THE CARDIAC SOCIETY OF AUSTRALIA AND NEW ZEALAND

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Dear Prof Sansom

Call for Submissions: Review of Anticoagulation Therapies in Atrial Fibrillation

Thank you for your letter of 22nd December 2011 seeking a submission on the review options for improving the health outcomes of patients treated with anticoagulation therapies.

We are pleased to provide the following submission on behalf of The Cardiac Society of Australia and New Zealand.

Yours sincerely

James Cameron
President

Richmond Jeremy
President Elect

Len Kritharides
Chair, CSANZ Scientific Committee

Andrew MacIsaac
Chair, CSANZ Interventional Council

THE CARDIAC SOCIETY OF AUSTRALIA AND NEW ZEALAND

CSANZ RESPONSE TO THE TERMS OF REFERENCE RAISED IN THE ENQUIRY LETTER FROM PROFESSOR LLOYD SANSOM SPECIAL ADVISOR ON NATIONAL MEDICINE'S POLICY FRAMEWORK FOR THE DEPARTMENT OF HEALTH AND AGEING

The terms of reference for the review are as follows:

a) To report on current and future options for improving health outcomes of patients with atrial fibrillation treated with oral anticoagulants.
b) To report on modes of health system delivery which may be used to optimise the use of currently available anticoagulants.
c) To report on what extent optimisation of the use of currently available anticoagulant treatments used in patients with atrial fibrillation would improve outcomes and at what cost.
d) To examine the future role of newer anticoagulant therapies for atrial fibrillation.
e) To report on any other matter relevant to items a. to d. above and on any other matters referred to it by the minister.

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

1. Background:

Atrial fibrillation is the most common serious arrhythmia with a prevalence of 1-2%. The incidence is expected to rise with an increasingly aged population and attendant increase in co-morbidities. Most patients present with symptoms such as palpitations, dyspnoea, chest pain, presyncope and syncope. A significant number of patients, estimated to be between 10-30% of the total cohort, are asymptomatic. Atrial fibrillation is categorised as paroxysmal (episodes that self-terminate in one week), persistent (episodes greater than one week), and permanent. The natural history of atrial fibrillation is to become permanent. 90% of cases are classified as non valvular, and 10% valvular and other causes. Factors, besides ageing, that predispose to atrial fibrillation include hypertension, structural heart disease including valvular disease and cardiomyopathy, obesity, sleep apnoea, diabetes, renal disease, chronic obstructive pulmonary disease, and thyroid disease. The prevalence of atrial fibrillation increases with age, being less than 0.5%

amongst those aged 40-50 years, increasing to 5-15% by 80 years of age with a lifetime risk of developing atrial fibrillation approximately 25% in those who reach the age of 40 years.

Please refer to recently published reviews on practice guidelines in Atrial Fibrillation (1,2).

2. Health consequences:

Patients may have symptoms related to disruption to cardiac function in relation to effects of rapid heart rate and loss of atrial contribution to cardiac filling, with added consequences including diminished exercise capacity and quality of life, left ventricular dysfunction, heart failure, increased rate of hospitalisations, and death. The major risk of atrial fibrillation relates to the associated risk (3 x 5 times risk)(1,2) of thromboembolic events to vital organs with the more common and serious of these being stroke. Stroke and recurrent stroke, in the context of atrial fibrillation is associated with a doubling of mortality for stroke (3,4). The risk of stroke is similar for episodes of paroxysmal atrial fibrillation of 48 hours duration as to persistent or permanent atrial fibrillation.

3. Current management:

The prevention of stroke in patients with non-valvular atrial fibrillation by use of oral anticoagulants is the key management priority to improve outcome in patients with atrial fibrillation (5). The optimal use of current agents such as antiplatelet drugs and Warfarin, along with newer oral anticoagulant agents, have potential to make a major impact on outcome in this serious disorder.

Treatment of symptoms where present includes strategies to either control rate or revert and maintain sinus rhythm "rhythm control". Despite "rhythm control" seeming to be the more intuitive strategy, studies demonstrate that the strategy of rate control and permanent anticoagulation actually show better outcomes than " rhythm control" with short-term anticoagulation.

