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Systematic review and cost-effectiveness evaluation of 'pill-in-the-pocket' strategy for paroxysmal atrial fibrillation compared to episodic in-hospital treatment or continuous antiarrhythmic drug therapy

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Systematic review and cost-effectiveness evaluation of 'pill-in-the-pocket' strategy for paroxysmal atrial fibrillation compared to episodic in-hospital treatment or continuous antiarrhythmic drug therapy

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 08/46/01. The contractual start date was in May 2009. The draft report began editorial review in September 2009 and was accepted for publication in March 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design.The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Systematic review and cost-effectiveness evaluation of 'pill-in-the-pocket' strategy for paroxysmal atrial fibrillation compared to episodic in-hospital treatment or continuous antiarrhythmic drug therapy

C Martin Saborido,[1] J Hockenhull,[1] A Bagust,[1] A Boland,[1] R Dickson[1]* and D Todd[2]

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Background: Atrial fibrillation (AF) is a tachyarrhythmia characterised by unco-ordinated atrial activation with consequent deterioration of impairment of atrial function and a rapid, irregular heartbeat. The annual incidence rate of paroxysmal AF (PAF) has been estimated at 1.0 per 1000 person-years (95% confidence interval 0.9 to 1.1), and reported prevalence rates show wide variations depending on age and country. Conventional treatment strategies for PAF focus on the suppression of paroxysms of AF and return to normal sinus rhythm.
Objectives: To summarise the results of the rapid reviews of the clinical effectiveness and cost-effectiveness literature describing the pill-in-the-pocket (PiP) approach for the treatment of patients with PAF; and to develop an economic model to assess the cost-effectiveness of PiP compared with in-hospital treatment (IHT) or continuous antiarrhythmic drugs (AADs) for the treatment of patients with PAF.
Data sources: Ovid MEDLINE and Ovid OLDMEDLINE 1950 to present with Daily Update were searched. The following electronic databases were searched for ongoing trials: Health Services Research Projects in Progress, ClinicalTrials.gov, metaRegister of Current Controlled Trials, BioMed Central, World Health Organization International Clinical Trials Registry Platform, ClinicalStudyResults.org and the National Library of Medicine Gateway.
Review methods: Inclusion criteria, which included patients suffering from PAF, were independently applied to all identified references by two reviewers (JH and CMS). Electronic searches were conducted to identify clinical effectiveness and cost-effectiveness evidence describing the use of a PiP strategy for the treatment of PAF, published since the release of the Royal College of Physicians' national guidelines on AF in June 2006. A Markov model was constructed to examine differences between three PAF strategies (PiP, AAD and IHT) in terms of cost per quality-adjusted life-year (QALY). A Markov model structure was chosen because it is assumed that PAF is a condition that causes patients to move between a limited number of relevant health states during their lives.
Results: The search strategies for clinical studies identified 201 randomised controlled trials (RCTs). Of the 201 RCTs identified, 12 were deemed to be relevant to the decision problem as they included drugs used to treat PAF; summary data were abstracted from these studies in order to inform the development of the economic model only. The model results indicate that the PiP strategy is slightly less effective than the other two strategies, but also less costly (incremental cost-effectiveness ratio of £45,916 per QALY when compared to AAD, and £12,424 per QALY when compared to IHT). The one-way sensitivity analyses performed do not show substantial changes in relative cost-effectiveness except in relation to the age of patients, where PiP dominates AAD in men over 65 years and in women over 70 years. At a threshold of £25,000 per QALY, IHT has the maximum probability of being cost-effective at this threshold. For threshold values between £0 and £9266 per QALY, PiP is the option exhibiting the maximum probability of being cost-effective. The AAD strategy has a very poor probability of being cost-effective under any threshold. However, none of the strategies considered has more than a 40% probability of being cost-effective at a threshold of £25,000 per QALY at any threshold

level. This demonstrates the uncertainty around the parameters and its effect on the decision to choose any one strategy over the others.
Limitations: Most of the data used to populate the model have been taken from studies with populations that do not match the patient population specified in the decision problem. Populating the model in this way was unavoidable as there was a paucity of published clinical effectiveness and cost-effectiveness data describing a PiP strategy for this highly specific group of patients.
Conclusions: Overall, a PiP strategy seems to be slightly less effective (i.e. fewer QALYs gained) than AAD and IHT, but is associated with cost savings. A PiP strategy seems to be more efficacious and cost-effective than an AAD strategy in men over 65 years and women over 70 years, but this is principally due to a very slight difference in QALY gained by the PiP strategy. A change in clinical practice that includes the introduction of PiP may save costs, but also involves a reduction in clinical effectiveness compared to existing approaches used to treat patients with PAF. Uncertainty in the available clinical data means there was insufficient evidence to support a recommendation for the use of PiP strategy in patients with PAF. Further research should identify outcomes of interest such as adverse events and recurrent AF episodes in an RCT setting because the only clinical study addressing these issues, even partially, is not an RCT but a descriptive analysis. Patient preferences also need to be considered in any future research designs.

Contents

List of abbreviations

AAD	antiarrhythmic drug
A&E	accident and emergency
AE	adverse event
AF	atrial fibrillation
CAF	chronic atrial fibrillation
CI	confidence interval
DC	direct current
ECG	electrocardiogram
EQ-5D	European Quality of Life-5 Dimensions
GP	general practitioner
HRQoL	health-related quality of life
HSRProj	Health Services Research Projects in Progress
HTA	*Health Technology Assessment*
ICER	incremental cost-effectiveness ratio
IHT	in-hospital treatment
LRiG	Liverpool Reviews and Implementation Group
MAE	mean absolute error
NA	not applicable
NICE	National Institute for Health and Clinical Excellence
NETSCC	National Institute of Health Research Evaluation, Trials and Studies Coordinating Centre
NLM	National Library of Medicine
*m*RCT	metaRegister of Current Controlled Trials
NSR	normal sinus rhythm
PAF	paroxysmal atrial fibrillation
PiP	pill-in-the-pocket
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RFA	radiofrequency ablation
RR	relative risk
SA	sensitivity analysis
SF-36	Short Form questionnaire-36 items
SF-6D	Short Form-6 Dimensions
WHO	World Health Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Objectives

1. To summarise the results of the rapid reviews of the clinical effectiveness and cost-effectiveness literature describing the pill-in-the-pocket (PiP) approach for the treatment of patients with paroxysmal atrial fibrillation (PAF).
2. To develop an economic model to assess the cost-effectiveness of PiP compared with in-hospital treatment (IHT) or continuous antiarrhythmic drugs (AADs) for the treatment of patients with PAF.

Background

Atrial fibrillation (AF) is a tachyarrhythmia characterised by unco-ordinated atrial activation with consequent deterioration of impairment of atrial function and a rapid, irregular heartbeat. The patient may experience palpitations, chest pain, dizziness or, in severe cases, loss of consciousness. In some cases, patients with AF may present without any symptoms. An incidence of AF may be self-terminating or require clinical intervention (for example, pharmacological or medical cardioversion). The annual incidence rate of PAF has been estimated at 1.0 per 1000 person-years (95% confidence interval 0.9 to 1.1), and reported prevalence rates show wide variations depending on age and country.

The classification of AF is called the 3 'P' classification: paroxysmal, persistent and permanent. When a patient experiences two or more AF episodes that terminate within 7 days (usually within 48 hours), AF is classified as paroxysmal. If a patient suffers more than one attack and the AF attack lasts longer than 7 days, the AF is classified as persistent. If the AF episode does not resolve for over a year and/or is not successfully terminated by cardioversion, the pattern is classified as permanent.

Conventional treatment strategies for PAF focus on the suppression of paroxysms of AF and return to normal sinus rhythm (NSR). AAD treatment can consist of (i) continuous prophylactic treatment or (ii) episodic IHT. Prophylactic treatment (daily dose) can include the use of beta-blockers, class Ic agents (e.g. flecainide, propafenone) or class III agents (sotalol, amiodarone). Episodic treatment of PAF consists of pharmacological cardioversion usually involving an intravenous infusion of AADs in a hospital setting or, if this fails, electrical direct current cardioversion.

Methods

Electronic searches were conducted to identify clinical effectiveness and cost-effectiveness evidence describing the use of a PiP strategy for the treatment of PAF, published since the release of the Royal College of Physicians' national guidelines on AF in June 2006. An additional search was also undertaken, excluding the term 'pill-in-the-pocket' in order to identify economic evaluations and costing studies describing the comparator treatments to support the development of the economic model.

A Markov model was constructed to examine differences between three PAF strategies (PiP, AAD and IHT) in terms of cost per quality-adjusted life-year (QALY). A Markov model structure was chosen because it is assumed that PAF is a condition that causes patients to move between a limited number of relevant health states during their lives. This type of model allows a large number of cycles to be simulated without having to create a new decision tree in each cycle. The three PAF strategies have the same five health states:

- NSR
- persistent/chronic atrial fibrillation (CAF)
- post-stroke without CAF
- post-stroke with CAF
- death state.

The economic evaluation has been undertaken from an NHS and Personal Social Services perspective. The model has been developed with a cycle length of 1 year and is simulated for the remaining lifetime of all patients.

Results

The search strategies for clinical studies identified 201 randomised controlled trials (RCTs). None of the identified RCTs compared PiP with any other treatment for PAF and therefore did not meet the inclusion criteria for the review. No relevant studies were identified by the search for ongoing trials.

Of the 201 RCTs identified, 12 were deemed to be relevant to the decision problem as they included drugs used to treat PAF; summary data were abstracted from these studies in order to inform the development of the economic model only. The 12 RCTs were all conducted in a hospital setting and prior to the publication of the current national guidelines. One additional study was identified that had informed the evidence considered in *Atrial fibrillation: national clinical guideline for management in primary and secondary care* developed by the National Collaborating Centre for Chronic Conditions in 2006.

The model results indicate that the PiP strategy is slightly less effective than the other two strategies, but also less costly (incremental cost-effectiveness ratio of £45,916 per QALY when compared to AAD, and £12,424 per QALY when compared to IHT). The one-way sensitivity analyses performed do not show substantial changes in relative cost-effectiveness except in relation to the age of patients, where PiP dominates AAD in men over 65 years and in women over 70 years.

The probabilistic sensitivity analysis demonstrates how close the three strategies are to each other, and the uncertainties in the data. All conclusions need to be considered in relation to these uncertainties.

Conclusions

The systematic review of clinical evidence did not identify any new studies that had not been included in the previously available guidelines.

Overall, a PiP strategy seems to be slightly less effective (i.e. fewer QALYs gained) than AAD and IHT, but is associated with cost savings.

A PiP strategy seems to be more efficacious and cost-effective than an AAD strategy in men over 65 years and women over 70 years, but this is principally due to a very slight difference in QALY gained by the PiP strategy.

A change in clinical practice that includes the introduction of PiP may save costs, but also involves a reduction in clinical effectiveness compared to existing approaches used to treat patients with PAF.

Uncertainty in the available clinical data means there was insufficient evidence to support a recommendation for the use of PiP strategy in patients with PAF. Further research should identify outcomes of interest such as adverse events and recurrent AF episodes in an RCT setting because the only clinical study addressing these issues, even partially, is not an RCT but a descriptive analysis.

Patient preferences also need to be considered in any future research designs.

Chapter 1
Introduction

In 2008, a scoping exercise was commissioned by the National Institute of Health Research Evaluation, Trials and Studies Coordinating Centre (NETSCC) in order to address the clinical effectiveness and cost-effectiveness of a pill-in-the-pocket (PiP) strategy for the treatment of patients with paroxysmal atrial fibrillation (PAF). This exercise was carried out by the Liverpool Reviews and Implementation Group (LRiG), Liverpool, UK and was submitted to the NETSCC in early 2009 (see Appendix 1). The scoping exercise concluded that the evidence base for recommending a PiP strategy was limited and that there were no new clinical effectiveness or cost-effectiveness data available to inform clinical decision-making. In order to make use of the limited data available, the NETSCC requested that the LRiG develop an economic model to assess the cost-effectiveness of the PiP strategy compared with other treatments. To inform the economic model, the original literature review searches were updated. This document reports the amalgamated results of the two rapid literature reviews and presents the development and findings of the de novo economic model.

Research question and scope

What is the cost-effectiveness of PiP treatment for those patients with PAF compared to in-hospital treatment (IHT) or antiarrhythmic drug (AAD) therapy?

Objectives of the project

1. To summarise the results of the rapid reviews of the clinical effectiveness and cost-effectiveness literature describing the PiP approach for the treatment of patients with PAF.
2. To develop an economic model to assess the cost-effectiveness of PiP compared with IHT or continuous AAD for the treatment of patients with PAF.

Chapter 2
Background

Overview

Atrial fibrillation (AF) is a tachyarrhythmia characterised by unco-ordinated atrial activation with consequent deterioration of impairment of atrial function and a rapid, irregular heartbeat. AF is characterised on the electrocardiogram (ECG) by the absence of consistent 'P' waves and the presence of irregular rough fibrillation or 'f' waves and irregular QRS complexes. The patient may experience palpitations, chest pain, dizziness or, in severe cases, loss of consciousness. In some cases, patients with AF may present without any symptoms. An AF attack may be self-terminating or require clinical intervention (for example, pharmacological or medical cardioversion).

