ASPEN AUSTRALIA SUBMISSION TO THE SANSOM REVIEW OF ANTICOAGULATION THERAPIES IN ATRIAL FIBRILLATION

Executive Summary

Reducing the burden of stroke in Australia through the improved measurement and management of NVAF - an Evidence-Based Submission to the Sansom Review

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Executive Summary

Stroke is one of the most serious consequences of Atrial Fibrillation (AF) and imposes substantial personal and economic costs. One in five Australians suffering a stroke will die within the first month and the impact on a stroke survivor's quality of life is considerable, often with reductions in mobility, conversation skills, memory, and perception. People suffering a stroke are likely to need the help of family, friends and other carers to perform everyday activities and will almost certainly require ongoing health care services.

Approximately 365,209 Australians aged 50 years and over received a Non-Valvular Atrial Fibrillation (NVAF) diagnosis in 2011, including 207,246 people at high stroke risk, 110,831 people with moderate stroke risk and 47,132 people at low stroke risk. Clinical studies further suggest there are an additional 10%-30% or 91,302 patients with undiagnosed NVAF.

Australian clinical practice and PBS dispensing data indicate that less than one third of NVAF patients at moderate-to-high stroke risk receive Warfarin and 40% of patients at moderate-to-high stroke risk are receiving no treatment. Evidence also suggest that healthcare professionals have decisional conflicts around the prescribing of anticoagulants generally in spite of a well accepted and efficacious treatment such as Warfarin and educational initiatives to improve the management of AF.

In March 2011, the PBAC recommended that Dabigatran (Pradaxa®) was suitable for inclusion on the Pharmaceutical Benefits Scheme (PBS) for the prevention of stroke or embolism in certain groups of patients with atrial fibrillation. Since the PBAC recommendation, the Therapeutic Goods Administration issued Safety Advisory Alerts for Dabigatran on 5 October and 3 November 2011, noting bleeding-related adverse event reports and advising of renal function monitoring requirements respectively. These alerts also reflect similar alerts being made in other major regulatory authorities internationally (including the FDA).

In September 2011 the Government announced that it would hold an enquiry of review and call for submissions on options for improving the health outcomes of patients treated with anticoagulation therapies, including optimising the use of currently available treatments in Australia as well as the future role of newer therapies for the treatment of atrial fibrillation, such as Dabigatran (Pradaxa®).

Significant issues identified in the reporting of the pivotal trials on the new agents coupled with the international regulatory scrutiny on the morbidities observed since registration of Dabigatran point to a rush to market and a need to interpret the findings of these trials cautiously.

In preparing this submission Aspen is aware that with new anticoagulant agents coming onto the market, each sponsor mounting their own scientific case relative to Warfarin (and other standard alternatives), the scientific debate will become very one sided. Generic manufacturers simply don't have the financial resources and product margins to redress such imbalances and particularly in this case where the new generation products potentially offer such a large economic incentive.

We acknowledge that, as a major generic manufacturer and supplier of Warfarin in Australia (the current main competitor to Dabigatran), we have a certain commercial interest in this matter however this does not automatically preclude that the arguments we make in this submission are valid. Aspen is not opposed to innovation and new drugs but believes that aggressive and unbalanced representation (particularly opposite relatively unsupported generics) can promote outcomes that are contra to the principles of the NMP- to achieve optimum use of medicines.

We believe that the recent market developments in the NAVF anticoagulant market highlights the need for a proper examination of the scientific evidence in the context of current treatment practices and of the opportunity costs associated with making new anticoagulant agents available. For this reason, we believe the review of anticoagulants used in the management of NVAF to be conducted by Emeritus Professor Lloyd Sansom is both a timely and a necessary government initiative.

In response to the call for submissions and a subsequent meeting held with the Professor Sansom , Aspen has adopted by necessity a selective approach with respect to the terms of reference (Warfarin having accumulated for example far more intellectual/clinical data than its newer counterparts). At the request of Professor Samson we have addressed the area of patient management in more detail. Given the limited time available since receiving this request should the Review require further detail and input in this area, Aspen would be pleased to pursue additional lines of enquiry and information where appropriate.

Key areas explored by Aspen in this response was constrained to:

1. critical appraisals and comparisons of important clinical trial outcomes on three new AC agents, [Dabigatran (registered), Rivaroxaban and Apixaban (under evaluation]
2. critical appraisal of the Deloitte economics report submitted in support to PBAC in conjunction with the PSD arising on Dabigatran on factors that would impact materially on the estimated incremental cost-effectiveness ratio (ICER)
3. Exploration of whether Warfarin's reputation as a burdensome therapy is justified by the evidence
4. Preliminary review of practices and initiatives in the management of NVAF in the Australian setting and
5. Recommendations on alternative management algorithms, which will offer significant cost effectiveness gains or cost reduced outcomes for patients and Government.

The Aspen submission constitutes the results of an extensive review of the literature which has been assembled in accordance with good evidential practices and performed by an independent research house commissioned by Aspen. The purpose of this work was to identify factors and key assumptions that would impact materially on the estimated incremental cost-effectiveness ratio (ICER), understand the perceptions of prescribers and patients towards Warfarin and anticoagulants and recommendations on initiatives to improve the management of patients on NAVF. This also included consideration of whether Warfarin is deserving of its reputation as a burdensome treatment in the treatment of NVAF. Most importantly, to provide a more balance scientific and cost effectiveness viewpoint with respect to the following objectives:

1. to quantify the extent of AF and the economic and patient burden of associated strokes in Australia; and
2. to assess how current clinical practice can be improved to reduce this burden.

Where appropriate new data reconstruction and statistical analysis have been conducted to shed light on critical areas of the investigation as detailed in the body of this submission. There are however a number of key findings of pivotal importance to the terms of reference which are highlighted in this executive summary.

Key Points of critical interest highlighted by this submission

1. Implications for cost-effectiveness evaluations of new ACs

With respect to the PBAC consideration of the submission requesting subsidy of Dabigatran, it is not possible, on the basis of the Public Summary Document (PSD) relating to this consideration, to exclude the possibility that the PBAC has not taken into consideration a number of factors that would materially impact the estimated incremental cost-effectiveness ratio (ICER). Whilst Dabigatran is the subject of this analysis the issues identified are also applicable to the new agents more generally.

2. Significant issues identified in the reporting of the pivotal trials on the new agents

Significant reporting issues coupled with the international regulatory scrutiny on the morbidities observed since registration of Dabigatran point to a rush to market and a need to interpret the findings of these trials cautiously.

3. Critical deficiency in Deloitte Access Economics Report submitted to PBAC

The pivotal mistake made in the Deloitte Access Economics Report in support of the assumptions driving the cost effectiveness analysis of Dabigatran, is in the area of preventable strokes. Specifically the proportion of preventable strokes in untreated patients at moderate-to-high stroke risk with Dabigatran appears to have been overestimated in their economics report. Importantly, these erroneous assumptions will have ongoing and potentially costly implications if they continue to be used in future new agent cost-effectiveness evaluations.

4. Revised rates of Preventable Strokes Calculated

Correspondingly in this review we have addressed the deficiencies in the Deloitte's Access Economics Report to recalculate the Deloittes Tables relating to the number of preventable strokes arising from the introduction of the new agents

5. Optimal Monitoring Frequency of INR monitoring

A sequential case series of Australian pathology cases indicated that Optimal Monitoring Frequency would appear to be around one to two measurements per month giving variability of only 4.6% and 78%. With access to improved and cost effective technologies (as exampled in this submission) there is now greater scope through improved management practices to improve INR monitoring to achieve optimal range maintenance.

6. Under-utilisation and sub-utilisation of anticoagulants

In the Australian setting the under-utilisation and sub-utilisation of anticoagulants remains a substantial obstacle to the translation of trial efficacy outcomes into practice and improving the quality of health care. Only one in three patients without a contraindication received Warfarin, consistent with other studies that have found Warfarin is prescribed for 15–44% of eligible patients. Deloitte Access Economics have put this figure in Australia at 32.2% (high risk) and 30.3% (moderate risk).

7. The economic impact of the proper utilisation of Warfarin

As the new agents derive their advantages over Warfarin when Warfarin is used sub-optimally (i.e outside the standard INR range 2.0-3.0), it is expected with the introduction of improved modes of health system delivery on outcomes achieved with anticoagulation therapy that this would lead to more patients taking Warfarin (currently 39 % of the high risk patients are on aspirin!). This would lead to even fewer strokes being prevented as a consequence of improving AC management practices whilst improving the QUMs in this critical area. The scope for improved overall cost benefit efficiencies to government are apparent.

8. Barriers to Proper AC Treatment & Patient Uptake

Confronting the under-utilisation and sub-utilisation of Warfarin is the apparent mythology around Warfarin, that it places a considerable burden on patients and prescribers through the need for frequent blood monitoring, fear of treatment-related bleeding, including difficult to treat and disabling stroke and major bleeds; drug-food interactions; and drug interactions. The high tolerability of Warfarin based on very small incidence rates of reported events to ADRAC (bleeding, drug-drug interaction and reduced laboratory efficacy), significantly better rates of discontinuation in the Dabigatran pivotal trial, and tolerability not rating as a significant barrier by prescribers or patients to treatment suggest the reality to be very different. In the absence of objective information and clinical data this mythology is self reinforcing and has already been exploited commercially by the competitors to Warfarin. This clearly points to need for better healthcare education and patient management support programs.

Warfarin is a well tolerated, well understood and efficacious product with wide patient care application and medical community understanding. There is a key point around patient management which can lead to unfavourable associated costs. As illustrated in this submission, Aspen believes there are demonstrable efficiencies to be gained in areas such as the management of INR levels through improved practices (such as Point of Care monitors and Patient Tracking Systems) which would have the impact of increasing the ICER estimated to be associated with the new anticoagulants agents versus Warfarin.

For a long time Warfarin was not just the standard it was really the only front line oral product (notwithstanding the use of Aspirin, Persantin, Plavix which have a role in anticoagulation). The new AC agents derive their advantages over Warfarin when Warfarin is used sub-optimally. In the Australian setting the under-utilisation and sub-utilisation of cost effective treatments such as Warfarin remains a substantial obstacle to the translation of trial efficacy outcomes into practice and improving the quality of health care. With the advent of new generation anticoagulants and identified opportunities to improve patient treatment management practices (including the use of available new technologies) and with clinical practice experience growing around the use these interventions, we believe informed medical practice requires the development of guidelines in this market area.

We believe these guidelines should take into account both a revision of the erroneous cost-effectiveness arguments (as highlighted in this review) currently being put forward but also the very tangible opportunities to improve anticoagulant treatment management practices that further improve the comparative effectiveness of Warfarin as a main line treatment. This should include better healthcare education to redress some of the apparent misconceptions regarding use and administration of Warfarin as highlighted in this review. Aspen is therefore prepared to work with Cardiologists, Haematologists and others to develop therapeutic guidelines for clotting disorders related to AF (and other associated disease states).

As evidenced in a separate literature review on patient utilisation in the Australian setting, clear barriers based on prevailing mythology have led to the under utilisation and sub optimal use of AC therapy in the proper care and management of patients. Aspen believes that with the appropriate government assistance there are important initiatives where generic manufacturers can provide educational support to doctors and the patient community (including interactive phone based support) to assist in the proper and effective use of critical care medicines such as AC therapy. Aspen would welcome such developments which are clearly called for based on the evidence brought to light in our response to this call for submissions.

We trust that this Review of Anticoagulation Therapies in Atrial Fibrillation called by the Minister of Health will provide an opportunity of looking at the management of AF from a broader perspective and provide a more "balanced outcome" where Warfarin may continue to play a leading role in the treatment of NVAF and importantly ensure that it is not inappropriately marginalised at an unwarranted cost to the public purse.

Introduction

To evaluate the optimisation of use of currently available anticoagulant treatments in AF patients which regards to health outcomes and cost, starts with a review of the clinical trial evidence and comparative analyses used to inform the economic analyses. Results of the economic analysis estimating the incremental cost-effectiveness ratio for new ACs versus Warfarin will be materially sensitive to assumptions relating to a range of factors that would have implications for inputs to the analysis.

With respect to the PBAC consideration of the submission requesting subsidy of Dabigatran, it is not possible, on the basis of the Public Summary Document (PSD) relating to this consideration, to exclude the possibility that the PBAC has not taken into consideration a number of factors that would impact materially on the estimated incremental cost-effectiveness ratio (ICER). For example:

(i) there are some serious deficiencies in the pivotal study (and post study publication revisions) that appear not to have been recognised by the PBAC and that the PBAC might therefore have assumed that the results from the trial may have provided adequate substantiation of the clinical claims made in the submission and that the results were appropriate for application, without adjustment, in the model used to generate the ICER for Dabigatran versus Warfarin; and

(ii) it is not clear that the potential for increased costs likely to be associated with management of patients on Dabigatran experiencing a bleed secondary to an accident (e.g., following a fall, which would not be an uncommon event in the elderly) due to the lack of availability of an antidote for Dabigatran have been factored into the economic and financial analyses. Notably, the trial did show a higher rate of transfusions were needed in Dabigatran-treated patients compared with Warfarin-treated patients.

In this submission we outline the additional factors that have a material impact on the estimated incremental cost-effectiveness ratio (ICER) and that we believe may not have been properly presented for evaluation by the PBAC for Dabigatran. We highlight these critical deficiencies in the trust that they can be taken into consideration by the imminent review of anticoagulants used in the management of NVAF.

Additionally, we delve further into some of the key assumptions to which these factors would be highly sensitive such as the clinical efficacy in the pivotal trials, the methodology used to estimate the impact of the new agents on preventable strokes and the improved management of NVAF in practice. This report will focus on three novel AC agents that are most advanced in development and likely to be the first to reach market in Australia (Dabigatran Etexilate, Rivaroxaban, Apixaban).

This submission is therefore divided into two sections:

SECTION 1:
Factors requiring consideration in the review of comparative effectiveness & cost effectiveness of Dabigatran and other new AC agents
SECTION 2:
Factors contributing to the under-utilisation and sub-utilisation in the treatment management of anticoagulants, and recommendations for improved management of patients with NVAF

SECTION 1

Factors requiring consideration in the review of comparative effectiveness & cost effectiveness of Dabigatran

Results of the economic analysis estimating the incremental cost-effectiveness ratio for Dabigatran versus Warfarin will have been materially sensitive to assumptions relating to the following factors that would have implications for inputs to the analysis:

- **comparative effectiveness of Dabigatran versus aspirin** in patients in whom Warfarin is either contraindicated or not tolerated or refused (both in terms of impact on endpoints of stroke and systemic embolism and in terms of impact on relevant adverse events including intracranial bleeding, gastrointestinal bleeding and other major bleeding); there is some suggestion in the PSD that aspirin may have been considered inferior to Warfarin and this differential may be a key driver of the overall outcomes of the economic analysis.

- the **generalisability of the results from the RE-LY trial to the Australian population**; it is suggested that:
  - whilst the profound post study publication revisions (identifying a further 81 new events and 28 new silent MIs for these critical outcomes) do not materially change the conclusions with respect to non-inferiority, they do alter the conclusions with respect to MIs. This is a very profound 'revision' of so many outcome measures for a published study and coupled with the significant morbidities observed in the international community since Dabigatran's registration unfortunately leaves one with some anxiety as to the veracity of all the results.
  - some adjustments should have been made to the results from the RE-LY trial prior to their application in an economic analysis due to some systematic differences between the Australian population with NVAF (+ at least one additional risk factor) and the population recruited to the RE-LY trial (e.g., the proportion of patients with well controlled INR) which would result in the baseline risk of stroke being higher in the trial population than the Australian population)
  - it may be necessary to incorporate adjustments for the open-label nature of the trial
  - the application of results based on an intention-to-treat (ITT) analysis would be inappropriate; although it is acknowledged that the ITT analysis is a preferred evaluation in most clinical trials because it minimises bias in follow up of patients and it can resemble "real world" effectiveness, the ITT analysis of the RE-LY trial is not the most appropriate evaluation) in the context of a non-inferiority trial (which are usually analysed on a per-protocol basis) and given that there are outcomes which reflect benefits (reduced stroke) and risks (increased bleeding) from treatment an ITT analysis does not capture the full extent of relative risk and benefit from the three study medications.

- **comparative effectiveness of Dabigatran 110mg bd vs 150mg bd** and the distribution of patients across these doses in the modelled economic analysis; this is important as the advantages for the lower dose of Dabigatran are associated with less than for the higher dose

- **proportion of Australian population with NVAF** (+ at least one additional risk factor) currently managed with Warfarin versus aspirin (particularly if differences in effectiveness of aspirin and Warfarin were assumed in the economic analysis)

- **proportion of preventable strokes in untreated patients at moderate-to-high stroke risk with Dabigatran** appear to have been overestimated in their economics report. Their report (Deloitte's) mistakenly include the non-diagnosed among the non-treated in whom strokes would be prevented by the introduction of either the new treatment or aspirin/Warfarin. The second point here is that the Dabigatran (i.e. 23% relative risk to no treatment) assumes that all diagnosed will go on to Dabigatran and there will be no diluting this to some aspirin etc.

- the estimated **impact on quality-adjusted survival for each of the competing adverse events** (i.e., what were the assumed consequences of intracranial bleeds, gastrointestinal bleeds and other major bleeds on quality-adjusted survival)

- the **consequences of irreversibility of the effect of Dabigatran versus Warfarin**; in the case of accident or emergency, the effect of Warfarin can be quickly reversed by administration of vitamin K whereas no such antidote is available for Dabigatran and also where a bleeding event occurs there may have been additional difficulties in controlling the bleed in the Dabigatran group (e.g., if difference in rate of transfusions across groups was observed, this should have been included in the economic analysis)- Notably, the trial did show a higher rate of transfusions were needed in Dabigatran treated patients compared with Warfarin-treated patients.

- the **consequences of discontinuation of medication** on both costs and quality-adjusted survival given that a larger proportion of patients discontinued treatment in the Dabigatran arm of the RE-LY trial than in the Warfarin arm

- **consideration of results for cost-effectiveness of Dabigatran versus aspirin separately from results for Dabigatran versus Warfarin** as it may be that although Dabigatran is very cost-effective vs aspirin in patients in whom Warfarin is contraindicated or not tolerated, the same may not be true for the comparison of Dabigatran versus Warfarin. It is possible that the key driver of cost-effectiveness is the inclusion of patients currently treated with aspirin and that it may be more cost-effective (and fiscally prudent) to only make Dabigatran available for the subset of patients in whom Warfarin is contraindicated or not tolerated or where patients have poor INR control.

Re-Evaluation of the key inputs into the ICER and comparative effectiveness

Underpinning the outcome and relative outcome rates used in the determination of comparative effectiveness and cost effectiveness of Warfarin and the new agents are the pivotal comparative trials. Since Dabigatran's international market release there has been a chorus of unexpected regulatory safety advisory alerts with regards to bleeding-related adverse event reports and advising of renal function monitoring requirements respectively.

To derive the extent to which anticoagulant therapies may prevent events in those with NVAF a population-based approach for calculations placing the available data (relative efficacies from RCTs) into a broad Australian population setting must be adopted. To do this, population estimates of key rates, e.g. strokes, AF, untreated AF, etc are required upon which to place outcome and relative outcome rates derived from the RCTs. The results of this approach are highly sensitive to how rigourously one obtains the population estimates and applies the appropriate calculations. A preliminary review of the economics report underpinning the Dabigatran submission would suggest an erroneous approach was adopted with respect to estimating the impact of Dabigatran on preventing strokes.

To gain a greater understanding and perspective on these key drivers of comparative effectiveness Aspen has undertaken a critical appraisal of the pivotal trials and economics report.

Critical appraisal of the pivotal drug trials

The most significant issues identified with the reporting of the RE-LY study (Dabigatran)

The increase in MI and PE rates is of clinical concern. Despite the large sample size the study is still not well powered for statistical comparison of these low rates.

Using the time to first event analyses approach ignores any multiplicity of events. It does not fully portray the relative costs and benefits of these agents. This issue is magnified as the number of contributing outcomes to a composite endpoint increases.

The study has established non-inferiority for the primary outcome and has shown superiority for the higher dose (DE 150mg). The absolute benefit in terms of this rare outcome, equating to a NNT per annum of 167 patients, should not be overstated.