The major treatment strategy in atrial fibrillation is anticoagulant therapy to minimise thromboembolic complications. Currently-used agents commonly include Aspirin, and Clopidogrel (alternatively Prasugrel or Ticagrelor)(antiplatelet therapy) and Warfarin (antithrombotic therapy). Therapy is guided by the use of risk scores which predict and categorise risk for thromboembolic events including stroke (although this risk is recognised to be a continuum), including CHADS2 and CHADS 2-Vasc scoring systems (6,7). These triage risk to low, intermediate and high risk, and generally antiplatelet therapy is used for low risk scores, antiplatelet or anticoagulant therapy is for intermediate risk, and anticoagulant therapy for high risk. Numerous trials including randomised trials and meta-analysis of trials have confirmed this approach and demonstrated the benefits of treatment.

CHADS2 scoring involves one point each for congestive heart failure, hypertension, age greater than 75 years, diabetes and two points for previous stroke. A score of 0 indicates low risk, 1 intermediate risk, and greater than 1 high risk. CHADS2-Vasc is a nine point score system incorporating presence of vascular disease with 0-1 low risk and greater than 1 high risk.

Bleeding risk is assessed as part of the decision to treat and is usually a subjective assessment, considering factors such as age, previous haemorrhage, frailty, falls risk. Risk scores for bleeding do exist, such as HAS-BLED (8), but are not widely used in clinical practice.

The decision to embark on therapy and choice of therapy ideally should take into account existing guidelines, along with individual patient assessment and use of risk scoring systems, but is often subject to subjectivity, dependent on Physician and patient attitudes and acceptance.

Peri-operative management is a complex and frequently difficult area of anticoagulant care and involves:

a) Close and prospective liaison and co-operation between Cardiologist, Surgeon, patient's General Practitioner and patient
b) Determination of ideal level of anticoagulation prior to carrying out the surgical procedure safely
c) Cessation of Warfarin for periods dependent on level of anticoagulation required, with determination of requirement for overlapping anticoagulant cover with Heparin (unfractionated or low molecular weight)
d) Careful re-institution of anticoagulant therapy post op to avoid bleeding complications.

Specific care is required in management of patients who are on Warfarin for non-valvular atrial fibrillation and who require coronary stenting, which involves a mandatory requirement for dual antiplatelet therapy including Aspirin and Clopidogrel (alternatively Prasugrel or Ticagrelor) for varying periods after stenting. Reports of increased bleeding risk in relation to the combination of Warfarin and dual antiplatelet therapy indicates this strategy is potentially high risk, and this may be compounded by the use of drug-coated stents which require use of dual antiplatelet therapy for 12 months at least. Various strategies in these patients include the use of bare metal stents, which require shorter duration dual antiplatelet therapy, or use of lower levels of Warfarin anticoagulation.

The remainder of this document will focus on antithrombotic therapies current and new.

4. Problems in relation to current treatment strategies in treatment of atrial fibrillation and use of Warfarin therapy:

There is good evidence that anticoagulant therapy with current drugs, i.e. Warfarin, is effective at preventing strokes in patients with atrial fibrillation. Meta-analyses of 13 randomised control trials, which have demonstrated significant reductions in stroke and mortality support the use of Warfarin (9). Nonetheless there is widespread evidence that application of current anticoagulant therapy in patients at risk of stroke is suboptimal. The EURO-HEART survey of atrial fibrillation found that only two-thirds of patients eligible for Warfarin anticoagulation actually received it (10). There is room to improve the efficacy of current anticoagulant therapy (Warfarin) to prevent stroke, as 8-40% of the international normalised ratio (INR) values in primary stroke prevention trials, and up to one-half of INR recordings in ambulatory care outside of research trials, are out of range (11).

Some clinical factors (e.g. acute illness, drug interactions, dietary changes) or genetic factors that are associated with poor adherence or maintenance of Warfarin anticoagulation are difficult to anticipate or modify. Modifiable factors include patient and Doctor attitudes and understanding, as well as technological improvements to simplify monitoring of anticoagulant status. These hold promise of better outcomes with anticoagulant management.

Non-adherence to daily Warfarin therapy is common – 21% of patient days in the IN-RANGE study (12) were out of treatment range for INR. It should be noted that non adherence to medication is widespread and that these issues are not unique to Warfarin, as experience with antihypertensive drugs over many years has shown. It is worth noting that many factors identified as associated with suboptimal compliance in general are also likely to impact adversely upon treatment adherence with anticoagulant drugs.