Atrial fibrillation can result in a degree of haemodynamic instability which can represent a critical condition that requires immediate intervention to alleviate the symptoms. The adverse effects of AF are the result of the haemodynamic instability related to the rapid irregular heart rhythm, and thromboembolic complications (thrombus formation) related to a prothrombotic state (intra-atrial blood stasis, structural heart disease or blood vessel abnormalities, and abnormal platelets and haemostasis). This prothrombotic state is associated with a predisposition to stroke with an approximately threefold greater risk than for people without AF.[1] Fast ventricular rates can cause heart failure in some patients, with a relative risk (RR) of 6.4 compared to people without AF;[1] uncontrolled AF may even precipitate a coronary event with an RR of 2.1 compared to people without AF.[1]

Diagnosis and classification

Atrial fibrillation is sometimes only detected after the patient presents with serious complications of AF (for example, stroke or heart failure). AF is often asymptomatic and can be discovered incidentally during a clinical examination. AF can be detected by screening patients at risk (such as the elderly), or following presentation with symptoms such as breathlessness, palpitations, dizziness or chest pain. When any of the former symptoms are present, manual pulse palpation should be performed to assess the presence of an underlying AF. Once the irregular pulse has been detected, an ECG should be performed. Sometimes the clinician may suspect that AF is paroxysmal (PAF), and in this situation an event-based ECG record or a 24-hour ambulatory ECG monitor is then used. Echocardiography is normally performed in patients with AF in whom there is a suspicion of underlying structural/functional heart disease.

The classification of AF is called the 3 'P' classification:[2] paroxysmal, persistent and permanent (*Table 1*). When a patient experiences two or more AF episodes which terminate within 7 days (usually within 48 hours), AF is classified as paroxysmal. If a patient suffers more than one attack and the AF attack lasts longer than 7 days, the AF is classified as persistent. If the AF episode does not resolve for over a year and/or is not successfully terminated by cardioversion, the pattern is permanent.[3]

Paroxysmal AF, in which the frequency of paroxysms is low, may degenerate into either PAF with more frequent paroxysm, or persistent AF; similarly, persistent AF may degenerate into permanent AF. Persistent AF can be reverted to a normal sinus rhythm (NSR) in those cases where a disease is present and is causing the AF, by treating the underlying condition.

Epidemiology

There is an increasing incidence and prevalence of AF with the increasing age of the population, coupled with comorbidities such as diabetes, hypertension, valve disease, congestive heart failure and stroke. AF may also be caused by some coexisting cardiac and non-cardiac conditions such as acute pneumonia, pulmonary embolism and lung carcinoma. In addition, AF can appear after cardiothoracic surgery such as coronary artery bypass grafting.[4]

A retrospective cohort analysis of the UK General Practice Research Database estimated the incidence

TABLE 1 *Classification of AF subtypes*

Terminology	Clinical features	Arrhythmia pattern
Paroxysmal	Spontaneous termination <7 days and most often <48 hours	Recurrent
Persistent	Not self-terminating	Recurrent
	Lasting >7 days or prior cardioversion	
Permanent ('accepted')	Not terminated	Established
	Terminated but relapsed	
	No cardioversion attempt	

Adapted from Levy *et al.* International consensus on nomenclature and classification of atrial fibrillation: a collaborative project of the Working Group on Arrhythmias and the Working Group on Cardiac Pacing of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Europace* 2003;**5**:119–22.[2]

of chronic AF (CAF) to be 1.7 per 1000 person-years[5] (40- to 89-year-old, and male and female population). It becomes more common with increasing age, occurring in about 5% of people aged over 65 years and in 17.5% of individuals aged over 80 years.[6] The annual incidence rate of PAF has been estimated at 1.0 per 1000 person-years [95% confidence interval (CI) 0.9 to 1.1]. Reported prevalence rates vary (e.g. 22% in France in a cardiology practice setting: age 19–95 years; to 66% in a UK general practitioner (GP) setting: age 40–89 years).[4,7]

In a study by Benjamin *et al.*[8] in 1998, AF was associated with an odds ratio for death of 1.5 for men and 1.9 for woman; the risk of mortality did not appear to be influenced by age. In PAF patients, there was no reported increase in risk of mortality, compared to an age- and gender-matched sample of the general population.

Paroxysmal atrial fibrillation

In clinical practice the presentation of AF is variable. Some patients present with short episodes of AF that cease spontaneously. Others may develop a type of AF that can only be converted to normal NSR by chemical or electrical cardioversion; in some patients NSR cannot be restored. In PAF, each episode comes on suddenly, but will frequently convert to NSR without any treatment within 7 days (usually within 2 days).[3] The period of time between each episode can vary greatly from case to case.

Clinical observation has suggested that PAF is a progressive condition resulting in persistent AF in between 6% and 9% of patients 6 months after the first episode, and persistent AF in up to 25% at 5 years.[4,9] Although this progression may be caused by the deterioration of underlying heart disease in some patients, progression has also been noted in patients without heart disease.[4]

Paroxysmal AF is heterogeneous in presentation and may appear, for example, as an episode lasting 1 or 2 minutes once a year or as an episode which lasts for 10 hours twice a day; clearly the impact of PAF on the quality of life of patients can vary quite considerably. The treatment of PAF must therefore be tailored to meet the requirements of individual patients.

Patients eligible for PiP treatment must by necessity be symptomatic of AF. Therefore, the patients included in the decision problem (*Table 2*) are those diagnosed by a cardiologist with events treated in an accident and emergency (A&E) setting, with intravenous AADs. This is classified as an IHT approach as explained in the next section.

Overview of treatments

Treatment aims

The three main aims of treatment for PAF are:[3]

1. To suppress paroxysm of AF and maintain long-term NSR.
2. To control heart rate during paroxysms of AF if they occur.
3. To prevent the complications associated with PAF (for example, stroke – and tachycardia – induced cardiomyopathy).

Conventional treatment options

Conventional treatment strategies for PAF focus on the suppression of paroxysms of AF and return to

TABLE 2 *Summary of the decision problem and key clinical outcomes*

Population	People with PAF who: have no history of left ventricular dysfunction, or valvular or ischaemic heart disease have a history of infrequent symptomatic episodes of PAF have a systolic blood pressure > 100 mmHg and a resting heart rate > 70 beats per minute are able to understand how, and when, to take the medication have no history of atrial flutter[a]
Intervention	Pill-in-pocket strategy: flecainide propafenone
Comparator	In-hospital episodic antiarrhythmic treatment: propafenone flecainide sotalol amiodarone Continuous prophylactic treatment: propafenone flecainide sotalol amiodarone Radiofrequency ablation (secondary comparator)
Outcomes	Mean time to conversion (from AF to normal sinus rhythm) Conversion rates (from AF to normal sinus rhythm) Frequency of hospital visits Frequency of recurrences Health-related quality of life All-cause death Progression to persistent AF Adverse events rate: conversion to atrial flutter proarrhythmia thromboembolic events

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation.
a This criterion is not included in the National Institute for Health and Clinical Excellence guideline, but was suggested by one clinical expert.

NSR. AAD treatment can consist of (i) continuous prophylactic treatment or (ii) episodic IHT. Prophylactic treatment (daily dose) can include the use of beta-blockers, class Ic agents (e.g. flecainide, propafenone) or class III agents (sotalol, amiodarone).[3] Episodic treatment of PAF consists of pharmacological cardioversion usually involving an intravenous infusion of AADs in a hospital setting, or if this fails electrical direct current (DC) cardioversion. Sometimes electrical DC cardioversion is used in cases where prophylactic treatment is not effective. Several studies have shown propafenone and flecainide can achieve similar efficacy rates in the restoration of NSR.[10–16]

Advice stated in the *British National Formulary*[17] suggests that class I and III agents should be administered under the supervision of a hospital physician, but it is stressed that this does not necessarily mean that the patient has to be hospitalised and that it is the decision to administer the drug that requires the necessary expertise.

Pill-in-the-pocket strategy

Pharmacological cardioversion requires IHT; however, with the development of oral AADs, immediate out-of-hospital treatment is possible.

This strategy is referred to as PiP. Patients meeting pre-established criteria are provided with an oral dose of an AAD which they self-administer at the onset of an episode of PAF. No training is needed, but treatment advice is given during the consultant appointment. This allows for immediate intervention with the objective of converting to NSR without the need for hospital-based treatment. Such a strategy also avoids the need for continuous prophylactic treatment. Drugs used in the PiP strategy are mainly flecainide or propafenone, changing to daily sotalol if the former drugs fail.[3]

Interventional procedures

Recently published studies[18–21] have described a new approach to the treatment of PAF: radiofrequency ablation (RFA). RFA has been described as an effective interventional treatment for PAF as it can reduce recurrence and costs. Despite the high costs of the procedure, this alternative has been reported to be cost-effective when compared with AAD therapy from as early as 2 years after the intervention.[19] Unfortunately, there are no data available to allow assessment of the effectiveness of RFA in reducing progression as well as recurrence, as the currently available studies all have short follow-up periods.

Adverse events

The three options mentioned above (IHT, PiP and AAD) have a common adverse event (AE) which is proarrhythmia. This is an arrhythmia paradoxically precipitated by antiarrhythmic therapy, which means it is a side effect associated with the administration of some existing AADs. The treatment for proarrhythmia is electrical DC cardioversion.

Another AE related to the use of continuous AADs (mainly associated to amiodarone) is drug toxicity which mainly affects the lungs. In the case of episodic in-hospital AAD treatment, AEs could also occur due to the nature of intravenous administration and the risks associated with hospitalisation.

Licensed indications

The licensed indications of the drugs prescribed or administered in hospital to treat PAF are quite similar, with the exception of amiodarone, which should be initiated in hospital or under specialist supervision. A complete list of indications can be found in *Table 32* in Appendix 2.

In 2006, the National Collaborating Centre for Chronic Conditions issued guidelines relating to the treatment of AF and PAF.[3] The guidelines state that where patients have infrequent paroxysms and few symptoms, or where symptoms are induced by known precipitants (such as alcohol, caffeine), a 'no drug treatment' strategy or a PiP strategy should be considered and discussed with the patient. In patients with PAF, a PiP strategy should be considered in those who:

- have no history of left ventricular dysfunction, or valvular or ischaemic heart disease
- have a history of infrequent symptomatic episodes of PAF
- have a systolic blood pressure > 100 mmHg and a resting heart rate above 70 beats per minute
- are able to understand how to, and when to, take the medication.

Costs

Costs of the drugs used in the treatment of PAF are included in the *British National Formulary*.[17] Costs vary depending on the number of tablets dispensed and whether generic or branded formulations are used. A summary of the drug costs used for PAF treatment is presented in *Table 33* of Appendix 2.

Overview

In summary, PAF is a condition that tends to progress to a chronic condition for many patients despite treatment. The current possible treatments for PAF are as follows:

- continuous prophylactic AAD treatment (class Ic agents such as flecainide, propafenone or class III agents such as sotalol, amiodarone).
- IHT with the same AADs.
- episodic PiP treatment with the same AADs.

Chapter 3

Methods for identifying published clinical effectiveness and cost-effectiveness evidence

Electronic searches were conducted to identify clinical effectiveness and cost-effectiveness evidence describing the use of a PiP strategy for the treatment of PAF published since the release of the Royal College of Physicians' national guidelines on AF in June 2006.[3]

Identification of evidence: clinical evidence

Search strategy

Using gold standard systematic review methodology, 'Ovid MEDLINE® and Ovid OLDMEDLINE® 1950 to present with Daily Update' was searched using the search strategies described in Appendix 3 to identify randomised controlled trials (RCTs), systematic reviews and economic evaluations. Search terms for electronic databases included a combination of index terms for AF and free text words for the technologies involved (e.g. drug names). Data from relevant papers were then extracted by one reviewer (JH) and cross checked by a second (CMS).

The following electronic databases were searched for ongoing trials:

- Health Services Research Projects in Progress (HSRProj).
- ClinicalTrials.gov.
- metaRegister of Current Controlled Trials (*m*RCT).
- BioMed Central.
- World Health Organization (WHO) International Clinical Trials Registry Platform.
- ClinicalStudyResults.org.
- National Library of Medicine (NLM) Gateway.

Reference lists of potentially relevant studies were searched to identify other relevant studies of clinical effectiveness, cost-effectiveness or costs. All of the references were exported to an ENDNOTE bibliographic database (Version X2, Thomson ISI ResearchSoft, CA, USA).

Methods for reviewing clinical effectiveness

Inclusion criteria

Inclusion criteria, as outlined in *Table 3*, were independently applied to all identified references by two reviewers (JH and CMS).

Exclusion criteria

Randomised controlled trials were excluded if they provided data on only a subgroup of the enrolled patients.

Data extraction

Where appropriate, data extraction was carried out by one reviewer (JH) and checked by another (CMS). Summary data were abstracted into pre-defined data extraction forms created within an ACCESS database (Microsoft Corporation). Data were abstracted under the following headings: study, treatment, comparator, number of patients, duration of AF prior to treatment, setting, follow-up, mean time to conversion, conversion rate, frequency of hospital visits, frequency of recurrence, health-related quality of life (HRQoL), progression to persistent AF, conversion to AF, proarrhythmia, thromboembolic events, death and AEs.

Quality assessment and data analysis

No studies met the inclusion criteria and therefore no quality assessment of the studies could be undertaken. Data relevant to other aspects of the project are presented in tables.

