Review of Anticoagulation Therapies in Atrial Fibrillation

The following submission to the Review of Anticoagulation Therapies in Atrial Fibrillation is divided into two Sections. Section 1 addresses current stroke prevention treatment in patients with AF with warfarin and seeks to characterise and quantify subgroups of such patients according to whether or not they receive adequate anticoagulant therapy. Section 2 presents a systematic review of various warfarin management programs that have been used to improve warfarin therapy and summarises the evidence available to show how effective these programs are.

1. Characterising AF patients considered for anticoagulant therapy

1.1. Disadvantages of oral anticoagulants and evidence of under-treatment around the world

The principal agents currently used for stroke prevention in AF (SPAF) patients are oral anticoagulants, such as warfarin, and antiplatelet agents such as aspirin. Warfarin is the most widely used oral anticoagulant (OAC) for SPAF and prevents blood coagulation by inhibiting an enzyme that recycles vitamin K to its active form after it has been involved in the carboxylation of factors II, VII, IX and X in the coagulation cascade (Ansell et al 2004). Hence, warfarin and other coumarins are known as vitamin K antagonists (VKA). Since the late 1980s a number of clinical trials have demonstrated the effectiveness of VKAs for SPAF (Hart et al 2007) and have since had an established role in this indication. However, VKAs have a number of disadvantages that make patient management challenging. The limitations of VKAs alongside aspirin are outlined in Table 1-1.

Table 1-1: Limitations of currently available treatments for SPAF

Treatment	Limitation	Comment
Warfarin	Narrow therapeutic window	The range between a dose that produces benefits and a dose that is potentially harmful is small
	Inter-patient variability in anticoagulant activity / Need for constant monitoring	Regular blood tests and dose adjustments are necessary to maintain the level of anticoagulant activity within the target range. This is inconvenient and time-consuming and can be particularly difficult for the elderly patient.
		Dosing problems can arise due to non-adherence by the patient and miscommunication between the patient and physician
	Drug and food interactions	A balance between the warfarin dose and the amount of vitamin K in the body is necessary and can be difficult for both the AF patient and the physician to manage.
		Dietary vitamin K, for example from green leafy vegetables, can affect the amount of warfarin needed to maintain the INR.
		Several commonly used drugs increase the anticoagulant activity of

Treatment	Limitation	Comment
		warfarin either by reducing its metabolism or reducing vitamin K levels. These include certain antibiotics (erythromycin, ciprofloxacin and metronidazole) cimetidine, omeprazole and amiodarone (of particular significance since it is frequently used in the management of AF patients). The activity of warfarin can be reduced by certain drugs including barbiturates and carbamazepine. These drug interactions may result in the patient experiencing serious side effects e.g. bleeding if the level of warfarin is too high or an increased risk of stroke if the level of warfarin is too low.
Aspirin	Efficacy / Mechanism of action	Aspirin is of only moderate efficacy and is significantly less effective than OACs. Aspirin is an antiplatelet agent not an anticoagulant.
	Adverse events	Aspirin is associated with bleeding events, mainly GI (Camm et al 2010).

Although guidelines recommend use of aspirin only for lower risk patients, in practice it is also used in high risk patients possibly due to concerns about risks of haemorrhage and limitations of VKAs. Two recent studies have shown the potential benefits of OACs over aspirin (Rash et al 2007, Mant et al 2007) and questions have arisen as to the actual benefits of aspirin even in low risk patients. A study of 871 low risk patients in Japan was stopped because the rates of the primary endpoint (cardiovascular death stroke or transient ischaemic attack (TIA)) were not markedly lower with aspirin than in the untreated control group, and a higher rate of major bleeds was found in the aspirin group (Sato et al 2006).

Guidelines for SPAF have been developed to encourage best practice and a systematic approach to treatment among physicians, with the intention of achieving the best outcome for the AF patient. Among the most current are those of the European Society of Cardiology (ESC) 2010, the AHA and American Stroke Association (ASA) (2010/11) (Camm et al 2010; Goldstein et al 2011). Earlier major and influential international guidelines were those of the ACCP (8th edition) published in 2008 and the joint guidelines of the ACC, AHA and European Society of Cardiology (ACC/AHA/ESC), from 2006 (Fuster et al 2006; Singer et al 2008); an update of specific sections of the ACC/AHA guideline was published in 2011 (Wann et al 2011).

The most recent guidelines from the American College of Chest Physicians (ACCP Evidence-Based Clinical Practice Guidelines, 9th ed.) recommend an OAC in AF patients with any additional risk factor for stroke, where there is no contraindication (Guyatt et al 2012). This is represented by a $CHADS_2$ score of 1 or more, where $CHADS_2$ is an assessment score for the risk of stroke in patients with atrial fibrillation incorporating the following risk factors: Congestive heart failure, Hypertension, Age, Diabetes and history of

Stroke (ischemic or unknown type) or TIA. $CHADS_2$ score ranges from 0 (1.9% per year risk of stroke without anticoagulation therapy) to 6 (18.2 % per year risk) and is based upon assignment of points for each of the following: 1 point each for the presence of congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus and 2 points for history of stroke or TIA. These recent guidelines recommend a target INR of 2.0−3.0 for those who receive a VKA. In individuals at moderate risk of stroke (AHA/ASA) an OAC is preferred. Although an antiplatelet agent (usually aspirin) is an option in such patients, it is not presented as a recommended alternative as in the older guidelines.

Despite the existence of guidelines for anticoagulant therapy in atrial fibrillation (AF), a high proportion of patients with AF who should be eligible for oral anticoagulation do not receive VKAs according to guideline recommendations. As mentioned above, VKAs are associated with several disadvantages, including demonstrating a narrow therapeutic window, requirement for regular monitoring of blood anticoagulation parameters (INR) and a range of drug and food interactions which complicate the maintenance of optimal anticoagulant activity. Concern about such issues may contribute to the underuse of OACs, with the result that many patients at high risk of stroke receive antiplatelet therapy, even where the guidelines recommend OACs. Concern about bleeding and particularly a risk of intracranial haemorrhage is another factor that influences the choice of treatment.

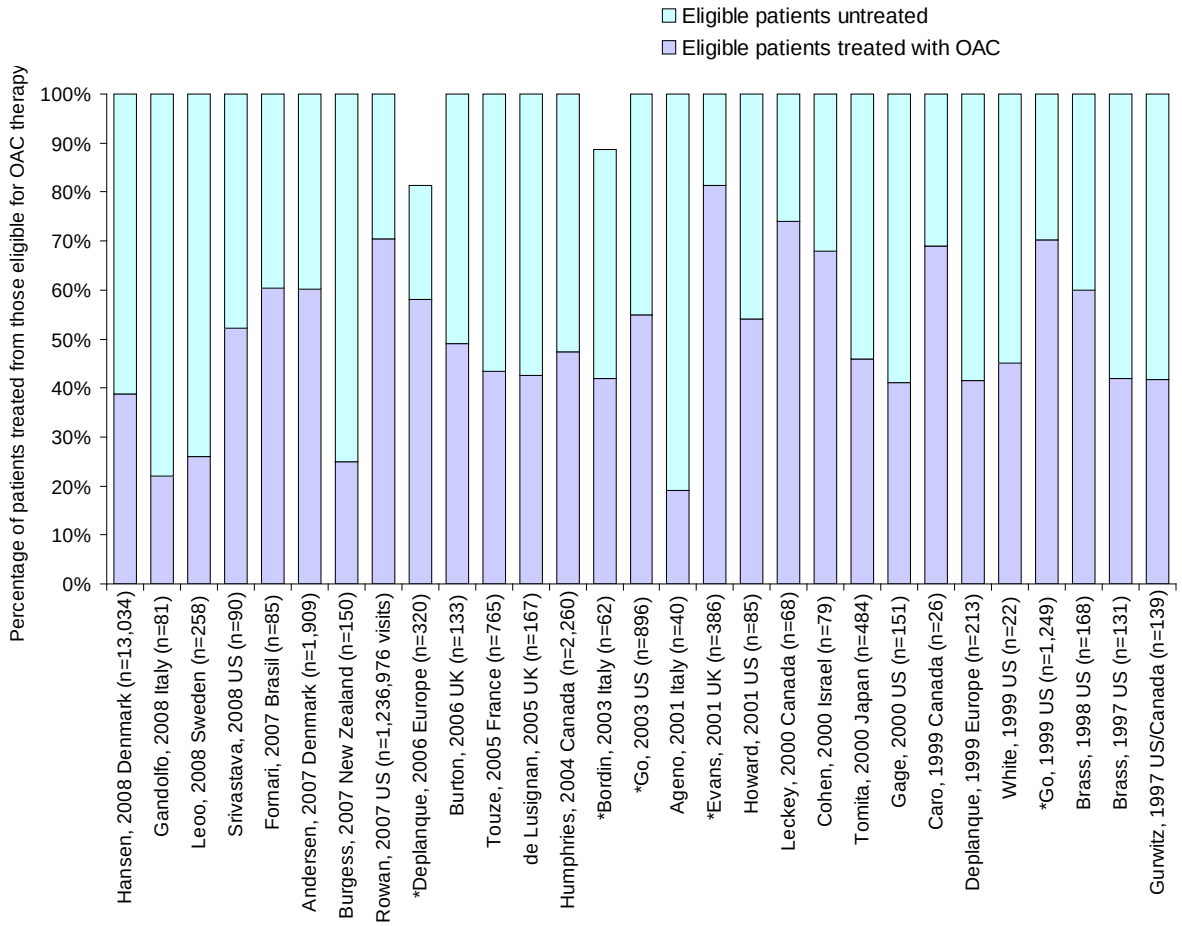
The following section reviews the evidence of under-prescribing of oral anticoagulants (OACs) even in patients at the highest risk of stroke. Data from around the world suggests that VKAs are extensively underused:

- A systematic review of studies in AF patients found that around 50% of eligible AF patients do not receive VKAs
- Studies in Europe in general practice demonstrate between 25% and 50% of AF patients eligible for OACs according to current guidelines actually receive them.

A systematic review of 98 papers compared current treatment practices for SPAF with current guidelines (Friberg et al 2006). The percentage of AF patients eligible for OAC due to elevated risk stroke was compared with those who actually received treatment. Under-treatment was defined as less than 70% of eligible AF patients receiving treatment (Friberg et al 2006). The majority of the 54 studies where risk levels for stroke was reported showed underuse of OACs. Among 29 studies of patients with a history of stroke or TIA, who would be eligible for OACs under the then current published treatment guidelines, 25 studies showed under-treatment. In the majority of these studies (21 of 29) fewer than 60% of

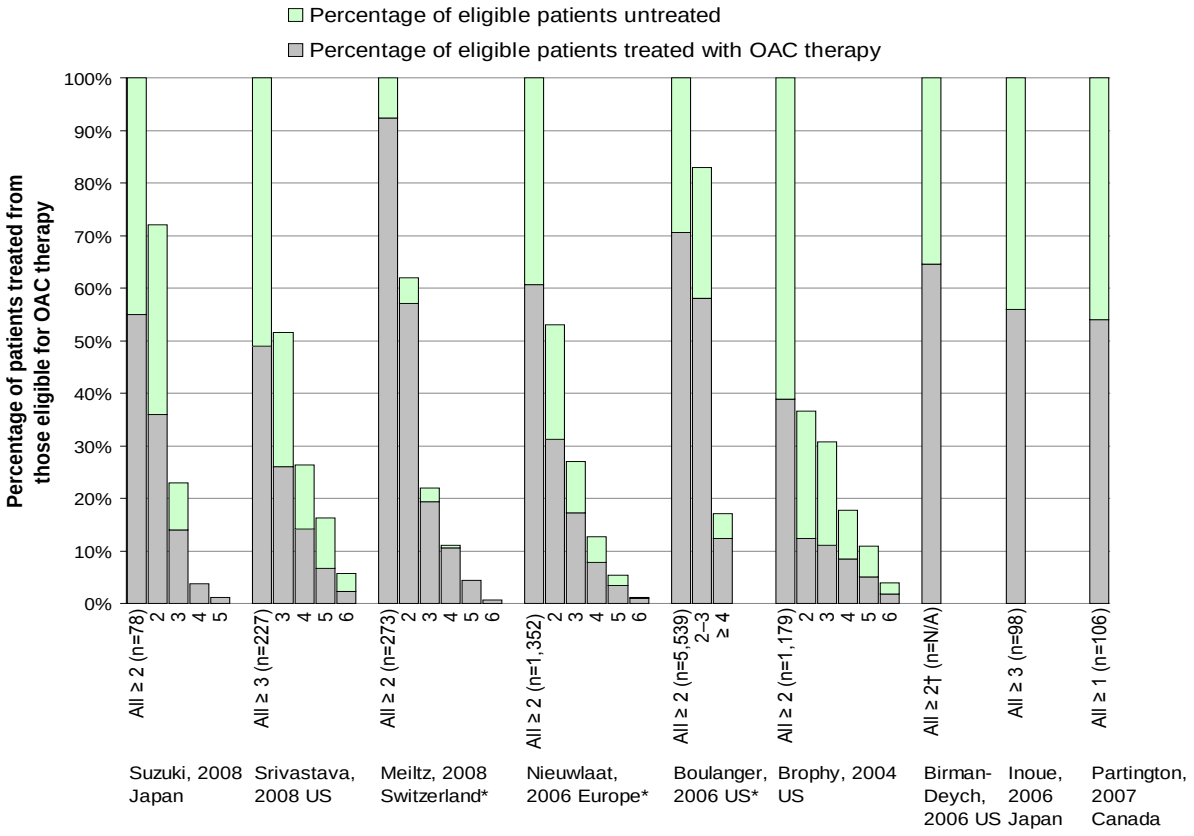
eligible patients received OACs (Figure 1-1). Additionally, in around half of the studies (15 of 29) fewer than 50% of eligible patients received OACs (Frost et al 2002).

