DOCTOR OF PHILOSOPHY

Development and trialling of a behavioural intervention for patients with atrial fibrillation initiating oral anticoagulation

the 'treat' study

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DEVELOPMENT AND TRIALLING OF A BEHAVIOURAL INTERVENTION FOR PATIENTS WITH ATRIAL FIBRILLATION INITIATING ORAL ANTICOAGULATION: THE 'TREAT' STUDY

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SUMMARY

Purpose: Atrial fibrillation (AF) is the most common heart arrhythmia and is associated with an increased risk of stroke. Stroke risk is commonly treated with oral anticoagulation (OAC) with a narrow therapeutic range (INR 2.0 to 3.0); which is poorly controlled in practice. Barriers to adherence include poor knowledge, and inaccurate perceptions surrounding illness and medications. Trial registration: ISRCTN93952605.

Systematic review: Seven trials of educational, self-monitoring and decision aid interventions were included in a systematic review. Pooled analysis suggested education OR, 95% CI 7.89 (5.54-10.24) and self monitoring OR (95% CI) 5.47(2.55-8.39) significantly improve TTR; whereas decision aids are no more effective in reducing decision conflict than usual care, OR (95% CI) -0.10 (-0.17 to -0.02).

Intervention development: The intervention was theoretically-driven (utilising the common sense and beliefs about medication models) and developed with expert patient feedback. Described using behavioural change techniques, the one-off group session included an educational booklet, 'expert-patient' focussed DVD, and worksheet.

Methods: Ninety seven warfarin-naïve AF patients were randomised to receive the intervention (n=43), or usual care (n=54). The primary endpoint was time within therapeutic range (TTR), secondary endpoints included knowledge, quality of life (AF-QoL-18), beliefs about medication (BMQ), illness perceptions (IPQ-B), and anxiety and depression (HADS).

Results: Intervention group had significantly higher TTR than usual care (78.5% vs. 66.7%; p=0.01). Knowledge changed significantly across time ($F(3, 47) = 6.4$; $p<0.01$), but not between groups ($F(1, 47) = 3.3$; $p = 0.07$). At six months knowledge predicted TTR ($r=0.245$; $p=0.04$). Illness concern negatively correlated with TTR ($r= -0.199$; $p=0.05$). General Harm scores at one month predicted TTR ($F(1, 72) = 4.08$; $p=0.048$). There were significant differences in emotional representations ($F(3, 49) = 3.3$ (3, 49); $p= 0.03$), anxiety ($F(3, 46) = 25.2$; $p<0.01$) and depression ($F(3, 46) = 37.7$; $p<0.01$) across time.

Conclusion: A theory-driven educational intervention can improve TTR in AF patients and potentially reduce the risk of adverse clinical outcomes. Improving education provision for AF patients is essential to ensure efficacious treatment.

Key words: Atrial Fibrillation; Health Intervention; Illness Perceptions; Beliefs about Medication; Oral Anticoagulation.

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Personally, I would like to thank my parents and grandparents for their endless support, belief and understanding throughout what has been an epic student career. Thank you for remaining both interested and enthusiastic. I particularly want to thank my mum for adding 'grammar and punctuation' to the numerous things she has taught me. I am also lucky enough to have some amazing friends, who have supported me both academically and emotionally over the years, and without whom I certainly wouldn't have got this far, thank you. To my lovely husband, whose wondrous charms, technical skills, love and support over the three years, have been invaluable, and have certainly kept me smiling every day; love you always. Finally, I want to say a special thanks to Deirdre, for her patience, guidance, time and support on a daily basis, I couldn't have got through it without her, thank you.

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACCP	American College of Chest Physicians
ACE	Angiogestin-converting-enzyme
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AFA	Atrial Fibrillation Association
AFFIRM	Atrial Fibrillation Follow-up Investigators of Rhythm Management
AFI	Atrial Fibrillation Investigators
AHA	American Heart Association
BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CHD	Coronary heart disease
CHF	Congestive heart failure
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ESC	European Society of Cardiology
HADS	Hospital anxiety and depression index
HR	Hazard ratio
IQR	Inter quartile range
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events
MI	Myocardial infarction

NICE	National Institute of Clinical Excellence
NHS	National Health Service
NVAF	Non-valvular atrial fibrillation
OR	Odds Ratio
PAF	Paroxysmal atrial fibrillation
PCI	Percutaneous coronary intervention
PR	Pulse rate
PVD	Peripheral vascular disease
QoL	Quality of Life
RACE	Rate Control versus Electrical Cardioversion
RR	Relative Risk
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SPAF	Stroke prevention in atrial fibrillation
TIA	Transient ischemic attack
TREAT	Trial of an Educational intervention for patients with Atrial fibrillation initiating anticoagulant Treatment with warfarin
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

CONTENTS

1 Introduction

This chapter aims to introduce both the patient group and the need for a theory driven health intervention. As such it will discuss patient barriers to adherence in general, before focussing on the particular group of study, atrial fibrillation (AF) patients. The epidemiological background of both the patient group and their prescribed treatment is particularly relevant for intervention design. Oral anticoagulation (OAC) is a treatment carrying significant risks. As such any factors which may influence why patients may or may not adhere to recommendations are particularly important. Furthermore, any factors that may be useful for intervention design are also discussed, including patients' decision making, knowledge, physical and psychological prognosis following diagnosis.

1.1 Adherence

Medical research has provided efficacious treatments for numerous chronic illnesses, many of which are self administered. However, the effectiveness of these treatments is often undermined by low levels of adherence (Sabate, 2003; Sackett & Snow, 1979). Research suggests that patients substantially over estimate their actual adherence rates. One study comparing self-reported adherence to electronic monitors found patients over-reported their adherence to cardiac medications 78.8% of the time; self-report correlated poorly with objective monitoring of electronic pillbox recordings (regression coefficients <0.1) (Zeller, Ramseier, Teagtmeyer, & Battegay, 2008). Treatment discontinuation rates have also been found to increase over time in patients with chronic conditions such as hypertension and diabetes (Bloom, 1998; Lerman, 2005). Patients' overestimation of adherence and their discontinuation of

treatment could be a result of numerous factors including a poor understanding of the treatment regimen, memory deficits, and in some cases demand characteristics (i.e. wanting to please the physician). It is important for health care practitioners to consider factors that impact upon adherence, particularly as both intentional and unintentional non-adherence can result in treatments being in-effective or even harmful. Furthermore, cumulative non-adherence represents a costly waste of resources (Horne, Weinman, Barber, Elliot, & Morgan, 2005).

Psychological theory suggests that patients develop beliefs about medications in general and the medications they are prescribed for their individual health concern, which may influence their interpretation of information and in turn affect their levels of adherence (Horne, Weinmann, & Hankins, 1999). Beliefs about medication have been found to predict intentional and non-intentional adherence in patients starting medication for a range of chronic illnesses (Clifford, Barber, & Horne, 2008).

Patient's perceptions of their illness (for an extended discussion see section 3.1.2) have been also been related to medication adherence in hypertension (Meyer, Leventhal, & Gutmann, 1985), and diabetes (Gonder-Frederick & Cox, 1991). Illness perceptions may be inaccurate, representing a barrier to patient adherence. One study found illness representations during convalescence predicted adherence to recommendations to attend cardiac rehabilitation classes following a first myocardial infarction (MI) (Petrie, Weinman, Sharpe, & Buckley, 1993). Where patients have a coherent understanding of their illness and its cause, timeframe and consequences, they may be more likely to understand the necessity of adherence to medication. Thus, theories surrounding patients' perception of both their medications and their

illness can allow for a greater understanding of the barriers to adherence, and further, can aid the development of theory-based interventions.

A huge amount of attention has been devoted to improving adherence in numerous patient groups, by targeting psychological barriers. The common sense model (CSM; for an extended discussion see section 3.1.2) focuses on patients' illness representations. The model suggests that when diagnosed with a chronic illness we form a representation of that illness, including an understanding of the cause, consequences and timeline, illness coherence and emotional representation of the illness. The CSM has been used to design effective interventions for serious illnesses, for example two studies found that training women with breast cancer in emotional regulation skills can confer benefits (Antoni, 2003; Cunningham, Edmonds, Hampson, Hanson, Havonec, & Jenkins, 1991). Further interventions with MI patients, targeting problem-focussed self-regulation, found significant positive changes in patients' views of their MI; patients felt more prepared for leaving hospital ($p<0.05$) and subsequently returned to work at a significantly faster rate than the control group ($p <0.05$). At the 3-month follow-up, patients in the intervention group reported a significantly lower rate of angina symptoms than control subjects (14.3% vs. 39.3%, $p <0.03$) (Petrie, Cameron, Ellis, Buick, & Weinman, 2002).

Another intervention targeted problem-focussed self-regulation in patients undergoing gastrointestinal endoscopy using an educational brochure. They found those patients receiving the education experienced less anxiety before and after the gastroscopy, and they also reported greater satisfaction with preparation for the procedure (Van Zuuren, Grypdonck, Crevits, Walle, & Defloor, 2006). These interventions have targeted a range of psychological barriers to adherence, and have

succeeded in improving symptom control, return to work rates and patient satisfaction. It is important that the methods utilised for intervention design have established effectiveness, thus research must trial various interventions before adopting techniques as a 'usual care' procedure.

In practice very few interventions have been rigorously tested and few have considered psychological barriers in their design and evaluation. One Cochrane review examined interventions that have targeted adherence for a range of conditions and prescribed medications (Haynes, Yao, Degani, Kripalani, Garg, & McDonald, 2006). They found that of the 25 studies (evaluating 29 interventions) which met the review criteria, nine interventions were associated with significant improvements in at least one adherence measure at six to twelve months. Several methods of increasing adherence have been highlighted, using both long term and short term strategies (see Table 1.1); but few have a theoretical-basis.

One theory-driven trial used an education and counselling intervention to improve adherence to HIV medication (Pradier, Bentz, Spire, Tourette-Turgis, Morin, & Souville, 2003). This intervention was founded on the principles of motivational psychology, using client-centred, empathic therapy to enhance participants' self efficacy. The intervention focused on cognitive, emotional, social and behavioural determinants affecting adherence and consisted of three individually delivered sessions by nurses lasting 45-60 minutes. Both self-reported adherence (available for 83% of patients) and mean difference in HIV ribonucleic acid between baseline and six months (for all patients) were significantly improved in the intervention group, versus control (Pradier, et al., 2003). However, the trial was criticised for basing measurements of adherence on self-report.

Problems with studying the phenomenon of adherence usually stem from a lack of objective measurement tools, often relying on subjective self-report, where patients may overestimate their adherence (Zeller, Ramseier, Teagtmeyer, & Battegay, 2008). Practical ways of overcoming this include checking those patients who appear not to respond to treatment increments or those who fail to attend appointments. However, most objective measures rely on biological assays where available (i.e. blood, saliva, and urine samples), which are susceptible to dosage and timing issues (Haynes, McDonald, & Garg, 2002).

The medical research council published a framework for the development and evaluation of randomised control trials (RCTs) for complex interventions to improve health (MRC, 2000), including a step-by-step guide for implementation. The initial stage of the process includes exploring the relevant theory to ensure the best choice of intervention, for which several trials fail to do so, perhaps due to the absence of formal guidance on how to incorporate theory. Many interventions do attempt to incorporate strategies to improve adherence (see Table 1.1), often with success in both the short- (e.g. reminder packaging, written instructions) and long-term (e.g. instructions, simplifying drug regime and counselling). However, most rely on pragmatic decision-making when choosing intervention components, rather than an established development technique.

Table 1.1: Successful strategies for improving adherence to medications based on a review by Haynes et al (Haynes, Yao, Degani, Kripalani, Garg, & McDonald, 2006).

Increasing adherence with short term strategies#	Increasing adherence with long term strategies (interventions involving ≥1 strategy)*
➢ Counselling about the importance of adherence	➢ Instructions and instruction manuals
➢ Written instructions about taking medicines	➢ Simplifying the regimen
➢ Reminder packaging (e.g. dosettes, calendar packs)	➢ Counselling about the regimen
	➢ Support group sessions
	➢ Reminders for medications and appointments
	➢ Cuing medications to daily events
	➢ Reinforcement and rewards (explicitly acknowledging patients efforts to adhere)
	➢ Self monitoring with regular physician review
	➢ Involving family members and significant others

based on studies by (McDonald, Garg, & Haynes, 2002; Sharpe & Mikeal, 1974; Linkewich, Catalano, & Flack, 1974; Dickey, Mattar, & Chudzik, 1975) *based on reviews by (McDonald, Garg, & Haynes, 2002; Haynes, 1979).

More recently health psychologists have published a list of validated 'behavioural taxonomies' for the development of behaviour change interventions (Abraham & Michie, 2006). This taxonomy represents a practical and accessible guide, whereby researchers can use applicable theory-based behaviour change techniques within their interventions. With the use of validated domains, we are able to operationalise our intervention descriptions and replicate successful interventions in practice. Provision of instruction, reminders, memory aids/cues, opportunities for social support and self monitoring, are examples of these taxonomies, which directly link

into numerous psychological theories (Abraham & Michie, 2006), many of which are also highlighted as successful strategies within the review by Haynes and colleagues (Haynes, et al., 2006). However, the decision as to which strategies should be included in the intervention remains with the researcher or practitioner, and there is little guidance on the most appropriate evaluation strategy.

One patient group, with a high risk of stroke, who have received little attention regarding theory-based intervention development are patients with atrial fibrillation (AF). Patients with AF are prescribed oral anticoagulation (OAC), to reduce their risk of stroke, and their adherence to treatment and recommendations can be objectively monitored over time (Rosendaal, Cannegieter, van der Meer, & Briet, 1993) (refer to Section 4.3.1). Furthermore, this group is particularly suited to a theoretically-driven intervention as evidence suggests they have little knowledge of their condition or treatment (Lane, Ponsford, Shelley, Sirpal, & Lip, 2006; Nadar, Begum, Kaur, Sandhu, & Lip, 2003; Coelho-Dantas, Thompson, Manson, Tracy, & Upshur, 2004), poor adherence (Connolly, et al., 2008; Morgan, McEwan, Tukiendorf, Robinson, Clemens, & Plumb, 2009), high levels of anxiety and depression (Thrall, Lip, Carroll, & Lane, 2007; Lane, Langman, Lip, & Nouwen, 2009) and inaccurate illness representations (McCabe, Barnason, & Houfek, 2011).

1.2 Atrial Fibrillation

1.2.1 Etiology and prevalence

AF is defined as an atrial tachyarrhythmia (commonly known as an irregular heart beat); characterised by uncoordinated atrial activation and consequently by the

deterioration of atrial mechanical function (ESC, 2010). Patients can be both symptomatic and asymptomatic, and symptoms vary in frequency and duration including: palpitations, chest pain, fatigue, dizziness and exercise intolerance (ESC, 2010). Acute clinical management includes the assessment of these symptoms and is based on the European Heart Rhythm Association (EHRA) score (see Table 1.2) (Lip, et al., 2011).

Table 1.2: Classification of AF-related symptoms

EHRA Class	Explanation
EHRA I	'No symptoms'
EHRA II	'Mild symptoms', normal daily life not affected.
EHRA III	'Severe symptoms', normal daily life affected
EHRA IV	'Disabling symptoms', normal daily life discontinued.

EHRA: European Heart Rhythm Association (Lip, et al., 2011).

The pattern of this arrhythmia varies from patient to patient and can change over time. For clinical purposes there are five types of AF based on presentation and duration (ESC, 2010):

1. Newly diagnosed AF: every patient fits into this category initially irrespective of the severity of symptoms or duration of the arrhythmia.
2. Paroxysmal AF: usually episodes terminate spontaneously (usually in less than 48 hours), although episodes may last for up to seven days.

3. Persistent AF: characterised by an episode lasting more than seven days, but less than one year duration, requiring termination via cardioversion.
4. Long standing persistent AF: permanent AF whereby a rhythm control strategy is adopted.
5. Permanent AF: continuous for more than one year and accepted by the patient and the physician (hence no rhythm control adopted) (ESC, 2010).

The five categories are not mutually exclusive. For example, patients with paroxysmal AF can have periods of persistent AF and the reverse may also occur. A further factor to consider is the term 'silent AF', whereby patients are asymptomatic and only diagnosed via electrocardiogram (ECG) or following an AF complication. Silent AF can occur with any of the above types of AF (ESC, 2010). Patients can experience a number of symptoms including dizziness, palpitations, breathlessness and exercise intolerance; however, the majority of AF patients are asymptomatic (ESC, 2010).

AF is the most common arrhythmia in clinical practice (Fuster, Ryden, Cannom, Crijins, Curtis, & Ellenbogen, 2006; Lloyd-Jones, et al., 2004; Heeringa, et al., 2006), and the incidence and prevalence is rising. One US population-based study (n=4618) found the age/sex-adjusted incidence of AF per 1000 person-years was 3.04 (95% CI 2.78-3.31) in 1980, increasing to 3.68 (3.42-3.95) in 2000; amounting to a relative increase of 12.6% (Miyasaka, Barnes, & Gersh, 2006). Similar findings in the European Rotterdam Study (n= 6806) found the overall prevelance of AF was 5.5% to 6.0% in men and 5.1% in women (Heeringa, et al., 2006). In Iceland the prevalence in 2008 was 2.0%, and is projected to increase to 3.5-4.8% in 2050 (Stenfansdottir, Aspelund, Gudnason, & Arnar, 2011). Projected incidence of AF in

the US assuming a continued increase in age-adjusted incidence [as evidenced by 1980-2000 data] would suggest that by 2050 16 million people will be treated for AF (Miyasaka, Barnes, & Gersh, 2006). As AF may remain undiagnosed, particularly when asymptomatic ('silent AF'), the true prevalence of the condition may be higher. A UK population-based study found that 534 000 people (281 000 men and 253 000 women) were being treated for AF in the UK in 1995, this equated to 0.9% of the whole population and 5% of those over 65 years. Based on this population they calculated that including hospital admissions, treatment costs and long-term nursing home care, AF accounts for 0.62% of total health care expenditure, with a projected cost of 0.82% of total expenditure in 2000 (Stewart, Murphy, Walker, McGuire, & McMurray, 2004).

The prevalence of AF dramatically increases with age, from 0.5% at 40–50 years, rising to 5–15% at 80 years (see Figure 1.1) (Stewart, Hart, & Hole, 2001; Go, Hylek, Borowsky, Phillips, Selby, & Singer, 1999; Miyasaka, Barnes, & Gersh, 2006; Heeringa, et al., 2006; Naccareli, Varker, Lin, & Schulman, 2009; Lloyd-Jones, et al., 2004), with the prevalence being slightly higher in men than in women (Lloyd-Jones, et al., 2004). However, these figures can only be applied to certain populations as AF in non-White populations is less well studied (ESC, 2010). Data from the Framingham Heart Study suggests that at age 40 both men and women have a one in four lifetime risk of developing AF (Lloyd-Jones, et al., 2004).

1.2.2 Risk factors for atrial fibrillation

Numerous risk factors have been identified as contributing to the development of AF. These factors can have an additive or cumulative effect by increasing the patient's

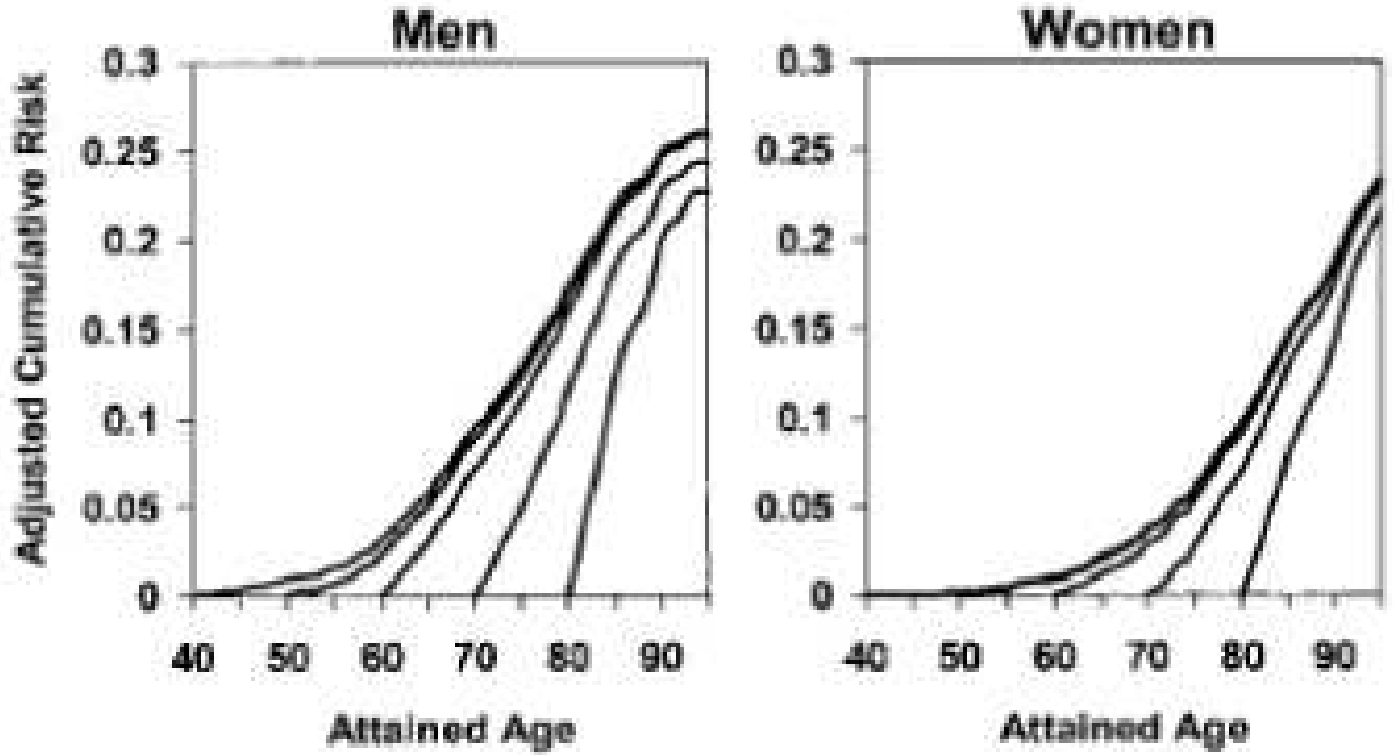
risk of developing the condition (Benjamin, et al., 2009). Where no predisposing factor can be identified, patients are classified as 'lone AF' (atrial fibrillation in the absence of overt cardiovascular disease or precipitating illness) (Kopecky, et al., 1987). Whilst the prevalence of lone AF appears to be small, a longitudinal study with over 30-years follow-up found the prevalence was 2.7% (n=97) (Kopecky, et al., 1987). A more recent review suggests the true prevalence of lone AF could range anywhere between 1.6% and 30% (Potpara & Lip, 2011), depending on patients age and study criteria. Further, evidence is often criticised for the inclusion of hypertensive and diabetic patients to the lone AF category.

AF appears to be progressive in both frequency and duration; evidence suggests it can progress from paroxysmal to permanent arrhythmia (Wijffels, Kirchhof, Dorland, & Allessie, 1995). EHRA recently published a comprehensive review of risk factors and markers for AF (Kirchhof, et al., 2011). Established and validated risk factors leading to the development of AF include age (see Section 1.2.2 for extended discussion), male gender, hypertension, valvular heart disease, heart failure, coronary artery disease, diabetes (Benjamin, Levy, & Vaziri, 1994; Gami, et al., 2007; Furberg, Psaty, Manolio, Gardin, Smith, & Rautaharju, 1994; Krahn, Manfreda, Tate, Mathewson, & Cuddy, 1995; Schnabel, et al., 2009), and genetic factors (Amar, et al., 2006; Fox, et al., 2004). Indeed, many of these risk factors, once identified form part of the patients risk stratification for stroke (see Section 1.2.3.2) and early intervention can help to prevent disease progression (Kirchhof, et al., 2011).

Hypertension is often considered one of the most important factors; the higher the blood pressure, the greater risk of AF (Conen, Tedrow, Koplan, Glynn, Buring, & Albert, 2009; Thomas, et al., 2008). In one large cohort study hypertension was

found in 49.3% of AF patients (Go, et al., 2001). The underlying pathophysiological link, as with other conditions such as heart failure, appears to be atrial pressure and/or overload (Benjamin, et al., 1994; Furberg, et al., 1994). Whilst male gender has an established link with the incidence of AF, it should be mentioned that fewer females are included in clinical trials. This also contrasts with female gender being a key additional risk factor for stroke in AF patients (ESC, 2010), a contradiction that has yet to be explained within the literature.

Figure 1.1: The increase in cumalative risk for AF at selected ages for men and women (Lloyd-Jones, et al., 2004; pg. 1044).



1.2.2.1 Less well established risk factors for AF

Some less established factors, such as obesity may provide further insight into AF and its progression (Krahn, Manfreda, Tate, Mathewson, & Cuddy, 1995). Evidence suggests that one in four AF patients are obese (Nabauer, et al., 2009). In one German AF registry survey the mean body mass index was 27.5 kg/m2 (equivalent to moderately obese; Nabauer, et al., 2009). Blood/pulse pressure (Conen, Tedrow, Koplan, Glynn, Buring, & Albert, 2009; Psaty, et al., 1997), height (Psaty, et al., 1997), sleep apnea syndrome (Gami, et al., 2007), subclinical hyperthyroidism (Sawin, et al., 1994), alcohol consumption (Conen, Tedrow, Cook, Moorthy, Buring, & Albert, 2008), chronic kidney disease (Iguchi, et al., 2008), competitive or athlete-level endurance sports (Mont, et al., 2008), chronic obstructive pulmonary disease (de Vos, et al., 2010), smoking (Furberg, et al., 1994; Krahn, et al., 1995; Benjamin, Levy, & Vaziri, 1994) and coffee consumption (Conen, Chiuve, Everett, Zhang, Buring, & Albert, 2010; Mattioli, Bonatti, Zennaro, Melotti, & Mattioli, 2008) are also less established risk factors.

Psychological determinants have also been highlighted as risk factors for AF. One study examined prevalence of acute psychological stress in patients with first presentation AF compared to an age- and sex-matched control group. Recent stress was associated with a greater risk of AF, alongside a high intake of coffee and obesity. Acute stress appeared to induce an increase in coffee consumption and changes in patient's lifestyle (Mattioli, Bonatti, Zennaro, Melotti, & Mattioli, 2008). The Framingham Offspring Study, following 3873 participants ('off-spring' of AF patients) found trait-anger (RR=1.1; 95% CI, 1.0 to 1.4; P=0.04), symptoms of anger (RR=1.2; 95% CI, 1.0 to 1.4; P=0.008), and hostility (RR=1.3; 95% CI, 1.1 to 1.5; P=0.003)

were predictive of 10-year incidence of AF in men (Eaker, Sullivan, Kelly-Hayes, D'Agostino, & Benjamin, 2004). Anger has also been found to trigger arrhythmias (OR, 1.8; 95% CI, 1.0 to 3.2) in patients with implantable cardioverter-defibrillators (Lampert, Joska, Burg, Batsford, McPherson, & Jain, 2002). Previous studies have only suggested a tentative relationship between emotion and arrhythmia, thus more evidence is needed to explain this relationship further.

1.2.3 AF prognosis

1.2.3.1 Morbidity and mortality

AF is associated with various clinical events, prevention of which is the main therapeutic goal. Stroke is the most common and feared complication, and strokes which occur in association with AF are often more severe, resulting in long-term disability or death, greater morbidity, poorer functional outcome, and longer hospital stays (Marini, De Santis, & Sacco, 2005; Steger, Pratter, & Martinek-Bregel, 2004; Savelieva, Bajpai, & Camm, 2007). AF is an independent risk factor for stroke, conferring a five-fold excess risk in AF patients compared to those in sinus rhythm and accounts for almost 10-15% of all ischemic strokes and approximately one in four strokes in those aged over 80 years (Lip & Edwards, 2006). Furthermore, undiagnosed 'silent AF' is a likely cause of some unexplained strokes (Kirchhof, et al., 2007; Knecht, et al., 2008).

The risk of stroke and thromboembolism is comparable whether AF is paroxysmal, persistent or permanent, symptomatic or asymptomatic (Flaker, Belew, & Beckman, 2005); and varies according to the number of risk factors present (Hughes & Lip,

2007). These factors include age (64-75 or ≥75 are at greater risk), presence of diabetes mellitus and hypertension, previous history of stroke or transient ischemic attack (TIA) and poor cardiac function (stroke risk stratification is discussed in more detail in Section 1.2.3.2).

Quality of life and exercise capacity are often impaired in AF patients when compared to healthy controls, patients with coronary heart disease or the general population (Thrall, Lane, Carroll, & Lip, 2006). However, as Thrall and colleagues discuss in their review, most of these studies were highly selective and focused on symptomatic patients receiving an intervention to improve quality of life, and as such may not relate to all AF patients. As patient's quality of life is often dependent on symptom control (symptomatic patients exhibit poorer quality of life outcomes), assessment of symptoms now forms part of the recommendations for physicians (ESC, 2010; for an extended discussion of AF related quality of life see Section 1.5.2).

Other factors which contribute to high levels of morbidity in this patient group include impaired left ventricular hypertrophy (LVH), caused by an irregular, fast ventricular rate (ESC, 2010). LV impairment represents an additional cardiovascular risk factor; the rate of fatal and non-fatal hospitalizations, cardiovascular events and all cause death is markedly greater in these patients (four-fold to five-fold) compared to patients without LVH, even when adjusting for other variables such as blood pressure (Bombelli, et al., 2009).

Cognitive dysfunction may also relate to AF; observational studies suggest that asymptomatic embolic events may contribute to long term cognitive impairment

(Knecht, et al., 2008). However, research also suggests that antiplatelet treatment may contribute to cerebral microbleeds, affecting a large percentage of older patients prescribed aspirin to reduce cardiovascular risk (adjusted odds ratio compared with non-users, OR, 1.71, 95% CI, 1.21-2.41) (Vernooij, et al., 2009). This was further supported by a pooled analysis of trial data suggesting that microbleeds increased the risk of transient ischemic attack (TIA) and intracerebral hemorrhage, the excess increased from 2.8 (odds ratio; range, 2.3–3.5) in non-antithrombotic users to 5.7 (range, 3.4 –9.7) in antiplatelet users and 8.0 (range, 3.5–17.8) in warfarin users (P difference=0.01) (Lovelock, Cordonnier, Naka, Al-shahi Salman, Sudlow, & Group, 2010). Thus the link between AF and cognitive decline may be linked to treatment history (use of anti-platelet drugs) rather than an inherent causal link. Hospitalizations are more frequent in patients with AF (than other arrhythmias) for various reasons including aggravation of heart failure, thromboembolic complications, and acute arrhythmia management (ESC, 2010).

1.2.3.2 Risk stratification

The risk of stroke in AF patients varies markedly between patients and is dependent upon the presence or absence of risk factors. The clinical management of AF involves stratification of individual stroke risk profiles to ensure each patient is treated appropriately. A recent review of stratification schemes found 12 schemes varying in complexity (Stroke Risk in Atrial Fibrillation Working Group, 2008). Among the twelve risk schemas, the most frequently employed variables for predicting stroke risk were previous stroke or TIA (100%), age (83%), hypertension (83%), and diabetes (83%). Other factors included were heart failure (50%), left ventricular systolic dysfunction (50%), systolic blood pressure (42%), coronary artery disease (CAD; 33%) and

female sex (25%). Schemes also varied in their definition of the age threshold (>65 or >75 years) and whether variables were continuous or ordered. Unsurprisingly, the fraction of patients categorised as being low or high risk varies substantially and this can greatly affect whether or not they are prescribed appropriate antithrombotic treatments (Stroke risk in atrial fibrillation working group, 2007).

The National Institute for Clinical Excellence (NICE, 2006) proposed a stroke risk algorithm for physicians to use when deciding upon appropriate antithrombotic treatment (warfarin, aspirin, or no antithrombotic therapy). Patients are categorised as low (aged <65 with no moderate or high risk factors), moderate (aged ≥65 with no high risk factors or aged <75 with hypertension, diabetes or vascular disease) or high risk (previous stroke/TIA/ thromboembolic event, aged ≥75 with hypertension, diabetes or vascular disease, clinical evidence of valve disease, heart failure, or impaired left ventricular function). The recommended antithrombotic therapy for low risk patients is aspirin, while moderate risk patients can be treated with either aspirin or warfarin (physician decision). High risk patients are recommended for warfarin, unless contraindicated (NICE, 2006).

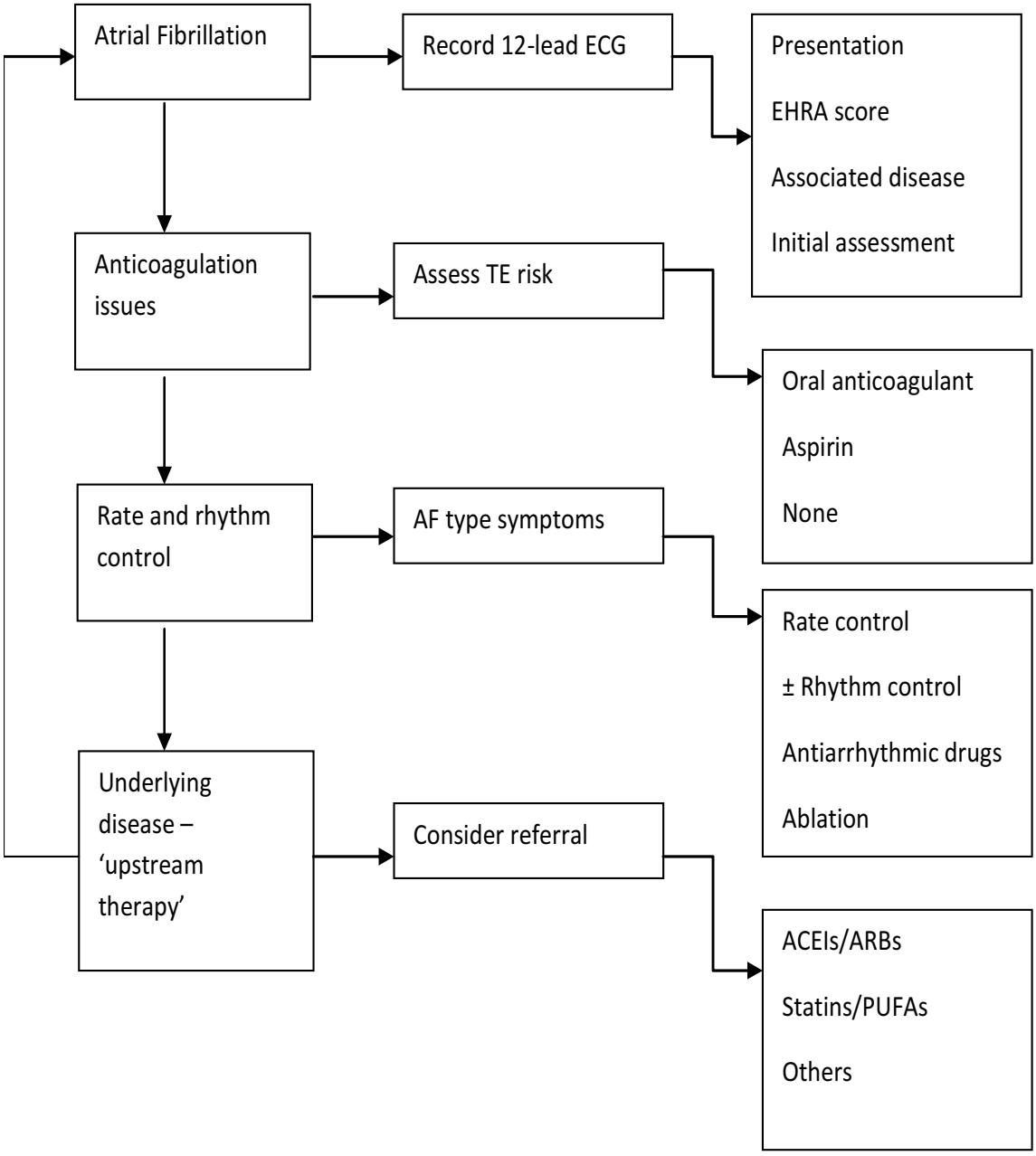
Since the development of the NICE stratification schema, it has become evident that stroke risk algorithms need to be simple and consider other risk factors that are evident within the literature. Furthermore, the strict categorisation into low, moderate and high risk categories may under or overestimate individual risk. Of particular concern is the intermediate risk category, where either aspirin or warfarin may be prescribed. This can leave physicians with a degree of uncertainty, and may explain why OAC is under-prescribed (Nieuwlaat, et al., 2006).

An alternative stroke risk stratification scheme, which is commonly used is the $CHADS_2$ index (see Table 1.3) which assigns one point for the presence of congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, and two points for previous stroke or TIA (Gage, Waterman, & Shannon, 2001). However, the $CHADS_2$ index has been criticised for underestimating patients' stroke risk. For example, a patient with previous stroke or TIA only, would have a risk score of two, which puts the patient in the moderate risk category, when they are high risk patients (Lip & Lim, 2007). However, both $CHADS_2$ and the National Institute for Health and Clinical Excellence (NICE, 2006) risk stratification schemes have similar value in predicting stroke and vascular events (Lip & Lim, 2007).

Previous risk stratification schemes have overlooked many potential risk factors, perhaps because many of these additional factors have not been systematically documented clinical trials (Lip, Nieuwlaat, Pisters, Lane, & Crijins, 2010). One systematic review carried out by the stroke working group found that in addition to the four major clinical predictors of stroke (prior stroke and/or TIA, advancing age, diabetes, and hypertension), there were also several factors with modest predictive value (Stroke risk in atrial fibrillation working group, 2007). For example, the Euro Heart survey data suggests female gender increases thromboembolic risk (Lane & Lip, 2009), as well as other vascular diseases such as myocardial infarction, peripheral vascular disease and aortic plaque (Schmitt, Duray, Gersh, & Hohnloser, 2009). Further, the BAFTA trial results suggest stroke risk increases in patients aged >65, thus patients risk score needs to be reassessed with increasing age (Lip & Lim, 2007; Mant, et al., 2007).

More recently the $CHADS_2$ scheme has been refined to include 'clinically relevant non-major' risk factors. These factors include vascular disease (defined as coronary artery disease, peripheral vascular disease, or previous thromboembolism other than stroke/TIA), age 65-74 years, and sex category (female sex). The updated schema, known by its acronym, CHA_2DS_2-VASc, allocates two points for patients that are 75 years and over and for those patients with a previous stroke/TIA/thromboembolism, highlighting the importance of age as a risk factor for stroke in AF. In addition to congestive heart failure, hypertension, and diabetes mellitus, CHA_2DS_2-VASc also allocates one point to the presence of vascular disease, age 65-74 years, and female gender (see Table 1.3). The Euro Heart survey group compared current risk stratification schemes and found the Birmingham 2009 schema (classified as CHA_2DS_2-VASC) proved the best predictor of thromboembolism (Lip, Nieuwlaat, Pisters, Lane, & Crijins, 2010). This approach of comprehensive risk factor assessment has been incorporated into the recent ESC guidelines for the management of AF patients. The management cascade shown in Figure 1.2, demonstrates how this risk factor approach to antithrombotic therapy is operationalised (ESC, 2010).

Figure 1.2: The management cascade for patients with AF taken from ESC guidelines (ESC, 2010, p. 12).



* ACEI = Angiotensin-converting enzyme inhibitor; ARB = Angiotensin receptor blocker, PUFA = polyunsaturated fatty acid, EHRA = European Heart Rhythm Association.

The ESC guidelines recommend that patients with a CHA_2DS_2-VASc score of zero can be treated with no therapy or aspirin with a preference for no antithrombotic therapy. Those with a CHA_2DS_2-VASc score of ≥1 should receive oral anticoagulation, unless contraindicated.

Table 1.3: CHA_2DS_2-VASc score risk factor-based approach based on the ESC guidelines (ESC, 2010).

CHADS2 Score	Risk factor	CHA2DS2-VASc Score
1	Congestive heart failure/LV* dysfunction	1
1	Hypertension	1
1	Age ≥75	2
1	Diabetes mellitus	1
2	Stroke/TIA*/thromboembolism	2
0	Vascular disease	1
0	Age 65-74	1
0	Sex category (i.e. female sex)	1
6	Maximum score	9

*TIA= transient ischemic attack; LV=Left ventricular

1.3 Antithrombotic therapy in AF

1.3.1 Warfarin versus placebo

Evidence from numerous RCTs supports the use of OAC for thromboprophylaxis in AF patients, demonstrating highly significant reductions in the incidence of stroke. A meta-analysis of the six RCTs (n=2900; five primary and one secondary prevention), comparing dose-adjusted warfarin (target International Normalised Ratio (INR) 2.0-3.0) with placebo demonstrated a 64% (95% CI 49%-74%) relative risk reduction in stroke with warfarin over placebo (Hart, Pearce, & Aguillar, 2007). Furthermore, the absolute risk reduction was greater for secondary stroke prevention (8.4%, number needed to treat (NNT) for 1 year to prevent a stroke was 12 vs. 2.7%, NNT 37, respectively), although only one secondary prevention study was included (Hart, Pearce, & Aguillar, 2007). The review suggested that the benefits of warfarin may in fact be underestimated, as many of the strokes that occurred in these studies occurred when patients were not taking anticoagulants or when the dose was sub-therapeutic (Hart, Pearce, & Aguillar, 2007). The risk reduction for ischemic strokes was particularly high (RRR 67%, 95% CI, 54% -77%).

1.3.2 Warfarin versus antiplatelets

A meta-analysis conducted by Hart and colleagues (Hart, et al., 2007) also demonstrated the effectiveness of dose-adjusted warfarin in reducing the risk of ischemic stroke or embolism (RRR 39%, 95% CI 22-52%) compared to antiplatelet therapy (11 trials) (Hart, et al., 2007). However, findings suggest that whilst the

increase in absolute risk of bleeding was small (0.2% per year), the risk of intracranial haemorrhage was doubled with adjusted dose warfarin compared with aspirin (RRR 128%, 95% CI -399% to -4%) (Hart, et al., 2007). However, the small number of strokes in this trial may limit the estimates of bleeding with warfarin versus antiplatelet therapy.

Since the meta-analysis of the earlier trials on antithrombotic therapy, the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study assessed whether warfarin, managed in primary care, reduced the primary endpoint of major stroke, arterial embolism or intracranial haemorrhage, compared with aspirin in 973 elderly (aged ≥75 years) patients. AF patients were followed up for an average of 2.7 years (Mant, et al., 2007). There were more adverse events among the aspirin patients (44 strokes, three systemic embolisms, one other intracranial haemorrhage), at a rate of 3.8% compared to 1.8% in warfarin patients (21 strokes, one systemic embolism, two other intracranial haemorrhage). Warfarin was associated with a 48% risk reduction (95% CI 0.28-0.80; p=0.003) for total number of events, while the risk of major haemorrhage (including intracranial and haemorrhagic stroke) was similar with warfarin and aspirin (Risk per year 1.9% vs. 2.0% respectively; RR 0.96, CI 95%, 0.53-1.75, p= 0.90). The BAFTA trial suggests that warfarin was more efficacious than aspirin in elderly AF patients, with a similar safety profile. The BAFTA trial also suggests that warfarin is still more efficacious than aspirin in patients >85 years old (RR 0.50, 95% CI, 0.17-1.31) and that there were no significant differences in risk reduction between age groups (age brackets included 75-79, 80-84, >85) (Mant, et al., 2007).

The anticoagulation and risk factors in atrial fibrillation (ATRIA) study, with a large retrospective cohort (n=13,559) of non-valvular AF patients, recently documented the net clinical benefit of risk (thromboembolism and bleeding) based recommendations for anticoagulation. The authors quantified net clinical benefit including estimated reduction in rate of thromboembolism, ischemic stroke, minus 1.5 times the estimated increased rate of intracranial haemorrhage attributable to warfarin therapy. The overall adjusted net clinical benefit with warfarin was 0.68% per year (95% CI, 0.34% to 0.87%). Adjusted net clinical benefit was greatest for patients with a history of ischemic stroke (2.48% per year [CI, 0.75% to 4.22%] and for those patients who were 85 years or older [2.34% per year [CI, 1.29% to 3.30%]) (Singer, et al., 2009).

1.3.3 Novel oral anticoagulants versus traditional antithrombotic therapy

The inherent difficulties associated with warfarin, such as regular blood monitoring, dietary and alcohol restrictions and interactions with other medications (see Section 1.4.3.2 for a full discussion), have led to the development of novel oral anticoagulant drugs which have sought to overcome these difficulties by reducing thromboembolic risk without substantially increasing the risk of major bleeding. Several new oral anticoagulant drugs have been tested in clinical trials, some of which have been completed (Granger, et al., 2011; Connolly, et al., 2011; Connolly, et al., 2009; Patel, et al., 2011) while others (Ruff, et al., 2010) are still ongoing. Table 1.4 illustrates that whilst many of the novel anticoagulants are non-inferior to warfarin in reducing incidence of stroke and mortality, some carry additional risks including increases in gastrointestinal bleeds. However, Apixaban appears to be both non-inferior and has a reduced risk of bleeding, with fewer treatment discontinuations (Granger, et al., 2011). In the future interventions targeting patients with atrial fibrillation may need to be adapted and/or relevant for novel OAC.

Table 1.4: Trials comparing new anticoagulants to warfarin in atrial fibrillation

Trial	Type of anticoagulant	Key findings
RE-LY	Dabigatran etexilate 150	Non-inferiority stroke
		Reduction in hemorrhagic & ischemic stroke
		Reduction in mortality
		Increased gastro intestinal bleeds
		Increased myocardial infarction
	Dabigatran etexilate 110	Non-inferiority stroke
		Reduction in hemorrhagic & ischemic stroke
		Reduction in major bleeding
		Increased myocardial infarction
ARISTOTLE	Apixaban	Non-inferiority stroke
		Reduction in hemorrhagic & ischemic stroke
		Reduction in mortality
		Reduction in major bleeding
		Fewer treatment discontinuations
ROCKET-AF	Rivaroxaban	Non-inferiority stroke
		Reduction in hemorrhagic & ischemic stroke
		Increased gastrointestinal bleeds

1.3.4 Bleeding epidemiology

Whilst the evidence discussed clearly highlights the net benefit of OAC for AF patients at risk of stroke, major bleeding events can be devastating if they do occur. Unfortunately, vitamin K antagonists, of which warfarin is the most commonly used, have a very narrow therapeutic range, and the INR needs to be maintained in the therapeutic range of 2.0–3.0 (Singer, et al., 2009). The risk of ischemic stroke increases when INR levels are below 2.0, and when they exceed 3.0, the risk of bleeding is increased (Singer, et al., 2009; Lip, et al., 2011). Hence, INR monitoring is necessary on a regular basis and dose adjustments may be required to reduce the risk of adverse bleeding. When deciding upon anticoagulant therapy, the risks of the treatment (i.e., bleeding risk) need to be assessed in conjunction with the risk of stroke (Lip, et al., 2011).

Anticoagulation intensity can be influenced by multiple drug and food interactions, as well as by alcohol consumption (Holbrook, et al., 2005). Furthermore, OAC is most often prescribed to elderly patients with multiple co-morbidities. The consequences of bleeding complications arising as the result of falls and overdosing, due to cognitive impairment, can be devastating. Ninety percent of the deaths associated with warfarin-related haemorrhage in AF patients are intra-cranial (Fang, Go, & Chang, 2007). A review carried out for the National Institute for Health and Clinical Excellence found several risk factors for anticoagulation-related bleeding, these include a history of myocardial infarction, diabetes, other bleeding and polypharmacy (particularly with aspirin and non steroidal anti-inflammatory drugs) (Hughes & Lip, 2007).