Identification of evidence: cost-effectiveness

The search used to identify relevant economic evaluations for inclusion in the review of cost-

TABLE 3 *Inclusion criteria for RCTs and systematic review*

Population	Paroxysmal atrial fibrillation
Intervention	Pill-in-pocket treatment, i.e. single oral dose
Comparator	Continuous prophylactic treatment with:
	propafenone
	flecainide
	beta blockers
	sotalol
	amiodarone
	In-hospital episodic antiarrhythmic treatment:
	propafenone
	flecainide
	beta-blockers
	sotalol
	amiodarone
	Radiofrequency ablation (secondary comparator)
Outcomes	Mean time to conversion (from atrial fibrillation to normal sinus rhythm)
	Conversion rates (from atrial fibrillation to normal sinus rhythm)
	Number of hospital visits

effectiveness evidence is described in Appendix 3. An additional search was also undertaken, excluding the term 'pill-in-the-pocket' in order to identify economic evaluations and costing studies that include the comparator treatments (i.e. searches with the specific name of several drugs in order to capture all data about the interventions). It was envisaged that this information would be used to support the development of the economic model.

Methods for reviewing cost-effectiveness

Inclusion criteria

In addition to the inclusion criteria outlined in *Table 3*, the following criteria had to be met for inclusion in the review of cost effectiveness evidence:

Study design Full economic evaluations that compared two or more options and considered both costs and consequences including: cost-effectiveness analysis, cost–utility analysis, cost–benefit analysis and cost-minimisation analysis.

Data extraction

Where appropriate, data extraction was carried out by one reviewer (JH) and checked by another (CMS). Summary data were abstracted into pre-defined data extraction forms created within an ACCESS database.

Quality assessment and data analysis

No studies met the inclusion criteria and therefore no quality assessment of the studies could be undertaken. Data relevant to other aspects of the project are presented in tables.

Chapter 4

Review of published clinical effectiveness and cost-effectiveness evidence

Randomised controlled trial clinical evidence

The search strategies described in Appendix 3 identified 201 RCTs. None of the RCTs identified were appropriate for inclusion in the review as none of the studies compared PiP with any other treatment for PAF. No relevant studies were identified by the search for ongoing trials.

One[22] of the 201 studies had been erroneously labelled as an RCT, but was in fact not a study, and included PiP as a treatment strategy; this investigation was conducted prior to the publication of the national guidelines.[3] As it was not a study it was not considered to be eligible for inclusion in the review. However, this Italian paper looked specifically at the feasibility of a PiP strategy for the treatment of PAF and appears to be the sole evidence considered in *Atrial fibrillation: national clinical guideline for management in primary and secondary care*[3] developed by the National Collaborating Centre for Chronic Conditions in 2006. The results of the Alboni *et al.*[22] 'before and after' paper suggested that, in a carefully selected patient population, a PiP strategy could yield reduced inpatient admissions and A&E visits compared to IHT.

Of the 201 studies identified, 12 RCTs[10–16,23–27] were deemed to be related to the decision problem as, although they did not included PiP as an intervention or comparator, they did include drugs used to treat PAF; summary data were abstracted from these studies (see Appendix 4, *Table 39*) in order to inform the development of the economic model only. The 12 RCTs were all conducted in a hospital setting prior to the publication of the national guidelines.[3]

In summary, the evidence described in these studies indicates that flecainide and propafenone have similar effectiveness in relation to conversion to NSR up to 8 hours. Some studies report that intravenous flecainide shows higher conversion rates than oral flecainde[23,24] and that oral flecainide shows similar conversion rates than intravenous propafenone. All studies assessing the efficacy of oral flecainide and propafenone reported favourable results in comparison to other treatment strategies. Oral sotalol was not found to be as efficacious as intravenous digoxin–quinidine.[25]

Systematic review clinical evidence

The search strategies described in Appendix 3 identified 11 systematic reviews.[28–38] Of these, five potentially relevant reviews were identified during the application of the inclusion/exclusion criteria (*Table 4*);[30,32,35–37] only one of the reviews was published after the publication of the national guidelines.[3] Again, none of the RCTs identified from these reviews were appropriate for inclusion in the review of clinical effectiveness as none compared PiP with any other treatment for PAF.

Four[30,32,35,36] of the five reviews focused solely on oral AADs and, of these, three[30,35,36] concluded that a single oral dose of propafenone was effective in converting PAF to NSR. One review[30] also considered flecainide and concluded that as flecainide had more favourable pharmacokinetics it was preferred to propafenone.

Economic evidence

The search strategies described in Appendix 3 identified 11 potentially relevant economic evaluations.[39–49] However, none of the economic evaluations identified were appropriate for inclusion in the review as none of the studies compared PiP with any other treatment for PAF.

An additional search of published references was then undertaken to identify any relevant cost studies describing any treatment for PAF. This additional search was not restricted to studies only describing a PiP strategy, as the aim was to identify cost or cost-effectiveness studies that included other drugs used to treat PAF, with the objective of including any relevant data in the economic

TABLE 4 *Summary of review evidence*

Review	Focus of review	Oral or IV	Conclusion
Deneer 2004[30]	Oral antiarrhythmic drugs in converting recent-onset AF	Oral	Propafenone and flecainide are effective in converting recent-onset AF
Ferreira 1997[32]	Effectiveness of sotalol in converting AF to sinus rhythm	Oral	Published studies did not support sotalol for the conversion of AF to sinus rhythm
Hughes 1997[35]	Oral propafenone for rapid conversion of recent-onset AF	Oral	A single 600-mg oral dose of propafenone is highly effective at restoring sinus rhythm in patients with AF with few adverse effects
Khan 2001[36]	Single oral dose of propafenone for pharmacological cardioversion of recent-onset AF	Oral	A single oral dose of propafenone is highly effective
Slavik 2001[37]	Pharmacological conversion of AF	Oral or IV	For recent-onset AF, procainamide is the preferred IV agent and propafenone is the preferred oral agent

AF, atrial fibrillation; IV, intravenous.

model. In total, nine studies[18–21,50–54] were identified and considered useful for the development of the economic model. Summary details of the nine studies are provided in *Table 5*. Only one of the studies[21] was published prior to the publication of the national guidelines.[3]

Implications of the evidence found

Owing to the lack of relevant information found in the published literature, we have had to use data from many different sources, which has lead us to make some assumptions. The resulting economic model has been built with these assumptions in mind and was based on the available information (e.g. probability of return to 'post stroke no CAF' health state after the second stroke, data from Lothian stroke registry)[55] or extracting single probabilities from several studies which addressed similar, but not identical, objectives (e.g. probability of progressing to CAF from NSR, data taken from Kerr *et al.*[9] and Ruigomez *et al.*[4]). Sometimes lack of available data might present some inconsistencies and these have been tested in the sensitivity analysis (SA) and probabilistic SA (PSA). In order to assess the quality of these studies, they have been classified in *Table 41* according to the kind of study. The cohort studies have been assessed in *Table 42*, the RCT and non-RCT in *Table 43* and the case–control study in *Table 44* (all these tables are in Appendix 5). The *Health Technology Assessment* (HTA) report has been described in *Table 5*.

TABLE 5 *Summary of relevant cost-effectiveness evidence*

Study	Author	Relevancy
Cost-effectiveness of atrial fibrillation catheter ablation	Andrikopoulos *et al.* 2009[20]	Review of studies describing the cost of AF catheter ablation
Epidemiology and economic burden of atrial fibrillation	Bajpai *et al.* 2007[50]	Summary of data from other studies and focusing on US setting
Cost-effectiveness of radiofrequency catheter ablation for atrial fibrillation	Chan *et al.* 2006[51]	Decision-analytic model to evaluate the cost-effectiveness of LACA in 55- and 65-year-old cohorts with AF at moderate and low stroke risk
Cost comparison of catheter ablation and medical therapy in atrial fibrillation	Khaykin *et al.* 2007[18]	Cost-analysis of the population in CARAF registry
Cost comparison of ablation versus antiarrhythmic drugs as first-line therapy for atrial fibrillation: an economic evaluation of the RAAFT pilot study	Khaykin *et al.* 2009[19]	Decision-analytic model using data on AF recurrence, hospitalisation rates, AAD use and treatment crossover rates derived directly from the Trial of RFA versus AAD as First-line Treatment of symptomatic atrial fibrillation (RAAFT)
The costs of care in atrial fibrillation and the effect of treatment modalities in Germany	McBride *et al.* 2009[52]	A 6-month multicentre prospective observational cohort study with additional 3-month retrospective clinical data collection was performed in physician practices. Cost calculation was from the health-care payer perspective
Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation	Rodgers *et al.* 2008[53]	Systematic review of clinical studies and economic evaluations of catheter ablation for AF and typical atrial flutter. A decision model was developed to evaluate a strategy of RFA compared with long-term AAD treatment alone in adults with paroxysmal AF
Costs of atrial fibrillation in five European countries: results from the Euro Heart Survey on atrial fibrillation	Ringborg *et al.* 2008[54]	This is a bottom-up cost study conducted for the five largest contributors in terms of patients enrolled from the Euro Heart Survey on AF in 2003 and 2004
Cost analysis of catheter ablation for paroxysmal atrial fibrillation	Weerasooriya *et al.* 2003[21]	The authors performed a retrospective cost comparison of RFA vs drug therapy for PAF

AAD, antiarrhythmic drugs; AF, atrial fibrillation; CARAF, Canadian registry of atrial fibrillation; LACA, left atrial catheter ablation; PAF, paroxysmal atrial fibrillation; RFA, radiofrequency ablation.

Chapter 5

Methods for economic evaluation and development of an economic model

Objective

The objective of this economic evaluation was to build a long term economic model in order to examine differences between three PAF strategies (PiP, AAD and IHT) in terms of cost per quality-adjusted life-year (QALY).

Economic evaluation framework

Treatment strategies

The three strategies to be compared were:

1. Pill-in-the-pocket

When a patient first experiences an episode of PAF, he or she is treated in hospital or possibly by a GP. The patient is then directed by the hospital consultant to take a single oral dose of a drug (flecainide or propafenone) each time he or she feels symptoms of tachycardia in order to try to cardiovert new PAF event recurrences. The patient must rest after taking the drug for at least 4 hours or until the palpitations have stopped. After this, the PAF event usually resolves, but a range of scenarios can occur:

(i) The patient's NSR returns.
(ii) The PiP does not work and the patient has to attend hospital for electrical DC cardioversion followed by 4 weeks of warfarin treatment.
(iii) The patient suffers a proarrhythmia event and needs to attend hospital for electrical DC cardioversion with warfarin treatment.
(iv) The patient suffers a minor AE (this is not included in the model).

Following events (ii) or (iii), the patient may either progress to persistent chronic AF (CAF in the model) or the patient may return to NSR. The patient could also suffer a stroke, a potentially serious consequence of PAF. If a stroke is suffered, the patient begins oral anticoagulation treatment with warfarin. After the first stroke, the patient will progress to the CAF state if the stroke is severe, or receive PiP treatment if the stroke is less severe. The model also allows a patient to suffer a subsequent stroke if the patient returned to PiP treatment after the first stroke. The reason for this is that the model is focused on the PiP strategy in PAF, not in CAF. As a consequence of oral anticoagulation treatment the patient can suffer bleeding events. Patients can also die from any cause. All patients in the three strategies who progress to CAF exchange their current drug treatment or episodic IHT for a rate control treatment consisting of a daily dose of beta-blocker or calcium-channel blocker (Appendix 6, *Figure 4*).

2. Antiarrhythmic drug treatment

In this strategy, the patient takes a drug (flecainide or propafenone) every day in order to reduce the frequency of PAF event recurrences. The possible scenarios are:

(i) The patient can suffer a proarrhythmia due to the drug intake and therefore may need treatment in hospital (electrical DC cardioversion) after which the patient may progress to CAF or return to NSR.
(ii) The patient can have a PAF event and need in-hospital chemical cardioversion (conversion to NSR with an intravenous drug treatment) or more likely an electrical DC cardioversion. After this cardioversion, the patient can return to NSR or progress to CAF if treatment fails. As in the PiP strategy, the patient can suffer from a stroke and stroke-related consequences (Appendix 6, *Figure 5*).

3. In-hospital treatment

This arm represents the patient going to hospital for emergency treatment whenever he or she feels symptoms to receive chemical cardioversion (conversion into a NSR with an intravenous drug treatment). The possible scenarios are then:

(i) The chemical cardioversion does not work (10–20% of patients) and the patient receives an electrical DC cardioversion, returning to NSR or progressing to CAF if DC cardioversion fails.

(ii) The patient can suffer a proarrhythmic AE during the treatment of the PAF event and need an electric DC cardioversion after which he or she moves to CAF or returns to NSR. The remaining pathways are similar to the other two strategies (Appendix 6, *Figure 6*).

Radiofrequency ablation was not considered as a strategy in the economic model for two reasons: firstly, there was very limited published evidence on clinical effectiveness, and secondly, the population characteristics of published economic evaluations and clinical studies describing RFA were very different from those described in the PiP protocol, i.e. the population in most of the RFA trials has been in AAD before randomisation and only a few of the trials have 100% of patients in PAF.

A summary of the different treatments at every stage is provided in *Table 6*. The pathways and events related to stroke events are not shown as there is no difference between strategies in relation to strokes.

Population

People with PAF who:

- have no history of left ventricular dysfunction, or valvular or ischaemic heart disease
- have a history of infrequent symptomatic episodes of PAF
- have a systolic blood pressure > 100 mmHg and a resting heart rate above 70 beats per minute
- are able to understand how, and when, to take the medication
- have no history of atrial flutter.

The patient characteristics described in the protocol are not matched by the patient populations described in any of the clinical or cost studies retrieved by the searches. The patient characteristics were extracted directly from the National Institute for Health and Clinical Excellence (NICE) clinical guideline on AF[3] which defines the patient characteristics of people receiving PiP treatment. Consequently, all of the parameters used in the economic model are derived using the best data approximations from a range of available published clinical and cost studies.