Figure 1-1: Patients with atrial fibrillation and prior stroke/TIA : OAC treatment levels as a proportion of patients eligible for OAC therapy (Frost et al 2002)



The $CHADS_2$ stroke risk stratification score was used in 9 of the 54 studies to identify AF patients at high risk of stroke, i.e. with a $CHADS_2$ score ≥2. OAC therapy was sub-optimal (<70% of eligible AF patients receiving OACs) in all but two of these studies. Indeed, in the majority of these studies (5 of 9) treatment levels were below 60% (Figure 1-2) (Frost et al 2002). However, in all 9 studies OAC usage increased with increasing $CHADS_2$ score with 41-100% of patients with a $CHAD_2$ score greater than 4 receiving OACs.

Figure 1-2: Patients with AF at high risk of stroke ($CHADS_2$ score): OAC treatment levels as a proportion of patients eligible for therapy (Frost et al 2002)



A comprehensive survey of the use of antithrombotic prophylaxis in AF patients, the European Heart Survey, involved 5,333 patients from cardiology practices in 35 European countries (Friberg et al 2006). In this study, 86% of patients had one or more risk factors for stroke and were eligible under the AHA/ACC/ESC criteria for OACs, but only 67% of these received OACs (including around 5% who received both OACs and antiplatelet agents) while most of the remainder received antiplatelet agents. In contrast to the under-treatment of some patients eligible for OACs, 47% of patients who were not eligible for OACs actually received them (Friberg et al 2006).

The European Heart Survey showed that prescriptions of antithrombotic drugs did not always correspond to patients' stroke risk profile. The study, which compared prescriptions of antithrombotics with risk stratification according to four different risk schemes (ACC/AHA/ESC 2001 guidelines, $CHADS_2$ score, Framingham score, and the ACCP 2001 Guidelines), found that although prescription of OAC therapy did increase with worsening stroke risk for all four stratification schemes, only some risk factors positively influenced OAC prescription (Garcia-Garcia et al 2005). Valvular heart disease and diabetes were associated with OAC prescription while prior stroke or TIA, hypertension, age >75 years and

coronary heart disease were not (Garcia-Garcia et al 2005). The study also found that although patients with paroxysmal AF had a comparable risk for thromboembolic events to patients with permanent or persistent AF, fewer paroxysmal AF patients at high risk of stroke received an OAC (Garcia-Garcia et al 2005).

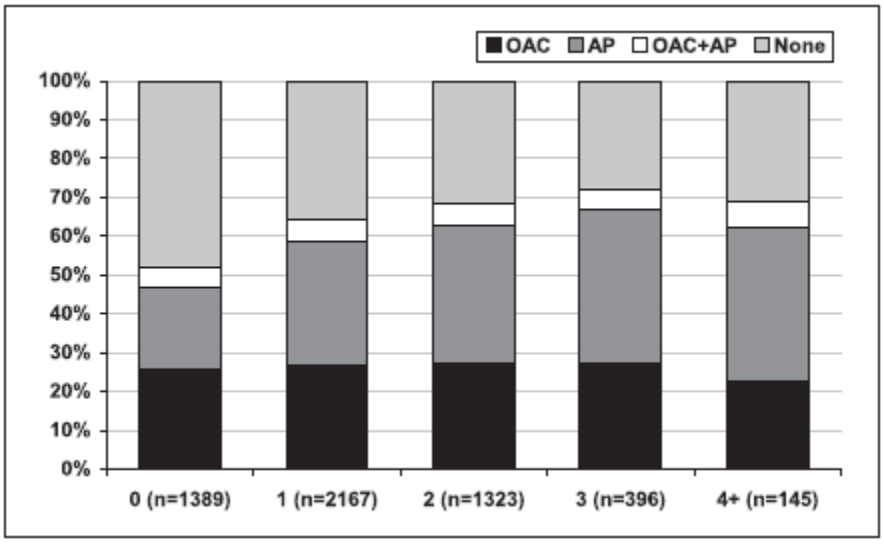
Underutilisation of OACs in clinical practice was also demonstrated using data from 400 Italian primary care physicians (Health Search/Thales Database). In the study period (2001 to 2005) amongst 5,420 new patients with AF, 26.6% were prescribed an OAC, 30.7% received an antiplatelet agent and 5.5% received both, but 37.2% received no antithrombotic treatment (Chien et al 2008).

This study also found that prescription of OACs did not correspond to the number of stroke risk factors in the $CHADS_2$ risk classification (see Figure 1-3). Only 23–27% of patients in any $CHADS_2$ risk category received OAC alone, with a further 5–7% receiving an OAC plus an AP. Even in the highest risk category, 31% of patients did not receive any antithrombotic drug (Chien et al 2008). However, antiplatelet, but not OAC, use significantly increased ($p < 0.0001$) with a worsening stroke risk as determined by $CHADS_2$ risk score: score 0 – 20.8%, score 1 – 31.7%; score 2 – 35.9%; score 3 – 39.4%; score ≥ 4 – 39.3% (Chien et al 2008).

A number of factors influenced the likelihood that patients would be prescribed an antithrombotic (Chien et al 2008):

- The date of diagnosis – patients diagnosed in 2004 were more likely to be treated than those diagnosed in 2001
- Concurrent heart valve disease, congestive heart failure and bone fracture were associated with an increased likelihood of OAC use. In contrast hypertension and peptic ulcer were associated with a decreased likelihood of OAC use.
- Antihypertensive drugs and lipid-lowering agents were positively associated with OAC use
- Elderly patients, 85 years of age or over, had an increased probability of receiving an AP agent, but not an OAC.

Figure 1-3: Italian primary care study – antithrombotic drug prescription per risk category according to the $CHADS_2$ score (Chien et al 2008)



Correlation between worsening stroke risk and change in antithrombotic prescription:
p-values: OAC, 0.7683; AP, <0.0001; OAC+AP, 0.7417.

Another analysis of antithrombotic treatment received by AF patients included data from 34 studies. This review found that the average percentage of untreated VKA eligible AF patients (i.e. those at moderate or high risk of stroke) across studies was 20%, with a range from 2-46%. This wide variation was thought to be in part attributable to differences in definitions of stroke risk. In the six studies that used the $CHADS_2$ score an average percentage for untreated VKA eligible patients of 12.5% was obtained (range: 2-28%) (White et al 2004).

A comparison of published international studies show the proportion of AF patients who receive OACs varies from country to country and clinical setting to clinical setting within these countries:

One published study was found for France.

- In this study in France in very elderly AF patients (mean age 84.7 ± 7 years), 48.8% were receiving OACs and 51.2% aspirin. The majority of patients receiving OACs (46.9%) were at very high risk according to the $CHADS_2$ risk stratification (Mahmud et al 2007). The investigators noted, however, that thromboembolic risk was underestimated, and haemorrhagic risk overestimated, so patients who may have been eligible for OACs did not receive them (Mahmud et al 2007).

Two studies in Germany showed varying rates of OAC use.

- An observational study in Germany, involving 361 patients (mean age 71 years) with AF recruited from physician practices, reported that 89% of AF patients, received OAC and 9% antiplatelet agents. The authors commented that this level of OAC usage contrasted with previous studies where rates of 20-30% and 35-65% have been reported (Sudlow et al 1998).
- In a study of 1,463 patients with a history of stroke of TIA, and consequently at high risk of further stroke, only 30.5% were receiving OACs on hospital discharge, with a further 13.9% receiving LMWH. Of 329 patients who were followed for 1-2 years (mean 1.52 ±0.42) 88.7% were still on OACs at follow up (Murdoch et al 2005).

Published Italian levels of reported levels of VKA usage varied widely, but frequently show underuse of OACs:

- The analysis of the Health Search Database which looked at antithrombotic usage among AF patients in general practice in Italy, demonstrated that only 26.6% of 5,420 new AF patients received OACs and 37.2% received no antithrombotic treatment at all (Chien et al 2008).
- A study by Bo et al. (2007) examined the usage of OACs before and after implementation of treatment guidelines in a study conducted in a teaching hospital in Northern Italy. The study showed that in 2000, 56.6% of patients (n=313) for whom OACs would be appropriate did actually receive them, and by 2004 this had risen to 81.9% (DeWilde et al 2006).
- In contrast, a study in 51 general practices in Northern Italy (Fillipi et al 2000), involving 719 patients with AF (40 years of age or more), reported that only 4% of patients were at low risk of stroke, while 3% were at moderate risk and 64% at high risk. The use of OACs was 29%, 14.3% and 22.8%, in low, moderate and high risk patients respectively, whereas the use of antiplatelet agents was 22.6%, 37.1%, and 65.1%, respectively. The investigators commented that almost 20% of the moderate and high risk patients received no antithrombotic treatment at all, and that warfarin was markedly underused, particularly in high risk patients (Boggon et al 2009).
- A more recent retrospective cohort of antithrombotic usage from 2001 to 2004 was included in a study conducted by Alacqua et al. (2008), using information from 400 Italian general practitioners. Of 5,420 patients diagnosed with AF, 37.2% did not receive a prescription for an antithrombotic agent, 26.6% were prescribed an OAC, 30.7% were prescribed an antiplatelet agent and 5.5% were prescribed both. As patients' stroke risk worsened (according to the $CHADS_2$ risk score), antiplatelet use increased significantly

($p<0.0001$), but OAC use did not ($p=0.7683$). Only 23-27% of patients in any $CHADS_2$ risk category received OAC alone, with a further 5-7% receiving an OAC plus an antiplatelet agent. Even in the highest risk category, 31% of patients did not receive any AT drug (Meiltz et al 2008).

- Further evidence of under prescribing of antithrombotic treatment in Italy comes from a study of 1,549 patients admitted to hospital with first-time stroke between 2000 and 2003. Of these, 238 patients (15.4%) had been previously known to have AF. Only 52.1% of patients with a known history of AF had been receiving any antithrombotic treatment: 13% had been receiving oral anticoagulants, and 34.9% antiplatelet agents (Rowan et al 2007).

In studies completed in Denmark, low overall levels of VKA treatment of AF patients have been reported.

- In a study conducted between 1995 and 2002, involving 68,546 patients (aged 50-99 years) with a diagnosis of AF who survived at least 3 months following hospital, 36% started warfarin treatment. Over the observation period, the proportion of patients who were prescribed warfarin increased, particularly among patients over 80 years of age where it rose from 13% to 23% (Boulanger et al 2006).
- Another study examined OAC prescribing in 2,699 men and 2,425 women with AF, aged 60-89 years, discharged from hospital in the 1991-1998 period. In this population, 31% of men and 23% had one or more recorded prescriptions of OAC (Go et al 1999).

Published data from Spain shows VKA use in eligible patients ranged from less than 30% to 71%.

- In a population-based study in primary care involving 416 patients diagnosed with chronic AF from a population of 28,447, the investigators considered that 81% of patients (96.8 with valvular AF and 78.2% with non-valvular AF received the correct antithrombotic treatment). A total of 71.4% received oral anticoagulants, 17.3% received aspirin and approximately 4.6% received other antiplatelet agents (clopidogrel, ticlopidine or trifusal) (Candel et al 2004).
- The CARDIOTENS study (1999), identified 6,194 patients with a history of previous cardiovascular disease from a cross-section of 32,051 outpatients seen on the same day by 1,159 physicians specialising in primary-care (79%) and cardiology (21%). Only 28% of patients with AF received OACs and 31% antiplatelet agents. There was a greater use of OACs among patients who had been seen by the cardiology specialists than among those seen in a primary care setting (37% vs. 21%; $p<.001$) (Miyasaka et al 2006).

- A small scale study, among 50 patients hospitalised for stroke, who had a history of AF of a least one year's duration, found that although 90% of the patients would have been eligible for OACs according to the then current guidelines, only 32% had actually received it (Fang et al 2004).