The factors contributing to suboptimal application of current oral anticoagulant therapy for atrial fibrillation may be grouped into three categories – those related to the patient, those related to the Physician and those related to the drug, and the systems/technology for its use. Clearly there are inter-relations between these factors.

Patient Factors:

Patient compliance is a major determinant of the efficacy and safety of medication including oral anticoagulants.

Factors identified with poor compliance included dose frequency, patient perception of treatment benefits, poor patient-physician communication, lack of motivation, poor socio-economic background, lack of family and social support, and young age. Other factors, including marital status, living arrangements and social problems can lead to non compliance (13). Non-compliance for Warfarin therapy in atrial fibrillation is also related to education level, employment status, mental health functioning, and cognitive impairment (12).

Many, if not most, of these factors will apply to new oral anticoagulants as well as Warfarin.

Several studies had found an inverse relationship between the number of doses prescribed and compliance. Compliance declines as dosage frequency increases (14). This may be an issue for newer anticoagulants which require twice daily dosage (as compared to once daily dosage of warfarin).

Patient perceptions about their own illness and risk are likely to be amongst the most important factors determining compliance. Thus, Cruess et al (15) found that patients reporting a lack of receptivity to details regarding their medical illness seem most at risk for Warfarin non adherence.

A note of caution about the impact of patient perceptions and compliance with medications upon the use of newer oral anticoagulants has also been sounded by Bellamy et al (13).

Clinical Factors:

There is evidence that attitudes and perceptions of medical practitioners do significantly impact upon the use of anticoagulants in patients with non-valvular atrial fibrillation, who are at increased risk of stroke. Physicians' reluctance to prescribe Warfarin is often due to perceived greater risk of bleeding, overestimation of associated risks, underestimation of stroke risk, and clinical uncertainty or inexperience of Warfarin (9).

Gattellary et al (16) conducted a study in nearly 600 Australian family physicians of whom 15.8% reported having a patient with non-valvular atrial fibrillation experience an intracranial haemorrhage with anticoagulation and 45.8% reported having had a patient with known non-valvular atrial fibrillation experience a stroke without anticoagulation. Practitioner sense of responsibility for adverse outcomes was significant with one-fifth of practitioners feeling *most responsible for intracerebral bleeding in a patient on anticoagulation* and one-third feeling *most responsible for an ischaemic stroke in a patient not receiving anticoagulation*.

The desire by practitioners to "do no harm" may result in their withholding anticoagulant therapy from patients they deem to be at risk of major bleeding (intracerebral or gastrointestinal), despite the fact that many of these patients are at significantly increased risk of ischaemic stroke. There appears to be considerable difficulty for patients in considering anticoagulation for elderly patients "at risk of falls" or with general frailty.

Older patients with atrial fibrillation are less likely to be prescribed Warfarin, because of the perception that there is an increased risk of bleeding in older people (due to polypharmacy, co-morbidities, risk of falls, or impaired cognitive function)(9).

The Bermingham atrial fibrillation treatment of the aged (BAFTA) trial (17), compared dose adjusted Warfarin (with a target INR of 2.5) with 75mg Aspirin in elderly patients aged greater than 75 years in a primary care setting. Warfarin was associated with a significant reduction in fatal or non-fatal disabling stroke with no difference in the risk of significant haemorrhage (intracranial or gastrointestinal) between the Warfarin and Aspirin groups.

Many practitioners report significant conflict in deciding about anticoagulant therapy for patients they consider to be high risk for haemorrhagic complications (16).

Although several bleeding risk stratification models have been proposed, the models are relatively complex and there is a need for further validation of these systems. As a result, these risk models are not currently widely used (18).

Provision of readily accessible clinical decision making support tools and regular updates to all prescribing Physicians may help address these concerns. Again, these very factors, which impede optimal use of current anticoagulants, are also likely to have some adverse impact as well upon the appropriate use of any new oral anticoagulants.

System and Technology Factors:

There are inherent limitations to Warfarin because of its narrow therapeutic range, and the fluctuation in INR, which occurs with change in diet, intercurrent illness or as a result of drug interactions. Monitoring of the INR and dose adjustment of Warfarin is critical for effective and safe treatment. Inadequate availability of or access to INR monitoring may pose a contraindication to Warfarin treatment. For many patients and practitioners

the logistics of regular INR testing, and dose management feedback are cumbersome. The use of self-monitoring for INR, using finger prick and test strips, has been effective for well-motivated patients. These patients appreciate the convenience of self-monitoring but comment on the cost of these test strips. The broader application of this innovation is hampered by cost for many patients, and it is likely that subsidy by government would improve patient uptake considerably.