The population in the economic model has a mean age of 60 years and includes 58% male patients as described in the Alboni *et al.* study.[21] The model only takes account of gender in relation to risk of death, allowing the simulation of a cohort of women or men. The model is used to simulate a cohort of 1000 patients.

Study perspective

The economic evaluation has been undertaken from an NHS and Personal Social Services perspective.

TABLE 6 *Summary of stages in all strategies*

Stages / Strategies	NSR	PAF event	PAF event treatment fail	Proarrhythmia event
PiP	No treatment	Single oral dose of flecainide or propafenone	Electrical cardioversion DC + warfarin treatment for 4 weeks and change antiarrhythmic treatment by rate control (CAF)	Electrical DC cardioversion + warfarin treatment for 4 weeks
AAD	Daily dose of flecainide or propafenone	Electrical DC cardioversion + warfarin treatment for 4 weeks	Change antiarrhythmic treatment by rate control (CAF)	Electrical DC cardioversion + warfarin treatment for 4 weeks
IHT	No treatment	IV infusion of flecainide or propafenone	Electrical cardioversion DC + warfarin treatment for 4 weeks and change antiarrhythmic treatment by rate control (CAF)	Electrical DC cardioversion + warfarin treatment for 4 weeks

AAD, antiarrhythmic drugs; CAF, chronic atrial fibrillation; DC, direct current; IHT, in-hospital treatment; IV, intravenous; NSR, normal sinus rhythm; PAF, paroxysmal atrial fibrillation; PiP, pill-in-the-pocket.

Time horizon

The model has been developed with a cycle length of 1 year and is simulated for the remaining lifetime of all patients.

Model framework

A Markov model was constructed to carry out the economic evaluation. A Markov model structure was chosen because it is assumed that PAF is a condition that causes patients to move between a limited number of relevant health states during their lives. This type of model allows a large number of cycles to be simulated without the need to create a new decision tree in each cycle.

The three PAF strategies described above have the same five health states:

- *NSR* Patients enter the model in this state following successful treatment of their first PAF event.
- *Persistent/chronic AF* This state follows progression of the condition due to proarrhythmia or failure of PAF treatment, or simply because PAF naturally tends to progress over time. People in this state are switched from their initial treatment strategy to rate control treatment (beta-blocker or calcium-channel blocker). This change follows the current national clinical guideline for management of AF in primary and secondary care.[3]
- *Post-stroke without CAF (returning to PiP, AAD or IHT strategy)* Any patient can suffer a mild stroke/transient ischaemic attack (remaining independent). In this health state, patients can suffer the same events as in NSR and may also experience bleeding events due to oral anticoagulation treatment (warfarin).
- *Post-stroke with CAF* Patients enter this state after a moderate or severe stroke (dependent patient). Patients are similar to those patients in post-stroke without CAF, but patients are receiving both oral anticoagulation treatment and rate control treatment.
- *Death state* This is the absorbent state. Patients may die from any other state with a general population mortality risk, or with a specific mortality risk related to a particular condition (e.g. stroke, AF).

While in these states patients may suffer from a variety of events depending on the strategy:

- *Initial stroke* This event is common to all strategies and is one of the most important events affecting PAF patients.
- *Subsequent stroke* Any event occurring after recovery from an initial stroke.
- *PAF* PAF is a recurrent PAF event.
- *AE* The main AE that a patient can suffer related to AADs is proarrhythmia. Other minor AEs can be present, but owing to their small cost and minor clinically importance, the model only takes account of proarrhythmia as an AE.
- *Bleeding events* These can occur in all three strategies and are related to the warfarin treatment administered to all patients following a stroke.

Parameters

All the parameters used in the model are listed with their sources with details presented in *Tables 7–12*. Parameters are derived from different sources owing to the lack of a single RCT to provide data on all the events needed to reflect the natural pathways of the disease and its treatment. Although the best data approximation has been attempted, a number of assumptions have been made in the development of the model. In the three strategies, some transition probabilities have been calculated based on the progression to CAF and the risk of death: this is because the latter changes over time and therefore the former needs to be able to reflect these changes. All probabilities are shown in *Table 7*.

Costs

- The cost of a chemical cardioversion in IHT strategy has been assumed equivalent to the cost of an 'Arrhythmia or Conduction Disorders without CC' in the 2007–8 *NHS reference costs*[56] and inflated to 2009 prices.
- The cost of being in the CAF state has been assumed to be the cost of treatment with sotalol 240 mg/day, but following recommendations from the clinical advisor, SA has been carried out using atenolol 50 mg or diltiazem LA 200 mg once a day. The annual cost of being in NSR in the PiP and IHT strategies is assumed to be zero, because patients do not receive any drugs in the absence of PAF events.
- The cost of a PAF event depends on the strategy: PiP costs are related only to the drug dose. IHT and AAD costs are those associated with hospital treatment of the event as stated previously.

- The cost associated with a stroke death has been included in order to reflect the use of resources from stroke until death, but no other costs for any other causes of death have been estimated. This is an acceptable approximation which has been found to have very little effect on the results of the model.

Utility

- The utility of death has been assumed to be zero.
- The disutility of suffering a PAF event has been assumed to be 7 days with the value of PAF (the maximum number of days a patient can be in AF before he or she progresses to CAF).[3]
- The disutility of suffering a proarrhythmia event has been assumed to be equivalent to 1 additional day in hospital after a PAF event.
- The disutility associated with the failure of PAF treatment and consequent electrical DC cardioversion has been assumed to be equivalent to 1 additional day in hospital for patients in all strategies.
- The disutility value of having suffered a stroke is assumed to be 0.38 (the utility value associated with a dependent patient after a stroke).
- To estimate the disutility associated with a bleeding event, it is assumed that a patient's previous utility value is reduced by 15% for 5 days.[57]

Transition probabilities

The transition probabilities used in the economic model have been estimated from several sources, but are derived mainly from the Alboni *et al.* study.[22] The transition probabilities that relate to stroke events have been calculated from several registries.[55,58–60] To estimate the rates of disease progression, data from a UK general practice registry of AF[4] have been used alongside data from the Canadian AF registry.[9] These are the most populated published registries as well as the most cited in the economic evaluation study from Rodgers *et al.*,[53] which is a systematic review and economic evaluation of curative catheter ablation in AF and atrial flutter, comparing ablation with long-term antiarrhythmic treatment. Some transition probabilities have been taken from a previous HTA report describing catheter ablation versus AAD.[53] This data source has been used primarily because of the limited data available to describe the PAF population specified in the NICE guidance[3] and also in the protocol.

The probability of remaining in NSR in the IHT and PiP strategies is assumed to be the same, but differs in the AAD strategy because (owing to the medication) the probability of remaining in NSR is higher. This is based on results of an RCT described by Pappone *et al.*[61] in which all the patients were in PAF and the main outcome was freedom from arrhythmia at 12 months.

The risk of bleeding has been calculated from a recent paper on bleeding risks associated with warfarin treatment,[62] which describes the risk of bleeding in people with AF in a UK setting. Because only 10% of the population in the published study had PAF and the mean age was 72.3 (standard deviation 10.3) years, an SA has been carried out as part of the economic evaluation to test the robustness of the model results to this parameter.

When treating PAF events, it is assumed that all of the available drugs are equally efficacious as used in all three strategies, because all the drugs (either oral or intravenous administration) achieve similar conversion rates within 24/48 hours.[10–16] It is also assumed that the probability of progressing from PAF to CAF is the same in the three strategies. The risk of death in the NSR state is taken to be the risk of death in the general population, taken from published mortality rates.[63] This assumption is based on the paper by Ruigomez *et al.*[4] which states that the RR of death from CAF versus PAF is 1.5. Finally, the transition probabilities from post-stroke without CAF (PiP, AAD or IHT) are assumed to be the same as in the NSR state, with the exception of the risk of bleeding,[62] risk of death[55] and risk of a new stroke[55,59] where the probabilities have been estimated from the published literature. All transition probabilities are listed in *Tables 7–10*.

The rate of progression from AF to CAF has been calculated from the paper by Ruigomez *et al.*,[4] which relates to a follow-up period of more than 4 years, and appears to indicate the presence of a long-term plateau in risk. However, clinical advice suggests that in clinical practice this effect is not apparent, and there seems to be a continuous upward trend in the risk of progression to persistent AF. To take account of this advice, an exponential function has been fitted to the data from the Ruigomez *et al.* paper[4] as shown in *Figure 1*. The model employs the original data for the first 4 years, combined with exponential projections thereafter with a maximum probability of progression of 45% (year 10).

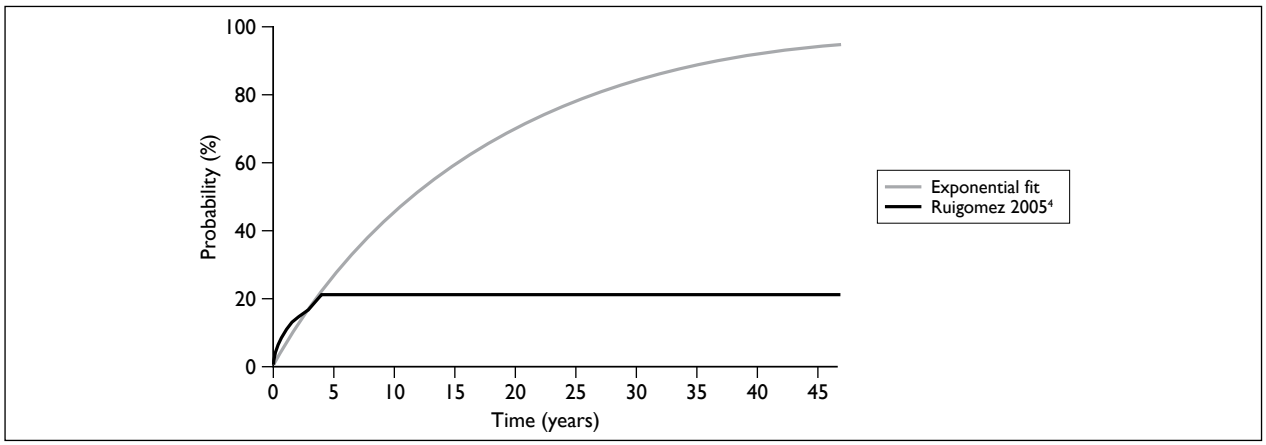

FIGURE 1 *Progression chart – progression to chronic atrial fibrillation.*

TABLE 7 *Transition probabilities used in all strategies*

Parameter	Value	Source
Probability of keeping an NSR in IHT and PiP	0.1952	Alboni 2004[22]
Probability of dying from post-stroke state in all strategies	0.25	Wardlaw 1998[58]
Probability of progressing after a (moderate and severe) stroke all strategies	0.3809	SPAF 1991[60]
Probability of first stroke in all strategies	0.022	SPAF 1998[57]
Probability of dying after being in post-stroke + CAF in all strategies	0.3750	Wardlaw 1998,[58] Ruigomez 2005[4]
Probability of return to NSR after a stroke in all strategies	0.5714	SPAF 1991[60]
Probability of death from NSR in all strategies (all-cause death)	Death risk (life tables)	Mortality rates[63]
Probability of death from CAF (RR = 1.5 risk of death) in all strategies	RR × life tables	Ruigomez 2005[4]
Probability of progressing to CAF from NSR in all strategies	Mean_progression	Kerr 2005,[9] Ruigomez 2005[4]
Probability of progressing to CAF from post-stroke in all strategies	Mean_progression	Kerr 2005,[9] Ruigomez 2005[4]
Probability of suffering a second stroke from post-stroke in all strategies	0.0175	Wardlaw 1998,[58] Birman-Deych 2006[59]
Probability of keeping post-stroke state in PiP and IHT strategies (after the first stroke)	0.1952	Alboni 2004[22]
Risk of a bleeding event in all strategies	0.0965	Wallerstedt 2009[62]
Probability of dying after the first stroke in all strategies	0.0476	SPAF 1991[60]
Probability of progress post-CAF after the second stroke	0.29	SPAF 1998[57]
Probability of dying after the second stroke	0.25	Wardlaw 1998[58]
Probability of return to post-stroke no CAF after the second stroke in all strategies	0.46	Author assumption

CAF, chronic atrial fibrillation; IHT, in-hospital treatment; NSR, normal sinus rhythm; PiP, pill-in-the-pocket; RR, relative risk; SPAF, Stroke Prevention in Atrial Fibrillation study.

TABLE 8 *Transition probabilities used in the PiP strategy*

Parameter	Value	Source
Probability of efficacy of the PAF treatment	0.9455	Alboni 2004[22]
Probability of proarrhythmia	0.0061	Alboni 2004[22]
Probability of return to NSR after proarrhythmia event	1.00	Alboni 2004[22]
Probability of progressing to CAF after proarrhythmia event	0.00	Alboni 2004[22]
Probability of PAF treatment fail	1 – probability of proarrhythmia Probability of efficacy	Author assumption
Probability of return to NSR after electrical DC cardioversion	0.7820	Dankner 2009[65]
Probability of progressing to CAF after DC electrical cardioversion	0.2180	Dankner 2009[65]
Probability of recurrences	1 – probability of keeping NSR Probability of a stroke Mean_progression Mortality risk	Author assumption
Probability of keeping CAF state	1 – relative risk × life table mortality risk	Author assumption
Probability of being in post-CAF	1 – probability of dying after being in post-stroke CAF	Author assumption
Probability of recurrences after post-stroke	1 – probability of keeping post + PiP Probability of suffering a new stroke in post + PiP Risk of bleeding event Probability of dying post + PiP Mean_progression risk	Author assumption

CAF, chronic atrial fibrillation; DC, direct current; NSR, normal sinus rhythm; PAF, paroxysmal atrial fibrillation; PiP, pill-in-the-pocket.