Patients are at greater risk of bleeding upon initiation of warfarin therapy, with the first 90 days of treatment appearing to be the most crucial period. In addition, elderly patients (those aged over 80 years), with supra-therapeutic INR (INR of ≥ 4.0), and high stroke risk ($CHADS_2$ score of 3 or more) are at greatest risk of major bleeding (Hylek, Evans-Molina, Shea, Henault, & Regan, 2007). However, for those with a high stroke risk, the benefits of anticoagulation often outweigh the risks. Hence, the risks of bleeding should reinforce the need for appropriate management and monitoring of treatment and INR, rather than to deter the use of OAC treatment all together.

In the same way that stroke risk stratification was developed, it is evident that bleeding risk may need a similar process. Previous bleeding risk stratification schemes are not AF specific and are validated with small samples (e.g. Beyth, Quin, & Landefeld, 2000; Kuijer, Hutten, & Prins, 1999). Four different stratification schemes have been published (Tay, Lane, & Lip, 2008). However, whilst age is accounted for in all schemes, female gender is only accounted for in two schema (Shireman, Mahnken, & Howard, 2006; Gage, Yan, & Milligan, 2006) anaemia in three (Gage, Yan, & Milligan, 2006; Shireman, Mahnken, & Howard, 2006) and recent myocardial infarction in one (Beyth, Quinn, & Landefeld, 1998). All schemas also take into account a range of varying factors, with limited predictive validity and clinical applicability (Tay, Lane, & Lip, 2008)

As alluded to earlier, treatment decisions regarding the most appropriate antithrombotic therapy for AF patients needs to consider both the risk of stroke and the risk of bleeding. However, the available schemas to assess bleeding risk have a

number of limitations as highlighted in the previous paragraph. Consequently, a new bleeding risk score was developed using data from the Euro Heart Study. This new bleeding clinical prediction rule is known by the acronym HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly; see Table 1.5). Results from the validation of HAS-BLED in the Euro Heart Survey cohort demonstrates that the risk of major bleeding rises sharply once the HAS-BLED score is ≥3 (Pisters, Lane, Nieuwlaat, de Vos, Crijns, & Lip, 2010), suggesting that such patients require close monitoring of their INR and assessment of associated risk factors to try to prevent treatment-associated bleeding complications.

HAS-BLED has been validated in the SPORTIF III (Stroke Prevention Using an ORal Thrombin Inhibitor in Atrial Fibrillation) and IV trials and compared against the other published bleeding risk tools (Lip, Frison, Halperin, & Lane, 2011). HAS-BLED score performed best in predicting bleeding events ($p<0.0001$). The c statistic (a measure of predictive accuracy) for bleeding was 0.65 (95% CI, 0.61 - 0.68) in the overall cohort and 0.66 (95% CI, 0.55-0.74) among patients naive to warfarin at baseline (n = 769). A further study compared the use of HAS-BLED with an older prediction scheme $HEMORR_2HAGES$ in a cohort of 'real world' AF patients (Olesen, et al., 2011). Using HAS-BLED (n = 44 771), 34.8% were categorized as 'low bleeding risk' and 47.3% using $HEMORR_2HAGES$. C-statistics for the two schemes were 0.795 (0.759–0.829) and 0.771 (0.733–0.806) respectively (Olesen, et al., 2011). Thus whilst the two schemes were comparable in predictive ability, HAS-BLED was deemed easier to use in clinical practice. This tool can be used to highlight high risk patients and decide whether they require extra monitoring or treatment review (ESC, 2010).

New bleeding risk stratification schemes such as the ATRIA bleeding risk score (Fang, et al., 2011), also have good predictive ability, the c-index for the continuous risk score for this scheme was 0.74 and 0.69 for the 3-category score (low- intermediate- and high-risk). Thus the predictive ability of this scheme is also good. The ESC guidelines have also endorsed formal assessment of bleeding risk when initiating antithrombotic therapy and suggest using a bleeding risk tool (ESC, 2010).

Table 1.4: Clinical characteristics comprising the HAS-BLED bleeding risk score (Lip, et al., 2011).

Letter	Clinical characteristic*	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (age >65)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

*'Hypertension' is defined as systolic blood pressure >160mmHG; 'Abnormal renal function' is defined as the presence of chronic dialysis or renal transplantation; 'Abnormal liver functions' is defined as chronic hepatic disease (cirrhosis) or biochemical evidence of significant hepatic derangement; 'Bleeding' refers to previous history of bleeding or predisposition to bleeding; 'Labile INRs' refers to unstable or high INRs and limited time within therapeutic range (<60%); 'Drugs/alcohol' refers to concomitant use of drugs such as antiplatelets, non-steroidal anti-inflammatory drugs and alcohol abuse.

1.3.5 Time within therapeutic range (TTR)

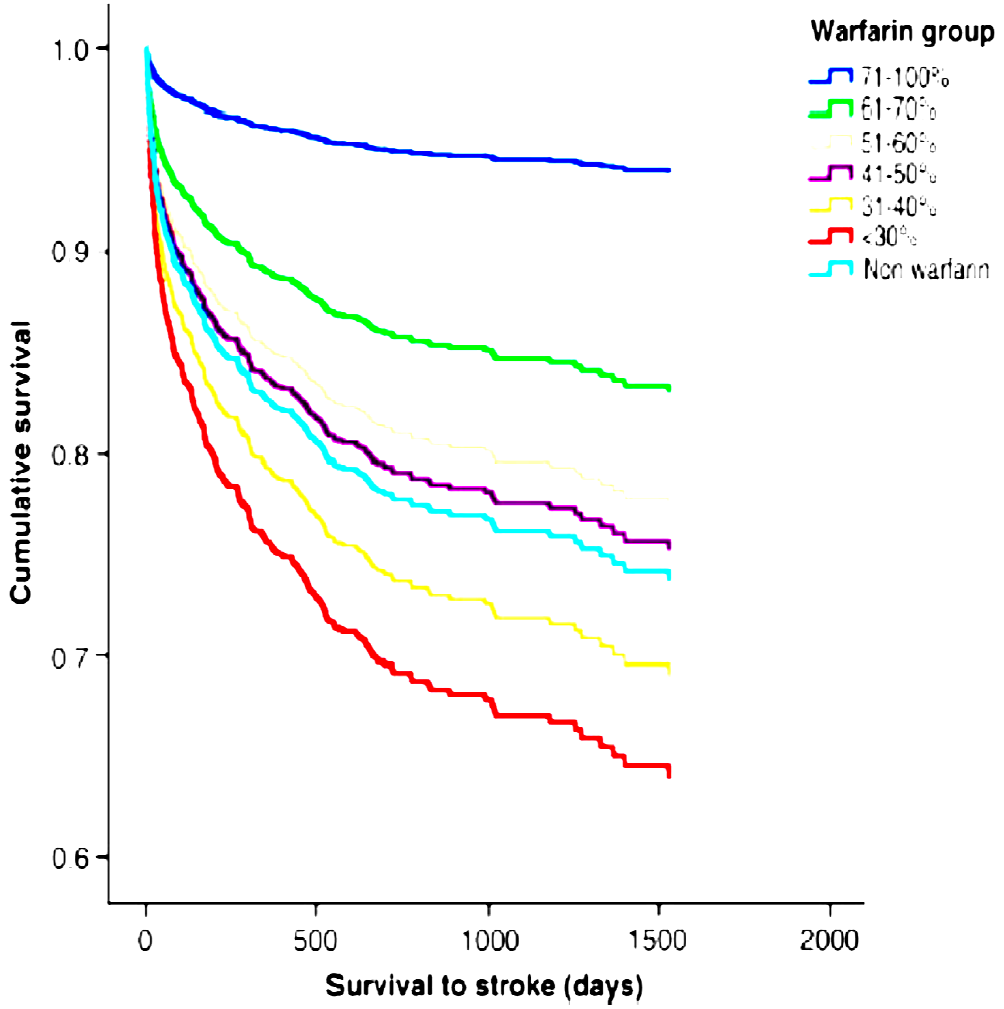
One of the most important goals of anticoagulation is to ensure that the international normalised ration (INR) is maintained within the target therapeutic range (TTR) of 2.0 to 3.0, where warfarin treatment offers the best benefit/risk ratio (Fuster, Ryden, Cannom, Crijins, Curtis, & Ellenbogen, 2006). Rosendaal (Rosendaal, Cannegieter, van der Meer, & Briet, 1993) first described a method for assessing the variability of INR target levels i.e. TTR (for details of its calculation see Section 4.3.1). This involves setting a study time-frame over which the cohort is observed, and gathering dates of all prothrombin time assessments; the INR is treated as gradually increasing or decreasing over the interval time frame (Rosendaal, Cannegieter, van der Meer, & Briet, 1993).

The ACTIVE-W trial explored the variation in INR control between centres and countries and observed how this variation impacted on the effectiveness of OAC therapy in patients with AF. The mean TTR of all patients in the trial varied by both centre and country (46 -78%) despite the parameters set by a clinical trial (such as the protocol-mandated target INR of 2.0-3.0 and minimum monthly measurements) (Connolly, et al., 2008). The findings suggested that where TTR values ≤ 58%, one cannot expect any net benefit from being on OAC, and a TTR >65% is critical to achieve clinical benefit (Connolly, et al., 2008).

Another study, using record-linkage data from hospitalised inpatients in Wales, sought to determine what proportion of TTR may be defined as good control in terms of reduced stroke and mortality for AF patients (Morgan, McEwan, Tukiendorf, Robinson, Clemens, & Plumb, 2009). This study found that 51% (n=248) of patients

with a $CHADS_2$ score ≥2 were outside the therapeutic range for 50% or more of the time for the duration of their warfarin treatment. The outcomes of this study suggest that warfarin treatment offers no or limited clinical benefit [reduced stroke and mortality] unless a patient can maintain their therapeutic range for more than 71% of the time (see Figure 1.3). Furthermore, there was a non-significant trend towards worse outcomes with TTR control lower than 30% for mortality and lower than 40% for stroke (Morgan, et al., 2009).

Figure 1.3: Cox proportional hazards model for survival to post-atrial fibrillation stroke, for patients at moderate or high risk of stroke CHADS2 ≥2, by level of warfarin control (Morgan, et al., 2009).

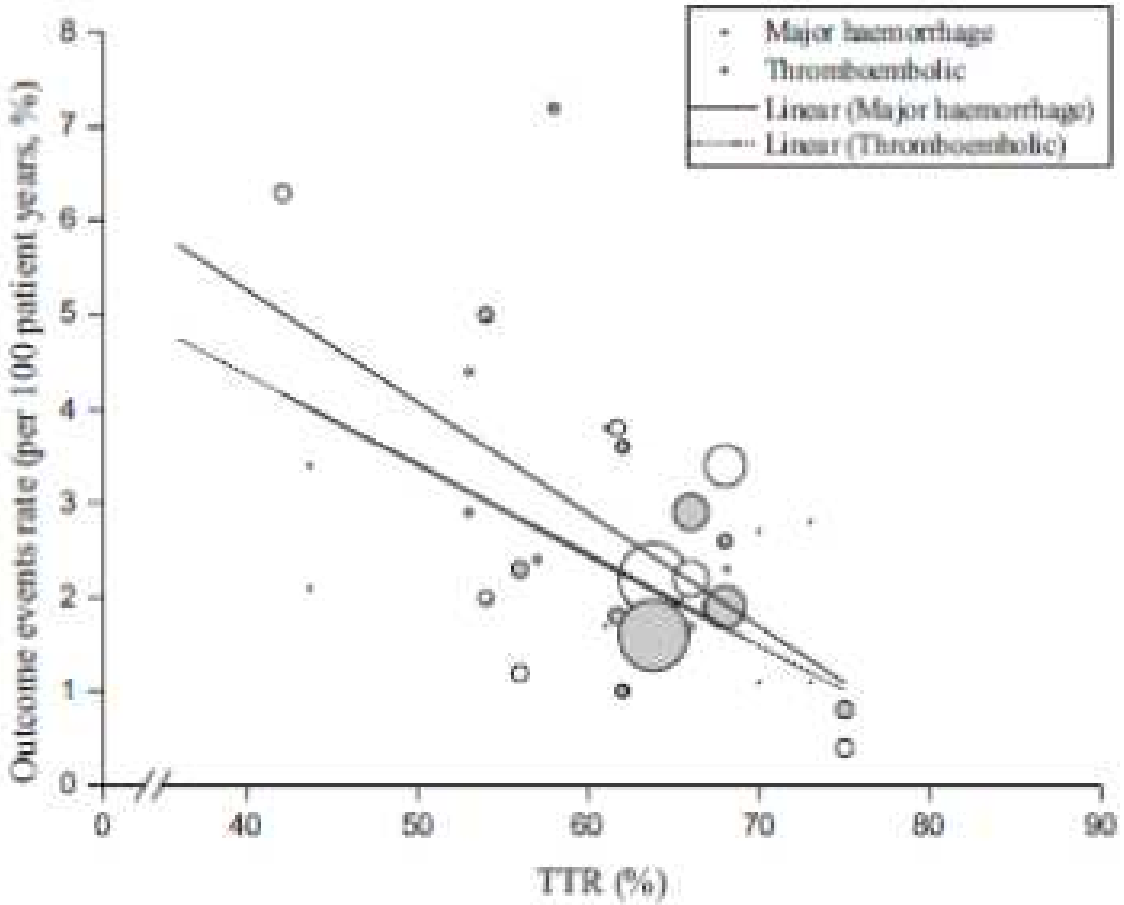


One meta-analysis of 32 studies (27 retrospective, 5 prospective) examined the relationship between INR control and the prediction of adverse events in patients with AF (Wan, et al., 2008). TTR was found to have a significant relationship with adverse outcomes in all of the studies, including thromboembolic events and major haemorrhage. The findings support the proposition that those patients with a higher percentage of time in therapeutic range have fewer adverse events (Figure 1.4). The authors suggest that a 7% improvement in TTR would lead to a reduction of one

major haemorrhage per 100 patient-years, and a 12% improvement in TTR would lead to a reduction of one thromboembolic event per 100 patient-years (Wan, et al., 2008).

More recently the RE-LY trial examined TTR in patients taking a novel OAC, dabigatran (110mg or 150 mg) versus warfarin. Patients were followed-up over a period of two years (n=18113). An increasing TTR in the warfarin group resulted in fewer strokes and systemic embolisms (at TTR <55.1% event rate per 100 person-years was 1.92, at >72.6% TTR event rates dropped to 1.34), but not fewer occurrences of intracranial bleeding. They also found no significant interactions between centre TTR control and total stroke with either dose of dabigatran (Wallentin, et al., 2010). There were however, lower rates of non-hemorrhagic stroke at higher quartiles of TTR in the dabigatran groups (in dabigatran 150 dose TTR >72.6% resulted in an event rate of 0.30 person-years, compared to 0.77 in the warfarin group), suggesting novel anticoagulants may be superior in reducing the incidence of bleeding, when patients remain within therapeutic range (Wallentin, et al., 2010).

Figure 1.4: TTR versus adverse events (weighted by sample size) for all studies (Wan, et al., 2008).



1.4 Barriers to Anticoagulation

Whilst it is clear that patients need to be assessed using appropriate risk stratification schemes and they need to remain within therapeutic range of their prescribed OAC treatment, there are many factors that influence whether patients are prescribed anticoagulation and indeed whether they adhere to recommendations. Barriers may be at the level of the health-care provider, the physician, or the patient themselves.

1.4.1 Health-care barriers

Achieving a good quality of OAC care can be problematic, particularly as the most cost effective method for monitoring patients requires them to travel to their nearest hospital or community clinic. Thus, the inconvenience of travelling and frequent venipunctures could impact upon adherence. However, anticoagulation control also varies extensively depending on the group, setting, drug types and type of management (i.e. self management; van Walraven, Jennings, Oake, Fergusson, & Forster, 2006). One systematic review and meta-analysis of warfarin therapy, found that studies set in the community, and those that did not use self-monitoring of INR, had the lowest percentage of TTR (van Walraven, et al., 2006). Unfortunately, this describes the majority of patients taking warfarin in both the UK and the US. The difference in TTR between community practices and anticoagulation clinics was significant in a meta-analysis (-8.3%; 95% CI, -4.4 to -12.1), with better INR control seen in anticoagulation clinics, however, there was no significant difference between anticoagulation clinics and randomised trials (van Walraven, et al, 2006). Thus patients taking part in trials and those receiving hospital care follow-up are more likely to achieve a better TTR and therefore, less warfarin-associated complications

Self-monitoring trials appear to achieve better TTR than traditional methods such as anticoagulation clinics (71.5% vs. 63.1% respectively) (van Walraven, et al., 2006). These patients are trained to self manage their treatment, and are also likely to demonstrate greater knowledge of the factors affecting TTR, taking more responsibility for their health outcomes. However, self-management is costly, few patients are suitable for this type of intervention, and self management trials often have high levels of attrition, perhaps due to a patients' lack of confidence in performing these tests.

1.4.2 Physician barriers

Despite the documented benefits of anticoagulation for AF patients, the Euro Heart Survey found that warfarin was prescribed in only 67% of eligible patients (Nieuwlaat, et al., 2006). Antithrombotic treatment needs to be tailored according to patients' individual risk profiles. However, in the Euro Heart Survey a similar proportion of patients received OAC therapy (40-50%) regardless of their stroke risk (see Figure 1.5). Evidence suggests that a high proportion of low risk ($CHADS_2$=0) patients (40-50%) are being prescribed warfarin, leaving them exposed to an avoidable bleeding hazard. Furthermore, some of the key risk factors such as prior stroke or TIA and age >75 were not associated with anticoagulant prescription (Nieuwlaat, et al., 2006). Factors that were associated with OAC prescription included valvular heart disease (OR 5.67, 95% CI, 3.83 – 8.38, p<0.001), AF type (paroxysmal, persistent, and permanent; p<0.001), diabetes (OR 1.47, 95% CI, 1.17 – 1.85), reason for hospital admission (i.e. AF only or another reason; p<0.001), lack of an OAC monitoring clinic (OR 0.75, 95% CI, 0.62-0.91, p=0.003), and type of heart rhythm control strategy (p<0.001) (Nieuwlaat, et al., 2006). Some of these non-traditional factors associated

provide cause for concern; for example, paroxysmal AF patients are less likely to be prescribed treatment, which could link to an inaccurate assumption that a low AF burden also confers a low risk of stroke (Nieuwlaat, et al., 2006).

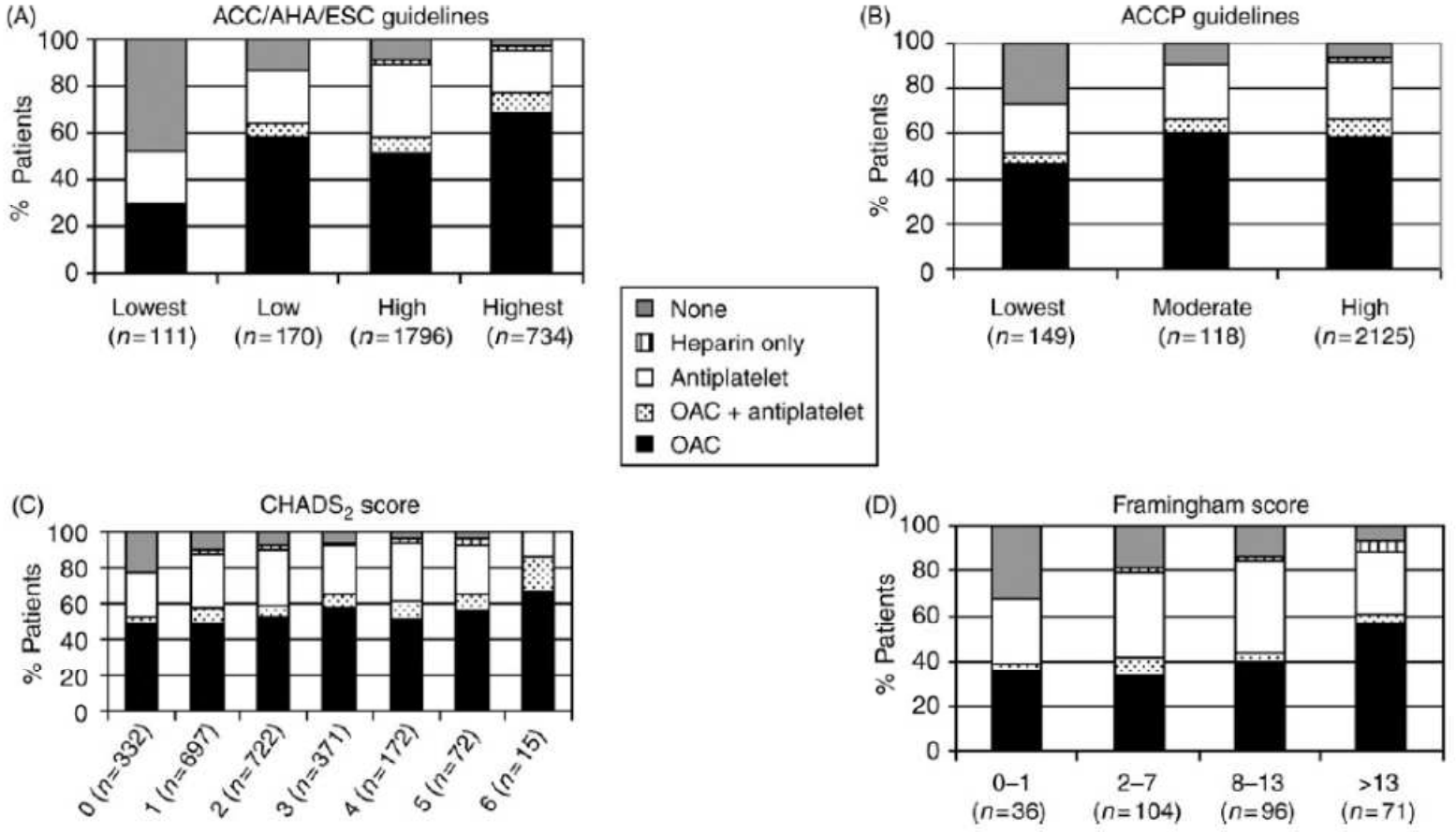
Evidently there are numerous factors that physicians consider, alongside traditional risk stratification factors for stroke. From the physician's perspective, there is reluctance to use warfarin, partly due to overestimation of bleeding risks (Marini, De Santis, & Sacco, 2005; Hart, Pearce, & Rothbart, 2000; Flaker, Belew, & Beckman, 2005; Choudry & Lip, 2004; Goldman, Pearce, & Hart, 1999). One study noted substantial differences between the amount of excess bleeding risk physicians and patients were willing to accept to reduce the potential risk of future stroke (Devereaux, Anderson, Gardner, Putnam, & Flowerdew, 2001). Participants were given descriptions of major and minor stroke and bleeding and completed four clinical scenarios to determine their thresholds for the minimum reduction in risk of stroke necessary to justify treatment [two warfarin and two aspirin scenarios]. Participants decided whether they would prescribe or agree to take warfarin in the given scenario. The stroke thresholds for warfarin were very different; 74% [n=45] of patients were willing to take warfarin if it prevented one stroke in 100 patients, whereas 38% [n=24] of physicians were willing to recommend warfarin for the same reduction in stroke.

Thus there was a significant difference between patient and physician threshold (P= 0.009).Thirty-five (57%) patients were willing to accept 22 more episodes of bleeding in 100 patients over a two year period; this is significantly different from physicians ($p<0.001$) (Devereaux, et al., 2001). Thus, the variability of physicians' bleeding thresholds may explain some of the under prescribing of OAC treatments. Physicians may not recommend warfarin if they think that the bleeding risks outweigh the

benefits. Thus it also follows that physicians are less likely to prescribe warfarin in scenarios where they perceive there to be a high risk of bleeding. One survey (Gattellari, Worthington, Zwar, & Middleton, 2007) utilising clinical vignettes to elicit OAC prescribing decisions, found that physicians prescribed warfarin less in scenarios where this risk of bleeding appeared high, e.g. due to a history of falls, recent bleeding and previous intracranial haemorrhage, despite a high risk of stroke.

Physicians' experiences of prescribing warfarin may also have an influence; as one survey also found that Australian family physicians felt more responsible for a stroke occurring whilst not on warfarin than a haemorrhage occurring whilst on warfarin. Approximately one fifth (17.6%) anticipated feeling most responsible for an intracranial haemorrhage on anticoagulation, whereas 31.5% anticipated feeling most responsible for an ischemic stroke in a patient without anticoagulation. Physicians who anticipated feeling most responsible for an intracranial haemorrhage were more likely to have previously experienced this outcome compared with physicians who anticipated feeling most responsible for a stroke (Gattellari, et al., 2007).

Figure 1.5: Antithrombotic drug prescription per risk category according to ACC/AHA/ESC guidelines (A) ACCP guidelines (B), $CHADS_2$ score (C), Framingham score (D) from an article by Nieuwlaat and colleagues (Nieuwlaat, et al., 2006).



Knowledge also plays an important role in physicians' confidence in treating AF (Murray, Lazure, Pullen, Maltais, & Dorian, 2011). One Canadian study found physicians lacked the confidence to provide optimal care for AF patients, predominantly because their knowledge was lacking. There was a lack of consensus over whether AF was a disease itself or a manifestation of another disease or condition. There was also a lack of confidence in identifying underlying factors of AF and detection of paroxysmal AF, as well as a lack of up-to-date knowledge surrounding appropriate treatment and the clinical decision making process. The study also identified contextual and communication barriers such as lack of access to specialists and incomplete referrals processes (Murray, et al., 2011). Evidently there are education gaps across the continuum of care that need to be addressed to ensure optimum treatment is provided for patients.

Whilst risk stratification models are improving in terms of clinical application, physicians may be less likely to adhere to the guidelines if their knowledge of them is poor (Lane & Lip, 2007). One qualitative study also highlighted this barrier and found senior physicians were often uncertain when prescribing OAC, 'certainty' in prescribing was expressed by <20% of physicians in any one vignette (Anderson, Fuller, & Dudley, 2007). Furthermore, physicians discussed a lack of availability of risk information, and their lack of AF-specific knowledge, leading to many of their decisions about patient treatment being influenced by experiential views (Anderson, Fuller, & Dudley, 2007).

More recent risk stratification schemes such as $CHADS_2$ (Gage, Waterman, & Shannon, 2001), and CHA_2DS_2-VASc (Lip et al, 2010), and HAS-BLED (Pisters, Lane, Nieuwlaat, de Vos, Crijns, & Lip, 2010), have led the way in proposing

standardised, easy-to-use schemes to help facilitate appropriate, and wider-ranging prescription of antithrombotic therapy among AF patients. Inadequate physician knowledge and appreciation of relevant data from clinical trials (Deplanque, Leys, & Parnetti, 2004), may also reflect a need for better dissemination of these guidelines (Lip & Lim, 2007).

1.4.3 Patient Barriers

Patient barriers to optimal OAC treatment are complex. There are several reasons why patients may choose not to take OAC or why they may not adhere to medication and lifestyle recommendations. The literature has focussed on patients' perceptions of the risks associated with treatment, the impact of the warfarin regime on quality of life, the decision making process itself and their knowledge and understanding surrounding AF and treatment choice.

1.4.3.1 Perception of risk

Risk index guidelines do not account for individual management of patients' complexities, co-morbidities and concerns. Patient related factors have been identified as barriers to anticoagulation and perception of risk is perhaps the most important consideration in deciding whether or not to start taking OAC.

It is presumed that we make rational decisions regarding treatment choice, opting for whichever plan of action results in the greatest benefit or usefulness to the individual. However, risk communication can also impact upon this process, particularly the 'framing' of the message. The way in which the risks and benefits are presented to

an individual in a consultation and how they are perceived will evidently affect their treatment choice (Dudley, 2001). Some physicians may communicate this information in a positive way by focussing on positive aspects of treatment and omitting negative aspects (positive framing), whilst others may focus on particular limitations or negative aspects of treatment, i.e. age, mobility or lifestyle changes (negative framing). This suggests that the physicians own opinions and perceptions of risk may also play an important role in determining patient risk perception (Dudley, 2001).

Qualitative evidence suggests that the majority of patients with atrial fibrillation are unaware that they are at risk of stroke (61% 34/56) (Howitt & Armstrong, 1999). Furthermore, of those patients that were aware, only two (2/56) felt able to estimate the level of risk (Howitt & Armstrong, 1999). These findings were also reflected in a local Birmingham-based study that found only half of the patients considered AF a serious condition, and only 9% considered it a 'very serious' condition. Furthermore, only 54% were aware that AF could predispose them to blood clots or stroke (Lane, Ponsford, Shelley, Sirpal, & Lip, 2006). One qualitative study suggests whilst patients may be aware of the name of their treatment, they are less likely to know the reason why they are taking it (Bajorek, Krass, Ogle, Duguid, & Shenfield, 2006). Without the knowledge to facilitate the link between their illness and the necessity for treatment, many patients may not view their condition as risky and indeed may underestimate the necessity of their medication.

Patients appear to have little knowledge of the risk associated with warfarin use or their potential risk of stroke, and the importance of their perception of risk has been highlighted in previous studies (Howitt & Armstrong, 1999). Patients' judgement of

the minimal level of benefit for which they would take warfarin (versus aspirin) predicted those patients who were going to start warfarin, with a mean minimal clinically important difference (between warfarin and aspirin) at the first interview of 2.56% and 4.86% for those not starting warfarin (t test 2.93, $p<0.05$) (Howitt & Armstrong, 1999). Clearly patients are managing risk based on the evidence acquired, or alternatively their perception of risk.

An example of the decision making process was highlighted in a decision aid study by Fuller and colleagues. They examined treatment choices of older patients when given information about the cumulative benefits of warfarin on stroke risks over a 10 year period (Fuller, Dudley, & Blacktop, 2004). Pictograms were used to illustrate the risks and benefits, both visually and numerically. Patients aged ≥ 65 were asked to choose a treatment option from treatment P (placebo) and treatment J (warfarin) for a patient with AF who has had a recent ischemic stroke. Pictograms illustrated the number of strokes suffered in both treatment arms at 10 years, participants were asked which treatment they would choose, all participants chose treatment J (n=81). As additional information was given regarding the risk of intracerebral haemorrhage, increasing from 0.1% risk (1 person in 10 years) to 4% (34 people after 10 years), the percentage of participants opting for treatment J was reduced from 99% (with 0.1%/year risk) to 49% (with 4%/year risk). However, even with the maximum bleeding risks nearly half of the participants were opting for treatment with warfarin suggesting that patients fear the risk of stroke more than the risk of bleeding on OAC (Fuller, Dudley, & Blacktop, 2004).

Patients' perception of risk plays an important role in their decision to start anticoagulation therapy, and information on the risk of bleeding significantly

attenuates the number of patients willing to take OAC, suggesting that patients 'trade-off' the risk of stroke with the risk of bleeding, to arrive at a decision about OAC therapy. Qualitative evidence suggests that patients who decide not to take warfarin do not perceive themselves at high risk of stroke (Howitt & Armstrong, 1999), thus they may place greater emphasis on the 'unnecessary' risks of bleeding.

However, not all patients feel able to make a judgement regarding the minimum clinically important difference between stroke and bleeding risk (Fuller, Dudley, & Blacktop, 2004). Thus for many patients it may be difficult to understand the risk information presented to them. In practice these patients would most probably seek the advice of the physician or social networks. Hence it is important when developing educational materials that they are piloted with patient groups to ensure understanding, as misunderstanding could attenuate the effects of the intervention. Further, physicians need to ensure that they are not framing the communication of risk in a way that may present a barrier to patient uptake.

1.4.3.2 Warfarin regimen

The warfarin regime requires several changes to a patients' lifestyle. Regular INR monitoring is achieved via blood testing, which often takes place at a community GP surgery or hospital outpatient clinic. Furthermore, patients are given lifestyle recommendations based on the numerous factors that can influence warfarin metabolism. Despite the burden of the treatment regimen the Boston Area Anticoagulation Trial for Atrial Fibrillation found that patients decided to take warfarin 93% of the time (Gottlieb & Salem-Schatz, 1994). However, 26% of patients (aged 80 years and over) in another study stopped taking warfarin within the first year. For

over 80% of these patients, physicians stopped their treatment due to concerns about safety (Hylek, Evans-Molina, Shea, Henault, & Regan, 2007). This may explain why surveys of prescribing physicians have found they may withhold warfarin based on the belief that patients would be non-adherent (Kutner, Nixon, & Silverstone, 1991). Whilst patients are prepared to take OAC based on recommendations, they may be reticent about doing so, influencing their decision to discontinue their treatment or perhaps not adhere to recommendations.

The impact of the warfarin regime varies, whilst the vast majority of patients in one qualitative study reported no warfarin complications, others report minor inconveniences (Coelho-Dantas, Thompson, Manson, Tracy, & Upshur, 2004). Those patients who regarded warfarin as having a significant impact on their day-to-day lives were more likely to have multiple co-morbid illnesses, multiple treatment plans, and struggle with the addition of the warfarin regime (Coelho-Dantas, et al., 2004). Therefore, it is important to find out which elements of the regime patients find difficult to integrate into their lifestyle.

One study by Fuller and colleagues (Fuller, et al., 2004) examined decision-making when faced with the additional information about warfarin (i.e. the need for blood tests, necessity of tablets and the risks of bleeding). INR (blood) checks did not substantially reduce the number of participants opting for warfarin from 12-weekly blood check (99%) to 2-weekly (84%), but 15% of participants were choosing not to take warfarin because of the inconvenience of the tests. Furthermore, whilst 98% of patients still opted for warfarin with the limitation of two units of alcohol per day, 11% of patients chose not to opt for this treatment if they were not able to drink alcohol at all (Fuller, et al., 2004).

A large scale European cross-sectional study (n=711) also suggested that patients felt that OAC treatment impacted on them in numerous ways. For 67% of the cohort the impact included diet, socialising, career, independence, and the impact was more prevalent in patients that were younger (74%) (Lip, Agnelli, Thach, Knight, Rost, & Tangelder, 2007). Therefore the burden of INR tests and lifestyles changes can present a challenge for patients; for some these changes may influence their decision to adhere to guidelines.

Evidently whilst patients are willing to start treatment to reduce the risk of stroke, they may not adhere to associated lifestyle recommendations. One qualitative study interviewing anticoagulation nurses suggested patients were unperturbed by the risk of bleeding, even to the point of ignoring safety measures (Bajorek, Krass, Ogle, Duguid, & Shenfield, 2006). When provided with the risks of bleeding, and lifestyle recommendations, many patients still choose not to adhere to treatment guidelines (i.e. 'informed dissent'). This could result from other influencing factors, for example, several studies highlight the lack of patient knowledge surrounding treatment and AF (Bajorek, Krass, Ogle, Duguid, & Shenfield, 2006; Lane, Ponsford, Shelley, Sirpal, & Lip, 2006; Bajorek, Ogle, Duguid, Shenfield, & Krass, 2007; Coelho-Dantas, Thompson, Manson, Tracy, & Upshur, 2004), therefore, perhaps patients are not aware of the extent of the risks associated with non-adherence, thus are less willing to make changes to their lifestyle.

1.4.3.3 Decision making

The decision to take warfarin can be a difficult one for patients, who may need to consider the associated risks and required lifestyle changes. One qualitative study of

patients taking warfarin (n=21) found several themes within patient narratives regarding perspectives on taking warfarin (Coelho-Dantas, Thompson, Manson, Tracy, & Upshur, 2004). Patients report that the decision to initiate warfarin therapy had been made by the doctors; typically there was no patient involvement in the decision-making process (Coelho-Dantas, et al., 2004). This lack of involvement in the decision-making process often coincided with a high level of trust in medical expertise, as illustrated by the commonly-used phrase “doctor knows best”.

The decision of whether or not to take OAC is an important one, particularly as it may impact on a patient’s morbidity and mortality. Several studies have designed patient decision aids to ascertain a patients’ ability to make decisions about their antithrombotic therapy (Man-Son-Hing, et al., 1999; Thomson, Robinson, Greenaway, & Lowe, 2002; Holbrook, Labris, Goldsmith, Ota, Harb, & Sebaldt, 2007; McAlister, et al., 2005). One RCT used a booklet, personal worksheet and audiotape to guide the trial group through the decision making process (Man-Son-Hing, et al., 1999). The materials highlighted the risk of stroke and haemorrhage for patients taking aspirin or warfarin using pictograms and descriptive examples. The results suggest patients in the intervention group were less likely to take warfarin than those patients not receiving the decision aid, despite the benefits of anticoagulation (n=12 [8%] in trial group, n=17 [11%] in control group, p=.02). However, using the decision aid did not improve patient satisfaction when compared to the control group even though trial patients believed they were more informed (-0.21 units; 95% CI, -0.34 to -0.08). Evidently, improving patient knowledge may reduce the number of patients prepared to take warfarin, and encouraging shared decision making may have a negative impact on patient satisfaction surrounding their consultation.

Another trial examined differences in patient outcomes/preferences based on (i) the format (decision board, decision booklet with audio tape or computer decision aid), (ii) the graphical presentation of risk data, and (iii) the names of the treatments (Holbrook, Labris, Goldsmith, Ota, Harb, & Sebaldt, 2007). The authors found knowledge improved significantly after the decision aid ($p < 0.01$), as indicated by an increase in the mean comprehension score (from 4.6, standard deviation [SD] 2.2) to 7.7 (SD 1.8), regardless of type of graphical presentation.

Interestingly more patients chose treatment with warfarin when blinded to treatment names; 39 participants chose treatment A (warfarin), 41 chose treatment B (aspirin), and 18 selected treatment C (no treatment). When told the treatment name the number of participants selecting warfarin decreased to 27 ($p = 0.023$), the number choosing no treatment decreased to 5 ($p < 0.001$), and the number selecting aspirin increased to 66 ($p < 0.001$) (Holbrook, Labris, Goldsmith, Ota, Harb, & Sebaldt, 2007). It is important to consider whether patients' decisions are influenced by preconceived ideas or beliefs about the available treatments. Evidently patients are not only influenced by the risks associated with the treatment, but also by their perceptions of it, which may derived from personal information-seeking through social networks or the media (for a discussion of beliefs about medication refer to Section 3.1.1). However, patients in this trial were not diagnosed with AF, the trial was examining pseudo-decision making, thus cannot be applied to 'real-life' decision making.

The DAAFI (Decision Aid in Atrial Fibrillation Investigators) trial examined the impact of a decision aid on the appropriateness of treatment (McAlister, et al., 2005). The patient decision aid was a self-administered booklet and audio-tape versus usual

care. This trial highlights the potential benefits of using a decision aid, as in the intervention group, the number of patients receiving therapy appropriate to their stroke risk increased by 9% (32% [69/219] at baseline vs. 41% [89/219] at 3 months). However, the proportion of patients whose therapy met the ACCP (American College of Chest Physicians) treatment recommendations did not differ between study arms at baseline ($p = 0.11$) or 3 months ($p = 0.44$). Thus decision aids maybe one step towards improving this decision making process. Furthermore, there were significantly more patients in the intervention group able to make accurate estimates of the stroke risk ($p<0.001$), signifying an increase in knowledge. Therefore, even a cohort with longstanding AF (such as in the DAAFI trial) can increase their knowledge regarding treatment choice and stroke risk. The potential impact an intervention may have on a warfarin-naive or newly diagnosed cohort maybe greater.

The results of these trials signify the importance of shared decision making between the patient and clinician. The benefits of improving patient knowledge and understanding of treatment risk could include more patients taking warfarin and adhering to recommendations. Equally improving knowledge of risk could also have a negative impact on patient anxiety and treatment uptake. More evidence is needed to evaluate the impact of decision aids of newly diagnosed AF patients.

1.4.3.4 Treatment knowledge

The importance of a patient's knowledge surrounding their illness and medication has been consistently highlighted in the literature. Patient knowledge surrounding treatment varies with age. Elderly patients (>75) demonstrate poorer knowledge, with less than half of one patient sample able to name even one specific benefit, risk or

lifestyle change associated with warfarin (Coelho-Dantas, Thompson, Manson, Tracy, & Upshur, 2004). In several cases spouses were more knowledgeable than patients and appeared to play a vital role in monitoring their treatment regime (Coelho-Dantas, et al, 2004). Furthermore, this study sample was from a patient population of an academic primary-care practice that is both well educated and of medium-high socio-economic status, thus a more heterogeneous sample may demonstrate even less treatment related knowledge. Indeed a pan European patient survey (n=711) found that only 7% of patients knew that OAC was taken to prevent stroke (Lip, Agnelli, Thach, Knight, Rost, & Tangelder, 2007). Perhaps this explains why 21% of patients admitted missing clinic appointments (Lip,et al., 2007).

One survey collected data from hospital emergency rooms in Finland (Koponen, Rekola, Ruotsalainen, Lehto, Leino-Kilpi, & Voipio-Pulkki, 2008). Patients only had moderate levels of knowledge about atrial fibrillation, which improved slightly three months after the visit. Patients exhibited the highest accuracy on questions about AF symptoms and its effects on everyday life. Fewer patients were knowledgeable about the disease, treatment, detection of symptoms and when to seek treatment. Knowledge level varied between participants, and factors associated with better knowledge included male gender and previous atrial fibrillation diagnosis (Koponen, et al., 2008).

Local studies (based in Birmingham) also found poor knowledge surrounding OAC (Lane, Ponsford, Shelley, Sirpal, & Lip, 2006; Lip, Kamath, Jafri, Mohammed, & Bareford, 2002; Nadar, Begum, Kaur, Sandhu, & Lip, 2003). One study examined whether knowledge and perceptions of OAC differed between ethnic groups (Nadar, et al., 2003). Knowledge scores were high for many of the questions i.e. drug name

(90%), type of drug (94%), name one or less side effects (91%). However, few patients were able to name two or more side effects (9%), or name the condition for which warfarin was being taken (54%). Furthermore, there was a significant difference between ethnic groups knowledge, Indo-Asian patients were less likely to know the name of the drug ($p<0.001$) or their target INR ($p=0.01$), Afro-Caribbean's were less likely to know which condition warfarin was for ($p=0.04$). Further, 45% of Indo-Asians, compared with 18% of white Europeans and 19% of Afro-Caribbean's, felt they had difficulty understanding their anticoagulant management ($p=0.04$). Whilst this study is cross-sectional and applied to multiple indications for warfarin, it does highlight the inconsistencies in patient knowledge surrounding OAC, particularly between ethnic groups (Nadar, et al., 2003).

A similar study examined ethnic differences in AF-related knowledge (Lip, Kamath, Jafri, Mohammed, Bareford, & McAlister, 2002), finding only 63% of patients were aware of their cardiac condition, with significantly less awareness in ethnic minority groups ($p<0.001$). Furthermore, the majority of patients did not perceive AF as a serious condition (61%), only 33% perceived AF as serious and 6% as very serious. The findings highlight the lack of patient knowledge surrounding their condition, as only 63% were aware of AF predisposing to 'blood clots' and 53% were aware of it predisposing to stroke (Lip, et al., 2002). Patients will understandably have inaccurate perceptions of the risk where their knowledge surrounding their illness is poor. This lack of knowledge and potential inaccurate illness perceptions may also impact on their ability to adhere to required regimens.

A prospective study of Chinese patients attending an anticoagulation clinic evaluated patients' treatment related knowledge and its relationship to anticoagulation control

(Tang, Lai, Lee, Wong, Cheng, & Chan, 2003). The knowledge of a random sample of patients (n=122) was moderate with an overall score of 0.48±0.18 (maximum score = 1.0), which did not differ for men and women. Tang and colleagues found an inverse relationship between age and knowledge score of the patient (r -0.43; $p<0.001$) and a positive association between duration of warfarin treatment and knowledge (r 0.18; p=0.044). Most importantly the proportion of patients with INR values within target range declined with age (r -0.30; $p<0.01$), and there was a positive correlation between patients' knowledge of warfarin treatment and the number of INR values within range (r 0.20; p=0.024). Thus more knowledgeable patients were more likely to be within therapeutic range (Tang, et al, 2003). This suggests that warfarin-experienced patients often lack knowledge surrounding their treatment, and whilst this study lacks the rigour of an RCT and had limited follow-up, it does suggest that increasing patient knowledge, may also increase time spent within therapeutic INR range.

A brief educational intervention (Lane, Ponsford, Shelley, Sirpal, & Lip, 2006) has successfully increased knowledge. These patients were predominantly White Europeans (95.7%), presenting at baseline with poor knowledge. Only half of the patients were aware that their cardiac condition was known as 'atrial fibrillation' (49%), 57% were aware that anticoagulation prevents blood clots and 19% were aware that OAC prevents stroke. A particular concern was patients' lack of awareness of the factors that may affect their INR levels, only 37% of patients at baseline were aware of these factors. A brief educational booklet significantly improved patients' knowledge of their target INR (p=0.001) and factors affecting INR levels (p=0.014), but not patients' awareness of AF related factors (Lane, et al.,

2006). Thus there is potential to improve knowledge and even improve INR control, with the use of appropriate interventions.

Where patients lack knowledge surrounding their condition, it is likely that they rely on other (possibly misleading) sources of information, potentially formulating inaccurate perceptions of AF. More importantly patients' lack of knowledge surrounding their treatment carries significant risks. Without sufficient knowledge of the factors affecting target INR patients cannot adhere to recommendations. Evidently even a brief intervention can improve patients' levels of knowledge, therefore theory-driven intensive interventions may have a significant impact with this group.

1.5 Psychological prognosis

In addition to the established cardiac prognosis, psychological factors have been implicated in the aetiology of AF and the potential prognosis for AF patients. Few studies have examined the significance of depression and anxiety among AF (Thrall, Lane, Carroll, & Lip, 2006; Lane, Langman, Lip, & Nouwen, 2009), those that have predominantly focus on quality of life (QoL) in symptomatic AF patients undergoing surgical or pharmacological interventions (Thrall, et al., 2006).

1.5.1 Depression and anxiety

Depression and anxiety in AF appears to be highly co-morbid, with 71% of patients reporting Beck's Depression Index (BDI) scores ≥10, and also exhibiting high levels of anxiety. Furthermore, symptoms of depression and anxiety also seem to persist in

follow-up studies (Thrall, et al., 2007). Thrall and colleagues compared the psychological wellbeing of AF patients (n=101) to a hypertensive “disease control” group (n=97) in sinus rhythm. AF and hypertensive patients displayed similar levels of depression and quality of life (QoL) at baseline. However, the AF group exhibited higher levels of trait anxiety ($p<0.02$) and percentage of scores (≥40 on STAI, $p=0.03$). Therefore, it is evident that the psychological prognosis for AF patients is similar to that of other cardiac disorders, with significantly higher anxiety levels than the disease control (Thrall, et al., 2007).

Lane and colleagues carried out a study examining anxiety, depression and QoL in ‘lone’ AF patients (Lane, Langman, Lip, & Nouwen, 2009). The study found few depressive symptoms at any of the time points. However, state anxiety (STAI-S ≥40) symptoms were elevated at all time points (38.5%, 30.9% and 35.7%, at baseline, six and twelve months respectively), with no significant differences over time. One influential factor determining a patient’s psychological prognosis was age. Those patients with elevated anxiety levels were found to be significantly younger than non-anxious patients ($p=0.02$). However, anxiety and depression levels in patients with ‘lone’ AF were not significantly different to age-matched general population norms, in contrast with the findings from Thrall’s study. The differences between the findings for ‘lone AF’ patients and a mixed AF patient group suggest that co-morbidities may also play an important role, as lone AF patients with no other co-morbidities suffer from fewer symptoms of depression and anxiety (Lane, et al., 2009).