Specifically in relation to INR testing, problems relate to the burden of frequent INR testing including access to INR testing, in particular where there is limited access to INR testing facilities in rural and remote areas. Further, patients who travel away from their usual location, including overseas, may encounter similar access difficulties. Additional problems include the time, disruption of schedule, cost of travel for patients, and in addition, costs of tests if a "gap payment" is required over and above the Item Number rebate.

Another innovative approach to anticoagulation management was reported by Oake et al (19) in Canada. The authors used an interactive voice response system to assist in managing Warfarin therapy for low risk patients. The system communicated results of INR testing, dosage schedules and dates of subsequent test to patients, as well as reminders of missed appointments. Although the study set was a group of well-motivated patients with good INR control previously, this interesting development holds promise as a new means to improve anticoagulant therapy.

5. Introduction of New Oral Anticoagulant Therapies:

There are several new oral anticoagulant agents. Dabigatran is currently available in Australia having been recommended for clinical use by the PBAC but not currently funded by the PBS scheme. Two other agents, Rivaroxaban and Apixaban have been the subject of study in 2 recent large multicentre randomised trials and are currently under assessment.

Dabigatran is a direct thrombin-inhibitor and is not subject to variations in drug efficacy such as Warfarin, and does not require INR testing. Dabigatran was the subject of large-scale multicentre randomised trial (RELY) (19) in which two dose schedules, 110mg twice a day and 150mg twice a day, were used. The 110mg twice a day schedule showed similar efficacy to Warfarin in terms of stroke prevention, but with lower bleed risk particularly intracranial bleeds whereas the 150mg dose twice daily schedule showed improved efficacy over Warfarin in terms of stroke prevention but with similar overall bleed risk and once again lower risk of intracranial bleed.

Dabigatran is contraindicated in patients with renal insufficiency with GFR <30mL/min and is contraindicated in patients with significant liver disease and impaired clotting function. It has a rapid onset of action and achieves maximum concentration in 0.5 – 2.0 hours with a half-life of 14-17 hours requiring twice daily dosing.

Dabigatran has no antidote, and if serious bleeding occurs, apart from ceasing the drug, management is supportive only. There is some evidence that the effect can be reduced by use of certain blood products along with consideration to dialysis.

Dabigatran cannot be directly monitored for efficacy but does raise APTT levels at any dosage, and this might be useful as a crude test of compliance. Dabigatran has important drugreactions with Amiodarone and Verapamil, both commonly used cardiac medications. Subgroup analysis in RELY suggested that the outcomes in patients with adequate levels of anticoagulation with Warfarin were similar to those of patients on Dabigatran. The direct cost of Dabigatran is higher than Warfarin, but may be offset by no requirement for INR monitoring with its attendant costs including disruption to patient schedules, requirement to travel for testing, along with reduced healthcare cost with reduced stroke and bleed rates.

Two other drugs, Rivaroxaban and Apixaban, which are both factor Xa inhibitors have recently shown efficacy in randomised studies in patients with atrial fibrillation and are currently being reviewed. Rivaroxaban 20mg once daily was not inferior to Warfarin in prevention of system embolism in stroke in the randomised study of 14,264 patients with non-valvular atrial fibrillation (20), while Apixaban 5mg twice daily was superior to Warfarin in a randomised trial in 18,201 patients with non-valvular atrial fibrillation with reduced risk of stroke, systemic embolus, bleeding and mortality (21).

6. Current and Future Options for Improving Healthcare Outcomes for Treatment of Atrial Fibrillation:

The increasing burden of AF and the attendant risk of stroke are major current and future health priorities.

In view of the observation that a significant cohort of patients with atrial fibrillation are asymptomatic, measures could be undertaken to detect and diagnose atrial fibrillation particularly in at risk groups such as greater than 50 years of age at primary care level including consideration for example to annual ECG checks in this group. The difficulty in detection of such patients, however, is compounded by the fact that many asymptomatic patients present with heart rates within the normal range albeit irregular, either in relation to intrinsic conduction disease or concomitant use of drugs which have AV nodal blocking effects. Nevertheless, greater awareness and measures to detect more of these patients may well be worthwhile.