Studies published using data from Ireland show VKAs are underused in AF patients, and that this is most marked among older patients.

- In a community-based study, a total of 70 patients with AF were identified among 2,684 patients in two clinical practices: 26 of these patients had contraindications to OAC. Among those for whom warfarin was indicated, 47% (21 of 44) received an OAC. Of those patients not on OACs and those for whom aspirin was not contraindicated 20 of 42 were not on aspirin (Gage et al 2000).
- In a large scale database study of patients in general practice, in which digoxin use was used as surrogate indicator for the presence of AF, 21,971 patients were identified with possible AF. In any given month 36% were receiving warfarin, 51% were receiving aspirin, 8% were receiving both and 5% were not receiving any antithrombotic treatment. In the ≥75 age range, 26% of patients were on warfarin, and 3% on both warfarin and aspirin (Baker et al 2009).

Studies across the United Kingdom (UK) showed the overall AF population on OAC therapy ranged from 21.4-65.2% (Gladstone et al 2009; McBride et al 2007).

- In a community-based cross-sectional study conducted in Glasgow, Scotland between 1999 and 2001, 1,416 patients (mean age 73-74) with AF were identified. Of these 53% were receiving OAC (warfarin), of those who did not receive warfarin 65% did not have any contraindications to its use (McBride et al 2007).
- In another community-based study, 4.7% (228) of 4,843 subjects screened from primary care practices in Northumberland had AF. Although 61% of these patients would have benefited from OAC according to risk stratifications based on the Stroke Prevention in Atrial Fibrillation (SPAF) study, only 23% actually received oral anticoagulation (Gladstone et al 2009).
- An analysis was conducted of practice data taken from eight general practices (81,811 patients) in the south of England. Of 944 patients with AF, 82.8% were ≥65 years. Of these patients 42.6% of men and 35.2% of women had been prescribed OACs, and 28.2% of men and 34.5% of women prescribed aspirin. The study looked at high risk groups to see if more intensive treatment was targeted at those most at risk, however,

warfarin and aspirin were prescribed in similar proportions to patients in the very high, high and moderate risk categories, with less prescribed to those at low risk.

- DeWilde et al. (2006) used data from 181 UK general practices to investigate changes in the prevalence of AF and of OAC use between 1994 and 2003. Over this period AF prevalence rose from 0.78% to 1.31% in men and from 0.79% to 1.15% in women. The proportion of patients with AF taking anticoagulants rose from 25% to 53% in men and from 21% to 40% in women; most other patients received antiplatelet agents. However, only 56.5% of patients at very high risk of stroke were taking warfarin, although most of the rest were taking antiplatelet drugs. In addition 38.2% of AF patients at low risk of stroke were receiving OACs (Hirsch et al 2001).
- A study based on information from the General Practice Research Database (GPRD), which comprises the computerised medical records of general practitioners in the UK, looked at the records of 35,083 AF patients. In a subset of 14,445 patients with incident AF, 49.6% received warfarin and 57.1% received aspirin. There was some overlap with 23.3% of the total receiving both aspirin and warfarin. However, 16.4% received neither antithrombotic (JCS 2008).

One published study was identified from Switzerland.

- A 2005 study in Switzerland in 23 cardiology practices in Geneva found that 92% of AF patients with a $CHADS_2$ score >2 were receiving an OAC. This is one of the highest usage rates of OACs with these specialists closely following guideline recommendations. However, in this study there was high usage of OACs (58%) in low risk AF patients, outside the current treatments guideline with may be due to concerns in this group of physicians about the risk of stroke in younger (<65 years) AF patients (Dolan et al 2008).

The overall picture of OACs use in Europe demonstrates that between a quarter and just over a half of AF patients who were eligible for OACs, according to current guidelines, actually receive them. However, it is important to note that in some studies where guideline recommendations are followed, levels of appropriate OAC usage are high (Sudlow et al 1998; Dolan et al 2008).

As is the case in Europe, there is evidence of the underuse of OACs among AF patients in the USA, although use of OAC has risen since the 1990s.

- An analysis of data from the National Ambulatory Medical Care Survey (NAMCS), a survey of US office-based medical practice, found that the overall frequency of OAC usage also increased from 40.3% of all patients with AF between 1994 and 1997 to

49.1% between 2001 and 2003 (Heneghan et al 2006). Interestingly, the increase in OAC use was greater among patients with comorbid risk factors for stroke than for those without. However, there was also increased use of OACs in younger patients at low risk of stroke, although guidelines do not recommend their use in such individuals (Heneghan et al 2006).

- A retrospective analysis of data from electronic medical records for approximately 14,000 patients treated for AF at US physician centres across the country was conducted between 1998 and mid-2003. It found that approximately two-thirds of these patients were prescribed warfarin alone or in combination, 12% of patients were prescribed aspirin alone, while 23% of patients did not receive any form of antithrombotic treatment (Ogilvie et al 2009).
- The Anticoagulation and Risk Factors in AF (ATRIA) study that included AF patients enrolled in a large Californian health maintenance organisation found that 55% received warfarin in 1996 and 1997 (CSD 2009).
- An earlier analysis of data from the NAMCS found that at 41% of visits by patients with AF in 1999 and 2000 the patients were receiving OACs (Jones et al 2005).
- A retrospective study of data from a Californian Medicaid population between 1993 and 1996 found that only 55% of 597 AF patients were prescribed antithrombotic therapy at hospital discharge: 34% received warfarin and 21% received aspirin (Gallagher et al 2008).

There is also evidence in Japan that patients do not receive OACs in line with treatment guidelines. For example, in a study of risk factors based on the database of the Japan Thrombosis Registry for AF, Coronary, or Cerebrovascular Events (J-TRACE)' approximately one-quarter of patients (n=2.242) with AF who had $CHADS_2$ scores ≥2 did not receive treatment with an oral anticoagulant (Reynolds et al 2006).

Evidence from Australia is limited but there is an indication that VKAs are also significantly underused here. Jackson et al. (2011) showed that among hospital in-patients, on admission and before risk assessment, only 16% of low risk patients were being treated with warfarin compared to 30% of moderate risk patients and 31% of high risk patients. In a study by Bajorek et al. (2002), elderly patients aged ≥80 years with AF who are generally at high risk of stroke were less likely to receive warfarin than those aged <80 years (25.5% versus 61.5%).

Despite the strong evidence for VKAs to prevent strokes in AF patients and the consistent recommendations of VKA use in the respective guidelines, data from around the world shows that there is a significant underuse of VKAs in patients with AF at high risk of stroke. The consistency of this phenomenon across the various geographies and healthcare systems is noteworthy and is likely to be associated with systematic deficiencies of VKAs. The next section investigates the efficiency of VKA management in those patients adherent to treatment and the persistence in treatment.

1.2. Quality of OAC management

Quality of warfarin management is commonly determined by measuring a patient's International Normalised Ratio (INR) and establishing the percentage of time the patient's INR is within therapeutic range (time in therapeutic range or TTR). A significant proportion of AF patients have INR values outside the recommended range for stroke prevention. The proportion of patients who achieve their target range can be improved by more frequent anticoagulant monitoring and monitoring in a specialised anticoagulation clinic, but this adds to the time expended by the patient and the burden on the healthcare services. Despite frequent monitoring, some patients are unable to maintain an adequate TTR (Hansen et al 2009; Tentschert et al 2004; Hamann et al 2003).

For stroke prevention in AF patients the optimal INR target range is usually 2.5 (range 2.0−3.0 (Abdelhafiz et al 2003). The Japanese guidelines, however, specify ranges of INR 2.0−3.0 for AF patients <70 years of age and 1.6–2.6 for AF patients ≥ 70 years of age (Abdelhafiz et al 2003). Once the clinician has established an appropriate target INR range for the patient, the OAC dose will be adjusted to keep the patient in the target range.

A meta-analysis by Baker et al. in 2009 reported a therapeutic treatment rate (that is the proportion of time patients spent in the therapeutic INR range) of 63% for patients monitored in anticoagulation clinic versus a therapeutic treatment rate of 51% for those monitored in community practices in the US.

An additional review of published studies showed that patients monitored in usual care (community and hospital based) settings were within the optimal INR range for only 56% (24 studies, range 29-69%) of the time and those monitored in specialist anticoagulation clinics were in INR range for 65% (24 studies, range 54–74%) of the time (Turpie 2008).

A second meta-analysis investigated the relationship between the time in target range and the setting and frequency of anticoagulant monitoring, in both treatment-experienced and treatment-naive AF patients on OAC therapy (Ogilvie et al 2011). The following observations were made:

- Patients who were monitored frequently (more than once per month) spent more time in the therapeutic range (64.3%) than those who were monitored less often (59.1%).
- In specialist care settings (anticoagulation clinics) patients spent significantly more time in range − 11% (95% CI: 0.1–21.7%) − compared with usual care.
- Naïve OAC users spent less time in range: 56.5% (95% CI: 45.5%–67.5%) than existing users 61.2%.

Many patients find the frequent monitoring and necessary dose adjustments associated with OACs inconvenient and time consuming and may miss appointments, leading to poor control of anticoagulation. Self-monitoring of anticoagulant activity, to involve the patient and reduce the inconvenience, has been investigated in a number of trials. These compared self-monitoring and self-adjustment of the warfarin dosage, with the patient's usual practice (e.g. at primary care practice or specialist anticoagulation centre). A review of 14 studies found improvements of 3·0% to 20·9% in maintaining INR within the therapeutic range among self-monitored patients (Youman et al 2003). Self-monitoring was associated with reductions in the risk of thromboembolic events and death. However, self-monitoring is not feasible for all patients, and requires identification and education of suitable candidates (Youman et al 2003).

A systematic review of studies with data on quality of anticoagulation identified 16 with sufficient information for review (Palmer et al 2005). Definitions of what constituted poor INR control varied between studies and where possible poor INR control was defined as patients spending less than 60% of the study time in therapeutic range (TTR). However, in some cases, poor INR control was defined in the study itself and in some others, the definitions had to be adapted to the information available in the study. Results are reported as the percentage of AF patients with poor INR control from the AF patients who received VKAs. Additional results from the review showed:

- Three studies had data on a 3-6 month follow-up; the average percentage of patients showing poor INR control was 49% (range: 46–52%)
- Three studies had data for a 6-9 month follow-up. The average percentage of patients with poor INR control was 38% (range: 33–44%).

- Eight studies had data for follow-up >9 months – for seven studies follow-up was one year, and five years in the other five years. The average percentage of patients with poor INR control was 58% (range: 23-80%).

A multicentre, observational study in Germany showed that patients with AF who were receiving VKAs were within the target INR range 56% of the time, above range 30% of the time (leading to an increased risk of bleeding) and below range 14% of the time (leading to an increased risk of stroke) (Hamann et al 2003).

A prospective observational study in France of around 800 AF patients who were managed by GPs or Cardiologists, found that over a six-month observation period, 32% of patients had spent less than 50% of their follow-up time in therapeutic range and only 38% of patients spent more than 75% of their time in the therapeutic range of INR, and were considered to have good anticoagulation control (Allender et al 2008).

Sub-therapeutic levels of INR were reported in a Canadian study of patients who were admitted to hospital with ischaemic stroke who had a known history of AF and no contraindications to OACs (Winter et al 2009). The results of this study showed:

- Only 40% of patients were receiving warfarin at the time of stroke admission and of those, three quarters had a sub-therapeutic INR (i.e. less than 2.0) which meant that 90% of patients were not optimally anticoagulated at the time of their stroke.
- Among the subset of AF patients with a history of stroke or TIA, and were at highest risk of stroke, 57.3% were taking warfarin before admission, but 68.3% had a sub-therapeutic INR at admission.
- That, not only was there considerable underuse of OAC in AF patients, but also that a majority of those patients receiving warfarin were below the target INR of 2.0-3.0.

In Japan, in large-scale prospective observational study, the J-RHYTHM registry, from January to July 2009, registered a total of 7,937 AF patients [5,468 men (68.6±10.0 years) and 2,469 women (72.2±9.0 years)] were from 158 institutions. Overall, 34.2% of the patients were over 75 years. In all 87.3% of patients were receiving warfarin (Ohsawa et al 2007). Additional results reported included:

- More than 25% of warfarin-prescribed patients had an INR <1.6, both among those <70 years and those >70 years of age.
- In both the <70 years of age and >70 years cohorts, 66% of had INRs in the range 1.2-2.6.

- 37% of patients in the <70 years cohort and 34% of patients <70 years had INRs in the range 2–2.99.
- Only 2.8% of patient <70 years and 2.9% of those >70 years had INRs ≥3.

This study suggests that although in Japan different INR ranges are recommended for AF patients <70 years (INR 2-3) and >70 years (INR 1.6-2.6), in practice there is little difference between older and young patients, with most being treated to the lower range. Furthermore, a quarter of patients had INR below the lower limit of even the lower normal range (Ohsawa et al 2007).

