consistent finding across all audited practices was that 46% of all patients with AF were on anticoagulation therapy. Pleasingly, of those who were on this therapy, 74% were in the therapeutic range.

4. To report on current and future options for improving the health outcomes of patients with atrial fibrillation treated with oral anticoagulants.

Indication clarity - Patient selection for anticoagulant therapy

The RACGP agrees with the concise indication as "patients with non-valvular atrial fibrillation (NVAF) who are at moderate to high risk of developing stroke or systemic embolism, who meet certain criteria."

The risk of thromboembolism in non-valvular AF is low in patients less than age 65[ii]. The $CHADS_2$ score is validated on patients aged greater than 65[iii]. This age characteristic is being overlooked and should be routinely incorporated into indication decisions.

The PBAC indication is subtly different to current guidelines for assessing risk for thromboembolic stroke. The $CHADS_2$ score was utilised by the RE-LY study and would be consistent with current guidelines. Multiple other trials investigating atrial fibrillation and new anticoagulants are also utilising the $CHADS_2$ system. For sake of consistency in guidelines, the $CHADS_2$ system for indication should be maintained.

Some groups are now advising to progress to using a CHA_2DS_2VASc score. This will have implications for the use of AF therapies and it is therefore essential to have clarity on which tool is the most appropriate and validated. One possible implication of the recent push to using CHA_2DS_2VASc score is that significantly more people will be calculated for anticoagulation therapy using this method.

The RACGP views with concern several marketing strategies employed by the pharmaceutical companies and we would suggest to the review that these be scrutinized:

(1) The indication for anticoagulants has been shortened to
   (a) "Atrial Fibrillation" – not all AF is moderate to high risk. Oral anticoagulation is clearly not recommended for all cases of atrial fibrillation.
   (b) "A warfarin substitute" – whereas both drugs are not interchangeable (e.g. renal failure). There is probably no clinical reason to change from warfarin in long term stable patients. Similarly, Dabigatran has no indication for anticoagulation in valvular forms of AF.
(2) The product familiarization programme was instituted without attempts to monitor drug safety or issues pertaining to quality prescribing.

Safety Clarity

Table 4 of the RE-LY trial suggests that Dabigatran has a statistically and clinically significant higher rate of serious adverse events. Information regarding adverse safety outcomes should be further explained to enable better clinical decision making and to provide clarity around this issue from a patient perspective.

For example, there is inconsistency in the recommendations of the Dabigatran product information leaflet. The concomitant use of Dabigatran with strong P-glycoprotein (P-gp) inhibitors, i.e. amiodarone, quinidine or verapamil in one section states it should be avoided, while other sections suggest a decreased dose. This issue should be clarified to ensure safe prescribing.

Guideline integration and consistency

Dabigatran is a moderate risk drug from a new drug class, and patient safety should be considered before marketing priorities. The RACGP believes the introduction of the drug class has been progressed before appropriate guidelines, prescribing practices (e.g. therapeutic options), and monitoring infrastructure has been implemented.

There are clear guidelines with respect to current use of aspirin and warfarin, however the indication proposed by the PBAC seemed out of the guideline framework.

Appropriate patient selection criteria for differing therapies have been determined and validated – i.e. the $CHADS_2$ score. This was based and validated on a minimum age of 65 years. Although the $CHADS_2$ score was part of the RE-LY trial, this screening process has been subtly changed for the new drug indication, and the 65 year age minimum has been dropped.

Recommendation

- The RACGP believes the $CHADS_2$ process is an acceptable and simple means of patient delineation for anticoagulation choice and should be maintained for all antithrombotic/anticoagulant choices unless clear evidence demonstrates otherwise.

Optimising current anticoagulant utilisation patterns

The RACGP believes this is a complex issue in a patient cohort where multi-morbidity is the norm. This can only occur through sophisticated computerised general practice systems, where years of accumulated history, co-morbidity and pathology are combined to produce a comprehensive medication evaluation system.

Clinical indicators for safety and efficacy in general practice are in the early stages of development by the RACGP. Typically though, indicators could be used to potentially flag suboptimal prescribing situations.

Recommendation

- The RACGP recommends to the review that to meet current and future demands for medication audit and safety, improved medication auditing processes be introduced into general practice.

Monitoring of Drug/Drug, Drug-disease interactions

As stated by the introductory comments, the RACGP believes improved monitoring systems that constantly monitor patient data and medication programmes need to be integrated into General Practice. The proportion of general practices having systematic surveillance systems for drug monitoring and ADE prevention is unknown. Most computerised practices have medication alerts within their IT systems at the point of prescribing. These alerts screen for Chronic Kidney Disease (CKD) in medical histories but do not consistently screen for eGFR. It is the view of the RACGP that this process will overlook patients with impaired renal function.

5. To report on modes of health system delivery which may be used to optimise the use of currently available anticoagulants.

Systems of care in general practice

Many of the patients on anticoagulant therapy are currently enrolled in regular structured reviews within general practice. Multi-morbidity is high in this group of patients and includes diabetes, hypertension, existing IHD, renal impairment and stroke/TIA. Many of these structured reviews include regular biophysical assessment. Polypharmacy is common in patients with AF, and approximately 70% of these patients are likely to be taking 8 or more medications.