Educational initiatives might include those aimed at the primary care Physician to improve compliance with guidelines, including improved understanding of guidelines and correct use of risk scoring systems for stroke and bleed.

Educational initiatives may be directed to patients to improve acceptance of need for treatment and adherence to treatment..

Risk scoring systems themselves could be re-evaluated, including potential development of “global” risk scores for combined adverse outcome measures of stroke and bleeding. Further research and development of such systems would involve examination of both prior randomised studies, existing clinical registries, and the development of future clinical registries providing real-time data for evaluation of new therapies.

Improved systems for monitoring Warfarin should include consideration of both patient-directed and practitioner-directed monitoring particularly where pathology services are scarce. There are data which support both of these measures as providing better

outcomes than standard Warfarin care services. Incentives for the primary practitioner to provide Warfarin therapy, and cost rebates for the patient in terms of monitoring equipment should be strongly considered to encourage these initiatives.

In addition, consideration can be given, on the basis of recent research studies, to less frequent requirement for INR testing in patients with very stable INR with recent evidence demonstrating that three monthly testing results in very similar outcomes to monthly testing.

Many research studies have demonstrated significant gaps in treatment efficacy with between 30 and 40% of patients on Warfarin outside of target INR range. Specific and successful measures to reduce the treatment gap may have a major impact with use of current Warfarin therapy in improving outcomes for such patients.

A survey of comments from Cardiac Society members indicated considerable reservation whether current systems for use of Warfarin could be significantly improved. As a result of this, Cardiac Society members did take a group view that new anticoagulants should be introduced, although with necessary caution as their use would be widespread and have a significant impact on current care. The group considered that the introduction of newer anticoagulants could provide a number of additional advantages to the current use of Warfarin.

Generally it was felt that there was no major disagreement regarding the data resulting from clinical trials completed to date, but that many noted that this was an evolving evidence base, and that newer agents should be carefully introduced over time in response to the rapidly accumulating evidence base. Any new drug should be evaluated in the context of the current treatment systems, but the group generally felt that the new drugs did offer advantages, including a choice of alternate therapies. Comments on the features of newer anticoagulants included the following advantages:

a) These agents are noted to generate reliable levels of anticoagulation without requirement for monitoring and hence are generally more flexible for patient use particularly a major advantage where access for INR testing is difficult. The “no requirement” for INR testing might be expected to increase patient acceptance and adherence.

b) New agents offer the possibility of greater efficacy and stroke prevention, and lower risk of bleeding particularly reduced levels of intracranial bleeding, compared to Warfarin. The newer agents offer flexible alternatives to Warfarin in terms of more rapid onset of action and this might improve efficiency in treatment of inpatients with ability to anticoagulate patients faster and then have reduced hospital stay. In pre-operative cases, drugs such as Dabigatran for example can be stopped one to two days prior to surgery (or three to five days if clearance <50mL/min) and then usually would not require “bridging” therapy with Heparin.

c) New agents offer high quality anticoagulation to those in rural and remote setting with difficult access to INR monitoring.

Some disadvantages of new oral anticoagulants compared to Warfarin include for example:

a) Contraindication in patients with renal insufficiency with drugs such as Dabigatran.

b) No antidote if bleeding occurs, so care would need to be exercised with patients with a risk of bleed or where these agents are re-introduced following surgery where there is a post-operative bleed risk. In such instances Heparin (unfractionated or low molecular weight) could be used as a "bridging" strategy with reintroduction of newer anticoagulants at a later time.

c) The cost of these agents is higher than Warfarin, but may be offset by no requirement for INR monitoring with its attendant costs, including disruption to patient schedules and requirement to travel for testing, along with reduced healthcare costs with reduced stroke and bleed rates. CSANZ notes that a "cost effective" analysis is beyond the scope of this report.

d) Anecdotal reports of higher bleeding rates in patients greater than 75 years of age with newer anticoagulants will need examination and monitoring if introduced in a more widespread fashion.

