AACP Submission to:

Review of Anticoagulation Therapies in Atrial Fibrillation

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About AACP

The Australian Association of Consultant Pharmacy Pty Ltd (AACP) was established to develop a national approach to the practice of 'consultant' pharmacy as an expansion of the professional health role of pharmacists in Australia. The AACP is jointly owned by the Pharmaceutical Society of Australia (PSA) and The Pharmacy Guild of Australia (the Guild).

The AACP promotes and seeks recognition for the practice of consultant pharmacy and the provision of value-added, professional services in Australia. AACP develops, implements and administers assessment, credentialing and accreditation procedures for the practice of consultant pharmacy. Over 2,100 registered pharmacists are accredited to conduct medication reviews – Home Medicine Reviews (HMRs) and Residential Medication Management Reviews (RMMRs), with a further 900 pharmacists currently in the process of accreditation. This represents over 10 percent of all registered pharmacists.

Overview

AACP provides the following feedback from accredited pharmacists on the use of anticoagulant therapies, including warfarin and dabigatran.

- Warfarin is a commonly prescribed oral anticoagulant and is very effective for primary and secondary prevention of thromboembolic events. Many patients, especially older people, have limited understanding on the risks and benefits of warfarin therapy. Education on warfarin therapy is often limited. Drug interactions with warfarin are common and often poorly understood by GPs and patients.
- Whilst the lack of the need to monitor dabigatran therapy has advantages, it may also create potential problems: the ability to objectively measure anticoagulation and determine adherence is lost and any currently unknown drug interactions will be hard to assess with potentially serious consequences.
- Safety alerts have been issued in Australia and internationally following increased reports of bleeding-related adverse events. Many of the serious events were related to gastrointestinal bleeding and occurred in patients over 75 years of age; some patients prescribed dabigatran have one or more of these risk factors.
- Dabigatran is significantly more expensive than warfarin even when the costs associated with anti-coagulation services are taken into account. The main advantage is the ability to reduce the impact of monitoring on patients' lives. In addition, recent evidence suggests monitoring for patients stabilised on warfarin may only require INR testing every 12 weeks.[1]
- Anecdotal evidence suggests that dabigatran has been prescribed during this interim period since approval to the PBS to patients in whom the medication is contraindicated or to be used with caution and require close monitoring:
    - Patients with severe kidney impairment (creatinine clearance < 30 mL/min) should not take dabigatran. Renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment, and not by relying on eGFR results.

[1] Schulman S, Parpia S, Stewart C, Rudd-Scott L, Julian JA, Levine M. Warfarin Dose Assessment Every 4 Weeks Versus Every 12 Weeks in Patients With Stable International Normalized Ratios. Ann Intern Med. 2011;155:653-659.

  - Patients aged ≥ 75 years, moderate renal impairment (CrCL 30-50 ml /min) or previous gastro-intestinal bleed may have an increased risk of bleeding.
  - P-glycoprotein inhibitors (e.g. amiodarone, verapamil) can reduce clearance and increase plasma levels & effect of dabigatran.
  - Concomitant antiplatelet drugs and NSAIDs increase the risk of bleeding.
- In addition, the labelling of dabigatran has been inconsistent or non-existent by GPs, creating confusion and the potential for harm.
- Major anti-coagulant service and pathway re-design is required if these drugs are to be used, with clear delineation of responsibilities between primary and secondary care with reference to prescribing initiation and continuation.

AACP suggests the following 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.