In other comparable cardiac conditions such as coronary heart disease, post-myocardial infarction, angina, CHF, depression further predicts clinical prognosis (Frasure-Smith & Lesperance, 2006; Lett, et al., 2004). Depression is a suggested

risk factor for stroke (Larson, Owens, Ford, & Eaton, 2001) and sudden death (Whang, et al., 2005). The AF-CHF trial data suggests that elevated BDI-II depression scores significantly predicted cardiovascular death (Hazard Ratio 1.30, 95% CI 1.16-1.46, p<0.001), arrhythmic death (HR 1.36, 95% CI 1.15-1.60, p=0.001) and all-cause mortality (HR 1.23, 95% CI 1.11-1.37, p<0.001) in both study groups (Frasure-Smith, et al., 2009). Thus, where AF patients exhibit elevated depression scores, there may be an increased risk of stroke and mortality.

1.5.2 Quality of life

AF can be a highly symptomatic condition, with patients reporting palpitations, dizziness, breathlessness, exercise intolerance and fatigue (ESC, 2010). Thus, it is unsurprising that patients report a reduction in QoL when compared to the age- and sex-matched general population in sinus rhythm (Howes, Reid, Brandt, Ruo, Yerkey, & Prasad, 2001; van den Berg, Hassink, & Tuinenburg, 2001; Dorian, Jung, & Newman, 2000; Thrall, Lip, Carroll, & Lane, 2007). Given that AF is a chronic condition which places patients at increased risk of mortality and morbidity, and often requires life-long treatment, including long-term oral anticoagulation, QoL is therefore an important treatment outcome when measuring a patient's physical, emotional and social functioning, as well as their perceived health (Smith, Lip, & Lane, 2010).

Thrall's review (2006) suggests AF patients score poorest on general health, vitality, physical, social and emotional role functions, however, QoL does improve with symptom alleviation (Thrall, Lane, Carroll, & Lip, 2006). The predictability of a patient's ventricular rate is an important determinant of QoL (Thrall, Lane, Carroll, & Lip, 2006). Of the five randomised controlled trials that compared pharmacological

rate-control versus rhythm-control, four reported QoL as an outcome (Carlsson, Miketic, Windeler, Cuneo, Haun, & Micus, 2003; Gronefield, Lilienthal, Kuck, & Hohnloser, 2003; Hagens, Ranchor, Van Sonderen, Bosker, Kamp, & Tijssen, 2004; Jenkins, Brodsky, Schron, Chung, Rocco Jr, & Lader, 2005). All four trials demonstrated improvements in QoL following intervention, three reported greater improvements in patients among those receiving rate-control strategies (Carlsson, Miketic, Windeler, Cuneo, Haun, & Micus, 2003; Gronefield, Lilienthal, Kuck, & Hohnloser, 2003; Hagens, Ranchor, Van Sonderen, Bosker, Kamp, & Tijssen, 2004) and the AFFIRM trial demonstrated similar improvements for both rate and rhythm-control treatment (Jenkins, Brodsky, Schron, Chung, Rocco Jr, & Lader, 2005). Physical QoL outcomes were more frequently improved, specifically domains such as general health, physical functioning, physical role and bodily pain. However, significant improvements to psychological domains such as mental health and social functioning were also reported (Thrall, et al., 2006). Patients undergoing invasive procedures are often highly symptomatic and the relief of these symptoms appears to lead to significant improvements in QoL.

Symptomatic relief may affect the patient in numerous ways (Smith, Lip, & Lane, 2010). First, some suggest that treatment may have a placebo affect whereby patients report fewer symptoms because they believe their treatment is successful (Berkowitsch, Neumann, Kurzidim, Reiner, Kuniss, & Siemon, 2003). Second, perhaps simply being informed that their heart rate is beating in a ‘normal’ rhythm may reduce patient anxiety and increase psychological wellbeing. Indeed one study (Pappone, Rosanio, Augello, Gallus, Vicedomini, & Mazzone, 2003) compared QoL in patients undergoing radiofrequency isolation of the pulmonary vein or pharmacological rhythm-control. At baseline both groups were clinically comparable

and both physical and mental functioning scores showed similar changes over time. However, a significant time trend (p=0.007) was found only in ablated patients (p=0.004), where QoL levels at six months were similar to those of healthy-matched controls, with no further improvements at 12 months. For both patient groups the maintenance of sinus rhythm was associated with a reduced risk of death (ablation: hazard ratio (HR), 0.66, 95% confidence interval (CI), 0.09 to 0.48; pharmacological: 0.46 (0.12 to 0.32)) and adverse event rates (ablation: 0.61 (0.16 to 0.68); pharmacological: 0.45 (0.08 to 0.21); 13). Therefore, whilst QoL outcomes could be attributed to many factors including placebo or expectancy effects of an invasive procedure, it is likely that the improvement in QoL was again related to a reduction in AF burden (Smith, Lip, & Lane, 2010).

If control of the ventricular rate improves QoL, patients with paroxysmal AF, particularly symptomatic paroxysms are likely to report lower QoL when compared to patients with permanent or persistent AF (Smith, Lip, & Lane, 2010). PAF patients experience intermittent periods of AF interspersed with episodes of normal sinus rhythm, normally lasting <7 days (Levy, Novella, Ricard, & Paganelli, 1995). PAF comprises from 25 to 62% of AF cases seen by physicians and GPs (Kannel, Wolf, & Benjamin, 1998; Takahashi, Seki, Imataka, & Fujii, 1981), and the prevalence of PAF varies due to differences in definition. When compared to patients with permanent sustained AF, PAF patients tend to be younger, have less hypertension and congestive heart disease and are more symptomatic (Flaker, Belew, & Beckman, 2005). However, as symptoms are often infrequent, unpredictable and hard to document, the subsequent clinical course is not as clear as persistent AF patients who may have relatively more ‘stable’ heart rates and fewer treatment options.

Hence QoL is often poorer among PAF patients (Thrall, et al., 2006) due in part to the uncertainity of their AF prognosis and treament options and outcomes.

Evidently the prognosis for patients with AF is poor, they are at risk of psychological and physical morbidity. Furthermore, OAC represents a burdensome treatment regime with additional risks, and patients appear to exhibit poor knowledge surrounding their treatment and are often subsequently non-adherent. This presents problems in clinical practice as non-adherence is costly, both for the patient and the health care system. It is therefore important that interventions are developed to improve patient knowledge surrounding their treatment with the aim of subsequently improving adherence. Finally, in order to design successful interventions it is important that we consider both the barriers patients face and the motivation to change, as well as the intervention components that have proven successful in previous studies.

This study aims to develop an intervention that will improve patient adherence to their medication and treatment regimen. This includes restricting vitamin K intake, alcohol consumption and monitoring other drugs or herbal remedies that may interfere with warfarin's metabolism, as well as ensuring they remember to take their tablets. The literature has highlighted several reasons why patients may not adhere, including poor knowledge of their treatment and illness, poor communication of risk by the health care professional, a lack of shared decision making and patients anxiety following diagnosis of AF. Chapter 2 aims to review previous randomised trials of educational and behavioural interventions for patients with atrial fibrillation taking warfarin. By gaining an understanding which interventions have been trialled previously, and whether they proved successful in increasing adherence, we are

more able to choose an effective intervention strategy. Chapter 3 aims to document the design of the theory-driven behavioural intervention, explaining how the intervention components attempt to targets patients' barriers to adherence, such as their beliefs about medications and their illness representations. Chapter 5 aims to evaluate the effectiveness of the intervention, examining differences between the group receiving the intervention and the group that received usual care. It further attempts to explain why these differences exist.

1.6 Objectives

To increase patients' adherence to their medication and lifestyle recommendations, as measured by their subsequent time spent in therapeutic INR range.

To improve patients' knowledge and understanding of their treatment regimen and their condition.

To reduce inaccurate beliefs about medication and illness perceptions and subsequently reduce potential barriers to adherence.

2 Systematic review

2.1 Importance of the review

Patients need sufficient information to make informed choices and actively participate in the management of their own treatment (Thrall, Lane, Carroll, & Lip, 2006). Patient education aims to influence patient behaviour and improve knowledge, attitudes and practices that are necessary to improve health outcomes (Wofford, Wells, & Singh, 2008). Techniques used in delivering patient education cover a wide spectrum, including the use of booklets and videos as media to transmit additional information, alone or in addition to other self management interventions (such as INR self monitoring) and interventions which used decision aids. Behavioural interventions include those which attempt to modify patients' behaviour towards treatment and symptoms such as cognitive behavioural therapy (CBT), motivational interviewing and heart rate variability bio-feedback. This review, for which the protocol has previously been published (Smith, Borg Xuereb, Pattison, Lip, & Lane, 2010), evaluates the value of educational and behavioural interventions for patients with AF, currently prescribed warfarin; including the impact on the time spent within the therapeutic INR range (TTR) and secondary outcomes such as patient knowledge and quality of life.

2.2 Objective

The aim of the review was to assess the effects of educational and behavioural interventions for OAC in patients with atrial fibrillation and whether the interventions increased time spent within therapeutic range.

2.3 Methods

2.3.1 Criteria for considering studies for this review

2.3.1.1 Types of studies

Randomised controlled trials (RCTs) of any type of intervention with any length of follow-up and in any language were included.

2.3.1.2 Types of participants

Adults (aged 18 years or older) with AF categorised according to the ESC guidelines (ESC, 2010) including; (1) First diagnosed AF, (2) Paroxysmal AF, (3) Persistent AF, (4) Long standing persistent AF and (5) Permanent AF. AF will have been diagnosed and documented by electrocardiogram (12-lead or holter monitoring). Patients who are eligible for or currently receiving OAC were considered eligible for inclusion in this review. Studies which included AF patients with other medical conditions, were also included in this review where the studies were RCTs comparing at least one intervention with a control group, and including patients with atrial fibrillation as either the study population or a subgroup. Studies were only included where patients are grouped per indication i.e. patients taking oral anticoagulants for AF, DVT/PE, valve replacements etc, and only AF patients data were included within the analysis.

2.3.1.3 Types of interventions

All types of educational and behavioural interventions given to AF patients who were taking OAC were considered for this systematic review. Educational interventions included those giving patient information, such as using booklets and videos as media to transmit additional information, alone or in addition to other self management interventions (such as INR self monitoring), interventions which used decision aids, and talking interventions. Behavioural interventions included interventions that attempt to modify patients' behaviour towards treatment and symptoms such as cognitive behavioural therapy (CBT), self monitoring and/or management, motivational interviewing and heart-rate variability bio-feedback. Interventions could be targeted at adults on the individual level or as a group intervention. The intervention may have taken place in an emergency department, hospital, home or in the community. The intervention could have been delivered by a nurse, pharmacist, educator, health or medical practitioner, or a multidisciplinary team associated with the hospital or referred to by the hospital. The intervention could be undertaken at any time point from diagnosis of AF or initiation of OAC (i.e. not only newly diagnosed AF patients or those newly referred for OAC). Trials were only considered where the comparison groups were; usual care, no intervention, or intervention in combination with other self management techniques. Usual care was defined as standard anticoagulation clinic practice, where patients attend routine INR checks (defined as usual care by the author). Any length of follow-up was included.

2.3.2 Types of outcome measures

2.3.2.1 Primary outcomes

The primary outcome measure was the percentage of time spent within the therapeutic range (TTR) of INR (2.0 to 3.0).

2.3.2.2 Secondary outcomes

The secondary outcomes were: major bleeding (defined as bleeds that result in death, are life threatening, cause chronic sequel or consume major health care resources) and minor bleeding (Schulman & Kearon, 2005); stroke and thromboembolic events; increased knowledge with regards to AF and anticoagulation therapy; patient satisfaction; acceptability of the anticoagulant therapy; quality of life; psychological well being; changes in perception towards AF and INR control; changes in the patients' illness beliefs and illness representations; self reported adherence to treatment and a change in the patients' beliefs about medications; economic costs of the intervention (cost-effectiveness); and decision conflict. Decision conflict was included as a secondary outcome in the final analysis. Whilst not specified as an outcome of interest in the original protocol, it was highlighted as a common secondary outcome measure in three of the studies included in the final review. For this reason the authors decided to include this data within the results. All outcomes could have been quantified using validated or non-validated questionnaires, ratings or scales.

2.3.3 Search methods for identification of studies

2.3.3.1 Electronic searches

The Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE) on *The Cochrane Library (Issue 2, 2010)*, MEDLINE OVID (1950 to June, week 2, 2010), EMBASE OVID (1980 to 2010 week 23), EMBASE OVID classic (1947 to 1979) PsycINFO OVID (1806 to June 2010 week 3) and CINAHL plus with full text were searched. All searches took place from 18th to the 21st June 2010 (See appendix for search strategies).

2.3.3.2 Searching other resources

Abstract books from national and international cardiology, psychology and psychiatry conferences were hand-searched, including:

- Society for Behavioural Medicine and the Division of Health Psychology Conference
- European Health Psychology Conference
- Royal College of Psychiatrists Annual Meeting
- Dissertation abstracts (UMI ProQuest Digital Dissertations)

Reference lists of all relevant papers were searched to identify other potentially relevant articles.

2.4 Data collection and analysis

2.4.1 Selection of studies

Two reviewers scrutinised the titles found from the search and decided on inclusion or exclusion. From the included titles these two reviewers (DEC and supervisor DAL) then selected the abstracts and papers for inclusion and exclusion. Where disagreements arose on which papers to include the reviewers discussed the article and agreed on a consensus.

2.4.2 Data extraction and management

Two reviewers independently extracted the data. For each trial, the following data was extracted using a specially designed data extraction form: participants (sample size, age, sex, ethnicity, marital status, type of AF); type of anticoagulation therapy (warfarin, other); type and duration of the interventions (intervention versus usual care or no intervention; other combinations); primary and secondary outcomes; length of follow-up; statistical methods employed; the effect size and its precision.

2.4.3 Assessment of risk of bias in included studies

Two reviewers independently assessed the methodological quality of each trial in accordance with guidelines in the Cochrane handbook for systematic reviews of interventions (Higgins & Green, 2009). Each study was assessed on several areas of bias (sequence generation, allocation concealment, degree of blinding, patient attrition rate, selective reporting bias). The risk of bias was determined using the

Collaboration's risk of bias tool. The domains listed below were considered when reviewing each study. There were three possible responses: yes, no, or unclear. Yes indicates a low risk of bias and no indicates a high risk of bias. If insufficient detail was reported the judgement on risk of bias will be unclear.

2.4.3.1 Sequence generation

Yes, if the allocation sequence was generated using techniques such as a random number table; a computer random number generator; coin tossing; shuffling cards or envelopes; or throwing dice. No, if the allocation sequence was generated using techniques such as odd or even date of birth; date (or day) of admission; hospital or clinic record number. Unclear, if there was insufficient information about the sequence generation process to permit judgement.

2.4.3.2 Allocation concealment

Yes, if the allocation concealment used methods such as central allocation (including telephone, web-based, and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered opaque, sealed envelopes. No, if the participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias such as allocation based on using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque, or not sequentially numbered); alternation or rotation; date of birth; case record number. Unclear, if there was insufficient information to permit judgement of Yes or No, if the method of concealment was not described or not

described in sufficient detail to allow a definite judgement (e.g. if the use of assignment envelopes was described but it remained unclear whether envelopes were sequentially numbered, opaque and sealed). Where the method of allocation is unclear, we contacted study authors to provide further details.

2.4.3.3 Blinding

Yes, if there was no blinding but the review authors judged that the outcome and the outcome measurement were likely to be influenced by lack of blinding; if blinding of participants and key study personnel was ensured and it was unlikely that the blinding could have been broken; if either participants or some key study personnel were not blinded but outcome assessment was blinded and the non-blinding of others was unlikely to introduce bias. No, if there was no blinding or incomplete blinding and the outcome or outcome measurement was likely to be influenced by lack of blinding; if blinding of key study participants and personnel was attempted but it was likely that the blinding could have been broken; if either participants or some key study personnel were not blinded and the non-blinding of others was likely to introduce bias. Unclear, if there was insufficient information to permit judgement of yes or no or the study did not address this outcome (e.g. where the blinding was described only as double-blind without any other details).

2.4.3.4 Incomplete data assessment

Yes, if there were no missing outcome data; reasons for missing outcome data were unlikely to be related to the true outcome; missing outcome data were balanced in numbers across intervention groups with similar reasons for missing data across

groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes was not enough to have a clinically relevant impact on observed effect size; missing data were imputed using appropriate methods. No, if the reasons for missing outcome data were likely to be related to the true outcome, with either imbalance in numbers or reasons for missing data across intervention groups. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was enough to introduce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes was enough to introduce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation. Unclear, if there was insufficient reporting of attrition or exclusions to permit judgement of yes or no (e.g. numbers randomised were not stated, no reasons for missing data were provided); or the study did not address this.

2.4.3.5 Selective outcome reporting

Yes, if the study protocol was available and all of the study's pre-specified (primary and secondary) outcomes that were of interest in the review were reported in the pre-specified way; the study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified. No, if not all of the study's pre-specified primary outcomes were reported; one or more

primary outcomes were reported using measurements, analysis methods or subsets of the data (e.g. sub scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely so that they could not be entered in a meta-analysis; the study report failed to include results for a key outcome that would be expected to have been reported for such a study. Unclear, if there was insufficient information to permit judgement of Yes or No.

2.4.3.6 Other sources of bias

Yes, if the study appeared to be free of other sources of bias. No, if there was at least one important risk of bias (e.g. the study had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; had been claimed to be fraudulent; had some other problem). Unclear, if there was either insufficient information to assess whether an important risk of bias existed or if there was insufficient rationale or evidence that an identified problem would introduce bias.

2.4.4 Measures of treatment effect

Statistical analyses were undertaken as follows: for continuous variables the weighted mean difference was used. As a summary measure of effectiveness, odds ratios with 95% confidence intervals were calculated for dichotomous variables.

2.4.5 Dealing with missing data

Authors were contacted for studies with incomplete information in published articles and for data clarifications.

2.4.6 Assessment of reporting biases

Publication bias was not assessed in this review as studies either included a protocol paper listing outcomes that corresponded with those reported, or they address each of the outcomes listed in their methods.

2.4.7 Data synthesis

Results of individual studies are initially combined within a narrative review. This takes into account methodological quality of the study. Where possible, meta-analysis was used to statistically combine results. If insufficient data are present to conduct a meta-analysis, we reported effect sizes and confidence intervals (CIs) of the included studies using a standard method of presentation. TTR data was only included if directly reported, or where available from personal communication with the authors.

2.4.8 Subgroup analysis and investigation of heterogeneity

Subgroup analyses were carried out looking at the type of intervention (educational alone, behavioural alone, and a combination of education and behavioural vs. usual care). However, due to insufficient number of trials it was not possible to examine the

effects of frequency (one session vs. multiple sessions) and duration (e.g. < 6 months vs. > 6 months) of the intervention, length of time on OAC, men vs. women, individual vs. group interventions and age of participant groups.

2.5 Results

2.5.1 Results of the search

The search retrieved 815 articles from all sources. Of these, 749 were excluded by assessing titles and abstracts. Sixty three full text articles were obtained for consideration. Fifty three articles were excluded based on the review of the full text article. Ten articles reporting on seven studies were included in this review (Khan, Kamali, Kesteven, Avery, & Wynne, 2004; Christensen, Magaard, Sorensen, Hjortdal, & Hasenkam, 2006; McAlister, et al., 2005; Man-Son-Hing, et al., 1999; Beyth, Quinn, & Landefeld, 2000; Thomson, et al., 2007). Features of the interventions are included in the 'characteristics of included studies' table (Table 2.1); see PRISMA flow chart for inclusion process (see Figure 2.1).

2.5.1.1 Methods

All seven included studies were randomised controlled trials. Four of the studies specifically recruited AF patients (Khan, Kamali, Kesteven, Avery, & Wynne, 2004; McAlister, et al., 2005; Man-Son-Hing, et al., 1999; Thomson, et al., 2007), a further three trials recruited patients with a range of indications (e.g. AF, venous thromboembolism, cardiovascular disease, heart valve prosthesis, peripheral vascular disease, myocardial infarction) and provided unpublished data on AF

patients (Beyth, Quinn, & Landefeld, 2000; Gadisseur, Kaptein, Breukink-Engbers, van Der Meer, & Rosendaal, 2004; Christensen, Magaard, Sorensen, Hjortdal, & Hasenkam, 2006).

2.5.1.2 Included studies

Figure 2.1: PRISMA flow chart for inclusion of studies within the systematic review.

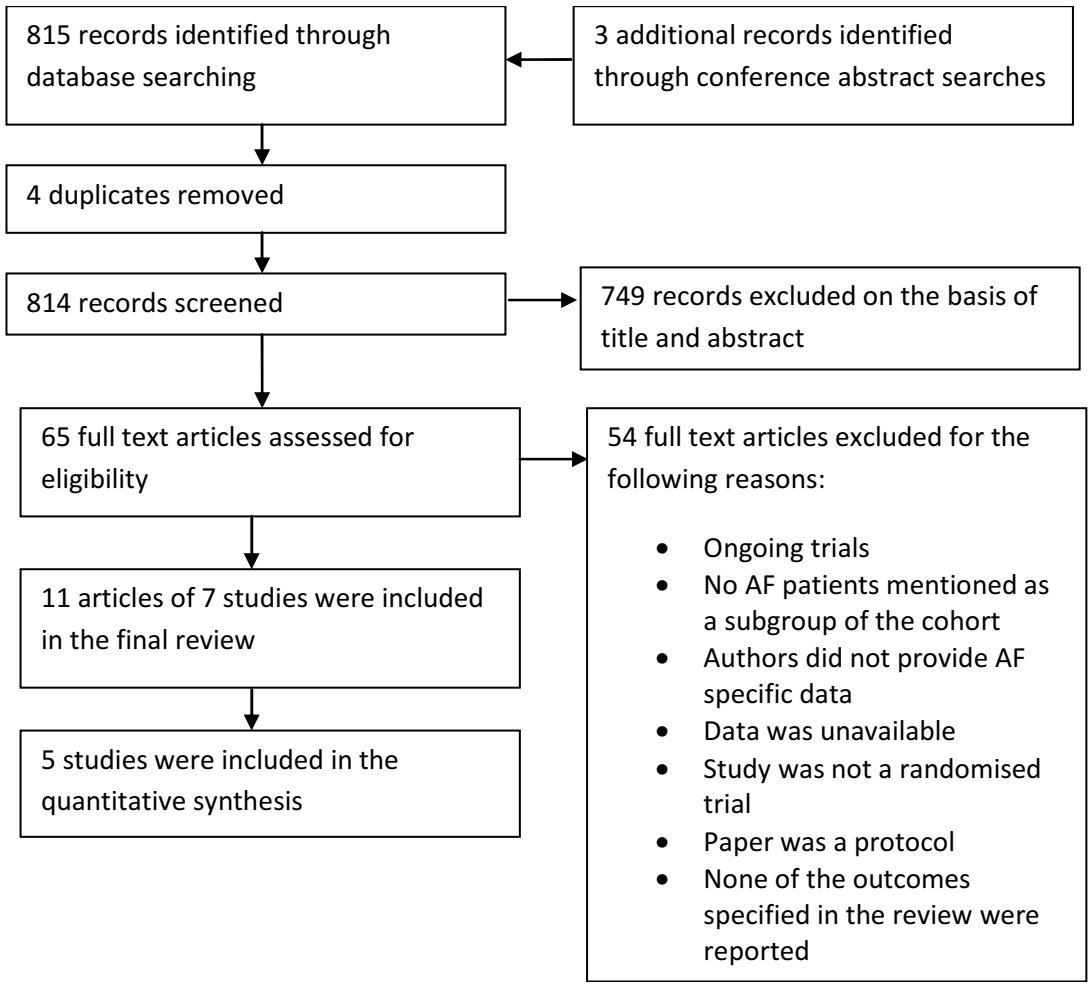


Table 2.1: Characteristics of included studies

Study Year Country	N of AF ppts	Age of AF patients; n± SD/ n(range)	Study design	Length of follow-up	Type	Duration	Facilitator Setting
Beyth 2000 USA	n=54	74.6±6.8 intervention versus 75.5± 6.2 UC	RCT, parallel groups design	6 months	Education and SM vs. UC	30-60 minutes (one-off)	Lay educator Hospital
Christensen 2007 Denmark	n=20	59±18 intervention versus 51 ±12 UC	RCT, cross-over design	6 months pre- and post-intervention	Education and SM vs. UC	#	# Hospital
Gadisseur 2003 Netherlands	n=58	#	Multi-centre RCT (4 trial arms)	6 months	(A) Self-testing vs. (B) SM. (C) educated UC vs. (D) UC	90-120 minutes (3 sessions)	Physician or Health care professional
Khan 2004 UK	n=125	71 (65-91) self-monitoring versus 75 (65-87) education versus 73 (65-93) UC	RCT (3 trial arms)	6 months	SM vs. education vs. UC	2 hour education session (one-off)	Physician or Health care professional Hospital

Man-Son-Hing 1999 USA	n=287	65 (#) for both groups	RCT	6 months	DA, PTOT vs. UC	#	Computerised/ audio tool Hospital
McAlister 2005 Canada	n=434	73±9 intervention versus 71 ±10 UC	Cluster RCT	1 year	DA, PTOT vs. UC	#	Physician or Health care professional GP Practice
Thomson 2007 UK	n=136	73.1±6.7 decision aid versus 73.7±6.2 guidelines	RCT	12 months	Computerised DA vs. guideline evidence	30-60 minutes (one-off session)	Computerised/ audio tool Research clinic

Not reported; PTOT = probability trade-off tool; RCT = randomised control trial; DA = decision aid; DC= decision conflict; SM=self-management; UC=usual care; n=number.

2.5.1.3 Participants

The total sample size of AF patients including published and unpublished data varied from 24 (Christensen unpublished) to 434 (McAlister, et al., 2005) participants. The mean age of the trial participants was 59 (±18 Standard deviations; Christensen unpublished) to 75 with a small range (65-87). One trial did not provide any demographical information for AF patients (Gadisseur, Kaptein, Breukink-Engbers, van Der Meer, & Rosendaal, 2004).

2.5.1.4 Type of studies

Of the seven studies that were identified, two compared education with usual care (Khan, Kamali, Kesteven, Avery, & Wynne, 2004; Gadisseur, Kaptein, Breukink-Engbers, van Der Meer, & Rosendaal, 2004), four compared self monitoring with usual care (Beyth, Quinn, & Landefeld, 2000; Khan, Kamali, Kesteven, Avery, & Wynne, 2004; Gadisseur, et al., 2004; Christensen, Magaard, Sorensen, Hjortdal, & Hasenkam, 2006), one also included a self-management group (Gadisseur, et al., 2004). A further three trials focused on the use of a decision support aid versus usual care (McAlister, et al., 2005; Man-Son-Hing, et al., 1999) or a comparison group (Thomson, et al., 2007).

2.5.1.5 Types of interventions

Interventions were either one to one (Beyth, Quin, & Landefeld, 2000; McAlister, et al., 2005) or group training session(s) (Gadisseur, Kaptein, Breukink-Engbers, van Der Meer, & Rosendaal, 2004; Khan, Kamali, Kesteven, Avery, & Wynne, 2004).

Three of the trials did not explicitly specify group or individual intervention type (Christensen, Magaard, Sorensen, Hjortdal, & Hasenkam, 2006; Man-Son-Hing, et al., 1999; Thomson, et al., 2007).

All of the interventions included an educational element, usually consisting of a description of the consequences of minor/major stroke and major haemorrhage, the blood monitoring required for warfarin and the probability of stroke and major haemorrhage for patients taking warfarin (for intervention components see Table 2.2). Most interventions also included information regarding the lifestyle factors influencing warfarin control. Self monitoring interventions included training on the use of INR monitoring devices (Khan, Kamali, Kesteven, Avery, & Wynne, 2004; Gadisseur, et al., 2004; Beyth, Quinn, & Landefeld, 2000; Christensen, et al., 2006). Decision aid interventions offered more detailed information on the risks of bleeding and thromboembolism (Man-Son-Hing, et al., 1999; McAlister, et al., 2005; Thomson, et al., 2007). All three trials using a decision support aid employed pictograms, depicting the risk of stroke and bleeding on either placebo, aspirin or warfarin; two utilised paper based charts (Man-Son-Hing, et al., 1999; McAlister, et al., 2005) and the third (Thomson, et al., 2007), employed a computerised version. The decision aid was presented and patients were asked to select which treatment they would prefer on the basis of the risk information (probability trade-off).

2.5.1.6 Duration of intervention

The duration of the educational training element of interventions varied: trials reported a one-off consultation of 30-60 minutes (Beyth, et al., 2007), a two hour session (Khan, et al., 2004) or three sessions each lasting 90-120 minutes (Gadisseur, et al., 2004). The other three trials did not specify how long the intervention lasted or the number of sessions (Christensen, et al., 2006; Man-Son-Hing, et al., 1999; McAlister, et al., 2005).

2.5.1.7 Intervention facilitator

One study did not specify type of facilitator (Christensen, et al., 2006). Of those that did, facilitators included a lay educator (Beyth, et al., 2000), a physician or health care professional (Gadisseur, et al., 2004; Khan, et al., 2004; McAlister, et al., 2005) and a computerised/audio tool (Man-Son-Hing, et al., 1999; Thomson, et al., 2007).

2.5.1.8 Country

The geographical settings of the studies were based in Europe, USA or Canada, but varied considerably; Denmark (Christensen, et al., 2006), The Netherlands (Gadisseur, et al., 2004), USA (Beyth, et al., 2000; Man-Son-Hing, et al., 1999), Canada (McAlister, et al., 2005), UK (Khan, et al., 2004; Thomson, et al., 2007).

2.5.1.9 Setting for intervention

Most of the interventions were conducted in a hospital/anticoagulation clinic setting (Beyth, et al., 2000; Man-Son-Hing, et al., 1999; Khan, et al., 2004; Christensen,et al., 2006; Gadisseur, et al., 2004). One of the trials took place in a GP practice (McAlister, et al., 2005), another in a research clinic within a GP practice (Thomson, et al., 2007).

2.5.1.10 Follow-up

Assessment of the impact of the intervention on outcomes over time ranged from three (Thomson, et al., 2007; McAlister, et al., 2005) to six months (Khan, et al., 2004; Beyth, et al., 2000; Gadisseur, et al., 2004; Christensen, et al., 2006; Man-Son-Hing, et al., 1999).

2.5.1.11 Funding

Two of the trials declared some funding input by drug companies (Gadisseur, et al., 2004; Man-Son-Hing, et al., 1999).

2.5.2 Outcome measures

Table 2.2: Intervention components and review outcomes included in each study.

Study	Intervention components	Primary review outcomes included	Secondary review outcomes included
Beyth 2000	**Patient education** - one to one teaching by a lay educator. **Self-monitoring training -** patients were taught to self-monitor prothrombin time. Patients instructed to use monitor three times in 1st week and once weekly after that. **Consultation -** assessed each patient's indication for therapy and potential risks for warfarin related bleeding, including specific recommendations about modifiable risk factors, such as use of non-steroidal anti-inflammatory drugs. **Coaching**- aimed to increase patient's participation in their care and improve information seeking-skills. **Workbook -** to teach them about warfarin, indications for its use, drug and food interactions, and the signs and symptoms of bleeding.	TTR	Major bleeding, stroke and thromboembolic events Mortality
Christensen 2007	**Patient education** - not explained in detail. **Self-monitoring training** - included patient practicing analysis of blood specimens. The patient gradually assumed management of OAC. **Examination -** after 27 weeks patients took an exam, if passed patient went onto self-manage.	TTR Complication outcome	#

Gadisseur 2003	**Patient education** - information about the study, the blood coagulation system, OAC, and the effects of some substances (e.g. Alcohol, certain medications and foods rich in vitamin k). **Self-monitoring training –** included being taught how to use monitoring device, and instructions on oral self-dosing of OAC. This also contained theoretical and practical self-dosing training. **Written information** - on all the topics discussed. **Telephone support -** to confirm whether they could adhere to their proposed dosing schedule or if they needed to adjust it (self management only).	TTR	Patient satisfaction QoL
Khan 2004	**Patient education** - patients were told about atrial fibrillation and the clinical benefits and risks of OAC. **Self-monitoring training** - in capillary INR testing. **Written information** - covering the issues raised. **Telephone dosing support -** based on the patients INR value, gave appropriate advice about warfarin daily dosage for the next seven days.	TTR	QoL
Man-Son-Hing 1999	**Decision aid –** included a 29-page booklet, personal worksheet (complete pre-intervention), and a 20-minute audiotape that guided the patient. **Patient education -** included a description of the consequences of minor/major stroke and major haemorrhage, the blood monitoring required for warfarin and the two-year probability of stroke and major haemorrhage for patients taking aspirin/warfarin using pictograms.	#	Patient knowledge Patient satisfaction Decision conflict

McAlister 2005	**Decision aid –** included a 30-page decision aid booklet, personal worksheet, 50-minute audiotape to guide participants through the booklet, and worksheet. Four versions of the decision aid were available depending on patient's baseline stroke risk. **Patient education –** provided background information about AF, the potential consequences of stroke and major haemorrhage, relative efficacy/bleeding risks with warfarin, and aspirin therapy. **Worksheet -** was completed by the patient after reviewing the booklet to clarify their personal values regarding desired outcomes, the therapy they are inclined to take, their preferred role in the decision process, and any questions they have for their physician.	Percentage of INR's in range Patient knowledge	Patient satisfaction Decision conflict
Thomson 2007	**Decision aid -** included risk/benefit presentation "implicit tool" [computerized decision aid]. **Patient education –** included benefits and harms of warfarin treatment, advantages/disadvantages, and personalized risk assessment [using the Framingham equation]. The presentation used graphical and numerical media.	#	Patient knowledge Decision conflict Anxiety

Not included in published article; QoL = quality of life; TTR = time in therapeutic range; INR= international normalised ratio.

2.5.2.1 Primary outcome

The percentage of time spent within the therapeutic range (TTR) of INR (2.0 to 3.0) was reported by four trials (Khan, et al., 2004; Gadisseur, et al., 2004; Beyth, et al., 2000; Christensen, et al., 2006). Two trials reported other indicators of INR control; percentage of in-range INRs (McAlister, et al., 2005) and combined INR and complication outcomes (Christensen, et al., 2006). Of those studies reporting TTR, all were self monitoring interventions but only one published AF specific data (Khan, et al., 2004). Thus, the remaining trial authors were contacted for AF-specific data, this was provided by three of the authors (Gadisseur, et al., 2004; Christensen, et al., 2006; Beyth, et al., 2000). AF specific data was not requested for outcomes that were not comparable, i.e. combined INR and complication outcomes (Christensen, et al., 2006).

2.5.2.2 Secondary outcomes

One study reported major bleeding, stroke and thromboembolic events (Beyth, Quin, & Landefeld, 2000). None of the studies reported minor bleeding. Three trials reported on patient knowledge (Thomson, et al., 2007; McAlister, et al., 2005; Man-Son-Hing, et al., 1999). Two trials assessed knowledge before and after the intervention (Thomson, et al., 2007; Man-Son-Hing, et al., 1999), one only tested after the intervention, thus cannot be included as a measure of the effect of the intervention. Three trials included patient satisfaction as a specified outcome (Gadisseur, et al., 2004; McAlister, et al., 2005; Man-Son-Hing, et al., 1999), one trial did not report on this outcome (McAlister, et al., 2005) thus data is not included. None of the studies reported on patients' acceptability of anticoagulant therapy. Two

studies reported QoL as an outcome (Gadisseur, et al., 2004; Khan, et al., 2004), using the SF-36 (Khan, Kamali, Kesteven, Avery, & Wynne, 2004) and a questionnaire originally validated by Sawicki and colleagues (Gadisseur, et al., 2004). The QoL data could not be pooled. Further, one of the trials did not publish AF specific data (Gadisseur, et al., 2004). The other trial (Khan, et al., 2004), only reported QoL data for those receiving education alone and education plus self-monitoring; QoL in the usual care arm is not reported. None of the studies reported changes in patients' illness beliefs, illness perceptions, self-reported adherence to treatment, beliefs about medication, or the economic costs of the intervention. Three studies reported decision conflict (McAlister, et al., 2005; Man-Son-Hing, et al., 1999; Thomson, et al., 2007). However, one of the studies did not have a usual care arm (Thomson, et al., 2007), thus was not included in the pooled data analysis. One study reported patient anxiety (Thomson, et al., 2007). One study reported on mortality (Beyth, et al., 2000), but do not state whether they have measured all cause or cardiac specific mortality outcomes.

2.5.3 Excluded studies

Fifty one papers on 47 studies were excluded for the following reasons:

Fifteen studies were excluded because they did not include AF patients (Baker, Roberts, Newcombe, & Fox, 1991; Bump & Campbell, 1977; Claes, et al., 2005; Claes, et al., 2006; Cromheecke, Levi, & Colly, 2001; Cordasco, et al., 2009; Cromheecke, et al., 2000; Fitzmaurice, et al., 2005; Holbrook, Labiris, Goldsmith, Ota, Harb, & Sebalt, 2007; Landefeld & Anderson, 1992; Mazor, Baril, Dugan,

Spencer, Burgwinkle, & Gurwitz, 2007; Pernod, et al., 2008; Vadher, Patterson, & Leaning, 1997; Vadher, Patterson, & Leaning, 1996; Waterman A, et al., 2001).

Ten studies were eligible for inclusion but the data presentation was inadequate and attempts to obtain the specific data from the authors, was unsuccessful. For nine of these trials/studies the authors could not be contacted (Stone, Holden, Knapic, & Ansell, 1989; Sawicki, 1999; Watzke, Forberg, & Svolba, 2000), or did not respond to e-mail/written requests for unpublished data (Barcellona, Contu, & Marongiu, 2006; Mendez-Jandula, Souto, & Oliver, 2005; Ryan, Byrne, & OShea, 2009; Siebenhofer, Rakovac, Kleepies, Piso, & Didjurgeit, 2007; Chan, Wong, Lau, Chan, Cheng, & You, 2006; Gardiner, Williams, Longair, Mackie, Machin, & Cohen, 2006). For one study (Machtinger, Wang, Chen, Rodriguez, Wu, & Schilinger, 2007) the author was successfully contacted but the data was unavailable.

Fifteen studies were not randomised controlled trials (Bajorek, Krass, Ogle, Duguid, & Shenfield, 2005; Blaise, et al., 2009; Burns, 2009; Corbella, et al., 2009; Davis, Billett, Cohen, & Arnsten, 2005; Leger, et al., 2004; Megden, Heidgen, & Vetter, 1999; Nedaz, 2002; Polzien, 2007; Satger, et al., 2009; Sawicki, et al., 2003; Taylor, Gray, Cohen, Gaminara, & Ramsay, 1997; Witt, Sadler, Shanahan, Mazzoli, & Tillman, 2005; Wurster & Doran, 2006; Woodend, 2005).

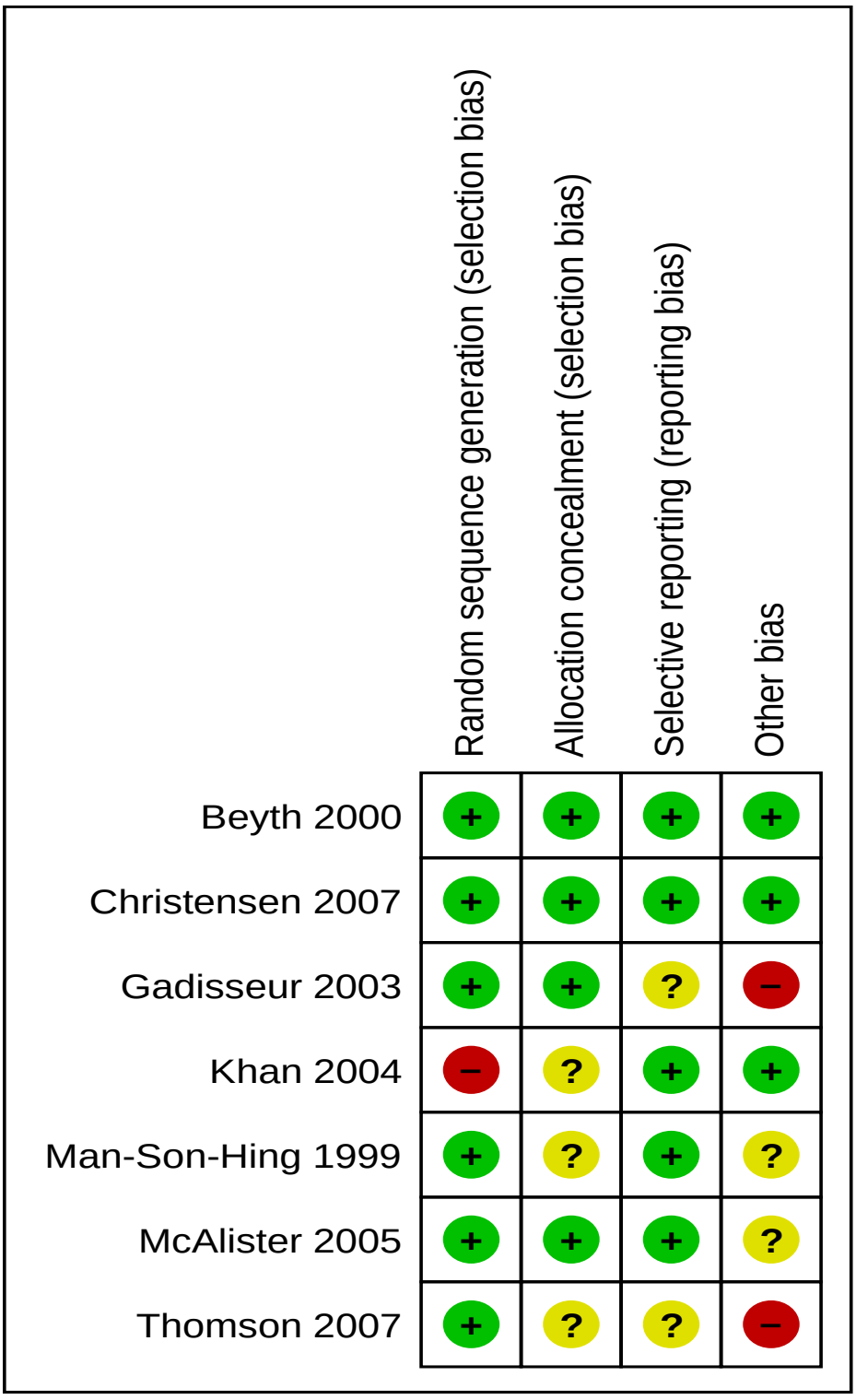
Four commentaries or protocol papers on three studies were identified (Fitzmaurice, Hobbs, Murray, Holder, Allan, & Rose, 2000; Fitzmaurice, et al., 2005; Mendez-Jandula , et al., 2005).

Seven studies did not fulfil our predefined inclusion criteria. Three did not include an educational or behavioural intervention (Fitzmaurice, Hobbs, Murray, Bradley, & Holder, 1996; Matchar, et al., 2005; Fitzmaurice, Hobbs, Murray, Holder, Allan, & Rose, 2000; Waterman, Miligan, Banet, Gatchel, & Gage, 2001). None of the studies were excluded for including participants >18 years. Three studies did not report any of the pre-specified outcomes (Batty, Oborne, Hooper, & Jackson, 2001; Jackson, Peterson, & Vial, 2004; Lees, et al., 2003).

2.5.4 Risk of bias

Risk of bias was assessed independently by two reviewers (DEC and supervisor DAL) in accordance with the Cochrane Handbook for Systematic Reviews of Interventions, Version 5 (Higgins & Green, 2009).

Figure 2.2: Risk of bias for each of the included studies



(+) suggests authors have considered methods to reduce type of bias, (-) suggests measures were not taken thus there is a risk of bias, (?) indicates not enough information was given to determine whether there was a risk of bias.

2.5.4.1 Allocation (selection bias)

Six of the included trials provided information about adequate sequence generation. For the majority this consisted of randomisation to intervention or usual care, according to a computer-generated sequence using block randomisation (Thomson, et al., 2007; McAlister, et al., 2005; Man-Son-Hing, et al., 1999; Christensen, Magaard, Sorensen, Hjortdal, & Hasenkam, 2006), a random numbers table (Khan, et al., 2004) or a two step partial-zelen design (Gadisseur, et al., 2004). The other trial provided information regarding patient stratification, but not specifically about sequence generation (Beyth, et al., 2000).

2.5.4.2 Blinding (performance bias and detection bias)

Blinding patients to which arm of the intervention they were receiving was not possible in this type of intervention, nor was it possible to blind the intervention facilitator to which arm the patients were receiving and this inevitably raises the risk of bias. However, blinding the data analyst or researcher to which intervention arm the patient was assigned to is possible in principle, and was undertaken in four trials (McAlister, et al., 2005; Christensen, et al., 2006; Gadisseur, et al., 2004; Beyth, et al., 2000). Three trials do not state whether their data analyst was blinded to which group the patients were randomised to (Thomson, et al., 2007; Khan, et al., 2004; Man-Son-Hing, et al., 1999) or indeed whether the individual delivering the intervention also carried out the analysis.

2.5.4.3 Incomplete outcome data (attrition bias)

The percentage of patients completing the final follow-up ranged from 72% (Thomson, et al., 2007) to 97% (McAlister, et al., 2005). Thus, all of the trials had low levels of attrition.

2.5.4.4 Selective reporting (reporting bias)

One of the studies published a protocol paper (McAlister, et al., 2005) and reported on all but one of the pre-specified outcomes (patient satisfaction). A further six studies did not publish protocol papers (Christensen, et al., 2006; Gadisseur, et al., 2004; Beyth, Quin, & Landefeld, 2000; Khan, et al., 2004; Man-Son-Hing, et al., 1999; Thomson, et al., 2007) but reported on all the outcomes specified within their method section.

2.5.4.5 Inclusion bias

All of the studies reported the number of eligible participants. However, for the mixed cohort trials, it was difficult to retrospectively assess which of the screened patients had AF. Of those trials specifically recruiting AF patients, the percentage of eligible patients randomised ranged from 30% (Thomson, et al., 2007) to 79% (Khan, et al., 2004). In the mixed indication cohort trials this percentage ranged from 18% (Gadisseur, et al., 2004) to 95% (Christensen, et al., 2006).Thus some of the trials are more representative than others and trials that randomised a low percentage of eligible patients may be at risk of inclusion bias.

2.6 Effects of interventions

Various methods of measuring outcomes were employed and this was the main obstacle when comparing study findings. This was further complicated by the different time points at which measurements were taken, depending on the length of the trial. Further, the included studies differed in type (behavioural and decision aids) and in their comparator group. Where data was comparable, i.e. using the same measurement tool and type of intervention, AF-specific data was requested.

2.6.1 Education

2.6.1.1 Time within therapeutic range

Two of the trials included a comparison between education only groups and usual care (Khan, et al., 2004; Gadisseur, et al., 2004). Khan et al found TTR in the education only group increased from a mean 61.1 ±15.1 during the 6 months prior, to 70.4 ±24.5 during the 6 months after the study began (mean difference 8.8, 95% CI: -0.2-7.8, p=0.054). However the difference between groups is not significant (intervention groups 0.25±0.30 vs. control 0.16± 0.30, p=0.12). Gadisseur and colleagues studied a mixed indication cohort taking OAC and provided additional unpublished data on the AF patients. TTR in the education group was 75% (95% CI: 66.19-83.80) compared with 67.1% (95% CI: 59.18-74.98) in the usual care alone group and 70.32% (95% CI: 55.33-85.31) in the self-monitoring plus education group.