CSANZ summary:

1. **The burden of AF and risk of stroke is increasing with attendant higher mortality and morbidity.**
2. **Current management is deficient in areas with "gaps" in treatment with some opportunity to improve efficiencies and outcomes.**
3. **New therapies may provide additional benefits to address "treatment gaps" but require judicious introduction.**

b) To Report on Modes of Health System Delivery which may be used to optimise the use of currently available anticoagulants:

Modes of System Care Delivery to consider to optimise use of oral anticoagulants include:

1. Educational initiatives to improve public and individual patient awareness and understanding of atrial fibrillation in terms of complications and treatment issues. These approaches should be individualized to be as meaningful as possible to the patient, and time should be spent in consultation between primary care Physicians and specialists with patients in relation to explanation and discussion of these complex matters and appropriate emphasis to treatment priorities. Education can be supplemented for example through educational tools, "lay language" brochures, and Practice Nurses. Education can be used to improve patient understanding and acceptance of anticoagulation therapy with likely resultant improved adherence. In addition, improved treatment outcomes and lower bleeding will alter community and patient perceptions and attitudes and this is likely to improve subsequent adherence to anticoagulant therapy.

Educational initiatives should also be directed towards primary care and specialist Physicians, in both the ambulatory and hospital care settings, including raising awareness in detection of atrial fibrillation, symptomatic and asymptomatic, in the population and

include introduction measures to detect more of this group, for example with regular ECGs in patients greater than 50 years of age. Educational initiatives should also be aimed at educating medical practitioners on current and new anticoagulant therapies, clinical pathways and guidelines, including incentives to accurate comply with guideline recommendations. As with patients, improved treatment outcomes and lower bleeding will alter and improve practitioner perceptions and attitudes and with a greater readiness and comfort to recommend anticoagulant therapy.

2. Development and adoption of standard clinical pathways for both ambulatory and hospital patients for difficult areas of care such as peri-operative anticoagulant management, post coronary stent management, cardioversion, with both intravenous or subcutaneous anticoagulants, and oral anticoagulants such as Warfarin and new anticoagulants. Expert groups in guideline writing such as the NHMRC, might provide leadership in development of such guidelines and clinical pathways for both Warfarin and newer anticoagulants.

3. Development of quality clinical registries for monitoring prospectively of introduction of current and new anticoagulant therapies. Such registries should collect appropriate co-morbidity data to allow development of risk modeling in individual systems of care, to allow accurate risk stratification and development of standard guidelines and clinical pathways, and to provide further feedback in improvement in such pathways over time.

Internationally, clinical registries have contributed enormous information to the development of risk models to predict outcomes with subsequent use of risk models to triage risk and therapies. The Cardiac Society of Australia and New Zealand has an interest in developing quality clinical and procedural registries, and currently is in the process of introducing a National Cardiac Procedures Registry, and a registry to monitor post-operative care and outcomes in indigenous people with cardiac surgery for rheumatic fever.

Clinical quality registries provide a number of advantages including stimulating improved patient care by feedback to clinicians and institutions in an education feedback loop of both positive and negative performance. Registries can provide advisory roles to institutions and/or regulatory bodies, including application of relevant emergency best practice principles, facilitating development of standard operational procedures and guidelines, identifying individual, cohort and system-related risk factors, providing accurate and transparent assessment of the safety of therapies and procedures, and identifying disparities in access for different geographic, ethnic or socio-economic groups.

Assessment of the major impact of current and new oral anticoagulants on clinical outcomes in AF would make this an ideal subject for a quality clinical registry.

4. Improvements in INR monitoring:

a) Widespread use with consideration of incentives for both patients and practitioners to undertake direct Warfarin care
b) Less requirement for INR tests in patients with very stable INR levels, reducing tests from monthly to two to three monthly

c) Optimisation of pathology rebates to minimise "gap" payments to patients to reduce the cost disincentive to patients.

5. Increase availability of newer anticoagulant therapies with introduction facilitated by:

a) Education.
b) Development of clinical pathways and guidelines.
c) Development of risk models facilitating risk assessment in individuals.
d) Development of prospective clinical registries.
e) Closer linking with pharmacy services with ambulatory and inpatient care.