1. **A Home Medicines Review is recommended for patients on warfarin according to clinical need.**
2. **Patients initiated on warfarin in hospital are routinely referred for a Home Medicines Review.**
3. **Warfarin (new prescription or poor control in therapeutic range) is added to the list of risk criteria for Home Medicine Reviews.**
4. **Prescribing of dabigatran be restricted to specialists and initiation in hospital.**
5. **The model of pharmaceutical company sponsorship of initial therapy should be discouraged.**

Modes of health system delivery which may be used to optimise the use of currently available anticoagulants

Recommendations:

1. **A Home Medicines Review is recommended for patients on warfarin according to clinical need.**
2. **Patients initiated on warfarin in hospital are routinely referred for a Home Medicines Review.**
3. **Warfarin (new prescription or poor control in therapeutic range) is added to the list of risk criteria for Home Medicine Reviews.**

Warfarin is a commonly prescribed oral anticoagulant and is very effective for primary and secondary prevention of thromboembolic events. Warfarin is used in the community setting for indications such as uncomplicated deep vein thrombosis (DVT) and stroke prophylaxis in atrial fibrillation (AF). Warfarin was first approved for use in 1954 and is now the 19th most commonly prescribed drug in Australia with 2.3 million prescriptions dispensed on the PBS in 2008-9, at a cost of over $28M.

Successful warfarin therapy requires a partnership between patients and their carers and health professionals including general practitioners, medical specialists, hospitals and pharmacists.

Point of care (POC) testing in pharmacies and GP surgeries is growing. Results using CoaguChek monitor correlate well with laboratory INR values.[2] Self-management by patients capable of self-testing and monitoring improves the quality of oral anticoagulation.[3]

Patient education and involvement on decision making is critical to optimal benefits with warfarin therapy and minimising risks. In a small Australian study less than 40 percent of GPs provided any patient education at commencement of warfarin therapy, with the others believing this was a role of the specialist, pathology service or dispensing pharmacist.[4] None of the GPs in this study provided routine follow-up of education.

A Home Medicines Review provides an opportunity to discuss the patient preferences and concerns on warfarin therapy, and provide education in their home environment. This patient-centred approach is likely to help patients gain the most benefit from warfarin, whilst minimising the risks. Accredited pharmacists with additional training in warfarin management have been shown to provide appropriate warfarin management

[2] Jackson SL, Peterson GM, Bereznicki LR, Misan GM, Jupe DML, Vial JH. Improving the outcomes of anticoagulation in rural Australia: an evaluation of pharmacist-assisted monitoring of warfarin therapy. J Clin Pharm Ther 2005;30:345-353.
[3] Heneghan C, Alonso-Coello P, Garcia-Alamino JM, Perera R, Meats E, Glasziou P. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis. Lancet 2006;367:404-411.
[4] Lowthian JA, Diug BO, Evans SM, Maxwell EL, Street AM, Piterman L, et al. Who is responsible for the care of patients treated with warfarin therapy? Med J Aust 2009;190:674-677.

recommendations as part of a collaborative management model.[5] AACP is committed to providing appropriate education and certification in warfarin management for accredited pharmacists.

Home Medicines Reviews have been shown to delay the time to next hospitalisation for bleeding in the period 2 to 6 months after the HMR. As this benefit is not sustained over time, six monthly HMRs have been recommended for patient on warfarin who are at high risk of bleeding.[6]

Intensive follow-up and testing of INR by pharmacists post-discharge after initiation of warfarin therapy in hospital significantly decreased the number of bleeding events and increases the number of patients with a therapeutic INR, compared to usual care by a GP.[7]

Pharmacist-monitored anticoagulation is associated with reduced thromboembolic events, an increase in minor bleeding events and no difference in major bleeding events.[8] Patients indicate that pharmacy-based monitoring helps them deal more effectively with warfarin.[2]

Warfarin management and patient support

The following information provides background information on the role of warfarin in the prevention of stroke in atrial fibrillation.

Extensive research in Australia supports an increased role for pharmacists in warfarin management through the provision of Home Medicine Reviews.