Table 2.3: Results of systematic review table

Author, year, country	Study population No. participants, mean (SD/Range) age, years	Study design, length of follow-up.	Type of intervention	Outcomes for AF patient data
Man-Son-Hing 1999, USA	N=287; control 67(#), intervention 65 (#).	RCT; 6 months.	DA, PTOT vs. UC	• Proportion choosing warfarin greater in control group • PTOT ↑ ability to make decision choice. • DA group significantly greater knowledge of treatment related information than usual care (p<0.001). • DA did not significantly affect patient satisfaction. • No significant differences between groups on DC (p=.14).

Thomson 2007, UK	N=136; guidelines 73.7(6.2), decision aid 73.1(6.7).	RCT, 12 months.	Computerised DA vs. guideline evidence.	• Computerised decision aid led to significantly fewer patients choosing warfarin. • NS differences between knowledge scores of 2 groups. • DC fell in both groups post-intervention with significant difference between groups (p=0.036), DA group reported less conflict. • Anxiety fell in both groups, but there was no significant difference between groups (p=0.98).
McAlister 2005, Canada	N=434; control 71(10), intervention 73(9).	Cluster randomised trial.	DA, PTOT vs. UC	• PTOT ↑ patient ability to choose 'appropriate' antithrombotic therapy in short term only. • INR control ↓ over time in UC arm, ↑ over time in SM arm. • DA group scored lower on DC than UC group (p=0.05).

Christensen 2007, Denmark	N=92; control 46.3(13.4), intervention 51.5(14.4).	RCT, cross-over design; 6 months pre- and post-randomisation.	Education and SM vs. UC	• ↑ % TTR in SM vs. UC (77% vs. 71.5%), differences NS.
Khan 2004, UK	N=125; control 73(56-93), self-monitoring 71 (65-91), education 75(65-87).	RCT (3 trial arms); 6 months.	SM vs. education vs. UC	• ↑ TTR in education group (p=0.054), ↑ TTR in self-monitoring group (p<0.001), NS differences between groups. • NS differences in QoL (SF-36) between groups, except on emotional role limitation (p=0.04).
Beyth 2000, USA	N=294; control 74.5 (6.6), intervention 74.9 (6.9).	RCT, parallel groups design; 6 months.	Education and SM vs. UC	• No differences in major bleeding, stroke and thromboembolic events between groups.
Gaddiseur 2003, Netherlands	N=161; (A) 54.8(25-74), (B) 53.9(24-75), (C) 56(21-73), (D) 62(32-75).	Multi-centre RCT (4 trial arms); mean=24 weeks.	(A) Self-testing vs. (B) SM. (C) educated UC vs. (D) UC	• ↑ % TTR in SM vs. UC (70.32% vs. 67.08%), differences NS. • DA did not significantly impact on patient satisfaction.

Not reported; PTOT = probability trade-off tool; RCT = randomised control trial; TTR = time in therapeutic range; DA = decision aid; DC= decision conflict; NS= non significant; SM=self-management; UC=usual care; QoL=quality of life, ↑= increase, ↓= decrease

Pooled analysis of the two studies reporting TTR (Gadisseur, et al, 2004; Khan, et al., 2004) demonstrated that education significantly improves TTR compared with usual care OR, 95% CI 7.89 (5.54-10.24).

2.6.1.2 Quality of life

Only one study reported QoL (Khan, et al., 2004), assessed using the SF-36. No significant difference in QoL scores on any of the SF-36 sub scales, other than emotional role limitation (difference 13.33, 95% CI 0.85 to 25.81, p=0.04) were evident between education alone and education plus self monitoring groups.

2.6.1.3 Patient satisfaction

One educational intervention trial reported patient satisfaction (Gadisseur, et al., 2004). Patients who were assigned to the self monitoring group showed a significant increase in their general treatment satisfaction ($P < 0.01$). There was no change from baseline to follow-up with the addition of the educational intervention (p=0.21).

2.6.2 Self monitoring plus education

2.6.2.1 Time within therapeutic range

Four trials examined the impact of self monitoring plus education (Beyth, et al., 2000; Christensen, et al., 2006; Gadisseur, et al., 2004; Khan, et al., 2004). In the self monitoring plus education group, Khan found that TTR increased from 57.0±17.0 to 71.1±14.5 (mean difference 14.1, 95% CI: 6.7-21.5, p<0.001). In the usual care

group there was no significant differences in TTR between the six months prior (60.0±18.8) to the six months after the study began (63.2±25.9) (mean difference: 3.2, 95% CI: -7.3-13.7, p>0.5). Khan and colleagues found no significant differences between self monitoring plus education, education only and usual care groups (intervention groups 0.25±0.30 vs. control 0.16± 0.30, p=0.12) (Khan, et al., 2004). Christensen (Christensen, et al., 2006) recruited patients with multiple indications for OAC, with only 20 AF patients: 11 receiving self management plus education and 9 in the usual care group. The findings suggest greater INR control in the intervention group (mean (SD) 77.3 (2.2) % vs. 71.5 (5) %, respectively).

Gadisseur (Gadisseur, et al., 2004) provided data on AF patients but numbers were also small in the self monitoring plus education (n=6) and usual care (n=43) groups. However, the mean % TTR was greater in the self monitoring plus education group than usual care (70.32%, SD=7.495 vs. 67.08%, SD=7.04 respectively).

Beyth et al (Beyth, et al., 2000) did not provide AF specific data on TTR outcomes and thus could not be included in these analyses.

The pooled analysis of the three studies reporting TTR (Gadisseur, et al., 2004; Khan, et al., 2004; Christensen, et al., 2006) demonstrated that self monitoring significantly improves TTR compared to usual care, OR (95% CI) 5.47(2.55-8.39).

2.6.2.2 Major bleeding, stroke and thromboembolic events

One study found the number of cases of major bleeding (cases n=1(1.8% of total AF cohort) intervention group, n=2(3.7% of total AF cohort) usual care), and stroke and

thromboembolic events (cases n=1 (1.8% of total AF cohort) intervention group, n=2 (3.7% of total AF cohort) usual care) were minimal in both groups (Beyth, et al., 2000).

2.6.3 Education versus self monitoring

Two trials compared self monitoring plus education with education only groups (Khan, et al., 2004; Gadisseur, et al., 2004). Khan and colleagues found that TTR increased from 57.0±17.0 to 71.1±14.5 (mean difference 14.1, 95% CI: 6.7-21.5, p<0.001) in the self monitoring plus education group. TTR in the education only group also increased from a mean 61.1 ±15.1 during the 6 months prior, to 70.4 ±24.5 during the 6 months after the study began (mean difference 8.8, 95% CI: -0.2-7.8, p=0.054). Khan and colleagues found no significant differences between self monitoring plus education, education only and usual care groups (intervention groups 0.25±0.30 vs. control 0.16± 0.30, p=0.12) (Khan, et al., 2004). Gadisseur (Gadisseur, et al., 2004) provided data on AF patients but numbers were small in the self monitoring plus education (n=6) and education only (n=17) groups. TTR in the self monitoring plus education group (70.32%, SD=7.495) compared to 75% (95% CI: 66.19-83.80) in the education only. The data from these trials was pooled and the analysis did not favour education or self monitoring plus education OR (95% CI) -2.79 [-7.91 to 2.33].

2.6.4 Decision aids

2.6.4.1 Percentage of INRs in range

McAlister (McAlister, et al., 2005) found that INR control deteriorated in the usual-care arm over time (INRs were between 2.0 and 3.0 on 66% of the days at 3 months vs. 70% of the days at baseline) while INR control improved in the intervention arm (INRs were between 2 and 3 72% of the days at 3 months vs. 65% at baseline) over time. The between group difference was statistically significant (p=0.02). By 12 months care in both arms had regressed back to baseline levels.

2.6.4.2 Patient knowledge

Two trials reported on patient knowledge (Thomson, et al., 2007; Man-Son-Hing, et al., 1999). Thomson used an extension of the decision conflict scale and found that although knowledge scores after the intervention had improved slightly, by the three month follow-up they had returned to pre-intervention levels (Thomson, et al., 2007). There were no significant differences between decision aid and guidelines groups at any point.

The second trial used an un-–validated scale, and demonstrated that patients in the decision aid group had significantly greater knowledge of treatment related information [difference (95% CI) aspirin-related, 15.9 (4.6-27.2) p<.001; warfarin-related, 14.9 (4.6-25.2) p<.001, in favour of decision aid group] than those in the usual care group (Man-Son-Hing, et al., 1999).

2.6.4.3 Patient satisfaction

One decision aid trial reported patient satisfaction as an outcome (Man-Son-Hing, et al., 1999).They found that use of the decision aid did not significantly affect patients' satisfaction with their physician consultation.

2.6.4.4 Decision conflict

Three studies (McAlister, et al., 2005; Man-Son-Hing, et al., 1999; Thomson, et al., 2007) reported decision conflict, all of which used the decision conflict scale (O'Connor, 1995).

Two of the trials reported patients' level of decision conflict post-intervention (Man-Son-Hing, et al., 1999; McAlister, et al., 2005). Man-Son-Hing and colleagues (Man-Son-Hing, et al., 1999) found no statistically significant differences in overall decision conflict between the decision aid group and the control group (p=.14). McAlister and colleagues (McAlister, et al., 2005) found that there was a small but statistically significant difference in the decision conflict between the decision aid and the usual care group, the decision aid group scored lower on decision conflict (m=1.6, SD 0.5) than the usual care group (m=1.7, SD 0.5, p=0.05).

The third trial reported levels of decision conflict at pre-clinic, post-clinic and three month follow-up (Thomson, et al., 2007). Thomson found that decision conflict fell in both groups post-intervention and the between group difference was significant

(r=2.12, df=107, p=0.036), with those in the decision aid group reporting less decision conflict, but this difference was not sustained at the three month follow-up.

Although three studies reported decision conflict as an outcome (Thomson, et al., 2007; Man-Son-Hing, et al., 1999; McAlister, et al., 2005), only two compared differences between usual care and decision aid groups (Man-Son-Hing, et al., 1999; McAlister, et al., 2005). Data from these two trials were pooled, and analyses favoured neither usual care nor the decision aid in terms of reducing decision conflict, OR (95% CI) -0.10 (-0.17 to -0.02).

2.6.4.5 Anxiety

Only one trial reported anxiety as an outcome (Thomson, et al., 2007). Anxiety fell significantly in both groups pre- to post-clinic, mean change -4.57 (95% CI) -6.30 to -2.84), but there was no evidence of a significant difference in anxiety between the two groups (F (1, 95) = 0.001; p=0.98).

2.7 Discussion

2.7.1 Summary of main results

This review found seven RCTs (Khan, Kamali, Kesteven, Avery, & Wynne, 2004; Christensen, et al., 2006; Man-Son-Hing, et al., 1999; Thomson, et al., 2007; Beyth, et al., 2000; Gadisseur, et al., 2004; McAlister, et al., 2005) of behavioural and educational interventions for anticoagulant therapy in patients with AF. Two trials compared education with usual care (Gadisseur, Kaptein, Breukink-Engbers, van Der

Meer, & Rosendaal, 2004; Khan, Kamali, Kesteven, Avery, & Wynne, 2004), four compared self monitoring plus education with usual care (Beyth, et al., 2000; Khan, et al., 2004; Christensen, et al., 2006; Gadisseur, et al., 2004) and one trial also compared a self management (consisting of self testing and self dosing) group (Gadisseur, et al., 2004). Three trials focused on the use of a decision support aid versus usual care (Man-Son-Hing, et al., 1999; McAlister, et al., 2005) or a comparison group (Thomson, et al., 2007).

Two trials reported TTR data for educational interventions versus usual care (Gadisseur, et al., 2004; Khan, et al., 2004). Pooled analysis of the two studies reporting TTR (Gadisseur, et al. 2004; Khan, et al., 2004) demonstrated that education significantly improves TTR compared to usual care OR, 95% CI 7.89 (5.54-10.24). This supports non-trial evidence from Tang and colleagues (Tang, et al., 2003), suggesting a link between treatment-related knowledge and INR control.
Three self monitoring plus education trials also reported TTR (Christensen, et al., 2006; Khan, et al., 2004; Gadisseur, et al., 2004). Pooled data for the AF patients demonstrated that self monitoring significantly improves TTR compared to usual care, OR (95% CI) 5.47(2.55-8.39). This evidence supports a previous Cochrane review into self monitoring trials for mixed indication patients taking OAC. In their review, pooled estimates showed significant reductions in both thromboembolic events (RR 0.50, 95% CI 0.36 to 0.69) and all-cause mortality (RR 0.64, 95% CI 0.46 to 0.89) (Garcia-Alamino, et al., 2010). Evidently, self-monitoring plus education can significantly improve TTR and clinical outcomes. However, the pooled TTR analysis from our review was largely driven by Christensen's study, which had a small AF sample (lacking statistical power); (Christensen, et al., 2006), with exclusively male participants in their intervention group.

Two trials compared self monitoring plus education with education only groups (Khan, et al., 2004; Gadisseur, et al., 2004). The data from these trials was pooled and the analysis favours neither education nor self monitoring (plus education) OR (95% CI) -2.79 (-7.91 to 2.33).

Findings suggest that education may be the key factor influencing whether patients spend more time in therapeutic range. As many of the trials (decision aid and self monitoring plus education) did not clearly specify the content of their intervention and all of the self monitoring groups also received education, it is difficult to decipher which component is contributing to patients improved TTR. Furthermore, the evidence is based on a small number of trials with small sample sizes, thus should be interpreted with caution. Studies included are heterogeneous, with varying sample sizes, intervention content and mixed indication cohorts.

Decision aid trials appear not to favour either the intervention or usual care group in minimising decision conflict (Thomson, et al., 2007; Man-Son-Hing, et al., 1999; McAlister, et al., 2005). Data from these two trials (Man-Son-Hing, et al., 1999; McAlister, et al., 2005) was pooled, and analysis favoured neither usual care nor decision aid in terms of reducing decision conflict, OR (95% CI) -0.10 (-0.17 to -0.02). However, the two trials with pooled data did not measure decision conflict prior to the intervention and therefore it is not possible to ascertain whether the intervention directly affected decisional conflict or not. The use of a decision aid did not have a significant impact on AF patients anxiety levels (Thomson, et al., 2007) or patient satisfaction (Man-Son-Hing, et al., 1999).

2.7.2 Overall completeness and applicability of evidence

Three of the included trials had mixed indication cohorts (Beyth, et al., 2000; Gadisseur, et al., 2004; Christensen, et al., 2006), and ten further trials were excluded as they did not provide AF specific data (Barcellona, Contu, & Marongiu, 2006; Mendez-Jandula, Souto, & Oliver, 2005; Ryan, Byrne, & OShea, 2009; Siebenhofer, Rakovac, Kleepies, Piso, & Didjurgeit, 2007; Chan, Wong, Lau, Chan, Cheng, & You, 2006; Gardiner, Williams, Longair, Mackie, Machin, & Cohen, 2006; Stone, Holden, Knapic, & Ansell, 1989; Sawicki, et al., 2003; Watzke, Forberg, & Svolba, 2000). Recruiting patients with mixed indications for warfarin can be problematic. Patients often have different INR ranges (e.g. with valve replacements) and each patient group is unique in their lifestyle and treatment recommendations. AF patients are often older (Kannel, Wolf, & Benjamin, 1998), prescribed treatment on a long-term basis (NICE, 2006) and susceptible to inaccurate illness representations (McCabe, Barnason, & Houfek, 2011), due to their symptoms being irregular and often unrecognised (Fuster, Ryden, Cannom, Crijins, Curtis, & Ellenbogen, 2006). Thus it is essential that interventions are disease specific, targeting the particular concerns of the target population.

Six of the trials recruited patients that had previously taken OAC (Christensen, et al., 2006; McAlister, et al., 2005; Gadisseur, et al., 2004; Khan, et al., 2004; Thomson, et al., 2007) and one recruited patients receiving anti-platelet treatment (Man-Son-Hing, et al., 1999). Most of the patients had been receiving antithrombotic treatment long term, for up to 5.5 years (Christensen, et al., 2006) prior to receiving the intervention. Whilst some trials included warfarin-naive patients (Thomson, et al., 2007) or in-patients starting OAC (Beyth, et al., 2000) none of the trial cohorts were exclusively

warfarin-naive. Patients TTR tends to improve in the months following their diagnosis, and their knowledge also increases (Tang, et al., 2003). Therefore, previous experience of taking warfarin may influence patients TTR treatment control. Further evidence suggests that previous warfarin experience also influences patients' treatment choice (Holbrook, Labris, Goldsmith, Ota, Harb, & Sebaldt, 2007; Lip, et al., 2011). Therefore, the results of these trials may not be representative of the effect of a behavioural or educational intervention may have on a sample of warfarin-naive patients and we cannot draw conclusions on the use of interventions for newly referred patients, who are at greatest risk of complications.

Prior treatment with warfarin may also influence patients' decision making. Patients may have had prior education pertaining to OAC, stroke and the risk of major and minor bleeding. Further, they may have developed specific beliefs about their medications that influence the decision making process, such as the inconvenience of regular blood tests, and reductions/abstinence of alcohol and dietary restrictions (Lane, et al., 2006; Lip, et al., 2002; Coelho-Dantas, et al., 2004). Patients may also feel a level of protection from harm (Lip, et al., 2011), thus increasing their likelihood of adopting a certain treatment. One of the trials in this review (Man-Son-Hing, et al., 1999) recruited patients that had previously taken part in the SPAF trial (Man-Son-Hing, et al., 1999). All of these patients had previously taken either anti-platelet (60% of decision aid group vs. 60% of the usual care group) or OAC (37% of the decision aid group vs. 38% of the usual care group). The patients within this trial are unlikely to be representative of patients that are making treatment decisions for the first time. Firstly, as they are ex-trial patients, thus are likely to have prior treatment related education and secondly, as they have had first-hand experience of one or both treatments. One study found that more patients chose warfarin in a decision aid trial

when the drug name was blinded, than when unblinded (Holbrook, et al., 2007). Thus their decisional conflict will be influenced by their prior knowledge of this treatment, and perhaps any adverse events they may have suffered from. Moreover, research suggests that patients are more likely to choose their current treatment over and above another, it has been suggested that this act prevents cognitive dissonance (i.e. the stress of choosing a preferred treatment over actual treatment choice) (Holbrook, et al., 2007; Howitt & Armstrong, 1999; Protheroe, Fahey, Montgomery, & Peters, 2000; Fuller, et al., 2004).

2.7.3 Quality of the evidence

The risk of bias was low in the majority of trials. Two types of bias were most prevalent within the studies. Firstly, blinding of patients to the intervention received was not possible, nor was it possible to blind the intervention facilitator, inevitably raising the risk of bias. However, blinding the data analyst or researcher to which intervention arm the patient was assigned to was undertaken in four trials (McAlister, et al., 2005; Christensen, et al., 2006; Gadisseur, et al., 2004; Beyth, et al., 2000). Trials must be explicit when reporting their methods and procedure to ensure accurate assessment of blinding bias and enable comparison of trials.

Inclusion bias was also evident in many studies where the trial patients may not have been representative of the number of eligible participants. The percentage of eligible patients randomised was as little as 18% (Gadisseur, et al., 2004) in one of the mixed cohort trials. Perhaps the reluctance of individuals to participate may relate to the extensive training required, particularly for self-monitoring trials. Furthermore, many patients may refuse consent due to physical limitations, time commitment

associated with multiple training sessions, or psychological barriers to performing self monitoring. AF patients in particular are mostly elderly (Kannel, Wolf, & Benjamin, 1998) and often highly symptomatic (Lip, et al., 2011), thus trial participation may be a particular burden.

The quality of care in the control groups may vary, affecting the benefit and control of standard anticoagulation monitoring. The educational element of the intervention may be one of the key factors improving TTR. However, trials vary in the intensity, duration and number of education sessions, thus we cannot draw conclusions about the influence of the educational components of these interventions.

Three studies did not record patients level of education (Gadisseur, et al., 2004; Christensen, et al., 2006; Thomson, et al., 2007), a factor which may impact on knowledge uptake and treatment control. Research suggests that patients with greater knowledge of their treatment spend more time in therapeutic range (Tang, et al., 2003). Thus the results of the trials which do not indicate education level may be influenced by individual differences in educational achievement between trial groups.

Interventions included within the review were largely self monitoring and decision aid trials that included some element of educational training. However, only two trials included an education only group (Khan, et al., 2004; Gadisseur, et al., 2004). To establish whether the differences in TTR control were a result of self monitoring (i.e. an increased level of responsibility for their therapeutic outcomes) or the education itself (improved knowledge), it is essential to specify the educational components included in both the self monitoring and education only intervention groups. Without this information we cannot draw conclusions as to whether self-

monitoring has significant additional benefits over purely providing patients with information; particularly as results suggest that education alone can improve patients' anticoagulation control. As usual hospital care currently includes educational components, such as an information session, or an education based consultation, improving this service may prove more cost effective than self management.

Whilst the educational components of the interventions did focus on important areas of risk (i.e. side effects, medication recommendations), they did not include education specific to patients' indication for treatment. Studies suggest that AF patients have limited knowledge of their condition (Lane, et al., 2006; Coelho-Dantas, et al., 2004; Tang, et al., 2003; Nadar, et al., 2003), which may influence the perceptions they form about their illness and their treatment (Steed, Newman, & Hardman, 1999). Thus it is essential that patients form an accurate understanding of their illness and make appropriate lifestyle changes.

Few studies provided AF specific data on psychological outcomes such as anxiety, depression and quality of life, and those that did found no significant differences between groups. Only one self monitoring study reported QoL as an outcome (Khan, Kamali, Kesteven, Avery, & Wynne, 2004), finding no significant difference in QoL scores on any of the SF-36 sub scales, other than emotional role limitation (mean difference 13.33, 95% CI 0.85 to 25.81, p=0.04). Only one decision aid trial reported anxiety as an outcome (Thomson, et al., 2007). They found that anxiety fell significantly in both groups pre- to post-clinic (mean change -4.57 (95% CI) -6.30 to -2.84), but there was no evidence of a significant difference in anxiety between the two groups (F (1, 95) = 0.001; p=0.98). None of the self-monitoring trials measured anxiety, a factor which may have an influence on patient's self-efficacy to perform

regular blood tests. Furthermore, the trial which measured QoL used a generic measuring tool (SF-36). It is necessary to include disease-specific measures of QoL to accurately assess the impact of the intervention. Numerous studies suggest that AF patients suffer from high levels of anxiety (Thrall, Lip, Carroll, & Lane, 2007), yet none of the interventions were designed with this in mind.

2.7.4 Potential biases in the review process

Our search strategy included a comprehensive search of several electronic databases, meticulous hand-searching of reference lists of included and excluded papers, recent conference proceedings, and personal communications with experts in this area. Further, the titles and abstracts of all studies identified by the search strategy were reviewed independently by two reviewers and disagreements were resolved by consensus. Data extraction of the included studies was also under taken independently by two reviewers. Therefore the potential for bias in the review process was minimal and it is unlikely that important studies were missed.

2.8 Conclusions

2.8.1 Implications for practice

Patients participating in both educational interventions and self-monitoring interventions (with education) spend more time within the therapeutic INR range (Christensen, et al., 2006; Gadisseur, et al., 2004; Khan, et al., 2004), inevitably decreasing the prevalence of adverse thromboembolic events and mortality. However, there are not enough trials to draw clear conclusions (about

whether self-monitoring has a greater influence on treatment control than education alone), consequently more trials are needed to examine the impact of intensive educational interventions on anticoagulation control. Further, self-management may not be a feasible option for the majority of the patients requiring anticoagulation, due to the training required (Fitzmaurice, Hobbs, Murray, Holder, Allan, & Rose, 2000). In addition, the associated costs of self-monitoring may prevent wide-scale uptake (Fitzmaurice, Hobbs, Murray, Holder, Allan, & Rose, 2000), particularly with imminent arrival of new anticoagulants which do not require monitoring (Lip, et al., 2011). Thus education may become the primary focus for clinical practice, as patients will still need to understand the disease, the need for treatment, and the risks and benefits of anticoagulation, as well as the importance of adherence to the treatment regimen in order to avoid adverse events.

2.8.2 Implications for research

This review highlights the need for AF-specific trials in larger cohorts and among warfarin-naive AF patients, since the number of AF patients within the trials was limited, with most patients being warfarin-experienced. Furthermore, the trials that were included all focused on self-monitoring and decision aids. None of the trials specifically looked at other types of intervention such as intensive education, or behaviour change interventions which are driven to improve psychological outcomes (i.e. motivational interviewing and cognitive behavioural therapy). In addition, such trials should account for the potential confounding effects of patient education levels and the varying quality of the control group care. Future studies should set out to understand the mechanisms by which interventions are successful, exploring the psychological implications for patients suffering from this long-term chronic condition.

3 Intervention development

Evidence from the systematic review (see Chapter 2) supports the need for a behavioural intervention that targets AF patients who are newly prescribed OAC. By improving knowledge of AF and OAC, it seems possible to increase patients' time spent within therapeutic INR range. However, it is also important to consider the mechanisms by which an intervention with this patient group is successful, and include a theoretical basis which considers the literature surrounding adherence to medication.

Complex interventions have been described as interventions that 'contain several interacting components' (Craig, Dieppe, Macintyre, Michie, Nazareth, & Petticrew, 2008). This type of intervention is used widely within public health practice and the National Health Service (NHS). The Medical Research Council (MRC) published a framework for the development and evaluation of RCTs for complex interventions, including a pre-clinical or theoretical phase (MRC, 2000). However, complex interventions have evolved in both the design and evaluation process, and the original framework has been criticised for lacking attention to the early phase of piloting and developing the intervention (Hardeman, Sutton, Griffin, Johnston, White, & Wareham, 2005). Rather than a linear development process, the new guidelines propose a more pragmatic process of intervention design, whereby each phase informs the other (Anderson, 2008). Thus, whilst the evaluation process is essential (primarily through an RCT design), the development of the intervention, through the literature reviews, theoretical models or modelling processes and outcomes, is equally as important (see Figure 3.1). Using these principles the development process may inform the piloting procedures and the evaluation of the intervention or

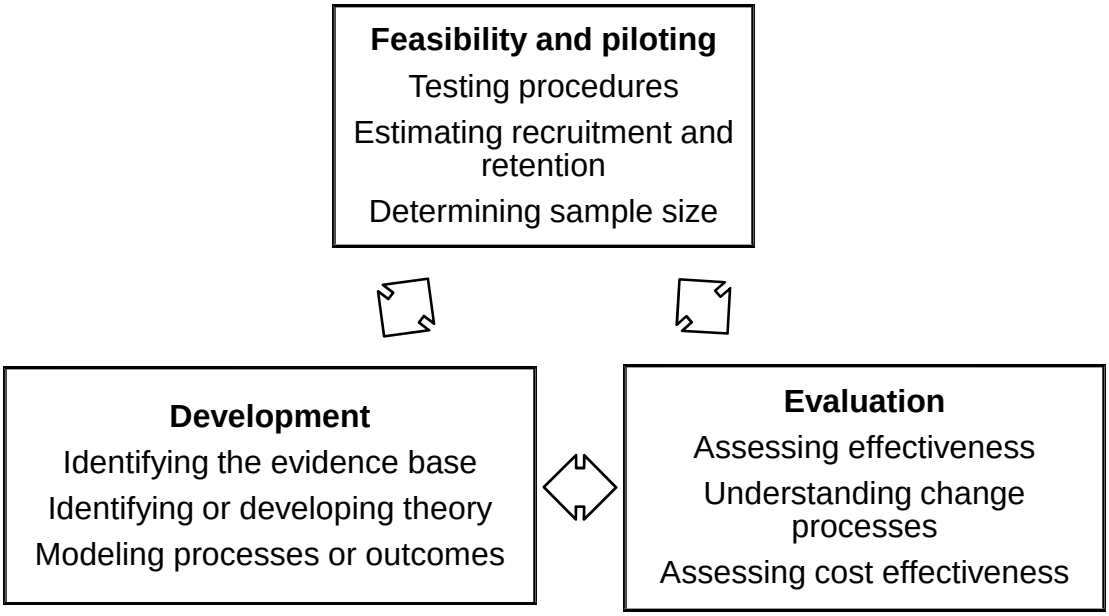
pre-specified outcomes. This chapter aims to document the development process of the intervention, including the components which informed its final development.

3.1 Theoretical background

3.1.1 Beliefs about medication

Research into patients' beliefs about medications suggests utilising the 'Necessity-Concerns Framework' to understand the key beliefs which are influencing whether patients adhere to prescribed treatment or not (Horne, Weinmann, & Hankins, 1999). The models suggests that patients hold beliefs about the necessity of their prescribed medication (Specific-Necessity), and concerns about prescribed medication, based on beliefs about danger of dependence and long-term toxicity, as well as the disruptive effects of the medication (Specific-Concerns). The model also describes general beliefs about medication, assessing beliefs that medicines are addictive and harmful, (General-Harm) and that medicines are over-prescribed by doctors (General-Overuse). These beliefs, and the way in which patients balance their concern about medications, have been widely used in predicting adherence in a variety of chronic conditions including rheumatoid arthritis (Neame & Hammond, 2005), asthma (Jessop & Rutter, 2003), type II diabetes (Farmer, Kinmonth, & Sutton, 2006) and depression (Aikens, Nease, Nau, Klinkman, & Schwenk, 2005).

Figure 3.1: Key elements of the development and evaluation process adapted from Craig et al (Craig, Dieppe, Macintyre, Michie, Nazareth, & Petticrew, 2008)



It has been suggested that several factors influence adherence, and these factors are either intentional or un-intentional. Intentional non-adherence can occurs when patients make a decision not to take their treatment as a result of their personal motivations and/or beliefs. Unintentional non-adherence can refer to an individual's skills or ability to take their medications (e.g. problems with remembering to take tablets). Patients may report either or both, and indeed there may be an overlap between the two concepts (e.g. where patients perceive medications as being unnecessary, they maybe more likely to forget to take it; Horne, 2001). The necessity-concerns framework has also been found to predict both intentional and non-intentional adherence in patients starting medication for a range of chronic illnesses (Clifford, Barber, & Horne, 2008).

Some patients are particularly at risk of non-adherence, which can be explained by the model. For example, asthma and cardiac patients are significantly more likely to perceive that the costs of their medication outweigh the benefits, in comparison to oncology or dialysis patients (Horne, Weinmann, & Hankins, 1999). Concerns about medication could have arisen from potentially mistaken beliefs, for example, that regular use results in adverse effects or dependence, as both groups often rely on medication for long-term management of their condition. These beliefs can result in intentional non-adherence (see Table 3.1).

Table 3.1: Examples of patients' self-reported reasons for non-adherence classified as unintentional and intentional (Clifford, Barber, & Horne, 2008).

Unintentional reasons	Intentional reasons
I was away from home and forgot to take my medicines with me.	I was worried about the side effects so I reduced the dose.
I was tired and I forgot.	I miss doses because I feel I am taking too many.
I went out for the evening and forgot to take medicines with me.	I do not take water tablets (diuretics) when going out of the house.
I was in a hurry and forgot.	I miss the evening dose because it keeps me awake.

A comparison of beliefs about medications between adherent, unintentional non-adherent and intentionally non-adherent patients, found significant differences in medication related beliefs in patients with a range of chronic illnesses, after being newly prescribed medication for the last ten days (Clifford, Barber, & Horne, 2008). Compared with adherers, intentional non-adherers had significantly lower scores on

the necessity subscale of the BMQ (p=0.012), higher scores on the concerns subscale (p=0.008), and lower scores on the necessity-concerns differential (p=0.001). There were no significant differences between adherers and unintentional non-adherers (Clifford, Barber, & Horne, 2008). Evidently whilst unintentional non-adherers may benefit from memory aids (i.e. reminders, tablet dosettes), intentional non-adherers may need to address both their perceptions of their medication and misinformation, by increasing patient education surrounding their treatment. Intentional non-adherers appear to doubt their personal need for their medication and have concerns about taking it compared to adherers. They may also view their concerns about the medication as more important than their concerns about the illness itself. Whilst these findings are not derived from a specific AF population, the study did test a cohort which was similar to AF patients (i.e. aged ≥75, stroke, coronary artery disease, asthma, diabetes, rheumatoid arthritis).

Other studies have given more insight into how we can utilise this model for the purpose of intervention development. A study examining beliefs about medication in diabetes patients found the majority strongly agreed with statements about the benefits of taking medication (Farmer, Kinmonth, & Sutton, 2006). However, negative beliefs that taking medication would cause unpleasant side effects and lead to weight gain were held by 24.1% and 13.9% of people, respectively. Beliefs about benefits were strongly associated with intention to take medication regularly. Two beliefs were associated with reduced medication adherence: firstly that changes to their daily would make it more difficult to take diabetes medicines regularly ($P < 0.001$), and secondly that taking medications led to weight gain ($P < 0.05$). Thus by emphasising the importance and the benefits of medication, it may be possible to increase

adherence. Further it seems pertinent to address any misconceptions surrounding the potential harm of the medication prescribed.

In heart failure patients, the most frequently identified benefit of medication adherence (to diuretics) was decreasing the chance of being hospitalized (81%), and the most commonly reported barrier was disruption of sleep (78%) (Bennett, Lane, Welch, Perkins, Brater, & Murray, 2005). Heart failure patients perceived both benefits of treatment and the barriers to adherence, which can inform tailored intervention development, in a similar way to the diabetes cohort. The implications of these findings suggest that in order to improve adherence rates, patients must understand the need for treatment and tackle any concerns they have about taking it. The intervention must incorporate the needs of both unintentional and intentional non-adherers (see Table 3.2).

Table 3.2: Key recommendations regarding beliefs about medications

Key recommendations based on the literature surrounding beliefs about medication
• Address unintentional non-adherence by using reminders/memory aids/dosettes. • Address intentional non-adherence by discussing with the patient their individual barriers to adherence and the benefits of their prescribed medication. • Discuss with patients the consequences of their illness, risks associated with treatment and how this related to their perceived barriers to medication adherence.

3.1.2 Illness perceptions

Patients' barriers to adherence may also relate to their perceptions of their illness. The common sense model (CSM) suggests there are five dimensions which form our illness representations, these include (i) *identity*- symptoms and the label attributed to the illness; (ii) *consequences*- expected physical, social and economic implications; (iii) *timeline*- acute, chronic or cyclical duration; (iv) *causes*- personal ideas about causes; and (v) *cure/control*- the extent to which a patient believes they will recover from or control their illness. Items of the illness perception questionnaire (IPQ) (Broadbent, Petrie, Main, & Weinmann, 2006) were theoretically-derived to assess each of the above components.

Illness representations have been studied with a range of chronic illnesses including; heart disease (Cooper, Lloyd, Weinman, & Jackson, 1999; Steed, Newman, & Hardman, 1999), cancer (Buick & Petrie, 2002), chronic obstructive pulmonary disease (Scharloo, Kaptein, Weinman, Hazes, Breedveld, & Roojimans, 1999), diabetes (Griva, Myers, & Newman, 2000; Paschalides, Wearden, Dunkerley, Bundy, Davies, & Dickens, 2004); myocardial infarction (French, Lewin, Watson, & Thompson, 2005) and rheumatoid arthritis (Scharloo, Kaptein, Weinman, Hazes, Breedveld, & Roojimans, 1999; Murphy, Dickens, Creed, & Bernstein, 1999; Pimm & Weinman, 1998). These studies suggest links between illness representations and outcomes such as coping (Scharloo, et al., 1998; Scharloo, Kaptein, Weinman, Vermeer, & Rooijmans, 2000; Moss-Morris, Petrie, & J, 1996) and medication adherence (Cooper, Lloyd, Weinman, & Jackson, 1999; Weinman, Petrie, Sharpe, & Walker, 2000).

In myocardial infarction (MI) patients illness representations predicted various outcomes; slower return to work was associated with higher concern ($r=.43$, $p<.03$) and higher treatment control beliefs ($r=.44$, $p<.03$). The Brief-IPQ at discharge further predicted cardiac anxiety (Eifert, et al., 2000) and quality of life (Spertus, et al., 1995; Ware, Snow, Kosinski, & Gandek, 1993) three months after MI. Thus, illness representations are a key aspect of a patient's recovery from their illness and play an important role in how individuals cope with their treatment strategy.

Whilst patients are encouraged to adhere to treatment recommendations, general practitioners and physicians rarely discuss the behaviours required to become adherent and overcome perceived barriers (Theunissen et al., 2003). The CSM of illness representations suggests that patients' appraisal of somatic changes such as symptoms and functions can explain both patient care seeking and a patient's management of their condition (Cameron, Leventhal, & Leventhal, 1993; Horne, 2003; Skelton & Croyle, 1991). For example, symptoms of illness may be attributed to 'normal' ageing (Horowitz, Rein, & Leventhal, 2004) or psychological stress (Cameron et al., 1993), thus not prompting treatment seeking behaviour.

Many patients may harbour strong, but medically unsupported beliefs about their medical condition, derived from the media, extreme cases, or general beliefs about health and illness. The CSM suggests that patients rely on a set of 'mental tools' to understand somatic stimuli such as duration, location and severity of symptoms; a concept supported by research with hypertensive (Meyer, Leventhal, & Guttman, 1985) and diabetes patients (Skinner & Hampson, 2001). For example, changes in adolescents' perception of the severity of their diabetes were associated with an increase in adherence. Further, the more diabetes patients believed their treatment would control their diabetes, the more likely they were to adhere to dietary

recommendations (Skinner & Hampson, 2001). By understanding patients' illness representations we are able to understand how patients self-regulate their illness and this represents an important opportunity for intervention development.

Two studies have examined illness representations in AF patients. One cross-sectional study compared the differences between symptomatic and asymptomatic AF patients (Steed, Newman, & Hardman, 1999); they found participants' representations differed on the identity subscale between symptomatic and asymptomatic patients (m (SD) 7.87 (3.4) vs. 4.00 (2.8) respectively; $p<0.001$), but not on the other subscales (Steed, Newman, & Hardman, 1999). As the identity sub-scale is particularly focussed on symptoms, there is an obvious difference between the two groups. However, the findings suggest that AF patients with different expressions of the arrhythmia are similar on the other subscales.

A recent cross-sectional study with mixed cohort of AF patients provided further insight into the role of illness perceptions. The authors found that patients believed psychological factors, such as age and heredity, caused AF (McCabe, Barnason, & Houfek, 2011). Stronger beliefs that AF is cyclic and unpredictable ($r=0.30$), having psychological causes ($r=0.36$) and greater consequences ($r=0.58$) were associated with more negative emotion. Those patients with the greatest illness coherence, reported fewer negative emotions relating to their AF ($r=-0.38$) and held stronger beliefs that their AF was controllable with treatment ($r= 0.33$) (McCabe, Barnason, & Houfek, 2011). The evidence from this study suggests that by improving patients' illness coherence, and their understanding of causality, we may improve their beliefs surrounding the controllability of their illness, potentially promoting adherence. However, the systematic review (Chapter 2) suggests that there are no studies to

date utilising the CSM within AF interventions, or indeed any studies examining illness perceptions in AF patients over time.

A behavioural intervention, utilising a CSM framework, integrating each of the five components that contribute to the formation of illness representations, may therefore be suitable for AF patients, who often exhibit poor knowledge of their condition and its treatment (Lane et al., 2006; Nadar et al., 2003). It is particularly important for this patient group to increase knowledge and illness coherence, as non-adherence to warfarin carries significant health risks. McAndrew and colleagues focussed on the use of CSM for intervention design and suggest integrating the five components and monitoring the change between current status and the desired endpoint(s) (McAndrew, et al., 2008).

The development of a 'top-down' conceptual framework for AF, involves ensuring patients recognise that AF is present, even if they are asymptomatic. For example, focussing on each of the common sense model components, to allow patients with AF to appraise information and formulate their own illness representation. Thus the top-down elements of the intervention are educational, providing information regarding causality, consequences, expected timeline and potential areas for the control of AF and its symptoms. This approach encourages patients to view AF as both chronic and treatable, and provides patients with a model to correctly interpret bottom-up inputs generated by their actions (i.e., their INR results and treatment outcomes). This strategy is relevant for AF patients, as depending on the type of AF (paroxysmal, persistent or permanent), each patient may represent and manage their condition in a different manner (e.g. they may only adhere to treatment when symptoms are acute, which may be infrequently), consistent with symptom severity.

Below the requirements for patients to create a cognitive representation of AF are summarised:

Create an illness identity: help patients understand which symptoms are/are not associated with AF, common co-morbidities, the risks of stroke in addition to the reasons for prescribing anticoagulant medication and the emotions individuals associate with the illness (e.g. 'I am afraid of what will happen').

Understand the consequences: help patients understand the physical, social and economic implications of both AF and treatment with anticoagulation. Patients need to be provided with information about the risks associated with atrial fibrillation e.g., the main risk associated with AF is stroke.

Identifying their illness timeline: patients can be made aware of the duration of their illness and treatment given information about the different types of AF, and how this relates to the risk of stroke.

Understanding the causes of AF: patients need to be made aware of their personal ideas about the causes of AF and how they relate to the scientific evidence.

Identifying a cure or control for their illness/symptoms: patients can be presented with information pertaining to the control of their INR (with control of factors affecting warfarin metabolism), pharmacological control of their AF symptoms, and explore the factors that may affect their symptoms including caffeine intake, exercise and

alcohol. Of particular relevance are the key lifestyle factors which affect INR control including diet, alcohol intake and other medications and supplements, as for many patients there is no ‘cure’ for AF.

Patients’ common sense models of their physical health and illness can be influenced by subjective cognitions (i.e. symptoms, moods, and experienced dysfunction). AF patients maybe particularly affected by the presence or absence of their symptoms; which in turn can impact on their quality of life (Smith, Lip, & Lane, 2010). However, all patients have the same risk of stroke, regardless of their symptom burden (Flaker, Belew, Beckman, & Investigators, 2005). Therefore it is important that patients do not use a symptom prototype as a subjective cue to identify their illness.

An additional intervention component which replaces automatic control with volitional control is needed within the intervention. This involves patients; (a) knowing what to do to minimise the risk, thus controlling their health outcomes (e.g. dietary change, alcohol intake and use of anticoagulants) and (b) relying on objective rather than subjective indicators (identity, using INR as a meter for control, rather than symptoms) to evaluate the efficacy of treatment (control and consequences); (Cameron & Leventhal, 2003; McAndrew, et al., 2008). The bottom-up approach focuses on behavioural change by using an action plan. By discussing their concerns about treatment and developing their own plan for integrating the treatment regimen; patients may be more likely to manage their illness effectively, a concept which also fits in with the Necessity-Concerns Framework (McAndrew, et al., 2008; Horne, Weinmann, & Hankins, 1999).

Table 3.3: Key recommendations regarding illness perceptions

Key recommendations based on literature surrounding illness perceptions
• Guide patients through the different components of the CSM, to increase illness coherence. • Focus on objective indicators of illness/treatment control (i.e. INR results) rather than symptoms. • Use a personal action plan to encourage volitional control over treatment success.

3.1.3 Behaviour change techniques

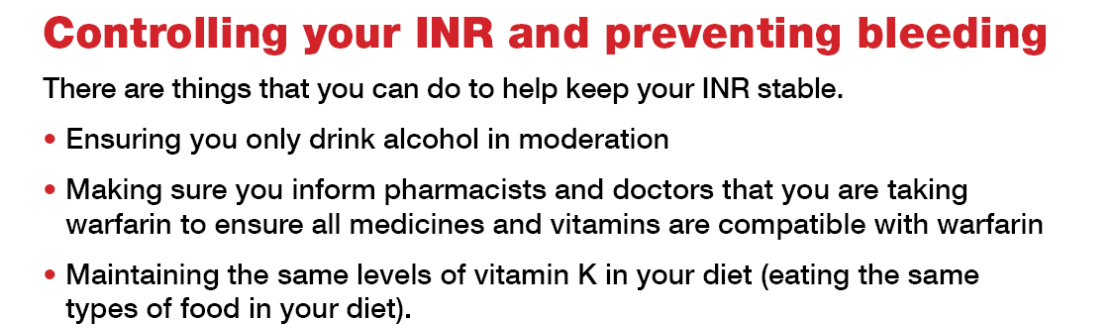
The NICE guidelines for behaviour change, specify three important goals in intervention design (1) be specific about content; (2) spell out what is done, to whom, in what social and economic context, and in what way; (3) make it clear which underlying theories have been utilised, with explicit links between actions and outcomes (NICE, 2007). Psychological theories are numerous and many have overlapping constructs (Michie, Johnston, & Abraham, 2005; NICE, 2007). In order to evaluate how and why an intervention works or doesn't work, these theories need to be simplified into an accessible format. A recent taxonomy of techniques developed a set of reliable and distinct theory-linked definitions of behaviour change techniques (BCTs; Abraham & Michie, 2008). Each of these 26 techniques has led to successful behaviour change in previous interventions with a range of chronic illnesses, based on several overlapping theories (Abraham & Michie, 2006).

Whilst the techniques chosen for this intervention are not specifically linked to one theory, each BCT did correspond with the key recommendations derived from the systematic review, theoretical models and focus groups. The techniques are listed below:

3.1.3.1 Provide general information on behaviour-health link

The common sense model suggests patients need to identify a cure or control for their illness (see Section 3.1.2). In order to gain control over symptoms and outcomes, it is essential to educate patients about the link between behaviour and health outcomes. The intervention group were presented with information relevant to their necessary behavior change, i.e. how they can maintain their INR and thus improve health outcomes (see example Figure 3.2). For patients taking warfarin this included advice on alcohol intake, diet, and other medications and supplements, and susceptibility to bleeding and stroke risk with non-adherence.

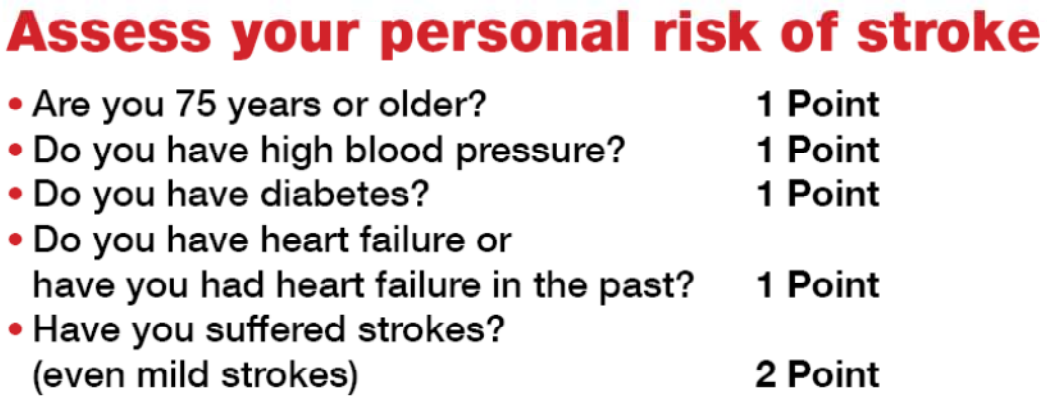
Figure 3.2: Excerpt from the patient information booklet highlighting the behaviour-health link (for more detail see the Patient Booklet, Appendix 3).



3.1.3.2 Provide information on consequences

The common sense model suggests that patients need to understand the consequences of their illness (Section 3.1.2). Thus as part of the intervention session patients are asked to calculate their own risk of stroke (Figure 3.3) using the $CHADS_2$ scoring system (Gage, Waterman, & Shannon, 2001) which assesses which antithrombotic treatment they will be prescribed based on current clinical guidelines. This process allows for the formulation of an AF illness identity, an awareness of the associated risks and the need for treatment. For AF patients the relationship between behaviour and health outcomes includes the susceptibility to stroke and thromboembolism. Patients are asked to draft action plans to minimise this risk. The consequences of not adhering to antithrombotic treatment and lifestyle recommendations are an increased risk of stroke and bleeding complications. These risks are presented as expert patient narratives, discussing their personal experiences of bleeding associated with warfarin and non-adherence to lifestyle recommendations in the DVD. Bleeding risks are also illustrated as annotated pie charts within the booklet to reinforce the information given during the educational session. Patients are provided with safety information regarding side-effects, when/how and who to contact in an emergency and the symptoms of a high INR (illness representations Section 3.1.2).