CSANZ summary:

Systems of health delivery optimisation might include:

1. **Educational initiatives aimed at community, patients and practitioners**
2. **Development of clinical pathways and guidelines perhaps led or directed by the NHMRC with key involvement of clinical groups such as CSANZ**
3. **Development of Clinical quality registries with key involvement by groups such as CSANZ**
4. **Improve current risk scoring systems and their more widespread if not universal use in clinical practice**
5. **Improvements in INR availability, accessibility, monitoring with incentives for extended practitioner and patient monitoring**
6. **Introduction of newer anticoagulant therapies.**

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

Results of research studies demonstrate that there are significant gaps in efficacy of Warfarin in terms of achievement of stable therapeutic INRs in patients. In many studies, 30-40% of patients on Warfarin are not adequately anticoagulated. These "treatment gaps" do indicate a significant important potential for improved outcomes by improving Warfarin efficacy in current treatment systems. Methods outlined in the previous discussion above indicate that there is a potential to have a major impact on improvement in health in these patients. However, even in the best controlled randomised controlled trials of warfarin, optimal INR control is well short of 100%. Members of the society were therefore somewhat reserved about to what extent these measures might be effective and that universal application of measures to achieve near perfect efficacy with Warfarin would seem unlikely.

Measures outlined above such as patient and practitioner incentives, optimisation of pathology gaps, would come at a cost and are beyond the scope of discussion of this document and outside the influence of CSANZ

CSANZ summary:

1. **Optimisation of use of current anticoagulant therapies has the potential to close "treatment gaps" and improve outcomes and should be undertaken but with some cost.**
2. **Clinical groups such as CSANZ have reservations as to what extent this is achievable.**

d) To examine the future role of newer anticoagulant therapies for atrial fibrillation:

New oral anticoagulant agents include Dabigatran which is currently available in Australia but not currently funded by the PBS scheme, as well as two other agents, Rivaroxaban and Apixaban, which have been the subject of study in 2 recent large multicentre randomised trials and are currently under assessment.

Dabigatran, Rivaroxaban and Apixaban can be considered as suitable alternatives to Warfarin for patients with non-valvular atrial fibrillation when anticoagulation is indicated, and some of the newer agents may be superior to Warfarin. These agents have the advantage of fewer drug, food and other interactions and lack of requirement for monitoring compared to Warfarin. This may result in improved compliance with anticoagulant therapy and may help to close the gap between evidence and practice, with more patients at high risk being adequately protected.

Risk of bleed with the newer agents will need to be closely monitored as there have been adverse reports excess bleeding in relation to these agents internationally particularly in the elderly.

The examination of newer anticoagulant therapies has largely focused upon stroke prevention in the long-term for patients with non-valvular AF.

A potential future role is for short-term anticoagulation in the setting of brief atrial fibrillation responding to chemical or DC cardioversion. Current practice is to treat such patients with warfarin for 3 weeks following cardioversion, because of the lingering risk of stroke. The long half-life of warfarin mitigates against such short term therapy. Newer anticoagulants, with shorter half-life and earlier onset of therapeutic effect may be useful in this setting.

One study, by Nagarakanti et al (2011) (22) reported a comparison of high and low dose dabigatran with warfarin for short term anticoagulation in patients undergoing cardioversion and concluded that dabigatran is a reasonable alternative to warfarin in patients undergoing cardioversion.

Another potential role for newer anticoagulants is for management of patients with AF who may require a surgical procedure, whereby easier termination of anticoagulation may be achieved with a shorter drug half-life, than is presently the case for warfarin.

It should be noted that the evidence base supporting the use of newer anticoagulants for stroke prevention in these short- term settings is relatively limited (in contrast to that for pulmonary embolism prophylaxis). The importance of building such an evidence base is underscored by the recent report of Lakkireddy et al (2012) (23) who examined the

feasibility and safety of periprocedural Dabigatran therapy in patients undergoing radiofrequency ablation for AF. In this multicentre study of 290 patients, periprocedural dabigatran use significantly increased the risk of bleeding or thromboembolic complications compared with uninterrupted warfarin therapy.

The potential role of newer anticoagulant drugs in patients with AF associated with valvular heart disease, particularly those with prosthetic heart valves, is presently undefined. Available reports are limited and it is not yet possible to draw a conclusion about the likely application of the new oral anticoagulants for AF in these settings.

The Cardiac Society of Australia and New Zealand members did not think that there was any major disagreement in interpreting recent studies of new oral anticoagulants and the current use of Warfarin, and did recommend introduction of these agents in a judicious fashion as the evidence-base accumulated. CSANZ members thought that the research trial results for new anticoagulants provided results which indicated consistent class effects, with only minor differences between agents. There was genuine belief that these drugs will provide advantages to current therapy with Warfarin. Newer emerging agents will allow greater alternatives for patients and should improve outcomes for patients with non-valvular atrial fibrillation who use anticoagulants.