1. BACKGROUND

Warfarin has been in widespread use since the 1950s and is currently the most commonly prescribed vitamin K antagonist. It has been conclusively demonstrated that long-term anticoagulation therapy with warfarin can reduce the risk of stroke by approximately 60% in patients with non-valvular atrial fibrillation (AF).[1-5] Warfarin is also established as an effective treatment for the management of venous thromboembolism (VTE), left ventricular dysfunction and valvular heart disease.[6] The number of elderly patients who are eligible for anticoagulation with warfarin is steadily expanding, partly because of the increasing prevalence of AF.[7] The prevalence of AF increases with age; approximately 10% of people over the age of 80 years are affected.[8]

[5] Stafford L, Peterson GM, Bereznicki LR, Jackson SL, van Tienen EC. Training Australian pharmacists for participation in a collaborative, home-based post-discharge warfarin management service. Pharm World Sci 2010;32:637-642.
[6] Roughead EE, Barratt JD, Ramsay E, Pratt N, Ryan P, Peck R, et al. Collaborative home medicines review delays time to next hospitalization for warfarin associated bleeding in Australian war veterans. J Clin Pharm Ther 2011;36(1):27-32.
[7] Jackson SL, Peterson GM, Vial JH, Jupe DML. Improving the outcomes of anticoagulation: an evaluation of home follow-up of warfarin initiation. J Intern Med 2004;256:137-144.
[8] Poon IO, Lal L, Brown EN, Braun UK. The impact of pharmacist-managed oral anticoagulation therapy in older veterans. J Clin Pharm Ther 2007;32:21-29.

While warfarin is a widely prescribed oral anticoagulant, the optimal use of the drug has been hampered by its greater than ten-fold inter-patient variability in the doses required to maintain therapeutic responses.[9] This variation arises from a range of genetic, physiological and environmental factors. Approximately 40% of a person's variability to warfarin dose can be explained by genetic polymorphisms; both the response to warfarin and its metabolism are affected by genetic polymorphisms.[10] Age-related changes in metabolism lead to elderly people being more sensitive to warfarin, which necessitates close monitoring in this group.[11] Warfarin is also subject to multiple drug and dietary interactions.[6] These include the dietary content or extent of absorption of vitamin K, the absorption and metabolism of warfarin (which are increased or decreased by many drugs), and the clearance of blood clotting factors. Intercurrent illness, starting or stopping therapy with other drugs and changes in diet or bowel function can all influence the anticoagulant effect of warfarin. These limitations necessitate regular monitoring of the international normalised ratio (INR) and dose adjustment of warfarin to prevent serious adverse events. Despite almost 60 years of clinical experience with its use, warfarin is still a major cause of adverse drug events and hospital admissions[12-14] and optimal management remains a challenge. Warfarin-related bleeding thrombotic events resulting from therapeutic failure result in significant morbidity and mortality to individual patients and substantial costs to the healthcare system.[15]

1.1. Warfarin in the elderly

Most individuals who receive oral anticoagulant therapy are elderly patients with AF and acute or recurrent VTE. Anticoagulation in elderly patients poses unique challenges because they are simultaneously at higher risk for recurrent thromboembolism and major bleeding, including catastrophic intracranial haemorrhage.[16, 17, 18] The fear of bleeding and the anticipated difficulty in controlling warfarin therapy are often reasons that warfarin is not prescribed to elderly people.[19] However, recent studies demonstrate that age alone should not be considered a contraindication to warfarin. In the BAFTA study, aspirin was compared to warfarin in people over the age of 75 years with AF.[20] Warfarin treatment was associated with a reduced risk of stroke or systemic embolism than aspirin, with a similar risk of major bleeding. While age alone is not a contraindication to warfarin treatment, it is important that true contraindications (e.g. bleeding disorders, previous gastrointestinal bleeding, uncontrolled hypertension, heavy alcohol intake, liver disease, unsupervised dementia or potential non-adherence with treatment or monitoring) are considered prior to warfarin treatment and periodically thereafter.