A patient's condition is often dynamic and prone to quick changes. To ensure prescribing safety in patients with multi-morbidities, practices may have to mandate 6 or 12 monthly reviews of this patient group, which could be incorporated into clinical governance of general practice.

The RACGP has concerns about the lack of evidence to support Home Medicine Reviews[iv,v].

Clinical Monitoring systems

The College's Standards for general practices are well established and well recognised as one of the pillars of safety and quality in the Australian healthcare system and provide a template for safe and effective care. The 4th edition of the Standards requires that general practices have clinical risk management systems in place to enhance the quality and safety of care. The RACGP re-iterates the need for medication audit systems to be incorporated into the infrastructure of general practice.

The only Medicare Benefits Schedule (MBS) supported tools to manage potential drug safety are medication reviews within a health assessment, or chronic disease management plan are those for the Department of Veterans Affairs. These have specific item numbers for medication reviews performed by general practitioners.

Anticoagulant compliance monitoring

The safety aspects of dedicated patient prescribing support for warfarin therapy has been detailed earlier in this submission. Dabigatran derives its advantages over warfarin when warfarin is used sub-optimally[vi]. It is noteworthy that references of effectiveness with warfarin with high time in therapeutic range (TTR) was mentioned in the PBAC statement, but not fully examined.

The PBAC statement is not clear as to why it chose to accept lower TTR results (between 50.4% and 68%) from unpublished and unreferenced surveys within Australia.

A TTR audit of the RE-LY trial is available in the appendix and is taken from Wallentin et.al.[vii]. The average TTR in the RE-LY trial was 67%. However, as previously noted, most of the effect occurs when warfarin TTR is low. What is not mentioned is the converse – "With a TTR of 72.4% or higher, dabigatran etexilate 150 mg does not reduce, and may even increase, the event risks from death, major bleeds and cardiovascular events. (Even though a small stroke benefit is still seen)[viii].

Clinically, these TTR rates are commonly found in general practice in Australia. This was effectively confirmed in the RE-LY Australian subgroup which provided a TTR of

74%. If TTR are constantly above 72.4%, warfarin dominates with lower cost and higher QALY compared to Dabigatran 150mg[viii]. With the introduction of Dabigatran into this environ, we may well be introducing an expensive drug, with more clinical adverse events, with no benefit.

(1) We believe "Warfarin Care" (S&N) type systems, that is centralised monitoring and medication advice to patients from centralised laboratories, offer superior anticoagulant services. This type of care can deliver about 70% in time spent in therapeutic range. This is much higher than was reported in by the PBAC. PBAC based its decision on published studies and an unpublished survey (both unreferenced) suggested that the time spent in target INR range was much lower.
(2) In rural areas where access is poor, co-ordinated GP services with point of care systems also have proven outcomes of close to 80% in time in therapeutic range[ix].
(3) Self-testing - Although not suitable for everyone, self-management improves the quality of oral anticoagulation. Patients capable of self-monitoring and self-adjusting therapy have fewer thromboembolic events and lower mortality than those who self-monitor alone. Although this provides independence to travel, increased training and test strips are negatives[x].

Recommendation

- The RACGP asks the review to re-examine current "time in therapeutic range" of existing systems within Australia, and consider systems and incentives to improve TTRs.

- The RACGP asks the review to consider POCT testing for rural patients who may not be able to access regular pathology and may be intolerant of Dabigatran (estimated 20% at 2 years – RE-LY trial).

Post Marketing Surveillance / Adverse event reporting

Current systems of adverse drug events reporting at a GP level are suboptimal. There is a plethora of untapped patient drug data that goes unreported on a daily basis in Australia. The current mechanism for reporting adverse drug events is cumbersome and inconsistent with modern standards of the digital age.

The RACGP would support integration of adverse event reporting into clinical software, with associated functionality to allow electronic transport of data to a centralised repository for further evaluation.

6. To report to what extent optimisation of the use of currently available anticoagulant treatments used in patients with atrial fibrillation would improve health outcomes and at what cost.

As stated in the RACGP submission to the ACQSHC in October 2010 in its response to the discussion paper on Patient Safety in Primary Health Care, the work that the College is involved in regarding patient safety, is grounded on the notion that 'clinical risk management systems' for general practices are driven by evidence-based interventions, and a strong patient safety culture. Interventions include:

- clinical governance arrangements
- business infrastructure, systems and processes
- patient information management systems
- staff training
- guidelines
- clinical education programmes
- clinical governance training
- clinical Indicators

The RACGP believes the basis for optimisation of medications relies on evidence, clear and consistent clinical guidelines detailing patient selection, therapeutic options to suit individual patient needs. Optimisation of treatments within a General Practice can be accomplished using known quality improvement tools within the General Practice.
To ensure quality improvement activities in anticoagulant prescribing occurs within a general practice, these QI activities can be incorporated into clinical governance and drug safety indicators.

With respect to the critical issue of quality of warfarin monitoring and TTR, this is beyond the capacity of the RACGP to determine infrastructure costs to achieve this.