A Korean study involving 1,502 patients with AF and no history of stroke reviewed the anticoagulant regimens of 422 patients with a $CHADS_2$ score of 1 or more. Anticlotting regimens were used in 33.9% (143 patients were receiving warfarin). The average INR in these patients was 2.00±0.48, and only 66 (46.2%) of the 143 patients maintained their INR within the range of 2-3 (Caro et al 1999).

There is a link between the level of INR control and the likelihood of an AF patient experiencing a clinical event. A UK study (Claesson et al 2000) in 2,223 patients with non-valvular AF, found that:

- Warfarin-treated patients were outside the INR target range 32.1% of the time, with 15.4% with INR values >3.0 and 16.7% with INR values <2.0.
- The quartile with the worst INR control spent 71.6% out of the target range, compared with only 16.3% out of range in the best controlled quartile.
- Time spent outside the target range decreased as the duration of INR monitoring increased, from 52% in the first three months of monitoring to 30% after two years
- An analysis showed that a 10% increase in time out of range was associated with an increased risk of mortality (odds ratio (OR) 1.29, p<0.001) and of an ischaemic stroke (OR 1.10, p=0.006) and other thromboembolic events (OR 1.12, p< 0.001). The rate of hospitalisation was higher when INR was outside the target range (Claesson et al 2000).

Like in many other countries, VKA patients in Australia are not optimally managed. Jackson et al. (2001) showed 45% of patients on hospital admission fell into an INR range of 2-3 and Jackson et al. (2005) showed 68% of patients were in the 2-3.5 range with an intensive management program. Pickering and Thomas (2007) showed in an audit of an urban indigenous community that patients on warfarin were in the target INR therapeutic range 44.9% of the time and Stafford et al. (2011) reported TTRs of 55.2% and 55.6% in patients

receiving usual care and patients receiving a post-discharge anticoagulant service, respectively.

1.3. Patient persistence with antithrombotic treatment

AF patients who start on OACs and/or antiplatelet agents may subsequently interrupt treatment or discontinue it altogether. This decision may be made by either the patients themselves or their physician and can be due to a range of different factors, including adverse events. Good compliance with both medication and INR monitoring is important to maintain therapeutic levels of anticoagulation, to avoid adverse effects and improve outcomes. Results of studies reporting persistence with VKA therapy are reported in Table 1-2.

Table 1-2: Persistence of OAC use in selected studies

Country/region	Patients persisting with OAC treatment			
	1 year	2 years	30 months	5 years
AF patients				
UK (Gallagher 2008)	70%[a]	60%[a]		35%[a]
Italy (Mazzaglia 2010)	42.5%[a]	24.3%[a]		
USA/Canada (Reynolds 2006)	49%[b]		44%[b]	
AF patients with stroke/TIA discharged from hospital on OAC				
Austria (Tentschert 2004)	72%			
Germany (Hamann 2003)	77.4%			

[a] Percentage of patients receiving OACs
[b] Percentage of patients in study – 65% were receiving OACs at baseline

In the UK, a study based on data from the General Practice Research Database (GPRD), involving chronic AF patients over 40 years of age, found that only a minority of patients continued their OAC therapy for more than a few years (Caro et al 1997). Regarding persistence, the study found:

- One-year persistence with treatment was 70% for warfarin and at two years 60% of patients who received warfarin were persisting with this treatment.
- After five years only 35% of warfarin-treated patients were still receiving treatment.
- Treatment persistence was higher in elderly patients and a higher $CHADS_2$ score was also associated with improved persistence.

A study conducted in the USA and Canada, which looked at antithrombotic prescribing in patients (mean age 65.9 years) newly diagnosed with AF, reported that although initially 65% of patients were prescribed warfarin, at 12 and 30 months only 49% and 44%, respectively, were still receiving it. Even among patients ideal for OACs (older patients with risk factors for stroke and no known contraindications) warfarin use fell from 70% at baseline

to 50% at 30 months (Dewey et al 2003). Factors that influenced continuing use of warfarin during follow-up, included recurrence of AF, a history of stroke or TIA, congestive heart failure and valvular heart disease (Dewey et al 2003). This suggests that such patients are more motivated to continue treatment.

Another US study which involved 472 AF patients aged 65 years and older reported that 28% of patients had stopped warfarin within one year. The predominant reason for patients <80 years discontinuing treatment was the return of normal heart rhythm, while in those ≥80 years safety concerns were the main reasons for withdrawal (Bo et al 2007).

In a study in general practices conducted in Italy, of 1,707 AF patients who received OACs after one year 42.5% of patients were persisting with treatment, 32.8% had interrupted treatment and 24.7% had discontinued therapy; after 2 years 24.3% of patients were persisting with therapy, 49.1% had interrupted therapy and 26.6% had discontinued (Chien et al 2008).

A large scale observational study from Denmark, based on registry data included 108,504 AF patients of whom 37% (40,133 patients) were prescribed OACs. Discontinuation of OACs mainly occurred in the first year of treatment, with 34% of patients who were alive (65-68%) having discontinued treatment, OAC usage remaining relatively stable thereafter (Bielik et al 2009).

In patients who have experienced a stroke or TIA, an Austrian study involving 401 patients who had experienced a stroke or TIA, reported that after one year 72% of patients discharged on an OAC and 46% discharged on an antiplatelet agent were adhering to their treatment regimen (Spieler et al 2002).

Data from the German Stroke Data Bank showed that after one year, 77.4% of the patients prescribed OAC were persisting with treatment, compared with 84% of the patients receiving aspirin and 61.6% of patients receiving clopidogrel. Under the conditions of this observational study, adherence to stroke prevention strategies was good (Winter et al 2009).

In a German study that included 329 AF patients who had experienced a stroke or TIA and were discharged from hospital on OAC therapy, 88.7% were still receiving OACs at follow-up after 1−2 years. The mean time to discontinuation of OAC was 10.4 months. Reasons given for discontinuation of OAC included cessation of former indication, (15%), new medical

indications (15%), preparation for operations (21%), prevention of bleeding complications (9%), adverse reactions (3%), and other or unknown reasons in 36% (Murdoch et al 2005).

In general, persistence with antithrombotic treatment in AF patients was better in patients who received antithrombotic therapy for secondary prevention of stroke, following a stroke or TIA, possibly because these patients were more motivated and followed-up more closely.

Reasons for stopping VKA therapy were collected in a UK study, conducted at a single anticoagulation centre involving 402 AF patients (Murdoch et al 2005; Ghatnekar et al 2008; Bruggenjurgen et al 2007). In total 13.7% of patients stopped warfarin over a mean follow-up of 18 months. Among the patients who discontinued warfarin:

- 38% discontinued because of bleeding complications
- 20% discontinued because of successful cardioversion
- 18% discontinued because or return to a normal heart rhythm
- general ill health led to 9.1% stopping treatment and 5.4% stopped treatment because of frequent falls (5.4%)
- other reasons for stopping treatment were metastatic cancer (3.6%), heart transplant (1.8%), jaundice (1.8%) and hair loss (1.8%).

Summary

The sections discussed above provide evidence that:

1. warfarin is under-utilised in patients eligible for anticoagulant therapy, especially in those at a high risk of stroke,
2. even in patients receiving warfarin, therapy is not optimally managed as demonstrated by a low TTR, and
3. there is a high rate of discontinuation from warfarin therapy.

1.4. AF patient subgroup analysis

The previous sections summarized that a large number of patients eligible for VKA therapy are not taking the appropriate medication and that patients on VKA have significant issues in achieving the relevant therapeutic range. This section aims to quantify AF patients, who are not well managed on VKAs, according to their treatment characteristics.

The AF patient subgroups were defined as follows:

1) VKA non-users: Those who should be on VKA according to clinical guidelines but are not treated during the study.

   a. Untreated: Those eligible for VKA therapy who are not treated with either VKA or antiplatelet therapy
   b. Antiplatelet treated: Those eligible for VKA therapy who are not treated with VKA but who receive antiplatelet therapy
   c. Treatment not specified: Those eligible for VKA therapy who are not treated with VKA but for whom other therapy or no therapy is not specified
2) VKA contraindicated: Those for whom VKA therapy is contraindicated
3) Warfarin naïve (newly diagnosed): Newly diagnosed patients eligible for warfarin but not treated so far with VKA
4) VKA discontinued: Those who should be on VKA according to clinical guidelines, but are not due to discontinuation of VKA therapy
5) VKA poorly controlled: Those on VKA with INR values frequently outside the target range (e.g. less than 65% in TTR)

A summary of the results of the subgroup analysis can be found in Table 1-3; each population subgroup is discussed below.

1a) VKA non-user – untreated

Forty-three studies contained data pertaining to AF patients eligible for VKA therapy, due to their moderate or high risk for stroke, and who are untreated (no VKA or antiplatelets). If all 43 studies were included, the average percentage of untreated VKA eligible AF patients across studies was 18.5%, with a range from 2.2% to 46.4% (Table 2). This large range is most likely due to differences in the definition of stroke risk categories among studies. In addition, differences in study populations and settings will also have an impact. To obtain a better comparison, studies were limited to those using the CHADS2 score (16 studies). An average percentage for untreated VKA eligible patients of 12.9% was obtained (range: 2.2%–34.0%). In addition, four studies which stratified patients according to ACC/AHA/ESC, 2001 guidelines were identified. An average of 27.5% of eligible AF patients remained untreated, according to these studies (range: 6.0% to 46.4%).

1b) VKA non-user – antiplatelet-treated

Current treatment practice literature was also examined for data pertaining to AF populations eligible for VKA therapy who are treated with antiplatelets rather than VKA. Forty-six studies had data pertaining to this population (Table 1-3). The average percentage of eligible AF patients treated with antiplatelets rather than VKA was 32.0% (range: 7.1% to 66.8%). If the analysis was limited to those studies that used a common stoke risk stratification scheme,

the average was 29.1% for 17 studies using the $CHADS_2$ score (range: 8.3% to 58.8%), and 26.9% (range: 7.1% to 53.4%) for four studies that used the ACC/AHA/ESC, 2001 guidelines.

1c) VKA non-user – other treatment not specified (AP or no treatment)

Twenty-seven studies contained population data for AF patients who were not treated with warfarin, but these studies did not specify whether these patients were treated with antiplatelets or had no treatment. In these studies, an average of 47.6% (range: 11.7% to 80.7%) of eligible AF patients fell into this category (Table 1-3). Of these studies, 17 used the $CHADS_2$ score to define eligible patients. The average percentage of Non-VKA unspecified patients stratified by $CHADS_2$ score was 48.1% (range: 11.7% to 80.7%).

Table 1-3: AF subgroup populations

AF subgroup	# of studies with usable information	Population	Average	Range	
				Min	Max
1) VKA non-users	43				
1a) Untreated: all records	43	% of VKA eligible AF patients	18.5%	2.2%	46.4%
1ai) Untreated: $CHADS_2$ score	16	% of VKA eligible AF patients	12.9%	2.2%	34.0%
1aii) Untreated: ACC/AHA/ESC guidelines	4	% of VKA eligible AF patients	27.5%	6.0%	46.4%
1b) Antiplatelet treated:	46	% of VKA eligible AF patients	32.0%	7.1%	66.8%
1bi) Antiplatelet treated: $CHADS_2$ score	17	% of VKA eligible AF patients	29.1%	8.3%	58.8%
1bii) Antiplatelet treated: ACC/AHA/ESC guidelines	4	% of VKA eligible AF patients	27.0%	7.1%	53.4%
1c) Treatment unspecified: all records	27	% of VKA eligible AF patients	47.6%	11.7%	80.7%
1ci) Treatment unspecified: $CHADS_2$ score	17	% of VKA eligible AF patients	48.1%	11.7%	80.7%
2) VKA contraindicated: all records	44	% of total AF patient population	24.2%	2.7%	83.9%
2a) Exclusions: Patients at long term care facilities and those with prior stroke	35	% of total AF patient population	21.2%	2.7%	48.2%
2b) Long term care populations only	3	% of total AF patient population	82.7%	80.4%	83.9%
3) Warfarin naïve: all records	53	% of total AF patient population	34.2%	3.2%	82.1%
4) Warfarin discontinued: all records	18	% of VKA treated AF population	20.3%	4.2%	45.9%
4a) Exclusions: population duplicate; studies of mixed indications	15	% of VKA treated AF population	22.2%	4.2%	45.9%
4b) 1 year follow-up. Exclusions: duplicate studies; studies of mixed indications	6	% of VKA treated AF population	25.3%	9.0%	45.9%
4c) >1 year follow-up. Exclusions: duplicate studies; studies of mixed indications	8	% of VKA treated AF population	21.9%	4.2%	40.0%
5) Poor INR control: all records	16	% of VKA treated AF population	N/A	N/A	N/A
5a) Poor INR control <65% TTR threshold	5	% of VKA treated AF population	61.9%	52.5%	73.8%
5b) Poor INR control: 3–6 months follow-up	4	% of VKA treated AF population	45.9%	37.6%	52.0%
5c) Poor INR control: 6–9 months follow-up	3	% of VKA treated AF population	38.0%	33.3%	44.0%
5d) Poor INR control: >9 months follow-up	11	% of VKA treated AF population	53.3%	23.3%	80.2%

2) VKA contraindicated

Forty-four studies from the current treatment practices literature contained information about the proportion of AF patients with contraindications to warfarin. Since these studies did not delineate the AF population by stroke risk, the results are given as a proportion of the whole

AF study population. While the average percentage of AF patients with contraindications to warfarin was 24.24%, the range was very wide with a minimum of 2.7% and a maximum of 83.9% (Table 2). Excluding AF populations in long term care, very elderly populations and those who have had a prior stroke who often have greater contraindications, 35 studies remained, giving an average of 21.2% and a smaller range of between 2.7% and 48.2%. As expected, when AF populations from long term care or very elderly population settings (3 studies) were examined alone, a very high level of contraindications to warfarin was found (average 82.7%; range: 80.4%–83.9%). The definition of contraindications given by studies varies widely, with some studies using very extensive categories, while others only include two or three contraindications; this probably accounts for much of the variation seen among studies. The most commonly mentioned contraindications include a history of bleeding or falling, along with alcohol abuse and cirrhosis. Additionally patients from different settings may have very different levels of contraindications, as seen with the patients from long term care facilities.