Figure 3.3: Excerpt from the patient booklet, used in combination with the patient worksheet to assess personal risk of stroke.



3.1.3.3 Prompt barrier identification

Patients are encouraged to think about potential barriers to adhering to recommendations (Figure 3.4) and to design a personal action plan to overcome these barriers. This technique addresses the concept of intentional non-adherence, derived from beliefs about medication theory (Section 3.1.1). This may include barriers to performing lifestyle changes (e.g. specific occasions where they are likely to drink more units of alcohol, or change their dietary intake) or psychological barriers (e.g. fear of taking a treatment that they associate with negative experiences with a former relative). This process takes place throughout the intervention session. Patients are presented with barriers which other patients have identified and ways in which they made these changes through the 'expert' patient narratives. Following the patient narratives on the DVD, patients are given a handout which asks them to list their main concerns about taking warfarin. Patients can then raise these concerns within the group discussion, or talk to the researcher following the session (beliefs about medication Section 3.1.1).

Figure 3.4: An excerpt from the patient worksheet used to prompt a discussion regarding barriers to OAC adherence.

SECTION C: Medication concerns
When prescribed a new life-long treatment such as warfarin, patients often come across problems and concerns which can prevent them from taking their medication and successfully reducing their risk of stroke. These can be psychological concerns for example; worrying about side effects and the burden of the medication or practical concerns for example; how you will remember to take the medication? what to do if you miss a dose etc.

3.1.3.4 Provide instruction

Many patients may also un-intentionally fail to adhere to treatment recommendations. This concept is linked into the beliefs about medication literature (Horne, Weinman, Barber, Elliot, & Morgan, 2005), suggesting that providing reminders and instructions could improve memory for certain behaviours, subsequently reducing the risk of unintentional non-adherence. This technique involves telling the patient how to perform specific health behaviours. For the purpose of this intervention this included consultant cardiologist narratives, describing in detail on the patient DVD, 'what do if you miss a dose of anticoagulation', 'how to remember to take your tablets', and 'when to seek medical attention'. Patients are also encouraged to formulate a personal action plan which will include memory aids for their tablets doses and what to do in an emergency (See patient DVD, Appendix 3).

3.1.3.5 Prompt self-monitoring of behaviour

The Cochrane systematic review (Chapter 2), suggests that self-monitoring can improve adherence to OAC medication. Whilst this intervention does not include INR self-monitoring, patients are encouraged to keep a record of their dietary intake, alcohol units, medications and supplements for two weeks (see Figure 3.5) following the intervention using the 'patient diary' booklet provided. Patients are asked to monitor whether their INR results are out of range and if this coincided with any changes in the recorded lifestyle factors. This encourages the use of INR results as an objective indicator of anticoagulation control, aiming to allow patients to formulate accurate illness representations. At the back of the booklet patients can refer to a list of questions (see Figure 3.6). This is a self-reflective tool, encouraging patients to assess what has changed within their lifestyle, and whether those changes may have had an impact on their INR scores. This diary is for patient self-monitoring only and does not form part of the outcome assessment (see patient diary, Appendix 3).

3.1.3.6 Teach to use prompts/ cues

A further technique, adopted to reduce un-intentional non-adherence, is the use of prompts or cues (see beliefs about medication, Section 3.1.1). Patients are encouraged to identify environmental prompts which can be used to remind them to take their tablets. This could include times of day or particular contexts. They also watch other 'expert' patients describe their memory-cues, including the use of tick lists, pill boxes and reminders. They discuss the roles of their partner (if they have one) within their treatment regimen. Patients are then encouraged to discuss their own memory-aid methods (see patient DVD, Appendix 3).

3.1.3.7 Provide opportunities for social comparison

It was evident when piloting the intervention materials with patient focus groups that patients benefit from discussing their experiences with others and from listening to patients' related treatment experiences. Thus, the intervention was designed to allow for social comparison between patients within the intervention sessions, via patient discussion. Social comparison is also employed by including patient narratives within the intervention DVD. During the intervention development stages 'expert' patients were invited to be filmed during an interview to discuss their illness perceptions, previous concerns about taking warfarin, the lifestyle changes they made, and their consultation when first diagnosed with atrial fibrillation (see patient DVD, Appendix 3). These narratives formed the basis of the patient DVD.

Figure 3.5: Example of patient diary to monitor alcohol intake, vitamin K rich foods and associated health problems.

Week 1: Start Date: ___/___/___

	Food & Fruit or Vegetable Juices Please note down the meals and snacks you ate today.	**Alcoholic Drinks** Please make a note of all the alcoholic drinks you had today.	**Units** Total number per day	**Health Problems** Have you noticed any health problems today? (e.g. bleeding, bruising, tiredness) If so, please write them down.
Mon				
Tue				
Wed				
Thu				

Figure 3.6: Self reflective tool from the patient diary

Medications

Did you miss any of your dosee of warfarin? Yes ☐ No ☐

If yes, which day?_____

Why did you miss the dose?_____

_____

Have you taken any new vitamin supplements/ herbal tablets/ new medication this week? Yes ☐ No ☐

If yes, which day?_____

What was it called?_____

_____

_____

INR

Have you had your INR checked at the hospital/clinic? Yes ☐ No ☐

If YES please answer the following questions:

What was your INR score?

___ . __

Was your score between 2.0 and 3.0? Yes ☐ No ☐

If No, please answer the next question.

Things to consider

If your INR score was between 2.0 and 3.0 you do not need to answer the following questions:

- Did you consume a lot of alcohol units in one day this week?
- Have you consumed a lot of high vitamin K foods such as green cabbage, watercress, soy beans, more than usual? (For a full list please see your copy of 'patient information on treatment with warfarin' booklet.)
- Have you been eating regular meals?
- Have you started taking any new tablets, this could include new prescribed or over the counter medicines, vitamin tablets or herbal remedies?

With these things to consider in mind and using your week's diary please list reasons why you may NOT have met your target INR :

1. _____
2. _____
3. _____

3.2 Developing the intervention materials

3.2.1 Piloting intervention materials with ‘expert’ patient focus groups

Once the theoretical basis for intervention development was established and appropriate educational information had been gathered (based on clinical guidelines published by the National Institute for Clinical Excellence) (NICE, 2006), various presentation methods were piloted. The key objective of the pilot study was to establish preferred communication methods for the educational information and to ensure the information could be understood by using the ‘teach back’ method. Patients were asked to relay the key message that the information was trying to convey, or to explain the information to the researcher and/or other participants. During the focus group six warfarin-experienced patients with AF (three males and three females) were presented with information slides. The same information was also presented to four patients who were new to warfarin (within the interviews). Four key areas were discussed which led to the subsequent modification of the intervention materials. Two of the topics focussed on illness identity information (i.e. the description of patient symptoms, the description of types of AF). The other two examples focussed on information that formed part of education regarding consequences (risks of treatment and risks of AF).

3.2.1.1 Description of symptoms

Patients were presented with a slide which described the symptoms associated with AF, taken from a published article outlining associated symptoms (Lane & Lip, 2009). They were asked whether this clearly described the symptoms they attributed to their

AF. Two key factors were raised. Firstly, some patients are asymptomatic and felt this should be clearly stated within the materials. One male AF patient stated [*M2*] - *"I can only say that on the last article on….other people with atrial fibrillation, I had no symptoms at all and it came about by a routine inspection... symptoms I am talking about the chest discomfort, the light headedness, the tiredness, or fainting... none of that".*

Secondly, for several patients their symptoms had previously been misattributed to other causes and a clear list of symptoms clarified the identity of their illness. One female patient explains, [F1] - *"when I first started experiencing palpitations and tiredness and slight shortage of breath... occasionally... I was told that it was all part of erm... oooh grief... … it was related to the work I was doing at the time and it was an occupational hazard... well you do get stuff with blood pressure don't you... high blood pressure".* Thus, a clear list of symptoms is included in the intervention materials, noting that some patients may also be asymptomatic (experiencing no symptoms at all).

3.2.1.2 Types of AF

Patients were presented with three clear definitions of the different types of AF derived from current clinical guidelines (NICE, 2006):

- Paroxysmal: multiple episodes that typically last less than 48 hours and stop by themselves
- Persistent: episodes that last longer than 7 days, or stop when treated
- Permanent: continuous AF for more than 1 year

Patients were asked whether they understood the definitions, which category they fitted into, and why. All of the patients appeared to be able to quickly categorise themselves (see quotations below), and thus the descriptions were kept the same.

[M2]- "out of that... number three will be the nearest to me... permanent continuous atrial fibrillation... for more than 1 year and I would say 50 years... [laughs] that's how long I can go back..."

Researcher – "how about everybody else?"

[F1] –"I have spent 3 years since I was diagnosed with it. With atrial fibrillation"

Researcher – "and which category would you fall into?"

[F1] –" mmm I would say probably the first one... comes and goes..."

3.2.1.3 Risks associated with warfarin

Patients were shown three different presentation methods for the same risk information. The information related to the risks of stroke associated with AF and the risks of bleeding associated with treatment with warfarin. Presentation methods included two traditional methods; [1] pie charts, [2] bar charts and one more novel method, [3] pictograms (denoting each percentage as a smiley face, previously used as a decision making tool by Man-Son-Hing and colleagues; Man-Son-Hing, et al., 1999). Patients were asked which method they preferred and which they understood. All patients agreed that the pie chart presentation method was clearer for a range of statistical risk information. One patient described how time-consuming the pictogram method was [F1]-*" because otherwise you are going to be sitting there ages as I say…counting how many faces are there on there…whereas with the circle you*

got…straight away". Based on the feedback from the focus group, pie charts were used to present risk information within the educational booklet.

3.2.1.4 Stroke risk associated with AF

Patients were presented with a diagram (of a torso, heart, nervous system and brain) describing the formation of clots within the atrium (top chamber) of the heart and the subsequent risk of stroke (see patient booklet, Appendix 3). They were asked whether the diagram was useful and whether they understood information they were presented with. The dialogue indicated that this diagram provided the informational link between the risk of blood clots and the risk of stroke.

[F1]- "well its explaining what can happen in the sections of the heart and how erm, as it there, clots can form and erm"
[M1] – "go to the brain"
[F1] – "yeah… can go to the brain and that can cause erm strokes or whatever and at the same time, it is also showing how the different movements of the heart, the pumping of the heart"
[M1] – "oh yes"
[F1] – "can effect erm… this distribution shall we say unless it is controlled with a thinning… drug or whatever. That's how I look at it"

Another patient described how the information provides an explanation for the need for anticoagulation with warfarin [F2]- *"it would help you to know why you have been given your medication and what it was gonna do to help prevent you… you know*

having the blood clot in first place". The original diagram was digitalised and adapted for use within the educational booklet.

This pilot study represents a pragmatic approach to intervention design. Patients were able to read the materials and comment on their understanding of the information, the method of presentation and the information they felt needed to be added to the final intervention session. Many of these patients also took part in the DVD filming, allowing them to voice their concerns about their personal barriers to taking warfarin, and how they were able to cope with their diagnosis and treatment. These interviews were presented as 'patient diary' clips within the DVD and provide one element of social comparison within the intervention. These AF patients played an important role in shaping the content of the intervention, to ensure it was both relative and relevant for the target group.

Table 3.4: Key recommendations based on focus group outcomes

Key recommendations based on the focus group pilot study
Symptoms –list the common symptoms, specifying that AF patients can be both symptomatic and asymptomatic *Risk presentation* –the use of pie charts, rather than other methods demonstrated. *Stroke diagram* –visual aids within the intervention materials can prove useful. *Social comparison* – patient narratives were added to the intervention materials, voicing barriers to adherence and questions to the physician.

3.2.2 Intervention outline

The intervention consists of a group session (between 2-6 patients) for one hour, where patients are shown a DVD of information, asked to complete worksheets, and take part in a group discussion. The intervention is delivered by the same researcher for each session (a Health Psychologist in-training, DEC), who designed and piloted the intervention under supervision. The information on the DVD consists of three chapters; (1) AF causes, etiology and warfarin (this section follows on to a worksheet and discussion about personal risks associated with AF and the need for anticoagulation treatment); (2) how to control INR (including key lifestyle recommendations such as diet, alcohol and other medications and supplements); and (3) expert patients discussing concerns, barriers to adherence and coping with lifestyle changes. An open discussion follows the DVD, eliciting key concerns surrounding lifestyle changes. Following each chapter patients are encouraged to note down the key lifestyle changes that they will make, including any barriers to adhering to recommendations, as part of their personal action plan. A consultant cardiologist is also filmed answering the frequently asked questions with an evidenced-based appraisal of the concern or problem. This section includes side effects, psychological morbidity, memory aids and maintaining INR control.

Patients are then encouraged to discuss their own concerns about their condition, and their treatment and draft a personal action plan to integrate lifestyle changes into their everyday routine. The DVD is presented with a variety of approaches; [1] expert patient narratives, [2] mock consultations, [3] pictorial examples of dietary components, alcohol and other medications and [4] expert consultant interview excerpts. In addition to the interactive group sessions, patients are also given an

educational booklet, which has more detailed information and reiterates key safety points. The complete intervention pack also contains a treatment diary (whereby patients can self-monitor the factors which affect the stability of their INR), an alert card and their session worksheet. The table below describes the content of the intervention, the mode of delivery and the relevant theoretical components (See Table 3.5).

Table 3.5: A table outlining the intervention components

Content	Mode of delivery	Description	Model component(s) and/or behavioural change technique
Definition	Booklet, DVD	Definition of AF given by consultant cardiologist and explained within the booklet. The booklet also includes symptoms associated with AF and the different types of AF are defined.	Illness identity
Diagnosis	DVD	Patients give narrative examples of their experiences of AF diagnosis. For some patients this maybe through routine health checks; for others it is following a TIA or stroke. Patients give further examples of what AF means to them and how they would describe the condition to other patients.	Illness identity Provide opportunities for social comparison
Cause	Booklet, DVD	The causes of AF are described by a consultant cardiologist; these include age and associated co-morbidities. The causes are also described within the educational booklet, documenting factors which increase the risk of AF and a graph illustrating the increase in numbers of AF patients with age.	Understanding the causes of AF

Prognosis	DVD, Booklet	The consultant describes the risk of stroke associated with AF on the DVD. The booklet describes the risk of stroke and uses a pictorial illustration of how blood clots can form and cause stroke.	Identifying an illness time-line Identifying a control for illness/symptoms Provide information on consequences
Stroke risk	DVD, Worksheet	The patient education booklet describes why AF patients are prescribed warfarin and how to calculate their risk of stroke. The booklet also uses pie charts to illustrate the potential risk of stroke and how this risk is reduced using different treatments. During the intervention session the patients calculate their personal risk of stroke and identify which treatment they would be recommended [using $CHADS_2$ risk stratification acronym (Gage, Waterman, & Shannon, 2001)]. Patients are also encouraged to document and discuss their own action plan for stroke risk reduction.	Provide information on consequences Identifying a control for illness/symptoms

Treatment	DVD, Booklet	The consultant cardiologist describes the need for warfarin and reasons for prescribing it within the DVD. There is further explanation of how antiplatelet [aspirin] and anticoagulant [warfarin] treatments work on different components within the blood. A pie chart illustrates the risks associated with warfarin i.e. bleeding and what types of bleeding can occur.	Identifying a control for illness Provide information on consequences
INR	DVD, Booklet, Patient Diary	Explanation of the process of INR monitoring and how to maintain an INR within therapeutic range are presented in various formats within the DVD. Lifestyle recommendations [including diet, alcohol intake and other medications and supplements] are given with visual examples. Further, a mock lifestyle consultation for each recommendation is presented. Finally patient narratives give examples of the changes that other patients have made in order to maintain their INR within therapeutic range. Patients are encouraged to formulate their own personal action plan which includes personal lifestyle changes, in order to maintain INR control. They are also asked to keep a self-monitoring diary for the first two weeks following the intervention session; this includes monitoring lifestyle factors that affect INR control.	Identifying a control for illness Prompt self-monitoring of behaviour

Memory aids	DVD	Patient narratives within the DVD give examples of the memory aids that patients use for remembering to take their tablets. The consultant cardiologist also gives instructions on what actions to take if patients miss a dose of warfarin.	Provide opportunities for social comparison Teach to use prompts/cues Provide information on consequences, provide instruction Target unintentional non-adherence
Side effects	DVD, Booklet	Patients give narrative examples on the DVD of the side effects they have experienced. These include bleeding, bruising, or in some cases no side effects at all. Patients also give examples of their initial concerns about bleeding side effects and how they overcame these concerns. The consultant cardiologist provides safety information on the DVD including what to do if patients experience bruising and/or bleeding side effects. Both patient narratives and the consultant explain how to ensure that medications are compatible with warfarin.	Provide opportunities for social comparison Provide information on consequences

Patient barriers	DVD, Worksheet	Patients describe their initial concerns about their diagnosis and treatment, and how they have coped with them. The consultant cardiologist describes the impact of AF and anticoagulation on quality of life and psychological health. During the discussion and using the worksheet patients are encouraged to discuss their own concerns about their illness and treatment, including ways in which they may overcome any perceived psychological barriers.	Provide opportunities for social comparison Prompt barrier identification Target intentional non-adherence

4 Method

The development of the TREAT intervention began in February 2009, a process which took 10 months. This process also included setting up the randomised controlled trial, which would form the evaluation of the intervention, including gaining ethical approval and consent from the local research and development group. This chapter documents the quantitative methods included in the trial evaluation (See Figure 4.1 for trial procedure timeline).

4.1 Patients

Between December 2009 and May 2011, all AF patients newly referred for anticoagulant therapy at the outpatient AF or OAC clinics at City Hospital, Sandwell District General Hospital, Good Hope Hospital, Russell's Hall Hospital and Heartlands Hospital who met the inclusion criteria, were eligible to participate. The diagnosis of AF was made by a cardiologist or general practitioner and documented by 12-lead electrocardiogram (ECG) or holter monitoring, demonstrating the presence of rapid, irregular fibrillatory waves and/or irregular ventricular response (Lip & Tse, 2007). Individualised annual risk of stroke was determined using stroke risk stratification schemes. At the beginning of the recruitment phase the most common stroke risk stratification schemes used were the NICE guidelines (low/moderate/high risk) (NICE, 2006) and $CHADS_2$ (Gage, Waterman, & Shannon, 2001). Those patients at moderate to high risk of stroke ($CHADS_2$ score ≥2) were eligible for OAC. In August 2010 new guidelines were published and therafter patients were stratified according to the latest ESC guidelines (ESC, 2010) and the updated CHA_2DS_2-VASc system (see section 1.2.3.2). Those patients with a CHA_2DS_2-VASc score ≥1 were eligible for OAC under the new guidelines. Patients who were eligible for OAC therapy received a standard explanation of the need for such therapy, and the risks/benefits of OAC treatment. Those

patients who were accepting of anticoagulant therapy with warfarin, were approached to participate in the present study. Patients were excluded from participation if they were aged <18 years old, had any contraindication to warfarin, had previously received warfarin, had valvular heart disease, were cognitively impaired or had dementia, were unable to speak or read English, or had any disease likely to cause their death within the subsequent 12 months.

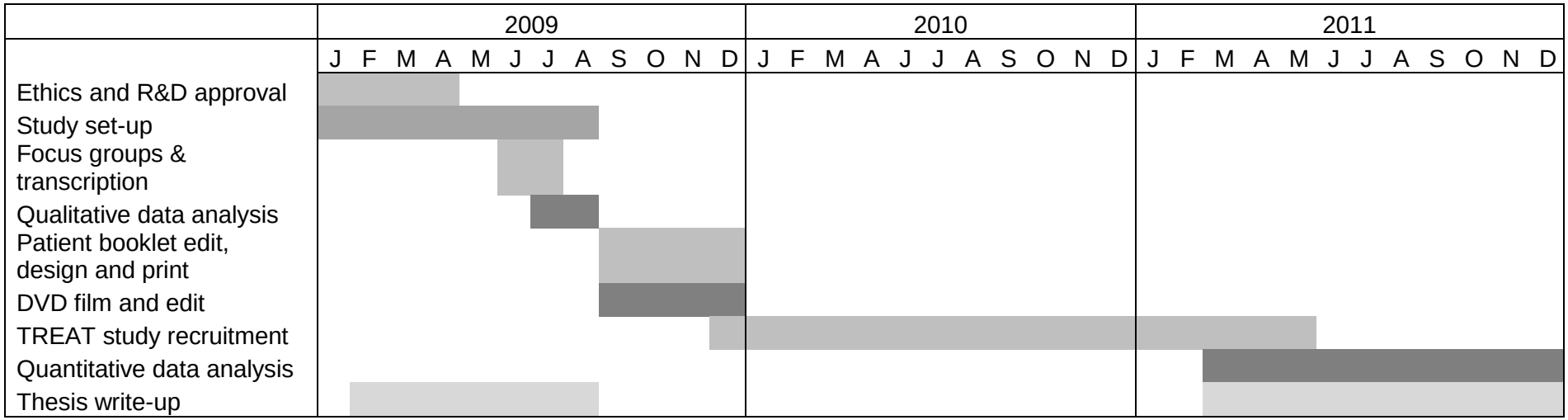
Power for the primary endpoint was calculated based on sample size calculations employed by Connolly and colleagues (Connolly, et al., 2008). A sample size of 78 patients (based on a 20% attrition rate) in each group was estimated to provide at least 95% power to detect a difference of 3% in the standard deviation of the TTR of INR, at a significance level of 0.05. This calculation assumes that usual care would have slightly poorer INR control than intervention (TTR between 58-65% in usual care and ≥65% in the intervention).

For the secondary endpoint of improvement in knowledge following the intervention, the sample size was calculated based a study by Khan and colleagues (Khan, Kamali, Kesteven, Avery, & Wynne, 2004). A sample size of 100 patients (allowing for a 20% attrition rate in completion of the questionnaires) would have at least 80% power to detect an 18.5% increase in knowledge about the condition and factors affecting INR control between baseline and follow-up.

During the study time period, 619 patients with documented AF, not currently on anticoagulant therapy, were assessed for eligibility. Three hundred and thirty one (53%) of the patients assessed were eligible for participation within the trial. Of those patients excluded from the study, 68 (21%) were scheduled for cardioversion, 156 (50%) had previously received warfarin, 24 (8%) had valvular heart disease, 63 (20%) were cognitively

impaired and 4 (1%) had terminal cancer that prevented them from taking part. Of 331 eligible participants, 234 (71%) declined to participate, most commonly due to mobility issues and time constraints. A further 97 (29%) chose to participate, provided written informed consent, and completed a baseline questionnaire. During the randomisation process 46 patients were randomised to the intervention group and 51 were randomised to usual care (for recruitment flow diagram see Figure 4.2).

Figure 4.1: Gant chart of study procedure

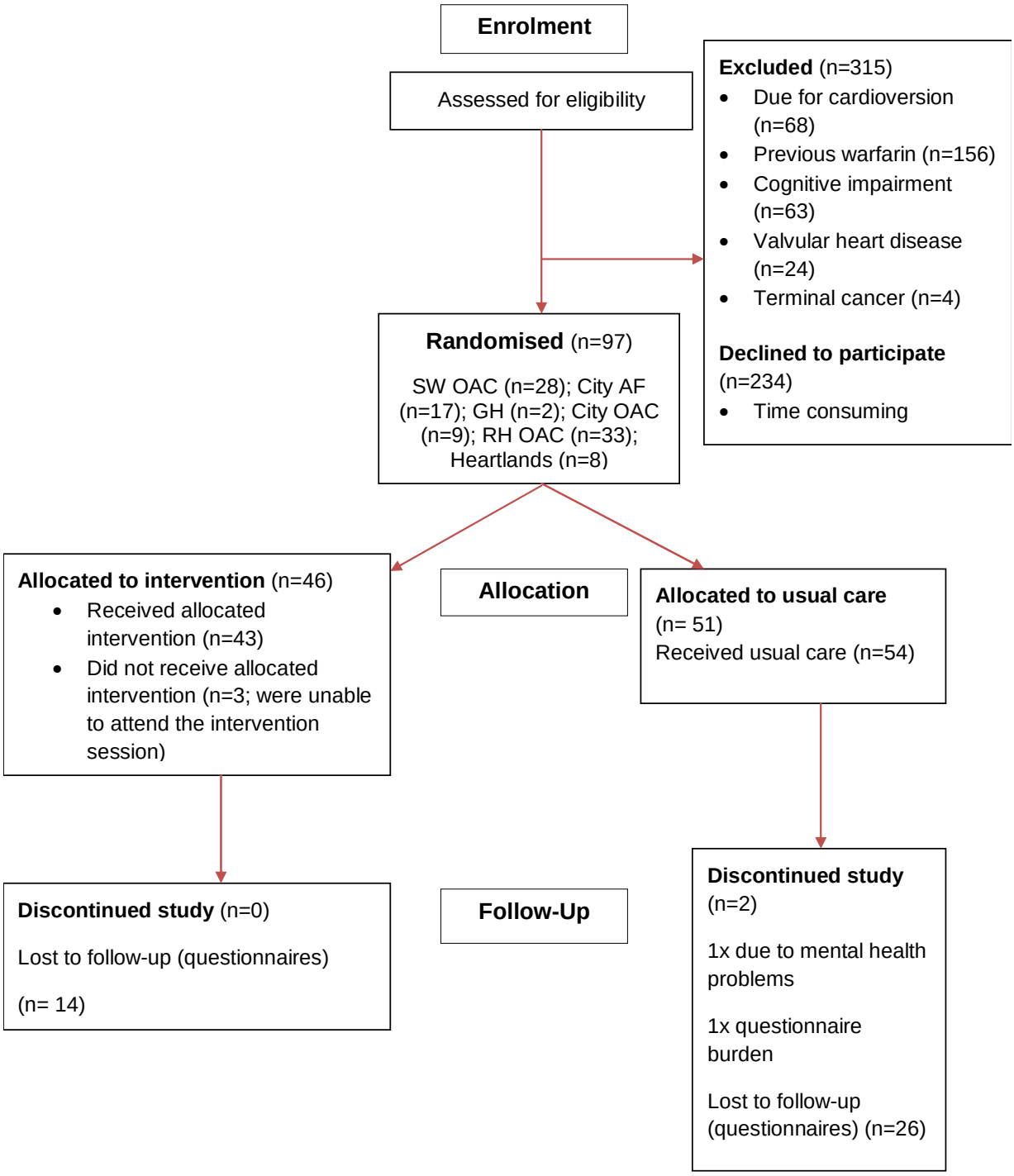


4.2 Procedure

All patients with documented AF, who were accepting of OAC were approached to participate in this study following their first outpatient appointment, prior to commencing warfarin treatment. The purpose of the study was explained to the patient and they were subsequently given an information sheet (see Appendix 1) detailing the study. The investigator then posted baseline questionnaires to the home address of patients willing to participate. Where the investigator could not explain the aims of the study face-to-face, patients were contacted by telephone. The research protocol and protocol amendments were approved by the Black Country Local Ethics Research Committee. Written informed consent was provided by each patient.

The telephone or face-to-face interview permitted the collection of social and demographic data including: age, gender, occupational status, number of years in education, body mass index (BMI), postcode (for socio-economic status index) and ethnicity. The patients were also posted a series of baseline questionnaires: The Beliefs about Medication Scale (Horne, Weinmann, & Hankins, 1999), the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983), the Brief Illness Perception Questionnaire (Broadbent, Petrie, Main, & Weinmann, 2006), the Atrial Fibrillation Quality of Life Questionnaire (Badier, Arribas, Ormaetxe, Peinado, & Sainz de los Terreros, 2007), and the Atrial Fibrillation Knowledge Questionnaire (Lane, Ponsford, Shelley, Sirpal, & Lip, 2006) to complete. Patients completed their baseline questionnaires at home and were provided with a stamped addressed envelope to return them. Further interrogation of hospital records allowed for collection of baseline clinical measures (e.g. body mass index (BMI), AF history, ECG, blood pressure, left ventricular function).

Figure 4.2: Consort flow diagram illustrating recruitment process and follow-up.



At the stage of randomisation the primary researcher checked to ensure the patient met the eligibility criteria and did not meet any of the exclusion criteria. If the patient was willing to

take part, consent was obtained prior to randomisation. A computer generated list randomised patients in blocks of four and on an individual basis with stratification by (a) age (<70 and ≥70 years)/sex and (b) specialist AF clinic versus 'general' cardiology clinic, to receive either 'usual care' or the intensive educational intervention, in addition to 'usual care'. The randomisation schedule was designed by an independent trials unit and the random allocation was obtained by the researcher telephoning an associate researcher (who was not involved in the data collection or data entry). The primary researcher was blinded to patient identification to ensure allocation concealment. A third researcher matched patient identification numbers (generated by the primary researcher) with randomisation codes (generated by the associate researcher). Once the random allocation was obtained, baseline data was collected and an intervention session arranged. Patients who refused to be randomised were offered their respective hospitals 'usual care' package. Follow-up questionnaires were sent to patients via the post at one, two, and six months after randomisation. Completeness of the questionnaires was checked by another researcher (not involved in the analysis of the data) and the patient was contacted via telephone if any questions were not completed.

4.2.1 Usual Care

Fifty one patients were randomised to receive usual care alone. All patients receive the standard 'yellow booklet' to identify that they are taking OAC therapy. This book contains is generic for all patients taking OAC (including deep vein thrombosis, pulmonary embolism etc) and including key safety information including dietary advice (a brief paragraph instructing patients not to miss meals and keep diet stable), medication (to inform GP/physician if they start a new medication) and emergency contact information. The usual care booklet does not provide any information on indications for warfarin (i.e. AF). A recent

addition to this process is the use of an education check list, used by prescribers. This includes areas the physician should cover in their initial warfarin consultation, including when and how to take tablets, factors that affect metabolism, and INR testing.

On observation, the usual care procedure varied slightly between the recruiting hospitals. At City and Heartlands Hospitals all new patients were seen within the general OAC clinic for an INR check. They were then counselled for approximately 5-10 minutes individually by the pharmacist or specialist nurses to discuss individual concerns. At Good Hope Hospital a specialist nurse manages a daily clinic for new patients; each patient has their INR checked and are counselled individually for approximately 10-15 minutes. This counselling also included a more comprehensive explanation of the link between AF and thrombosis. At Russell's Hall Hospital patients are counselled firstly as a group (nurse talks; this takes approximately 15-20 minutes). Patients are then seen individually to prescribe the dose and discuss personal recommendations. This process is generic for all patients taking OAC, and not specific to AF.

4.2.2 Educational Intervention

Forty six patients were randomised to the intensive educational intervention arm of the study. Three patients did not receive the intervention. Two patients were ill during the month following warfarin commencement; one patient could not be contacted. Those patients that did not receive the intervention were moved to the usual care arm. These participants attended a group session where they were shown a DVD containing information about the need for oral anticoagulants, the risks and benefits associated with OAC therapy, potential interactions with food, drugs, and alcohol, and the importance of monitoring and controlling their INR. The DVD (see Appendix 3) also included an expert patients' discussion of

experiences with AF and warfarin. The group sessions were interactive and patients were given the opportunity to ask questions throughout. Patients were also given a copy of the intervention booklet. The booklet (see Appendix 3) served to reinforce the information and enable the patient to refer to it in the future. The intervention development and components are described in more detail in Chapter 3.

4.3 Measures

4.3.1 Primary outcome: Time within therapeutic range

All patients attended the anticoagulant outpatient clinic at their respective hospital to have their INR checked using a capillary sample. The frequency of the INR visits was at the discretion of the OAC clinic. The OAC clinic staff were blinded to the intervention arm the patient was randomised to, ensuring monitoring and follow-up were as 'naturalistic' as possible. Every INR result, from baseline to the end of the study (6-months), was recorded on an INR log sheet. INR is a measure of blood clotting time. It gives an indication of whether patients are within the therapeutic range necessary to reduce their risk of clotting and potentially stroke. The INR reading is extremely sensitive and can be influenced by non-adherence to medications and lifestyle recommendations. Thus, INR is an objective measure of patient adherence. The proportion of time each patient spent in the therapeutic INR range (2.0 to 3.0) was calculated by the method of linear interpolation using data from months one to 12 (to allow attainment of the correct dose of warfarin during the first four weeks). Time spent within target therapeutic range (TTR) was calculated using a method developed by Rosendaal and colleagues (Rosendaal, Cannegieter, van der Meer, & Briet, 1993). Linear interpolation assumes that the INR value between two measurements will vary linearly from the value of the first, to the values of the second INR measurement. The INR is

treated as gradually increasing or decreasing over the interval. Person-time spent at each intensity of anticoagulation can then be calculated as a percentage of total person-time which lies within the target range. INR results from the first seven days after treatment is started or restarted, the time after permanent discontinuation of OAC, and time >5 days from temporary discontinuation, were not included in the calculation. Whilst it was not possible to blind the researcher to which arm patients were randomised to for the purpose of intervention facilitation, all of the follow-up data, including INR results were collected and added to a coded database. Patients were followed-up by an associate researcher, who had not input into the study to reduce bias. The randomisation code was only broken when the data had been analysed. However, the same researcher (DEC) delivered the intervention and carried out the analysis.

4.3.2 Secondary outcome: Patient knowledge

The knowledge questionnaire was previously designed and piloted by our research group (Lane, Ponsford, Shelley, Sirpal, & Lip, 2006) to assess patients' knowledge of their condition, AF, and anticoagulant treatment. The 14 questions encompass knowledge on the name of their condition; their awareness of consequences of, and severity of, the disease and potential benefits/side effects of anticoagulant therapy (see Appendix 2).The questions can be divided into two subscales (1) knowledge of atrial fibrillation and (2) knowledge of oral anticoagulation. Patients gave qualitative answers to questions which were later coded, indicating whether the patients were 'aware' or 'not aware' of the answer. Some of the questions provided qualitative evidence such whether patients perceived AF as a low risk, moderate risk or high risk condition. Seven questions directly tested patients' knowledge of their treatment and their condition. Where questions were answered correctly they were given a score of one, this gave a total knowledge score of zero to seven. The original piloted

questionnaire was delivered as an interview. The wording of the questions was adapted slightly to ensure they were suitable as a postal questionnaire.

4.3.3 Explanatory outcomes

4.3.3.1 The Beliefs about Medication Scale (BMQ)

The BMQ (Horne, Weinmann, & Hankins, 1999) is an 18-item questionnaire that has been widely used in studies assessing beliefs about medications in patients with a variety of chronic conditions including rheumatoid arthritis (Neame & Hammond, 2005), asthma (Jessop & Rutter, 2003), Type II diabetes (Farmer, Kinmonth, & Sutton, 2006) and depression (Aikens, Nease, Nau, Klinkman, & Schwenk, 2005). It was designed to assess commonly held beliefs about medication; including both specific and general medication beliefs (Horne, Weinmann, & Hankins, 1999).

The BMQ was derived from a pool of items (from common beliefs about medications within the literature). Further items were also formed from interviews with haemodialysis and myocardial infarction patients. Principal Component Analysis (PCA) found a high degree of separation between general and specific medication beliefs. This resulted in an 18-item, 4-factor structure. The BMQ-Specific comprises two 5-item factors assessing beliefs about necessity of prescribed medication (Specific-Necessity) and concerns about prescribed medication based on beliefs about danger of dependence, long-term toxicity and the disruptive effects of the medication (Specific-Concerns). The BMQ-General comprises two 4-item factors assessing beliefs that medicines are addictive, harmful, poisons which should not be taken continuously (General-Harm) and that medicines are over-prescribed by doctors (General-Overuse). The two sections can be used separately or in combination.

Items within each scale are both positive and negative statements. Each statement is scored using a five-point Likert scale. A score of “1” indicates that a patient strongly disagrees, ranging to a score of “5” if the patient strongly agrees with the statement. The patients are asked first to score a set of statements based on their beliefs about their specific AF medications. They are then asked to score a second set of statements based on their beliefs about medications in general. Scores for each scale are summed, divided by the total number of items in the scale, and multiplied by 5 to give a scale score ranging from 5 to 25. Higher scores on the scales indicate stronger beliefs in the concepts represented by the scale. The necessity-concerns differential is also calculated by subtracting the concerns subscale from the necessity subscale score. If the score on the differential is negative, this indicates that the patients rate their concerns about their medication higher than their beliefs about the necessity of taking it. If the score is positive, then the opposite applies; suggesting that a patient’s belief in the necessity of taking the medication is stronger than their concerns about potential adverse effects. Scores range from -20 to 20.

Discriminant validity of the scales was originally tested on the basis of each scale’s ability to distinguish between different illnesses and treatment modalities. For example, as expected, patients attending a complementary clinic had significantly higher scores on the General-Overuse ($t=5.89$, $p<0.001$) and General-Harm ($t= 1.94$, $p<0.05$) scale than those patients presenting a prescription at a pharmacy (Horne, Weinmann, & Hankins, 1999).

The assessment of criterion validity of each of the sub scales was based on several predictions. For example, the subscale Specific-Necessity should predict that patients with stronger beliefs in the necessity of their medication would be less likely to cope without it. This was evident as there were negative correlations between the scale scores and the statement “I can cope without my medicines” ($\rho= -0.44$; $p<0.001$).

BMQ-Specific and BMQ-General scales have satisfactory internal consistency scores in all of the patient groups tested (asthmatic, renal, diabetic, cardiac, psychiatric and general medical); with the exception of General-Harm scale in three groups. Cronbach's alpha coefficients range from α = 0.47 to 0.83 for General-Harm, 0.60-0.80 for General-Overuse, 0.63-0.80 for specific concerns and 0.55- 0.80 for Specific-Necessity. The low internal consistency of the General-Harm sub-scale was found in some illness groups (asthmatic, cardiac and general) and not others. The authors attributed this disparity to the premise that patients with certain illnesses develop a more coherent representation of medication in general, which may be influenced by their personal experience with prescribed medication.

4.3.3.2 The Hospital Anxiety and Depression Scale (HADS)

The HADS is a widely used self-assessment scale for detecting states of depression and anxiety in the setting of a hospital medical outpatient clinic (Zigmond & Snaith, 1983). The scale has been used to predict post–intervention outcomes in conditions such as myocardial infarction (Mayou, et al., 2000); to screen for depression in patients who manage chronic conditions, such as diabetic patients (Engum, Mykletun, Midthjell, Holen, & Dahl, 2005) and as a screening tool for general hospital populations (Michopoulos, et al., 2007).

The HADS is a 14-item questionnaire, incorporating an anxiety subscale (HADS-A, n=7) and a depression subscale (HADS-D, n=7). It is possible to obtain separate anxiety and depression scores, and an overall 'distress' score. This test was not intended to measure somatic illness outcomes; hence any symptoms of anxiety and depression which were also related to physical disorder (i.e. such as headaches, fatigue and insomnia) were excluded.

Patients are presented with four statements and asked to indicate to what extent they agree with each statement and are given a choice ranging between “not at all” and “very often”. The order of the responses were alternated in an attempt to prevent response bias. The scoring device is not present on the patient questionnaire to prevent biased responses. The scores on each item range from zero to three. Overall scores range from zero to 42, with higher scores indicating greater distress.

Analyses of sensitivity and specificity can also be carried out. For each scale a score of seven or less was classified a non-case, 8-10 a doubtful case and 11 or more a definite case (Zigmond & Snaith, 1983). Reliability testing revealed a 1% false positive and 1% false negative rate for the depression subscale; analogous figures for the anxiety scale were 5% and 1%, respectively (Zigmond & Snaith, 1983). The optimal balance between sensitivity and specificity for HADS as a screening instrument has been achieved most frequently using a cut-off score of ≥8 for both scales. This gives sensitivities and specificities for both sub-scales of approximately 0.80 (Zigmond & Snaith, 1983). Bjelland and colleagues suggest that this cut-off score is higher in community samples (score of ≥9), but consistently found that with relative variability, a score of ≥8 was the optimal threshold for primary care populations (Bjelland, Dahl, Haung, & Neckelmann, 2002). In studies which found much lower cut-off values, this was attributed to differences in the administration of the scale, as in both studies the HADS was administered in part (as separate sub scales) or as an interview (Lam, Pan, Chan, Chan, & Munro, 1995; Johnson, Burvill, Anderson, Jamrozik, Stewart-Wynne, & Chakera, 1995).

The internal consistency was calculated for the original validation, anxiety item correlations ranged from 0.41 to 0.76 ($p<0.01$). Analysis of the depression scale led to the elimination of one weak subscale item; remaining items had correlations ranging from 0.30 to 0.60

($p<0.02$). The weakest of the anxiety items were also removed to ensure an equal balance of items on the two subscales. Cronbach's alpha coefficient of internal consistency was reported in 15 of the reviewed studies and ranged from 0.68-0.93 (mean 0.83) for HADS-A and 0.67-0.90 (mean 0.82) for HADS-D (Bjelland, Dahl, Haung, & Neckelmann, 2002).

4.3.3.3 The Atrial Fibrillation Quality of Life Questionnaire (AF-QoL-18)

The AF-QoL is an 18-item health-related quality of life scale, developed specifically for AF patients, which can be applied to any of the types of AF (e.g. paroxysmal or permanent) (Badier, Arribas, Ormaetxe, Peinado, & Sainz de los Terreros, 2007). The pool of items was derived from a bibliography review of the most relevant descriptions of the impact of AF on patient quality of life. Items generated formed the basis for an elaborated survey for identifying AF-related symptoms, which was then assessed by three AF specialists. Further specialist focus groups were undertaken to eliminate any discrepancies and semi-structured interviews of AF patients identified appropriate phrases and expressions. By means of Classic Test Theory (Krahn, Manfreda, Tate, Mathewson, & Cuddy, 1995), Item Response Theory (Croker & Algina, 1986) and Rasch Analysis (Bond & Fox, 2001), the original item pool was reduced to 40. Following a pilot study and subsequent factor analysis seven items dealing with psychological QoL and 11 items focussing on physical QoL remained (Badier, Arribas, Ormaetxe, Peinado, & Sainz de los Terreros, 2007).

Response scales include instructions to indicate how strongly the patient agrees with each statement as a possible outcome of their AF. Responses range from "strongly disagree" to "strongly agree". The scoring for each dimension and the global scoring are calculated by adding up the corresponding items and standardizing the result. Values close to zero show a

worse health state while values close to 100 show a better health state of the patient with AF. In order to standardise the scoring, recommended formulas were used.

Internal consistency is excellent for the global questionnaire (α 0.91) and both the psychological AF-7 (α 0.89) and physical AF-11 (α 0.90) domains. The original AF-QoL-40 and reduced AF-QoL-18 versions were also compared and correlations were above 0.80 for the original instrument and the each of the reduced domains. Each factor showed high correlation with the AF-QoL-18 global score, but correlations with the reduced domains were lower (α 0.51) (Badier, Arribas, Ormaetxe, Peinado, & Sainz de los Terreros, 2007).

4.3.3.4 The Brief Illness Perception Questionnaire (IPQ-B)

The original Illness Perception Questionnaire is a widely used measure of illness representations outlined by Leventhal's Self-Regulatory Model (Leventhal, Nerenz, & Steele, 1984; Leventhal, et al., 1997). The model suggests five components underlie the cognitive representation of illness. These translate to the five scales assessing (i) *identity*- symptoms patients associated with the illness and what they attribute to the illness; (ii) *consequences*- expected physical, social and economic implications; (iii) *timeline*- acute, chronic or cyclical duration; (iv) *causes*- personal ideas about causes; and (v) *cure/control*- the extent to which a patient believes they will recover from or control their illness. Items of the original IPQ (Weinman et al, 1996) were theoretically-derived to assess each of the above components. Subsequent studies following the initial validation revealed a variation in internal consistency of the subscales and a revised version was released, incorporating changes to the cure/control and timeline subscales, i.e. the revised IPQ-R (Moss-Morris, Weinman, Petrie, Horne, Cameron, & Buick, 2002). Analysis of the data suggested that items loaded onto two separate factors within the cure/control subscale; (1) personal control and self-efficacy

beliefs and (2) belief in the treatment or recommended advice. Hence, two separate subscales were derived. Problems with low internal consistency on the timeline subscale led to the development of new items to assess cyclical time beliefs, which were previously overlooked (Moss-Morris, Weinman, Petrie, Horne, Cameron, & Buick, 2002). The revised questionnaire also incorporated items assessing emotional representation, a concept which formed part of the original model but was not included in the original version.

The IPQ-R has over 80 items and is particularly prohibitive where patients are very ill, elderly and when repeated measures designs are employed (Broadbent, Petrie, Main, & Weinmann, 2006). Thus a Brief Illness Perception Questionnaire (Brief-IPQ) was devised using a single-item scale approach to assess perceptions on a linear scale (Broadbent, Petrie, Main, & Weinmann, 2006). The Brief-IPQ has eight items which represent the best summarised question from each subscale of the IPQ-R. All of the items are rated on a zero to ten response scale. The first five items assess illness representations i.e. consequences (item 1), timeline (item 2), personal control (item 3), treatment control (item 4) and identity (item 5). Two items assess emotional representations i.e. concern (item 6) and emotions (item 8). One item assesses illness comprehensibility (item 7). The final item is part of the causal scale from the IPQ-R; patients are asked to list in rank-order the three most important factors that have caused their illness. Responses can be grouped into categories (e.g. such as heredity, stress and lifestyle) and analysed. The term ‘illness’ in the questionnaire is replaced with AF and the term ‘treatment’ replaced with warfarin, to ensure the scale is illness specific.

Structural validity was determined using principal component analysis (PCA). Items loading onto more than one factor were eliminated and items with loadings of more than 0.5 were interpreted as being representative of a particular factor. Good test-retest reliability was

demonstrated for both time points ranging from .48 to .70 (p<.001) at 3 weeks, and .42 (p<.01) to .75 (p<.001) at 6 weeks (Broadbent, Petrie, Main, & Weinmann, 2006). Concurrent validity measures were carried out in the renal, diabetes and asthma samples, patients were asked to complete both the Brief-IPQ and the IPQ-R. The majority of items correlated moderately and significantly with their corresponding subscale; personal control and treatment control α = .80; emotional representations α =.88) (Broadbent, Petrie, Main, & Weinmann, 2006). Data from renal dialysis inpatients was used to evaluate test-retest reliability over a three week period. The dimensions showed good stability over this period with significant but low correlations (.33 and .32; p<.001) (Broadbent, Petrie, Main, & Weinmann, 2006).

4.3.3.5 Reliability Analysis for the TREAT sample

Where the measures used for the TREAT study were recorded as scale data and included more than one item for each scale they were analysed for internal consistency. Baseline results from the TREAT study sample were entered into the analysis. All of the scales demonstrated high levels of internal consistency with α scores ranging from 0.632 to 0.914 (See Table 4.1).

Table 4.1: Cronbach's alpha coefficient outcomes for the TREAT study sample

	Number of items	Cronbach's alpha coefficient
HADS-Anxiety	7	0.884
HADS-Depression	7	0.821
BMQ-General harm	4	0.632
BMQ-General overuse	4	0.833
BMQ-Specific concern	5	0.767

BMQ-Specific necessity	5	0.796
AF-QOL-Physical	8	0.914
AF-QoL-Psychological	7	0.868

4.3.4 Clinical Variables

Baseline clinical variables including concomitant medications, type of AF (paroxysmal, persistent, and permanent), duration of AF, ECG details, blood pressure, left ventricular function, smoking status, and alcohol intake were recorded from patients' hospital records. In addition, the numbers of stroke risk factors ($CHADS_2$ and CHA_2DS_2-VASc) were also documented from patient records (ESC, 2010; Gage, Waterman, & Shannon, 2001) (for more detail on these guidelines see section 1.2.3.2). IMD scores were calculated using patients post-code to an indication of socio-economic status (from: https://www.npeu.ox.ac.uk/birthplace/lcm/imd).