Model validation

The model has been validated clinically by a clinical advisor and methodologically by the LRiG team.

Clinical outcome data

Clinical outcomes in published studies

The main clinical effectiveness outcomes in the published studies and therefore considered in this economic evaluation were:

- mean time to conversion (from AF to NSR)
- conversion rates (from AF to NSR)
- frequency of hospital visits
- frequency of recurrences
- HRQoL
- all-cause death
- progression to chronic condition of AF
- AEs rate:
  - conversion to atrial flutter
  - proarrhythmia
  - thromboembolic events.

Efficacy

Conversion rates from AF to NSR appear to be very similar for each of the drugs employed in the three strategies;[11–13,15,23,24] as described by the papers summarised in the literature search. In all cases, the conversion rates are very similar at 8 hours between intravenous and oral administration of flecainide and propafenone. However, there are no published studies that directly compare the three strategies in terms of clinical effectiveness.

In order to reflect the HRQoL associated with the three strategies, the number of PAF recurrences, rate of all-cause death, progression rate from PAF to CAF and a range of AEs are taken into account in the model as they affect the estimates of the QALYs used to calculate incremental cost-effectiveness ratios (ICERs) in the economic evaluation.

TABLE 9 *Transition probabilities used in the IHT strategy*

Parameter	Value	Source
Probability of efficacy of the PAF treatment	0.5920	Dankner 2009[65]
Probability of proarrhythmia	0.006	Kaufman 2009[66]
Probability of return to NSR after proarrhythmia	1.00	Alboni 2004[22]
Probability of progressing to CAF after proarrhythmia	0.00	Alboni 2004[22]
Probability of PAF treatment fail	1 – probability of proarrhythmia Probability of efficacy	Author assumption
Probability of return to NSR after DC electrical cardioversion	0.7820	Dankner 2009[65]
Probability of progressing to CAF after electrical DC cardioversion	0.2180	Dankner 2009[65]
Probability of recurrences	1 – mean progression Mortality risk Probability of keeping NSR Probability of a stroke	Author assumption
Probability of keeping CAF state	1 – relative risk × life table mortality risk	Author assumption
Probability of being in post-CAF	1 – probability of dying after being in post-stroke CAF	Author assumption
Probability of recurrences after post-stroke	1 – probability of keeping post + IHT Probability of suffering a new stroke in post + IHT Risk of bleeding event Probability of dying post + IHT Mean_progression risk	Author assumption

CAF, chronic atrial fibrillation; DC, direct current; NSR, normal sinus rhythm; PAF, paroxysmal atrial fibrillation; PiP, pill-in-the-pocket.

Health-related quality of life

Health-related quality of life data used in the model were estimated from several published papers that have reported the results of Short Form questionnaire-36 items (SF-36) and Short Form-6 Dimensions (SF-6D) surveys in patients with AF.[67,68] From the paper of Dorian *et al.*,[67] SF-6D scores were taken and transformed into a single index using the algorithm published by Ara *et al.*,[69] in order to calculate the utility value associated with being in AF. The utility value associated with being in NSR was taken from McKenna *et al.*;[70] this author reviewed the literature, searching for the best data related to the NSR state and this value was used in the model. The disutility associated with each event was calculated by estimating the number of days spent suffering from the event and multiplying the transformed utility value by this number of days. The number of days in every event was taken from McKenna *et al.*[70] and the utility values for post-stroke health states from Dorman *et al*.[69] All HRQoL data are listed in *Table 11*.

All QALYs have been discounted using a 3.5% annual rate.

Costs

Where appropriate, costs have been extracted mainly from *NHS reference cost 2008/09* documents[56] and the *British National Formulary* from 2009;[17] the costs of treatments and drugs were inflated as required.

To estimate the costs of stroke events, the number of days in hospital for patients after a mild stroke, after a severe or moderate stroke, and dying following a stroke, have been taken from the Lothian Stroke Registry[55] and have been multiplied by the daily average cost of inpatient treatment in a stroke unit and a general ward as described by Saka *et al*.[71] The study by Saka *et al.*[71] is a recent study of the cost of stroke in the UK using mean unit costs. All costs have been inflated to reflect 2009 prices.

TABLE 10 *Transition probabilities used in the AAD strategy*

Parameter	Value	Source
Probability of efficacy of PAF treatment (electrical DC cardioversion)	0.7820	Dankner 2009[65]
Probability of keeping an NSR	0.3535	Pappone 2006[61]
Probability of proarrhythmia	0.006	Kaufman 2009[66]
Probability of returning to NSR after proarrhythmia	1.00	Rodgers 2008[53]
Probability of progressing to CAF after proarrhythmia	0.00	Rodgers 2008[53]
Probability of recurrences	1 – mean progression Mortality risk Probability of keeping NSR Probability of a stroke Probability of proarrhythmia	Author assumption
Probability of keeping CAF state	1 – relative risk × life table mortality risk	Author assumption
Probability of keeping post-stroke (after the first stroke)	0.3535	Alboni 2004[22]
Probability of being in post-CAF	1 – probability of dying after being in post-stroke CAF	Author assumption
Probability of recurrences after post-stroke	1 – probability of keeping post + AAD Probability of suffering a new stroke in post + AAD Risk of bleeding event Probability of dying post + AAD Mean_progression risk	Author assumption
Probability of progression after DC cardioversion due to PAF event	0.2180	Dankner 2009[65]

AAD, antiarrhythmic drug; CAF, chronic atrial fibrillation; DC, direct current; NSR, normal sinus rhythm; PAF, paroxysmal atrial fibrillation.

TABLE 11 *Utility values used in the model*

Parameter	Data	Source
Utility value of being in CAF state	0.71	Dorian 2000[67]
Utility of being dependent after a stroke	0.38	LSR-Dorman 2000[63]
Utility of being independent after a stroke	0.74	LSR-Dorman 2000[63]
Utility during AF event	0.71	Dorian 2000[67]
Utility in NSR	0.89	Rienstra 2006[72]
Utility of death	0	Author assumption
Loss of utility for suffer a PAF event (7 days: maximum number of days in the definition of PAF in the national clinical guideline[3])	0.0035	Author assumption
Loss of utility for suffer a proarrhythmia event (1-day more with AF utility)	0.0005	Author assumption
Loss of utility for suffer a bleeding (5 days with a 15% reduction in previous utility)	0.0015	Eckman 2009[63]
Loss of utility due to the fail of the PAF treatment	0.0005	Author assumption

AF, atrial fibrillation; CAF, chronic atrial fibrillation; LSR, Lothian Stroke Registry; NSR, normal sinus rhythm; PAF, paroxysmal atrial fibrillation.

The annual cost of being in a health state following either a mild stroke or a moderate-to-severe stroke has been calculated using the annual cost of stroke from Saka *et al.*[71] and from the Chambers *et al.*[73] model.

The costs of PAF events in the PiP strategy involve only the cost of a single dose of the drug treatment prescribed. In the AAD strategy, the PAF cost consists of the cost of an A&E visit and the cost of electrical DC cardioversion because the daily treatment has not prevented the event, or the cost of electrical DC cardioversion because the patient is experiencing symptoms. In the IHT strategy, the cost of the PAF event is the cost of a chemical cardioversion as first treatment, and an electrical DC cardioversion if the former fails (see *Table 12*).

The cost of treating proarrhythmia in all strategies has been assumed to be equal to the cost of an electrical DC cardioversion procedure plus the cost of the 4-week warfarin treatment as stated in the *NHS reference costs 2008/09*.[51] Other relevant prices and costs have been taken from the published literature and are presented in *Table 12*.

All costs have been discounted using a 3.5% annual rate.

TABLE 12 *Cost parameters used in the model in all strategies*

Parameter	Data	Source
All strategies		
Annual cost of long-term care in post-stroke CAF (dependent)	£9334.98	Chambers *et al.* model,[73] Saka 2009[71]
Annual cost of long-term care in post-stroke (independent)	£724.20	Chambers *et al.* model,[73] Saka 2009[71]
Cost of a stroke dependent event (51 days inpatient stay)	£8181.61	Wardlaw 1998,[58] Saka 2009[71]
Cost of a stroke independent event (14 days inpatient stay)	£2245.93	Wardlaw 1998,[58] Saka 2009[71]
Cost of a stroke event followed by death (33 days inpatient stay)	£5293.98	Wardlaw 1998,[58] Saka 2009[71]
Annual cost of being in CAF (rate control drug sotalol 240 mg daily)	£38.91	*British National Formulary*[17]
Annual cost of warfarin treatment	£3.95	Abdelhafiz 2003[74]
Cost of bleeding events prices 2009	£102.93	Abdelhafiz 2003[74]
PiP strategy		
Cost of PAF event in PiP (cost of flecainide 100 mg 60-tablet pack = £15.04) (2009)	£0.75	*British National Formulary*[17]
Cost of proarrhythmia event (electrical cardioversion plus warfarin)	£741.37	*NHS reference costs 2008/09*[56]
Cost of PAF treatment fail (electrical cardioversion plus warfarin)	£741.37	*NHS reference costs 2008/09*[56]
Annual cost of being in NSR in PiP	£0.00	Author assumption
AAD strategy		
Cost of PAF event in AAD (90% patients electrical cardioversion plus warfarin and 10% pharmacological cardioversion)	£703.55	*NHS reference costs 2008/09*[56]
Cost of proarrhythmia event in AAD (electrical cardioversion plus warfarin)	£741.37	*NHS reference costs 2008/09*[56]
Annual cost of being in NSR in AAD (200 mg daily of flecainide)	£182.99	*British National Formulary*[17]
IHT strategy		
Cost of PAF event in IHT returning to NSR (cost of an intravenous infusion A&E room)	£363.15	*NHS reference costs 2008/09*[56]
Cost of proarrhythmia event (electrical cardioversion plus warfarin)	£741.37	*NHS reference costs 2008/09*[56]
Cost of PAF treatment fail (electrical cardioversion plus warfarin)	£741.37	*NHS reference costs 2008/09*[56]
Annual cost of being in NSR in IHT	£0.00	Author assumption

AAD, antiarrhythmic drug; A&E, accident and emergency; CAF, chronic atrial fibrillation; IHT, in-hospital treatment; NSR, normal sinus rhythm; PAF, paroxysmal atrial fibrillation; PiP, pill-in-the-pocket.

Chapter 6

Economic evaluation and economic model: results

The results of the cost-effectiveness analyses are summarised below showing mean costs, life-years and QALYs per patient and the resulting incremental ICERs.

Base-case analysis

The results of the simulated cohort of patients (1000 patients) are presented in *Table 13*.

In the base-case analysis, the PiP strategy results in lower costs (more than £800 per patient), but is less clinically effective (QALYs) than the other strategies. The main cost differences are due to the cost of daily prophylactic treatment in the AAD strategy and the cost of treating PAF events in the IHT strategy. The differences in 'time in states' (deaths, patients progressing to CAF and QALYs) between the three treatments are very small (*Table 14*). Also 'time in state' in NSR differs between strategies mainly because of the relative effectiveness of PAF treatment which is better in PiP and worse in AAD and in IHT.

The number of recurrences in the AAD strategy (*Table 15*) is low because the prophylactic treatment reduces the risk of new events. The number of proarrhythmia events in AAD strategy is higher than in the other two strategies because there are more patients at risk in the AAD option. There is a marked difference in the number of PAF treatment failures, as a consequence of the differences in efficacy between the three strategies (see *Table 7*).

Table 16 shows the proportion of patients returning to NSR following a proarrhythmia event, or PAF treatment failure or success. The main difference lies in the proportion of patients who return to NSR after successful treatment of a PAF recurrence. IHT has a poorer outcome because chemical cardioversion (used in the treatment of PAF events in the IHT strategy) is less effective than the PAF treatment used in the other two strategies (single drug dose in PiP, and electrical DC cardioversion in AAD).

Table 17 indicates that the majority of health costs are incurred while patients are in NSR, progressive

TABLE 13 *Results from the model (per patient)*

Treatment strategy	Mean cost	Mean life-years	Mean QALYs	Incremental cost (vs PiP)	Incremental QALYs (vs PiP)	ICER (£/QALY)
PiP	£1512.33	17.01	9.21			
AAD	£2389.25	17.10	9.23	+£876.92	+0.02	£45,915.84
IHT	£2340.13	17.06	9.29	+£843.37	+0.07	£12,423.61

AAD, antiarrhythmic drug; ICER, incremental cost-effectiveness ratio; IHT, in-hospital treatment; PiP, pill-in-the-pocket; QALY(s), quality-adjusted life-year(s).

TABLE 14 *Time spent in health states in the model by strategy (months)*

Treatment strategy	NSR	Progressive CAF	Post-stroke CAF	Post-stroke without CAF	Death
PiP	3220	13,588	98	100	29,993
AAD	2274	14,677	76	80	29,902
IHT	2683	14,198	86	89	29,943

AAD, antiarrhythmic drug; CAF, chronic atrial fibrillation; IHT, in-hospital treatment; PiP, pill-in-the-pocket.

TABLE 15 *Number of estimated events by strategy*

Treatment strategy	PAF recurrences	PAF treatment failures	Proarrhythmia	Strokes
PiP	2422	117	15	93
AAD	1403	306	20	72
IHT	2153	865	13	81

AAD, antiarrhythmic drug; IHT, in-hospital treatment; PAF, paroxysmal atrial fibrillation; PiP, pill-in-the-pocket.