The post-publication correction of outcome measures (based on events identified post-database lock) casts doubt over the conduct and reporting of the study. Notably these results mean the elevation in MI rates from Pradaxa is no longer statistically significant. Note the final sentence in the opening paragraph of the original NEJM article ("All the authors vouch for the accuracy and completeness of the data and the analyses").

Discontinuation rates are much higher in the Pradaxa arm (15.5% vs 10.2%). The introduction and substantial justification for the study was that VKAs (Warfarins) are not easy to use and discontinuations rates are therefore high. Pradaxa does not seem to remedy this issue.

The manner in which the differential exposure to study drug is handled within the analyses. It is evident that patients are stopping DE treatment (either dose) at a higher rate than they are stopping Warfarin and the ITT analysis which does not integrate the timing of the exposure with the timing of the outcomes (i.e. whether the event occurs while on treatment) does not provide a comprehensive picture of the relative risks and benefits of these treatments. 'Safety outcomes', e.g. bleeding, appear to have been analysed with an ITT approach rather than using a 'safety analysis' approach. The lack of retention of patients on DE when it apparently has many administration advantages over Warfarin is an important result.

The treatment differences in the primary outcome manifest later in the follow-up where there are many fewer patients. Longer and more complete exposure to Pradaxa may explain this apparent effect.

The increase in MI and PE rates should be of some concern, and despite the very large sample size the study is not well powered for statistical comparison of these rates, or whether these were factored into costs.

The time to first event analyses approach ignores any multiplicity of events and therefore does not provide the full picture in relation to the clinical benefits and risks of these agents.

The NEJM letter to the editor outlining the 'revised' outcome measures based on events identified post-database lock casts an unfortunate pale over the study. Identifying a further 81 new events and 28 new silent MIs (none were reported in the original analyses) for these critical outcomes reflects very badly on the conduct of the study and the evident haste to publish. While these results do not materially change the conclusions with respect to non-inferiority, they do alter the conclusions with respect to MIs and leaves one with some anxiety as to the veracity of all the results.

Dabigatran derived its advantages over warfarin when warfarin is used sub-optimally. Superiority of dabigatran compared to warfarin is demonstrated when dabigatran subjects are compared to subjects on warfarin whose mean percent of time of INR in 2-3 was <65% as indicated in the below table. The mean time in therapeutic range (TTR) for patients enrolled from different countries in the RELY trial, for warfarin at different levels of international normalised ratio (INR) control (2-3) (Wallentin 2010) indicated that patients enrolled in Australian sites had a mean time in therapeutic range for warfarin of 74% based on a small number of patients.

Hazard ratios and 95% CI for stroke/SEE by INR control for warfarin

Mean % of the time of INR in range 2-3 ≥ 65%		
	DE 110 mg vs. Warfarin	DE 150 mg vs. Warfarin
#Events/N	183/6015 vs. 89/3195	134/6076 vs. 89/3195
Hazard ratio	1.12	0.81
95% CI	0.87, 1.44	0.62, 1.05
Mean % of the time of INR in range 2-3 < 65%		
	DE 110 mg vs. Warfarin	DE 150 mg vs. Warfarin
#Events/N	183/6015 vs. 113/2827	134/6076 vs. 113/2827
Hazard ratio	0.73	0.53
95% CI	0.58, 0.92	0.41, 0.67

[Source: Reviewer's results]

The complete expert critical appraisal on the RE-LY study is located in Annexure 1.

The most significant issues identified with the reporting of the ROCKET (Rivaroxaban) study:

The most significant weakness/anomaly with the study is the high rate of events in the Rivaroxaban study in the 30 days after study drug is discontinued. The manner in which this result is reported adds to the confusion associated with this outcome. There are 3 different reports of this phenomenon alls how higher rates in Rivaroxaban. The first reported in the NEJM paper (table 2, figure2) shows these figures for all those discontinuing during the study period and show an elevated rate 4.7%/annum (81 events) for Rivaroxaban and 4.3%/annum (66 events) for Warfarin, p=0.58. The reported median follow-up for these patients is reported as being 117 days-which is not consistent with figure 2B. The second reporting of this for patients discontinuing prematurely during the study period who then underwent Warfarin treatment showed 42 events in those previously on Rivaroxaban and 36 in those previously on Warfarin. Of note there was a difference in the time to first therapeutic INR in the Rivaroxaban group median 13 days compared with 3 days. The third reporting of this is for those ending treatment at the end of the study, and the transitioning to VKAs (presumably predominantly Warfarin) where there were 22 events in those previously on Rivaroxaban and 7 for those previously on Warfarin, p=0.008, figure 2 online. Again there was a difference in the time to first therapeutic INR in the Rivaroxaban group median 13 days compared with 3 days. While these results are curious and deserve some scrutiny, they do NOT impact on the key results from the study.

Non-inferiority is established in both the per-protocol and the intention to treat analysis where these outcomes are largely included (i.e. those results from those prematurely discontinuing) and superiority was not established in the intention-to-treat analysis.

The key unresolved issue would be the impact of the inclusion of follow-up data say to 30 days post study termination (i.e. after the study ended) in the ITT primary outcome analysis, irrespective of the treatment patients are then placed on. If non-inferiority were still apparent in the intention-to-treat population this issue would largely go away. However, the clinical utility of the results post study termination, particularly in the context of standard treatment with either agent, needs to be considered.

The time to first event analyses approach ignores any multiplicity of events and therefore does not provide the full picture in relation to the clinical benefits and risks of the Rivaroxaban and Warfarin.

The most significant issues identified with the reporting of the ARISTOTLE (Apixaban) study:

The only weakness in this study is the lack of further sensitivity analyses of the key outcome measures based on the per-protocol population. While it appears unlikely this would alter the key results this may shed some further light on the interpretation of the overriding significant advantage seen in all key outcomes on Apixaban. Additionally, the reporting of the adverse events is inadequate. A table of these as is routinely reported in papers describing randomised controlled trials should be presented .

The sub-group analyses of the TTR for Warfarin are not helpful in assisting the interpretation of the results from this study. The key assumption in these analyses is that greater adherence to Warfarin monitoring and treatment will lead to better outcomes in the Warfarin treated patients. Why do they not test this outside the constraints of the crude center quartile classifications? Further it is very evident from these analyses that poor compliance with Warfarin monitoring and treatment at the center level is strongly associated with a suite of confounding demographic, clinical and concomitant medication variables. The centre classification is capturing a host of factors, which is why the primary outcome rates drop in the Apixaban arm across the centre quartiles. There are other more sensitive and efficient analyses that could be undertaken addressing this issue. Of some note the sums of the key outcomes across the Apixaban group in this presentation do not sum to those presented in the NEJM publication.

Indirect Comparison New Agents vs Warfarin:

The three studies being compared are the RE_LY (150mg dab1gatran only), ROCKET_AF and ARISTOTLE trials each comparing a stroke prevention medication with Warfarin, in patients with atrial fibrillation. The study designs are broadly similar. However, (i) RE_LY is not double-blinded and is likely therefore to overestimate the treatment effect of the new agent, (ii) the inclusion/exclusion criteria differ so that particularly the ROCKET_AF study has patients at greater risk of stroke, (iii) the populations used for analysis are different with ROCKET_AF appropriately incorporating a per-protocol population for the primary non-inferiority comparison, and (iv) follow-up definitions differ with some outcomes only included while on treatment and others to study termination.

The indirect comparisons are undertaken using the pooled variances on a log scale from the individual study hazards ratios, to calculate the 95% confidence intervals for the ratios of the hazard ratios. Hazard ratios are used as all the outcomes presented are time-dependent. Warfarin with a target INR of 2-3 was the common comparator across the three studies.

All three of the above mentioned studies identify key predictor variables when showing baseline comparability of randomised groups (table 1 in each publication). While appropriately no statistical comparisons of baseline measures are undertaken all three studies correctly identify no clinically relevant

confounding due to any such imbalances. With the exception of the allowance for baseline stratification variables (e.g. ARISTOTLE, baseline Warfarin status and geographical region) none of the studies perform any multivariate statistical comparisons to produce adjusted risk ratios allowing for baseline predictor measures. Key predictors identified in all studies are age, gender, $CHADS_2$ category, hypertension, previous event (stroke, TIA, SE) and previous (long-term) VKA therapy. The actual role of these variables is not determined in any of the studies however. It is our sense that the risk ratios from all three studies are robust, there is little evidence of confounding so we don't believe that these ratios would be altered to any great degree by analyses which incorporate these variables. The roles of these measures in outcome prediction would nevertheless provide very informative additional analyses.

The clinical populations for the three studies do differ somewhat in regards to these measures and this is an important consideration in making indirect comparisons between the studies. Additionally, while the relative efficacy of the randomised treatments may not change the clinical population to whom the results are generalisable will differ if the study populations are different. Notably the $CHADS_2$ category formed part of the inclusion criteria for all 3 studies; ROCKET ($CHADS_2$ >=2) ARISTOTLE ($CHADS_2$ >=1-34 % CHADS group 1) and Connolly ($CHADS_2$ >=0). In general however, with regards to the other perceived predictors of outcome age, gender, existing hypertension and prior VKA therapy the clinical populations for the studies are broadly similar. A further consideration in this context is that none of the studies showed any differential efficacy (New agent vs Warfarin) in the sub-groups defined by these predictors.

Additionally, the outcomes are not consistently assessed across the three studies.

1. RE-LY. This is probably the best in this regard. They assess efficacy and safety outcomes on the ITT population and apparently all events are evaluated over the entire follow-up period.
2. ROCKET-AF. The majority of the analyses, efficacy and safety are performed on either (a) the per-protocol (i.e. took at least one dose, no major protocol violations and are only followed up to 2 days after terminating treatment (if early discontinuation) or (b) the as treated safety population which is the same as the per-protocol but doesn't require adherence to the protocol.
3. ARISTOTLE. All efficacy outcomes were appropriately evaluated on the ITT population and included all events up to the follow-up dates irrespective of whether they discontinued treatment or not. The bleeding outcomes were however, assessed on all patients who took at least one dose and only included events up to 2 days post study medication for those who discontinued early.

In keeping with these points we have generated Summaries and Comparisons of important outcomes, with modifications for the relevant populations, on these new agents and Warfarin to a more explicit defintion of which populations we were comfortable to compare on. The ITT populations were used for the RE-LY and ARISTOTLE comparisons and we were also able to get ITT populations for ROCKET-AF for SSE and all cause -mortality. The ROCKET ARISTOTLE comparisons are on the as treated populations. All 3 studies had as their treatment strategy for the Warfarin arm, as an INR target of 2.0-3.0.

The following tables and figures represent individual study estimates and indirect comparisons between the three studies.

Table 1 notably highlights the poorer stroke prognosis for ROCKET_AF with evidence of more prior VKA use, more diabetics, more prior stroke/systemic embolism and TIA and much higher (worse) $CHADS_2$ status. This prognosis is further evidenced in the outcome tables where those in ROCKET_AF have higher stroke/systemic embolism, stroke and myocardial infarction rates, but notably lower overall mortality.

Table 1. Baseline measures in all participants.

Baseline measure	ROCKET_AF	RE_LY	ARISTOTLE
Age (Median)	73	71.6(mean)	70
Gender (F)	39.7	37.8	35.3
Prior VKA	62.4	49.4	57.1
CHF	62.5	31.9	N/A
Hypertension	90.5	78.9	87.4
Diabetes	40.0	23.2	25.0
Prior SSE/TIA	54.8	20.1	19.4
Prior MI	17.2	16.5	14.2
AF Persistent/permanent	81.0	66.8	84.7
Mean CHADS	3.5	2.2	2.1
% $CHADS_2$ 3-6	87.0	32.4	30.2
Aspirin	38.5	39.6	30.9
Beta-Blocker	65.4	62.7	63.1
Follow-up (Yrs)	1.9	2.0	1.8

Table 2. Populations used for study outcomes.

Outcome	ROCKET_AF	RE_LY	ARISTOTLE
Death all-cause	ITT/As treated	ITT	ITT
Death vascular	As treated	ITT	
IC bleeding	As treated	ITT	As treated
Major Bleeding	As treated	ITT	As treated
Myocardial infarction	As treated	ITT	ITT
Stroke	As treated	ITT	ITT
Stroke/Systemic Embolism	ITT/As treated	ITT	ITT

The indirect comparisons are undertaken using the pooled variances on a log scale from the individual study hazards ratios, to calculate the 95% confidence intervals for the ratios of the hazard ratios. Hazard ratios are used as all the outcomes presented are time-dependent.

The indirect comparisons (Tables 3-6) highlight three significant differences, with ARISTOTLE showing a significantly greater reduction than ROCKET in terms of major bleeding ($p<0.05$) and stroke/systemic embolism (the primary outcome in all studies) was significantly reduced with Dabigatran 150mg in the RE_LY study compared with the ITT population comparison in ROCKET_AF. An important factor in the consideration of these findings is that the new agents derived their advantages over Warfarin when Warfarin was used sub-optimally (<65% of time within INR standard range of 2.0-3.0).

We have also seen that the advantages espoused in the Dabigatran trial have not translated as expected into practice but have been the focus of much unexpected morbidity and regulatory concern worldwide. It is not unreasonable to assume therefore that effective translation of comparative benefits observed in these controlled trials to general/community practice in the short term are unlikely to be realised.

Table 3: Comparisons of important outcomes, with modifications for the relevant populations, on the new agents and Warfarin

Study	*corrected/revised values	Rates Comparator	Warfarin	HR	Lower CI	Upper CI	Comparisons	RRR	LL	UL
RE-LY	Stroke/systemic embolism*	1.11	1.71	0.65	0.52	0.81	rely vs rock	0.739	0.561	0.972
ARISTOTLE	Stroke/systemic embolism	1.27	1.6	0.79	0.66	0.95	rely vs aris	1.215	0.910	1.623
ROCKET	Stroke/systemic embolism	2.1	2.4	0.88	0.75	1.03	rock vs aris	1.114	0.873	1.422
RE-LY	Death-all cause	3.64	4.13	0.88	0.77	1	rely vs rock	0.957	0.802	1.141
ARISTOTLE	Death-all cause	3.52	3.94	0.89	0.8	0.998	rely vs aris	1.011	0.848	1.206
ROCKET	Death-all cause	4.5	4.9	0.92	0.82	1.03	rock vs aris	1.034	0.879	1.216
RE-LY	Stroke	1.01	1.57	0.64	0.51	0.81				
ARISTOTLE	Stroke	1.19	1.51	0.79	0.65	0.95		1.234	0.909	1.676
RE-LY	Myocardial Infarction*	0.81	0.64	1.27	0.94	1.71				
ARISTOTLE	Myocardial Infarction	0.53	0.61	0.88	0.66	1.17		0.693	0.457	1.051
ARISTOTLE	Major Bleeding	2.13	3.09	0.69	0.6	0.8				
ROCKET	Major Bleeding	3.6	3.4	1.04	0.9	1.2		1.507	1.226	1.854
ARISTOTLE	IC bleeding	0.33	0.8	0.42	0.3	0.58				
ROCKET	IC bleeding	0.5	0.7	0.67	0.47	0.93		1.595	0.978	2.601

Dabiga better than Rivarox

Rivarox inferior to Apixiban

Derivation of estimates:

For Warfarin vs non-treatment the RR for STROKE is 0.33, for Aspirin vs non treatment it is 0.79 -both figures from the HART meta-analysis.

The figure used for Dabigatran vs non treatment, from Roskell and based on Ischaemic stroke is 0.23.

Loosely these figures are for different outcomes so shouldn't be compared BUT the figure we get for Dabigatran vs Warfarin from this is 0.70, (i.e. .23/.33).

If we have the correct outcomes we can work these out: so for stroke Warfarin vs non treatment was 0.33 and Dabigatran vs Warfarin 0.64, so the figure for Dabigatran vs non treatment would be 0.21

Table 4: Comparisons of important outcomes, with modifications for the relevant populations, on the new agents and Warfarin

