21st February, 2012

RE: Review of anticoagulant therapies in atrial fibrillation

Thank you for your email informing me that the Committee investigating anticoagulant use had been formed and that my expertise, both clinical and research over 3 decades was not needed but that I could make a submission to the Committee.

I am a Cardiologist in private practice and have been in private practice almost 30 years. I have a private research unit which I set up 2 decades ago and have been involved in investigator driven research and multicentre international trials. My primary research interest initially and still remains is diet and heart disease and psychosocial factors and over the years I have played a number of roles in the Heart Foundation Committees. I was nominated by the National Heart Foundation of Australia to attend the 2020 Summit and I was the only Cardiologist to be invited.

With regard to anticoagulation and heart disease I was an investigator in the seminal RELY Trial, the ACTIVE-W and ACTIVE-A Trials and currently am an investigator in the ongoing ENGAGE (Endoxaban) trial. I have been involved in numerous studies using anti-platelet agents in acute coronary syndromes. As a clinician managing patients with atrial fibrillation is very much a part of my day to day practice. Of the 20 patients I saw yesterday, 4 have chronic atrial fibrillation, 2 are currently on Warfarin, 2 on Dabigatran. One of the Dabigatran patients had been on Warfarin for more than 20 years and is most grateful that he switched to Pradaxa via the special access scheme last year. The other patient is on Dabigatran as follow up therapy from being a patient in the RELY Trial. Over the years as a busy Cardiologist in private practice I have come across literally thousands of patients with atrial fibrillation where anti-coagulation needs to be considered and also hundreds of patients who have other indications for anti-coagulation therapy.

I write to you, not to reiterate the science which is clear regarding the new anti-coagulation versus Warfarin, but more as a clinician with a vast experience with day to day contact with patients where decisions have to be made regarding anticoagulation therapy and balancing risk versus benefit. The other practical issues of the frequent blood testing and side effects and how these can be devastating has a very personal face. I may be able to provide some insights into your committee.

I have just finished reviewing these seminal trials regarding the anti-coagulation such as the RELY Trial, ARISTOTLE Trial and ROCKET Trial for the Pharmaceutical Society's refresher course in April this year. I am the key-note speaker giving four major lectures and three 2 hour workshops. One of the workshops is on the new anticoagulants.

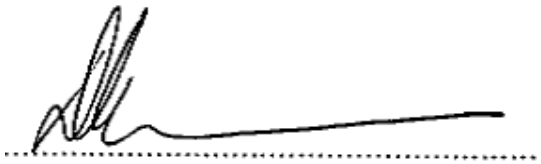
Rather than reiterate these trials, which I am sure you will be well acquainted with, it would be worthwhile to note two patients of mine on anticoagulation and their clinical sequelae. These are direct personal case histories of patients whom I have seen over the last few months. One is an example of a patient who was stable on Warfarin therapy for many years who then unaccountably had sudden prolongation of his INR and had a near catastrophic bleed and was admitted to hospital for a number of weeks. In contrast is another patient who had a stable INR, again for many years, whose INR dropped below 2 and had a stroke. In addition to the index stroke there was evidence on CT scanning of a previous stroke. This patient was started on Dabigatran which he is paying for rather than go back on to Warfarin. It is important to note both patients were highly compliant, were attending very good anticoagulation clinics run by our large pathology carriers in Queensland and they were being frequently monitored with target levels of 2 to 3 INR (usual targets which are agreed internationally).

These two patients illustrate the two ends of the spectrum where Warfarin is inferior to the new anticoagulants regarding hard endpoints. This is separate to the tremendous inconvenience that patients (who are usually elderly) have by attending pathology departments, sometimes a few times a week, for many months on end. Many of my elderly patients find it very stressful and painful having blood taken, particularly from their frail veins. The inconvenience and the suffering patients endure is not assessed in the clinical trials but at the coalface it is an enormous issue. We are inflicting needless pain and suffering on many of our frail elderly patients.