TABLE 16 *Effectiveness of treatment strategies in restoring NSR following PAF recurrence or proarrhythmia*

		Number of patients		
Treatment strategy	PAF recurrences	Returning to NSR after proarrhythmia	Returning to NSR after PAF treatment failure	Returning to NSR after PAF treatment success
PiP	2422	15 (100%)	92 (78.2%)	2290 (94.55%)
AAD	1403	20[a] (100%)	NA[b]	1097 (78.20%)
IHT	2153	13 (100%)	677 (78.2%)	1275 (59.20%)

AAD, antiarrhythmic drug; IHT, in-hospital treatment; NA, not applicable; NSR, normal sinus rhythm; PAF, paroxysmal atrial fibrillation; PiP, pill-in-the-pocket.
a Proarrhythmia in AAD strategy occurs when the patient is in NSR with daily medication.
b In AAD strategy when PAF treatment fails patients progress to CAF.

CAF or post-stroke CAF states. PiP treatment costs in the NSR state are low because the cost of PAF treatment is cheap compared with the other two strategies (single drug dose versus electrical DC cardioversion or chemical cardioversion), avoiding most hospital admissions for PAF recurrences.

Costs in the progressive CAF state involve the cost of daily rate control treatment together with the transitional costs of patients suffering proarrhythmic events or PAF treatment failures.

In the post-stroke CAF health state, costs are higher for PiP than for the other two strategies, because PiP has more patients in this state (see *Table 14*).

Costs in the post-stroke without CAF state relate to patients suffering a non-fatal stroke who have NSR restored and return to their original treatment strategy.

Table 18 shows that the differences between treatment strategies in terms of estimated QALYs per patient are very small, and arise predominantly from the balance of time spent in NSR or with progressive CAF: PiP maximises utility in NSR, whereas AAD leads to the largest expected utility in the progressive CAF state.

Deterministic sensitivity analysis

Several SAs were conducted to test the influence of key assumptions and to investigate the impact of data uncertainty on the results of the cost-effectiveness analyses. One-way deterministic SA was carried out on the following parameters:

- risk of bleeding events
- effectiveness of proarrhythmia treatment in returning patients to the NSR state
- utility value of stroke
- gender and age of population
- annual cost of CAF drug treatment
- utility index value
- progression to CAF.

Risk of bleeding

In the source paper[43] for the risk of bleeding, only 10% of the population had PAF. In order to explore the uncertainty around this parameter, the size of the risk was varied by 50% and the effect on the ICER (cost/QALY ratio) calculated. As *Table 19* shows, there are no significant changes to cost-effectiveness in any of the strategies.

TABLE 17 *Summary of estimated health-state costs per patient*

Treatment strategy	NSR	Progressive CAF	Post-stroke CAF	Post-stroke without CAF	Death[a]	Total
PiP (% of total)	£80.61 (4.50%)	£529.40 (29.54%)	£1019.23 (57%)	£158.21 (8.83%)	£30.04 (1.68%)	£1817.48
AAD (% of total)	£974.29 (36.17%)	£793.54 (29.46%)	£785.87 (29%)	£138.93 (5.01%)	£23.46 (0.87%)	£2712.16
IHT (% of total)	£974.16 (36.37%)	£670.80 (25.04%)	£886.87 (33.11%)	£138.93 (5.19%)	£26.37 (0.98%)	£2697.13

AAD, antiarrhythmic drug; CAF, chronic atrial fibrillation; IHT, in-hospital treatment; NSR, normal sinus rhythm; PiP, pill-in-the-pocket.
a The costs of death are only those related to the cost of a fatal stroke.

TABLE 18 *Summary of estimated health-state QALYs per patient*

Treatment strategy	NSR	Progressive CAF	Post-stroke CAF	Post-stroke without CAF	Death[a]	Total
PiP (% of total)	2.784 (22.15%)	9.339 (74.30%)	0.030 (0.24%)	0.053 (0.42%)	0.353 (2.81%)	12.559
AAD (% of total)	1.904 (15.10%)	10.261 (81.41%)	0.024 (0.19%)	0.047 (0.37%)	0.360 (2.86%)	12.596
IHT (% of total)	2.381 (18.82%)	9.831 (77.69%)	0.027 (0.22%)	0.052 (0.41%)	0.353 (2.79%)	12.644

AAD, antiarrhythmic drug; CAF, chronic atrial fibrillation; IHT, in-hospital treatment; NSR, normal sinus rhythm; PiP, pill-in-the-pocket.
a The QALYs assigned to death are only those related to a fatal stroke episode.

TABLE 19 *Sensitivity analysis: changing the risk of bleeding events*

Treatment strategy	Cost per patient	QALYs per patient	Incremental cost	Incremental QALYs	ICER
Base case: risk=0.0965					
PiP	£1512.33	9.211	–	–	–
AAD	£2389.25	9.230	+£876.92	+0.019	£45,916
IHT	£2355.70	9.279	+£843.37	+0.068	£12,424
50% increase: risk=0.14475					
PiP	£1512.74	9.211	–	–	–
AAD	£2391.17	9.232	+£878.43	+0.021	£42,542
IHT	£2356.63	9.279	+£843.89	+0.068	£12,434
50% decrease: risk=0.04825					
PiP	£1511.92	9.211	–	–	–
AAD	£2387.33	9.228	+£875.41	+0.017	£49,886
IHT	£2354.78	9.279	+£842.86	+0.068	£12,413

AAD, antiarrhythmic drug; ICER, incremental cost-effectiveness ratio; IHT, in-hospital treatment; PiP, pill-in-the-pocket; QALYs, quality-adjusted life-years.

Effectiveness of proarrhythmia treatment in returning NSR state

Owing to the lack of published clinical evidence supporting the use of the PiP strategy, the clinical effectiveness of proarrhythmia treatment was extracted from Alboni *et al*.[22] However, this paper reported only one patient suffering from proarrhythmia who returned to the NSR state after the AE occurred, suggesting 100% effectiveness for proarrhythmia treatment. To test this parameter, the probability of returning to NSR after proarrhythmia was reduced across a wide range. *Table 20* shows that there was no significant impact on the size of the estimated ICER as the number of QALYs gained decreased by no more than 0.8%.

Utility value of stroke

Because some costs have been included in the pathway to death via a fatal stroke (see *Table 12*), it was considered appropriate to assign a utility value to this terminal episode of care. In the model, a utility value of 0.38 was assumed, similar to the utility value of being in a persistent AF-dependent stroke health state. To test uncertainty in this parameter, this value was increased and decreased by 50%. *Table 21* shows the results of this SA which led to only minor changes to the size of the ICER.

Annual cost of chronic atrial fibrillation drug

In the base-case evaluation, the drug used to treat patients in CAF health state is sotalol (see *Table 12*), but two alternative drugs (diltiazem and atenolol) are used in clinical practice and should also be considered. *Table 22* shows the results of SA using these two drugs; changes in the ICERs are minor in either case.

Gender and age of population

The base-case ICER has been calculated for a population aged 60 years. However, ICERs have also been calculated for a range of ages, and both genders. *Table 23* indicates that the PiP strategy dominates AAD in men above 65 years of age and in women above 70 years of age, while PiP is never dominant compared to IHT. The alternative strategies are generally less cost-effective for older people. This is because when people are getting older, the probability of death from any cause is higher and the probability of death from CAF is 1.5 times higher than death from any cause. Because people in AAD spend more time in the CAF state than people in PiP, at some point between 60 and 65 years the QALYs gained in the CAF state by the AAD strategy begin to decrease, but people in the PiP strategy gain more QALYs from the NSR health state where the mortality risk is lower than in CAF.

Utility index value

As stated in Health-related quality of life, the single utility index for the AF state has been estimated using an algorithm from Ara and Brazier.[69] Because all such calculations are subject to some error, an SA has been carried out using the mean absolute error (MAE) value taken from Ara and Brazier.[69] *Table 24* shows that when the MAE is used to reduce the utility value, the AAD strategy is dominated by the PiP strategy. When the MAE is used to increase the value of the utility index, both ICERs decrease. This indicates that using algorithms to

TABLE 20 *Sensitivity analysis: changing the probability of recovering NSR after proarrhythmia*

Effectiveness of proarrhythmia treatment	ICER (AAD vs PiP) (£/QALY)	ICER (IHT vs PiP) (£/QALY)
Base case: 100%	£45,916	£12,424
90%	£45,309	£12,475
80%	£44,718	£12,526
70%	£44,140	£12,579
60%	£43,576	£12,631
50%	£43,026	£12,685
40%	£42,488	£12,738
30%	£41,963	£12,793

AAD, antiarrhythmic drug; ICER, incremental cost-effectiveness ratio; IHT, in-hospital treatment; PiP, pill-in-the-pocket.

TABLE 21 *Sensitivity analysis: changing utility of stroke*

Treatment strategy	Cost per patient	QALYs per patient	Incremental cost	Incremental QALYs	ICER (£/QALY)
Base case: utility = 0.38					
PiP	£1512.33	9.211	–	–	–
AAD	£2389.25	9.230	+£876.92	+0.019	£45,916
IHT	£2355.70	9.279	+£843.37	+0.068	£12,424
50% increase: utility = 0.57					
PiP	£1512.33	9.211	–	–	–
AAD	£2389.25	9.230	+£876.92	+0.019	£46,161
IHT	£2355.70	9.279	+£843.37	+0.068	£12,451
50% decrease: utility = 0.19					
PiP	£2355.00	9.210	–	–	–
AAD	£2389.25	9.230	+£876.92	+0.019	£45.673
IHT	£2355.70	9.278	+£843.37	+0.068	£12,396

AAD, antiarrhythmic drug; ICER, incremental cost-effectiveness ratio; IHT, in-hospital treatment; PiP, pill-in-the-pocket; QALYs, quality-adjusted life-years.

TABLE 22 *Sensitivity analysis: changing drug used in the CAF state*

Treatment strategy	Cost per patient	QALYs per patient	Incremental cost	Incremental QALYs	ICER (£/QALY)
Base case: sotalol					
PiP	£1512.33	9.211	–	–	–
AAD	£2389.25	9.230	+£876.92	+0.019	£45,916
IHT	£2355.70	9.279	+£843.37	+0.068	£12,424
Alternative: atenolol					
PiP	£1262.44	9.211	–	–	–
AAD	£2115.16	9.230	+£852.72	+0.019	£44,649
IHT	£2093.59	9.279	+£831.19	+0.068	£12,244
Alternative: diltiazem LA					
PiP	£1935.50	9.211	–	–	–
AAD	£2853.39	9.230	+£922.36	+0.019	£48,061
IHT	£2799.56	9.279	+£870.00	+0.068	£12,728

AAD, antiarrhythmic drug; ICER, incremental cost-effectiveness ratio; IHT, in-hospital treatment; PiP, pill-in-the-pocket; QALYs, quality-adjusted life-years.

TABLE 23 *Results of the model with population data disaggregated by age and gender*

		AAD vs PiP			IHT vs PiP		
		Incremental			Incremental		
	Years	Costs	QALYs	ICER (£/QALY)	Costs	QALYs	ICER (£/QALY)
Men	35	£913.84	0.136	£6729	£881.68	0.134	£6570
	40	£911.68	0.121	£7558	£879.66	0.126	£7004
	45	£907.98	0.100	£9066	£876.04	0.114	£7684
	50	£902.47	0.076	£11,916	£870.47	0.100	£8689
	55	£894.36	0.048	£18,569	£862.03	0.085	£10,194
	60	£882.44	0.018	£49,742	£849.29	0.067	£12,627
	65	£862.78	−0.014	PiP dominates	£828.02	0.049	£16,900
	70	£832.97	−0.044	PiP dominates	£795.53	0.032	£25,217
	75	£781.11	−0.069	PiP dominates	£739.90	0.017	£43,651
	80	£696.73	−0.082	PiP dominates	£651.96	0.007	£88,043
	85	£535.58	−0.078	PiP dominates	£495.99	0.004	£123,005
Women	35	£916.26	0.148	£6175.03	£884.03	0.141	£6257
	40	£914.36	0.136	£6735.77	£882.26	0.134	£6577
	45	£911.67	0.118	£7724.63	£879.71	0.124	£7088
	50	£907.38	0.096	£9430.19	£875.49	0.112	£7831
	55	£902.09	0.072	£12,568.03	£870.16	0.098	£8883
	60	£893.94	0.044	£20,468.40	£861.67	0.082	£10,506
	65	£881.23	0.012	£71,039.80	£848.03	0.064	£13,203
	70	£859.71	−0.021	PiP dominates	£824.52	0.045	£18,269
	75	£820.80	−0.052	PiP dominates	£782.06	0.027	£29,129
	80	£748.39	−0.079	PiP dominates	£704.12	0.010	£68,778
	85	£565.26	−0.083	PiP dominates	£524.35	0.002	£257,093

AAD, antiarrhythmic drug; ICER, incremental cost-effectiveness ratio; IHT, in-hospital treatment; PiP, pill-in-the-pocket; QALY, quality-adjusted life-year.

convert SF-36 values to European Quality of Life-5 Dimensions (EQ-5D) values when patient level data are not available could change the model results.

