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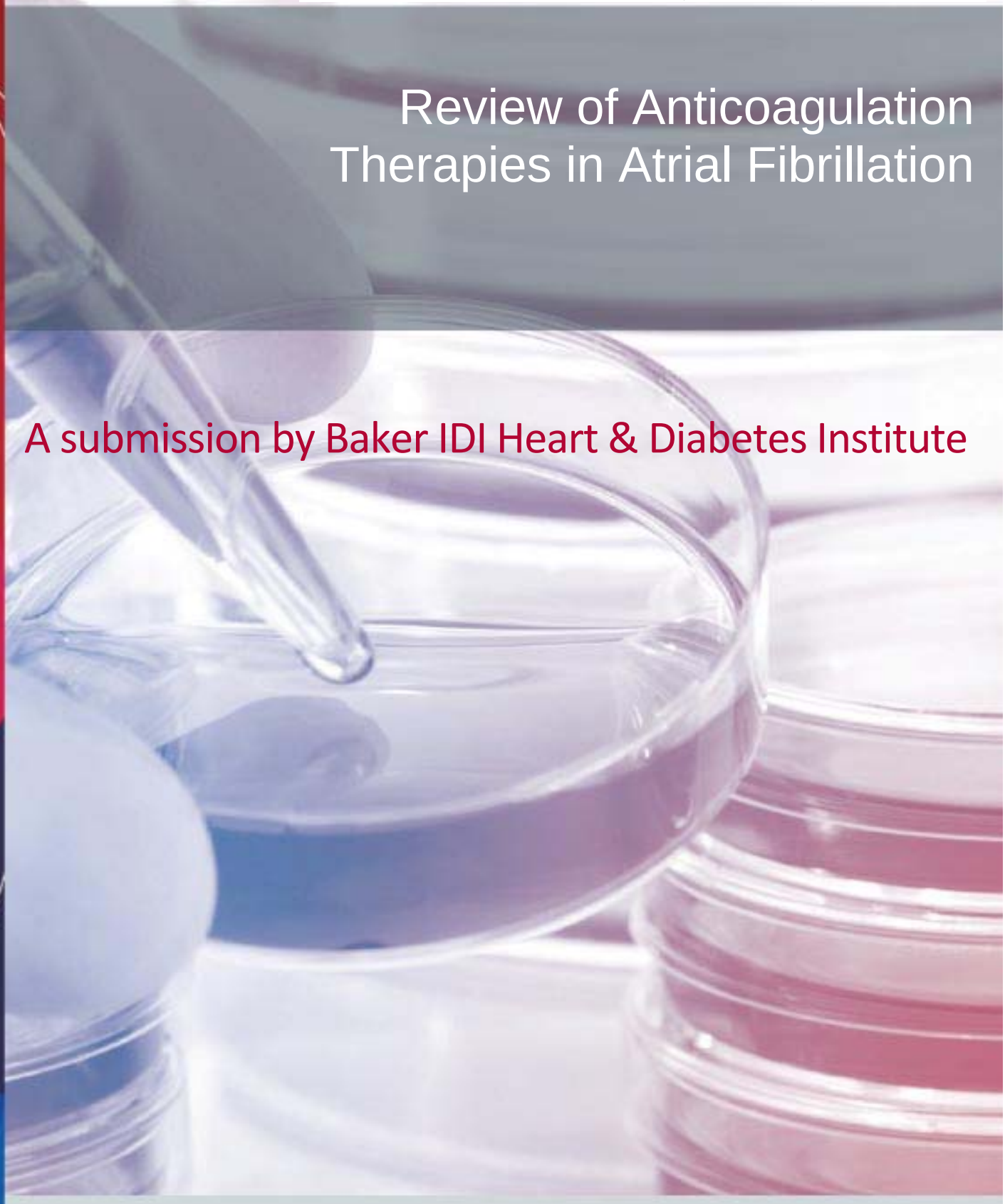
Review of Anticoagulation Therapies in Atrial Fibrillation

A submission by Baker IDI Heart & Diabetes Institute



Review of Anticoagulation Therapies in Atrial Fibrillation

The Baker Heart & Diabetes Institute

The Baker Heart & Diabetes Institute is an independent health and medical research institute with activities ranging from fundamental discovery research to health services and public health research, surveillance and clinical services delivery. Thrombosis and its consequences including stroke and acute coronary syndromes is an important element in the prevention, study and cure of cardiovascular disease and stroke and therefore a substantial component of our work. We welcome the opportunity to contribute a submission to this review.