4.3.4.1 Concomitant medication

Prescription of all other concomitant medications at baseline was also recorded. In particular, any other antithrombotic treatment (e.g. heparin, clopidogrel, and aspirin), antihypertensives, antiarrhythmics, metabolic and anti-inflammatory treatment and other drugs which may affect INR, including vitamins, antibiotics H^2 blockers and herbal remedies were documented. For example, some antibiotics, particularly co-trimoxazole, macrolides and fluoroquinolones increase the risk of haemorrhage when taken with warfarin, by inhibiting vitamin K synthesis or hepatic warfarin metabolism (Juurlink, 2007). Therefore, it

was necessary to record any medications which may affect whether a patient remains within optimum therapeutic INR range (2.0-3.0).

4.3.4.2 Stroke and bleeding incidence

The incidence of minor and major bleeding, stroke, TIA and mortality was recorded at each of the follow-up points using clinical records. Data concerning the cause of death (cardiac or non-cardiac), reasons for any interruption of anticoagulation and the number of, and reasons for hospitalisation were also recorded.

Definitions of major bleeding were determined by using the International Society of Thrombosis and Haemostasis guidelines (Schulman & Kearon, 2005). Major bleeding constitutes a clinically important primary endpoint in many randomised trials, particularly in anticoagulation studies. Major bleeds are defined as those which result in death, are life threatening, cause chronic sequelae or consume major health-care resources. The criteria are as follows:

1) Fatal bleeding, and/or

(2) Symptomatic bleeding in critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome and/or

(3) Bleeding causing a fall in haemoglobin level of 20 g L-1 (1.24 mmol L-1) or more, or leading to transfusion of two or more units of whole blood or red blood cells (Schulman & Kearon, 2005).

4.4 Study outcomes

The *primary* endpoint is the proportion of time spent in the therapeutic INR range, 2.0 to 3.0, calculated by the method of linear interpolation (Rosendaal, Cannegieter, van der Meer, & Briet, 1993). *Secondary* endpoint is patients' knowledge. *Explanatory* outcomes are (1) beliefs about medication and (2) illness representations. Ancillary analyses will explore the relationship between INR control and incidence of minor and major bleeding, stroke, and thromboembolic events (given that the trial is not powered to detect these differences).

4.5 Data reduction and analysis

Data was analysed using SPSS for windows (Version 18.0). All tests were two tailed, where p-values ≤ 0.5 they were considered statistically significant. All nominal data was coded. Categorical variables were analysed using the chi-square statistic. The fisher's exact test was used where there were expected frequencies of less than five in any cell. Continuous variables were compared using independent t-tests. Where descriptive statistics suggest that the data was not normally distributed (or the Levene's test for variance is significant $p<0.05$) a Mann Whitney-U test for non-parametric data was used. Analysis for the primary outcome was an on- treatment analysis, an intention-to-treat analysis is also included, controlling for any effects of drop-out or cross-over of participants. Three patients that were randomised to the intervention group did not receive the intervention. These patients were included as usual care in the on-treatment analysis, and as intervention group in the intention-to-treat analysis. The cross-over participants TTR results were 64%, 42%, and 62%.

To measure the change in variables across time (at four time points including baseline, one, two and six month follow-ups) and between groups (intervention and usual care groups),

data for each psychological outcome was entered into separate two-factor mixed ANOVA analyses. Where the assumptions of the test were violated (via Mauchley's test of sphericity $p<0.05$), a more conservative p-value was reported (Greenhouse-Geisser).

To test whether outcome variables such as; beliefs about medication subscale scores and illness representation scores predicted TTR multiple stepwise entry multiple regression analyses were used. Where it was of interest to determine whether factors correlated with the primary outcome (TTR), but data was not normally distributed, Spearman's correlation coefficient was used. This test works by ranking the data and then applying the Pearson's equation.

The primary analysis was a comparison of the primary outcome (TTR) between the intervention and usual care groups, including factors which may predict TTR. Secondary analysis was a comparison of knowledge scores between groups. Explanatory analyses considered factors which may predict the differences in TTR between groups, such as illness perceptions and beliefs about medication. Further analyses examined psychological morbidity of the two groups to ensure the intervention did not have an adverse effect on patients.

5 Results

5.1 Baseline demographic characteristics of the AF patients

There were 46 patients randomised to the intervention group, of which 3 crossed-over to the usual care arm, leaving 43 patients. Fifty two patients were randomised to usual care, but with the addition of the cross-over patients the group was eventually 55 patients. At baseline all of the intervention group patients completed the questionnaire follow-ups, three failed to complete all of the questionnaires in the usual care arm. The attrition rates from the questionnaire follow-ups increased over time, with the greatest attrition at the two month follow-up (see Table 5.1).

Table 5.1: Attrition rates from baseline to 6 month follow-up

	Baseline	1 month	2 months	6 months
Usual Care	52	40 (77%)	30 (57%)	32 (61%)
Intervention	43	32 (74%)	27 (63%)	29 (67%)

Data for the primary outcome (TTR) was collected for 38 patients in the intervention group (minus cross-over patients) and 52 patients in the usual care arm (plus cross-over patients).

5.1.1 Patient demography

The demographic characteristics of the patients in the intervention and usual care groups are summarised in Table 5.2. No significant differences were found between the intervention and usual care groups with regard to age, sex, socio-economic status, education level or ethnicity. The mean (SD) age of the total cohort was 72.9 (8.2) years. The majority (48.5%)

of the patients were aged between 65 and 74 years old, male (63.6%), White British, Irish or European (97%), with a median (IQR) of 10 (9.5 to 12) years in education. The median socio-economic status scores suggest a moderate level of deprivation; however, there were a large variation of scores within the cohort (IQR = 9.3 to 37.1).

5.1.2 Clinical Characteristics

Analysis of the baseline clinical characteristics (Table 5.3) found no significant differences between the intervention and usual care groups on any of the variables including body mass index (BMI), type of AF, duration of AF, and alcohol/tobacco consumption. The majority of patients were overweight, with a mean (SD) BMI of 28.4 (5.4). There were more paroxysmal AF patients (30.9%) overall than persistent and permanent AF patients, although there were no significant differences between groups. Most of the patients had only been recently diagnosed with AF (median 3.0 months; IQR 1.0-14.0). Both patient groups reported drinking fewer units of alcohol than the recommended weekly number (Median=4; IQR = 0 to 12); few patients were current smokers (4%), but nearly half (46.5%) of the total patient cohort were ex-smokers.

5.1.3 Stroke risk factors

There were no significant differences between patients in the intervention and usual care groups in their baseline stroke risk factors (Table 5.4). Both groups had a high proportion (65.7% of total cohort) of hypertensive patients. More patients in the usual care group were 75 or older (42.6%) than in the intervention group (30.2%), although this difference was not significant. The median $CHADS_2$ score for the total cohort was 2 (IQR 1-3), suggesting a

high risk of stroke among patients overall. More patients had suffered a previous TIA (10.1%) than a previous stroke (5.1%).

5.1.4 Current medication

There were no significant differences between the intervention and usual care groups in their baseline prescribed medication (Table 5.5). Only about one third of the patients were prescribed a beta blocker (36.4%), statin (34.3%), and/or diuretic (31.3%), with a slightly higher proportion receiving an angiotensin-converting enzyme inhibitor (ACE-I; 40.4%). Of note, few patients received antiplatelet therapy for stroke thromboprophylaxis prior to initiating warfarin.

5.1.5 Baseline psychological factors

Patients exhibited similar baseline levels of depression and anxiety in both groups (Table 5.6). However, the intervention group demonstrated a significantly worse baseline quality of life ($p=0.01$) than the usual care group. Anxiety scores were relatively high (in both groups) at baseline. All patients demonstrated good baseline knowledge scores, with patients answering more than half of the questions correctly.

Table 5.2: Patient baseline demographic characteristics

Demographic characteristics	All participants	Intervention	Usual Care	x^2	t	z	p-value
Age, years	72.9 (8.2)	72.5 (7.4)	73.2 (8.7)		0.43		0.67
Age, years				2.90			
<65	14(14.4)	5(11.6)	9(16.7)				0.25
65-74	47(48.5)	25(58.1)	22(40.7)				
≥75	36(37.1)	13(30.2)	23(42.6)				
Sex				0.21			
Males	63(63.6)	29(67.4)	34(63)				0.67
Females	34(34.3)	14(32.6)	20(37)				
Ethnicity				0.81			
White (British, Irish and European)‡	96 (97)	43(100)	53(98.1)				1.00
Years in education †	10 (9.5 to 12)	10 (10 to 12)	10 (9 to 12)			-0.41	0.82
Socio-economic status†	20.9 (9.3 to 37.1)	23.6 (9.7 to 37.9)	20.6 (8.4 to 34.7)			-0.59	0.61

‡ Only one patient in the study was not White British/Irish/European; Chi-squared, independent samples t-test, Mann-Whitney and Fishers exact tests used as appropriate; Mean (SD) or N (%) are reported where appropriate; † Median (IQR) is reported where data is not normally distributed.

Table 5.3: Patient baseline clinical characteristics

Clinical characteristics	All participants	Intervention	Usual Care	x^2	t	z	p-value
Body Mass Index (kg/m^2)	28.4 (5.4)	28.9 (5.6)	27.98(5.22)		-0.85		0.39
Type of AF				0.21			
PAF	30 (30.9)	12(31.6)	18(47.4)				0.26
Persistent	22 (22.6)	11(28.9)	11(28.9)				
Permanent	24 (24.7)	15(39.5)	9(23.7)				
Duration of known AF in months †	3.0 (1.0 to 14.0)	3.0 (1.0 to 24.0)	2.0 (1.0 to 9.75)			-0.47	0.52
Alcohol units per week †	4.0 (0 to 12)	4.0 (0 to 14)	3.5 (0 to 10)			-0.92	0.39
Current smoker	4 (4)	2 (4.7)	2 (3.8)	1.15			0.63
Ex smoker	46 (46.5)	23 (53.5)	23 (43.5)				
Non smoker	46 (46.5)	18 (41.9)	28 (42.8)				

Chi-squared, independent samples t-test, Mann-Whitney and Fishers exact tests used as appropriate.
Mean (SD) or N (%) is reported where appropriate; † Median (IQR) is reported where data is not normally distributed.

Table 5.4: Patient baseline stroke risk factors

Stroke risk factors N (%) †Median (IQR)		All participants	Intervention	Usual Care	x^2	z	p-value
C	Congestive Heart Disease/ LV dysfunction‡	17 (17.2)	9 (33.3)	8 (36.4)	0.05		1.00
H	Hypertension	65 (65.7)	33 (86.8)	32 (82.1)	0.33		0.39
A	Age ≥75	36 (37.1)	13 (30.2)	23 (42.6)	2.90		0.25
D	Diabetes mellitus	15 (15.2)	7 (18.9)	8 (21.1)	0.05		0.52
S_2	Stroke/TIA	5 (5.1)	1(2.6)	4 (10.3)	2.78[a]		0.35
		10 (10.1)	5(13.2)	5 (12.8)	0.01		1.00
	Total $CHADS_2$ score†	2 (1-3)	2 (1-2)	2 (1-3)		-0.89	0.29

LV = Left ventricular; TIA = transient ishaemic attack, Chi-squared or Mann Whitney-U tests were used where appropriate, [a]Fisher's exact tests used to calculate p-value.

Table 5.5: Patient baseline medication

Current medication n (%)	All participants	Intervention	Usual Care	x^2	p-value
Calcium channel blockers	23 (23.2)	9(21.4)	14(26.9)	0.38	0.63
Beta-blocker	36 (36.4)	20(47.6)	16(30.8)	2.79	0.14
Anti-platelet	11 (11.1)	6 (14)	5 (9.3)	0.49[a]	0.53
Angiotensin-converting-enzyme inhibitor	40 (40.4)	21(50)	19(36.5)	1.72	0.21
Statin	34 (34.3)	16(38.1)	18(34.6)	0.12	0.83
Digoxin	16 (16.2)	7(16.7)	9(17.3)	0.01	1.00
Diuretic	31 (31.3)	15(35.7)	16(30.8)	0.26	0.66

[a]Fisher's exact test used to calculate p-value, Chi squared test used were appropriate, n (%) reported.

Table 5.6: Patient baseline scores for psychological variables

Psychological factors	All participants	Intervention	Usual Care	t	z	p-value
Anxiety†	7.0 (3.0 to 10.0)	6.0 (3.8 to 9.0)	7.0 (3.0 to 10.7)		-0.28	0.76
Depression†	4.0 (2.0 to 8.0)	4.0 (2.0 to 7.0)	4.0 (2.0 to 8.0)		-0.07	0.97
Quality of life	45.9 (22.2)	39.7 (20.2)	50.9 (22.6)	-0.14		0.01
Knowledge	5.6 (2)	5.9 (1.8)	5.4(2.1)	-1.05		0.29

Independent t test and Mann-Whitney tests used as appropriate. Mean (SD) reported; † Median (IQR) is reported where data is not normally distributed.

5.2 Primary outcome analyses

5.2.1 Time within therapeutic range

Patients receiving the intervention spent significantly more time in therapeutic INR range than patients receiving usual care (78.5% vs. 66.7% respectively; t=-2.65; p=0.01, see Table 5.7 and Figure 5.1). Patients in the usual care group spent significantly more time with a sub-therapeutic INR (INR<2.0) than patients in the intervention group (23.1% vs. 13.3% respectively; t=2.51; p=0.01). There were no significant differences between the groups in the proportion of supra-therapeutic INRs. Both the intervention and usual care groups attended the anticoagulant clinic a similar number of times (mean number of visits 6.7 vs. 7.2 respectively; t=0.94; p=0.35).

Table 5.7: The proportion of time spent within therapeutic range stratified by treatment group.

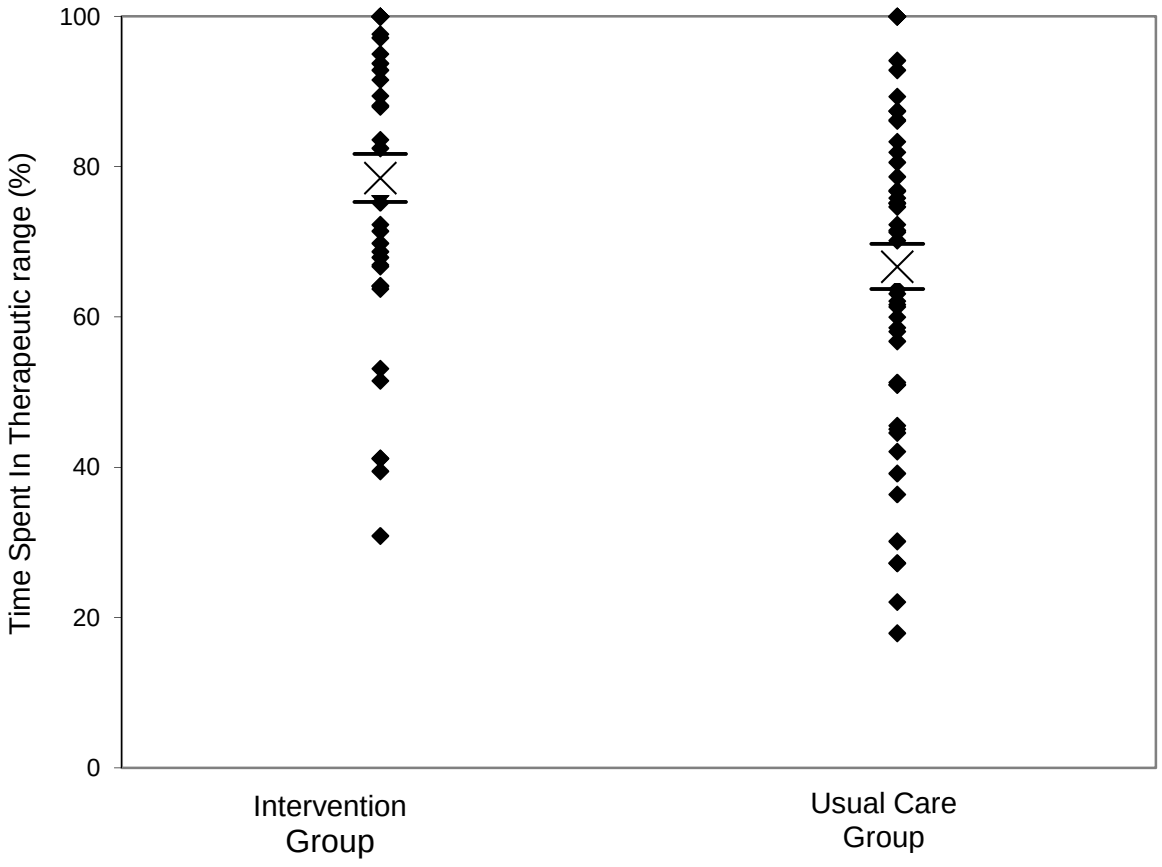
			On-treatment analysis		Intention-to-treat analysis	
Mean % (SE)	Intervention* (n=38)	Usual*Care (n=52)	t	p-value	t	p-value
TTR Overall	78.5 (3.2)	66.7 (3.0)	-2.65	0.01	-2.18	0.03
INR>3	10.2 (2.9)	13.2 (2.3)	0.82	0.42	0.98	0.33
INR<2	13.3 (2.2)	23.1 (2.9)	2.51	0.01	1.91	0.06
Number INR visits	6.7 (2.0)	7.2 (3.0)	0.94	0.35	0.28	0.83

INR = international normalised ratio, TTR = time in therapeutic range, *percentage of TTR is based on the on-treatment analysis

5.2.2 Predicting time in therapeutic range

To establish whether any of the key baseline demographics influenced the TTR, sex, age and education were included in a multiple regression model as predictors of TTR. Whilst TTR was slightly higher in women than in men (74.74% vs. 70.23% respectively; t=-0.93, p=0.37), differences were not significant. There were also no significant differences between age categories (<65, 65-74, ≥ 75 years; p=0.48), or years spent in education (p=0.31).

Figure 5.1: Graph illustrating mean TTR percentages for each patient, between groups.



5.3 Secondary outcome analyses

5.3.1 Knowledge

5.3.1.1 Knowledge of atrial fibrillation

There are no baseline differences between the intervention and usual care groups on any of the knowledge questions (Table 5.8). Baseline scores were high for both groups, with 90.7% of the intervention group and 82.7% of the usual care group aware of their primary diagnosis of AF. At one month more patients in the intervention group were aware that AF is a cardiac rhythm abnormality (96.9% vs. 82.9%; χ^2 3.58; $p<0.05$). At the one month follow-up the intervention group were significantly more aware of the risks of AF (i.e. predisposing to stroke and clots) than the usual care group (χ^2 9.30; $p<0.01$). However, there are no significant differences between groups for any of the other knowledge questions relating to AF.

5.3.1.2 Knowledge of oral anticoagulation

There were no baseline differences between groups in their knowledge of any of the questions relating to OAC (Table 5.9). However, at the one month follow-up there were significant differences between the intervention and usual care group's knowledge of risks associated with OAC. The majority (84.4%) of the intervention group were aware of the factors affecting INR compared to only about a third in the usual care group (36.7%). However, differences between groups were not significant. More patients in the intervention groups were aware of their target INR (87.5%), than in the usual care group (72.5%) at one month, but these differences were non-significant ($p=0.06$). At one month the majority of patients in the intervention group were aware of the bleeding risks associated with oral

anticoagulants (78.1%), compared to just over half of the patients in the usual care group (53.7%); the differences between groups were significant (χ^2 4.69; $p<0.05$). At six months the majority of patients in the intervention group were still aware of the risks associated with OAC (89.7%) compared to just over half of the usual care patients (56.3%); a difference that was significant (χ^2 8.44; $p<0.01$).

5.3.1.3 Total knowledge scores

Analysis of the total knowledge scores for both groups demonstrates that patients scored highly at baseline (Table 5.10), as they answered six out of nine questions correctly on average. Knowledge scores increased slightly in the intervention group over time, remaining at a median score of seven at all subsequent time points. Total knowledge scores for the usual care group remained the same from baseline to the two month follow-up (median = 6), increasing slightly to a median of seven at the six month follow-up.

Table 5.8: Patient perceptions of atrial fibrillation, at each time point, by group allocation

	Baseline			1 month			2 months			6 months		
	Intervention	Usual care	χ^2	Intervention	Usual care	χ^2	Intervention	Usual care	χ^2	Intervention	Usual care	χ^2
Patients awareness of primary diagnosis of AF												
Aware	39 (90.7)	43 (82.7)	1.27	31 (96.9)	37 (90.2)	1.23	26 (96.3)	30 (96.8)	0.01	29 (100)	29 (93.5)	na
Not aware	4 (9.3)	9 (17.3)		1 (3.1)	4 (9.8)		1 (3.7)	1 (3.2)		0 (0)	2 (6.5)	
Patients understanding that AF is a cardiac rhythm abnormality												
Aware	35 (83.3)	41 (78.8)	0.30	31 (96.9)	34 (82.9)	3.58*	26 (96.3)	29 (93.5)	0.22	27 (93.1)	25 (80.6)	2.01
Not aware	7 (16.7)	11 (21.2)		1 (3.1)	7 (17.1)		1 (3.7)	2 (6.5)		2 (6.9)	6 (19.4)	
Perception of the severity of AF												
Not serious	3 (7)	8 (14.8)	2.75	5 (15.6)	9 (14.6)	0.46	5 (18.5)	5 (16.1)	0.06	5 (17.2)	5 (15.6)	1.01
Serious	25 (58.1)	33 (61.1)		22 (68.8)	26 (63.4)		18 (66.7)	21 (67.7)		20 (69)	25 (78.1)	
Very serious	13 (30.2)	10 (18.5)		5 (15.6)	6 (14.6)		4 (14.8)	5 (16.1)		4 (13.8)	2 (6.3)	

Awareness of AF predisposing to stroke												
Aware	23	32	0.42	29	24	9.30**	23	22	1.01	22	17	2.42
	(56.1)	(62.7)		(90.6)	(58.5)		(82.1)	(71)		(75.9)	(56.7)	
Not aware	18	19		3	17		5	9		7	13	
	(43.9)	(37.3)		(9.4)	(41.5)		(17.9)	(29)		(24.1)	(43.3)	

*P<0.05; **p<0.01

Table 5.9: Patient perceptions of anticoagulation therapy between groups, at each time point

	Baseline			1 month			2 months			6 months		
	Intervention	Usual care	χ^2	Intervention	Usual care	χ^2	Intervention	Usual care	χ^2	Intervention	Usual care	χ^2
Awareness of anticoagulation therapy preventing blood clots												
Aware	39 (90.7)	42 (79.2)	1.07	28 (87.5)	36 (87.8)	0.002	24 (88.9)	27 (90)	089	26 (89.7)	29 (93.5)	0.29
Not aware	4 (9.3)	11 (20.8)		4 (12.5)	5 (12.2)		3 (11.1)	3 (10)		3 (10.3)	2 (6.5)	
Awareness that anticoagulation prevents stroke												
Aware	36 (83.7)	39 (75)	2.32	29 (90.6)	32 (78)	2.07	23 (85.2)	24 (77.4)	0.56	25 (86.2)	23 (74.2)	1.35
Not aware	7 (16.3)	13 (25)		3 (9.4)	9 (22)		4 (14.8)	7 (22.6)		4 (13.8)	8 (25.8)	
Aware of bleeding risks associated with anticoagulants												
Aware	30 (69.8)	30 (56.6)	1.75	25 (78.1)	22 (53.7)	4.69*	21 (77.8)	17 (54.8)	3.36‡	26 (89.7)	18 (56.3)	8.44**
Not aware	13 (30.2)	23 (43.4)		7 (21.9)	19 (46.3)		6 (22.2)	14 (45.2)		3 (10.3)	14 (43.8)	
Aware of target INR												
Aware	27	32	0.07	28	29	2.43	21	18	2.07	21	22	0.02

	(64.3)	(61.5)		(87.5)	(72.5)		(77.8)	(60)		(72.4)	(71)	
Not	15	20		4	11		6	12		8	9	
aware	(35.7)	(38.5)		(12.5)	(27.5)		(22.2)	(40)		(27.6)	(29)	
Aware of factors which may affect INR levels												
Aware	20	26	0.05	27	27	2.70	22	17	3.15	22	21	0.49
	(47.6)	(50)		(84.4)	(36.7)		(78.6)	(56.7)		(75.9)	(67.7)	
Not	22	26		5	13		6	13		7	10	
aware	(52.4)	(50)		(15.6)	(32.5)		(21.4)	(43.3)		(24.1)	(32.3)	

*P<0.05; **p<0.01; ‡ Differences almost reaching significance at p=0.06; Na= test value unavailable as there were limited cell counts

Table 5.10: Overall knowledge scores

Knowledge score Median (IQR)	Intervention	Usual care
Baseline	6 (5-7)	6 (4-7)
1 month	7 (7-8)	6 (5-8)
2 months	7 (6-8)	6 (5-8)
6 months	7 (6-7)	7 (4-7)

To determine whether there were any significant differences in knowledge across the follow-up time points between the intervention and usual care groups and in relation to age and sex, a two-factor mixed model ANOVA was carried out (Table 5.11). There were significant differences in knowledge within groups across time ($F(3, 47) = 6.4$; $p<0.01$). There were no significant differences between groups ($F(1, 47) = 3.3$; $p = 0.07$) and the interaction between knowledge and the treatment group was not significant ($F(3, 47) = 1.9$; $p=0.13$).

Table 5.11: Differences in knowledge between groups and across time

	F	df	p-value
Time	6.4	3	<0.01
Group	3.3	1	0.07
Time*group	1.9	3	0.13

5.3.1.4 Knowledge and time within therapeutic range

As the knowledge scores were not normally distributed, a Spearman's correlation coefficient was carried out to determine whether knowledge at baseline, one, two and six months predicted TTR across the follow-up period (Table 5.12). The findings suggest that patient knowledge at baseline, one and two month follow-ups do not predict TTR, whereas knowledge at the six month follow-up significantly predicts overall TTR (r=0.245; p=0.04).

Table 5.12: Knowledge as a predictor of time within therapeutic range

	Correlation coefficient	p-value
Baseline knowledge	0.105	0.17
1 month knowledge	-0.029	0.41
2 month knowledge	0.094	0.25
6 month knowledge	0.245	0.04

5.3.2 Explanatory outcome analyses

5.3.2.1 Illness Perceptions

At baseline 59 (61%) patients gave an answer for the perceived 'cause' of their illness, with most non-respondents stating that they did not know the cause. However, of those patients that named a possible cause at baseline (see Table 5.13), the majority of patients in the intervention and usual care groups thought there was a psychological cause (40.0% vs. 41.1% respectively). At the 1 month follow-up, more patients in both groups believed that there was an external cause of their AF (48.5% intervention group vs. 50.0% in the usual care group), although around a third still believed there was a psychological cause (33% in both groups). At the 2 and 6 month follow-ups, patients in the intervention group were more

likely to believe there was an external cause of their illness (i.e. age, other cardiac illness/surgery or hereditary disposition), compared to usual care patients who more often stated a psychological cause.

There were no significant differences between the groups in their perception of cause of AF at any time point, other than at the six month follow-up. The change in the perception of cause of AF appears to be due to the changing perceptions of the intervention group who were more likely to perceive the cause as external (73.9%) (e.g. age, hereditary or previous illness), whereas patients in the usual care group were more likely to perceive the cause of their AF as psychological (42.9%). Differences between groups at perception of cause at six months were significant (χ^2=6.31; p=0.04). IPQ scores between groups (see Table 5.14) suggest that; (1) patients in both groups view their illness as having a moderate affect on their life (consequences); (2) patients perceived their illness as long-term (timeline); (3) patients felt they had a moderate level of control over their illness (personal control), this increased slightly in both groups by the six month follow-up; (4) patients felt their treatment could have a 'helpful' impact on their illness in both groups, at all time points (treatment control); and (5) patients scored a moderate score for 'how much do you experience symptoms?' (Identity), suggesting that some patients maybe very symptomatic, whilst others are asymptomatic. Patients in the intervention group scored higher on illness coherence, lower on emotional representation (how much their illness affected them emotionally), and lower on illness concern than the usual care group. However, none of these differences were significant.

Mixed two-way ANOVAs were carried out to determine whether illness perceptions changed across time (within groups) and whether the group patients were assigned to (between groups) influenced illness perceptions. There were no significant differences within or

between groups on perceived consequences of AF, perception of the timeline of AF, personal control of illness, treatment control, illness identity, illness coherence or illness concern (Table 5.15). There were significant differences within groups emotional representation of illness (F (3, 49) = 3.3 (3, 49); p= 0.03) across time. However, there were no significant differences between groups.

5.3.2.1.1 Illness perceptions and time within therapeutic range

Separate multiple regression analyses were carried out entering all of the IPQ factors for a given time point, from baseline, month 1, 2, and 6. None of the models predicted TTR. However, at 1 month follow-up, there was a significant negative correlation between illness concern and TTR (r= -0.199; p=0.05). Thus the higher patients concern, the lower the TTR.

Table 5.13: Patients' perceived cause of atrial fibrillation

N (%)	Baseline		X^2	1 month		X^2	2 months		X^2	6 months		X^2
	Intervention (n=25)	Usual care (n=34)		Intervention (n=24)	Usual care (n=24)		Intervention (n=19)	Usual care (n=19)		Intervention (n=23)	Usual care (n=21)	
Psychological	10 (40.0)	14 (41.2)	1.38	8 (33.3)	8 (33.3)	0.15	3 (15.8)	9 (47.4)	4.47	3 (13.0)	9 (42.9)	6.31*
External	6 (24.0)	12 (35.3)		11 (45.8)	12 (50.0)		12 (63.2)	8 (42.1)		17 (73.9)	8 (38.1)	
Lifestyle	9 (36.0)	8 (23.5)		5 (20.8)	4 (16.7)		4 (21.1)	2 (10.5)		3 (!3.0)	4 (19.0)	

*P<0.05; psychological: includes answers relating to psychological morbidity including stress, anxiety, depression and bereavement; lifestyle: includes factors related to patients lifestyle habits such as smoking, excess drinking, obesity and excessive exercise; externals: includes factors that patients cannot control including hereditary disposition, following surgery or other chronic illness.

Table 5.14: Mean (SD) scores for IPQ factors from baseline to 6 month follow-up.

Mean (SD)	Baseline		1 month		2 months		6 months	
	Intervention	Usual care	Intervention	Usual care	Intervention	Usual care	Intervention	Usual care
Consequences	4.3 (2.3)	5.0 (2.5)	4.1 (2.6)	4.6 (2.7)	4.7 (2.8)	4.9 (2.4)	4.2 (2.8)	4.9 (2.5)
Timeline	8.8 (2.5)	9.2 (1.7)	8.8 (2.1)	8.2 (2.7)	8.8 (1.9)	8.8 (1.9)	8.6 (2.5)	8.5 (2.6)
Personal control	4.3 (3.1)	4.9 (3.1)	4.2 (2.9)	4.7 (2.6)	4.8 (2.8)	5.0 (2.7)	5.6 (2.9)	5.6 (2.9)
Treatment control	7.1 (2.3)	7.7 (2.3)	7.9 (1.9)	7.6 (1.7)	7.9 (1.6)	7.2 (1.8)	7.3 (1.9)	7.8 (2.1)
Identity	4.2 (2.7)	4.1 (2.9)	4.3 (3.0)	4.1 (2.7)	4.6 (2.8)	4.1 (2.6)	3.8 (2.8)	4.2 (3.1)
Coherence	6.0 (7.8)	5.9 (2.9)	6.2 (2.6)	5.7 (3.1)	7.1 (2.4)	5.9 (2.9)	7.2 (2.3)	6.1 (2.8)
Emotional representation	4.2 (2.7)	5.8 (3.3)	4.2 (2.9)	5.8 (3.3)	4.9 (3.0)	5.7 (3.1)	3.8 (2.9)	5.1 (3.1)
Illness concern	5.8 (3.1)	7.3 (3.1)	5.6 (3.1)	7.3 (2.9)	5.9 (2.9)	6.6 (3.1)	5.4 (3.1)	6.3 (3.1)

Scores range from 1 to 10 for each of the outcomes.

Table 5.15: Time and group differences in illness perceptions

	F	df	p-value
Time *(Consequences)*	0.9	3	0.46
Group (Consequences)	0.9	1	0.36
Time*Group	0.4	3	0.79
Time *(Timeline)*	1.7	3	0.19
Group (Timeline)	0.2	1	0.89
Time*Group	1.6	3	0.21
Time *(Personal control)*	1.7	3	0.18
Group (Personal control)	0.3	1	0.61
Time*Group	0.2	3	0.92
Time *(Treatment control)*	0.5	3	0.70
Group (*Treatment control*)	<0.01	1	0.99
Treatment control*Group	1.9	3	0.15
Time *(Identity)*	0.4	3	0.78
Group (*Identity*)	0.01	1	0.91
Time*Group	0.6	3	0.63
Time *(Coherence)*	0.8	3	0.51
Group (*Coherence*)	2.3	1	0.14
Time*Group	1.2	3	0.23
Time *(Illness concern)*	1.5	3	0.23
Group (*Illness concern*)	2.5	1	0.12
Time*group	1.9	3	0.14
Time *(Emotional representation)*	3.3	3	0.03
Group *(Emotional representation*)	2.8	1	0.10
Time*Group	0.7	3	0.57

5.3.2.2 Quality of life

Descriptive statistics (Table 5.16) indicate that patients in the intervention group scored lower at baseline on all subscales, suggesting worse QoL than in the usual care group. QoL increases in the intervention group at the one month follow-up. At subsequent follow-ups there are no significant differences in scores between groups. Large standard deviation scores suggest a large variation of scores in both groups.

Mixed two-way ANOVAs were carried out to determine whether there were differences in QoL between the intervention and usual care groups and across time (Table 5.17). Results suggest there are no significant differences between groups or within groups QoL. Thus group allocation does not affect QoL outcomes, and QoL did not change over time.

5.3.2.2.1 Changes in quality of life over time

Baseline QoL analyses suggest significant differences between the intervention and usual care groups (see Table 5.6). ANOVA analyses suggested no differences in QoL over time or between groups (Table 5.17), but these methods do exclude any patients that did not take part in all follow-ups. QoL change scores were subsequently calculated between each time point to determine whether there was a significant difference between intervention and usual care groups (Table 5.18). The psychological and global QoL scores in the intervention group and usual care group increased from baseline to one month. Physical QoL scores increased in the intervention group from baseline to one month, but they neither increased nor decreased in the usual care group. There was a significant difference between the intervention and usual care groups global quality of life scores improved significantly more than in the intervention group (9.7 vs. 3.5; $z = -2.4$; $p=0.01$) from baseline to one month.

Table 5.16: Mean (SD) scores for patient quality of life between groups, from baseline to 6 month follow-up

	Baseline (n = 97)		1 month (n = 72)		2 months (n = 55)		6 months (n =59)	
QoL Subscale	Intervention	Usual care	Intervention	Usual care	Intervention	Usual care	Intervention	Usual care
Physical	36.1 (26.4)	50.2 (27.3)	46.6 (26.2)	50.6 (29.9)	44.1 (25.9)	43.3 (25.2)	42.6 (20.9)	47.8 (26.9)
Psychological	39.5 (20.8)	50.6 (26.3)	53.5 (24.9)	50.5 (28.8)	51.9 (25.2)	46.4 (29.2)	53.6 (24.9)	50.5 (28.8)
Global	39.6 (20.2)	50.9.6 (22.6)	51.3 (21.8)	50.4 (24.8)	48.6 (21.8)	44.7 (23.3)	48.6 (21.8)	44.7 (23.3)

Table 5.17: Group and time differences in patient quality of life

	F	df	p-value
Time *(Physical QoL)*	0.97	3	0.40
Group (*Physical QoL*)	0.05	1	0.82
Time*Group	1.14	3	0.34
Time *(Psychological QoL)*	0.52	3	0.67
Group (*Psychological QoL)*	0.09	1	0.77
Time*Group	1.59	3	0.19
Time *(Global QoL)*	0.95	3	0.37
Group (*Global QoL*)	0.04	1	0.83
Time*Group	2.54	2	0.09

Table 5.18: Change in quality of life scores across time and by group

	BL to 1 month			BL to 2 months			BL to 6 months			1 to 2 months			2 to 6 months		
	Intervention	Usual care	z	Intervention	Usual care	z	Intervention	Usual care	z	Intervention	Usual care	z	Intervention	Usual care	z
Psychological	12.5 (-2.8 to 32.2)	7.1 (-10.7 to 14.3)	-1.8	3.5 (-3.6 to 32.1)	5.4 (-12.5 to 14.3)	-0.8	12.5 (-2.7 to 32.1)	7.1 (-10.7 to 14.3)	-1.8	-1.9 (-14.1 to 7.1)	-0.5 (-8 to 3.6)	-0.2	1.9 (-21.6 o 15.0)	0.5 (-7.1 to 14.3)	-0.2
Physical	6.7 (-4.7 to 14.8)	0 (-8.6 to 10.9)	-1.8	0 (-3.1 to 12.5)	-3.1 (-18.7 to 12.5)	-1.3	0 (-3.1 to 12.5)	3.1 (-13.3 to 10.9)	-0.5	0 (-7.0 to 3.9)	-9.4 (-15.6 to 9.4)	-1.2	1.6 (-12.5 to 3.3)	10.9 (-3.1 to 15.6)	-1.6
Global	9.7 (0.7 to 18.1)	3.5 (-6.6 to 9.7)	-2.4**	4.2 (-5.5 to 15.3)	-1.4 (-13.5 to 11.1)	-1.7	4.2 (-5.5 to 15.3)	-1.4 (-13.5 to 11.1)	-1.7	-0.7 (-9.7 to 4.5)	-3.5 (-10.8 to 2.4)	-0.5	0 (0 to 0)	0 (0 to 0)	1.0

BL = Baseline, QoL = quality of life; IQR = inter-quartile range, **p=0.01, Mann Whitney-U test was used to calculate p-value and z scores.

5.3.2.3 Beliefs about medication

Patients' beliefs about medication (Table 5.19) scores suggest that the usual care group scored higher on specific concerns about medication at all time-points than the intervention group. The usual care group also score higher on general harm scales at all time points. Whilst the mean score for perceived general harm drops in the intervention group after baseline, the score for this subscale increases in the usual care group. Scores on the specific necessity subscale are similar for both groups. The scores on the subscale 'general overuse' remain consistent across time in the intervention group, while perceived general overuse scores increase after baseline in the usual care group. Scores for the necessity-concerns differential are positive for both the usual care and the intervention group, thus patients beliefs in the necessity of taking medication are stronger than their concerns about adverse events. This differential is more apparent in the intervention group, who also score lower on specific concerns about their medications at all time points.

Several mixed two-way ANOVAs were carried out to determine whether patient group influenced beliefs about medication outcomes and further whether beliefs about medication changed across time. There was a significant difference between groups' perception of general harm of medication ($F(3, 51) = 2.16$; $p<0.01$). There was also a significant interaction between general harm scores across time and between groups ($F(3, 51) =1.85$; $p = 0.03$).

Table 5.19: Mean (SD) scores on beliefs about medication subscales from baseline to 6 month follow-up

Mean (SD) †Median (IQR)	Baseline		1 month		2 months		6 months	
	Intervention	Usual care	Intervention	Usual care	Intervention	Usual care	Intervention	Usual care
General Harm	8.1 (2.1)	9.1 (2.2)	8.3 (2.1)	10.1 (2.9)	8.5 (1.7)	10.2 (2.5)	7.9 (2.0)	10.3 (2.6)
General overuse	10.4 (3.0)	11.3 (2.9)	10.4 (3.7)	12.9 (2.9)	10.9 (3.4)	12.0 (2.9)	10.7 (3.5)	12.0 (2.6)
Specific necessity	18.3 (3.7)	18.7 (4.2)	18.7 (3.5)	18.4 (3.9)	18.9 (3.6)	18.8 (3.4)	19.1 (3.2)	18.8 (4.1)
Specific concern	14.0 (3.7)	16.6 (4.2)	13.2 (3.4)	15.3 (2.3)	13.5 (3.5)	14.8 (4.6)	13.0 (3.9)	15.8 (5.3)
Necessity-concerns differential†	4.0 (1.0 to 8.0)	3.0 (-1.0 to 5.5)	5.0 (2.0 to 8.0)	2.5 (0.25 to 6.0)	5.0 (1.0 to 10.0)	3.0 (0 to 7.0)	5.0 (1.5 to 9.5)	3.0 (-1.0 to 5.75)

Table 5.20: Group and time differences in perceived general harm

	f	df	sign
Time	2.55	3	0.06
Group	10.53	1	0.002
Time*Group	1.85	3	0.03

There were no significant changes across time in perception of general overuse of medication (Table 5.21). However, differences between groups' perceptions were nearly significant (F (3, 50) = 2.65; p=0.06), as was the interaction between time and group (F (3, 50) = 2.14; p = 0.11).

Table 5.21: Group and time differences in perceived general overuse

	f	df	sign
Time	1.98	3	0.13
Group	3.53	1	0.06
Time*Group	2.14	3	0.11

There were no significant differences between groups or across time in perceptions of the specific necessity of treatment for AF (Table 5.22).

Table 5.22: Group and time differences in specific necessity

	f	df	sign
Time	0.64	3	0.59
Group	0.003	1	0.96
Time*Group	0.39	3	0.76

There were significant differences between groups' perception of their specific concerns related to their current medication (F (1, 51) =5.84; p=0.01; Table 5.23). However, there were no significant differences across time and the interaction between time and group factors were not significant.

Table 5.23: Group and time differences in specific concerns about medication

	F	df	p-value
Time	2.19	3	0.11
Group	5.84	1	0.01
Time*Group	0.85	3	0.44

There were significant differences across time (F (3, 51) = 2.87; p=0.04) and between groups (F (1, 51) = 4.09; p=0.04) in the differential between perceived medication necessity and perceived medication concerns (Table 5.24). However, the interaction between time and group factors was not significant.

Table 5.24: Group and time differences in necessity-concern differential

	F	df	p-value
Time	2.87	3	0.04
Group	4.09	1	0.04
Time*Group	6.19	3	0.57

5.3.2.3.1 Beliefs about medication and time within therapeutic range

When entering all scores for BMQ subscales, General Harm scores at 1 month were the only scores that predicted TTR ($F(1,72)= 4.08$; $p=0.048$). The Pearson's r correlation suggests a negative correlation ($r=-0.241$; $p= 0.021$) suggesting that as perceived general harm scores increase, TTR decreased.

Spearman's correlation coefficient was used to determine whether the necessity concern differential at each time-point correlated with TTR (Table 5.25). Baseline differential scores significantly correlated with TTR at six months ($r=0.217$; $p=0.04$). The correlation was positive suggesting patients with lower scores on specific concern and higher scores on specific necessity (thus higher differential scores) also spent more time in the therapeutic range.

Table 5.25: Correlations between necessity-concerns differential scores and 6 month TTR

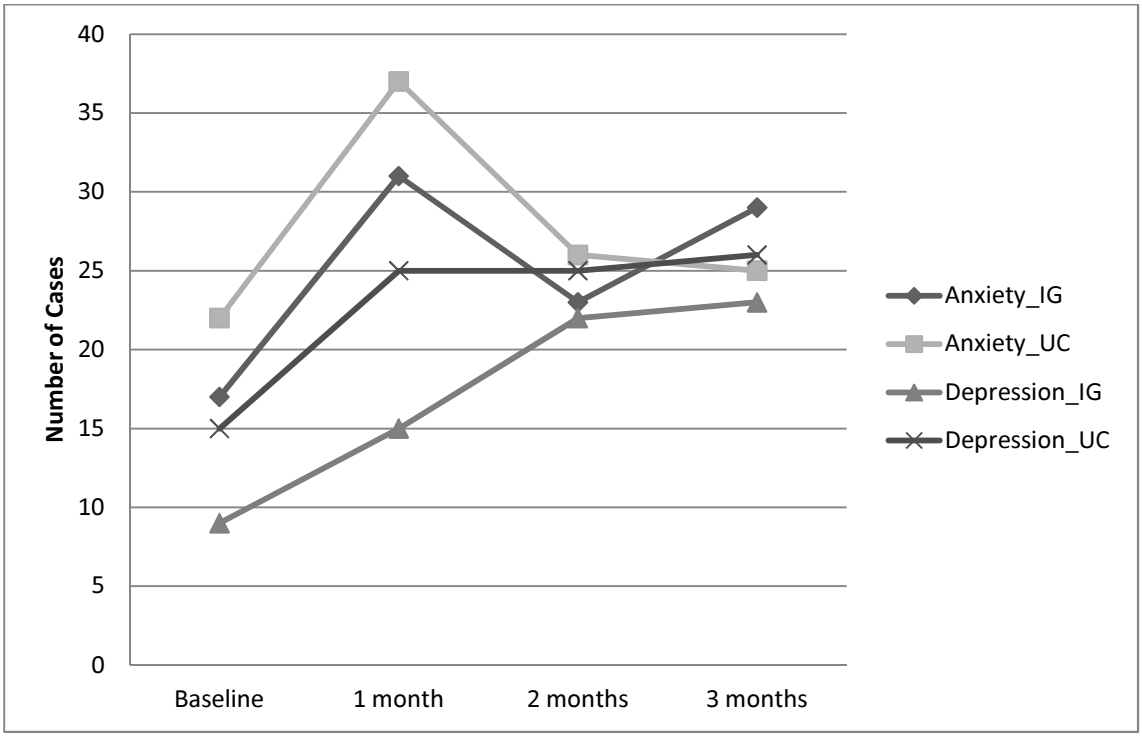
	Correlation coefficient	p-value
Baseline	0.217	0.04
1 month	0.202	0.09
2 months	0.129	0.35
6 months	0.090	0.51

5.3.3 Anxiety and Depression

At baseline, median anxiety scores for the total cohort were just below the cut-off for clinical significance (≥ score of 8; Table 5.26). At subsequent follow-ups anxiety scores in both

groups increased significantly, indicating that patients are highly anxious (>10). A similar pattern was exhibited with regard to depression scores. Whilst at baseline patients have lower scores (median (IQR) 4.9 (2-8), these scores increased significantly at each follow-up above the clinical cut-off (score ≥8) suggesting over half of the patients in both groups were depressed (See Figure 5.2). The prevalence of depression cases doubled from baseline to one month (25.5% to 55.6%), as did the prevalence of anxiety (41.5% to 95.4%).

Figure 5.2: Number of anxiety and depression cases over time by treatment group



A case of anxiety or depression was determined by a patient scoring ≥8 on the subscales of the HADS questionnaire.

A mixed model two-way ANOVA was used to determine whether there were differences in anxiety between intervention and usual care groups and across time. A conservative p-value (Greenhouse-Geisser) was adopted as the assumptions of the test were violated. There were significant changes in anxiety scores across time ($F(3, 46) = 25.2$; $p<0.01$; Table

5.26), but there were no significant differences in anxiety scores between the intervention and usual care groups (F (1, 46) = 0.57; p = 0.45).