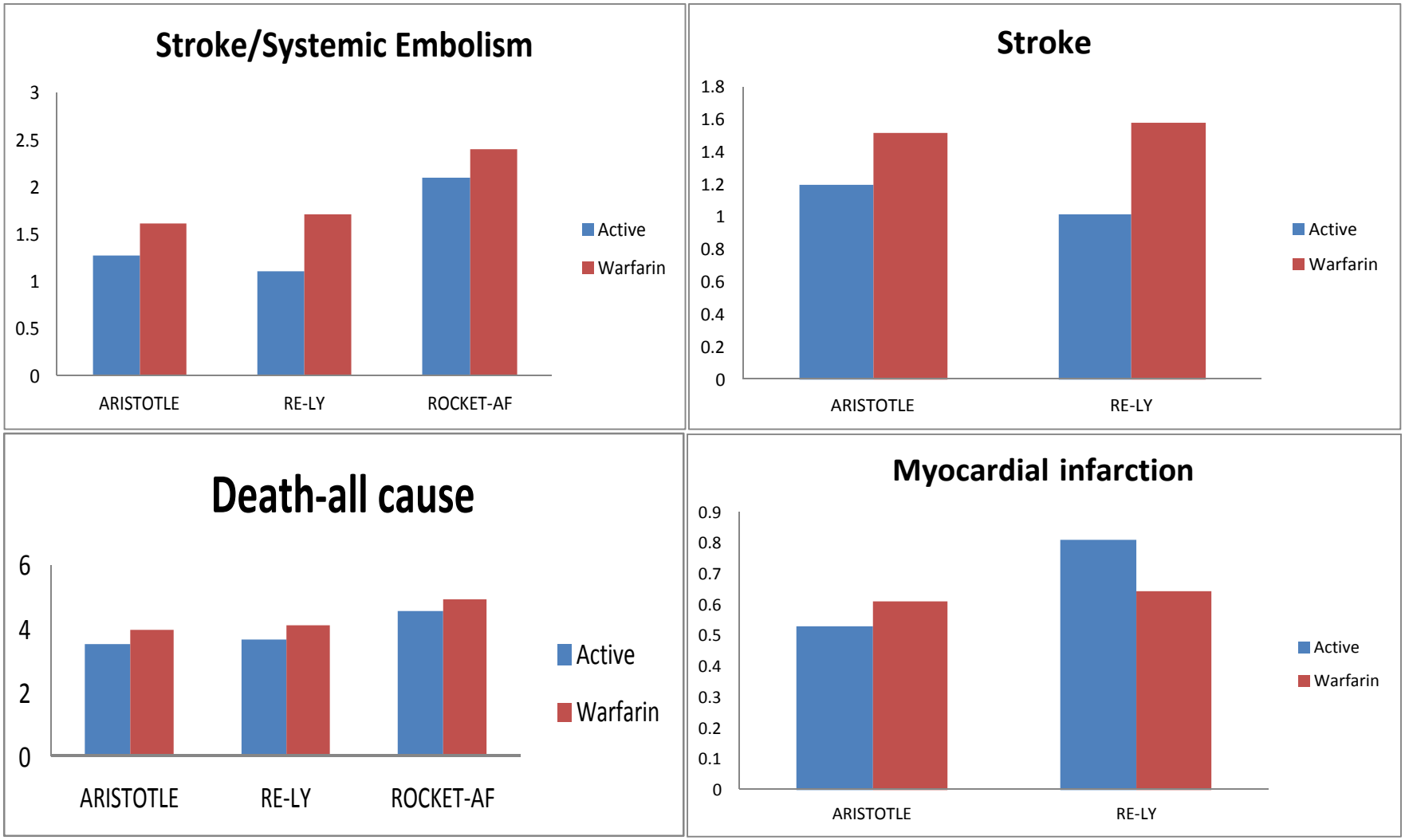
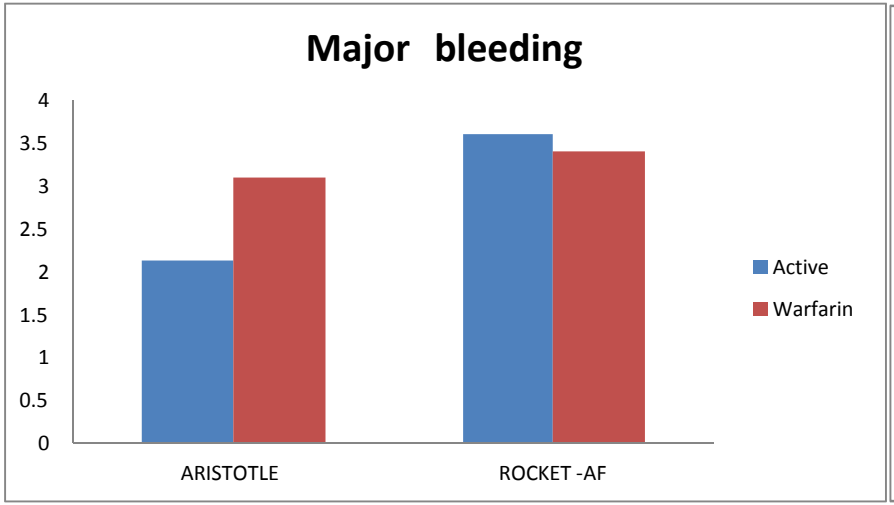
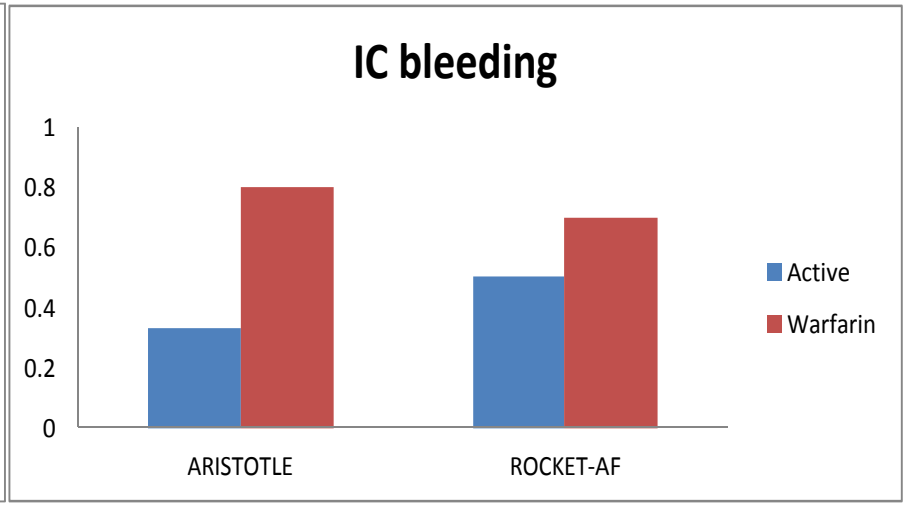
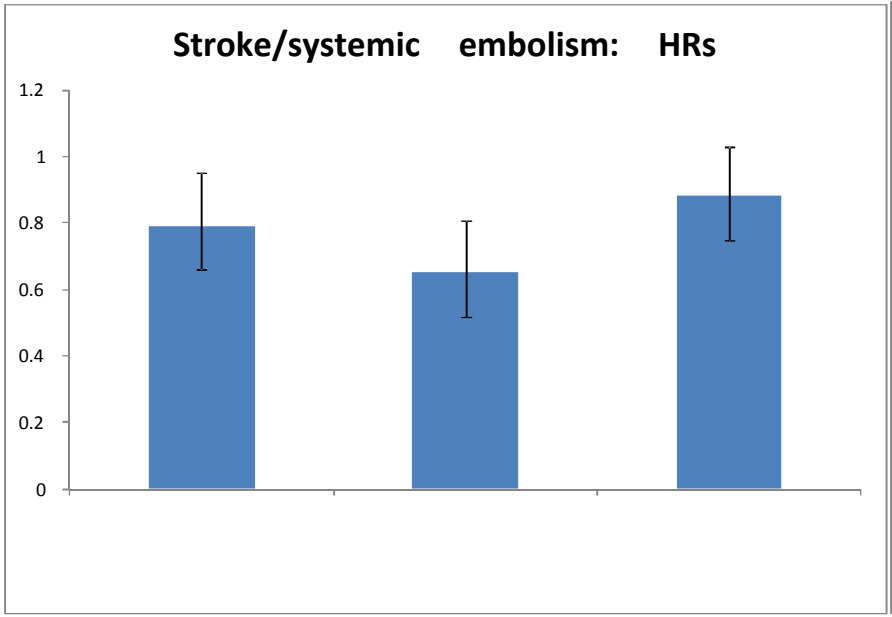


Table 5: Comparisons of important outcomes, with modifications for the relevant populations, on the new agents and Warfarin







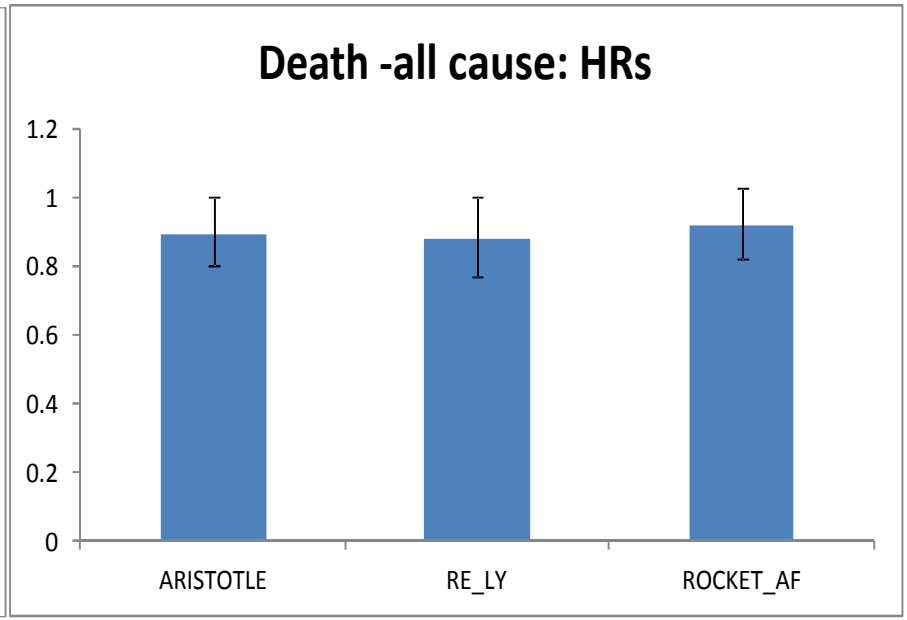
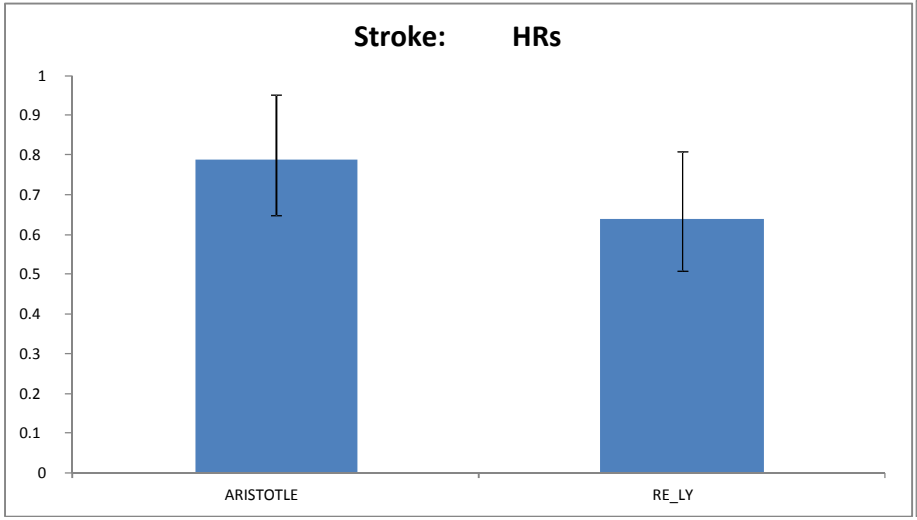
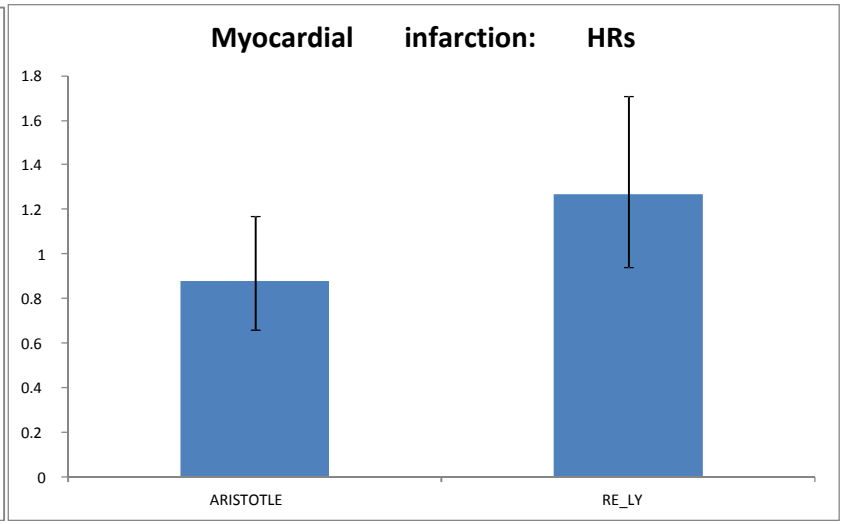
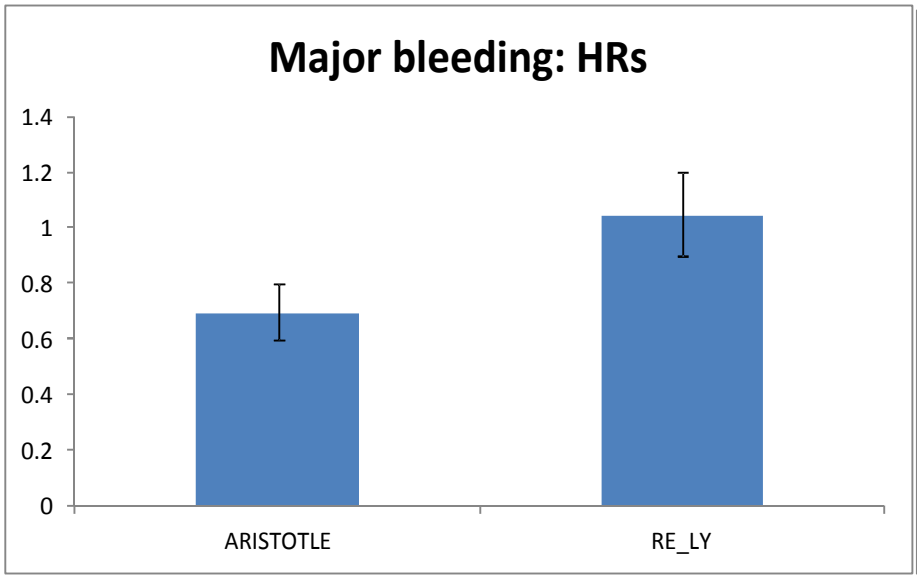
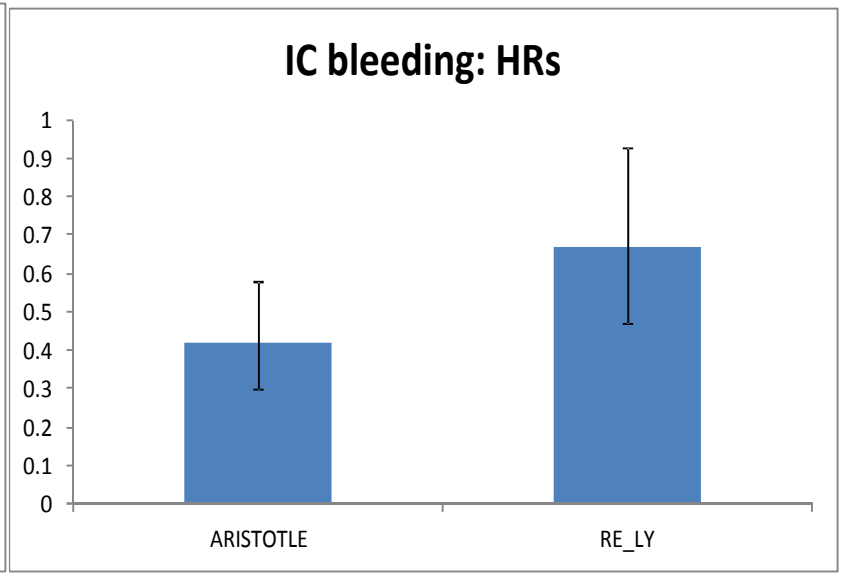


Table 6: Comparisons of important outcomes, with modifications for the relevant populations, on the new agents and Warfarin









Critical appraisal on the Deloitte Access Economics report -the impact of the new agents on preventable strokes at moderate-to-high stroke risk:

Methodology

To derive the extent to which anticoagulant therapies may prevent events in those with NVAF a population-based approach for calculations placing the available data (relative efficacies from RCTs) into a broad Australian population setting was adopted. To do this, population estimates of key rates, e.g. strokes, AF, untreated AF, etc are required upon which to place outcome and relative outcome rates derived from the RCTs.

The Deloitte Access Economics publication ***Off Beat:*** **The Case for 21st Century Stroke Prevention** was used in this review to ascertain the likely impact of the new agents on preventable strokes. A recent report (November 2011) it was commissioned by Boehringer-Ingelheim and attempts to derive the extent to which their anticoagulant therapy Dabigatran may prevent events in those with NVAF in the Australian setting. This report is thorough and well done. The main flaw with it is the assumptions they are forced to make when the data is not available, but mostly they are explicit about this.

The Deloitte approach is very different of course from the approach of the RCTs which are attempting to elucidate efficacy and relative efficacy in the clinically relevant population. For this reason the Deloitte report could only sensibly estimate rates for key input groups (e.g. age and gender) for which published outcome rates (e.g. strokes) are available. Inherently there will not be many groups for which these rates are available.

The Deloitte report uses age, gender, VKA treatment (including non-compliance with Warfarin) as explicit determinants of outcomes rates. They have acquired stroke rates for the age-gender, stroke risk and current treatment subgroups and then coupling this with the prevalence of these groups have estimated preventable strokes. To some degree they have not overcomplicated the model by incorporating too many predictors of stroke, and they have captured the key readily quantifiable population determinants. They have not however, applied sub-group specific relative outcomes (as given in e.g. pg 1149 Connolly) to the sub-groups but have used overall relative rates. Again this is defensible; firstly the rates in Connolly do not differ significantly between any of the sub-groups (min p-value =0.10) and secondly the model will potentially lose clinical credibility by being excessively complicated and giving an impression of being removed from clinical reality.

The pivotal mistake made in the Deloitte Access Economics Report submitted to PBAC in support of the assumptions driving the cost effectiveness analysis of Dabigatran, is in the area of preventable strokes.

In the Deloitte's report they state that 3532 (approx 10/day) could be prevented if those currently untreated were placed on aspirin and Warfarin as per current guidelines. Referring to Table 5.1 clearly indicates that approx 50% of the high and moderate risk groups not being treated are NOT diagnosed with

NVAF. Deloitte's make this very clear hence the recommendation for better diagnosis. No-one would suggest treating all over 50s on the assumption that some might have NVAF.

The estimate of 3532 preventable does not take into account those who are unwilling to take meds. It merely indicates what ratios would wind up on aspirin or Warfarin in the high and mod risk groups (table 5.2), they may have played with these figures.

The second clear error they make is stating that Warfarin is taken by 'fewer than 40% of patients who should get anticoagulation therapy' -It is very clear that this figure also includes undiagnosed NVAF.

In keeping with these points we have regenerated the Deloitte Tables 5.1 to 5.4. Two key points here which these tables highlight:

1. **Deloitte's mistakenly include the non-diagnosed among the non-treated in whom strokes would be prevented by the introduction of either the new treatment or aspirin/Warfarin.** Surely the new treatment of itself would not improve the diagnosis of NVAF. It is more apt therefore to calculate the preventable based on those untreated BUT diagnosed. As we have done with the yellow highlighting to the right of the sheet. This shows quite different figures (Table XX).

2. The second point here is that the Dabigatran (i.e. 23% relative risk to no treatment) assumes that all diagnosed will go on to Dabigatran and there will be no diluting this to some aspirin etc. While Warfarin does have side effects and perceptions are such that many will be tried on aspirin or moved to aspirin from Warfarin - there are also many who are wary of any AC treatment and therefore even in Dabigatran if widely available would not be given to all for whom it is indicated. Some might get aspirin or a combo.... we have estimated this effect based on the Deloitte Access Economics Report and have allowed for this in the calculations (Table 8). We have also repeated this method with the new agents Apixaban and Rivaroxaban (Tables 9-10). The recalculated number of preventable strokes with Dabigatran, Apixaban, Rivaroxaban are estimated at 2005, 1899 and 1857 respectively based on current utilisation figures.

As the new agents derive their advantages over Warfarin when Warfarin is used sub-optimally (i.e outside the standard INR range 2.0-3.0), it is expected with the introduction of improved modes of health system delivery on outcomes achieved with anticoagulation therapy that this would lead to more patients taking Warfarin (currently 39 % of the high risk patients are on aspirin!). Even fewer strokes being prevented as a consequence of the use of the new agents whilst improving the QUMs in this critical area.