In terms of introduction of newer agents, at present it would appear that, in patients who have stable INR in the therapeutic range on Warfarin, where testing is infrequent and where costs regarding patients are low, outcomes with Warfarin are similar to those of Dabigatran. Therefore there may be no advantage for such patients to change to newer agents.

There were some unanswered questions in relation to the newer agents, including their interaction with coronary artery disease, as some studies have indicated the potential for an increase in myocardial infarction with direct thrombin inhibitors (24). No such disadvantage has been noted in Warfarin, and in fact, Warfarin in previous studies does have some advantages in these patients. Further evidence will be required in relation to this.

Newer anticoagulant drugs will need to be assessed in terms of development of clinical pathways in relation to treatment of peri-operative anticoagulation, post-stent management, and cardioversion. Expert writing groups will be required to develop such guidelines prospectively.

CSANZ summary:

1. **Several new oral anticoagulants may become available for use in the near future.**
2. **These drugs offer clinical advantages compared to warfarin and might provide opportunities to close "treatment gaps."**
3. **Specific areas of advantage might include patients who have suffered bleeding complications on warfarin - particularly intracranial bleed- and who require ongoing use of anticoagulants, along with patients whose INR levels are poorly controlled or who require frequent INR testing.**
4. **Patients who are currently stable on warfarin with infrequent requirement for INR monitoring and no side effects might not derive signifcant advantage in changing to Dabigatran but this view might need to be reconsidered over time as further evidence regarding new oral anticoagulants emerges.**
5. **Significant differences exist between warfarin therapy and new oral anticoagulants and judicious introduction of these drugs should occur over time as their treatment outcomes in trials, clinical registries, and clinical use are determined, along with development of appropriate clinical pathways and practice guidelines.**

EXECUTIVE SUMMARY

1. The burden of AF and risk of stroke is increasing with attendant higher mortality and morbidity.

2. Current management is deficient in areas with "gaps" in treatment with some opportunity to improve efficiencies and outcomes including:

- **a) Educational initiatives aimed at community, patients and practitioners.**
- **b) Development of clinical pathways and guidelines perhaps led or directed by the NHMRC with key involvement of clinical groups such as CSANZ.**
- **c) Development of Clinical quality registries with key involvement by groups such as CSANZ.**
- **d) Improve current risk scoring systems and their more widespread if not universal use in clinical practice.**
- **e) Improvements in INR availability, accessibility, monitoring with incentives for extended practitioner and patient monitoring.**

3. Optimisation of use of current anticoagulant therapies has the potential to partially close "treatment gaps" and improve outcomes and should be undertaken, but with some cost and reservations as to what extent this is achievable.

4. Several new oral anticoagulants may become available for use in the near future, and are notable for the following:

- **a) These drugs offer clinical advantages compared to warfarin and might provide opportunities to close "treatment gaps."**
- **b) Specific areas of advantage might include patients who have suffered bleeding complications on warfarin particularly intracranial bleed, and who require ongoing use of anticoagulants, along with patients whose INR levels are poorly controlled or who require frequent INR testing.**
- **c) Patients who are currently stable on warfarin with infrequent requirement for INR monitoring and no side effects might not derive much advantage in changing to Dabigatran but this view might need to be reconsidered over time as further evidence regarding new oral anticoagulants emerges.**
- **d) Significant differences exist between warfarin therapy and new oral anticoagulants and judicious introduction of these drugs should occur over time as their treatment outcomes in trials, clinical registries, and clinical use are determined, along with development of appropriate clinical pathways and practice guidelines.**

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Disclaimer

The use of literature references cited in this report is meant to be illustrative and the collators of this document accept that this report does not comprise an exhaustive literature review.

Statement of Process

The process for the CSANZ response involved circulation of the letter from Prof Sansom widely to experts and general membership within CSANZ. The responses to this survey have been collated from the CSANZ Board including through the Chairs of the Continuing Education and Recertification Committee, the Scientific Committee , and the President and President Elect of the Society. The collators declare no conficts of interest in relation to the preparation of this response. CSANZ does derive sponsorship from commercial companies in the way of undifferentiated sponsorship to the CSANZ Annual Scientific Meeting. The organisation of the education content of the ASM is undertaken independently by the Society without influence from sponsors.