Table 5.26: Anxiety and depression during first 6-month

	Baseline		1 month		2 months		6 months	
	Intervention	Usual care	Intervention	Usual care	Intervention	Usual care	Intervention	Usual care
Anxiety cases (HADS-A score ≥8)	17 (40.5)	22 (42.3)	31 (96.9)	37 (92.5)	23 (92.0)	26 (89.7)	29 (100)	25 (89.3)
Anxiety Score†	6 (3.7-9)	7.0 (3-10.7)	13 (11-13.7)	12 (10-14)	12 (10-14)	12 (9-14)	12 (11-14)	12 (10-13.7)
Depression cases (HADS-D score ≥8)	9 (21.4)	15 (28.8)	15 (46.9)	25 (62.5)	22 (88.0)	25 (86.2)	23 (79.3)	26 (92.9)
Depression score†	4 (2-7)	4 (2-8)	7 (5-9)	8 (7-9)	8 (8-9)	9 (8-10)	9 (8-9)	9 (8-10)

HADS-A = anxiety; HADS-D = depression; †Median (IQR) or n (%) reported

Table 5.27: Differences in anxiety scores across time and between groups

	F	df	p-value
Time	25.2	3	<0.01
Group	0.57	1	0.45
Time*Group	27.4	3	0.09

Friedman's ANOVA was carried out to determine whether there were significant differences in anxiety across time for the total patient cohort. This test was chosen as the data violates

the assumptions of the repeated-measures ANOVA, as it is not normally distributed. Results suggest that there were significant differences in the anxiety scores across the different time points (χ^2 = 26.49; p<0.001; Table 5.28). Patients exhibited the highest anxiety levels at 6 months and the lowest anxiety at baseline.

Table 5.28: Anxiety changes across time for the total cohort

	Mean rank	Chi square	p-value
Baseline	1.71	26.49	<0.001
1 month	2.76		
2 month	2.63		
6 month	2.90		

A mixed model two-way ANOVA was used to determine whether there were differences in depression between intervention and usual care groups and across time (Table 5.29). A conservative p-value (Greenhouse-Geisser) was adopted as the assumptions of the test were violated. There were significant changes in depression scores across time (F (3, 46) = 37.7; p<0.01), but there were no significant differences in depression between groups (F (3, 46) = 0.69; p = 0.55).

Table 5.29: Differences in depression scores across time and between groups

	F	df	p-value
Time	37.7	3	<0.01
Group	0.69	3	0.55
Time*Group	2.54	1	0.12

Friedman's ANOVA was also carried out to determined whether there were any significant differences within groups' depression across time in the total patient cohort (Table 5.30). Results suggest that there were significant differences in depression across time (r=50.65; p<0.001). Patients' depression scores got progressively worse over time, exhibiting the lowest levels at baseline and the highest at six months.

Table 5.30: Depression changes across time

	Mean rank	Chi square	p-value
Baseline	1.50	50.65	<0.001
1 month	2.41		
2 month	2.88		
6 month	3.21		

5.3.4 Adverse events

Observations of adverse events in both groups suggest more events occurred in the usual care group (total events = 8); including three ischaemic (non-fatal) strokes, three episodes of bleeding (one major and two minor) and one death (not cardiac related) versus one event (peripheral embolism) in the intervention group.

5.4 Overall study model

Factors that had been found to be significantly associated with TTR in the exploratory analyses were entered into a linear regression model (backwards entry). These factors included six month follow-up knowledge scores, the assigned group (usual care and intervention), one month follow-up scores for general harm and illness concerns and

baseline scores for the necessity-concerns differential. One factor remained in the model as a significant predictor of TTR, group assignment was a significant predictor (t=2.0, SE= 5.8, p=0.05).

6 Discussion

6.1 Discussion of the key findings

6.1.1 Time within therapeutic range

The primary outcome for the TREAT study was time spent within therapeutic INR range (TTR), a measure which is sensitive to whether patients adhere to treatment recommendations. There was a statistically significant difference between the intervention and usual care group (78.5% vs. 66.7% respectively; p=0.01); suggesting greater adherence to medication and lifestyle recommendations in those patients receiving the intervention (see results Section 5.2.1). TTR is an objective measure (utilising blood samples to calculate INR), therefore, these results are a reliable indicator of differences in levels of adherence, in contrast with subjective self-report studies. By increasing the provision of information required to formulate accurate beliefs and perceptions surrounding AF and warfarin, patients may be more able and willing to adhere, in the long-term, to treatment recommendations. The clinical implications of this finding are important as the effectiveness of treatment, including warfarin, is often undermined by low levels of adherence (Sabate, 2003; Wan, et al., 2008; Gladstone, et al., 2009); and maintaining the therapeutic range of 2.0 to 3.0 is imperative for stroke risk reduction (Singer, et al., 2009; Hylek, Evans-Molina, Shea, Henault, & Regan, 2007) and to reduce the risk of treatment-associated bleeding complications.

Findings from the ACTIVE-W trial suggested that where TTR values ≤ 58%, one cannot expect any net benefit (i.e. stroke risk reduction, from being on oral anticoagulation (OAC)), and that a TTR ≥65% is critical to achieve clinical benefit

(Connolly, et al., 2008). Thus, the mean TTR for both groups in the TREAT study were relatively good, perhaps an indication of improvements made to usual care education procedure (e.g. a recently introduced mandatory education checklist). However, another study, using record-linkage data from hospitalised inpatients, suggested warfarin treatment offered no or limited clinical benefit (reduced stroke and mortality) unless a patient could maintain their therapeutic range for more than 71% of the time (Morgan, McEwan, Tukiendorf, Robinson, Clemens, & Plumb, 2009). Thus, the use of a theory-driven intervention could help to ensure that patients starting warfarin would benefit from 'good' INR control.

The number of visits in both the intervention and usual care groups were comparable in the TREAT study (6.7 vs. 7.2, respectively), with very little variation. This suggests that the intervention improved INR control without requiring additional resources from OAC clinics (i.e. an increased number of visits). At the individual level fewer visits to OAC clinics has also been associated with better INR control, perhaps because only those patients with unstable INR results are reviewed more frequently (Smith, Lip, & Lane, 2011)

The usual care group spent significantly more time with sub-therapeutic (<2.0) INRs (23.1% vs. 13.3%; p= 0.01), thereby increasing their risk of ischaemic stroke (Morgan, McEwan, Tukiendorf, Robinson, Clemens, & Plumb, 2009; Gladstone, et al., 2009). Patients in both the intervention and usual care groups spent less time with a supra-therapeutic INR (INR >3.0) (10.2% vs. 13.2% respectively); however, any time spent with an INR >3.0 increases the risk of bleeding events (Hylek, Evans-Molina, Shea, Henault, & Regan, 2007). It is important that patients are aware of factors which affect INR control, such as how many units of alcohol are safe to drink per day, which foods are high in vitamin K, what to do if they miss a dose of warfarin

and which medications can impact on warfarin metabolism. When equipped with this information, patients have the potential to make informed decisions about their own treatment adherence. Previous research has demonstrated that a brief educational intervention (the precursor/pilot to the present study) covering these topics can significantly improve knowledge of factors influencing INR control (Lane, Ponsford, Shelley, Sirpal, & Lip, 2006). Physicians also need to ensure they are using appropriate risk stratification guidelines (Fang M. C., et al., 2011; ESC, 2010; Kirchhof, et al., 2011), to ensure that where the risk of bleeding significantly outweighs the level of risk reduction provided by OAC, patients are considered for an alternative treatment and that discussion of a patient's treatment preferences are considered in clinical-decision making.

6.1.2 Patient knowledge

The TREAT study results suggest there were significant changes in patients' knowledge of OAC and AF across time ($F(3, 47) = 6.4$; $p<0.01$). However, there were no significant differences between the intervention and usual care group ($F(1, 47) = 3.3$; $p = 0.07$). Both groups scored highly on knowledge questions at baseline, thus any differences between groups on follow-up were small (see results Section 5.3.1). The high baseline knowledge scores could stem from recent improvements made to the usual care hospital procedure, such as an educational check list received by both groups prior to their baseline assessment.

Subsidiary analysis of the relationship between knowledge and TTR suggests that knowledge could play a role in patient adherence. At baseline, one and two month follow-ups knowledge did not predict TTR, whereas their knowledge score at six months did ($p=0.04$). This indicates that where patients' knowledge regarding their

illness and their treatment is sustained, patients are more likely to remain within target therapeutic range. The relationship between knowledge and adherence is unclear; however, it is possible that improving patient knowledge could reduce intentional and unintentional non-adherence (Horne, Weinman, Barber, Elliot, & Morgan, 2005). Non-adherence is intentional when patients make a decision not to take their treatment as a result of their personal motivations or beliefs. Where these beliefs are inaccurate, or they perceive the barriers as too great, they are unlikely to adhere. Equally, improved knowledge of specific questions (e.g. 'what should I do if I miss a dose of warfarin?') could reduce unintentional non-adherence; which refers to an individual's skills or ability to take their medications (e.g. problems with remembering to take tablets). Evidence suggests that patients often report either or both types of non-adherence, with occasional overlap between the two concepts (e.g. where patients perceive medications as being unnecessary, they maybe more likely to forget to take it) (Horne, 2001; Horne, Weinman, Barber, Elliot, & Morgan, 2005).

Previous studies have also highlighted the link between knowledge and INR control (Tang, Lai, Lee, Wong, Cheng, & Chan, 2003; Khan, Kamali, Kesteven, Avery, & Wynne, 2004). One prospective study examined knowledge and INR control in a mixed indication Chinese cohort (n=122), taking warfarin for varying lengths of time (mean months = 43.1±39.8). Tang and colleagues provided brief counselling and an educational booklet, and focussed on factors that affect INR control, including drug interactions, alcohol and dietary advice. They found poor baseline knowledge with an overall score of 0.48±0.18 (maximum score = 1.0), and, similarly to the present study, there was a positive correlation between patients' knowledge of warfarin treatment and the number of INR values within range (r 0.20; p=0.024) (Tang, Lai, Lee, Wong, Cheng, & Chan, 2003). However, they also found an inverse relationship between age and knowledge score of the patient (r -0.43; p<0.001) and a positive association

between duration of warfarin treatment and knowledge (r 0.18; p=0.044). The TREAT findings do not support the relationship between age and knowledge, and as patients were new to warfarin, the relationship between duration of treatment and knowledge was not explored. Thus, it is difficult to compare these results for several reasons including the use of a non-trial design, a mixed indication cohort, and patients with varying durations of treatment; all factors that may influence the outcomes. However, findings do indicate that improving knowledge has a significant benefit on therapeutic outcomes; highlighting the impact of educating patients about the potential risks associated with their treatment.

The systematic review (Chapter 2) found that the provision of an educational intervention improved TTR when compared to usual care and self monitoring (Khan, Kamali, Kesteven, Avery, & Wynne, 2004; Gadisseur, Kaptein, Breukink-Engbers, van Der Meer, & Rosendaal, 2004). Two of the trials included a comparison between education only groups and usual care (Khan, Kamali, Kesteven, Avery, & Wynne, 2004; Gadisseur, Kaptein, Breukink-Engbers, van Der Meer, & Rosendaal, 2004). Both of these studies provided similar interventions to TREAT by including educational materials, and a group training session. Khan and colleagues recruited AF patients and found TTR in the education group increased from a mean 61.1 ±15.1 during the six months prior, to 70.4 ±24.5 during the six months after the study began (mean difference 8.8, 95% CI: -0.2-7.8, p=0.054) (Khan, Kamali, Kesteven, Avery, & Wynne, 2004). Gadisseur and colleagues provided unpublished data on the AF patients in the trial and found, following the intervention, TTR in the education group was 75% (95% CI: 66.19-83.80) compared with 67.1% (95% CI: 59.18-74.98) in the usual care alone group and 70.32% (95% CI: 55.33-85.31) in the self-monitoring plus education group (Gadisseur, Kaptein, Breukink-Engbers, van Der Meer, & Rosendaal, 2004). TTR in the TREAT intervention group is comparable with these

two trials; however, the intervention differs substantially, with the inclusion of theory-driven components. Furthermore, the TREAT trial recruited patients who were newly-prescribed OAC, rather than those patients who had prior experience of warfarin, as duration is known to have an impact on knowledge and potentially INR control (Tang, Lai, Lee, Wong, Cheng, & Chan, 2003). Thus TREAT highlights the benefits of intervening at the commencement of OAC, when patients are initially adapting to the integration of the warfarin regime.

Between groups analysis of specific knowledge questions suggests that patients in the intervention group were more aware of risk information pertaining to bleeding (associated with OAC) and clot or stroke (associated with AF) (see Section 5.3.1). Patients' perception of risk can have an important influence on their adherence, and furthermore their decision to initiate warfarin (Protheroe, Fahey, Montgomery, & Peters, 2000; Howitt & Armstrong, 1999; Man-Son-Hing, et al., 1999; McAlister, et al., 2005; Devereaux, Anderson, Gardner, Putnam, & Flowerdew, 2001; Fuller, Dudley, & Blacktop, 2004; Thomson, et al., 2007). Previous qualitative evidence suggests that patients who decided not to take warfarin do not see themselves at high risk of stroke (Howitt & Armstrong, 1999). Further evidence suggests that provision of a decision aid (including risk information) reduces the number of patients prepared to take warfarin (Fuller, Dudley, & Blacktop, 2004). The impact of increased knowledge of risk in the intervention group could therefore play an important role in treatment adherence; enhancing patients' understanding of the link between AF and stroke, and hence the need for adherence. Behavioural change techniques, such as social comparison, may have aided the process of increased risk awareness. Patient narratives on the intervention DVD discuss risks associated with AF and treatment, and provide a clear link between health and behaviour. Risk information was also presented as pie charts, in addition to stroke algorithms (i.e. $CHADS_2$), whereby

patients calculated their own risk of stroke. The intervention highlights the importance of giving patients adequate information to make informed decisions; this allows them to 'trade-off' the risk of stroke with the risk of bleeding and justify their lifestyle changes, a concept which has been highlighted by previous decision aid studies (McAlister, et al., 2005; Man-Son-Hing, et al., 1999).

Many patients do not view AF as a 'high risk' condition, despite its association with stroke. A previous study carried out by our research group found that only half of the patients considered AF a serious condition, and only 9% considered it a 'very serious' condition (Lane, Ponsford, Shelley, Sirpal, & Lip, 2006; Nadar, Begum, Kaur, Sandhu, & Lip, 2003; Lip, Kamath, Jafri, Mohammed, & Bareford, 2002). The results of the TREAT study suggest that more patients perceive AF as 'serious or very serious', than previously found; at baseline 61% of the usual care patients and 58% of the intervention group viewed AF as a 'serious condition', a further 18.5% vs. 30% respectively, viewed their condition as 'very serious'. This may explain why TTR is high in both groups, as where patients view their condition as serious; they may place more value on the treatment that is required for risk reduction. Since Lane and colleagues published the pilot study (Lane, Ponsford, Shelley, Sirpal, & Lip, 2006) there have been more initiatives focussing on the role of education locally, which may explain this change in perception (such as the use of an education checklist).

The communication of risk information is important. Several decision aid trials have proposed new ways of communicating OAC risk with patients (Man-Son-Hing, et al., 1999; Thomson, et al., 2007; McAlister, et al., 2005), and those measuring the impact on INR control have found significant benefits (McAlister, et al., 2005). The communication of risk within the TREAT intervention included the provision of information regarding risk of stroke and potential risks of bleeding, avoiding either

‘positive’ or ‘negative’ framing of the treatment. It is possible that by allowing patients to formulate their own decision to take a treatment, based on the risk information available, that they maybe more satisfied with their decision; indeed one study found that patients’ judgement of the minimal level of benefit for which they would take warfarin (versus aspirin), predicted those patients who were prepared to start taking it (Howitt & Armstrong, 1999).

6.1.3 Beliefs about medication

There is a dearth of trialled theory-based interventions, despite the overwhelming evidence and guidelines to support their use (Horne, Weinman, Barber, Elliot, & Morgan, 2005; MRC, 2000; NICE, 2007). For example, previous evidence has highlighted the link between patients’ beliefs about their medication and adherence (see Section 3.1.1 for a full discussion). By targeting those beliefs, and potentially improving adherence to medication, we may subsequently improve clinical outcomes.

Where patients view their medication as harmful, they are less likely to adhere (Clifford, Barber, & Horne, 2008; Menckeburg, et al., 2008; Horne, Weinman, Barber, Elliot, & Morgan, 2005). This has been related to perceived ‘toxicity’ of medications, and patients’ views surrounding the impact of side effects in the long- and short- term (Horne, Weinman, Barber, Elliot, & Morgan, 2005). Indeed, the present study found significant differences between the intervention and usual care group in their perception of medication harm in general ($F(3, 51) = 2.16$; $p<0.01$) and a significant interaction between general harm scores across time and between groups ($F(3, 51) =1.85$; $p = 0.03$). The usual care group perceived medication as more harmful than the intervention group at all time points. At the one month follow-up, patient scores for the general harm subscale predicted the amount of time patients spent within

therapeutic range (p=0.04). It seems an obvious assumption that perceiving medications as harmful represents a barrier to adherence, and yet this is rarely considered in intervention design. Patients must undergo a personal risk evaluation when choosing to start a new medication, perhaps taking into consideration potential side effects (i.e. bleeding and bruising), perceived toxicity/potency of medication (Horne, Weinman, Barber, Elliot, & Morgan, 2005) and risk reduction associated with warfarin. This procedure is reliant on their ability to balance the risks associated with their treatment with those associated with their condition (i.e. stroke risks associated with AF vs. bleeding risks associated with warfarin).

Many AF patients may have preconceived ideas about how harmful warfarin is; for example patients are more willing to take warfarin when they are blinded to the name of the treatment (Holbrook, Labiris, Goldsmith, Ota, Harb, & Sebalt, 2007; Fuller, Dudley, & Blacktop, 2004), highlighting the negative connotations this treatment has. It is important that patients do not rely on inaccurate perceptions of harm, and that their risk evaluation draws upon reliable knowledge. The TREAT findings suggest that by reducing patients' perception of harm, it may be possible to increase adherence levels. This was achieved by discussing patient barriers within the intervention session; including inaccurate perceptions. 'Expert' patient narratives discussed their own experiences of bleeding and bruising, and the intervention group were able to assimilate this risk information into their own belief system.

The intervention group scored lower on perceived over-prescription and overuse of medication by health care professionals at all time points (including baseline); these differences were greater following the intervention, but there were no significant differences between groups. Previous cross-sectional (n=321) evidence has suggested our general beliefs about medication remain stable over time, including

our general beliefs about whether medicines are over-used or over-prescribed (Porteous, Francis, Bond, & Hannaford, 2010). This may explain why there were no significant changes post-intervention. However, it is also possible that experiencing a new treatment regime, and receiving an appropriate intervention, could change perceptions, as evidenced by the fluctuating perception of general harm across time in this study. An assessment of patients' general beliefs about medication can prove useful, even if we are unable to target them within a behavioural intervention; as where patients perceive medications as overused and even harmful, they may be less likely to adhere (Horne, Weinman, Barber, Elliot, & Morgan, 2005).

There were no significant differences between groups or across time in their perception of the specific necessity for the medications for AF. Both groups scored highly on this subscale at all time-points, suggesting that all patients within the trial view their medication for AF as highly necessary. Previous research has found that those patients scoring higher on the necessity sub-scale are more likely to adhere to treatment recommendations (Horne, Weinmann, & Hankins, 1999; Menckeburg, et al., 2008; Bane, Hughes, & McElnay, 2006; Horne, Weinman, Barber, Elliot, & Morgan, 2005). Data from one cross-sectional study, found significant associations between specific necessity scores and both self-reported adherence and prescription refill adherence for the previous 12-months (Menckeburg, et al., 2008). Whilst this was a retrospective study and with a younger sample (18-45 year old asthmatics), it does highlight the link between patients' beliefs about medication and their adherence levels. Similarly, a cohort of patients attending a cardiac outpatient clinic (n=122), were more likely to adhere to treatment where they scored highly on the specific necessity subscale (Bane, Hughes, & McElnay, 2006). Although specific necessity did not predict TTR in the TREAT study, it may have influenced whether patients adhered to behavioural recommendations; as there was no inclusion of a

self-reported adherence measure, which has been significantly associated with perceived necessity for numerous conditions (Horne, Weinmann, & Hankins, 1999).

There were significant differences between the intervention and usual care groups perception of specific concern about their AF medications ($F(1, 51) = 5.84$; $p=0.01$). Patients in the intervention group were less concerned about their medication at all time points; with no significant changes across time. Previous evidence suggests that those patients scoring higher on the specific concern subscale are less likely to adhere to medication (Horne, Weinmann, & Hankins, 1999; Menckeburg, et al., 2008; Neame & Hammond, 2005). This could provide some explanation as to why the intervention group spent more time in therapeutic range, although results do not suggest a causal link between specific concerns and TTR.

Using the sub-scales of the beliefs about medication questionnaire, it is possible to calculate a necessity-concerns differential score. This represents the difference between patients' concerns about their AF medication and their perception of its necessity; and there were significant differences across time ($F(3, 51) = 2.87$; $p=0.04$) and between groups ($F(1, 51) = 4.09$; $p=0.04$) on this measure. The intervention group scored higher, suggesting patients perceived the necessity for warfarin as more important than their concerns about taking it. Baseline differential scores significantly correlated with TTR at six months ($p=0.04$), suggesting those patients with lower scores on specific concern, and higher scores on specific necessity (thus higher differential scores), also spent more time in therapeutic range. This supports previous evidence with depressed patients taking selective serotonin reuptake inhibitors; whereby high necessity and low concern scores surrounding their anti-depressants were associated with greater self-reported adherence (Aikens, Nease, Nau, Klinkman, & Schwenk, 2005).

In both the intervention group and the usual care group, the median differential score was positive at all time points. This suggests that all patients regarded the necessity of their treatment to outweigh the concerns or costs of the regime, supporting evidence from a cross-sectional study with cardiac clinic patients, where 94.5% of patients scored highly on the necessity of medication sub-scale (Bane, Hughes, & McElnay, 2006). Evidently AF patients view the reduction of stroke risk, and subsequently the need for treatment, as more important than the potential bleeding risks associated with warfarin. This also supports qualitative evidence surrounding patients' perceptions of warfarin and their willingness to accept bleeding risks in order to reduce their risks of suffering from a stroke (Fuller, Dudley, & Blacktop, 2004). Thus, AF patients' perception of risk is extremely important, as those patients who understand the necessity of the warfarin regime are more likely to adhere.

6.1.4 Quality of life

At baseline the intervention group had significantly poorer quality of life (QoL) than those receiving usual care, although these differences were not apparent at subsequent time points (see results section 5.3.2.2.1). However, due to attrition rates at the two and six month follow-ups, the analyses of variance only included those patients who took part at each time point. Therefore the findings may not be representative of those patients who did not complete the questionnaire at each time point. Subsidiary analyses of the change in QoL from baseline to the one month follow-up suggest significant differences in the global QoL subscale between groups ($p=0.01$). Global QoL (an inclusive measure of psychological and physical quality of life) increased in both groups following baseline; therefore this increase was significantly greater in the intervention group. When compared to healthy controls,

patients with coronary heart disease or the general population (Thrall, Lane, Carroll, & Lip, 2006; Howes, Reid, Brandt, Ruo, Yerkey, & Prasad, 2001; Dorian, Jung, & Newman, 2000), QoL is substantially impaired in AF; patients score poorest on general health, vitality, physical, social and emotional role functions (Carlsson, Miketic, Windeler, Cuneo, Haun, & Micus, 2003; Gronefield, Lilienthal, Kuck, & Hohnloser, 2003; Hagens, Ranchor, Van Sonderen, Bosker, Kamp, & Tijssen, 2004; Thrall, Lane, Carroll, & Lip, 2006). As many AF patients are highly symptomatic (ESC, 2010) symptom relief can improve reported quality of life (Thrall, Lip, Carroll, & Lane, 2007; Smith, Lip, & Lane, 2010). However, where the burden is psychological or stemming from other factors, such as the warfarin treatment regime, improving QoL may be more difficult.

Few studies have examined how quality of life changes over time, following diagnosis and/or treatment onset. The TREAT results suggest that both groups appear to have a relatively stable QoL score across time, with similar physical and psychological burden. As the majority of patients are older (≥65 years), at moderate to high risk of stroke ($CHADS_2$ score 3), with numerous co-morbidities (e.g. diabetes, hypertension, chronic obstructive pulmonary disease), they may also be dealing with the treatment and symptom burden of other conditions or older age; and it may be difficult to determine specific causal factors. One study examining psychological morbidity in 'lone' AF ('lone' signifying the absence of other cardiac morbidity and predisposing factors) found no significant differences in QoL between AF patients and mean population norms (Lane, Langman, Lip, & Nouwen, 2009); therefore, perhaps the psychological morbidity exhibited in AF is largely determined by the co-morbidities that are common in older patient groups.

6.1.5 Illness perceptions

Numerous studies in the literature have examined at the relationship between illness perceptions and whether or not patients adhere to their treatment regimes (Cooper, Lloyd, Weinman, & Jackson, 1999; Steed, Newman, & Hardman, 1999; Buick & Petrie, 2002; Scharloo, et al., 1998; Griva, Myers, & Newman, 2000; French, Lewin, Watson, & Thompson, 2005). Very few studies have developed interventions which aim to change illness perceptions, and subsequently improve adherence levels. The present study findings suggest that there were no significant differences between groups across any of the illness perception questions other than perceived cause (see results Section 5.3.2.1). This contradicts previous evidence where interventions using the principles of the common sense model have found changes illness perceptions (Petrie, Weinman, Sharpe, & Buckley, 1993; Fischer, et al., 2010). For example one 12-week rehabilitation programme, consisting of individualised counselling, tailored exercises and group education for patients with chronic obstructive pulmonary disease, found significant increases in personal control and perceived timeline following the intervention (Fischer, et al., 2010). However, previous studies have used a more individualised intervention approach; assessing unique illness perceptions, and targeting specific problematic areas (Petrie, Weinman, Sharpe, & Buckley, 1993; Fischer, et al., 2010). Thus, the TREAT intervention, which aims to be accessible for the lay educator within usual hospital care, and generic in its approach, may not have the same impact, but rather help to prevent the formation of inaccurate illness representations.

At baseline, the majority of patients thought that there was a psychological cause (e.g. stress or bereavement; 41%), or an external cause of their illness (e.g. age or

previous morbidity; 31%); fewer blamed lifestyle factors (e.g. smoking, diet or lack of exercise; 29%). At the one month follow-up, more patients believed that there was an external cause of their AF (48%), rather than a psychological cause (33%). At each follow-up, the intervention group were more likely to perceive the cause as external, while patients in the usual care group were more likely to perceive the cause of their AF as psychological. These differences were significant at 6 months (p=0.04). This indicates that patients did change their perception of cause after receiving the intervention.

Patients in the intervention group had a more accurate perception of their illness following the intervention, stating established causal factors including age, male gender, hypertension, valvular heart disease, heart failure, coronary artery disease, diabetes (Benjamin, Levy, & Vaziri, JAMA, 1994; Gami, et al., 2007; Furberg, Psaty, Manolio, Gardin, Smith, & Rautaharju, 1994; Krahn, Manfreda, Tate, Mathewson, & Cuddy, 1995; Schnabel, et al., 2009), and genetic factors (Amar, et al., 2006; Fox, et al., 2004). AF patients have previously reported psychological causes of AF (McCabe, Barnason, & Houfek, 2011), despite evidence to the contrary; which could contribute to the emotional burden of their illness. On the contrary coronary artery disease (CAD) patients are more likely to believe that lifestyle factors caused their illness (Astin, Closs, McLenachan, Hunter, & Priestly, 2009); and changing lifestyle factors represents an area patients are able to control, as opposed to external factors such as age, or other co-morbidities. This may explain why AF patients in both treatment groups felt in control of their treatment, but not of their illness.

The lack of symptom predictability; or the cyclic nature of symptom presentation may leave patients feeling out of control (McCabe, Barnason, & Houfek, 2011). Indeed patients with paroxysmal AF and those with unpredictable symptoms have exhibited

the poorest QoL in a previous study (Thrall, Lane, Carroll, & Lip, 2006). The treatment regimen may provide them with an opportunity to feel in 'control' of their medication regime by providing regular feedback from blood tests and INR results, as well as an opportunity to adapt their lifestyle to ensure they remain within therapeutic range. The intervention aimed to enhance patients' perceived control by focussing on the objective indicators of treatment regulation, and ensuring patients are aware that the presence or absence of symptoms is not an indication of illness control or recovery.

There were significant differences within groups for emotional representation of illness across time; suggesting that the extent to which AF affects patients emotionally fluctuated across the six month period. Previous evidence with lone-AF patients has found significant changes in energy and general health perception across time, but no change in physical and social functioning (Lane, Langman, Lip, & Nouwen, 2009). These changes could be a result of diagnosis, as McCabe and colleagues found that a diagnosis of AF induces negative emotions (McCabe, Barnason, & Houfek, 2011). Having AF made patients feel anxious (59%), afraid (43%), depressed (37%) and angry (26%) (McCabe, Barnason, & Houfek, 2011) and the psychological burden of AF was also apparent in other studies (Carlsson, Miketic, Windeler, Cuneo, Haun, & Micus, 2003; Gronefield, Lilienthal, Kuck, & Hohnloser, 2003; Hagens, Ranchor, Van Sonderen, Bosker, Kamp, & Tijssen, 2004; Thrall, Lane, Carroll, & Lip, 2006). Thus the emotional impact of diagnosis and treatment may fluctuate over time; and the psychological morbidity associated with AF appears to be similar to other cardiac conditions, including patients treated with PCI (Astin, Closs, McLenachan, Hunter, & Priestly, 2009), or awaiting CABG (Hermele, Olivio, Namerow, & Oz, 2007).

Illness concern at the first follow-up was found to predict TTR (r= -.199; p=0.05). This evidence contradicts previous studies with MI patients, which found illness perceptions do not predict attendance to cardiac rehabilitation (French, Lewin, Watson, & Thompson, 2005). Our findings suggest that patients who are more concerned about their illness were less likely to adhere, and overcoming these barriers or concerns by discussing them with the health care practitioner should form part of the usual care procedure. Qualitative evidence suggests that AF patients' concerns surrounding illness can include worry about the impact upon their family and relationships; including being viewed as lazy or unproductive by co-workers when symptoms prevented them from being able to carry out work related tasks (McCabe, Schumacher, & Barnason, 2011). It is possible that those patients who are most concerned about their illness and its impact, may avoid the further social 'burden' of treatment recommendations (including attending regular blood checks, avoiding excessive alcohol intake, and dietary limitations).

The high scores on the 'timeline' question suggest that patients viewed their illness as continuing indefinitely, a result that did not fluctuate significantly over time or between groups. This perception could be an accurate reflection of their diagnosis, as AF is often a lifelong illness, typically treated with anticoagulation indefinitely (ESC, 2010). One problem with using the IPQ-B is that it does not assess patients' perception of the cyclic nature of their illness. Previous evidence suggests AF patients view their illness as cyclic rather than long-term (McCabe, Barnason, & Houfek, 2011). However, McCabe and colleagues had a higher percentage of symptomatic paroxysmal patients (64%) in their study, thus the results may be affected by the differences between samples.

There is limited evidence evaluating psychological burden and changes across time within this patient group, thus the TREAT intervention is the first of its kind to utilise psychological theory as a basis for an intervention for AF patients and may provide a design platform for future development. Finally, the validity of the IPQ-B has been deliberated in recent articles (van Oort, Schroder, & French, 2011). Thus, it is possible that some of the differences between groups were not identified due poor sensitivity of the evaluation tools (for an extended discussion see limitations, Section 6.2).

6.1.6 Anxiety & depression

There were no significant differences between groups in terms of anxiety and depression levels at baseline or throughout follow-up. This suggests the intervention did not have a positive or negative effect on psychological morbidity. Whilst the intervention was not designed to reduce anxiety or depression levels, findings do indicate that giving patients more information did not have a negative impact on their psychological morbidity. Of those trials included in the systematic review of behavioural interventions (see Chapter 2), only one measured anxiety (Thomson, et al., 2007). Anxiety fell significantly in both groups pre- to post-intervention, mean change -4.57 (95% CI) -6.30 to -2.84), but there was no evidence of a significant difference in anxiety between the two groups ($F(1, 95) = 0.001$; $p=0.98$) (Thomson, et al., 2007). This supports the present findings, that receiving more information does not increase anxiety. However, in the study by Thomson and colleagues anxiety levels dropped, in contrast to the increase in the TREAT study; which may be partly explained by differences between cohorts. Notably, patients in the Thomson et al study had previously taken warfarin, thus may have been less anxious about the medication regime due to prior experience. Furthermore, they trialled a decision aid,

whereby not all patients chose to take warfarin (some took aspirin), thus the study findings are not comparable.

The levels of anxiety and depression increased dramatically in both groups following post-baseline ($p<0.001$; see results section 5.3.3). As all patients were diagnosed prior to baseline, this indicates that the diagnosis of AF was not causing the distress, but rather the commencement of treatment with warfarin was having a significant negative impact. The warfarin regime requires several changes to a patient's lifestyle. Regular INR monitoring is achieved via blood testing, which often takes place at a community GP surgery or hospital outpatient clinic. Furthermore, patients are given lifestyle recommendations based on the numerous factors which can influence warfarin metabolism (including dietary intake, alcohol restrictions and potential medication interactions). This may explain the significant increase in anxiety in both groups after baseline and the continued feelings of anxiety during the ensuing six months. Despite the necessary lifestyle changes, very few patients chose not to take warfarin; a finding supported by Fuller and colleagues (Fuller, Dudley, & Blacktop, 2004). One qualitative study suggested that whilst patients reported the impact the treatment regime had, from minor inconveniences (e.g. INR tests affecting travel plans) to major complications (e.g. severe bleeding), the medication regime was placed at the centre of their daily routine (Coelho-Dantas, Thompson, Manson, Tracy, & Upshur, 2004). Thus, whilst patients continue to take their treatment, they may remain reticent or anxious about doing so.

Findings support those of other studies suggesting patients with AF in general have higher levels of anxiety and depression than population norms or healthy- and disease- controls (Frasure-Smith, et al., 2009; Thrall, Lip, Carroll, & Lane, 2007; Lane, Langman, Lip, & Nouwen, 2009). Whilst the TREAT intervention did not aim to

improve psychological morbidity, the findings support the additional need for inclusion of intensive behavioural interventions aimed at reducing anxiety levels specifically for AF patients initiating warfarin or other anticoagulation treatment, in conjunction with a routine psychological screening process within outpatient clinics.

Screening is particularly important as previous studies with AF and comparable cardiac conditions, such as heart failure, suggest that those patients with significant psychological morbidity also face poorer clinical prognosis in terms of cardiovascular mortality (Frasure-Smith & Lesperance, 2006; Lett, et al., 2004). Psychological mood state, specifically anger, has been found to trigger ventricular arrhythmia in patients with implantable cardioverter-defibrillators (Lampert, Joska, Burg, Batsford, McPherson, & Jain, 2002). Moreover, the AF-CHF trial of 974 AF patients with congestive heart failure found elevated BDI-II depression scores significantly predicted cardiovascular death (Hazard Ratio 1.30, 95% CI 1.16-1.46, $p<0.001$), arrhythmic death (HR 1.36, 95% CI 1.15-1.60, $p=0.001$) and all-cause mortality (HR 1.23, 95% CI 1.11-1.37, $p<0.001$) (Frasure-Smith, et al., 2009). Thus, physicians need to consider the impact of psychological morbidity on patients' clinical outcomes.

Psychological morbidity is an important factor predicting arrhythmic disturbance, stroke and mortality (Frasure-Smith & Lesperance, 2006; Lampert, Joska, Burg, Batsford, McPherson, & Jain, 2002; Lett, et al., 2004). The systematic review reported in Chapter 2 found none of the interventions specifically targeted psychological morbidity in this high risk AF group. In a similar cohort of coronary artery disease patients, one review (of 16 trials) found behavioural interventions (including cognitive behavioural therapy (CBT), psychodynamic psychotherapy and counselling) targeting depression, have had a small but beneficial effect on depression severity and remission rates when compared to usual care; these effects

were significant in the short and long term (Baumeister, Hutter, & Bengel, 2011). Short term effects were also found in pharmacological intervention studies with selective serotonin reuptake inhibitors; with a significant 1.8-fold (95% CI 1.18 to 2.74) reduction in depression (Baumeister, Hutter, & Bengel, 2011). However, there appears to be a dearth of high quality trials examining the impact of intensive psychological interventions in chronic physical illness (Lane, Chong, & Lip, 2009; Baumeister, Hutter, & Bengel, 2011).

It essential that AF patients are screened for depression and anxiety within outpatient clinics at diagnosis and post-treatment initiation when they face the greatest risk of psychological morbidity; as the results of the TREAT trial suggest that this may occur when patients begin a new and complex treatment regime. The AF-CHF trial identified patient characteristics significantly associated with depression, including those patients who were women, non-white, unmarried, and with fewer years in education ($p<0.001$) (Frasure-Smith, et al., 2009). By identifying more factors associated with depression and anxiety it may be possible to development a risk profile and screening procedure to form part of the usual care process.

6.2 Strengths and Limitations

There are some limitations with the TREAT study design and evaluation which need to be considered when interpreting the findings. The demography of the cohort reflects the typical presentation of AF, for example, there were more males than females (63.6% vs. 34.3%), this reflects the prevalence of AF in clinical practice (Lloyd-Jones, et al., 2004). Similarly, the TREAT cohort were mostly 65-74 years (48.5%), or older (aged ≥75; 37.1%), which also supports previous epidemiological findings (Stewart, Hart, & Hole, 2001). Whilst a specific diagnosis of ‘type’ of AF was

not available for all patients, for those who were categorised, there were a high percentage of PAF patients (30.9%). Similarly in clinical practice PAF patients represent 25 to 62% of AF cases seen by physicians and GPs (Kannel, Wolf, & Benjamin, 1998; Takahashi, Seki, Imataka, & Fujii, 1981).

The majority of the TREAT participants were of white ethnicity, which does not reflect the multi-ethnic community of the West Midlands; but it does reflect the disease prevalence, as AF is predominantly seen in White populations (Shen, et al., 2010). Inclusion of a more ethnically diverse population may have altered the findings; as one local study found ethnic differences in patient knowledge surrounding OAC (Nadar, Begum, Kaur, Sandhu, & Lip, 2003). However, cross-sectional research in the US (n= 430,317), searching electronic echocardiography archives, suggests the prevalence of AF is much higher in Whites (44.9%), than Black (9.4%), Asian (7.5%) or Hispanic (19%) ethnicities (Shen, et al., 2010). Thus perhaps the TREAT participants are more representative of those patients presenting with AF, than of the local ethnic population. Nonetheless, to ensure that the intervention materials are applicable for all AF patients, they would need to be available in a range of languages, as well as being culturally sensitive (e.g. including specific dietary requirements).

The symptoms patients experience and the predictability of a patient's ventricular rate is an important determinant of QoL (Thrall, Lane, Carroll, & Lip, 2006) and therefore patients who are more symptomatic, with uncontrolled AF, may be more likely to report poorer quality of life (Smith, Lip, & Lane, 2010); yet the TREAT study did not include an assessment of patients' symptoms at baseline or over time, which may be reflected within the results. Equally symptoms may influence patients' illness perceptions, as the identity question within the IPQ-B specifically asks about

symptoms, and there have been significant differences between symptomatic and asymptomatic patients on this item in previous studies (Steed & Newman, 1999). Since the design of the TREAT trial, the new ESC guidelines recommend classification of symptoms using the EHRA scoring system (see Section 1.2.1) as an important indicator of AF burden (Lip, et al., 2011). Therefore, future research should include an indication of the level of symptom burden for AF patients, and potentially examine any differences between groups.

This trial was also limited by its small sample size. Whilst other trials have found significant differences between groups with similar samples e.g. (Khan, Kamali, Kesteven, Avery, & Wynne, 2004), it is possible that many important relationships between factors studied remained undetected, due to a lack of statistical power (type II error). This is especially the case in the follow-up outcomes, as attrition increased as the study progressed, with the most notable levels at the two and six month follow-ups (44% and 42% attrition respectively, see results section 5.1). Furthermore, the use of a mixed models analysis allowed some flexibility in treating time as a continuous variable, accurately assessing the model regression line for time, rather than relying on an estimate of means. However, the use of a repeated measure design only includes a participant's data where they respond at all time points, excluding any patients who did not respond to all follow-ups. Nonetheless, the primary outcome does not rely on repeated measure analyses, and still indicated significant differences between groups. Furthermore, where necessary, conservative p-values were adopted to ensure relationships between variables were not over-estimated. Moreover the findings do give an indication of the impact of a one-off educational intervention on treatment control, and future studies may replicate the study with larger sample sizes to further explore interrelationships between variables, with correspondingly greater statistical power.

The systematic review (Chapter 2) highlighted the difficulties in blinding the data analyst or researcher to which intervention arm the patient was assigned. It is possible to blind the analyst to group assignment, but this was only undertaken in four of the trials included in the review (McAlister, et al., 2005; Christensen, Magaard, Sorensen, Hjortdal, & Hasenkam, 2006; Gadisseur, Kaptein, Breukink-Engbers, van Der Meer, & Rosendaal, 2004; Beyth, Quin, & Landefeld, 2000). However, the TREAT study integrated a systematic randomisation procedure (see methods Section 4.2). Furthermore, the use of randomisation codes ensured that the researcher carried out blinded questionnaire scoring, reducing the risk of bias.

The number of patients eligible for the study was 331, thus 29% of those eligible were included in the final cohort. Reasons given for non-participation included mobility issues, how time-consuming participation would be and the burden of other co-morbidities. This leaves a possibility of inclusion bias, as the demographic differences between participants and non-participants is well established. Those patients taking part in randomised trials are often healthier (Osler & Schroll, 1992), more educated (Alkerwi, Sauvageot, Couffignal, Albert, Lair, & Guillaume, 2010) and more motivated to change their behaviour (Graham, et al., 2008), than non-participants. Thus the results of this trial may not generalise to all AF patients, and the intervention may have a greater or poorer impact if used as a usual care procedure. Based on those trials included in the review, the percentage of eligible patients randomised into trials can be as little as 18% (Gadisseur, Kaptein, Breukink-Engbers, van Der Meer, & Rosendaal, 2004). Therefore, the TREAT study is comparable, if not more representative, than some other trialled interventions with this group.

The development of the TREAT intervention included piloting the materials with 'expert' patient groups, the integration of current clinical guidelines, guidance from expert cardiologists and the use of theoretical models (see intervention development Chapter 3). The MRC framework for interventions recommends additional theoretical modelling to determine whether the components of the intervention are relevant to the patient group (MRC, 2000). Whilst we took into consideration the findings from previous studies (McCabe, Barnason, & Houfek, 2011; Steed, Newman, & Hardman, 1999), neither of these studies examined illness perceptions as a predictor of treatment adherence. Therefore, whilst the development stage did not include a formal pilot study to trial which intervention components were most successful; the trial findings do allow for future development of the materials, focussing specifically on the key beliefs and perceptions that significantly predict TTR.

In order to determine the effectiveness of an intervention, we rely on the validity and reliability of the measurement tools. Recently, the validity of the Brief-IPQ has been called into question. Originally this questionnaire was included as an alternative to the IPQ-Revised, in order to reduce patient fatigue. However, reviews of the questionnaire have challenged the level of criterion validity (i.e. the extent to which questionnaire items test what they are supposed to be testing) (van Oort, Schroder, & French, 2011). The validation paper of the IPQ-B suggests that it is developed by forming one question which summarised the items on each subscale of the IPQ-Revised. The authors of the critique paper suggest that construct validity is flawed, as one questionnaire item cannot assess all aspects of a construct (van Oort, Schroder, & French, 2011). Patients appear to have problems in completing the questionnaire, particularly personal control, identity, illness coherence, emotional representation and causal attribution items. Items relating to cause and control were

often misinterpreted and the identity item caused the most difficulty (van Oort, Schroder, & French, 2011).

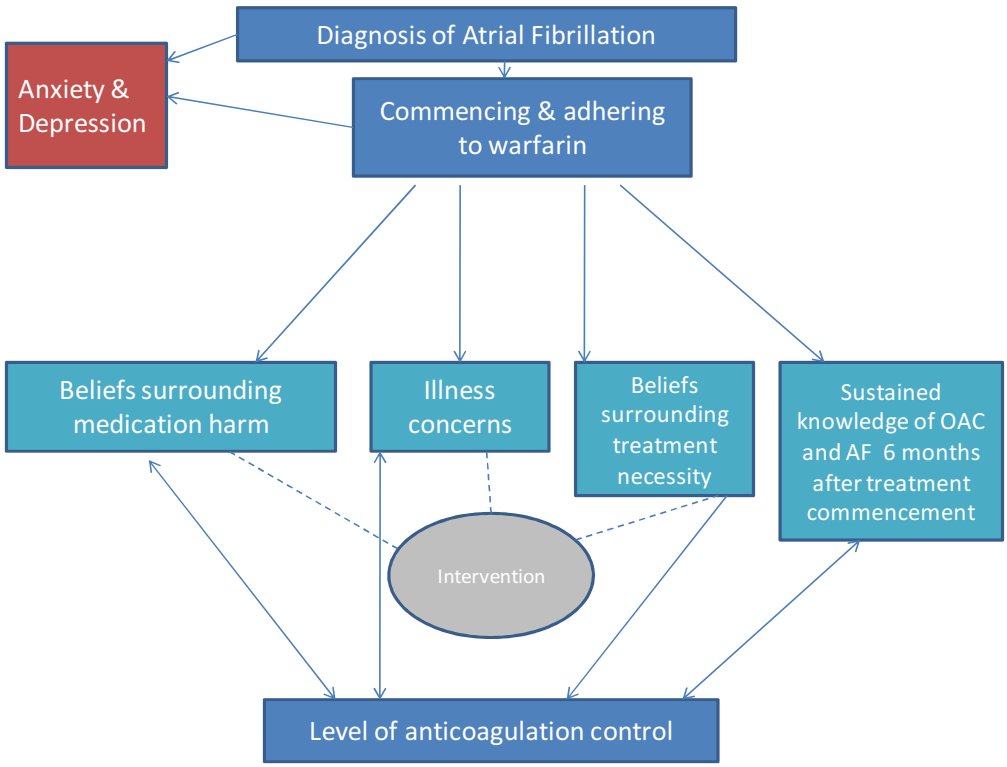
Similarly in the TREAT study it is clear that the identity item could give misleading results. The question focussed on symptoms 'How much do you experience symptoms from your illness?', and patients with AF vary in their presentation of symptoms, and have responded differently to the identity question in a previous study (Steed & Newman, 1999). Thus the questionnaire may lack construct validity in not assessing the entirety of the identity component. The results from the 'think aloud study' also suggest that patients do not answer the questionnaire for one illness specifically (van Oort, Schroder, & French, 2011). This could be problematic, as the TREAT cohort has a range of co-morbidities, including diabetes, heart failure, and hypertension. Thus our results may not give an accurate or 'complete' evaluation of the impact of the intervention on patients' AF-specific illness perceptions.

6.3 Clinical implications

Patient beliefs about their health can influence their decision to accept, decline, or comply with anticoagulant therapy, particularly warfarin. Several barriers to oral anticoagulation therapy can be related to patients' beliefs, including fear of the increased bleeding risks with warfarin, and the inherent difficulties associated with warfarin such as drug-, diet-, and alcohol-interactions, as well as lifestyle changes because of regular monitoring and dose adjustments. The results of the TREAT study suggest that by informing patients about their illness and targeting their beliefs about their medication, we can improve their understanding and subsequently improve patient adherence. The TREAT intervention differs from usual care by including 'patient focussed' educational materials, for example, using a DVD with

'expert patient' narratives, and including patients themselves in the development process. The intervention also provides a variety of different media to appeal to all learning styles and reinforce the key messages. By using the findings of the TREAT study we can begin to understand factors that may improve patients levels of anticoagulation control (see Figure 6.1). The study findings suggest that sustained knowledge, beliefs surrounding treatment necessity and harm and patients concerns about their AF can all play a role. The TREAT intervention can have an affect on these perceptions. For example, where patients have concerns about their AF or their treatment these may be alleviated, reducing the risk of intentional non-adherence.