1.2. INR control

The safety and efficacy of warfarin therapy depends on maintaining the INR within the established therapeutic range.[21, 22] The INR is often monitored daily until INR is stable in the therapeutic range. Australian consensus guidelines for warfarin therapy recommend that the INR should be measured daily or second-daily during the first week of treatment.[23] The interval should then be increased depending on the response. Once stabilised, most patients can then be well controlled with testing every four to six weeks, although some may require more frequent monitoring.[23] The INR should be tested more frequently if there are changes in the patient's condition, including intercurrent illness (e.g. heart failure, hepatic disease, GI disturbances, infections, thyroid disorders), concurrent drugs, amount of alcohol consumed, or diet (e.g. green leafy vegetable consumption).

The optimal INR for patients on warfarin for AF is between 2.0 and 3.0 (target 2.5).[24] A target INR range of 2.0 to 3.0 is also appropriate for the treatment and prevention of subsequent VTE and for the majority of patients with bioprosthetic and mechanical heart valves. A minority of patients require an increased target INR range of 2.5 to 3.5; indications for a higher target range include the presence of AF in patients with a mechanical heart valve and those with a mechanical or bioprosthetic heart valve placed in the mitral position.

This monitoring process is time consuming and has been cited as one reason for the non-prescription of warfarin.[25] It can reduce patient adherence and increase the risks associated with the treatment,[26] especially with people who are housebound, live far from a monitoring site, or who have a regular job and find it difficult to attend regular appointments.[27]

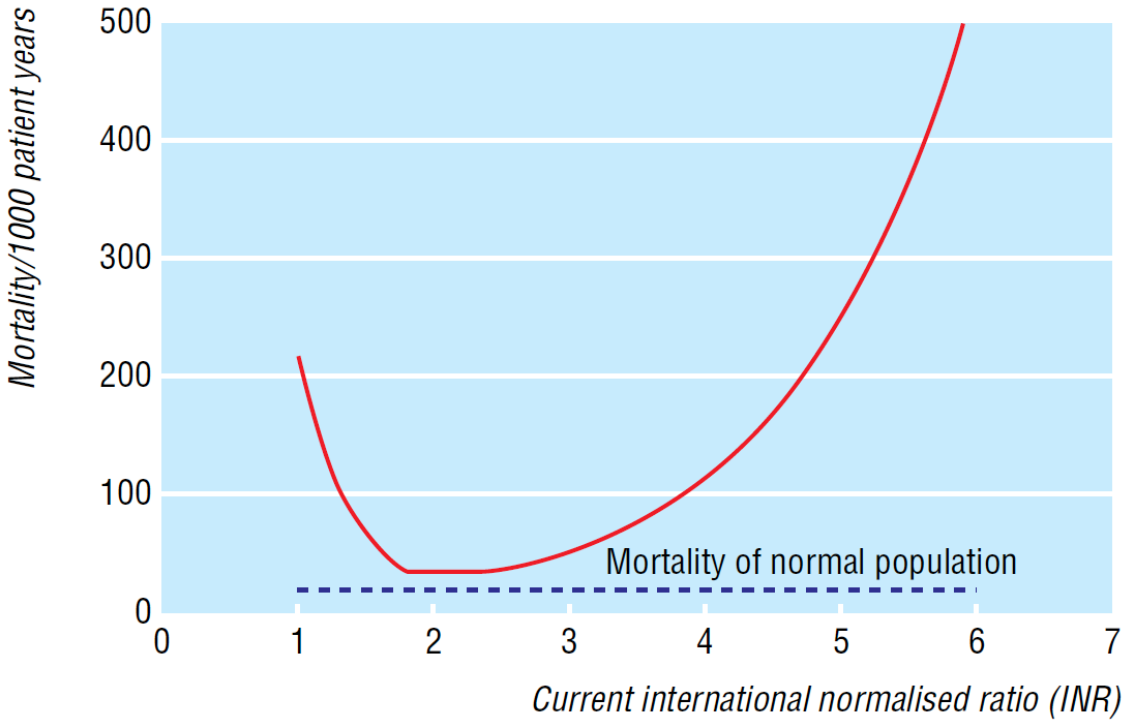
The benefit of warfarin therapy is strongly linked to the proportion of time that patients spend in the target INR range (time in therapeutic range; TTR).[21, 28] The risk of death, myocardial infarction, major bleeding and stroke or systemic embolism are all related to INR control.[22] In community-based practice, the TTR is usually only 50-60%,[29] with some studies estimating that patients on warfarin may be in the therapeutic range as little as one-third of the time.[30] INR control in prospective randomised controlled trials (RCTs) is typically higher than that achieved in community practice. On the other hand, patients who self-monitor their INR typically spend a greater proportion of time in range than patients managed by usual care.[29] It is worth noting that improvements in TTR of even 5 to 10% are clinically important.[22, 31] A systematic review of 67 randomised controlled studies (RCTs) and observational studies found that anticoagulated patients were within their target range 64% of the time across all study populations.[29] However, patients managed outside of RCTs or specialised anticoagulation clinics spent significantly less time in their target range. For patients managed in an RCT setting, an anticoagulation clinic setting or a community setting, the average proportions of time in target range were 66%, 66% and 57%, respectively.[29] A subsequent systematic review and meta-analysis of international studies focussed on patients with AF provided similar findings,[32] demonstrating that patients who receive long-term anticoagulation have similar INR control, regardless of their indication for anticoagulation. Recent data from the Australian general practice setting suggests that the TTR of people taking warfarin is in the order of 60-70%. In the recently published Australian Point of Care Testing in General Practice trial, patients spent a mean of 68% of their time within their target INR range.[33]