Table 7: Estimates of Preventable Strokes with Warfarin Based on Current Management of NVAF

Table 5.1

Risk	*Diag not treated*	*undiagnosed*	*total untreated*	*% likelihood of stroke*	*No. Strokes In untreated*
High	49559	51811	101370	5.7	5778
Moderate	30333	27708	58041	2.8	1625
Low	32199	11783	43982	1.9	836
total	112091	91302	203393		8239

Table 5.2

Risk	*To aspirin*	*To Warfarin*
High	39	61
Moderate	52	48

	Aspirin	*Warfarin*
RR	0.79	0.33

Includes non-diagnosed

Doesn't include non-diagnosed

Table 5.3 (Warfarin)

Risk	*Weighted risk*	*No. Strokes In untreated*	*Preventable*	*No. Strokes In untreated*	*Preventable*
High	0.5094	5778	2835	2825	1386
Moderate	0.5692	1625	700	849	366
Total		7403	3535	3674	1752

Table 8: **Estimates of Preventable Strokes with Dabigatran Based on Current Management of NVAF**

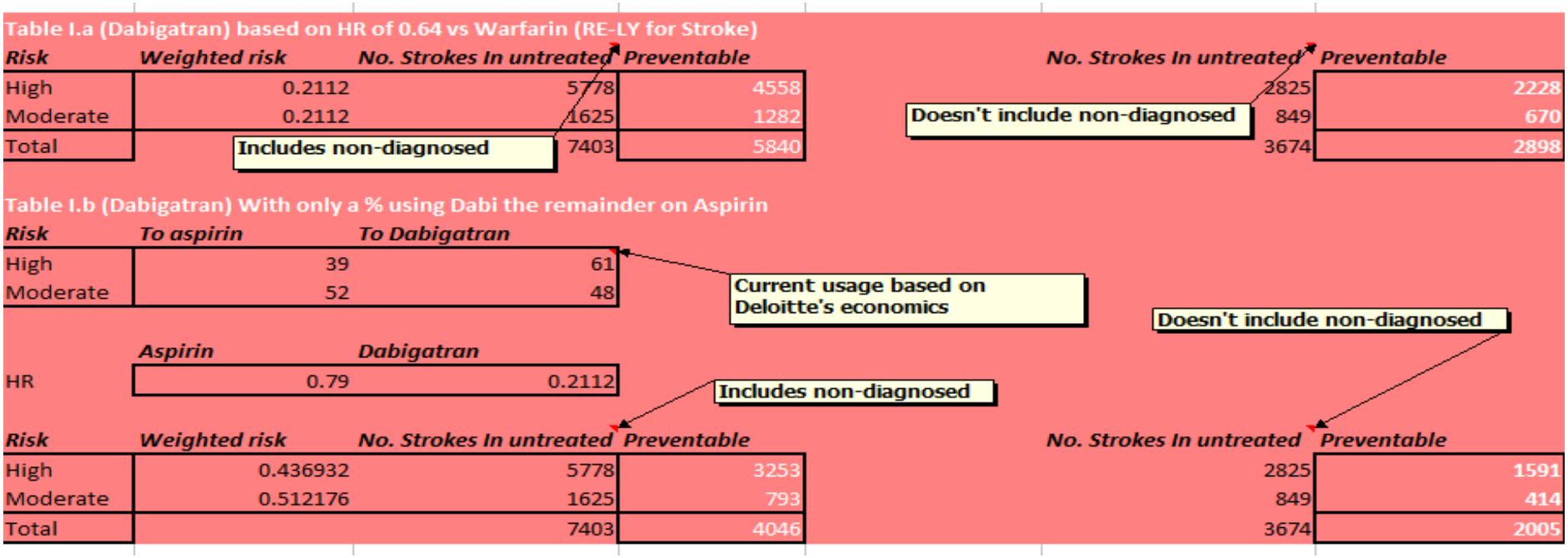


Table 9: Estimates of Preventable Strokes with Apixaban Based on Current Management of NVAF

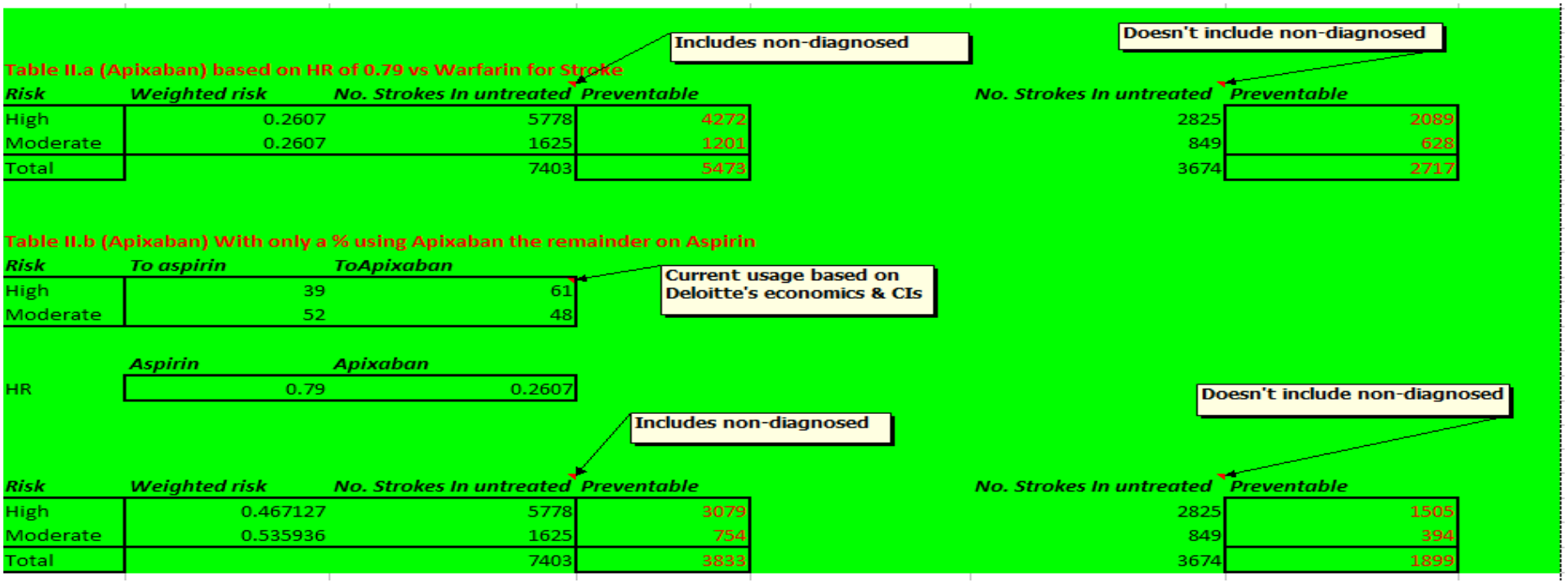
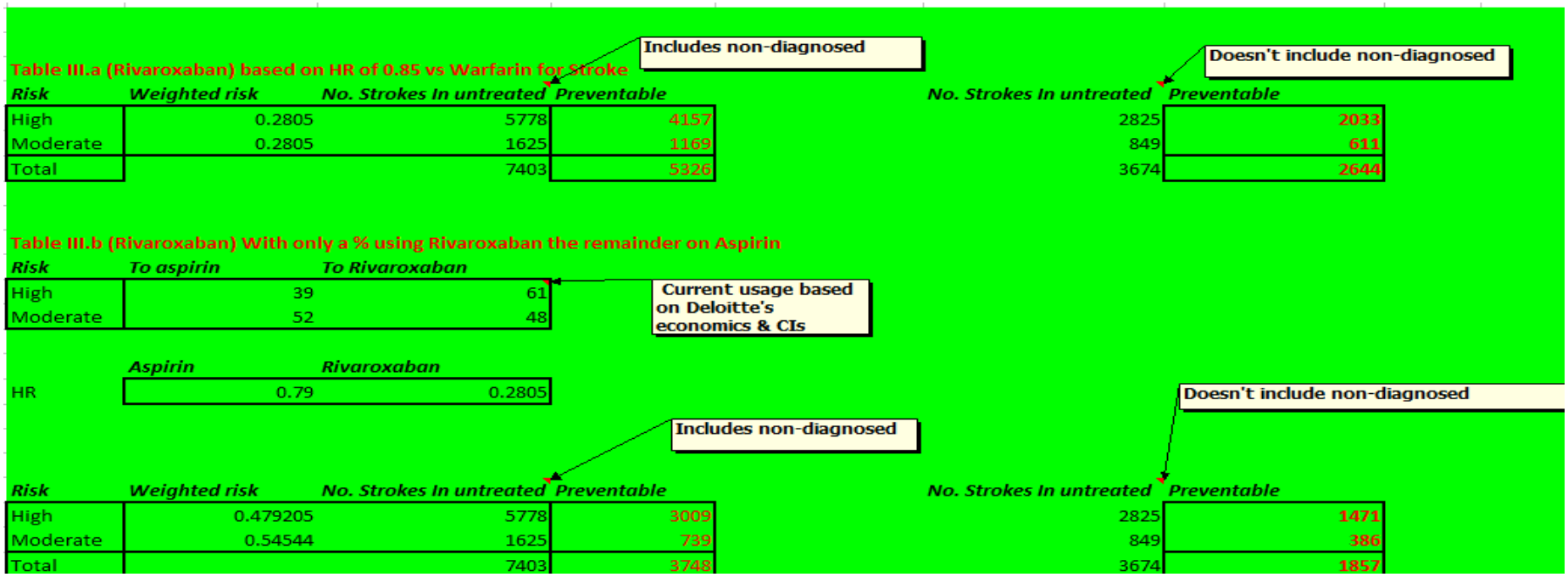


Table 10: Estimates of Preventable Strokes with Rivaroxaban Based on Current Management of NVAF



Overall Conclusion to Section 1

In Summary: SECTION 1 explores in some detail the factors that would have material implications for inputs to the economic analysis estimating the incremental cost-effectiveness ratio for Dabigatran (and other new ACs) and Warfarin namely; the quality of the reporting and results of the comparative pivotal trials and calculations derived from the economics report underpinning the assumptions used to populate the ICER model.

In this appraisal process we identified a number of issues which we believe impact materially on the effectiveness and cost effectiveness of the new agents relative to the established therapies.

We also noted in the trials that the new agents derived their advantages over Warfarin when Warfarin was used sub-optimally i.e. when patients spend <65% time within the standard INR range of 2.0-3.0. This latter fact has relevance in the following respects:

1. the mean time in therapeutic range (TTR) for patients enrolled from different countries in the RELY trial, for warfarin at different levels of international normalised ratio (INR) control (2-3) (Wallentin 2010) indicated for patients enrolled in Australian sites which had a mean time in therapeutic range for warfarin of 74%
2. improved therapeutic management of patients with NVAF based on these outcomes, would diminish the impact of the new agents observed in the pivotal trial.

SECTION 2: Factors contributing to and evidence of the impacts of under-utilisation and sub- utilisation of patient management anticoagulants.

In SECTION 1 we explored in some detail the factors that would have material implications for inputs to the economic analysis estimating the incremental cost-effectiveness ratio for Dabigatran (and other new ACs) and Warfarin.

Several recent randomised clinical trials of anticoagulation in atrial fibrillation have demonstrated that the new AC agents derive their advantages over Warfarin when Warfarin is used sub-optimally (RE-LY, ARISTOTLE). In the Australian setting the under-utilisation and sub-utilisation of anticoagulants remains a substantial obstacle to the translation of trial efficacy outcomes into practice and improving the quality of health care.

There appears to have built over time a mythology around Warfarin, that it places a considerable burden on patients and prescribers through:

- the need for frequent blood monitoring especially for patients living in rural or regional areas;
- fear of treatment-related bleeding, including difficult to treat and disabling stroke and major bleeds;
- requirements for patients to follow specific and consistent diets due to drug-food interactions; and
- interactions between Warfarin and many common medicines.

In the absence of objective information and clinical data this mythology is self reinforcing and has already been exploited commercially by the competitors to Warfarin.

In this Section we seek to qualify through an evidence-based approach the impact of Warfarin on the barriers to prescribing in the Australian setting through the review of pivotal trials on the new agents and the literature.

Additionally this Section discusses current stroke prevention management practice and interventions in Australia, including the:

- perceptions of healthcare practitioners and patients towards existing drug therapies in particular evidence on factors contributing to the under-utilisation and sub-utilisation of Warfarin and anticoagulants.
- evidence of the impact of education initiatives, or other Quality Use of Medicine initiatives, on health outcomes for patients on anticoagulant therapy.
- the impact of different modes of health system delivery on outcomes achieved with anticoagulation therapy including discussions on Point of Care Testing, compliance monitoring, continuum of care arrangements, pharmacogenetic testing and collaborative (shared care) arrangements.

Perceptions of healthcare practitioners and patients towards existing drug therapies in particular factors contributing to and evidence of the impacts of under-utilisation and sub-utilisation of Warfarin and anticoagulants

Pivotal Drug Trials

VKAs are not easy to use….

The introduction and substantial justification for the RE-LY study was that VKAs such as Warfarin are not easy to use and discontinuations rates are therefore high. ["Vitamin K antagonists are cumbersome to use, because of their multiple interactions with food and drugs, and they require frequent laboratory monitoring. Therefore, they are often not used, and when they are, rates of discontinuation are high. Many patients receiving Warfarin still have inadequate anticoagulation. Thus, there is a need for new anticoagulant agents that are effective, safe and convenient."].

The corresponding data from the Re-Ly study suggests that Praxada does not seem to remedy this issue. Discontinuation rates are much higher in the Dabigatran arm (*significantly, p<0.001 for both,* 15.5% vs 10.2% at 1 year and 21,2% vs 16.6% at 2 years).

Literature Review

A search was conducted on PubMed, Cochrane Library and the Grey literature interrogating the perceptions and barriers to the prescribing of Warfarin and anticoagulants generally in the Australian setting and interventions explored in improving health system delivery on outcomes achieved with anticoagulation therapy. The search methodology, search outputs and data extraction of the characteristics and outcomes on eligible reports can be viewed in Annexure 4

Adverse event reporting - ADRAC (TGA) reports

ADRAC (TGA) Reports

ADRAC reports from the Australian TGA adverse event reporting system were reviewed as an objective source of safety outcomes on Warfarin. Whilst passive reporting is associated with recognised biases and under-reporting, such systems, implemented nationally, provide signals of public health importance generated through spontaneous reporting mechanisms which can be evaluated on at risk groups, risk factors and clinical features of known serious ADRs.

The significance of under reporting on safety outcomes on determining the benefit/risk ratio of treatment with Warfarin must be considered within the context of the:

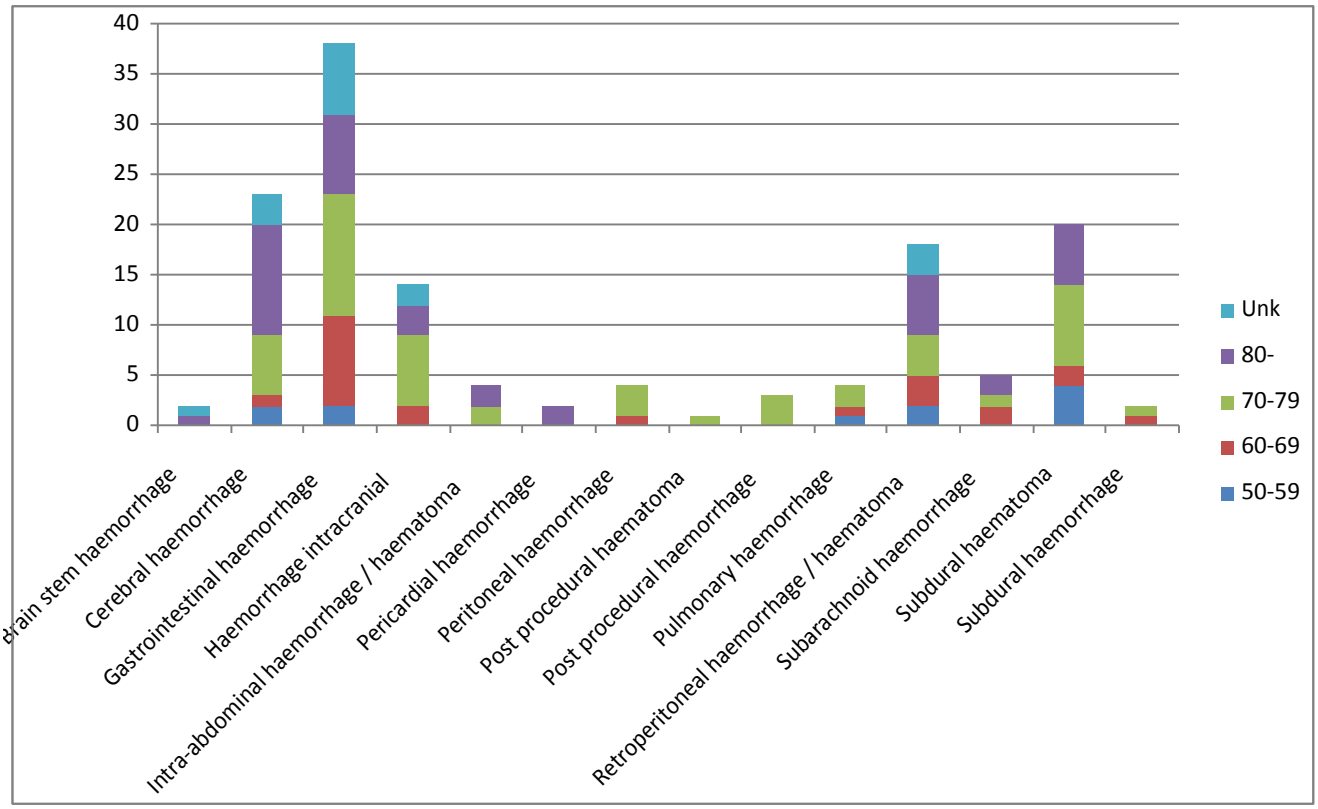
- very low historical signal in AERs for Warfarin
- plausibility and,
- research from prescription-event monitoring studies which confirms that there is both selective reporting and underreporting of safety outcomes with serious events significantly more likely to be reported than non-serious events[(Heeley 2001, Vandenbroucke 2001, Taylor 2004)]. It is not unreasonable to postulate that major or serious bleeds for example are likely to be reported in most cases of AC involved events.

Review of the ADRAC reports on Warfarin (which cover all indications) show with respect to:

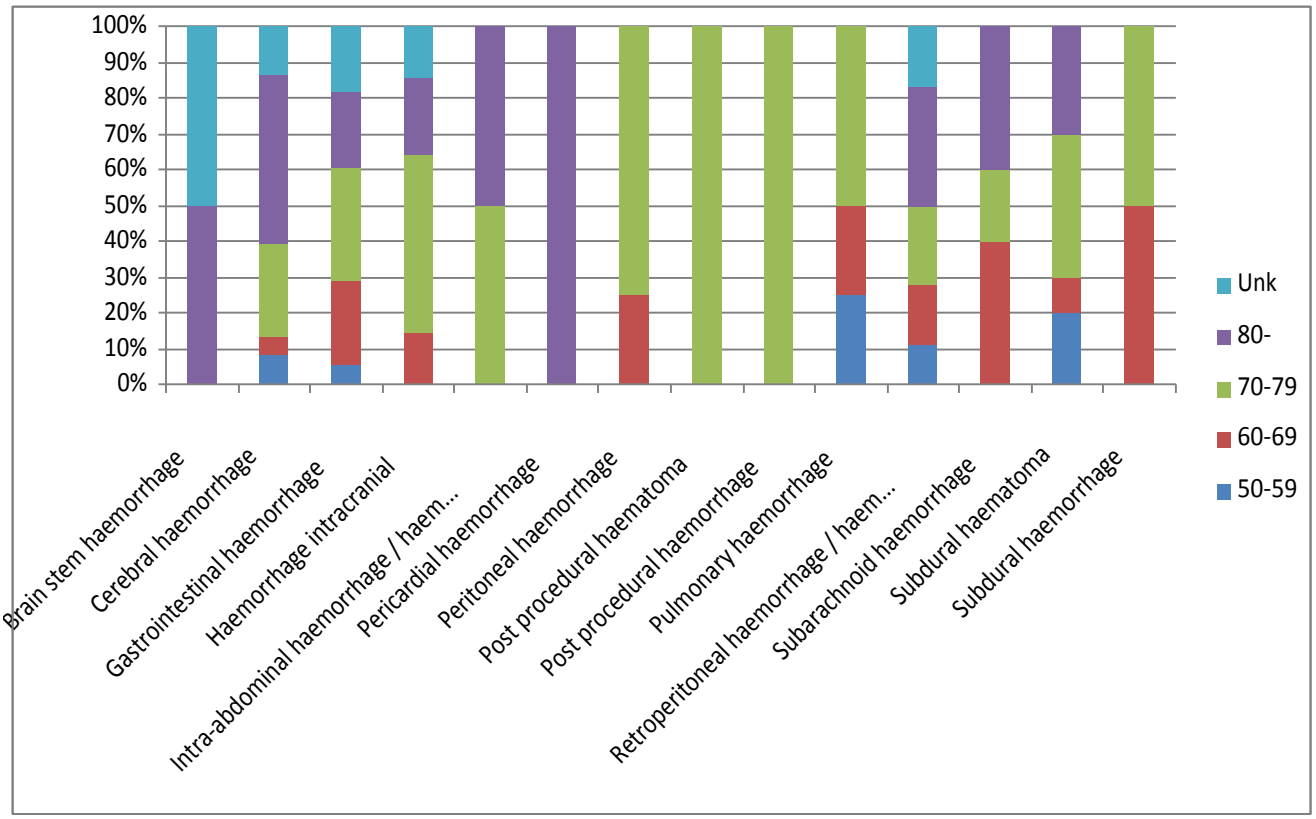
A/ Major bleeds:

- 1931 reactions (for 967 patients) involving Warfarin have been reported to ADRAC since 2000 on all indications. One hundred & forty or 7% of these reactions have involved major bleeds - at least 65% (to a maximum of 76%) of the major bleeds were reported in the 70-80+ age group and approx 8% in the 50-59 age group. The IMS data report 3.1 million Warfarin packs totalling 373.6 million mg were dispensed via the Pharmaceutical Benefits Scheme (PBS) in 2009, with 53% of those prescriptions (198.0 million mg) attributable to AF. The average daily dose of adjusted-dose Warfarin for stroke prevention in Australian practice is estimated to be 4.5mg (Gallus et al, 2000). Based on these data, PBS-dispensed Warfarin in 2009 accounted for 44.0 million patient days or 120,547 patients on Warfarin due to AF, which is nearly one-third of the estimated number of people with diagnosed NVAF at a moderate-to-high stroke risk in Australia (Section 1). In 2009 there were 105 reactions reported to ADRAC for all indications of Warfarin (12 major bleeds). Using a similar average dose for the non AF indications translates to a conservative 227,458 patients on Warfarin in 2009 or a very conservative incidence rate of major bleeds of 12/227,458 or 10^{-3}% in the community for that year. Translating this to all years since inception of reporting we're looking at a conservative cumulative incident rate for major bleeds of 12/227,458 per yr since 2000 or 5.27×10^{-6} %
- In this dataset of major bleeds Cerebral, GI, IC, Retroperitoneal and Subdural Haemorrhage were present at greatest frequency (18-38 events) with GI events most represented at 38/140 or 27%. IC haemorrhage is present at a frequency of 14/140 or 10% of the major bleeds.
- The distribution of the age groups within the dataset of major bleeds appear proportionally distributed.
- In the dataset of major bleeds with greatest frequency, 38/113 or 34% of the events were definitively resolved with an additional 46/113 or 41% of the events with unknown recovery status. There were 29/113 or 26% events derived from patients who died. Of this cohort 28/29 or 96.5% of these events were derived from patients who died of causes unrelated to Warfarin treatment.