Figure 6.1: TREAT model of factors influencing INR control.



Some self-management trials have demonstrated that interventions with atrial fibrillation (AF) patients can increase time spent within the therapeutic INR range (Khan, Kamali, Kesteven, Avery, & Wynne, 2004; Gadisseur, Kaptein, Breukink-Engbers, van Der Meer, & Rosendaal, 2004; Christensen, Magaard, Sorensen, Hjortdal, & Hasenkam, 2006), thus potentially decreasing the prevalence of adverse thromboembolic and haemorrhagic events (Wan, et al., 2008). Whilst self-management improves anticoagulation control, this may not be a feasible option for the majority of the patients requiring anticoagulation, due to the training required (Fitzmaurice & Machin, 2001). In addition, the associated costs of self-monitoring may prevent wide-scale uptake (Fitzmaurice & Machin, 2001), particularly with the arrival of new oral anticoagulants which do not require monitoring (Lip, et al., 2011; Wrigley, Lip, & Shantsila, 2010).

Whilst novel OAC provides an alternative treatment, without the burden of INR monitoring and lifestyle changes; there is likely to be further resistance to prescribing them due to cost compared to warfarin. In addition, patient preferences for OAC treatment are also important (Lane & Lip, 2007; Nadar, Begum, Kaur, Sandhu, & Lip, 2003) in facilitating a shared decision-making process; and many patients may choose warfarin, or be unable to take the new OACs. Clinicians are often reluctant to prescribe warfarin (due to lack of knowledge surrounding OAC and inexperience prescribing it to patients) and the intervention may help to alleviate some of these fears, increase uptake and adherence, and translate into fewer adverse outcomes. Thus a one-off intensive intervention package provides a cost-effective alternative in improving INR control, and this intervention could be adapted for use with novel anticoagulant drugs.

While there are usual care practices in place which provide educational materials for newly referred patients, these procedures vary substantially between hospitals and are often generic, not specifically considering the illness and reason for OAC prescription. It is evident that there needs to be a greater focus on disease-specific patient education for high risk treatments, so that patients understand the link between their treatment and the risks associated with their condition.

6.4 Future directions

In AF, warfarin has been the mainstay oral anticoagulant for the past 50 years; however novel oral anticoagulants are in development and have been tested in Phase III clinical trials. For example, the recent results of the Randomized Evaluation of Long- Term Anticoagulation Therapy (RE-LY) study suggest dabigatran is non-inferior to warfarin in reducing the risk of stroke, with fewer bleeding complications (Connolly, et al., 2009). In addition, novel OAC do not require regular blood tests (i.e., no INR monitoring) and do not appear to have drug-, food- and alcohol- restrictions, as seen with warfarin.

However, there is a lack of evidence on patients' perceptions of novel oral anticoagulants and the impact of patients' beliefs about novel oral anticoagulants on uptake and adherence. Further, the availability of novel oral anticoagulants will shift the pattern of initiating anticoagulants from secondary to primary care. Therefore, it is pertinent to understand how physicians perceive novel anticoagulants, how they make decisions about whether or not to prescribe antithrombotic therapy, the choice of appropriate anticoagulant therapy, and whether or not there are important differences between general practitioners and cardiologists in these factors affecting anticoagulant treatment decisions.

In the future the TREAT intervention materials will also need to be developed, aiming to [1] adapt the intervention for use with a range of OAC including the new anticoagulants, [2] to ensure that the intervention is widely available in a number of hospitals and GP practices across the country, and [3] to provide the existing and updated educational materials to patient organisations for inclusion within their patient materials (physical) and on-line.

To disseminate the intervention so that it is widely available for use in both research and clinical practice, it is possible to develop a website allowing specific focus on the psychological and practical barriers to adhering to anticoagulant therapy and lifestyle recommendations that have been highlighted in numerous studies (Coelho-Dantas, Thompson, Manson, Tracy, & Upshur, 2004; Hylek, Evans-Molina, Shea, Henault, & Regan, 2007; Fuller, Dudley, & Blacktop, 2004). Filmed patient narratives could also be available from the original TREAT intervention, alongside filmed expert-responses to some of the key patient concerns (i.e. missed dose, side effects and psychological side effects). This will aim to increase awareness of patient barriers and act as a social comparison tool for patients who are concerned about their treatment or condition. Our research group have existing links with charities, patient organisations and professional bodies that already provide educational materials to AF patients (e.g. Atrial Fibrillation Association (AFA); Anticoagulation Europe (ACE); StopAFib) and it may be possible to collaborate with these groups to improve the educational resources for patients.

6.5 Conclusion

The TREAT intervention provides a simple one-off behavioural session, which could be delivered by any health care practitioner (with appropriate training), and significantly improves adherence to warfarin as evidenced by greater TTR. Improving understanding about a disease and its treatment allows patients to make informed decisions about the management of their condition and treatment and can make a significant difference to adherence outcomes. The intervention's ability to improve adherence is reliant on providing adequate information surrounding risks so that patients can 'trade-off' the risks and benefits of their new medication. It further highlights the importance of AF patients' perceived necessity of medication and concerns or barriers about taking warfarin, which in turn will influence adherence, TTR, and subsequently clinical outcomes. By integrating theory-driven behavioural change techniques into usual care practices, and improving our methods of communication we may endeavour to improve patients' health outcomes in both the short- and long-term.

Table 6.1: Key findings from the TREAT study

Key findings
➢ Disease specific education can significantly improve INR control, even where TTR is relatively well controlled within usual care. ➢ Those patients with sustained knowledge over time, lower illness concern, and decreased perception of treatment harm are more likely to adhere to OAC medication. ➢ Patients with AF commencing OAC are at increased risk of psychological morbidity and clinical guidance should reflect that by improving screening and intervention provision.

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Appendix 1

Patient Information Sheet

Part 1

Study title

TRial of an Educational intervention on patient's knowledge of Atrial fibrillation and anticoagulant therapy, INR control, and outcome of Treatment with warfarin (TREAT)

Dear Patient

We would like to invite you to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
The purpose of this study is to examine whether giving patients like you, with atrial fibrillation (an irregular heart rhythm) more detailed information about your condition, the need for treatment with a blood-thinning medication called warfarin and the risks and benefits of taking warfarin, will help to improve how well-controlled your warfarin treatment is, compared to patients receiving usual care. In addition, this study will also assess whether extra education improves your knowledge about atrial fibrillation and if it changes your beliefs about atrial fibrillation and how it is treated. The study will also assess what impact your treatment has on your everyday quality of life and emotional well-being. Our previous studies and those of others have shown that knowledge about atrial fibrillation among patients with this condition is often poor and many patients do not understand the risks and benefits of warfarin treatment. Our previous study showed that after a short educational session, patients with atrial fibrillation were more aware of their target INR level (a measure of how thin or thick your blood is when taking warfarin), the things which may affect their INR, and the risks and benefits of taking warfarin.

Why have I been invited?
You have been asked to take part in this research study because you have atrial fibrillation (an irregular heart rhythm). This means that your heart does not beat in a regular rhythm, some or all of the time. As your doctor will have explained to you, having atrial fibrillation can increase your risk of having stroke (a blood clot in your brain). Other conditions, such as having high blood pressure, diabetes, heart failure, having had a previous stroke or mini stroke (transient ischaemic attack) and being 75 years of age or older, can increase your risk of having a stroke further. Your doctor has offered you treatment with a blood-thinning medication called warfarin, to decrease your risk of a blood clot forming and reduce your risk of having a stroke. We are asking all patients with atrial fibrillation who have agreed to start taking warfarin if they will take part in this study.

Do I have to take part?
It is up to you to decide whether or not to take part in the study. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show that you have agreed to take part. If you decide to take part, you are still free to change your mind at any time and stop taking part in the study, and you do not have to give a reason. A decision to withdraw at any time or a decision not to take part will not affect the standard of care you receive.

What will happen to me if I take part?
If you agree to take part in this study you will be asked to attend the *ASCOT centre if attending City Hospital anti-coagulation clinic/ SMRU if attending Sandwell Hospital anticoagulation clinic/Good Hope Hospital* [delete as applicable] before your first anti-coagulation clinic appointment to sign the consent form. We are trying to find out whether giving people more information about atrial fibrillation and its treatment can improve INR control and increase patients' knowledge compared to standard care. We put people into different groups and give each group a different treatment. The results are compared to see if one is better than the other. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). There are two groups in this study: usual care or the educational intervention. You have an equal chance of being allocated to either group.

After you have signed the consent form, you will be asked to complete seven questionnaires. These questionnaires ask about how you feel about taking warfarin and about having atrial fibrillation, how much you know about atrial fibrillation and the risks and benefits of taking warfarin, your experiences of taking warfarin and the impact your atrial fibrillation has on your life. You can either complete the questionnaires with the researcher or by yourself at home. If you decide to complete them at home you will be given a stamped addressed envelope in which to return then to the hospital.

You will be asked to complete six of these questionnaires on four further occasions: 1, 2, 6 and 12 months after starting to take warfarin. The questionnaires will be sent to your home address, with a pre-paid envelope in which to return the completed questionnaires to the hospital. Four weeks after you start taking warfarin one of the study researchers will contact you via telephone to as you about the financial costs you have incurred by travelling to the hospital. This will take 5 minutes and consist of 7 questions.

If you are put into the usual care group, you will receive the standard Yellow Book given to all patients who start taking warfarin, which explains the need for taking warfarin.

If you are put into the education intervention group, you will also be asked to attend the ASCOT centre at City Hospital for a one hour group education session. During this time, a doctor will go through a slide presentation and talk through all the information you need to know about regarding atrial fibrillation and warfarin treatment. You will be given the opportunity to ask questions and the doctor will answer your questions. After this session you will be given an information booklet containing all the information presented for you to keep and take home with you to read.

Regardless of which group you are put into, you will attend the anticoagulation clinic to have your first INR check, approximately seven days after starting to take warfarin. The International Normalised Ratio (INR) is a measure of how thin or thick your blood is when taking warfarin. The target level for your INR is between 2.0 and 3.0. At your first

visit, the dosing officer will go through the standard information contained in the Anticoagulation Yellow Book regarding the use of warfarin. You will attend the anticoagulation clinic for all INR tests and the results of each test will be written into you Anticoagulant Yellow Book. You will be followed up as part of the TREAT study for 12 months for the date you start taking warfarin. However, it is important to note that warfarin is a life-long medication to thin the blood and reduce the risk of stroke in patients with atrial fibrillation, and you will continue to take warfarin after the trial has finished, unless you decide that you do not wish to take warfarin any longer.

Expenses and payments
You will have your travel expenses (bus fare, fuel allowance and parking) reimbursed for the visit to the hospital when written informed consent is obtained and the first set of questionnaires are completed. If you are put into the education group you will also receive travel expenses (bus fare, fuel allowance and parking) for the visit to the hospital for the group education session.

What are the alternatives for diagnosis or treatment?
Currently, warfarin is the best blood-thinning medication for people like you who are at moderate- to high-risk of suffering a stroke. If during the course of this study other medications to thin the blood become available that are as good as or better than warfarin, at reducing stroke risk, then you will be informed about them and offered the alternative therapy.

What are the possible disadvantages and risks of taking part?
There are no disadvantages or risks to you in taking part in this study. This study is comparing the effect of extra education on atrial fibrillation patients' INR control and knowledge and beliefs about taking warfarin.

What are the side effects of any treatment received when taking part?
There are no side effects of the educational intervention.

What are the possible benefits of taking part?
We cannot promise that the study will help you but the information we get from this study may help to improve the treatment of people with atrial fibrillation in the future. If you receive the extra education you may benefit from increasing your understanding of this condition and the medication used to treat it.

What happens when the research study stops?
We will follow-up you up for the first 12 months after you start to take warfarin. At the end of the study, you will continue to take warfarin, as this is a life-long medication to thin the blood and reduce your risk of having a stroke, and you will continue to have your INR monitored at the anticoagulant clinic.

What if there is a problem?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2

What if new information becomes available?
If new blood-thinning medications become available during the course of this study that you doctor feels may be of benefit to you compared to taking warfarin, then your doctor will tell you and discuss whether you should continue in the study. If you decide to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study, your doctor may ask you to sign an updated consent form.

Alternatively, your research doctor might decide that you should withdraw from the study. He/she will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What will happen if I don't want to carry on with the study?
You can withdraw from the study at any point but we would like to keep in contact with you to follow-up your progress. If you decide not to continue taking warfarin you will be withdrawn from the study and your reasons for stopping warfarin will be recorded.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to one of the researchers who will do their best to answer your questions (contact Prof Lip 0121-507-5080/5678). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital Complaints and Litigation Department on 0121-507-4346.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence than you may have grounds for a legal action for compensation against *Sandwell and West Birmingham Hospitals NHS Trust/Good Hope Hospital* [delete as applicable] but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in this study be kept confidential?
If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the company sponsoring the study and by authorised employees of the NHS Trust. They may also be looked at by representatives of regulatory authorities and by people authorised to check that the study is being carried out correctly. We all have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

Involvement of the General Practitioner/Family doctor (GP)
Your GP will be informed about your participation in this research study if you agree to this on the consent form.

What will happen to the information I give?
All information that is collected about you during the course of the research will be kept strictly confidential. The questionnaires will not contain your name; instead you will be given a unique code known only to the Principal Investigator and the researchers. The completed questionnaires will be kept in a secure location within the hospital and data stored on computers will be anonymised (using your unique code) and the computers will be password protected. Only the researchers will have access to this data.

What will happen to the results of the research study?
At the end of the study, we hope to publish the results. You will not be identified in any report or publication. If you wish, we will send you a summary of our findings.

Who is organising and funding the research?
This research is being organised by the University Department of Medicine, City Hospital. The study is being funded by Bayer Healthcare Pharmaceuticals to cover the running costs of the study. No payments will be made to members of staff involved in this study.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, well-being, and dignity. This study has been reviewed and given favourable opinion by Black Country Research Ethics Committee.

Further information and contact details
If you have any questions about the study, please call the person listed below. They will answer your questions or give you advice.

Principal Investigator: Danielle Smith 0121-507-5053

If you have any concerns about this study, please call Balvinder Baines (R&D department on 0121-507-4946).

Thank you for taking the time to read this Patient Information Sheet and considering whether to take part in the study.

Consent form

Patient Identification Number:

CONSENT FORM

Title of Project: TRial of an Educational intervention on patient's knowledge of Atrial fibrillation and anticoagulant therapy, INR control, and outcome of Treatment with warfarin (TREAT)

Name of Researchers: Danielle Smith, Dr DA Lane, Professor GYH Lip

Please initial the box

1. I confirm that I have read and understand the information sheet dated 24/08/2009, Version 5 for the above study. I have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected d the study may be looked at by individuals from QED, from regulatory authorit from the NHS Trust, where it is relevant to my taking part in this research. I g permission for these individuals to have access to my records. ☐
4. I agree to my GP being informed of my participation in this study. ☐
5. I agree to take part in the above study. ☐

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature
Name of person taking consent (if different from researcher)	Date	Signature

Appendix 2

Baseline demographics

A: PATIENT DEMOGRAPHICS

1. Date of Birth: ☐☐ ☐☐ ☐☐

2. Age: ☐☐ years

3. Sex: ☐ M ☐ F

4. Height: ☐☐☐ . ☐ cm

5. Weight: ☐☐☐ ☐ kg BMI: ☐☐☐☐

6. Education level [please indicate [x] appropriate level]

Secondary school ☐

College ☐

University ☐

Post-graduate/ Other professional qualification ☐

7. Post-code ☐☐☐☐☐

8. Current occupation

_____

9. Previous occupation (if different from that specified in q8)

_____

10. What is your ethnic group?

A. White ☐ British ☐ Irish ☐ Any other white background

B. Mixed ☐ White and black Caribbean ☐ White and Black African ☐ Any other

C. Asian or Asian British ☐ Indian ☐ Pakistani ☐ Bangladeshi ☐ Other Asian

D. Black or Black British ☐ Caribbean ☐ African ☐ Other Black

E. Chinese ☐

F. Other (please specify)

_____

B: AF HISTORY

1. Specify type of AF? ☐ Persistent ☐ Paroxysmal ☐ Permanent

2. Date of AF diagnosis: ☐☐ ☐☐ ☐☐

day *month* *year*

3. Current antithrombotic treatment for AF

☐Aspirin ☐None ☐ Other (specify) _____

4. Has the patient ever taken Warfarin Previously?

☐Yes ☐No

If yes, please give details

_____

5. Previous stroke? ☐Yes ☐No

6. Previous TIA? ☐Yes ☐No

7. Previous systemic embolism? ☐Yes ☐No

8. Valvular heart disease? ☐Yes ☐No

9. ECG tested: ☐YES ☐ NO

10. Date of ECG: ☐☐ ☐☐ ☐☐

Day *Month* *Year*

11. ECG result:

a) Rhythm: ☐Atrial Fibrillation ☐Atrial Flutter ☐ Sinus

☐Atrial paced ☐Ventricular paced

☐Other (specify):_____

b) Ventricular rate: ☐☐☐ bpm

c) Was left ventricular hypertrophy present on ECG? ☐YES ☐ NO

C: BLOOD PRESSURE

1. Average Bp ☐☐☐/☐☐☐ mmHg

2. Average Heart Rate ☐☐☐ bpm

D: LEFT VENTRICULAR FUNCTION

1. Has Ventricular Function been assessed in the past year? ☐YES ☐ NO

1a) Date of assessment: ☐☐ ☐☐ ☐☐

day *month* *year*

1b) LV Ejection Fraction: ☐☐ % OR ☐ ≤40% ☐ > 40%

OR ☐Unknown

2. How was VF assessed?

☐ Echocardiogram ☐MUGA ☐TOE ☐ Other

(please specify below)

_____

E: SUBSTANCE USE

1. a) Is the patient currently using tobacco? ☐YES (please specify below)

☐ NO

b) Has the patient previously used tobacco regularly?

☐YES (please specify below) ☐NO

c) Type of tobacco use:

☐ cigarettes ☐pipes/ cigars ☐chewing tobacco other

(specify): _____

d) ☐☐☐ per day (cigarettes)

e) Age started ☐☐ Age stopped (if relevant) ☐☐

2. Current weekly alcohol consumption: ☐☐ (units)

F: INCLUSION CRITERIA

1. AF confirmed on ECG? ☐ Yes ☐ No

2. Stroke risk factors (please indicate [x] all that apply)

   Congestive Heart Failure ☐

   Aged ≥ 75yrs ☐

   Hypertension ☐

   Diabetes mellitus ☐

   Previous stroke ☐

   Previous TIA ☐

   Previous systemic embolism ☐

   Peripheral vascular disease ☐

   Female gender ☐

3. NICE guidelines stroke risk ☐ Low ☐ Moderate ☐ High

4. $CHADS^2$ Score ☐ (0-6)

Are all the Inclusion Criteria met? ☐YES ☐ NO

G: EXCLUSION CRITERIA

1. Does the patient require Warfarin for any indication other than AF?
   ☐Yes ☐No

Are any of the Exclusion Criteria met? ☐YES ☐ NO

No ⟶ Patient is eligible

Yes ⟶ Patient is ineligible

Concomitant medication	BASELINE	NO CHANGE	STARTED DATE: DD/MM/YY	STOPPED DATE: DD/MM/YY
A: ANTITHROMBOTIC THERAPY				
1. ASA				
2. AGGRENOX				
3. TICLOPIDINE				
4. PARENTERAL ANTICOAGULANT				
5. CLOPIDOGREL				
6. DIPYRIDAMOLE				
7. VITAMIN K ANTAGONIST				
B: ANTIHYPERTENSIVE FALIURE				
1. ARB				
2. SPIRONOLACTONE				
3. ALPHA BLOCKER OR OTHER VASODILATOR				
4. DILTIAZEM				
5. BETA BLOCKER				
6. ACE INHIBITOR				
7. OTHER DIURETIC				
8. VERAPAMIL				
9. OTHER CCB				
10. DIGOXIN				
C: ANTIARRHYTHIMIC DRUGS				
1. SOTALOL				
2. FLECANIDE				
3. DRONEDARONE				
4. AMIODARONE				
5. OTHER ANTIARRHYTMIC				
6. PROPAFENONE				
7. PROCANAMIDE				
8. MEXILENTINE				
9. QUINIDINE				
D: METABOLIC AND ANTI-INFLAMMATORY				
1. STATIN				
2. COX II INHIBITOR				
3. INSULIN				
4. NON-STATIN LIPID LOWERING DRUG				
5. OTHER NSAID				
6. ORAL HYPOGLYCEMIC				

F: OTHER DRUGS				
1. VITAMINS				
2. PROTON PUMP INHIBITORS				
3. HERBAL REMEDIES				
4. H2 BLOCKERS				
5. ANTIBIOTICS				
OTHER 1				
Specify_____				
OTHER 2				
Specify_____				
OTHER 3				
Specify_____				

IPQ-B

For the following questions, please circle the number that best corresponds to your views:

How much does your illness affect your life?

0 1 2 3 4 5 6 7 8 9 10

no affect at all — severely affects my life

How long do you think your illness will continue?

0 1 2 3 4 5 6 7 8 9 10

a very short time — forever

How much control do you feel you have over your illness?

0 1 2 3 4 5 6 7 8 9 10

Absolutely no control — extreme amount of control

How much do you think your treatment can help your illness?

0 1 2 3 4 5 6 7 8 9 10

not at all — extremely helpful

How much do you experience symptoms from your illness?

0 1 2 3 4 5 6 7 8 9 10

no symptoms at all — many severe symptoms

How concerned are you about your illness?

0 1 2 3 4 5 6 7 8 9 10

not at all concerned — extremely concerned

How well do you feel you understand your illness?

0 1 2 3 4 5 6 7 8 9 10

don't understand at all — understand very clearly

How much does your illness affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?

0 1 2 3 4 5 6 7 8 9 10

not at all affected emotionally — extremely affected emotionally

Please list in rank-order the three most important factors that you believe caused your illness. *The most important causes for me:-*

1. _____

2. _____

3. _____

Knowledge questionnaire

1. What is the name of your heart condition?

_____

2. How long have you been diagnosed with having atrial fibrillation?

_____

3. What is atrial fibrillation?

_____

4. What are the symptoms of atrial fibrillation (or what were your symptoms?)

_____

5. What can cause atrial fibrillation? (What caused you to have atrial fibrillation?)

_____

6. Do you perceive atrial fibrillation as a serious condition?

☐ Very serious ☐ Serious ☐ Not very serious

7. What types of problems can atrial fibrillation cause?

_____

8. What anticoagulant therapy are you taking?

_____

9. Why you are taking warfarin?

_____

10. What are the side effects of taking warfarin?

_____

11. What are the benefits of taking warfarin?

_____

12. How do you perceive the risk of taking warfarin?

_____

13. What is your target INR?

_____

14. What factors may affect your INR levels?

_____

BMQ

We are interested in your beliefs about the medicines which YOU TAKE SPECIFICALLY FOR YOUR ATRIAL FIBRILLATION. Read each of the following statements and then circle the appropriate number to the right of the statement to indicate your belief.

	Strongly disagree	Disagree	Uncertain	Agree	Strongly agree
1. My health, at present, depends on my medicines	1	2	3	4	5
2. Having to take medicine worries me	1	2	3	4	5
3. My medicines control my heart rate	1	2	3	4	5
4. Without my medicines I would be very ill	1	2	3	4	5
5. I sometimes worry about the long-term effects of my medicines	1	2	3	4	5
6. My medicines are a mystery to me	1	2	3	4	5
7. My medicines disrupt my life	1	2	3	4	5
8. I sometimes worry about becoming too dependent on my medicines	1	2	3	4	5
9. My health in the future will depend on my medicines	1	2	3	4	5
10. My medicines prevent my heart from beating too fast	1	2	3	4	5

We are also interested in your beliefs about medicines IN GENERAL. There are no ‘right’ or ‘wrong’ answers, so choose the most accurate answer for YOU - not what you think ‘most people’ would say. Read each of the following statements and then circle the appropriate number to the right of the statement to indicate your belief.

	Strongly disagree	Disagree	Uncertain	Agree	Strongly agree
1. Most medicines are additive	1	2	3	4	5
2. People who take medicines should stop their treatment for a while every now and again	1	2	3	4	5
3. Medicines do more harm than good	1	2	3	4	5
4. All medicines are poisons	1	2	3	4	5
5. Natural remedies are safer than medicines	1	2	3	4	5
6. Doctors place too much trust on medicines	1	2	3	4	5
7. If doctors had more time with patients they would prescribe fewer medicines	1	2	3	4	5
8. Doctors use too many medicines	1	2	3	4	5

AF-QoL-18

The following phrases refer to your feelings or thoughts about your arrhythmia (Atrial Fibrillation). Your answers will allow us to know more about how you have been feeling and how your illness has interfered with your regular activities in the last 30 days.
Below each phrase you will find a possible answer. Please read each phrase thoroughly. After reading each phrase, make an X next to the option which best describes what you think is happening to you. There are NO correct or incorrect answers. We are only interested in knowing about the consequences of your arrhythmia (Atrial Fibrillation).

	Due to my atrial fibrillation…….	*Totally Disagree*	*Sufficiently Disagree*	*Neither Agree Nor Disagree*	*Sufficiently Agree*	*Totally Agree*
1	What affects me the most is the helplessness I feel during a crisis					
2	I am afraid that my disease complicates things					
3	I am afraid of pain or suffering from a heart attack					
4	I am afraid of having a sudden or unexpected tachycardia					
5	I feel depressed when I find that I get tired					
6	I feel depressed when I think that my disease will last forever					
7	I have negative thoughts about my future					
8	I get more tired than usual when I perform physical exercise					
9	I get tired during a brisk walk					
10	I felt more vitality before I was diagnosed with the disease					
11	I have stopped performing physical exercise					
12	My disease has impaired my quality of life					
13	I feel affected by the impossibility of carrying out certain activities, “I want to but my body cannot”					
14	Sexual relationships are less frequent than before I was diagnosed with the disease					
15	I get tired when I walk for thirty minutes and I have to rest					
16	Changes have occurred in my sexual activity due to the medications I take					
17	I am afraid that my heart is “triggered” during sexual intercourse					
18	I find it difficult to get out of the house and carry out any activity					

Hospital Anxiety and Depression Scale

Please read each item below and place a tick in the box opposite the reply which comes close to how you have been feeling in the last week. Don't take too long over your replies: your immediate reaction will

1. I feel tense or 'wound up':

Most of the time……	
A lot of the time ……..…….	
Time to time, Occasionally ...…..…..	
Not at all……	

7. I can laugh and see the funny side of things:

As much as I always could……	
Not quite so much now……..	
Definitely not so much now……..	
Not at all……	

3. I still enjoy the things I used to enjoy:

Definitely as much……	
Not quite so much…….……	
Only a little……...	
Hardly at all……..	

9. Worrying thoughts go through my mind:

A great deal of the time…….	
A lot of the time……...….	
From time to time but not too often..	
Only occasionally……..	

5. I get a sort of frightened feeling as if something awful is about to happen:

Very definitely and quite badly…….	
Yes, but not too badly……..…	
A little, but it doesn't worry me……	
Not at all……	

11. I feel cheerful:

Not at all……	
Not often……	
Sometimes…….	
Most of the time……...…….	

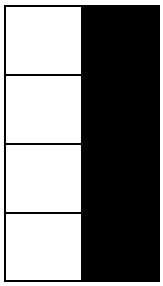
13. I can sit at ease and feel relaxed:

Definitely…..…….

Usually……..…..……

Not often……..……...

Not at all……



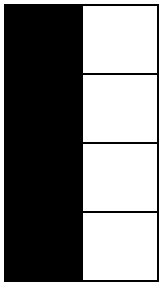
2. I feel as if I am slowed down:

Nearly all the time…….….

Very often…….…..

Sometimes……..

Not at all…….



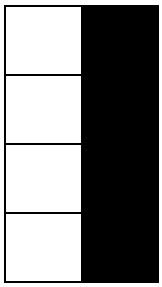
4. I get a sort of frightened feeling like 'butterflies' in the stomach:

Not at all……..……

Occasionally…….……..

Quite often……..

Very often……...



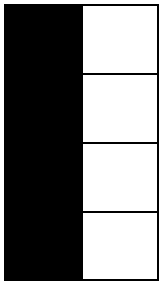
6. I have lost interest in my appearance:

Definitely…….…

I don't take so much care as I should..

I may not take quite as much care…...

I take just as much care as ever……...



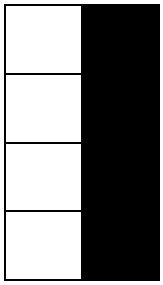
8. I feel restless as if I have to be on the move:

Very much indeed……...

Quite a lot……

Not very much…….

Not at all……..



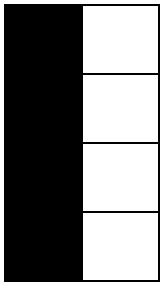
10. I look forward with enjoyment to things:

As much as I ever did…….

Rather less than I used to……

Definitely less than I used to……..

Hardly at all……



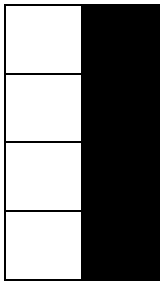
12. I get sudden feelings of panic:

Very often indeed……...

Quite often……..

Not very often…….…...….

Not at all…….



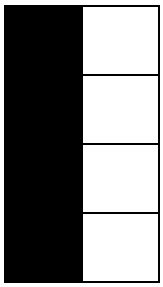
14. I can enjoy a good book or radio or TV programme:

Often……...

Sometimes……..…....

Not often……

Very seldom……



Adverse event	**Date** dd/mm/yy	**Event Status** 1=resolved 2=unresolved	**Intensity** 1=mild (symptom awareness, easily tolerated) 2=moderate (discomfort, tolerable) 3=Severe (incapacitating) 4=Not assessable/ unknown	**Outcome** 1=recovered 2=not yet recovered 3=sequelae 4=fatal 5=unknown	**Action Taken** 1=none 2=observation only 3=out-patient medical management 4=Hospitalised-medical management or observation 5=Hospitalised-surgical intervention 6=other	**Action Taken with Study Med** 1=continued 2=permanent discontinuation 3=temporary discontinuation-No restart 4=temporary discontinuation-Restart 5=N/A, patient previously permanently discontinued	**Event Serious** 1=yes 2=no	**Causal relationship to study drug** 1=yes 2=no
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								

Stroke report

PART A. Stroke details

1. Date of onset of event ☐☐ ☐☐ ☐☐ (dd/mm/yy)

2. Was the patient hospitalised for this event ☐ Yes ☐ No

3. Criteria for diagnosis of a stroke (must be YES to at least one)

a) Rapid onset of focal neurological deficit lasting ≥ 24 hours ☐ Yes ☐ No

NOTE: If stroke resulted in death please complete Death Report CRF (?) in addition to this stroke report.

4. Symptoms and signs (Mark [x] all symptoms present for at least 24 hours)

☐ i. Weakness/ paralysis (mark all that apply) ⟶ ☐ arm ☐ face ☐ lower extremity

☐ ii. Numbness/ sensory loss (mark all that apply) ⟶ ☐ arm ☐ face ☐ lower extremity

☐ iii. Change in condition ☐ iv. Aphasia ☐ v. Hemianopia ☐ vi. Sensory

☐vii. Change in levels of consciousness ☐viii. Cerebeller signs

☐ix. Other _____(please specify)

5. This event has been evaluated by (Mark [x] all that apply)

☐ MRI ☐ Autopsy ☐ CT ☐ Vascular imaging

6. Final diagnosis (Mark [x] only one)

☐ a) Ischemic stroke → ☐ Y ☐ N Secondary haemorrhagic transformation

☐ b) Haemorrhagic stroke

☐ b) Stroke of uncertain classification

Death report

PART A. Stroke details

1. Date of death ☐☐ ☐☐ ☐☐ (dd/mm/yy) 2. Time :

3. Death Witnessed: ☐ Yes ☐ No

4. Cause of death (Indicate vascular or Non-vascular):

☐ a) VASCULAR (Mark (x) one only)

☐ i) Sudden/arrhythmic death (mark [x] all that apply)

☐ Documented asystole

☐ Documented VF

☐ Recent MI

☐ Other, Specify_____

☐ ii) Pump failure death (mark [x] all that apply)

☐ CHF/ Cardiac Shock

☐ Cardiac tamponade

☐ Recent MI

☐ Other, Specify_____

☐ iii) Stroke (Complete STROKE Report CRF_☐☐ Report #

☐ iv) Pulmonary Embolus

☐ v) Peripheral Embolus

☐ vi) Aortic Dissection/ Rupture

☐ vii) Haemorrhage

☐ viii) Unknown cause

☐ ix) Other (specify):_____

b) NON-VASCULAR (Specify):

☐ Infection

☐ Cancer

☐ Trauma

☐ Respiratory Failure

☐ Other, Specify_____

5. Summary of details of death (provide a brief summary of events leading up to patient death)

_____

_____

Appendix 3

(For intervention DVD and Booklet please request loose materials)

Warfarin Worksheet

SECTION A: Assess your personal risk of stroke

One way to work out your risk of stroke is to use the acronym CHADS2. The CHADS2 gives 1 point to each of the risk factors mentioned above except for stroke which gets 2 points. The higher the total number of points, the higher the risk of stroke.

If a question below does not apply to you, write 0 in the 'your score' column

Questions	Points	Your Score
Are you 75 years or older?	**1**	
Do you have high blood pressure?	**1**	
Do you have diabetes?	**1**	
Do you have heart failure or have you had heart failure in the past?	**1**	
Have you suffered a stroke (even a mild stroke)?	**2**	
Total	**–**	

Recommendations depending on your total

- If a score of 0 or 1 is recorded, patients are usually advised to take aspirin (75-300 mg daily).
- If a score of 2 or more is recorded, patients are usually advised to take warfarin (INR 2.0-3.0).

SECTION B: Your personal warfarin plan

What is your target INR? _____ . _____

<u>Lifestyle changes:</u>

Target daily alcohol intake _____ units

Your usual alcoholic drinks

1. _____ units _____

2. _____ units _____

3. _____ units _____

SECTION C: Medication concerns

When prescribed a new life-long treatment such as warfarin, patients often come across problems and concerns which can prevent them from taking their medication and successfully reducing their risk of stroke. These can be psychological concerns for example; worrying about side effects and the burden of the medication or practical concerns for example; how you will remember to take the medication, what to so if you miss a dose etc.

In the space below list some of your key concerns about taking warfarin:

_____

_____

_____

_____

_____

_____

_____

_____

You should always discuss these concerns with a doctor or other health care professional. You can raise them in the group session or if you would prefer to talk privately about your concerns you can contact one of the investigators at a later date.

Appendix 4

The Cochrane Library

#1 MeSH descriptor patient education as topic this term only

#2 MeSH descriptor attitude to health explode all trees

#3 MeSH descriptor patient participation this term only

#4 MeSH descriptor behavior therapy this term only

#5 MeSH descriptor cognitive therapy this term only

#6 MeSH descriptor counseling explode all trees

#7 MeSH descriptor motivation this term only

#8 MeSH descriptor goals this term only

#9 MeSH descriptor Biofeedback (Psychology) this term only

#10 MeSH descriptor decision support techniques this term only

#11 MeSH descriptor Communications Media explode all trees

#12 education in All Text

#13 (training in All Text or train in All Text)

#14 (teaching in All Text or teach in All Text)

#15 (behaviour* in All Text or behavior* in All Text)

#16 "patient knowledge" in All Text

#17 counsel* in All Text

#18 (cognitiv* in All Text near/3 therapy in All Text)

#19 (cognitiv* in All Text near/3 intervention* in All Text)

#20 motivation* in All Text

#21 contingency next management in All Text

#22 (biofeedback in All Text or bio-feedback in All Text)

#23 (goal in All Text or goals in All Text)

#24 (decision* in All Text near/3 aid* in All Text)

#25 pamphlet* in All Text

#26 booklet* in All Text

#27 video* in All Text

#28 decision next aid* in All Text

#29 "patient participation" in All Text

#30 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)

#31 (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)

#32 (#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29)

#33 (#30 or #31 or #32)

#34 MeSH descriptor warfarin this term only

#35 MeSH descriptor Coumarins explode all trees

#36 MeSH descriptor anticoagulants this term only

#37 MeSH descriptor vitamin k explode all trees with qualifiers: AI

#38 oral next anticoagula* in All Text

#39 Oral next anti-coagula* in All Text

#40 ("vitamin K" in All Text and (antagonist* in All Text or inhibitor* in All Text))

#41 "antivitamin K" in All Text

#42 "anti-vitamin K" in All Text

#43 warfarin in All Text

#44 acenocoumarol in All Text

#45 sintrom in All Text

#46 sinthrome in All Text

#47 jantoven in All Text

#48 marevan in All Text

#49 coumadin* in All Text

#50 waran in All Text

#51 phenprocoumon in All Text

#52 nicoumalone in All Text

#53 VKA in All Text

#54 coumarin* in All Text

#55 dicoumarol in All Text

#56 dicumarol in All Text

#57 (#34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43)

#58 (#44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56)

#59 (#57 or #58)

#60 (#33 and #59)

MEDLINE on Ovid

1. Warfarin/

2. acenocoumarol/

3. Coumarins/

4. Phenindione/

5. Dicumarol/

6. Anticoagulants/

7. oral anticoagula$.tw.

8. exp Vitamin K/ai [Antagonists & Inhibitors]

9. warfarin.tw.

10. acenocoumarol.tw.

11. sintrom.tw.

12. sinthrome.tw.

13. jantoven.tw.

14. marevan.tw.

15. coumadin$.tw.

16. waran.tw.

17. Phenprocoumon/

18. nicoumalone.tw.

19. (vitamin k adj3 antagonist$).tw.

20. vitamin k inhibitor$.tw.

21. oral anticoagula$.tw.

22. oral anti-coagula$.tw.

23. vka.tw.

24. antivitamin k.tw.

25. anti-vitamin k.tw.

26. or/1-25

27. Patient Education as Topic/

28. exp Attitude to Health/

29. Patient Participation/

30. ((educat$ or train$ or teach$) adj3 (program$ or intervention$)).tw.

31. (patient$ adj3 (train$ or teach$ or educat$ or inform$)).tw.

32. patient knowledge.tw.

33. Behavior Therapy/

34. Cognitive Therapy/

35. exp counseling/

36. (behavi$ adj3 (therap$ or manage$ or modif$ or chang$ or intervention$)).tw.

37. (cogniti$ adj3 (therap$ or intervention$)).tw.

38. counsel$.tw.

39. Motivation/

40. motivational interview$.tw.

41. contingency management.tw.

42. biofeedback.tw.

43. bio-feedback.tw.

44. goals/

45. (goal$ adj3 set$).tw.

46. decision support techniques/

47. decision$ aid$.tw.

48. exp communications media/

49. pamphlet$.tw.

50. booklet$.tw.

51. video$.tw.

52. or/27-51

53. 26 and 52

54. randomized controlled trial.pt.

55. controlled clinical trial.pt.

56. randomized.ab.

57. placebo.ab.

58. clinical trials as topic.sh.

59. randomly.ab.

60. trial.ti.

61. 54 or 55 or 56 or 57 or 58 or 59 or 60

62. exp animals/ not humans.sh.

63. 61 not 62

64. 53 and 63

EMBASE OVID

RCT filter as recommended in the Cochrane Handbook (Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 (updated September 2009). The Cochrane Collaboration, 2009. Available from www.cochrane-handbook.org.) applied.

1. phenindione/

2. antivitamin K/

3. exp coumarin anticoagulant/

4. anticoagulant agent/

5. warfarin.tw.

6. acenocoumarol.tw.

7. sintrom.tw.

8. sinthrome.tw.

9. jantoven.tw.

10. marevan.tw.

11. coumadin$.tw.

12. waran.tw.

13. nicoumalone.tw.

14. (vitamin k adj3 antagonist$).tw.

15. vitamin k inhibitor$.tw.

16. oral anticoagula$.tw.

17. oral anti-coagula$.tw.

18. vka*.tw.

19. antivitamin k.tw.

20. anti-vitamin k.tw.

21. coumarin$.tw.

22. vitamin K group/po [Oral Drug Administration]

23. or/1-22

24. patient education/

25. attitude to health/

26. patient participation/

27. ((educat$ or train$ or teach$) adj3 (program$ or intervention$)).tw.

28. (patient$ adj3 (train$ or teach$ or educat$ or inform$)).tw.

29. patient knowledge.tw.

30. behavior therapy/

31. cognitive therapy/

32. exp counseling/

33. (behavi$ adj3 (therap$ or manage$ or modif$ or chang$ or intervention$)).tw.

34. (cogniti$ adj3 (therap$ or intervention$)).tw.

35. counsel$.tw.

36. motivation/

37. motivational interview$.tw.

38. contingency management.tw.

39. biofeedback.tw.

40. bio-feedback.tw.

41. (goal$ adj3 set$).tw.

42. decision support system/

43. decision$ aid$.tw.

44. (decision$ adj3 support).tw.

45. mass medium/

46. pamphlet$.tw.

47. booklet$.tw.

48. video$.tw.

49. or/24-48

50. random$.tw.

51. factorial$.tw.

52. crossover$.tw.

53. cross over$.tw.

54. cross-over$.tw.

55. placebo$.tw.

56. (doubl$ adj blind$).tw.

57. (singl$ adj blind$).tw.

58. assign$.tw.

59. allocat$.tw.

60. volunteer$.tw.

61. crossover procedure/

62. double blind procedure/

63. randomized controlled trial/

64. single blind procedure/

65. or/50-64

66. (animal/ or nonhuman/) not human/

67. 65 not 66

68. 23 and 49 and 67

PsycINFO

1. anticoagulant drugs/

2. warfarin.tw.

3. acenocoumarol.tw.

4. coumadin$.tw.

5. waran.tw.

6. nicoumalone.tw.

7. (vitamin k adj3 antagonist$).tw.

8. oral anticoagula$.tw.

9. vka*.tw.

10. coumarin$.tw.

11. or/1-10

12. client education/

13. client participation/

14. behavior therapy/

15. cognitive therapy/

16. exp counseling/

17. motivation/

18. exp goals/

19. biofeedback/

20. decision making/

21. exp communications media/

22. ((educat$ or train$ or teach$) adj3 (program$ or intervention$)).tw.

23. (patient$ adj3 (train$ or teach$ or educat$ or inform$)).tw.

24. patient knowledge.tw.

25. health knowledge/

26. (behavi$ adj3 (therap$ or manage$ or modif$ or chang$ or intervention$)).tw.

27. (cogniti$ adj3 (therap$ or intervention$)).tw.

28. health attitudes/

29. counsel$.tw.

30. motivational interview$.tw.

31. contingency management.tw.

32. biofeedback.tw.

33. bio-feedback.tw.

34. (goal$ adj3 set$).tw.

35. decision$ aid$.tw.

36. (decision$ adj3 support).tw.

37. pamphlet$.tw.

38. booklet$.tw.

39. video$.tw.

40. or/12-39

41. 11 and 40

42. random$.tw.

43. factorial$.tw.

44. crossover$.tw.

45. cross-over$.tw.

46. placebo$.tw.

47. (doubl$ adj blind$).tw.

48. (singl$ adj blind$).tw.

49. assign$.tw.

50. allocat$.tw.

51. volunteer$.tw.

52. control*.tw.

53. "2000".md.

54. or/42-53

55. 41 and 54

CINAHL

S76 S57 and S75

S75 S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73 or S74

S74 TX cross-over*

S73 TX crossover*

S72 TX volunteer*

S71 (MH "Crossover Design")

S70 TX allocat*

S69 TX control*

S68 TX assign*

S67 TX placebo*

S66 (MH "Placebos")

S65 TX random*

S64 TX (doubl* N1 mask*)

S63 TX (singl* N1 mask*)

S62 TX (doubl* N1 blind*)

S61 TX (singl* N1 blind*)

S60 TX (clinic* N1 trial?)

S59 PT clinical trial

S58 (MH "Clinical Trials+")

S57 S17 and S56

S56 S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55

S55 (TI video*) or (AB video*)

S54 (TI booklet*) or (AB booklet*)

S53 (TI pamphlet*) or (AB pamphlet*)

S52 (MH "Communications Media+")

S51 (TI decision* N3 support) or (AB decision* N3 support)

S50 (TI "decision* aid*") or (AB "decision* aid*")

S49 (MH "Decision Support Techniques+")

S48 (TI goal* N3 set*) or (AB goal* N3 set*)

S47 (TI bio-feedback) or (AB bio-feedback)

S46 (TI biofeedback) or (AB biofeedback)

S45 (TI "contingency management") or (AB "contingency management")

S44 (TI "motivational interview*") or (AB "motivational interview*")

S43 (MH "Motivation+")

S42 (TI counsel*) or (AB counsel*)

S41 (TI cogniti* N3 intervention*) or (AB cogniti* N3 intervention*)

S40 (TI cogniti* N3 therap*) or (AB cogniti* N3 therap*)

S39 (TI behavi* N3 intervention*) or (AB behavi* N3 intervention*)

S38 (TI behavi* N3 chang*) or (AB behavi* N3 chang*)

S37 (TI behavi* N3 modif*) or (AB behavi* N3 modif*)

S36 (TI behavi* N3 manage*) or (AB behavi* N3 manage*)

S35 (TI behavi* N3 therap*) or (AB behavi* N3 therap*)

S34 (MH "Counseling+")

S33 (MH "Cognitive Therapy")

S32 (MH "Behavior Therapy")

S31 (TI "patient knowledge") or (AB "patient knowledge")

S30 (TI patient* N3 inform*) or (AB patient* N3 inform*)

S29 (TI patient* N3 educat*) or (AB patient* N3 educat*)

S28 (TI patient* N3 teach*) or (AB patient* N3 teach*)

S27 (TI patient* N3 train*) or (AB patient* N3 train*)

S26 (TI teach* N3 intervention*) or (AB teach* N3 intervention*)

S25 (TI teach* N3 program*) or (AB teach* N3 program*)

S24 (TI train* N3 intervention*) or (AB train* N3 intervention*)

S23 (TI train* N3 program*) or (AB train* N3 program*)

S22 (TI educat* N3 intervention*) or (AB educat* N3 intervention*)

S21 (TI educat* N3 program*) or (AB educat* N3 program*)

S20 (MH "Consumer Participation")

S19 (MH "Attitude to Health")

S18 (MH "Patient Education")

S17 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16

S16 (TI dicumarol) or (AB dicumarol)

S15 (TI dicoumarol) or (AB dicoumarol)

S14 (TI coumarin*) or (AB coumarin*)

S13 (TI VKA*) or (AB VKA*)

S12 (TI phenprocoumon) or (AB phenprocoumon)

S11 (TI coumadin*) or (AB coumadin*)

S10 (TI sintrom) or (AB sintrom)

S9 (TI acenocoumarol) or (AB acenocoumarol)

S8 (TI warfarin) or (AB warfarin)

S7 (TI "antivitamin K") or (AB "antivitamin K")

S6 (TI "vitamin K" N2 inhibitor*) or (AB "vitamin K" N2 inhibitor*)

S5 (TI "vitamin K" N2 antagonist*) or (AB "vitamin K" N2 antagonist*)

S4 (TI oral N2 anti-coagula*) or (AB oral N2 anti-coagula*)

S3 (TI oral N2 anticoagula*) or (AB oral N2 anticoagula*)

S2 (MH "Warfarin")

S1 (MH "Anticoagulants")