1.3. Risks associated with warfarin therapy

The effectiveness and safety of warfarin is maximised by maintenance of a target INR range, below which effectiveness is lost, and above which the bleeding risk is unacceptably high.[34] The major complication of anticoagulant therapy is bleeding.[17, 35, 36] Clinical trial data indicates that the intensity of warfarin therapy is the most important risk factor for haemorrhage from any site, independent of other risk factors.[37, 38] In a large medical record linkage study, mortality related to bleeding was lowest at an INR between 2.0 and 2.4 for 42,451 patients (mean age 71 years) with any indication for warfarin therapy.[21] The risk of death increased with increasing INR such that the risk increase per INR unit above 2.5 was 2.2 for all indications.[21] Interestingly, the risk of bleeding related mortality was similar for

INR ranges 1.5-1.9 and 2.0-2.4; however, the annual risk of all cause mortality was 1.8% lower when the INR was between 2.0-2.4. Above an INR of 2.9, the risk of bleeding-related mortality increased exponentially. This is confirmation that for patients who are receiving warfarin, the risk of serious adverse events is lowest within the target range, and suggests that clinicians should avoid attempting to manage elderly patients at lower than normal target ranges. Figure 1 shows the relationship between the INR and mortality of patients taking warfarin.

Figure 1. The relationship between INR achieved during warfarin therapy and mortality. Taken from Oden et al. 2002.[21]



Based on estimates from randomised trials, the average annual frequencies of fatal, major, and major or minor bleeding during long-term warfarin therapy are 0.6%, 3.0%, and 9.6%, respectively; these frequencies are approximately five times those expected without warfarin therapy.[35, 36, 39] The definition of major bleeding is generally bleeding which requires treatment, medical evaluation or at least 2 units of blood). The definition of minor bleeding is generally bleeding that is reported by patients, but does not require treatment, medical evaluation or visits.[6] Major independent risk factors for bleeding during long-term warfarin therapy include co-morbid conditions other than the indications for therapy, history of stroke, history of gastrointestinal bleeding, advanced age (> 65 years) and the intensity of anticoagulant therapy.[35, 36, 39-41]