7. To examine the future role of newer anticoagulant therapies for atrial fibrillation.

The RACGP welcomes the new class of anticoagulant therapies and we believe they can be an advance clinically and a reduced burden for patients. However, this is only the case if they are adopted in an evidence-based manner.

The RACGP has a measure of concern associated with the enthusiasm to introduce Dabigatran into the Australian market. The results are based on one trial – the RE-LY trial. This trial's design, conduct and reporting were influenced by the drug company. In addition, the trial has been criticised because of its lack of access to, and the gaps in safety data (Therapeutics Initiative at the University of British Columbia is concerned by gaps in the published data).

We have seen rigorous activity by the drug company to pressure government into subsidizing the drug, even during the midst of a safety review. We have witnessed subtle changes in indications and other marketing strategies that cause concern. We have seen these activities filter to the general practice level.

The RACGP queries the standards that companies who produce new drugs or new drug classes are answerable to.

The introduction of new therapies also highlights an ongoing concern for the RACGP; the migration of moderate risk medications (serious adverse event rate 2.7%) into primary care in the absence of suitable infrastructure to monitor drug efficacy, drug interaction, and post-marketing surveillance in general.

Recommendation

- Educational material and clinical governance systems need to be implemented prior to introduction of new drug classes.

- Further medication safety infrastructure needs to be provided to general practice to enable quality and efficacy processes to ensure safe and optimal prescribing.

Appendix – Dabigatran outcomes by TTR

Comparison of Warfarin vs Dabigatran in Groups according to TTR
Source: Wallentin et.al. [vii]
Copy at - WEST YORKSHIRE CARDIAC NETWORK Economic Appraisal of Dabigatran Etexilate 150 mg

Table 2.2: Outcomes by each quartile based on TTR from RE-LY DG 150mg AR	DG 150mg AR	Warfarin AR	RR	ARR
TTR <56.9%	Dabigatran 150mg	Warfarin		
Total death	3.85%	5.72%	0.67	1.87%
Major bleeding	2.54%	3.59%	0.71	1.05%
All cardiovascular events	6.83%	10.13%	0.67	3.30%
Stroke or systemic embolism	1.10%	1.92%	0.57	0.82%
TTR 56.9% - 65.4%	Dabigatran 150mg	Warfarin		
Total death	3.75%	4.09%	0.92	0.34%
Major bleeding	3.33%	4.13%	0.81	0.80%
All cardiovascular events	7.09%	8.03%	0.88	0.94%
Stroke or systemic embolism	1.04%	2.06%	0.5	1.02%
TTR 65.4 - 72.4%	Dabigatran 150mg	Warfarin		
Total death	3.64%	3.70%	0.98	0.06%
Major bleeding	3.80%	3.40%	1.12	-0.40%
All cardiovascular events	7.41%	7.13%	1.04	-0.28%
Stroke or systemic embolism	1.04%	1.51%	0.69	0.47%
TTR >72.4%	Dabigatran 150mg	Warfarin		
Total death	3.30%	3.04%	1.09	-0.26%

Major bleeding	3.60%	3.11%	1.16	-0.49%
All cardiovascular events	7.07%	6.42%	1.1	-0.65%
Stroke or systemic embolism	1.27%	1.34%	0.95	0.07%

[i] Jared M Dart, Claire L Jackson, Helen J Chenery, Paul N Shaw and David Wilkinson Meeting local complex health needs by building the capacity of general practice: the University of Queensland GP super clinic model. MJA 2010; 193 (2): 86-89

[ii] Camm J et al -Guidelines for the management of atrial fibrillation The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC) European Heart Journal 2010; 31, 2369–2429

[iii] Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285:2864-2870

[iv] Easton K, Morgan T, Williamson M. Medication safety in the community: a review of the literature. Sydney: National Prescribing Service, June 2009

[v] Holland R, Desborough J, Goodyer L, Hall S, Wright D, Loke Y. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. Br J Clin Pharmacol 2008; 65:303–16.

[vi] PUBLIC SUMMARY DOCUMENT PBAC - Product: Dabigatran etexilate, capsules, 110 mg and 150 mg (as mesilate), Pradaxa Available at http://www.health.gov.au/internet/main/publishing.nsf/Content/1863CE366CA53443CA2578BE001241DB/$File/Dabigatran%20PRADAXA%20Boehringer%20Ingelheim%206-3%202011-03%20PSD%20FINAL.pdf

[vii] Wallentin L. et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. The Lancet 2010; 376: 975–83

[viii] WEST YORKSHIRE CARDIAC NETWORK Economic Appraisal of Dabigatran Etexilate 150 mg compared to Warfarin or Aspirin in Patients with Atrial Fibrillation Updated report available at http://www.yorksandhumberhearts.nhs.uk/upload/WYCN/Dabigatran/YHEC%20Dabigatran%20Feb%202011.pdf

[ix] Hodge K, Janus E, Sunararajan V, Taylor S , Brand W, Ibrahim J, Wolff A (2008) Coordinated anticoagulation management in a rural setting Australian Family Physician 37: 280-3

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