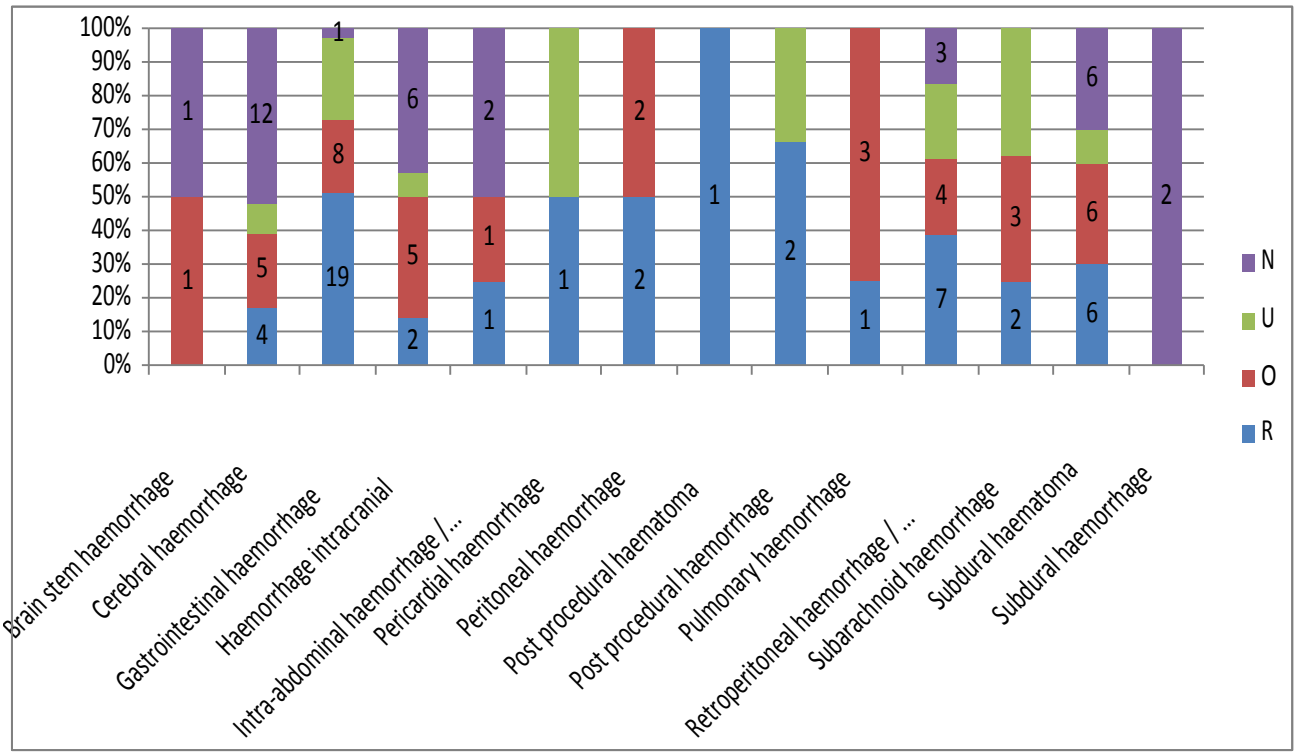
Frequency of major bleeds by age group n=140 ADRAC reports on Warfarin since 2000



Proportion of major bleeds by age group n=140 ADRAC reports on Warfarin since 2000



Recovery status by major bleed n=140 ADRAC reports on Warfarin since 2000

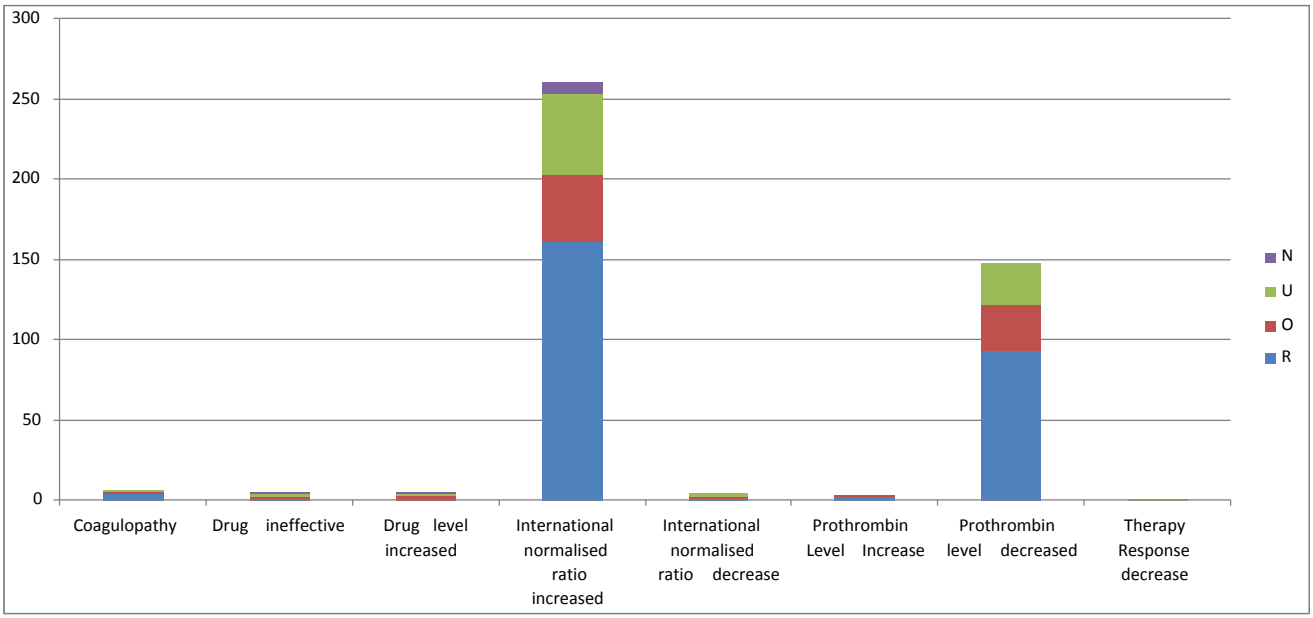


Legend: R=recovered; O=ongoing; U=unknown; N=not recovered/death; Death=unrelated

B/ Reduced laboratory efficacy:

- There were 452/1931 or 23% of the events reported involving reduced laboratory efficacy, of these 316/452 or 70% (to a maximum of 83%) were incurred in the 70-80+ age group and approximately 42/452 or 9% in the 50-59 age group. Based on the algorithm developed for calculations on the Major Bleeds this translates to an incidence rate of $1.81xe^{-7}$ over the 11 years of reporting. The most prominent group of coagulopathy issues reported involved increased INR (including decreased Prothrombin levels) accounting for 428/452 or 95% of the events reported in this category. The events resolved definitively in 262 or 58% of the cases and potentially in the majority or 94% of the cases. Death occurred in 15 patients 9 of which were reported as unrelated to Warfarin treatment.

Frequency of coagulopathies and recovery status

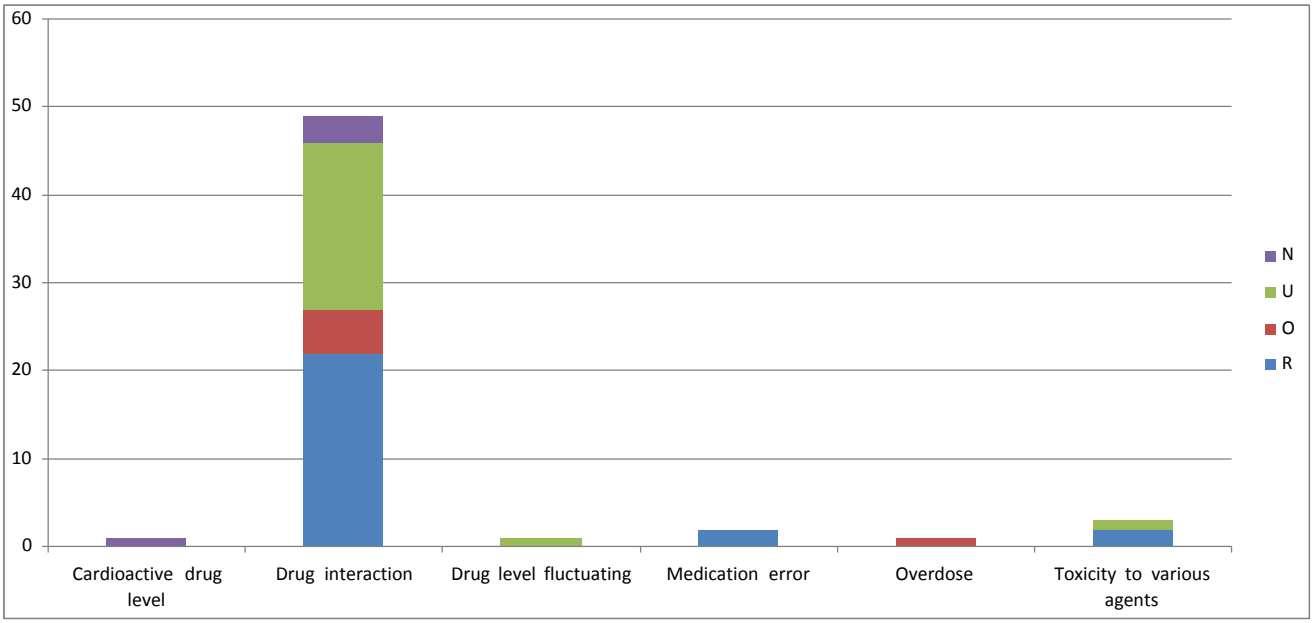


Legend: R=recovered; O=ongoing; U=unknown; N=not recovered/death; Death=unrelated

C/ Drug-Drug Interactions:

- There were 51/1931 or 2.6% events reported for drug-drug interactions (including drug toxicity). Twenty seven (27) or 53% of these were incurred in the 70-80+ age group with 4 or 8% incurring in the 50-59 age group.

Frequency of drug-drug interactions and recovery status



In Summary, since 2000 reactions in patients taking Warfarin irrespective of indication have been reported at an incidence rate of 7.72 $x10^{-7}$. Seven percent of the reports concerned major bleeds. Reduced efficacy in the laboratory and drug-drug interactions accounted for 23% and 2.6% of events reported respectively. Notwithstanding the general biases associated with passive reporting of adverse events, major events are expected for the most part to be reported. Taking this point the incidence of major bleeds observed in these reports is indicative of a very low safety signal on serious events. These figures concord with other

types of spontaneous reporting systems such as Community Treatment Reports example of which can be viewed at http://www.patientslikeme.com/treatments/show/105-Warfarin-side-effects-and-efficacy.

Current utilisation patterns of anticoagulants including data regarding the number of patients not currently being treated with Warfarin and/or aspirin, who may transfer to newer anticoagulation agents. Factors contributing to and evidence of the impacts of under-utilisation and sub-utilisation of anticoagulants.

Under-utilisation of ACs in practice

The literature review confirmed the under-utilisation and sub-utilisation of AC in the absence of contraindication to their use - In Singh 2011 only 38% of 1737 patients with AF (65%≥85 yrs) were prescribed Warfarin; 16% (40/255) did not receive any AC despite more than 80% of population being at high risk of stroke and 9% with a contradindication to Warfarin or AP. In Evans 2002, prior to admission, 87/111 (78%) patients had thrombo-embolism, yet only 14 (16%) were receiving Warfarin. 56 (64%) patients could have been receiving AC. 40 episodes of thrombo-embolism could have been avoided. In this same period 18 patients were admitted with haemorrhage related to Warfarin for stroke prophylaxis in NVAF. The authors in found that the medical comorbidities known to heighten the risk of stroke with NVAF did not influence decision on whether Warfarin was used for stroke. In Comino 2005 17/81 (26%) of patients with moderate to high risk of stroke did not receive Warfarin. Warfarin was prescribed for 42 (52%) and there were contradindications for Warfarin identified in 15/39 (39%) not taking Warfarin. The authors concluded that the number of preventable strokes far outweighed morbidity due to Warfarin in the management of NVAF. Physicians were hesitant to prescribe Warfarin in NVAF. In the Gattellari study contraindications to Warfarin "usually" or "always" applied to the patients of 40.6% of GPs (n = 242) when considering whether or not to prescribe Warfarin for their patients with NVAF. One-third of GPs (31.0%) indicated that this reason for not prescribing Warfarin applied to their patients "sometimes".

Only one in three patients without a contraindication received Warfarin, consistent with other studies that have found Warfarin is prescribed for 15–44% of eligible patients. Deloitte Access Economics have put this figure in Australia at 32.2% (high risk) and 30.3% (moderate risk).

Quality control of Warfarin

In Gattellari 2008 most GPs stated that they would measure INR levels monthly (n = 463, 77.7%) for a 78 year old patient diagnosed with NVAF after a stroke who was currently receiving Warfarin. Only 84 GPs (14.1%) indicated measurement of INR levels fortnightly. Almost 90% of GPs selected a target INR within the recommended range of 2.0–3.0 (n = 531, 89.1%) although 16.8% (n = 100) selected a target at the lower end of this range (2.0–2.5). A small minority selected a sub-therapeutic or supra-therapeutic target (n =25, 4.2% and n = 34, 5.7%, respectively). In Wolff 2008, patients (N=227, 55% with AF) were maintained within standard INR range (2.0-3.0) 69% of the time when tested fortnightly. AC related complications were 0.03 per patient year. INR testing every 14 days resulted in 78% of time spent in therapeutic range.

In a sequential case series from the Australian pathology group Pacific Knowledge Systems de-identified data were gathered from 236 individuals involving INR measurements over a minimum period of a year based on a frequency defined by the patient's health professional. Key statistics of the dataset can be viewed in Tables 11 and 12.

Table 11: Key statistics of pathology case series

	Mean +/- SD	Range
INR Levels	2.39 +/- 0.623	1.0 – 5.0
Period of Collection (Yrs)	1.84 +/- 0.222	0.901 – 1.981
Mean Visits / Patient	34.4 +/- 18.935	3.2 - 92
Visits / Patient / Year	19.15 +/- 12.615	2.6 – 94.6

Table 12: Monitoring statistics of pathology case series

Monitoring Frequency	INR - Mean	INR – S.Dev	INR – CV (%)
1 per 2 months	**2.55**	**0.73**	**28.90**
1 per month	**2.44**	**0.19**	**7.84**
2 per month	**2.59**	**0.11**	**4.59**

Commentary:

- Therapeutic levels of Warfarin (reference range 2.0 – 4.5) are highly variable within an individual. Circulating levels regularly fall below and rise above these target values. Random variation of INR values may occur in a patient on stable oral anticoagulant dosage, as a result of both biological and analytic variation. This total random variation has been estimated at ~10%.
- There is an even greater variation observed in the frequency of Warfarin measurement from patient to patient.
- At the extreme ends of the frequency spectrum, patients measurements were taken as irregularly as once per five (5) months or up to twice per week. On average patients were being tested 1.6 times a month
- Greater control of the frequency of measurement regulated by an automated monitoring tool may well improve the stability of circulating Warfarin levels in these patients.
- Optimal Monitoring Frequency would appear to be around one to two measurements per month resulting in variability of only 4.6% to 7.84%
- An automated monitoring and decision support system combined with a patient information program could improve the management and clinical outcomes of Warfarin patients.

Barriers to prescribing

Seventy two barriers to Warfarin use were identified in the literature review in the Australian setting which could be classified into 4 groups: patient medical characteristics (n = 26), health care system factors (n =21), patient capability (n = 18), and patient preference (n = 6).

Following are factors that strongly influenced physicians' decisions not to prescribe Warfarin in the local setting. A full description of the factors identified in the studies included in the review can be viewed in Annexure 3. A summary is located in Table 11 on page of this report.

(Patients Medical Characteristics): Frailty/Risk of Falls

In Perera 2009 frail patients were less likely to receive Aspirin than non frail on admission (p=0.002) and discharge (p<0.001). During hospitalisation, frail pts prescribed Warfarin decreased by 10.7% & non frail increased by 6.3%. 6 month follow up (n=207), 43 (20.8%) major or severe haemorrhages, 20 (9.7%) cardio embolic strokes, 40 (19.2%) deaths.

Age and psychosocial deficits (Patients Medical Characteristics):

In Shen 2008 (1)Elderly, (2)Elderly/mild dementia ,Elderly with MD living alone (4) Elderly with severe dementia (5) Very elderly plus adherence to INR monitoring, tendency to fall, heavy alcohol usage, cognitive function were less likely to be prescribed AC. In Bajorek 2012, there was less prescribing in patients aged $\geq$80 yrs. In Bajorek's 2002 study 202 (79%) pts were discharged on AT. Pts > 80 were as likely to receive AT therapy as those < 80 years (75.8% versus 81.9%, p = 0.23), but a significantly lower proportion received Warfarin than did those under 80 years (25.5% versus 62.5%, p = 0.0001). In Castelino 2010 Age (p=0.2) was significantly associated with AT use p <0.001. Interestingly, in the small study by Taylor 2005 variations were revealed in the management of acute AF in previously well, haemodynamically stable young pts suggesting other concerns at work than age and risk factors. In Evans 2002 study, physicians recommended Warfarin less often for case vignettes 85 yrs old compare to 65 yr olds. The authors identified a trend suggesting antithrombotic prescribing for older patients was less likely to be appropriate compared with younger patients.

Variations between Australian tertiary-care hospitals and types of speciality units in prescribing (Healthcare system factor):

In Duffy 2003 acute stroke care varied between Australian tertiary-care hospitals and types of speciality units. Patients from stroke units are more likely to be discharged with AP.

Medical experience of GPs (Healthcare system factor) –

In Gattellari 2008 GPs with shorter standing practice, decisional conflict and older age (75 vs 65) were associated with reduced prescribing of Warfarin.

Factors associated with patient capability and preference:

In the Gattellari 2008 study GPs referred to non compliance of patients with regular follow up, patients' reluctance or refusal ("usually","always" - 133/596 = 22.3%) to take Warfarin as some of the factors identified for reduced prescribing. Almost 60% (59.1%) of GPs reported that patient inability to comply with requirements for regular follow-up "never" or "rarely" applied to their patients, with only 10% endorsing this reason as "usually" or "always" applying to their patients when they considered whether or not to prescribe Warfarin. GPs were asked to indicate how often patient reluctance to take Warfarin applied to their patients when making decisions about Warfarin. Just over two-thirds of GPs (69.8%) indicated that this reason for not prescribing Warfarin applied to their patients at least "sometimes". Just over one-half of GPs (52.7%) stated that patient refusal precluded them prescribing Warfarin at least "sometimes"

With the advent of the new AC treatments it is predicted that a number of other barriers will become relevant to the consideration of AC management including Reversal of anticoagulant effect, long vs short half life, Rapid vs slow onset, Knowledge of genotype to assist dosage.