3) Newly diagnosed/VKA Naïve

Studies concerning the epidemiology of AF and current treatment practices were examined for information concerning the proportion of newly diagnosed AF patients or warfarin naïve patients; 53 studies were identified (Table 1-3). An assumption that newly diagnosed AF patients had not been treated with warfarin previously was made for the purposes of this analysis. The average percentage of newly diagnosed patients in AF populations was 34.1% and the range was from 3.2% to 82.1%.

4) VKA discontinued

Current treatment practice literature and discontinuation studies were considered for the extraction of population data for AF patients who permanently discontinue warfarin for any reason. As most studies concern AF populations on VKA therapy at the start of the study, results are reported as the percentage of AF patients who permanently discontinue treatment from the population of AF patients on VKA therapy in each study. Eighteen studies were found that contained information on permanent discontinuation of warfarin therapy. On average, 20.3% (range: 4.2% to 45.9%) of patients on warfarin discontinued therapy (Table 1-3). Study follow-up times varied from 1 year to 5 years. When duplicate study populations and study populations with indications other than AF were excluded, an average of 22.2% of patients discontinued warfarin (range: 4.2% to 45.9%; 15 studied). Studies were further categorised by follow-up time into those with a follow-up of one year (6 studies), and those with follow-up times of more than one year (8 studies). No difference was seen between

studies of one year follow-up (average: 25.3% of patients discontinued; range: 9.0% to 45.9%) and greater than one year follow-up (average: 21.9% of patients discontinued; range: 4.2% to 40.0%).

5) Poor INR control

Studies of INR control and monitoring were examined for data on the proportion of AF population with poor INR control while on oral anticoagulant therapy. Definitions of what constitutes poor INR control vary between studies. Where possible, poor INR control was defined as patients spending less than 65% of the study time in therapeutic range (TTR). However, in most studies, poor INR control was defined inconsistently and the definition given in the indicated study was used. Sixteen studies were identified as containing pertinent data (Table 1-3).

Most studies presented INR control data averaged over the follow-up duration of the study, therefore the duration of patient follow-up was reported and studies were placed into the following categories; 3–6 month follow-up, 6–9 month follow-up and more than 9 months follow-up. Results are reported as the percentage of AF patients with poor INR control from the cohort of AF patients receiving VKA therapy. It was not possible to obtain population information from INR control data reported as TTR alone. In addition, studies with patients on VKA for mixed indications were excluded.

Five studies defined poor control and less than 65% of TTR or greater (68% to 100% TTR); the average percentage of patients showing poor INR control was 61.9% (range: 52.5%-73.8%).

Four studies contained data for a 3-6 month follow-up; the average percentage of patients showing poor INR control was 45.9% (range: 37.6%-52.0%). Two of these studies defined poor INR control as being outside the therapeutic range, with no information concerning time in range; one study defined poor INR control as at least one INR reading outside the therapeutic range; and the last study defined poor control as spending less than 50% of time in the therapeutic range.

Three studies gave data for a 6-9 month follow-up. The average percentage of patients with poor INR control was 38.0% (range: 33.3%-44.0%). Poor INR control was defined as being outside the therapeutic range with no information concerning time in range in two studies, and as spending under 20% of the time in the target range in the third.

Eleven studies were available with data for a longer follow-up >9 months—for most studies follow-up was 1 year, in 2 studies follow-up was 18 months and for the final study follow-up was 5 years. The average percentage of patients with poor INR control was 53.3% (range: 23.3% to 80.2%). Poor INR control was defined as spending <60% of time in the target range in two studies; <68% of time in the target range in 1 study, <70% of time in the target range in one study, <75% of time in the target range in two studies and 100% in 1 study. The remaining studies defined poor INR control as INR outside the therapeutic range; no information was available concerning the amount of time spent outside this range.

In conclusion, the available data confirms that many patients with AF at risk of stroke are not appropriately managed as per guidelines. For a patient with AF who has a well-controlled INR and who is compliant when taking medication and receiving INR monitoring, VKA's may be effective. However many subgroups of AF patients do not fall into this category. The literature suggests that a significant proportion of patients who are eligible are not taking VKAs due to contraindications. For some of these patients, novel oral anticoagulants may be a viable alternative. For patients currently untreated, patients discontinuing treatment or treatment-naïve patients who have not yet initiated VKAs, it remains to be determined whether they are unwilling to take warfarin, whether they are inappropriately treated with treatments other than VKAs or whether other factors prevent them from taking VKAs. Patients with poorly controlled INRs would benefit from novel treatment alternatives or potentially through measures for optimizing warfarin management. The costs and effectiveness of such systems are further discussed in the next section.

2. Systematic review of warfarin management programs

Oral anticoagulation therapy has been available for prophylactic use and to reduce the risk of thromboembolic events in patients with atrial fibrillation for over 60 years. The widely used oral anticoagulant warfarin has a narrow therapeutic index and must be continually monitored based on the international normalised ratio (INR) traditionally measured using plasma obtained from venepuncture. Appropriate dosing can only be determined using INR as a guide; however, even with close monitoring thromboembolic events and bleeding are common. Due to the strong association between INR levels and adverse outcomes, maximising time spent in therapeutic range is very important for effective OAT therapy (Ansell et al 2001).

Optimised management of warfarin improves the quality of treatment and helps to reduce morbidity and mortality event rates. Traditionally anticoagulation management has been conducted by the general practitioner (GP) and this is still considered the standard of care (Samsa et al 2000). In most cases the GP will use personal judgement and experience to determine anticoagulation dose adjustments.

The rationale for anticoagulation management services is that a specialist anticoagulation manager takes responsibility for dosing changes, scheduling, patient education and other aspects of anticoagulation management rather than have this function performed by the patient's GP. The most effective means of management has been evaluated for years and several different types of program have been identified as effective for the management of OAT. Different methods of managing OAT include: management by the general practitioner (GP), pharmacist or nurse managed, computer assisted dosing programs, specialised anticoagulation clinics utilising nomograms, computer dosing and point of care testing (POCT), patient self-testing (PST) and patient self-management (PSM). All of these services (which are inconvenient for the patient and have a cost involved) would be unnecessary if the patient was on a NOAC.

Pharmacist managed programs are in place in both the community and hospital setting. In Australia, pharmacists also manage anticoagulation through the home management review (HMR) process (Stafford et al 2011).

Specialist anticoagulation management clinics are designed to optimise anticoagulation treatment by providing the patient with expert advice and education along with all the

associated anticoagulation monitoring and dosing assistance (Matchar et al 2002). These clinics may be managed by a pharmacist, nurse, nurse practitioner, physician, physician's assistant or some combination of these.

Computerised dosing programs enhance the quality of OAT by utilizing a standardised computer generated nomogram to assist physicians in making dosing decisions and to schedule appointments (Manotti 2001).

Patient self-management consists of the patient utilising a self-testing device to actively manage the dosing of anticoagulation. The difference between PST and PSM is in PST the patient uses the self-testing device to determine INR and dosage decisions are made by a health care professional whereas in PSM the patient makes dosing decisions themselves.

The percentage time that INR is within therapeutic range (TTR) is a useful indicator of efficacy and is one of the most common methods for evaluating anticoagulation management programs. Most clinical studies evaluating the effectiveness of anticoagulation management report TTR while other studies report clinical outcomes as a means of evaluating effectiveness. Both are important indicators.

The objectives of this assessment were to examine the various models used in the management of anticoagulation, to assess the value of anticoagulation management programs and to determine if there is a quantifiable value added by these programs.

The overall aim was to identify and compare all of the anticoagulation management programs that have been published, describe the details of the programs and examine the outcomes reported.

A comprehensive literature search was undertaken to identify all the relevant trials comparing the effectiveness of warfarin management programs in the control of anticoagulation for patients with atrial fibrillation.

Forty three trials directly comparing anticoagulation management programs were identified. A hand search of the literature revealed a further 9 trials that presented results directly related to the effectiveness of anticoagulation management programs in AF which were also included, giving a total of 52 studies.

These studies were then grouped by type of anticoagulation management program

- Pharmacist managed – Studies clearly identifiable as managed by a pharmacist included both hospital managed patients and patients managed in the community.
- Computer managed – Studies identified as using a computerised dosing system to manage the dose and schedule follow-up with patients.
- Specialist anticoagulation management – Studies that included more than one type of intervention i.e. computerised dosing, the use of standardised nomograms for dosing decisions, point of care testing and managed by a health professional (nurse, pharmacist, physician or a combination) specifically trained in OAT.
- Patient self-managed (PSM) or self-tested (PST) – Studies that compared the effects of PST or PSM with standard of care.

These groups were further stratified by geographic region before the average change in TTR between treatment groups was calculated. A weighted average of the change was calculated first by geographic region and then for the overall anticoagulation management program. The weighted average was also calculated for event rates and percentages were used to compare between treatment groups. Rates of adverse events were extracted from the literature and the weighted average for percentage of events was calculated.

Of the 52 studies that were selected for further analysis not all reported data on both TTR and event rates. As such, results were separated into results for efficacy measured using TTR and results for adverse event rates.

Table 2-1: Summary of Results

Type of warfarin management program	N studies identified	Total number of patients assessed	Average improvement in TTR	Major Bleeding	Minor Bleeding	Any Thrombotic Event	Stroke/TIA	Death
Pharmacist managed	15	93,628*	8.44%	1.31%	8.34%	0.83%	0.22%	0.65%
Computer managed	5	10,362	3.76%	1.26%	3.82%	1.38%	0.05%	0.88%
Specialist AC management	11	2161	11.53%	1.30%	17.25%	2.20%	1.51%	12.73%
Patient self-managed/tested	13	2835	4.75%	7.34%	35.64%	1.08%	1.89%	9.30%

*Includes 84,219 patients from a single study Bond et al 2004

The following tables illustrate the efficacy of anticoagulation management programs by comparing TTR and averaging the change between interventions. The change in the weighted average can then be used to compare between programs and to assess which programs provided the greatest percentage change from standard of care.

Nine studies presented in Table 2-2 compared the TTR of pharmacist managed anticoagulation services with that of standard care. Pharmacist managed anticoagulation programs improved the percentage TTR on average by over 8%.

Table 2-2: Efficacy of pharmacist managed anticoagulation management programs compared to GP managed programs

	Standard of Care			Pharmacist Managed			
Author (Date) Country	n	TTR	INR test frequency (mean weeks)	n	TTR	INR test frequency (mean weeks)	Average change after intervention
North America							
Airee et al (2009) USA	50	0.62	-	50	0.68	-	0.06
Garwood et al (2008) USA	40	0.48	5	40	0.76	2.92	0.28
Hall et al (2011) USA	175	0.546	6.93	175	0.672	3.77	0.126
Poon et al (2007) USA	1081	0.464	16.37	440	0.481	5.37	0.017
Thompson et al (2009) USA	145	0.479	-	145	0.457	-	-0.022
Wilson et al (2003) Canada	109	0.59	0.99	112	0.63	1.17	0.04
Witt et al (2005) USA	3322	0.552	3.11	3323	0.635	2.96	0.083
Young et al (2011) Canada	81	0.65	2.08	112	0.73	1.79	0.08
				Weighted Average Change North America			8.60%
Australia							
Stafford et al (2011) AU	100	0.552	1.52	86	0.556	1.5	0.40%
Weighted Average		0.53			0.62		8.44%

Five studies presented in Table 2-3 compare the management of anticoagulation dosing by computerised system compared to standard of care. The implementation of computerised dosing management systems increased the percentage of TTR by on average 3.76%.