Progression to chronic atrial fibrillation

As stated in Chapter 5, Transition probabilities, we have assumed an exponential fit to reflect the advice from the clinical advisor concerning the progression rate to CAF. To test this parameter, an SA has been undertaken using data from the Ruigomez *et al*. paper[4] which shows an increase in progression rates in the first 5 years after diagnosis and a plateau beyond this point. The results of the SA in *Table 25* show that the flat trend beyond the fifth cycle changes the costs which increase slightly in the three strategies. QALYs also increase but less so in AAD than in PIP and IHT, resulting in a dominant situation for PiP versus AAD and in an increase in the ICER between PiP and IHT. The dominance of PiP is due to the fact that AAD patients spend more time in CAF states, and therefore the QALYs gained in this health state decrease if the progression rate is low.

Probabilistic sensitivity analysis

Owing to uncertainty around the input parameters of the model, a PSA has been performed to indicate how this uncertainty affects the mean economic results. The parameters subjected to stochastic uncertainty, the central parameter estimates and uncertainty distributions applied are shown in *Tables 45–50* (see Appendix 7). These parameters have been calculated from the same

TABLE 24 *Sensitivity analysis on utility index value*

Treatment strategy	Costs per patient	QALYs per patient	Incremental cost	Incremental QALYs	ICER (£/QALY)
Base case: 0.71					
PiP	£1512.33	9.211	–	–	–
AAD	£2389.25	9.230	+£876.92	+0.019	£45,916
IHT	£2355.70	9.279	+£843.37	+0.068	£12,424
Mean absolute error (–0.041): 0.669					
PiP	£1512.33	8.836	–	–	–
AAD	£2389.25	8.822	+£882.441	–0.014	PiP dominates
IHT	£2355.70	8.887	+£849.288	+0.051	£16,673
Mean absolute error (+0.041): 0.751					
PiP	£1512.33	9.585	–	–	–
AAD	£2389.25	9.638	+£882.441	+0.053	£16,525
IHT	£2355.70	9.671	+£849.288	+0.033	£9900

AAD, antiarrhythmic drug; ICER, incremental cost-effectiveness ratio; IHT, in-hospital treatment; PiP, pill-in-the-pocket; QALYs, quality-adjusted life-years.

TABLE 25 *Sensitivity analysis on progression to CAF rate*

Treatment strategy	Mean cost	Mean QALYs	Incremental cost (vs PiP)	Incremental QALYs (vs PiP)	ICER (£/QALY)
PiP	£1638.65	9.27			
AAD	£2544.43	9.26	+£905.78	–0.01	PiP dominant
IHT	£2551.19	9.32	+£912.54	+0.05	£19,292.84

AAD, antiarrhythmic drug; ICER, incremental cost-effectiveness ratio; IHT, in-hospital treatment; PiP, pill-in-the-pocket; QALY(s), quality-adjusted life-year(s).

sources as the deterministic values listed earlier. All the distributions chosen to address the uncertainty around probability parameters are Beta (α,β parameters) distributions. In the case of costs, the distributions chosen are Gamma (α,β parameters). For the utility parameters, Beta distributions have been chosen if the values are not close to zero. If the value is close to zero, the Gamma distribution is chosen.[75]

The cost-effectiveness plane (*Figure 2*) shows the high degree of uncertainty evident in both comparisons (PiP versus AAD and PiP versus IHT), where neither comparison falls clearly into one quadrant of the plane. Some of the iterations are below and inside the right of the threshold line of £30,000 per QALY and some of them are above and to the left. Only a few are in the south-east quadrant showing dominance, but around half of the iterations are in the north-west quadrant which means the option is dominated. There does not seem to be a clear trend in the results of the PSA.

The cost-effectiveness acceptability curve (with the cost-effectiveness acceptability frontier) (*Figure 3*) shows that at a threshold of £25,000 per QALY, the option chosen under the rule of maximising net benefit is IHT, i.e. IHT is the option that has the maximum probability of being cost-effective at this threshold. For threshold values between £0 and £9266 per QALY, PiP is the option exhibiting the maximum probability of being cost-effective. The AAD strategy has a very poor probability of being cost-effective under any threshold. However, none of the strategies considered has more than a 40% probability of being cost-effective at a threshold of £25,000 per QALY at any threshold level. This demonstrates the uncertainty around the

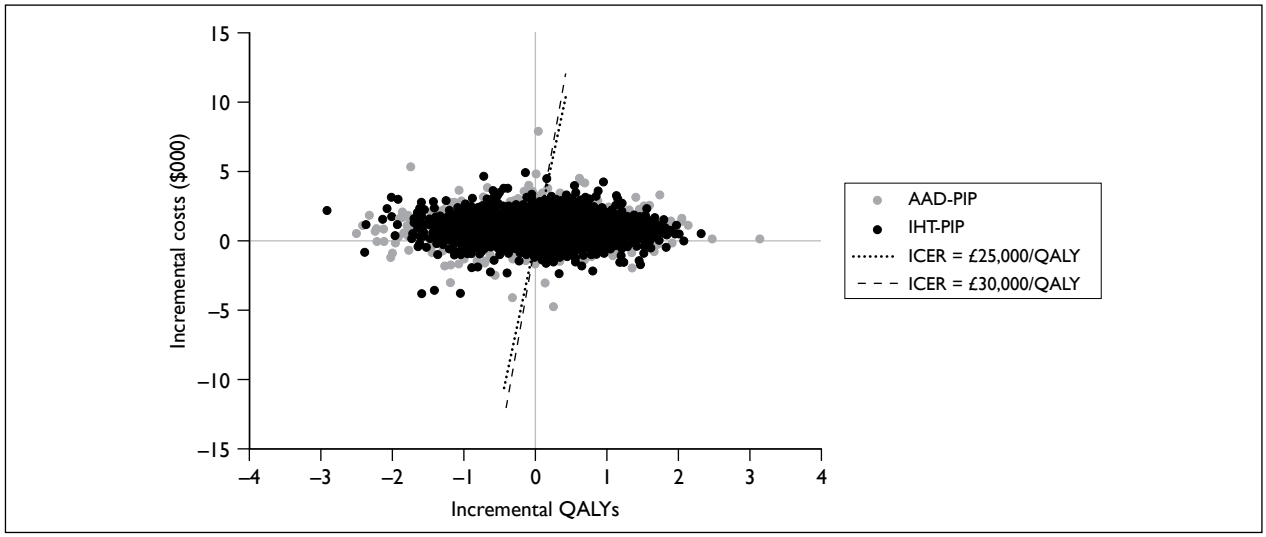

FIGURE 2 *Cost-effectiveness plane comparing PiP with AAD and IHT.*

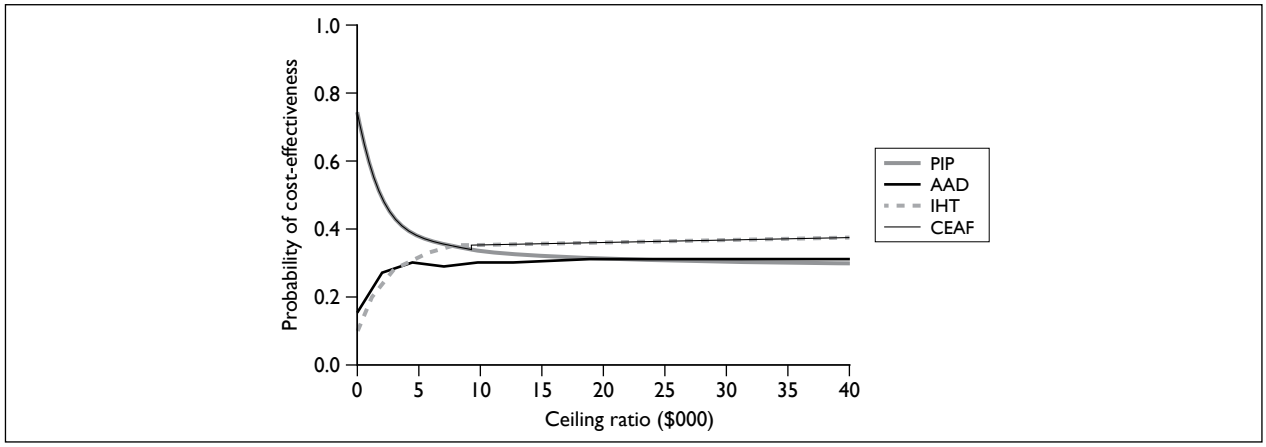

FIGURE 3 *Acceptability curve and cost-effectiveness acceptability frontier. CEAF, cost-effectiveness acceptability frontier.*

parameters and its effect on the decision to choose any one strategy over the others.

None of the alternatives show a high probability of being cost-effective. The uncertainty around parameters is not equally shared; AE parameters are often poorly reported in trial reports, and event rates have been incorporated into the model with caution and managed in the deterministic SA (i.e. bleeding events) and in the PSA (i.e. risk of proarrhythmia and bleeding events). The proportion and frequencies of these AEs are low and do not lead to any important changes in the size of the ICER.

Chapter 7
Discussion

This economic evaluation appears to be the first of its kind to estimate the cost-effectiveness of a PiP strategy compared with alternative treatments for PAF.

The economic model reflects the relevant literature which states that a PiP strategy is a safe way to treat PAF and is as efficacious as intravenous alternatives.[10,12,24] The results of the economic model are consistent with the conclusions of Alboni *et al.*[22] who state that a PiP strategy is associated with a marked reduction in A&E visits and hospital admissions. The results of this economic evaluation show that a PiP strategy is less clinically effective than the other two strategies; however, the number of QALYs yielded by each of the three strategies is very similar (see *Table 13*). The results also show that the costs incurred by the adoption of a PiP strategy are the lowest of the three strategies.

The AAD strategy, despite its low recurrence rate compared to PiP and IHT, shows the highest number of A&E visits; all recurrences in the AAD strategy are resource intensive.

The IHT strategy, in spite of the need for hospital visits every time a new PAF event occurs, does not incur the highest costs. This is mainly because recurrences are treated in the first instance with chemical cardioversion which is less expensive than electrical DC cardioversion.

The numbers of strokes and bleeding events are also very similar across the three strategies and the impact on both QALYs and costs is negligible (see *Table 14*).

When age and gender subgroups are analysed, PiP is a dominant strategy in people over 65 years compared to AAD, and PiP is more cost-effective for both men and women aged below 65 years than AAD. This is because in the AAD strategy people tend to progress to CAF faster than in the PiP strategy, and mortality risk from the CAF state is higher than from the NSR health state, resulting in a decrease in QALYs gained in the AAD strategy.

The PSA indicates that for IHT the maximum probability of being cost-effective at a threshold of £25,000 per QALY is only 40%.

The most cost-effective treatment strategy is either PiP or IHT; if the willingness-to-pay threshold is below £9266 per QALY, PiP is more likely to be cost-effective. The AAD strategy is not cost-effective at any threshold level, as can be seen in *Figure 3*. There is a high level of uncertainty attached to these findings owing to two main causes: (1) small differences in cost and more importantly small differences in QALYs between the strategies; and (2) the lack of relevant evidence and the poor quality of the existing data.

Another relevant issue that must be taken into account when interpreting the results of the economic model is that most of the data used to populate the model have been taken from studies with populations that do not match the patient population specified in the decision problem. Populating the model in this way was unavoidable as there is a paucity of published clinical effectiveness and cost-effectiveness data describing a PiP strategy for this highly specific group of patients.

Most of the registry data that were used to source parameter values in the economic model are inclusive of patients of all ages with heart disease; again, this does not match the patient population specified in the decision problem. These issues have been managed by conducting extensive SA as part of the economic evaluation. In order to inform future long-term models in this clinical area, new clinical studies are required.

Finally, it should be mentioned that patient preferences are an important factor when making decisions regarding the most appropriate treatment option for PAF. The alternatives of episodic treatment interventions (individual or hospital based) versus continuous prophylactic treatment have significant impacts on the life of the patient and therefore future studies need to investigate patient preferences alongside clinical effectiveness. As the current treatments (IHT and AAD) are virtually cost equivalent and PiP is much cheaper, if PiP is deemed to be clinically acceptable and is preferred by specific patients, it can be confidently implemented in the knowledge that it will incur no net additional cost to the NHS.

Chapter 8
Conclusions

The systematic review of clinical evidence did not identify any new studies that had not been included in the previously available guidelines.

Overall, a PiP strategy seems to be slightly less effective in terms of QALYs than AAD and IHT, but is associated with cost savings.

A PiP strategy seems to be more efficacious and cost-effective than AAD in men over 65 years and women over 70 years, but this is due to a very slight difference in QALYs gained by the PiP strategy.

A change in clinical practice that includes the introduction of PiP may save costs, but also carries a reduction in clinical effectiveness in the treatment of patients with PAF.

Uncertainty in the available clinical data means there is not enough evidence to support the use of PiP strategy in patients with PAF. Further research should identify outcomes of interest such as AE events and recurrent AF episodes in an RCT setting if possible.

Patient preferences also need to be considered in any future research designs.

Research recommendations

Research recommendations are required to address the following uncertainties detailed in our report:

- long-term progression to CAF
- effectiveness of PiP in the treatment of patients with PAF
- AEs related to the treatment
- compliance with treatment
- PAF recurrence rates
- all-cause mortality rates in this population
- progression probabilities from PAF to CAF
- AE event rates
- direct EQ-5D values in NSR and during/after PAF events, and duration of the effects of PAF events.

Data from observational studies and registries could be used in addition to data from RCTs.

The current lack of published evidence would appear to justify not supporting the general use of a PiP strategy in patients with PAF. Further evidence on the clinical effectiveness of PiP and its preference by patients may lead to this technology being implemented in the knowledge that it will not incur net additional cost to the NHS.