Our views are informed by the following considerations:

- Health care costs are rising rapidly and the government and health care providers have a responsibility to ensure that the community obtains full value from investment in health care and is not faced with unaffordable growth in health expenditure.
- Innovations including new drugs and devices contribute significantly to increased health costs. Given the need to curb growth there is an opportunity cost in introducing new therapies if they do not result in savings elsewhere.
- On the other hand the public has enjoyed significant increase in life expectancy and other benefits due in no small measure to health innovations, especially new therapies. Assessing the real cost implications of a new therapy is fraught given the multiplicity of budget holders involved in health care, management of disability, and the knock on effects to the general economy. In particular the cost implications of new drug therapies go way beyond the immediate impact on Pharmaceutical Benefits Scheme (PBS) expenditure. There are clear examples where 'front loading' of investment in prevention and care provides long lasting human and economic benefits, such as in the management of acute coronary syndromes or stroke.
- New anticoagulants have been developed by a number of pharmaceutical companies in response to an unmet need that has been clearly expressed over many years by both consumers and clinicians. This is largely driven by the problematic nature of Warfarin therapy, the only existing alternative for best practice management in the prevention of stroke associated with Atrial Fibrillation and for a number of other clinical conditions. Warfarin has been used for over 50 years or so with little improvement in its application in community practice. As a community we hope and expect that the pharmaceutical industry working with academics in health and medical research will respond to unmet needs. This necessarily means a return on investment if the system is to be sustainable.

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- Delay in reimbursement of medications is effective in curbing PBS expenditure in the short term. In the longer term delays such as occurred with the reimbursement of statins and ACE inhibitors which were considered expensive at the time resulted in a measurable consequences on rates of subsequent heart failure and acute coronary events (although in fairness the evidence for these consequences was not available at the time). On the other hand premature reimbursement of medications that are subsequently found to have rare but serious adverse effects e.g. Vioxx is also undesirable as it widens the population exposed to the drug. At present newer anticoagulant drugs (specifically Dabigatran) have emerged after many relevant international guidelines were published but recommendations for their use are emerging in more recent publications including a class I recommendation from the ACC/AHA/American heart Rhythm Society (for review of guideline status see Manolis et al J Hypertension 2012, 30:239-252)
- In the course of this submission Baker IDI does not intend to comment on the cost benefit of the introduction of new anticoagulants over existing practice involving Warfarin as these will be available from other sources. However the institute did provide technical and clinical advice to a recent analysis performed by Deloitte Access Economics (Off beat: Atrial fibrillation and the cost of preventable strokes 2011). Nor do we feel we need to comment on the efficacy of Warfarin relative to the newer agents as this information is widely available in the public domain. We do however have considerable experience and recent data on the management of Atrial Fibrillation in the Australian community that we feel may be of assistance in the present debate. These data are available in detail but briefly:
    - There is substantial opportunity for improvement in the use of Warfarin amongst people with Atrial Fibrillation and other indications amongst the Australian community. This reflects a need for better patient and provider education, introduction of specific pathways of care for remote populations and newer disease management programs. Recent data on point of care testing also points towards potential improvement in efficacy and safer use of oral anticoagulants (Lancet meta-analysis ePub 2012). In at least one recent publication the margin over standard monitoring was of the same order or greater than seen between Warfarin and newer anticoagulants in published major outcome trials. However data from community surveys in Australia show that maintenance of adequate and safe anticoagulation falls far short of that reported from clinical trial data in a good proportion of the population.
    - Atrial Fibrillation and stroke are associated with disadvantage. A striking example in relation to anticoagulation therapies is Aboriginal and Torres Strait Islander communities. The most obvious issue here relates to anticoagulation and rheumatic valvular surgery (RHD). Although not strictly the subject of the present review it presents an example where therapy that is equal or more effective than Warfarin but does not require local monitoring would be enormously beneficial

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and should be available. Whilst data is relatively thin, the only long term data collated on surgical outcomes suggests that thrombotic and bleeding events (representing both over and under-coagulation) in Aboriginal patients after surgery are very high and largely associated with mortality (rather than just morbidity). Importantly some of the problem stems from choice of surgical intervention (repair v replacement v mechanical v bioprosthesis) in people who are likely to experience significant problems with routine anticoagulation (adherence, unstable social circumstances, low health literacy, high mobility and poor and unstable dietary intakes).