Table 2-3: Efficacy of computerised dosing systems in anticoagulation management

	Standard Care			Computerised Dosing			
Author (Date) Country	n	TTR	Frequency of INR tests (mean) (in weeks)	n	TTR	Frequency of INR tests (mean) (in weeks)	Average change after intervention
Europe							
Cafolla et al (2011) Italy	1876	0.5038	2.74	1876	0.623	2.48	0.1192
Gouin-Thibault et al (2010) France	199	0.483	0.476	108	0.586	0.374	0.103
Manotti et al (2001) Italy	458	0.682	NR	458	0.712	NR	0.03
Poller et al (2008) Italy	6447	0.647	7.78	6605	0.659	7.99	0.012
Poller et al (2009) UK and Europe	1316	0.634	10.6	1315	0.668	9.49	0.034
Weighted Average		0.62			0.66		3.76%

Nine studies compared anticoagulation management by a specialist anticoagulation clinic with standard care (Table 2-4). One study by Ansell et al (2007) did not compare management but provided results for patients in treatment centres in 5 different countries. In

2 countries, (Italy and Spain) the patients' anticoagulation was managed by a specialist anticoagulation clinic and in the other 3 countries (USA, Canada and France) the patients anticoagulation was managed under standard of care.

Table 2-4: Efficacy of specialist anticoagulation services compared to standard of care

	Standard of Care				Specialist AMS				
Author (Date) Country	n	TTR		Frequency of INR tests (mean) (in weeks)	n	TTR		Frequency of INR tests (mean) (in weeks)	Average change after intervention
Europe									
Ansell et al (2007) USA, Canada, France, Italy, Spain	686	0.581	398.566	3	-	-	-	-	-
	152	0.628	95.456	2.9	-	-	-	-	-
	278	0.593	164.854	3	-	-	-	-	-
	-	-	-	-	177	0.695	123.015	3	-
	-	-	-	-	218	0.649	141.482	4.6	-
Holm et al (2002) Denmark	97	0.552	53.544	-	124	0.65	80.6	-	0.098
					Weighted Average Change Europe				7.76%
Asia									
Lee et al (2011) Taiwan	44	0.537	23.628	4.97	44	0.609	26.796	3.13	7.20%
North America									
Coghlan and Fish (2010) USA	467	0.57	266.19	-	200	0.73	146	-	0.16
Franke et al (2008) USA	30	0.308	9.24	6.6	37	0.321	11.877	4.03	0.013
					35	0.459	16.065	4.56	0.459
Matchar et al (2002) USA	317	0.523	165.791	-	173	0.556	96.188	-	0.033
Nichol et al (2008) USA	756	0.4207	318.0492	2.63	251	0.6814	171.0314	2.04	0.2607
Samsa et al (2000) USA	61	0.469	28.609	-	43	0.603	25.929	-	0.134
Thomson et al (2011) Canada	67	0.822	55.074	0.7	55	0.774	42.57	0.96	-0.048
					Weighted Average Change North America				14.55%
Weighted Average		53.43%				64.96%			11.53%

The 13 studies presented in Table 2-5 compare the TTR of patients self-managing or self-testing with that of standard care. Patient self-management or self-testing improved the percentage TTR on average by 4.75%.

Table 2-5: Efficacy of patient self-management and self-testing compared to standard of care

	Standard of Care			Self-managed/Self-testing			
Author (Date) Country	n	TTR	Frequency of INR tests (mean) (in weeks)	n	TTR	Frequency of INR tests (mean) (in weeks)	Average change after intervention
North America							
Beyth et al (200) USA	162	0.32	-	163	0.56	-	0.24
Grunau et al (2011) Canada	5	0.797	-	6	0.822	-	0.025
Matchar et al (2010) USA*	1457	0.624	3.3	1465	0.662	1.08	0.038
Sunderji et al (2004) Canada	70	0.587	-	69	0.648	-	0.061
				Weighted Average Change North America			5.83%
Europe							
Christensen et al	50	0.689	-	50	0.787	-	0.098

Author (Date) Country	Standard of Care n	TTR	Frequency of INR tests (mean) (in weeks)	Self-managed/Self-testing n	TTR	Frequency of INR tests (mean) (in weeks)	Average change after intervention
(2006) Denmark Cromheecke et al (2000) Netherlands	24	0.49	-	25	0.55	-	0.06
Menendez-Jandula et al (2005) Spain	369	0.688	-	368	0.679	-	-0.009
Siebenhofer et al (2008) Austria	96	0.645	-	99	0.613	-	-0.032
Voller et al (2005) Germany	101	0.585	-	101	0.678	-	0.093
				Weighted Average Change Europe			1.41%
UK							
Fitzmaurice et al (2005) UK	280	0.68	-	337	0.7	-	0.02
Khan et al (2004) UK	41	0.632	-	44 44	0.704 0.711	-	0.072 0.079
McCahon et al (2007) UK	40	0.64	4.43	38	0.7	2.43	0.06
				Weighted Average Change UK			3.13%
Israel							
Goldberg et al (2010) Israel	32	0.4	3.25	13 13	0.58 0.61	3.7 2.26	0.18 0.21
				Weighted Average Change Israel			19.50%
Weighted Average		0.62			0.66		4.75%

*Compared results from patient self-testing to results of POCT in a specialised clinic

Outcome data for the pharmacist managed anticoagulation programs compared with standard of care is presented in Table 2-6. Comparing the weighted averages for event rates the percentage of thrombotic events and stroke decreased while percentage of major and minor bleeding increased for patients managed by pharmacists.

Table 2-6: Major outcomes of pharmacist managed anticoagulation management programs compared to GP managed programs

Trial ID	Standard of Care Major Bleeding	Minor Bleeding	Any Thrombotic Event	Stroke or TIA	Death	Pharmacist Managed Major Bleeding	Minor Bleeding	Any Thrombotic Event	Stroke or TIA	Death
UK										
Abdelhafiz 2004	-	-	-	-	-	2.74%	26.62%	2.49%	-	5.47%
North America										
Airee 2009	2.00%	2.00%	0.00%	-	2.00%	0.00%	2.00%	0.00%	-	0.00%
Bond and Raehl 2004	-	9.15%	-	-	7.07%	-	8.41%	-	-	6.66%
Bungard 2008	-	-	-	-	-	5.15%	-	2.06%	0.52%	-
Fowler 2012	-	-	-	-	-	0.72%	0.89%	0.50%	0.07%	-
Garwood 2008	-	30.00%	2.50%	-	-	-	5.00%	0.00%	-	-
Menzin 2005	-	-	-	-	-	3.00%	-	-	0.83%	-
Poon 2007	0.19%	1.57%	1.11%	0.65%	-	0.68%	11.36%	0.45%	0.00%	-
Willey 2003	-	-	-	-	-	1.75%	17.25%	2.29%	-	0.00%
Wilson 2003	0.92%	-	1.83%	0.00%	5.50%	1.79%	-	0.89%	0.89%	4.46%
Witt 2005	0.93%	-	1.23%	0.54%	0.21%	0.87%	-	0.51%	0.18%	0.15%
Young 2011	0.00%	-	1.23%	1.23%	-	1.79%	-	0.89%	0.89%	-
Australia										
Stafford 2011	5.00%	14.00%	7.00%	-	2.00%	2.33%	3.49%	1.16%	-	3.49%
Weighted Average Event Rates	0.754%	9.14%	1.22%	0.57%	7.03%	1.30%	8.33%	0.82%	0.22%	6.34%

Outcome data for computerised dosing of anticoagulation compared with standard of care is presented in Table 2-7. Comparing the weighted averages for event rates the percentage of major and minor bleeding, thrombotic events and stroke all decreased for patients managed by computerised anticoagulation dosing.

Table 2-7: Major outcomes of computer managed anticoagulation dosing programs compared to standard of care

	Standard of Care					Computerised Dosing				
Trial ID	Major Bleeding	Minor Bleeding	Any Thrombotic Event	Stroke or TIA	Death	Major Bleeding	Minor Bleeding	Any Thrombotic Event	Stroke or TIA	Death
Europe										
Cafolla 2011	0.48%	5.76%	2.03%	0.11%	0.27%	0.32%	4.21%	1.23%	0.05%	0.16%
Gouin-Thibault 2010	2.01%	-	-	-	-	2.78%	-	-	-	-
Poller 2008	1.54%	4.47%	1.64%	-	0.96%	1.41%	3.83%	1.47%	-	1.06%
Poller 2009	1.06%	3.27%	1.75%	-	0.91%	1.75%	3.19%	1.14%	-	0.99%
Weighted Average Event Rates	1.28%	4.55%	1.73%	0.11%	0.82%	1.26%	3.82%	1.38%	0.05%	0.88%

Outcome data for the specialist anticoagulation clinics compared with standard of care is presented in Table 2-8. Comparing the weighted averages for event rates the percentage of major bleeding, thrombotic events and stroke decreased while percentage of minor bleeding increased for patients managed in the specialist anticoagulation clinics.

Table 2-8: Major outcomes of specialist anticoagulation management services compared to standard of care

	Standard of Care					Specialist AMS				
Trial ID	Major Bleeding-	Minor Bleeding	Any Thrombotic Event	Stroke or TIA	Death	Major Bleeding	Minor Bleeding	Any Thrombotic Event	Stroke or TIA	Death
North America										
Hodge2008	-	-	-	-	-	3.08%	-	0.44%	0.44%	-
Matchar 2002	1.58%	11.67%	3.47%	2.21%	-	1.73%	15.61%	5.78%	3.47%	-
Marques 2009	-	-	-	-	-	0.00%	16.98%	-	-	-
Nichol 2008	2.91%	-	-	1.32%	-	1.40%	-	-	1.42%	-
Thomson 2011	4.48%	-	2.99%	-	10.45%	5.45%	-	0.00%	-	12.73%
Asia										
Lee 2011	-	22.73%	4.55%	4.55%	-	-	27.27%	0.00%	0.00%	-
Weighted Average Event Rates	2.63%	13.02%	3.50%	1.70%	10.45%	1.30%	17.25%	2.20%	1.51%	12.73%

Outcome data for patients self-managing or self-testing anticoagulation compared with standard of care is presented in Table 2-9. Comparing the weighted averages for event rates

the percentage of major bleeding, thrombotic events and stroke decreased while percentage of minor bleeding increased for patients that self-managed or self-tested anticoagulation.

Table 2-9: Major outcomes of patients self-managing and self-testing compared to standard of care

	Standard of Care					Self-management and Self-testing				
Trial ID	Major Bleeding-	Minor Bleeding	Any Thrombotic Event	Stroke or TIA	Death	Major Bleeding	Minor Bleeding	Any Thrombotic Event	Stroke or TIA	Death
North America										
Beyth et al (200) USA	12.96%	-	0.00%	0.00%	26.54%	6.75%	-	0.00%	0.00%	25.15%
Matchar 2010	9.81%	27.52%	0.00%	2.13%	10.78%	10.03%	36.86%	-	2.12%	10.38%
Sunderji et al (2004) Canada	1.43%	-	2.86%	-	0.00%	0.00%	-	0.00%	-	0.00%
Europe										
Christensen et al (2006) Denmark	0.00%	-	0.00%	0.00%	0.00%	0.00%	-	0.00%	0.00%	2.00%
Cromheecke et al (2000) Netherlands	4.17%	-	8.33%	-	0.00%	0.00%	-	0.00%	-	0.00%
Menendez-Jandula et al (2005) Spain	1.90%	-	5.69%	-	4.07%	0.82%	-	0.82%	-	1.36%
Siebenhofer et al (2008) Austria	11.46%	-	13.54%	-	11.46%	6.06%	-	6.06%	-	15.15%
Voller et al (2005) Germany	0.00%	0.00%	0.99%	-	0.00%	1.98%	0.00%	0.00%	-	0.00%
UK										
Khan et al (2004) UK	-	-	-	-	0.00%	2.50%	5.00%	0.00%	0.00%	0.00%
Fitzmaurice 2005	1.07%	0.36%	1.07%	0.71%	0.36%	0.59%	0.59%	1.19%	1.19%	0.59%
Israel										
Goldberg 2010	0.00%	-	3.13%	3.13%	0.00%	0.00%	-	0.00%	0.00%	0.00%
Weighted Average Event Rates	8.19%	27.75%	4.93%	1.95%	9.87%	7.34%	35.64%	1.08%	1.89%	9.30%

Most studies did not report on the associated costs related to anticoagulation management programs. The 7 studies in Table 2-10 reported on the costs associated with anticoagulation management. Cost data was reported differently in each study and in different currencies dependent upon geographic location. Where possible cost estimations were extracted on a per patient per year basis. The main findings related to cost are narratively described below.