Bleeding complications with anticoagulant drugs appear to occur more frequently in older patients than in younger individuals,[16, 18, 35, 39, 42-45] although this remains controversial.[46, 47] Older patients may be at an increased risk for anticoagulant-related bleeding because of their generally increased incidence of adverse drug reactions, increased prevalence of

comorbidity and polypharmacy, and increased vascular and endothelial fragility.[48] Torn et al. found that of 4,202 patients who were treated with oral anticoagulation therapy due to the presence of a heart valve prosthesis, AF, or recent acute myocardial infarction, the rate of major haemorrhage increased from 1.5 to 4.2 per 100 patient-years, as the age of the patient rose from less than 60 years to more than 80 years.[49]

1.4. Role of medication reviews in people taking warfarin

Critical roles for pharmacists in improving the outcomes of warfarin therapy involve minimising the risk of bleeding, educating patients about their treatment, and assisting with the monitoring of warfarin treatment. Warfarin is very effective at reducing the risk of thrombosis, but possesses a narrow therapeutic index and requires careful monitoring and dosing in the elderly. Management in the elderly is complicated by factors such as the increased risk of bleeding, compliance, polypharmacy, and concomitant diseases that require careful individualisation of treatment.[50]

The DVA introduced a system of providing formal medication reviews for Australian Veterans in 1999, which was followed by the HMR program (available to all members of the Australian public) in 2001. These reviews provide an opportunity for patient education and review of warfarin management in the community setting. General practitioners refer patients to an accredited pharmacist who undertakes a home visit, identifying any medication related problems, including potential underuse, overuse, adverse effects, compliance and knowledge problems, or hoarding. The pharmacist provides a report to the doctor who has responsibility for follow-up with the patient. The potential benefits of patients receiving a pharmacist-conducted medication review were established in several large research projects performed in the late 1990s.[51-53] Most of these studies found that HMRs resulted in the resolution of drug-related problems (DRPs) and showed trends in reduced medication costs.

Recent studies in Australia involving a combination of pharmacist interventions and point-of-care (POC) INR monitoring based on the Home Medicines Review have found that pharmacist intervention reduces the risk of complications with warfarin therapy in the early post-discharge period.[54, 55] The first of these studies was an RCT comparing a trained pharmacist providing home-delivered post-discharge care to usual care for patients initiated on warfarin in hospital.[54] During this trial, patients received four home visits and POC INR monitoring on alternate days commencing two days post-discharge. Compared with usual care, the service resulted in improved attainment of therapeutic INRs and a reduced rate of supratherapeutic INRs at eight days post-discharge, and reduced rates of haemorrhagic complications to 90 days post-discharge. However, most of the beneficial effect of the intervention was due to a reduction in minor bleeding, and not events that resulted in hospitalisation. A second study compared the clinical outcomes of usual post-discharge care (UC) with those of a collaborative, home-based post-discharge warfarin management service (PDS). The PDS comprised two or three home visits by a trained HMR-accredited pharmacist to patients taking warfarin in their first eight to 10 days after discharge from hospital.[55] The PDS was associated with a statistically significant reduction in the rate of combined major and minor bleeding events to 90 days post-discharge (5.3% vs. 14.7%; p=0.03) when compared with usual community-based care.[56] The rate of combined

bleeding and thromboembolic events to Day 90 was also decreased (6.4% vs. 19.0%; p=0.008), and there was a non-statistically significant trend towards a reduction in major bleeding events (4.3% vs. 2.2%, p=0.39).

A recent study by Roughead et al. assessed the effect of HMRs in Australian veterans and war widows taking warfarin retrospectively using administrative claims data.[57] This study identified a 79% reduction in the likelihood of hospitalisation for bleeding between two and six months following the HMR (hazard ratio 0.21, 95% CI 0.05 - 0.87). This beneficial effort was not evident 6 to 12 months following the review. As INR testing and TTR were not assessed in the study, it is unclear whether improved INR control occurred as a result of the HMR, or whether the benefits occurred independently of improved INR control.

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