- That being said, even in a well-chosen cohort, Warfarin can be extremely difficult to monitor and titrate, and POC INR monitoring is not as widely available as we would like. We have experience in Central Australia where an individual will present to a clinic, have their blood taken (if lucky), the blood is spun and refrigerated, waits for the next trip into town to centralised path labs, is analysed then the result automatically sent through to the clinic. The clinic then may take some time to review the result, and then have to recall the patient for discussion and decisions on titration. The turnaround time is often one week or more. Rheumatic heart disease raises plenty of issues in relation to women of child-bearing ages as well. The toxicity of Warfarin during pregnancy (given the young age of RHD clients and the preponderance of females) is a significant consideration (fetal loss up to 30% especially in 1st trimester), and long term heparinisation or the use of LMWH has been suggested. However, heparin has been associated with prosthetic valve thrombosis in up to 20% of women (and requires careful monitoring) and bleeding complications peripartum. Australian guidelines for managing RHD have not yet incorporated any discussion of newer agents. It is likely to be some time until we have a trial to establish safety and effectiveness of newer agents in Aboriginal patients (although an argument could be made). We are aware however of significant advocacy work in NZ to ensure listing, particularly from the Maori arm of Pharmac (Marama Pamore personal communication).
- Cognitive impairment is another barrier to the successful use of warfarin and is much more common in a community sample with atrial fibrillation than in the major clinical trial populations. The table below show a comparison of findings in the SAFETY trial a community based disease management study presently underway in Australia compared to the published patient characteristics from major outcome trials of atrial fibrillation management (unpublished, abstract submitted to ESC 2012, not for reproduction).

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Characteristic	SAFETY	RE-LY	ROCKET-AF	ARISTOTLE
Mean (± SD)/median (IQR) age (years)	71.0 ± 11.0	71.4 ± 8.6	73.0 (65-78)	70 (63-76)
Male (%)	53.0	64.3	60.3	64.5
Paroxysmal AF (%)	3.9	32.1	18.9	15.1
Persistent AF (%)	87.1	32.4	81.1	84.9 (pers. + perm.)
Permanent AF (%)	9.0	35.4	-	See above
Mean (± SD) $CHADS_2$ score	1.9 ± 1.3	2.1 ± 1.1	3.48 ± 0.94	2.1 ± 1.1
Prior Stroke/TIA (%)	13.1	19.9	54.9	19.2
Prior myocardial infarction (%)	26.4	16.8	16.6	14.5
Diabetes (%)	31.8	23.4	40.4	25.0
Hypertension (%)	72.5	78.8	90.3	87.3
Cognitive impairment (%)	70.0	-	-	-

Carrington MJ, Ball J, Horowitz JD, Marwick TH, Mahadevan G, Wong C, Abhayaratna WP, Haluska B, Thompson DR, Scuffham PA, Stewart S. Navigating the fine line between benefit and risk in chronic atrial fibrillation: Rationale and design of the Standard versus Atrial Fibrillation spEcific managemenT studY (SAFETY). International Journal of Cardiology 2012. In press.

Conclusions

We estimate that around 30% of the population with indications for oral anticoagulation are either not suitable for Warfarin therapy or unduly exposed to risk with its use. We have identified a important segments within the community that would clearly benefit from availability of newer anticoagulants, and in whom the economic and human cost of continuing with present practice is prohibitive. There are others in whom warfarin therapy is both safe and efficacious and an important group who could achieve better control and efficacy with more widespread availability of point of care testing and disease management programs. These clinical considerations argue for wide availability of newer anticoagulants through reimbursement to some at the very least. The extent that this should be offered to a broader proportion of the population requiring oral anticoagulant therapy needs to take into account extensive and sophisticated cost benefit analysis.

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