Table 13

Summary of Barriers: current management and perceptions

	Barriers #	Impact of Barriers
Patient Medical Characteristics		
Bleeding Episodes	4	Product information for Warfarin sets out full list of contraindications and concomitant medication
Fall Risk	7	
Hepatic Disease	1	
Alcoholism	4	
Renal impairment	1	
Haematuria, thrombocytopenia	1	
Cancer	3	
Use Non Steroid Anti-Inflammatory	1	
Severe anaemia	1	
Allergy to Warfarin	3	
Total Barriers Identified	**26**	
% Barriers Identified/Total Barriers	**33%**	
Patient Capabilities		
Language and Cultural Diversity	3	Impacts ability to mgt dosage variation/ INR testing, comply with alcohol, dietary and non-prescription restrictions, comprehend medication instructions, communicate with health care professionals, receive support, education and resources
Social isolation/ living alone	2	
Impaired mobility/ gait with no falls risk	1	
Visual/ hearing impairment	1	
Dementia/ impaired cognition	4	
Patient non compliance	4	
Depression	2	
Inadequate patient health literacy	1	
Total Barriers Identified	**18**	
% Barriers Identified/Total Barriers	**23%**	
Patient Preference		
Patient reluctance/refusal	1	Impacts patient concern/anxiety on bleeding/bleeding risks/adverse affects, motivation, quality of life etc.
Fear of bleeding/bleeding risk	3	
Risk of adverse events	2	
Total Barriers Identified	**6**	
% Barriers Identified/Total Barriers	**8%**	
Health Care Barriers		
Access to specialised information/ resources	1	Impacts (1) patient care/support/resources/ education/training (2) health professionals support/ resources, education/training (3) access to quality services (4) adequate financial support to HCPs (5) increased workload (6) exposure to litigation.
Knowledge/ experience of health care professionals	4	
INR - guidelines differ from path labs, monitoring remote areas,	3	
INR not remunerated	1	
Education/ counselling time consuming, W difficult to mgs	3	
Roles and responsibilities in A-T mgt not clearly defined	2	
Conflicting prescribing patterns	7	
Total Barriers Identified	**21**	
% Barriers Identified/Total Barriers	**26%**	
Age	9	Independent barrier affecting other barriers
	11%	
Grand Total Barriers Identified	**80**	

In Conclusion, a review of the literature, pivotal trials and pathology case series on the tolerability of Warfarin and barriers to AC prescribing confirmed:

- The high tolerability of Warfarin based on very small incidence rates of reported events to ADRAC (bleeding, drug-drug interaction and reduced laboratory efficacy), significantly better rates of discontinuation of Warfarin vs Dabitgatran in the Dabigatran pivotal trial , and tolerability not rating as a significant barrier by prescribers or patients to treatment.
- Our review of the literature suggests that only one in three patients without a contraindication received Warfarin, consistent with other studies that have found Warfarin is prescribed for 15–44% of eligible patients. Deloitte Access Economics have put this figure in Australia at 32.2% (high risk) and 30.3% (moderate risk).
- Australian hospital statistics indicated that the most prominent group of coagulopathy issues reported involved increased INR (including decreased Prothrombin levels) accounting for 428/452 or 95% of the events reported in this category. The events resolved potentially in the majority or 94% of the cases. Death occurred in 15 patients 9 of which were reported as unrelated to Warfarin treatment.
- INR levels are being measured on average 1.6 times a month with patients measurements taken as irregularly as once per five (5) months or up to twice per week. Optimal Monitoring Frequency would appear to be around one to two measurements per month resulting in variability of only 4.6% and 78%. Less frequent testing has been associated with acceptable clinical outcomes (studies have reported equivalent clinical outcomes for once, twice and thrice monthly testing). However a more frequent schedule of testing has both the benefits of a high amount of time spent in therapeutic range and a means to regularly assess the patients who will be for the most part elderly. It also provides the physician the opportunity for patient education and the earlier detection of problems. It allows the practitioner the ability to tailor the intensity of anticoagulant therapy for patient-specific factors, such as for patients on single or dual antiplatelet therapy, or for those patients with an increased bleeding risk. Lastly, it may make it difficult to determine if the specific therapy has failed. If a patient develops a thromboembolic event on Warfarin, the INR is measured to determine if the event is truly a failure of therapy or whether the patient was sub therapeutic (due to noncompliance or other factors influencing the INR). In the latter case, dosing can be adjusted to increase the INR, and patient education can be provided if thought to be necessary.
- Seventy two barriers to Warfarin use were identified in the literature review in the Australian setting which can be classified into 4 groups: patient medical characteristics (n = 26), health care system factors (n =21), patient capability (n = 18), and patient preference (n = 6). Key barriers identified included patient medical characteristics such as age, at risk of falls, at risk of bleeding and health care system factors such as conflicting prescribing patterns (say between specialist & GP) and knowledge/experience of healthcare professionals.

- With the advent of the new ACs a number of other barriers will become relevant to the consideration of AC management including Reversal of Anticoagulant Effect, Rapid/Slow onset, Predictable Anticoagulant Affect, Knowledge of genotype to assist dosage

Interventions to Barriers

It is clear on review of these studies that reform in this space would need to address the following considerations:

- Characteristics of average patients on stroke prevention medication-the prevalence of AF is highest in the 70+ age group-this is reflected in the studies retrieved from the literature review with the mean age of patients in the studies at 75+. In the RE-LY, ROCKET and ARISTOTLE studies patient ages were a median of 70 years probably indicating a number below this age. A lot of our elders are coping with at least one of the following conditions, and many are dealing with two or more of the following: depression, cognitive impairment, Dementia, including Alzheimer's disease, Parkinson's disease, frequent falls, which can lead to fractures. The so-called **geriatric giants** are the major categories of impairment that appear in elderly people, especially as they begin to fail. These include immobility, instability, incontinence and impaired intellect/memory.

  Impaired vision and hearing loss are common chronic problems among older people. Hearing problems can lead to social isolation, depression, and dependence as the person is no longer able to talk to other people, receive information over the telephone, or engage in simple transactions, such as talking to a person at a bank or store. Vision problems lead to falls from tripping over unseen objects, medicine being taken incorrectly because the written instructions could not be read, and finances being mismanaged.

- Reduced access to pathology testing and medical management in the Rural settings

- These findings suggest that elderly patients on Warfarin should be reviewed regularly for psychosocial deficits and a stroke prevention solution tailored to patient capabilities, preference and location. Selected patients such as a patient with 'mild' medical characteristics and capable for example, should be considered for self point of care monitoring. Combined with a Patient Anticoagulation Tracking System this would pose a convenient and cost effective approach to INR testing and dose adjustment. Additionally this would enable regular monitoring of the health status of these patients with growing vulnerability to the deficits of growing age. The regular monitoring of INR could be combined with other medical and psychosocial tests thereby providing an opportunity to keep on top of any would be issues–thereby improving the QUMs.

- Practice resources to adequately prepare the healthcare practitioner to manage stroke prevention such as newer technology (eg Point of Care INR testing to provide immediate INR blood test results during consultations), Patient educational resources outlining the pros and cons of available

treatments, a computerised risk calculator to quantify the risk of stroke in patients with NVAF, means to flag patients for follow-up, monitor INR levels and refer to GP for the management of out of range INRs (e.g. practice nurse).

Tables 14 and 15 summarise the interventions studied in the reports identified in the literature search.

Details on some of the findings on these interventions from the literature review are offered below:

Control of assessment of stroke risk by 3rd professional parties such as pharmacists

Elliott 2002- Multidisciplinary feedback resulted in increased antithrombotic prescribing. The intervention had a greater impact on Asperin prescribing compared to Warfarin. Jackson 2011-The pharmacist led stroke risk assessment resulted in a significant increase in the proportion of pts receiving AT.

This could relate to the fact that prescribers are sometimes reluctant to use Warfarin in very old patients. This may have been due to the multifaceted nature of the intervention which included: presentation of feedback at multidisciplinary educational meetings, inclusion of comparative data from other hospitals, presentation and discussion of evidence supporting antithrombotic use in older patients with AF, provision of a written summary of the information, and use of educational posters placed in ward areas. High medical staff attendance rates at feedback sessions were considered to be important, and this was achieved by scheduling sessions to coincide with regular unit meetings. Also important was involvement of a respected senior geriatrician in the feedback sessions. The multidisciplinary nature of the intervention may also have been beneficial since pharmacists and nurses can influence prescribing decisions [24]. To avoid decline back to baseline ongoing regular audit and feedback is likely to be required to maintain the improvements achieved.

Antithrombotics were under-prescribed for older patients with AF at nine Australian hospitals. Application of an evidence-based prescribing indicator, combined with multidisciplinary feedback, increased antithrombotic use. Improved prescribing was still evident after 6 months, although there appeared to be a partial decline towards baseline, suggesting that ongoing feedback at regular intervals may be required to maintain improvements. The intervention had a greater impact on aspirin prescribing compared with Warfarin, indicating that further research is required to find ways to increase Warfarin use.

Point of Care Monitors

Jackson 2004 in rural areas-GPs generally confident in accuracy of monitor; foresaw little problem with widespread use in general practice; pts preferred near-patient testing. GP's more confident in prescribing Warfarin. It is not clear if testing was only done on AF pts or those with venous thrombolism as well. High correlation (r=0.89) between measurements; 88% of dual INR measurements were within 0.5 INR units of each other; monitor more likely to underestimate the INR value, particularly at values > 3.5.

Wolff 2008 in rural areas- Anticoagulation clinic (with specially trained personnel), point of care INR testing in remote centres, development of A-C protocols for GP use, comprehensive pt education program over 3

yrs. Time in the therapeutic range was 69% for the standard range (2.0 -3.0) and 81% in the expanded range 91.8-3.0). The A-C related complication rate was 0.03 per pt year (95% CI:0.01,0.08). INR testing every 14 days resulted in 78% of time spent in therapeutic range (in the new comparative drug trials patients on Warfarin with >65% time spent with INR in therapeutic range had similar outcomes to the new agents).

Educational Initiatives

Jackson 2004- letter with guidelines, visit, additional material - 272 guidelines mailed and 162 GPs visited Educational program significantly improved the prescribing of Warfarin for stroke prevention in AF; reduction in incidence and costs related to stroke in patients with AF if implemented

Mandryk 2008 NPS Intervention active (voluntary); passive (mail outs). The use of Warfarin is steadily increasing and neither this NPS intervention (non significant regression intervention effect, p= 0.1002) nor Beach data are suggestive of NPS impact on W

Newall 2008 – Parents of children with congenital heart disease - requiring Warfarin invited to participate in educational program (which also incorporated a pilot study of home monitoring for W. Parents demonstrated a statistically significant improvement in Warfarin knowledge immediately following completion of the program ($p<0.0001$), with the improvement being sustained over time.

Table 14: Interventions - Optimising prescribing of AT Therapy

First author	Year	Setting	Age	Patients n	AF Pts n	Response %	Intervention	Intervention Outcome - Use of AT
Bajorek	2012	Sydney teaching hospital	all 65+, mean 79.8±7.8	201	201	69%	Retrospective. "Time" - 2 audits on use of A-T and comparing presribing against TAG guidelines.	W ± AP's increased 34.5% to 46.3% (P<0.01); prop eligible & receiving W increased 39.0% to 55.5% (P<0.01). A-T 85% audit 2 vs 79.2% audit 1. Pts 80 yrs less likely to receive W compared to pts < 80 (40.2 vs 52.5), p = 0.1.
Bajorek	2005	Sydney teaching hospital and community setting	all 65+, mean 85.2	218	218	99.10%	Before/After Study. Pharmacist led multidisciplinary intervention to optimise A-T prescribing using evidence based algorithm (stroke risk vs contradictions) elderly at risk pts + design/implementation of review process by dedicated project pharmacist.	Significant increase in AT use (59.6% vs 81.2%, p < 0.001). Fewer patients received W post-intervention (20.7% versus 17.4%, P=0.39). Overall less pts experienced strokes. Slightly more (minor) bleeding compared to non AC therapies.
Elliott	2002	6 Aged Care and three General Medicine units (9 hospitals)	65 + (median age 81)	1146	Audit 1-112, Audit 2-105	n/a	Multifaceted intervention centred around feedback of audit results at multidisciplinary staff meetings - older pts. Cross sectional notes based audit, before and after feedback.	AT prescribing increased from 81/112 (72% immediately prior to feedback to 97/105 (92%) 4-8 weeks later (p=0.0001).6 mths after feedback, AT prescribing declined slightly, to 85% (p=0.36). Increased A prescribing accounted for most improvement in AT use while W continued to be underutilised. At 6 mths - audit 3 AT prescribing slightly declined towards base line, but was not statistically significant.
Jackson	2011	Hospital	Mean age 79	134	134	20.5%	Prospective risk assessment.Formal stroke risk assessment from a pharmacist. The pts' risk of stroke was assessed/documented according to Australian guidelines and a recommendation regarding AT was made on a specially designed stroke assessment form.	High risk of stroke (with no contradiction) - 98% were receiving W on discharge compared to 74% on admission (p < 0.001). 50 (37%) assessments recommended a change in therapy, where 44 (88%) resulted in change in AC compared to admission therapy. 30 (68%) assessments resulted in upgrade to more effective treatment - for example from no therapy to any agent from aspirin to W.
Jackson	2004	Controlled before-after study using a historical cohort	median age 75	patients: 245 pre and 157 post	patients: 245 pre and 157 post	=60% of GPs visited. 76% completed survey	Educational intervention: letter with guidelines, visit, additional material - 272 guidelines mailed and 162 GPs visited	Intervention area: overall pre-intervention 33% on warfarin at admission, post-intervention 43% (P=0.05); up to 25% in subgroups (demographic/clinical characteristics pre/post the same). Control area: also increase, but less than in intervention area (p<0.001). Educational program significantly improved prescribing of Warfarin in prevention of stroke in AF.

Table 15: Interventions - Management of AT

First author	Year	Setting	Type of participants	Pts/HCW's n	Patients n	AF Pts n	Response %	Intervention	Intervention Outcome
Gattellari	2011	Primary care- GP practices	Pts with NV AF > 65	Not published yet	Not published yet	Not published yet	Not published yet	Cluster randomised controlled trial with concealed allocation and blinded outcome. Educational intervention (DESPATCH) tailored to the self identified needs of Australian GPs, recognising their high perceived risk of AC use- designed to improve uptake of AC (with expert decisional support from clinical experts in stroke medicine).Multifaceted.	Not reported - study results not yet published
Jackson	2004	15 rural medical practices - 19 staff	Anticoagulated patients (validating device); practice staff (evaluation device)	n/a	169 patients (401 paired samples)	N/R	N/R	Survey. Diagnostic intervention: portable INR monitor (CoaguChek S) - near pt testing	High correlation (r=0.89) between measurements; 88% of dual INR measurements were within 0.5 INR units of each other; monitor more likely to underestimate the INR value, particularly at values > 3.5. GPs generally confident in accuracy of monitor. Pts preferred near testing.
Mandryk	2008	Primary care	GP's	NR	n/a	n/a	N/R	Multiple educational NPS Intervention active (voluntary); passive (mail outs). NPS intervention promoted Warfarin in NVAF pts at risk of stroke.	Intervention - modest success. Authors stated that the use of W is steadily increasing and neither this NPS intervention (non significant regression intervention effect, p= 0.1002) nor Beach data are suggestive of NPS impact on W. The SAND report also supports a significant rise in W prescribing of W by GP's, but because these data come from 2 cross sectional surveys , it is impossible to attribute any of the rise to the NPS intervention.
Newall	2008	Paediatric Hospital	Parents of children with congenital heart disease - required W	14	n/a	n/a	16.28%	Validated educational intervention for parents (which also incorporated a pilot study of home monitoring for W).	Parents demonstrated a statistically significant improvement in W knowledge immediately following completion of the program ($p<0.0001$), with the improvement being sustained over time.
Wolff	2008	Rural hospital and rural general practices	Pts. Mean age - 72 yrs, with 25% over 78 yrs	227	227	AF - 125 (55%)	n/a	Multifaceted intervention. Anticoagulation clinic (with specially trained personnel), point of care INR testing in remote centres, development of A-C protocols for GP use, comprehensive pt education program over 3 yrs	Time in the therapeutic range was 69% for the standard range (2.0 -3.0) and 81% in the expanded range 91.8-3.0). The A-C related complication rate was 0.03 per pt year (95% CI:0.01,0.08). INR testing every 14 days resulted in 78% of time spent in therapeutic range.

In Summary: medicine is entering an exciting phase of development and for selected patients this will result in greater empowerment in the area of self care. Selected patients on Warfarin for stroke prevention will have access to newer technologies such as Point of Care devices and Patient Tracking Systems enabling them to self monitor at a frequency that would maintain variability of their INR levels at a minimum whilst also remaining cost effective to the public purse. Patients with less capability will also benefit from reforms in technology such as POC devices and risk calculators for GPs and other healthcare practitioners involved in the community monitoring of these patients.

Overall Conclusion to Section 2

An objective wide spread review of the biomedical literature, local adverse reporting information and outcomes from the pivotal trials on the new ACs did not confirm Warfarin's reputation as a burdensome treatment for stroke prevention. On the contrary, discontinuation rates in comparative trials, patient reluctance/refusal rates from well conducted social studies and low safety signal in the community are all suggestive of a well tolerated and accepted medicine. Warfarin's long, effective half-life of approximately 40 hours, may work to the providers' advantage in a non adherent patient, Therefore, a degree of non adherence may have a negligible effect on anticoagulation levels, compared with an anticoagulant with a short half-life. With the use of a non monitored drug, such determinations cannot be made. Other potential disadvantages include dosing adjustment for renal and/or hepatic dysfunction. The absence of an antidote may be problematic for patients who are at a high risk of bleeding or for those who present with a bleed. This may not be as important a problem as some suggest, as rapid reversal of Warfarin is not simple and requires infusions of fresh frozen plasma or factor concentrates, the latter of which have been shown to be able to reverse anticoagulation with several of the new agents. Specific antidotes are also being developed for factor Xa inhibitors. Other potential disadvantages include dosing adjustment for renal and/or hepatic dysfunction.

The new AC agents derive their advantages over Warfarin when Warfarin is used sub-optimally. In the Australian setting the under-utilisation and sub-utilisation of cost effective treatments such as Warfarin remains a substantial obstacle to the translation of trial efficacy outcomes into practice and improving the quality of health care. Barriers to optimal management of patients with NVAF include patient medical characteristics, patient capabilities, patient preference and healthcare barriers. Reform through the address of these barriers through for example, better risk assessment profiling (of psychosocial and stroke risk status), new testing technologies and patient tracking systems and educational initiatives is expected to reduce the burden on both patients and on their care providers, increase the time patients spend in the INR therapeutic range and improve monitoring of the health status of these elderly patients.

Aspen has since acquisition of Warfarin revamped the Warfarin books and made them more freely available having distributed more than 80,000 books since June 2011.

Aspen is prepared to assist in the development of guidelines to help define a treatment regime reserving the newer treatments for those patients in whom Warfarin is contraindicated or who may be unable to maintain a steady INR in the 2.0 to 3.0 range for significant periods.

Aspen has already reminded doctors of the benefits of Warfarin through mailings which has led to an increase in uptake. We believe awareness alone will increase diagnosis and treatment of AF significantly, and this may double the estimated cost of the newer agents in patients for whom Warfarin will be an effective treatment.

Finally, Warfarin is available as a generic medication and is relatively inexpensive. $14.03 for 5mg x 50 tabs dispensed price and given the average dose is below this (4.5mg quoted above) is $8.42 per 30 day period. The cost of an INR assessment through a pathology lab from $23.47 which may be incurred between twice a month and once every 2 months and newer self care options may reduce this further. New agents will be significantly more expensive and third-party payers may require prior approval based on prespecified criteria. Patients who are unable to afford their medications may sometimes not take them, or skip days to extend the supply, as recently shown in a physician survey indicating that many patients were not filling their prescriptions or were skipping their pills due to financial stresses.

Submission Conclusion and Recommendations

We trust that this Review of Anticoagulation Therapies in Atrial Fibrillation called by the Minister of Health will provide an opportunity of looking at the management of AF from a broader perspective and provide a more "balanced outcome" where Warfarin may continue to play a leading role in the treatment of NVAF and importantly ensure that it is not inappropriately marginalised at an unwarranted cost to the public purse.