Table 2-10: Costs associated with anticoagulation management programs

	Standard Care			Intervention		Reported cost or cost savings (-)
Trial ID	Type of program	n	Cost	n	Cost	
Connock (2007)UK	PSM/PST	-	-	-	£180.21	£180.21
Jowett (2005) UK	PSM/PST	280	£122	337	£417	£295
McCahon (2007) UK	PSM/PST	40	£117.60	38	£193.01	£75.41
Bond and Raehl (2004) USA	Pharmacist	633,177	$17,167	84,219	$16,797	-$370
Hall (2011) USA	Pharmacist	175	$1,480,661	175	$754,191	-$3,697
Menzin (2005) USA	Pharmacist	-	-	600	$257	$257

Trial ID	Standard Care			Intervention		Reported cost or cost savings (-)
	Type of program	n	Cost	n	Cost	
Matchar (2010) USA	PSM/PST	1457	-	1465		$1,249

The cost savings reported in Bond and Raehl (2004) represents a per patient savings and was calculated from charges to Medicare for hospitalised patients that were being treated either in a hospital with access to an anticoagulation management service or hospitals that did not have access to this service.

The cost of patient self-management was determined to be £180.21 per patient per year over 5 years in the health technology assessment completed by Connock et al (2007). Connock included only studies that contained a full economic evaluation that compared costs and effects of PSM control with usual care. The results from Jowett et al (2005) were included in the evaluation.

Jowett et al (2005) was a cost-utility analysis conducted in the UK to determine the cost-effectiveness of PSM per patient per year. Costs were measured from both a healthcare and societal perspective. These included costs for training and assessment, costs for routine anticoagulation management, and primary and secondary care contacts for thrombotic and haemorrhagic complications.

Hall et al (2011) reported cost savings per patient in a pharmacist managed anticoagulation service compared to standard of care in hospitalised patients in the USA. Accounting for anticoagulation service operational costs and pharmacy expenditures the net savings was $647,024 or $3,697 per patient in the pharmacist managed group during the 1 year study period.

Matcher et al (2010) compared the per patient costs associated with POC testing in a group that self-tested compared to POC testing in patients tested in a specialist clinic. Costs were higher in the self-testing group but the difference was not significant.

McCahon et al (2007) evaluated the cost of PSM compared to standard of care in the UK. PSM is more costly than standard UK care, with NHS costs per patient per year estimated to be £75.41 more expensive than standard of care.

Menzin et al (2005) collected patient data from 3 anticoagulation clinics in the USA managed by a pharmacist and nurse. The mean overall cost of warfarin monitoring per patient over a

mean follow-up time of 10 months was calculated for each site. The average cost for the 3 sites was $257 per patient.

The data presented above provide a comprehensive outline of the impact of anticoagulation management programs, indicating that all programs increased the percentage TTR which translated into reduced thrombotic events. The impact of anticoagulation management represents a potential benefit to some patients at varying costs depending on the type of service being used.

The results of this study support results published previously in van Walraven et al (2006) and Baker et al (2009). Baker et al (2009) reported patients managed in anticoagulation clinics spent on average 11% more time in therapeutic INR target range than did patients managed by a GP.

This study reveals the most effective means of anticoagulation management are the specialist anticoagulation management services. These specialist clinics optimise anticoagulation treatment by determining the appropriateness of treatment, managing dose changes, monitoring INR results, providing dietary assistance and other education in regards to medications and disease states that may impact dosing. Specialist anticoagulation management clinics increased the time spent in therapeutic INR range by on average 11.5%. Comparing the weighted averages for event rates the percentage of major bleeding, thromboembolic events and stroke decreased while percentage of minor bleeding increased. When compared to standard of care the percentage of major bleeding decreased from 2.6% to 1.3%. The percentage of thromboembolic events also fell from 3.5% to 2.2% and the rates for stroke were reduced from 1.7% to 1.5%. While these results demonstrate the effectiveness of specialist anticoagulation clinics, it should be noted that clinics such as these do not currently exist in Australia.

Pharmacist managed anticoagulation programs have been assessed in Australia and these were shown to improve TTR by an average of 8.4% across all studies from the UK, USA and Australia. In the only Australian study, however, this improvement was only 0.4%. The percentage of any thrombotic event across all pharmacist managed studies was reduced from 1.2% to 0.8% and stroke or TIA fell from 0.6% to 0.2%. However, major bleeding unexpectedly increased from 0.7% to 1.3%.

Overall, the data show that improvements to warfarin therapy can be made with management programmes, but it remains unclear which subgroups would benefit most, as not all patients could be expected to improve.

3. Conclusion

Patients with AF are at risk of stroke, yet a large proportion do not receive adequate anticoagulation therapy that can effectively reduce this risk. This is despite the current standard of care with vitamin K antagonists, such as warfarin, being inexpensive and readily available. Many efforts have been made to improve warfarin management but the associated cost and the benefits for individual patients remains uncertain. The fact that warfarin has been available for such a long time and intensively studies, yet many patients worldwide continue to receive inadequate anticoagulation, highlights the limitations of this therapy and the need for alternatives.

4. References

Abdelhafiz AH, Wheeldon NM. Use of resources and cost implications of stroke prophylaxis with warfarin for patients with nonvalvular atrial fibrillation. Am J Geriatr Pharmacother 2003 Dec;1(2):53-60.

Abdelhafiz AH, Wheeldon NM. Results of an open-label, prospective study of anticoagulant therapy for atrial fibrillation in an outpatient anticoagulation clinic. Clin Ther 2004 Sep;26(9):1470-8.

Airee A, Guirguis AB, Mohammad RA. Clinical outcomes and pharmacists' acceptance of a community hospital's anticoagulation management service utilizing decentralized clinical staff pharmacists. *Annals of Pharmacotherapy*. 2009;43:621-628.Allender S, Scarborough P, Peto V, Rayner M. European Cardiovascular Disease Statistics 2008. European Heart Network; 2008 Feb.

Ansell J, Hollowell J, Pengo V et al. Descriptive analysis of the process and quality of oral anticoagulation management in real-life practice in patients with chronic non-valvular atrial fibrillation: The international study of anticoagulation management (ISAM). Journal of Thrombosis and Thrombolysis. 2007; 23:83-91.

Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):204S-33S.

Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. J Manag Care Pharm 2009 Apr;15(3):244-52.

Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin. A randomized, controlled trial. *Ann Intern Med*. 2000;133:687-695.

Bielik J, Tomek D, Visnansky M, Foltan V, Lednar M. Costs of atrial fibrillation in Slovakia from a payer perspective. Value Health. 2009.
Ref Type: Abstract

Bo S, Valpreda S, Scaglione L, Boscolo D, Piobbici M, Bo M, et al. Implementing hospital guidelines improves warfarin use in non-valvular atrial fibrillation: a before-after study. BMC Public Health 2007;7:203.

Boggon R, Gallagher R, van Star T. Resource utilisation and outcomes in atrial fibrillation (AF) stroke prevention in England. GRPD; 2009.

Bond CA, Raehl CL. Pharmacist-provided anticoagulation management in United States Hospitals: Death rates, length of stay, medicare charges, bleeding complications, and transfusions. *Pharmacotherapy*. 2004;24:953-963.Boulanger L, Kim J, Friedman M, Hauch O, Foster T, Menzin J. Patterns of use of antithrombotic therapy and quality of anticoagulation among patients with non-valvular atrial fibrillation in clinical practice. Int J Clin Pract 2006 Mar;60(3):258-64.

Bruggenjurgen B, Rossnagel K, Roll S, Andersson FL, Selim D, Muller-Nordhorn J, et al. The impact of atrial fibrillation on the cost of stroke: the berlin acute stroke study. Value Health 2007 Mar;10(2):137-43.

Bungard TJ, Gardner L, Archer SL et al. Impact of a pharmacist-managed anticoagulation clinic on clinical events. *Canadian Pharmacists Journal*. 2008;141:278-284.

Cafolla A, Melizzi R, Baldacci E et al. "Zeus" a new oral anticoagulant therapy dosing algorithm: A cohort study. *Thrombosis Research*. 2011;128:325-330.

Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010 Oct;31(19):2369-429.

Candel FJ, Matesanz M, Cogolludo F, Candel I, Mora C, Bescos T, et al. [Prevalence of atrial fibrillation and relationed factors in a population in the centre Madrid]. An Med Interna 2004 Oct;21(10):477-82.

Caro JJ, O'Brien JA, Klittich W, Jackson JD. The economic impact of warfarin prophylaxis in nonvalvular atrial fibrillation. Dis Manage Clin Outcomes 1997;1(2):54-60.

Caro JJ, Huybrechts KF. Stroke treatment economic model (STEM): predicting long-term costs from functional status. Stroke 1999 Dec;30(12):2574-9.

Cegedim Strategic Data (CSD). Quality and cost of anticoagulation for SPAF and VTET in French clinical practice. 2009.

Chien KL, Su TC, Hsu HC, Chang WT, Chen PC, Chen MF, et al. Atrial fibrillation prevalence, incidence and risk of stroke and all-cause death among Chinese. Int J Cardiol 2008 Nov 29.

Christensen TD, Maegaard M, Sorensen HT et al. Self-management versus conventional management of oral anticoagulant therapy: A randomized, controlled trial. *Eur J Intern Med*. 2006;17:260-266.

Claesson L, Gosman-Hedstrom G, Johannesson M, Fagerberg B, Blomstrand C. Resource utilization and costs of stroke unit care integrated in a care continuum: A 1-year controlled, prospective, randomized study in elderly patients: the Goteborg 70+ Stroke Study. Stroke 2000 Nov;31(11):2569-77.

Coghlan L, Fish J. Quality outcomes in traditional versus point-of-care testing anticoagulation management system. *Journal of General Internal Medicine*. 2010;25 SUPPL. 3:S374.

Connock M, Stevens C, Fry-Smith A et al. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: A systematic review and economic modelling. *Health Technology Assessment*. 2007;11:iii-50.

Cromheecke ME, Levi M, Colly LP et al. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison. *Lancet*. 2000;356:97-102.

Dewey HM, Thrift AG, Mihalopoulos C, Carter R, Macdonell RA, McNeil JJ, et al. Lifetime cost of stroke subtypes in Australia: findings from the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke 2003 Oct;34(10):2502-7.

DeWilde S, Carey IM, Emmas C, Richards N, Cook DG. Trends in the prevalence of diagnosed atrial fibrillation, its treatment with anticoagulation and predictors of such treatment in UK primary care. Heart 2006 Aug;92(8):1064-70.

Dolan G, Smith LA, Collins S, Plumb JM. Effect of setting, monitoring intensity and patient experience on anticoagulation control: a systematic review and meta-analysis of the literature. Curr Med Res Opin 2008 May;24(5):1459-72.

Fang MC, Stafford RS, Ruskin JN, Singer DE. National trends in antiarrhythmic and antithrombotic medication use in atrial fibrillation. Arch Intern Med 2004 Jan 12;164(1):55-60.

Fitzmaurice DA, Murray ET, McCahon D et al. Self-management of oral anticoagulation: Randomised trial. *British Medical Journal*. 2005;331:1057-1059.

Fowler S, Gulseth MP, Renier C et al. Inpatient warfarin: Experience with a pharmacist-led anticoagulation management service in a tertiary care medical center. *American Journal of Health-System Pharmacy*. 2012;69:44-48.

Franke CA, Dickerson LM, Carek PJ. Improving anticoagulation therapy using point-of-care testing and a standardized protocol. *Annals of Family Medicine*. 2008;6:S28-S32.

Friberg J, Gislason GH, Gadsboll N, Rasmussen JN, Rasmussen S, Abildstrom SZ, et al. Temporal trends in the prescription of vitamin K antagonists in patients with atrial fibrillation. J Intern Med 2006 Feb;259(2):173-8.

Frost L, Johnsen SP, Pedersen L, Toft E, Husted S, Sorensen HT. Atrial fibrillation or flutter and stroke: a Danish population-based study of the effectiveness of oral anticoagulation in clinical practice. J Intern Med 2002 Jul;252(1):64-9.

Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). Eur Heart J 2006 Aug;27(16):1979-2030.

Gage BF, Boechler M, Doggette AL, Fortune G, Flaker GC, Rich MW, et al. Adverse outcomes and predictors of underuse of antithrombotic therapy in medicare beneficiaries with chronic atrial fibrillation. Stroke 2000 Apr;31(4):822-7.

Gallagher AM, Rietbrock S, Plumb J, van Staa TP. Initiation and persistence of warfarin or aspirin in patients with chronic atrial fibrillation in general practice: do the appropriate patients receive stroke prophylaxis? J Thromb Haemost 2008 Sep;6(9):1500-6.