Attached are a few key slides of the patients I mentioned above. These practical issues are a major barrier to patient compliance. A major problem in patients who are compliant is that in the best places in the world at least 20% of patients are outside the therapeutic window. This is not due to poor patient compliance and lack of expertise of the doctors and nurses who run coagulation clinics, it is the nature of the medication and the nature of patient genetics and lifestyle.

Finally, the estimated rate of emergency admissions to hospital for adverse side effects in the United States has recently been published [(1).] This 2011 paper estimated that one third of all admissions to hospital due to major side effects of medication is due to Warfarin. It is estimated that the major bleeding that can be catastrophic and fatal is responsible for hundreds of millions of dollars in medical therapy in the United States. It would be reasonable to assume that these data reflected in Australia.

Kind regards,



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[redacted]

Ref: Budnitz DS. N Engl J Med 2011;365:2002-12

- 18/9/09 Admitted Emergency: Short onset and progressive swelling in (L) groin & scrotum with increasing pain, 1st noted playing golf earlier that day
- Chronic AF (stable INR on Warfarin for past 10 years) no new medications, supplements or diet and no illness. Sudden loss of control for no accountable reason. Previous readings in therapeutic range, monitored regularly by Warfarin clinic.
- **18/09/09 INR 6.5** (15/9/09 INR 3.0) Hb 91 (27/9/09)
- 25/9/09 US: haematoma (L) adductor longus muscle 16.6 x 7 x 12cm

Date	Lab Id.	INR	Warfarin Dosage
18/09/09		6.5	Managed by referring Practitioner.
15/09/09		3.0	5.5 mg Mon to Fri, 5.0 mg Sat and Sun
24/08/09		2.6	5.5 mg Mon to Fri, 5.0 mg Sat and Sun
10/08/09		2.7	5.5 mg Mon to Fri, 5.0 mg Sat and Sun
29/07/09		2.8	5.5 mg Mon to Fri, 5.0 mg Sat and Sun
16/07/09		3.1	5.5 mg Mon to Fri, 5.0 mg Sat and Sun

- 26/9/09: surgical drainage of haematoma in theatre, however still persisting 28/9/09, no sign of DVT
- 6/10/09: peri scrotal oedema post drainage of haematoma, US: (R) testis 4.5x3cm,
  (L) 4.7x2.7cm
- Pt unable to mobilise for the first 2 weeks of admission
- 17/10/09: Discharged
- Warfarin contraindicated permanently

- 12/1/12: Admitted with stroke affecting (L) side, background chronic AF
- Recent INR 1.9 (sub therapeutic). Previous readings in therapeutic range, monitored regularly by Warfarin clinic
- Sudden loss of control for no accountable reason.
- Gradual recovery with continuing (L) sided weakness and neglect
- CT revealed two areas of cerebral ischaemia
- P Hx: Angiogram (‘94) - moderate double vessel disease.
- Angina free

Date	Lab No	PT	INR	Dosage
29/03/11		24	2.2	3.5/ 4 mg warfarin alternating daily
24/05/11		23	2.0	3.5/ 4 mg warfarin alternating daily
29/06/11		25	2.2	3.5/ 4 mg warfarin alternating daily
08/08/11		22	2.0	3.5/ 4 mg warfarin alternating daily
06/09/11		24	2.2	3.5/ 4 mg warfarin alternating daily
25/10/11		24	2.2	3.5/ 4 mg warfarin alternating daily
10/01/12		22	1.8	4.5 mg for 1 day, then 3.5 / 4 mg warfarin alternating daily
12/01/12		19	1.9	Patient admitted to hospital.
Current Result:				
12/01/12	2770151	18	1.9	

- Dramatic increased risk of stroke in patients with AF when INR is below 2
- Patient switched to Dabigatran 150mg bd
  - Requires no monitoring
  - Superior to Warfarin in preventing stroke
  - Less bleeding (especially decreased risk of intracranial bleeds)
- Not currently subsidised by the government – costs $150-200/month