In summary, we conclude that his submission provides following points in support of the above viewpoint:

- Warfarin is an effective agent in the prevention of AF sequelae and seems to have a lower incidence of MI, PE & GI bleeding than the newer agents may have.
- Warfarin is a well tolerated anticoagulant and is as well tolerated as the newer agents.
- Warfarin is very cost effective based on outcomes, the cost of the medicine, the cost of the INR testing and when all potential costs contributing to the economic analyses of increased MI, PI, GI bleeding etc have been considered with newer agents.
- Warfarin's cost effectiveness increases when used optimally, the new agents deriving their advantages over Warfarin when Warfarin is used sub-optimally i.e. outside standard 2.0 to 3.0 INR range
- Increased Warfarin education and educational materials will increase intention to use, compliance and improve therapeutic outcomes.

- Switching all 125,000 patients on Warfarin with AF to the newer agents is unwarranted and presents a very large incremental cost to public health estimated to be in the vicinity of $1B over 5 years.

- Treating all untreated (diagnosed and undiagnosed) patients with the newer agents is unwarranted and further increases the above estimates up to a doubling of this incremental cost.

In the Australian setting the under-utilisation and sub-utilisation of cost effective treatments such as Warfarin remains a substantial obstacle to the translation of trial efficacy outcomes into practice and improving the quality of health care. With the advent of new generation anticoagulants and identified opportunities to improve patient treatment management practices (including the use of available new technologies) and with clinical practice experience growing around the use these interventions, we believe informed medical practice requires the development of guidelines in this market area.

Aspen is therefore very willing to assist in the development of guidelines to help define a treatment regime reserving the newer treatments for those patients in whom Warfarin is contraindicated or who may be unable to maintain a steady INR in the 2.0 to 3.0 range for significant periods.

Aspen believes that with the appropriate government assistance there are important initiatives where generic manufacturers can provide educational support to doctors and the patient community (including interactive phone based support) to assist in the proper and effective use of critical care medicines such as AC therapy. Aspen would welcome such developments which are clearly called for based on the evidence brought to light in this submission.

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Bajorek, B. V., I. Krass, et al. (2005). "Optimizing the use of antithrombotic therapy for atrial fibrillation in older people: a pharmacist-led multidisciplinary intervention." J Am Geriatr Soc **53**(11): 1912-1920.

OBJECTIVES: To develop, implement, and evaluate a pharmacist-led multidisciplinary intervention in a hospital setting that would optimize antithrombotic use in elderly atrial fibrillation patients. The hypothesis that there would be an increase in the proportion of patients receiving antithrombotic therapy at discharge was tested. DESIGN: Evidence-based algorithms were developed to define the criteria (stroke risk vs contraindications) by which an elderly patient's requirement for antithrombotic therapy was assessed. SETTING: A major Sydney teaching hospital. PARTICIPANTS: Two hundred eighteen consecutively admitted elderly patients (mean age 85.2) were recruited over a 6-month period. INTERVENTION: A pharmacist-coordinated multidisciplinary review process was implemented to coordinate risk assessments and subsequently recommend appropriate antithrombotic therapy, as per the algorithms. MEASUREMENTS: The proportion of patients receiving antithrombotic therapy was assessed on admission (preintervention), at discharge (postintervention), and postdischarge (follow-up at 3 and 6 months). RESULTS: As a result of the intervention, 78 patients (35.8%) required changes to their existing antithrombotic therapy. Of these changes, 60 (76.9%) were "upgrades" to more-effective treatment options (e.g., from no therapy to any agent or from aspirin to warfarin). The remaining 18 (23.1%) changes were "downgrades" to less-effective, albeit safer, options. Despite a significant increase in anti thrombotic use overall (59.6% vs 81.2%, P<.001), fewer patients received warfarin postintervention, after having been assessed as inappropriate candidates (20.7% vs 17.4%, P=.39). CONCLUSION: A pharmacist-led multidisciplinary process was successfully developed and implemented within the hospital setting to increase overall antithrombotic use. Having addressed some of the known barriers and limitations to warfarin use, these algorithms may allow allied health workers, patients, and clinicians to work collaboratively to achieve optimal and, importantly, appropriate (i.e., safe and effective) antithrombotic use in at-risk elderly patients.

Bajorek, B. V., S. J. Ogle, et al. (2007). "Management of warfarin in atrial fibrillation: views of health professionals, older patients and their carers." Med J Aust **186**(4): 175-180.

OBJECTIVE: To identify the views of health professionals, patients and their carers on strategies to improve the use and management of warfarin in older patients with atrial fibrillation. DESIGN: Qualitative study based on analysis of group interviews. SETTING: A major metropolitan teaching hospital, from 1 March to 30 April 2003. PARTICIPANTS: 14 patients (>/= 65 years) with established atrial fibrillation and taking warfarin, three carers, 12 specialists, eight general practitioners, six community pharmacists, nine hospital pharmacists, and 11 nurses volunteered in response to flyers promoting the study. RESULTS: Suggested strategies to improve warfarin management targeted support services for GPs and patients. Hospital-based clinicians felt that dissemination of trial evidence to GPs to support treatment recommendations is required, and that GPs need to enlist allied health professionals in the management of patients taking warfarin. GPs preferred access to practical advice from expert colleagues on the day-to-day management. Patients requested more information about warfarin therapy, as access to information is inadequate, particularly from primary sources (GPs, community pharmacists). Verbal and written information are equally important, but a single counselling session or supply of a booklet was viewed as inadequate. Participants identified various interventions for all levels of warfarin management; from the collective input, a framework for management strategies was developed. CONCLUSIONS: Health professionals and patients require more customised information to support warfarin use and

management.

Bajorek, B. V. and S. Ren (2012). "Utilisation of antithrombotic therapy for stroke prevention in atrial fibrillation in a Sydney hospital: then and now." Int J Clin Pharm **34**(1): 88-97.

Objective Evidence from pivotal clinical trials conducted more than a decade ago supports the use of antithrombotic therapy, particularly warfarin, for stroke prevention in atrial fibrillation (AF). Despite the wide dissemination of this evidence since that time, there is anecdotal evidence that utilisation of therapy remains suboptimal, especially in the target elderly population, which is reflected in the development of practice tools such as the TAG Clinical Indicator ('Antithrombotics in AF' Indicator 1.6, 2007). Therefore, the objective of this study was to determine the current utilisation of antithrombotic therapy for elderly patients with AF in the local setting, and to compare this utilisation with the results of a prior audit (AUDIT 1), as well as against the recommendations of the TAG Clinical Indicator (TAG IND). Setting A major teaching hospital in Sydney, Australia. Method A retrospective audit (AUDIT 2) of medical records of hospital inpatients (aged 65 years, with a significant diagnosis of AF), pertaining to admissions over the 12-month period 1st June 2006-31st May 2007, was conducted. Main outcome measure Proportion of patients receiving antithrombotic therapy at the point of discharge from hospital. Results A total of 201 patients (mean age 79.8 +/- 7.8 years) were reviewed in AUDIT 2. Most (85%) patients received antithrombotic therapy (vs. 79.2%, AUDIT 1), with "warfarin +/- antiplatelets" most frequently (46.3%) used (vs. 34.5%, AUDIT 1), followed by "aspirin +/- other antiplatelet" (33.3% AUDIT 2 vs. 43.1% AUDIT 1). Patients aged 80 years were significantly less likely to receive warfarin therapy, compared to those <80 years (40.2% vs. 52.5%, P = 0.01). Of those patients who were deemed 'eligible' for warfarin according to AUDIT 2 (n = 155), only 55.0% of patients were actually prescribed this treatment. Results obtained by AUDIT 2 and TAG IND were overall comparable. Conclusion Whilst there have been temporal improvements in the overall utilisation of antithrombotic therapy, including warfarin, there are still significant gaps in the translation of evidence from clinical trials to clinical practice. Further sustainable intervention is warranted to help apply treatment recommendations to the target population.

Castelino, R. L., T. F. Chen, et al. (2010). "Use of evidence-based therapy for the prevention of cardiovascular events among older people." Eval Health Prof **33**(3): 276-301.

Evidence-based therapies (EBTs) for the prevention of cardiovascular disease (CVD) are reportedly underutilized in older people. The primary purpose of this study was to evaluate the use of EBTs for the prevention of CVD events in older people and secondarily whether a Home Medicines Review (HMR) service by pharmacists' predicts the use of these medicines. A retrospective cross-sectional audit of HMR reports pertaining to 608 community-dwelling older people (>or=65 years) was conducted. EBTs considered for this audit included four guideline-recommended therapies for CVD: antithrombotic therapy (warfarin +/- antiplatelet therapy), beta-blockers, statins, and angiotensin agents (angiotensin-converting enzyme inhibitors [ACEI] +/- angiotensin II receptor blockers [ARBs]). The prevalence of EBT use among the older people, mean age (SD) 75.6 (7.5) years, was: 73% for antithrombotic therapy, 75% for statins, 74% for angiotensin therapy, and 35% for beta-blockers. CVD risk factors warranting treatment with these EBTs were frequently associated with use of EBTs. EBTs were least likely to be used in those with coronary interventions like coronary artery bypass grafting (CABG)/stent insertion (all EBTs except angiotensin agents) and angiotensin agents in those with a history of myocardial infarction or chronic heart failure. A pharmacist-led HMR service was significantly associated with the prescribing of all 4 EBTs. The results from this study show good adherence to evidence-based guidelines in general, although there is still room for improvement to further optimize clinical outcomes in these complex patients. The study also adds to the available literature on the effectiveness of pharmacists' collaborative contribution to the care of these high-risk patients.

Comino, N. J. (2005). "Automatic Drug Use Audit in Primary Care." Australian Family Physician **34**(9): 798-800.

Connolly, S. J., M. D. Ezekowitz, et al. (2009). "Dabigatran versus warfarin in patients with atrial fibrillation." N Engl J Med **361**(12): 1139-1151.

BACKGROUND: Warfarin reduces the risk of stroke in patients with atrial fibrillation but increases the risk of hemorrhage and is difficult to use. Dabigatran is a new oral direct thrombin inhibitor. METHODS: In this noninferiority trial, we randomly assigned 18,113 patients who had atrial fibrillation and a risk of stroke to receive, in a blinded fashion, fixed doses of dabigatran--110 mg or 150 mg twice daily--or, in an unblinded fashion, adjusted-dose warfarin. The median duration of the follow-up period was 2.0 years. The primary outcome was stroke or systemic embolism. RESULTS: Rates of the primary outcome were 1.69% per year in the warfarin group, as compared with 1.53% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.91; 95% confidence interval [CI], 0.74 to 1.11; P<0.001 for noninferiority) and 1.11% per year in the group that received 150 mg of dabigatran (relative risk, 0.66; 95% CI, 0.53 to 0.82; P<0.001 for superiority). The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group receiving 110 mg of dabigatran (P=0.003) and 3.11% per year in the group receiving 150 mg of dabigatran (P=0.31). The rate of hemorrhagic stroke was 0.38% per year in the warfarin group, as compared with 0.12% per year with 110 mg of dabigatran (P<0.001) and 0.10% per year with 150 mg of dabigatran (P<0.001). The mortality rate was 4.13% per year in the warfarin group, as compared with 3.75% per year with 110 mg of dabigatran (P=0.13) and 3.64% per year with 150 mg of dabigatran (P=0.051). CONCLUSIONS: In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. (ClinicalTrials.gov number, NCT00262600.)

Connolly, S. J. (2010). "Newly Identified Events in the RE-LY Trial." New England Journal of Medicine **363**(19).

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Diug, B., S. Evans, et al. (2011). "The unrecognized psychosocial factors contributing to bleeding risk in warfarin therapy." Stroke **42**(10): 2866-2871.

BACKGROUND AND PURPOSE: Warfarin is an effective drug for the prevention of thromboembolism in the elderly. The major risk for patients taking warfarin is bleeding. We aimed to assess the impact of psychosocial factors, including mood, cognition, social isolation, and health literacy on warfarin instability among community-based elderly patients. METHODS: A case-control study was conducted between March 2008 and June 2009 in a community-based setting. Cases were patients previously stabilized on warfarin who recorded an international normalized ratio>/=6.0. Control subjects were patients whose international normalized ratio measurement was maintained within the therapeutic range. Patient interviews investigated potential predisposing factors to elevated International Normalized Ratio levels. RESULTS: A total of 486 patients were interviewed: 157 cases and 329 control subjects, with an approximate mean age of 75 years. Atrial fibrillation was the most common primary indication. Adjusted multivariate logistic regression revealed impaired cognition (OR, 1.9; 95% CI, 1.0 to 3.6), depressed mood (OR, 2.2; 95% CI, 1.2 to 3.9), and inadequate health literacy (OR, 4.0;95% CI, 2.1 to 7.4) were associated with increased risk of an elevated International Normalized Ratio. CONCLUSIONS: This study identified impaired cognition, depressed mood, and inadequate health literacy as risk factors for warfarin instability. These had a similar impact to well-recognized demographic, clinical, and medication-related factors and are prevalent among the elderly. These findings suggest that elderly patients prescribed warfarin should be reviewed regularly for psychosocial deficits.

Duffy, B. K., P. A. Phillips, et al. (2003). "Evidence-based care and outcomes of acute stroke managed in hospital specialty units." Med J Aust **178**(7): 318-323.

OBJECTIVES: To assess the use of evidence-based investigations and treatments in patients with acute stroke in selected Australian hospitals and to compare management and outcomes between stroke and other types of hospital specialty unit. DESIGN: Retrospective, multicentre audit of hospital case files. SETTING: Eight metropolitan tertiary-care hospitals from five Australian States. SUBJECTS: 300 consecutive patients from each hospital admitted between 17 September 1999 and 23 May 2001 and having a discharge diagnosis of stroke or transient ischaemic attack. MAIN OUTCOME MEASURES: Use of investigations and treatments supported by best available evidence; comparison of management and outcomes between stroke, neurology, general medical and geriatric units. RESULTS: 2383 patients were audited (median age, 72.7 years; 52% men); 72% had ischaemic events, and 28% haemorrhagic events. Use of investigations and treatments varied between hospitals and types of unit. Stroke units or teams cared directly for 23% of patients (range across hospitals, 0-100%). Although 47% of patients with ischaemic events presented within 3 hours of symptom onset (when thrombolysis might provide benefit), only nine (2%) received thrombolysis. Angiotensin-converting enzyme (ACE) inhibitors were given to 28% of survivors at discharge (range, 14%-38%). Stroke units were more likely to use diagnostic tests, while neurology units were more likely to prescribe heparin acutely for patients with ischaemic stroke (not recommended for patients in general), and geriatric units were less likely to discharge patients with atrial fibrillation on anticoagulation therapy. Outcomes also varied significantly between types of unit. In-hospital survival rates were 90% (stroke units), 91% (neurological units), 82% (general medical units) and 79% (geriatric units) ($P < 0.001$). Stroke units and neurological units sent more patients home than the other units. Stroke units also sent fewer patients to rehabilitation and had longer mean length of stay. CONCLUSIONS: Acute stroke care varies between Australian tertiary-care hospitals and types of specialty unit, with suboptimal use of many evidence-based interventions.

Elliott, R. A., M. C. Woodward, et al. (2002). "Antithrombotic prescribing in atrial fibrillation: application of a prescribing indicator and multidisciplinary feedback to improve prescribing." Age and Ageing **31**(5): 391-396.

BACKGROUND: Atrial fibrillation is common in older people, and is associated with an increased risk of ischaemic stroke. Antithrombotic therapy reduces stroke-risk, but is known to be under-prescribed. OBJECTIVES: To use an evidence-based indicator to audit antithrombotic prescribing for older hospital inpatients with atrial fibrillation, and to assess whether feedback of audit results to hospital staff increases antithrombotic use. DESIGN: Cross-sectional notes-based audits, before and after feedback. SETTING: Six Aged Care and three General Medicine units at nine Australian public teaching hospitals between September 1998 and May 1999. SUBJECTS: 1416 hospital inpatients aged 65 years and over (median age 81). METHODS: Medication charts were reviewed to identify patients prescribed digoxin or amiodarone. Presence of atrial fibrillation was confirmed by review of the patients' medical notes. To be considered appropriate, patients with atrial fibrillation had to be receiving either warfarin or aspirin (or both), or have documented contraindications to both agents. Feedback of audit results was provided to medical, pharmacy and nursing staff at multidisciplinary meetings. Changes in antithrombotic prescribing 4-8 weeks and 6 months after feedback were assessed. Prescribing 8 weeks prior to feedback was assessed retrospectively. RESULTS: Appropriateness of the decision to prescribe (or not prescribe) antithrombotic therapy increased from 81/112 (72%) immediately prior to feedback to 97/105 (92%) 4-8 weeks later ($P<0.0001$). Six months after feedback, appropriateness of prescribing declined slightly, to 85% ($p=0.36$). Over the 8 weeks prior to feedback, appropriateness of prescribing did not change (74% versus 77%, $p=0.80$). Increased aspirin prescribing accounted for most of the improvement in antithrombotic use after feedback, while warfarin continued to be under-used. CONCLUSIONS: Antithrombotics were under-prescribed for older patients with atrial fibrillation. Audit and multidisciplinary feedback resulted in increased antithrombotic prescribing. The intervention had a greater impact on aspirin prescribing compared with warfarin.

Enis J et al (1997). "Stroke prevention in patients with non-valvular atrial fibrillation: a current community perspective." J Clin Neuroscience **4**(3): 320-321.

Fahridin S et al(2007). "Atrial fibrillation in Australian general practice." Australian family Physician **36**(7): 490-491.

Gattellari, M., D. Y. Leung, et al. (2011). "Study protocol: the DESPATCH study: Delivering stroke prevention for patients with atrial fibrillation - a cluster randomised controlled trial in primary healthcare." Implement Sci **6**: 48.

BACKGROUND: Compelling evidence shows that appropriate use of anticoagulation in patients with nonvalvular atrial fibrillation reduces the risk of ischaemic stroke by 67% and all-cause mortality by 26%. Despite this evidence, anticoagulation is substantially underused, resulting in avoidable fatal and disabling strokes. METHODS: DESPATCH is a cluster randomised controlled trial with concealed allocation and blinded outcome assessment designed to evaluate a multifaceted and tailored implementation strategy for improving the uptake of anticoagulation in primary care. We have recruited general practices in South Western Sydney, Australia, and randomly allocated practices to receive the DESPATCH intervention or evidence-based guidelines (control). The intervention comprises specialist decisional support via written feedback about patient-specific cases, three academic detailing sessions (delivered via telephone), practice resources, and evidence-based information. Data for outcome assessment will be obtained from a blinded, independent medical record audit. Our primary endpoint is the proportion of nonvalvular atrial fibrillation patients, over 65 years of age, receiving oral anticoagulation at any time during the 12-month posttest period. DISCUSSION: Successful translation of evidence into clinical practice can reduce avoidable stroke, death, and disability due to nonvalvular atrial fibrillation. If successful, DESPATCH will inform public policy, providing quality evidence for an effective implementation strategy to improve management of nonvalvular atrial fibrillation, to close an important evidence-practice gap. TRIAL REGISTRATION: Australia and New Zealand Clinical Trials Register (ANZCTR): ACTRN12608000074392.

Gattellari, M., J. Worthington, et al. (2008). "Barriers to the use of anticoagulation for nonvalvular atrial fibrillation: a representative survey of Australian family physicians." Stroke **39**(1): 227-230.

BACKGROUND AND PURPOSE: Anticoagulation reduces the risk of stroke in nonvalvular atrial fibrillation yet remains underused. We explored barriers to the use of anticoagulants among Australian family physicians. METHODS: The authors conducted a representative, national survey. RESULTS: Of the 596 (64.4%) eligible family physicians who participated, 15.8% reported having a patient with nonvalvular atrial fibrillation experience an intracranial hemorrhage with anticoagulation and 45.8% had a patient with known nonvalvular atrial fibrillation experience a stroke without anticoagulation. When presented with a patient at "very high risk" of stroke, only 45.6% of family physicians selected warfarin in the presence of a minor falls risk and 17.1% would anticoagulate if the patient had a treated peptic ulcer. Family physicians with less decisional conflict and longer-standing practices were more likely to endorse anticoagulation. CONCLUSIONS: Strategies to optimize the management of nonvalvular atrial fibrillation should address psychological barriers to using anticoagulation.