Garcia-Garcia J, Calleja-Puerta S, de lV-C, V, Benavente-Fernandez L, Rodriguez-Rodriguez S, Hernandez-Lahoz C. [Adequacy of anticoagulant prevention in patients with atrial fibrillation]. Rev Neurol 2005 Oct 1;41(7):399-403.

Garwood CL, Dumo P, Baringhaus SN et al. Quality of anticoagulation care in patients discharged from a pharmacist-managed anticoagulation clinic after stabilization of warfarin therapy. *Pharmacotherapy*. 2008;28:20-26.

Ghatnekar O, Glader EL. The effect of atrial fibrillation on stroke-related inpatient costs in Sweden: a 3-year analysis of registry incidence data from 2001. Value Health 2008 Sep;11(5):862-8.

Gladstone DJ, Bui E, Fang J, Laupacis A, Lindsay MP, Tu JV, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. Stroke 2009 Jan;40(1):235-40.

Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Ann Intern Med 1999 Dec 21;131(12):927-34.

Goldberg H, Gordon L, David YB et al. Feasibility of pre-discharge training in the self-management of oral anticoagulation. *Journal of Evaluation in Clinical Practice*. 2010;16:661-664.

Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, et al. Guidelines for the Primary Prevention of Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2011 Feb;42(2):517-84.

Gouin-Thibault I, Levy C, Pautas E et al. Improving anticoagulation control in hospitalized elderly patients on Warfarin. *Journal of the American Geriatrics Society*. 2010;58:242-247.

Grunau BE, Wiens MO, Harder KK. Patient self-management of warfarin therapy: Pragmatic feasibility study in Canadian primary care. *Canadian Family Physician*. 2011;57:e292-e298.

Hall D, Buchanan J, Helms B et al. Health care expenditures and therapeutic outcomes of a pharmacist-managed anticoagulation service versus usual medical care. *Pharmacotherapy*. 2011;31:686-694.

Hamann GF, Weimar C, Glahn J, et al. Adherence to secondary stroke prevention strategies--results from the German Stroke Data Bank. Cerebrovasc Dis 2003;15(4):282-8.

Hansen ML, Gadsboll N, Rasmussen S, Gislason GH, Folke F, Andersen SS, et al. Clinical consequences of hospital variation in use of oral anticoagulant therapy after first-time admission for atrial fibrillation. J Intern Med 2009 Mar;265(3):335-44.

Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007 Jun 19;146(12):857-67.

Heneghan C, Ward A, Perera R. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. Lancet 2012; 379:322-334.

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 Feb 4;367(9508):404-11.

Hodge K, Janus E, Sundararajan V et al. Coordinated anticoagulation management in a rural setting. *Australian family physician*. 2008;37:280-283.

Holm T, Deutch S, Lassen JF et al. Prospective evaluation of the quality of oral anticoagulation management in an outpatient clinic and in general practices. *Thrombosis Research*. 2002;105:103-108.

Japanese Circulation Society Joint Working Groups. Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2008). Circulation Journal 72[Suppl IV], 1639-1658. 2008.

Jones M, McEwan P, Morgan CL, Peters JR, Goodfellow J, Currie CJ. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvar atrial fibrillation: a record linkage study in a large British population. Heart 2005 Apr;91(4):472-7.

Jowett S, Bryan S, Murray E et al. Patient self-management of anticoagulation therapy: a trial-based cost-effectiveness analysis. *Br J Haematol*. 2006;134:632-639.

Khan TI, Kamali F, Kesteven P et al. The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation. *Br J Haematol*. 2004;126:557-564.

Lee T-Y, Po HL, Lin Y-J et al. A collaborative care model of anticoagulation therapy in patients with stroke. *Neurology Asia*. 2011;16:111-118.

Mahmud A, Bennett K, Okechukwu I, Feely J. National underuse of anti-thrombotic therapy in chronic atrial fibrillation identified from digoxin prescribing. Br J Clin Pharmacol 2007 Nov;64(5):706-9.

Manotti C, Moia M, Palareti G et al. Effect of computer-aided management on the quality of treatment in anticoagulated patients: A prospective, randomized, multicenter trial of. *Haematologica*. 2001;86:1060-1070.

Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the

Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007 Aug 11;370(9586):493-503.

Marques F, Quintao S, Bastos C et al. Point-of-care testing and computerized decision support for anticoagulation management: A reliable and practical method. *European Journal of Heart Failure, Supplement*. 2009;8 SUPPL. 2:ii83.

Matchar DB, Samsa GP, Cohen SJ et al. Improving the quality of anticoagulation of patients with atrial fibrillation in managed care organizations: Results of the managing anticoagulation services trial. *American Journal of Medicine*. 2002;113:42-51.

Matchar DB. Do anticoagulation management services improve care? Implications of the Managing Anticoagulation Services Trial. *Cardiac electrophysiology review*. 2003;7:379-381.

Mazzaglia G, Filippi A, Alacqua M, Cowell W, Shakespeare A, Mantovani LG, et al. A national survey of the management of atrial fibrillation with antithrombotic drugs in Italian primary care. Thromb Haemost 2010 May;103(5):968-75.

McBride D, Bruggenjurgen B, Roll S, Willich SN. Anticoagulation treatment for the reduction of stroke in atrial fibrillation: a cohort study to examine the gap between guidelines and routine medical practice. J Thromb Thrombolysis 2007 Aug;24(1):65-72.

McCahon D, Murray ET, Jowett S et al. Patient self-management of oral anticoagulation in routine care in the UK. *Journal of Clinical Pathology*. 2007;60:1263-1267.

Meiltz A, Zimmermann M, Urban P, Bloch A. Atrial fibrillation management by practice cardiologists: a prospective survey on the adherence to guidelines in the real world. Europace 2008 Jun;10(6):674-80.

Menendez-Jandula B, Souto JC, Oliver A et al. Comparing self-management of oral anticoagulant therapy with clinic management: a randomized trial. *Ann Intern Med*. 2005;142:1-10.

Menzin J, Boulanger L, Hauch O et al. Quality of anticoagulation control and costs of monitoring warfarin therapy among patients with atrial fibrillation in clinic settings: A multi-site managed-care study. *Annals of Pharmacotherapy*. 2005;39:446-451.

Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006 Jul 11;114(2):119-25.

Murdoch DL, O'Neill K, Jackson J, McMahon A, Rumley A, Wallace I, et al. Are atrial fibrillation guidelines altering management? A community based study. Scott Med J 2005 Nov;50(4):166-9.

Nichol MB, Knight TK, Dow T et al. Quality of anticoagulation monitoring in nonvalvular atrial fibrillation patients: comparison of anticoagulation clinic versus usual care. *Ann Pharmacother* . 2008;42:62-70.

Ogilvie IM, Dourdin N. Atrial Fibrillation- population subgroup analysis. Quebec, Canada: Bio Med Com Consultants; 2009. Report No.: BAST03.

Ogilvie IM, Welner SA, Cowell W, Lip YH. Ischemic stroke and bleeding rates in 'real world' AF patients. Thromb Haemost. In press 2011.

Ohsawa M, Okayama A, Okamura T, Itai K, Nakamura M, Tanno K, et al. Mortality risk attributable to atrial fibrillation in middle-aged and elderly people in the Japanese general population: nineteen-year follow-up in NIPPON DATA80. Circ J 2007 Jun;71(6):814-9.

Palmer AJ, Valentine WJ, Roze S, Lammert M, Spiesser J, Gabriel S. Overview of costs of stroke from published, incidence-based studies spanning 16 industrialized countries. Curr Med Res Opin 2005 Jan;21(1):19-26.

Poller L, Keown M, Ibrahim S et al. An international multicenter randomized study of computer-assisted oral anticoagulant dosage vs. medical staff dosage. *Journal of Thrombosis and Haemostasis*. 2008;6:935-943.

Poller L, Keown M, Ibrahim S et al. A multicentre randomised assessment of the DAWN AC computer-assisted oral anticoagulant dosage program. *Thrombosis and Haemostasis*. 2009;101:487-494.

Poon IO, Lal L, Brown EN et al. The impact of pharmacist-managed oral anticoagulation therapy in older veterans. *Journal of Clinical Pharmacy and Therapeutics*. 2007;32:21-29.

Rash A, Downes T, Portner R, Yeo WW, Morgan N, Channer KS. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). Age Ageing 2007 Mar;36(2):151-6.

Reynolds MR, Shah J, Essebag V, Olshansky B, Friedman PA, Hadjis T, et al. Patterns and predictors of warfarin use in patients with new-onset atrial fibrillation from the FRACTAL Registry. Am J Cardiol 2006 Feb 15;97(4):538-43.

Rowan SB, Bailey DN, Bublitz CE, Anderson RJ. Trends in anticoagulation for atrial fibrillation in the U.S.: an analysis of the national ambulatory medical care survey database. J Am Coll Cardiol 2007 Apr 10;49(14):1561-5.

Samsa GP, Matchar DB, Goldstein LB et al. Quality of anticoagulation management among patients with atrial fibrillation: Results of a review of medical records from 2 communities. *Archives of Internal Medicine*. 2000;160:967-973.

Sato H, Ishikawa K, Kitabatake A, Ogawa S, Maruyama Y, Yokota Y, et al. Low-dose aspirin for prevention of stroke in low-risk patients with atrial fibrillation: Japan Atrial Fibrillation Stroke Trial. Stroke 2006 Feb;37(2):447-51.

Siebenhofer A, Rakovac I, Kleespies C et al. Self-management of oral anticoagulation reduces major outcomes in the elderly. A randomized controlled trial. *Thromb Haemost*. 2008;100:1089-1098.

Singer DE, Albers GW, Dalen JE, Fang MC, Go AS, Halperin JL, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):546S-92S.

Spieler JF, Lanoe JL, Amarenco P. Socioeconomic aspects of postacute care for patients with brain infarction in France. Cerebrovasc Dis 2002;13(2):132-41.

Stafford L, Peterson GM, Bereznicki LRE et al. Clinical outcomes of a collaborative, home-based postdischarge warfarin management service. *Annals of Pharmacotherapy*. 2011;45:325-334.

Sudlow M, Thomson R, Thwaites B, Rodgers H, Kenny RA. Prevalence of atrial fibrillation and eligibility for anticoagulants in the community. Lancet 1998 Oct 10;352(9135):1167-71.

Sunderji R, Gin K, Shalansky K et al. A randomized trial of patient self-managed versus physician-managed oral anticoagulation. *Can J Cardiol*. 2004;20:1117-1123.

Tentschert S, Parigger S, Dorda V, Bittner K, Unterbuchschachner D, Greisenegger S, et al. Recurrent vascular events in patients with ischemic stroke/TIA and atrial fibrillation in relation to secondary prevention at hospital discharge. Wien Klin Wochenschr 2004 Dec 30;116(24):834-8.

Thomson BKA, MacRae JM, Barnieh L et al. Evaluation of an electronic warfarin nomogram for anticoagulation of hemodialysis patients. *BMC Nephrology*. 2011;12.

Turpie AG. New oral anticoagulants in atrial fibrillation. Eur Heart J 2008 Jan;29(2):155-65.

Van Walraven C, Jennings A, Oake N et al. Effect of study setting on anticoagulation control: a systematic review and metaregression. *Chest*. 2006;129:1155-1166.

Voller H, Glatz J, Taborski U et al. Self-management of oral anticoagulation in nonvalvular atrial fibrillation (SMAAF study). *Z Kardiol*. 2005;94:182-186.

Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NA, III, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011 Jan 4;123(1):104-23.

White S, Feely J, O'Neill D. Community-based study of atrial fibrillation and stroke prevention. Ir Med J 2004 Jan;97(1):10-2.

Willey ML, Chagan L, Sisca TS et al. A pharmacist-managed anticoagulation clinic: Six-year assessment of patient outcomes. *American Journal of Health-System Pharmacy*. 2003;60:1033-1037.

Wilson SJA, Wells PS, Kovacs MJ et al. Comparing the quality of oral anticoagulant management by anticoagulation clinics and by family physicians: A randomized controlled trial. *Canadian Medical Association Journal*. 2003;169:293-298.

Winter Y, Wolfram C, Schaeg M, Reese JP, Oertel WH, Dodel R, et al. Evaluation of costs and outcome in cardioembolic stroke or TIA. J Neurol 2009 Jun;256(6):954-63.

Witt DM, Sadler MA, Shanahan RL et al. Effect of a centralized clinical pharmacy anticoagulation service on the outcomes of anticoagulation therapy. *Chest*. 2005;127:1515-1522.

Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. Pharmacoeconomics 2003;21 Suppl 1:43-50.:43-50.

Young S, Bishop L, Twells L et al. Comparison of pharmacist managed anticoagulation with usual medical care in a family medicine clinic. *BMC family practice*. 2011;12:88.