Gattellari, M., J. M. Worthington, et al. (2008). "The management of non-valvular atrial fibrillation (NVAF) in Australian general practice: bridging the evidence-practice gap. A national, representative postal survey." BMC Fam Pract **9**: 62.

BACKGROUND: General practitioners (GPs) are ideally placed to bridge the widely noted evidence-practice gap between current management of NVAF and the need to increase anticoagulant use to reduce the risk of fatal and disabling stroke in NVAF. We aimed to identify gaps in current care, and asked GPs to identify potentially useful strategies to overcome barriers to best practice. METHODS: We obtained contact details for a random sample of 1000 GPs from a national commercial data-base. Randomly selected GPs were mailed a questionnaire after an advance letter. Standardised reminders were administered to enhance response rates. As part of a larger survey assessing GP management of NVAF, we included questions to explore GPs' risk assessment, estimates of stroke

risk and GPs' perceptions of the risks and benefits of anticoagulation with warfarin. In addition, we explored GPs' perceived barriers to the wider uptake of anticoagulation, quality control of anticoagulation and their assessment of strategies to assist in managing NVAF. RESULTS: 596 out of 924 eligible GPs responded (64.4% response rate). The majority of GPs recognised that the benefits of warfarin outweighed the risks for three case scenarios in which warfarin is recommended according to Australian guidelines. In response to a hypothetical case scenario describing a patient with a supratherapeutic INR level of 5, 41.4% of the 596 GPs (n = 247) and 22.0% (n = 131) would be "highly likely" or "likely", respectively, to cease warfarin therapy and resume at a lower dose when INR levels are within therapeutic range. Only 27.9% (n = 166/596) would reassess the patient's INR levels within one day of recording the supratherapeutic INR. Patient contraindications to warfarin was reported to "usually" or "always" apply to the patients of 40.6% (n = 242/596) of GPs when considering whether or not to prescribe warfarin. Patient refusal to take warfarin "usually" or "always" applied to the patients of 22.3% (n = 133/596) of GPs. When asked to indicate the usefulness of strategies to assist in managing NVAF, the majority of GPs (89.1%, n = 531/596) reported that they would find patient educational resources outlining the benefits and risks of available treatments "quite useful" or "very useful". Just under two-thirds (65.2%; n = 389/596) reported that they would find point of care INR testing "quite" or "very" useful. An outreach specialist service and training to enable GPs to practice stroke medicine as a special interest were also considered to be "quite" or "very useful" by 61.9% (n = 369/596) GPs. CONCLUSION: This survey identified gaps, based on GP self-report, in the current care of NVAF. GPs themselves have provided guidance on the selection of implementation strategies to bridge these gaps. These results may inform future initiatives designed to reduce the risk of fatal and disabling stroke in NVAF.

Granger, C. B. (2011). "Apixaban versus Warfarin in Patients with Atrial Fibrillation." The new england journal of medicine **365**(11): 981-992.

Hankey, G. J. (2000). "Transient ischaemic attacks and stroke." Med J Aust **172**(8): 394-400.
Stroke is the third most common cause of death and a major cause of disability in Australia. Effective prevention is the most powerful strategy for reducing the burden of stroke. Major modifiable causal risk factors for stroke include hypertension, cigarette smoking, diabetes, atrial fibrillation, and carotid stenosis. Atrial fibrillation, in particular, is under-treated in the community; almost all patients should be prescribed warfarin or aspirin, depending on their absolute risk of stroke and risk of bleeding complications. Patients with suspected acute stroke should be referred immediately to a specialist stroke unit for urgent assessment and care by an interested, organised, multidisciplinary team of stroke experts. They should undergo immediate computed tomography brain scan and, if intracranial haemorrhage is excluded, be given aspirin (160-300 mg). Rehabilitation and secondary prevention of recurrent stroke should begin on day one after stroke.

Heeley E, H. (2010). "Cardiovascular risk perception and evidence–practice gaps in Australian general practice (the AusHEART study)." MJA **192**: 254-259.

Jackson, S. L. and G. M. Peterson (2011). "Stroke risk assessment for atrial fibrillation: hospital-based stroke risk assessment and intervention program." J Clin Pharm Ther **36**(1): 71-79.
BACKGROUND: Despite the proven effectiveness of antithrombotic therapy for atrial fibrillation (AF), the treatment remains suboptimal. The aim of this study was to implement and evaluate a system to improve the appropriate use of antithrombotics for stroke prevention in AF utilizing a clinical pharmacist as a stroke risk assessor. METHOD: Hospital in-patients with AF were prospectively identified and they received a formal stroke risk assessment from a pharmacist. The patients' risk of stroke was assessed and documented according to Australian guidelines and a recommendation regarding antithrombotic therapy was made to the medical team on a specially designed stroke risk assessment form. RESULTS: One hundred and thirty-four stroke risk assessments were performed during the intervention period. For those patients at high risk of stroke and with no contraindication present (warfarin-eligible patients), 98% were receiving warfarin on discharge from hospital compared to 74% on admission (P < 0.001). Of the 50 (37%)

assessments that recommended a change of therapy, 44 (88%) resulted in a change in the patient's current antithrombotic therapy compared to their admission therapy. Thirty (68%) of the assessments resulted in an 'upgrade' to more-effective treatment options for example from no therapy to any agent or from aspirin to warfarin. DISCUSSION AND CONCLUSION: The pharmacist-led stroke risk assessment program resulted in a significant increase in the proportion of patients receiving appropriate thromboprophylaxis for stroke prevention in AF. The methods used in this study should be evaluated in a larger trial, in multiple hospitals, with different pharmacists performing the intervention.

Jackson, S. L., G. M. Peterson, et al. (2004). "A community-based educational intervention to improve antithrombotic drug use in atrial fibrillation." Ann Pharmacother **38**(11): 1794-1799.

BACKGROUND: Despite evidence that antithrombotics are effective in reducing the risk of stroke in atrial fibrillation (AF), they remain underused. OBJECTIVE: To perform a controlled trial of a comprehensive educational program promoting the rational prescribing of antithrombotics for stroke prevention in AF. METHODS: The intervention was conducted in Southern Tasmania, Australia, using Northern Tasmania as a control area. General practitioners were sent locally produced guidelines on stroke risk stratification and antithrombotic drug use in AF, which were followed by academic detailing visits. Outcomes were measured using evaluation feedback from the general practitioners, and drug utilization data were provided by a series of patients presenting to the hospital with an admission diagnosis of AF and dispensing of antithrombotic therapy under the Australian Pharmaceutical Benefits Scheme. RESULTS: During the educational intervention, 272 guidelines were mailed and, subsequently, 162 general practitioners were visited and the guidelines discussed. Hospital admission data before and after the intervention revealed a significant increase in the use of warfarin in patients at high risk of stroke (33% vs 46% of eligible patients; $p < 0.05$). Analysis of prescription data for warfarin also indicated that the increase in use of warfarin within the intervention region was significantly greater than for the control region ($p < 0.001$). CONCLUSIONS: The educational program described here led to a significant increase in the prescribing of warfarin for stroke prevention in patients with AF.

Janice, C. (2010). "Atrial fibrillation Changes 2000 to 2009." Australian Family Physician **39**(7): 461-.

Lowthian, J. A., B. O. Diug, et al. (2009). "Who is responsible for the care of patients treated with warfarin therapy?" Med J Aust **190**(12): 674-677.

OBJECTIVE: To identify potential weaknesses in the system of managing warfarin therapy. DESIGN, PARTICIPANTS AND SETTING: A structured interview-based study of 40 community-dwelling patients taking warfarin and with an international normalised ratio > or = 6.0 and 36 of their treating doctors (35 general practitioners and 1 specialist), conducted between July and November 2007. Patients all received services from and were recruited sequentially by a large, private metropolitan pathology provider in Melbourne. MAIN OUTCOME MEASURES: Patients' demographic, clinical, cognitive and psychosocial characteristics, warfarin knowledge, medication complexity and adherence; and doctors' experience with, approach to and involvement in warfarin management, and their perception of responsibility for warfarin management and patient education. RESULTS: Interviews revealed multiple difficulties, including cognitive dysfunction, possible depression, and medication non-adherence, in 30 of 40 patients. Of 36 doctors interviewed, 12 were unaware of these difficulties in their patients. Five doctors considered they had sole responsibility for their patients' anticoagulation, while 15 confirmed a mutual relationship with the pathology service, and 16 deferred total responsibility to the pathology provider. Only 14/36 doctors reported conducting patient education at commencement of warfarin therapy, with the other 22 stating this was the responsibility of the initiating specialist, pathology service or dispensing pharmacist. CONCLUSIONS: There is a need for improved role clarification in coordinating warfarin management. We propose exploring the possibility of a Warfarin Suitability Score to assist better recognition of patients in whom treatment may be problematic, along with a model of care using practice nurses with GPs to facilitate optimal patient care.

Mandryk (2008). "Evaluating the impact of educational interventions
on use of antithrombotics in Australia." pharmacoepidemiology and drug safety **17**: 160-171.

Newall, F., L. Johnston, et al. (2008). "Optimising anticoagulant education in the paediatric setting using a validated model of education." Patient Educ Couns **73**(2): 384-388.

OBJECTIVE: Providing education to patients requiring anticoagulant therapy may be associated with improved outcomes. This study investigated the knowledge outcomes of a validated educational intervention. METHODS: Parents of children with congenital heart disease requiring warfarin therapy took part in an educational intervention. Warfarin knowledge was assessed prior to commencing the program, immediately following its completion and 6 months following completion. RESULTS: Parents demonstrated a statistically significant improvement in their warfarin knowledge immediately following completion of the program ($p < 0.0001$), with this improvement being sustained over time. CONCLUSION: Current approaches to educating parents of children requiring warfarin therapy are likely suboptimal. Using a validated model of education may be associated with improved knowledge outcomes for patients. PRACTICE IMPLICATIONS: Consideration to the processes used in delivering patient education may result in improved patient knowledge outcomes.

Patel M et al (2011). "Rivaroxaban versus Warfarin in non-Valvular Atrial Fibrillation." New England Journal of Medicine **365**: 883-891.

Perera, V., B. V. Bajorek, et al. (2009). "The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation." Age Ageing **38**(2): 156-162.

OBJECTIVE: to investigate the impact of frailty on the utilisation of antithrombotics and on clinical outcomes in older people with atrial fibrillation (AF). DESIGN: prospective study of a cohort of 220 acute inpatients aged > or =70 years with AF, admitted to a teaching hospital in Sydney, Australia (April-July 2007), with 207 followed up over 6 months. RESULTS: a total of 140 patients (64%) were identified as frail using a validated tool. Frail patients were less likely to receive warfarin than non-frail on hospital admission ($P = 0.002$) and discharge ($P < 0.001$). During hospitalisation, the proportion of frail participants prescribed warfarin decreased by 10.7% and that of non-frail increased by 6.3%. Over the 6-month follow-up, 43 major or severe haemorrhages (20.8%), 20 cardioembolic strokes (9.7%) and 40 deaths (19.2%) were reported. Compared to non-frail, frail participants were significantly more likely to experience embolic stroke (RR 3.5, 95% CI 1.0-12.0, $P < 0.05$), had a small non-significant increase in risk of major haemorrhage (RR 1.5, 95% CI = 0.7-3.0, $P = 0.29$) and had greater mortality (RR 2.8, 95% CI 1.2-6.5, $P = 0.01$). CONCLUSION: frail older inpatients with AF are significantly less likely to receive warfarin than non-frail and appear more vulnerable to adverse clinical outcomes, with and without antithrombotic therapy.

Peterson, G. M., K. Boom, et al. (2002). "Doctors' beliefs on the use of antithrombotic therapy in atrial fibrillation: identifying barriers to stroke prevention." Intern Med J **32**(1-2): 15-23.

AIMS: To assess the attitudes of Australian doctors towards the use of antithrombotic drug therapy for stroke prevention in patients with non-valvular atrial fibrillation (AF), and investigate the barriers to prescribing warfarin. METHODS: A postal survey was undertaken among approximately 10% of all registered general practitioners (GPs), cardiologists and physicians in Australia. The anonymous questionnaire used case scenarios to assess doctors' knowledge of current guidelines for the therapeutic management of AF and sought opinions on potential barriers to the use of anticoagulation. RESULTS: Completed questionnaires were received from 711 doctors (30% response rate). The GPs performed better than the cardiologists and other specialists in estimating the risk of stroke in case scenarios. However, the cardiologists were more likely to select the recommended treatment, with GPs being more hesitant to use anticoagulation and tending to underestimate its reported benefit for stroke prevention in non-valvular AF. The GPs were also more likely to overestimate the reported risk of major bleeds with warfarin. In contrast, over one-third of the cardiologists went as far as to give warfarin to a low-risk patient and they were more likely to overestimate the reported benefit of aspirin and warfarin in AF. Only half the doctors

correctly classified a patient without a previous stroke (but with other risk factors) as being at high risk. Increased experience as a registered medical practitioner was generally related to a poorer performance on classifying patients according to the risk of stroke. The principal barriers to the use of anticoagulation were nominated as: (i) active gastrointestinal bleeding, (ii) previous intracranial haemorrhage, (iii) alcoholism, (iv) a history of daily falls, (v) liver disease, (vi) severe anaemia and (vii) concurrent use of non-steroidal anti-inflammatory drugs. CONCLUSION: There is scope for improvement in doctors' knowledge about the appropriate use of antithrombotic drug therapy in non-valvular AF and awareness of the results of recent clinical trials. Compilation and dissemination of clear guidelines and focused education on some of the other risk factors (apart from previous stroke or transient ischaemic attacks) in patients with non-valvular

Public Summary Document, Dabigatran (2011). "Public Summary Document." (March): 1-7.

Shen, Q., D. Cordato, et al. (2008). "Anticoagulant usage for primary stroke prevention: a general practitioner survey in local areas of metropolitan Sydney." J Clin Neurosci **15**(2): 166-171.

We assessed the hypothesis that having a non-English-speaking background (NESB), being very elderly, living alone, and having cognitive impairment were contributing factors to anticoagulant under-utilisation for atrial fibrillation in our local community. A questionnaire was mailed to 532 general practitioners (GPs) in three areas of metropolitan Sydney, Australia. The questionnaire included five case scenarios, regarding either an English-speaking background (ESB) patient, or an NESB patient, each characterised by potential barrier(s) for anticoagulant usage: being (1) elderly; (2) elderly with mild dementia; (3) elderly with mild dementia and living alone; (4) elderly with severe dementia; and (5) very elderly. The overall response rate was 34%. The percentage of GPs recommending anticoagulation was 57%, 50%, 6%, 25% and 23%, respectively, for the ESB scenario, and 48%, 32%, 4%, 14% and 18%, respectively, for the NESB scenario. Eighty-eight percent of GPs rated 'adherence to International Normalized Ration monitoring' as 'very important' in their decision. In conclusion, the factors proposed in our hypothesis were associated with a lower likelihood for anticoagulant prescription for atrial fibrillation.

Shen, Q., D. J. Cordato, et al. (2005). "Comparison of stroke risk factors and outcomes in patients with English-speaking background versus non-English-speaking background." Neuroepidemiology **24**(1-2): 79-86.

This study examined stroke risk factor profiles, management and outcomes for elderly patients with English-speaking background (ESB) and non-English-speaking background (NESB). This is an observational cohort study with both retrospective and prospective components. In total, 186 consecutive acute stroke patients aged > or =65 years admitted to our hospital were recruited over a 12-month period. Patient characteristics, stroke risk factors and management, in-hospital mortality, functional independence measurement scores before admission and at discharge, and discharge destination were recorded. On admission, NESB patients with atrial fibrillation (AF) were less likely to be taking warfarin than ESB patients (1 out of 19 with NESB vs. 19 out of 41 with ESB, p = 0.001). More NESB patients had a history of diabetes mellitus (DM) than ESB patients (41.4 vs. 10.2%, respectively; p = 0.001). However, ESB and NESB patients were comparable in terms of age, gender, preadmission functional status as well as other stroke risk factors (including smoking and alcohol drinking pattern, prevalence of hypertension and lipid disorder) and their management. In-hospital mortality was similar between ESB and NESB patients (10.2 vs. 8.6%). In conclusion, we found an association with our population of elderly NESB patients and an underutilization of warfarin for AF as well as a higher frequency of DM. Determination of the underlying reasons for such differences may be of value in the primary health care of NESB patients.

Singh, P., P. S. Arrevad, et al. (2011). "Evaluation of antithrombotic usage for atrial fibrillation in aged care facilities." J Clin Pharm Ther **36**(2): 166-171.

WHAT IS KNOWN AND OBJECTIVE: Warfarin is an important drug for the prevention of thromboembolic events such as stroke in patients with atrial fibrillation (AF). However, it is commonly implicated in major adverse drug events, which may result in reluctance to prescribe warfarin, especially in the institutionalised elderly population. This study aimed to assess the current trends in the antithrombotic management of AF in aged care facilities (ACFs) in Tasmania,

Australia, and to compare this with current recommendations. METHODS: We performed a non-experimental, retrospective cohort study designed to evaluate antithrombotic usage for AF in ACF residents in Tasmania. Residents with AF were identified on a patient-by-patient basis from residential case-note summaries collected from 29 of the 64 ACFs in Tasmania. The CHADS-2 score and the presence or absence of documented contraindications were used to determine the appropriateness of the current antithrombotic therapy prescribed. RESULTS AND DISCUSSION: Fifteen per cent (262/1737) of the ACF residents were diagnosed with AF. Nine per cent of the residents with AF had a contraindication to antithrombotic therapy (either warfarin or antiplatelet therapy). Eighty-one per cent of residents were eligible for treatment with warfarin according to the CHADS-2 score and did not appear to have a contraindication to warfarin. Of these, only 38% were prescribed warfarin; 16% (40/255) did not receive any antithrombotic treatment, despite being eligible for treatment with warfarin or antiplatelet therapy. Residents who did not receive any antithrombotic treatment or who received antiplatelet treatment were significantly older than those treated with anticoagulants. WHAT IS NEW AND CONCLUSION: Our results indicate that antithrombotic therapy, particularly warfarin, is underused in ACF-dwelling elderly patients who are eligible for treatment.

Taylor, D. M. (2004). "Use of Incident Reports by Physicians and Nurses to Document Medical Errors in Pediatric Patients." PEDIATRICS Vol. 114 **114**(No. 3 September): 729-735.

Taylor, D. M., A. Aggarwal, et al. (2005). "Management of new onset atrial fibrillation in previously well patients less than 60 years of age." Emerg Med Australas **17**(1): 4-10.

OBJECTIVE: This study reviewed the ED management of new onset atrial fibrillation (AF) in previously well patients aged less than 60 years. METHODS: We undertook a retrospective review of ED patients from 1998 to 2002 inclusive. The main outcome measures were approaches to rate or rhythm control and anticoagulation, the use of echocardiography, the value of diagnostic testing and the frequency of hospital admission. RESULTS: Fifty-two patients were identified. In general, all patients were haemodynamically stable. One patient had mild cardiac failure and one was clinically thyrotoxic. Serum potassium was measured in 51 (98%) patients, magnesium in 23 (44%) and cardiac enzymes in 30 (58%); results were generally unhelpful. Thyroid function tests were carried out in 40 (77%) patients; results were unremarkable except for the clinically thyrotoxic patient. No patient had echocardiography in the ED; however, 6 patients (12%) were later found to have major cardiac abnormalities. Forty-four (85%) patients received a variety of medications; 37 (71%) received an anti-arrhythmic and 24 (46%) an antithrombotic. Overall, 17 (33%) patients received theoretically effective therapy for conversion to sinus rhythm. Twenty-two (42%) patients were admitted to hospital. CONCLUSIONS: This study reveals variation in the management of acute AF in previously well, haemodynamically stable, young patients. Pathology testing was frequently carried out with a low yield. There were high rates of attempts to cardiovert, use of antithrombotics and of admission to hospital. Although cardioversion attempts appeared to be contrary to existing guidelines, decisions may have been based primarily on patient symptoms. Echocardiography should be considered prior to anti-arrhythmic therapy.

Vandenbroucke Jan (2001). "In Defense of Case Reports and Case Series." Annals of Internal Medicine **134** (4): 331-334.