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Contributions of authors

Dr Carlos Martin Saborido was the review co-ordinator, provided input into the background and was responsible for the development of the economic model and the conduct of the economic evaluation. Ms Juliet Hockenhull was the author of the scoping report and gave input into all aspects of the clinical review. Professor Adrian Bagust supervised all aspects of the economic model and economic evaluation. Dr Angela Boland gave input into the economic model and overall report production. Ms Rumona Dickson was the project manager and gave input into all aspects of the clinical component of the review. Dr Derick Todd provided clinical input into the background and the economic model. All contributors took part in the editing and production of this report.

About the assessment group

The LRiG was established within the Department of Pharmacology and Therapeutics of The University of Liverpool, Liverpool, UK in April 2001. It is a multidisciplinary research group whose purpose, in the first instance, is to conduct health technology assessments commissioned by the HTA programme.

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Appendix 1
Commissioning brief

What are the clinical effectiveness and cost-effectiveness of 'pill-in-the-pocket' treatment for those with paroxysmal atrial fibrillation compared with hospital-based administration or continuous antiarrhythmic therapy?

NCCHTA commissioning brief

This commissioning brief was developed in response to recommendations from NICE guideline CG036 issued in June 2006: *Atrial fibrillation: the management of atrial fibrillation*.[3] The full guideline produced by the National Coordinating Centre for Chronic Conditions[76] states that 2 years after publication of the guidelines NICE will commission a national collaborating centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. This scoping exercise therefore aims to determine whether there has been any expansion in the evidence base regarding PiP treatment of PAF since June 2006.

The NCCHTA [National Coordinating Centre for Health Technology Assessment; now known as National Institute of Health Research Evaluation, Trials and Studies Coordinating Centre (NETSCC)] commissioning brief outlines the aims of the research as: to compare the clinical effectiveness and cost-effectiveness of a PiP treatment strategy for those with PAF with hospital-based administration or continuous antiarrhythmic therapy. The suggested drug is flecainide. However, flecainide is not the only drug to have been considered for a PiP treatment strategy and therefore other drugs able to be taken in a single oral dose have been considered in this scoping exercise, e.g. propafenone and sotalol.

Introduction

Atrial fibrillation is a cardiac arrhythmia involving the two upper atria of the heart, the heart beat is irregular, frequently faster than normal and, if left untreated, a significant risk factor for stroke and other morbidities. PAF refers to an episode of AF which, without treatment, lasts for less than 7 days and often less than 48 hours. The episode may terminate as suddenly as it started with the heart returning to a normal rate and rhythm. Not all patients are symptomatic and episodes can be infrequent (e.g. less than once a month). However, some episodes require emergency room intervention or hospitalisation.

Conventional treatment strategies for PAF focus on the suppression of paroxysms of AF and the return of sinus rhythm. Treatment can consist of either continuous prophylactic treatment or episodic treatment. Prophylactic treatment can include the use of beta-blockers or low dose sotalol, particularly as first-line or class Ic agents (e.g. flecainide, propafenone), or class III agents (sotalol, amiodarone).[76]

Treatment of an episode consists of pharmacological cardioversion usually involving an intravenous infusion of an AAD or, in cases where the episode lasts in excess of 7 days, electrical cardioversion. Both pharmacological and electrical cardioversion require IHT; however, with the development of oral AADs, immediate out of hospital treatment is possible. This strategy is referred to as PiP. Patients meeting pre-established criteria are provided with an oral dose of an AAD that they self-administer at the onset of an episode of PAF. This allows for immediate intervention with an objective of converting to sinus rhythm without the need for hospital admission. Such a strategy also precludes the need for continuous prophylactic treatment.

Advantages

The advantages of a PiP treatment strategy are suggested to include the following:

- *Faster treatment* Being able to treat an episode of PAF at onset enables early relief of symptoms and reduces the risk of thromboembolic complications.[77]
- *Fewer visits to hospital* For the patient, fewer visits to hospital is of great importance in terms of both convenience and cost.[78] For the hospital, the reduction in hospital visits is advantageous in terms of both physical and financial resources.[39]
- *Patient compliance* A PiP treatment strategy negates the need for continuous prophylactic arrhythmic drug treatment, meaning that the issue of patient compliance in the taking of such medication is removed. In addition, the occurrence of side effects to prophylactic treatment, which often leads to either a change in dosage or indeed discontinuation of treatment, is also eliminated.

Disadvantages

The disadvantages of a PiP treatment strategy involve safety. Some commentators have raised concerns over the risk of proarrhythmias (a new or more frequent occurrence of pre-existing arrhythmias), paradoxically precipitated by antiarrhythmic therapy,[57] thromboembolic events[79,80] and drug interactions, particularly antithrombotic therapy.[81] In the trials so far conducted on the efficacy of a single oral dose of an AAD in converting PAF to sinus rhythm, the patient populations have been well defined, and recommendations for the use of a PiP strategy highlight the need for strict selection criteria.[57] In the one study assessing the efficacy of out of hospital treatment it was uncertain whether the PiP strategy was associated with more AEs, or reduced episode duration when compared to IHT.[21] Research on the safety of out of hospital treatment is limited.

NICE guidelines 2006

In 2006, NICE published guidelines on the management of AF.[3] The full guideline was produced by the National Collaborating Centre for Chronic Conditions[76] and included a section on the treatment of PAF; the recommendation was:

> Where patients have infrequent paroxysms and few symptoms, or where symptoms are induced by known precipitants (such as alcohol, caffeine), a no drug treatment strategy or a pill-in-the-pocket strategy should be considered and discussed with the patient.

In patients with PAF, a PiP strategy should be considered in those who:

- have no history of left ventricular dysfunction, or valvular or ischaemic heart disease
- have a history of infrequent symptomatic episodes of PAF
- have a systolic blood pressure > 100 mmHg and a resting heart rate above 70 beats per minute
- are able to understand how, and when, to take the medication.

Scoping methodology

This scoping exercise examined both the clinical effectiveness and cost-effectiveness evidence for the use of a PiP treatment of PAF, published since the release of the guidelines in June 2006.[3] Using gold standard systematic review methodology 'Ovid MEDLINE (R) and Ovid OLDMEDLINE (R) 1950 to present with Daily Update' was searched using search strategies described in Appendices 2–4 to identify RCTs, systematic reviews and economic evaluations. Inclusion criteria, as outlined in *Table 26*, were independently applied to all identified references by two reviewers (JH and CMS). Data from relevant papers were then extracted by one reviewer (JH) and cross-checked by a second (CMS).

Ongoing trials were searched for using the following databases:

- HSRProj
- ClinicalTrials.gov
- *m*RCT
- BioMed Central
- WHO International Clinical Trials Registry Platform
- ClinicalStudyResults.org
- NLM Gateway.

Existing evidence base: scoping search for clinical effectiveness evidence

Controlled trials

The search strategy described in *Table 27* identified 197 RCTs. By applying inclusion criteria (see *Table 26*), 11 RCTs and one non-study were identified and these are summarised in *Table 28*.

All studies assessing the efficacy of oral flecainide and propafenone found favourable results in comparison to other treatment strategies. Oral

TABLE 26 *Inclusion criteria RCTs and reviews*

Population	Paroxysmal atrial fibrillation
Intervention	Pill-in-pocket, i.e. single oral dose
Comparator	Continuous treatment with Beta-blockers Solatol Amiodarone Propafenone Flecainide In-hospital treatment Infusion Electro cardioversion
Outcomes	Mean time to conversion (from atrial fibrillation to sinus rhythm) Conversion rates (from atrial fibrillation to sinus rhythm) Number of hospital visits

TABLE 27 *Search strategy for clinical effectiveness: RCTs*

Term		Hits
1	exp Atrial Fibrillation/	22,324
2	atrial fibrilation.mp.	30
3	atrial fibrillation.mp.	28,939
4	1 or 3 or 2	28,953
5	pill in the pocket.tw.	12
6	pill in the pocket.mp.	12
7	episodic treatment.mp.	76
8	single oral dose.mp.	6377
9	exp Administration, Oral/	93,316
10	oral.mp.	369,659
11	5 or 6 or 7 or 8 or 9 or 10	371,084
12	exp Anti-Arrhythmia Agents/	172,834
13	flecainide.mp. or exp Flecainide/	1670
14	flecanide.mp.	7
15	propafenone.mp. or exp Propafenone/	1434
16	Amiodarone.mp. or exp Amiodarone/	7212
17	exp Sotalol/or sotalol.mp.	2527
18	quinidine.mp. or exp Quinidine/	7635
19	digoxin.mp. or exp Digoxin/	13,335
20	exp Disopyramide/or disopyramide.mp.	1932
21	verapamil.mp. or exp Verapamil/	22,002
22	exp Procainamide/or procainamide.mp.	3965
23	dofetilide.mp.	550
24	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	185,177
25	4 and 11 and 24	671
26	exp Randomized Controlled Trial/	261,353

continued

TABLE 27 *Search strategy for clinical effectiveness: RCTs (continued)*

Term		Hits
27	"Randomized controlled trial".pt.	261,353
28	"controlled clinical trial".pt.	77,884
29	(random$or placebo$).ti,ab,sh.	600,933
30	((singl$or double$or triple$or treble$) and (blind$or mask$)).tw,sh.	107,944
31	(retraction of publication or retracted publication).pt.	2100
32	30 or 27 or 31 or 26 or 29 or 28	665,038
33	25 and 32	231
34	limit 33 to (english language and humans)	197

TABLE 28 *Summary of clinical evidence*

Study	Treatment	Comparator	*n*	Duration of atrial fibrillation prior to treatment	Conversion rate data (unless otherwise stated)
Alboni 2004[22] (non-randomised)	Flecainide pill-in-pocket	Propafenone pill-in-pocket	F = 74 P = 136	280 ± 368 minutes	Fewer visits to A&E were reported compared with the year before
Alp 2000[24]	Oral flecainide	IV flecainide	Oral F = 40 IV F = 39	Oral F = 10.8 hours IV F = 11.0	*2 hours* Oral F = 68% IV F = 64% *8 hours* Oral F = 75% IV F = 72%
Blanc 1999[10]	Oral propafenone	Oral amiodarone	Oral P = 43 Oral A = 43	1 day	*4 hours* Oral P = 37% Oral A = 16% *24 hours* Oral P = 56% Oral A = 47%
Boriani 1995[12]	Oral propafenone	IV propafenone	Oral P = 29 IV P = 29	Oral P = 9 ± 10 hours IV P = 8 ± 7 hours	*1 hour* Oral P = 3% IV P = 28% *3 hours* Oral P = 55% IV P = 41% *8 hours* Oral P = 69% IV P = 66%

TABLE 28 *Summary of clinical evidence (continued)*

Study	Treatment	Comparator	*n*	Duration of atrial fibrillation prior to treatment	Conversion rate data (unless otherwise stated)
Boriani 1998[11]	Oral flecainide	IV amiodarone IV propafenone Oral propafenone Oral flecainide	Oral F = 69 IV A = 51 IV P = 57 Oral P = 119	28–31 hours	*1 hour* IV A = 6% IV P = 39% Oral P = 8% Oral F = 13% *3 hours* IV A = 25% IV P = 58% Oral P = 45% Oral F = 56.5% *8 hours* IV A = 57% IV P = 75% Oral P = 76% Oral F = 75%
Botto 1998[13]	Oral propafenone	IV propafenone	Oral P = 41 IV P = 40	Oral P = 17 ± 20 hours IV P = 11 ± 19 hours	*1 hour* IV P = 48% Oral P = 15% *4 hours* IV P = 50% Oral P = 71% *8 hours* IV P = 53% Oral P = 78%
Capucci 1994[14]	Oral quinidine	Oral propafenone	Oral Q = 29 Oral P = 29	Oral P = 19 ± 8 hours Oral Q = 22 ± 8 hours	*6 hours* Oral Q = 38% Oral P = 62% *12 hours* Oral Q = 48% Oral P = 83% *24 hours* Oral Q = 76% Oral P = 86% *48 hours* Oral Q = 79% Oral P = 86%
Capucci[a] 1999[16]	Oral propafenone	IV digoxin + oral quinidine IV digoxin + oral propafenone	Oral P = 66 ID D + oral Q = 70 IV D + oral P = 70	Oral P = 17.8 ± 21.1 hours IV D + oral Q = 14.7 ± 17.7 hours IV D + oral P = 16.0 ± 18.2 hours	Mean duration to conversion Oral P = 4.0 ± 4.1 hours IV D + oral Q = 5.4 ± 4.5 hours IV D + oral P = 5.0 ± 8.6 hours

continued

TABLE 28 *Summary of clinical evidence (continued)*

Study	Treatment	Comparator	*n*	Duration of atrial fibrillation prior to treatment	Conversion rate data (unless otherwise stated)
Capucci 1992[15]	Oral flecainide	IV amiodarone followed by oral amiodarone	Oral F = 22 IV A + oral A = 19	Oral F = 28 ± 29.4 hours IV A + oral A = 29.8 ± 30.2 hours	*3 hours* Oral F = 68% IV A + oral A = 16% *8 hours* Oral F = 91% IV A + oral A = 37%
Crijns 1988[23]	Oral flecainide	IV flecainide	Oral F = 14 IV F = 13	68% < 24 hours	Achieved acute conversion, i.e. within 5 hours for oral and 30 minutes for IV Oral F = 10/14 IV A + Oral A = 10/13
Halinen[a] 1995[25]	Oral sotalol	IV digoxin–quinidine	Oral S = 33 IV DQ = 28	Oral S = 12.4 ± 10.8 hours IV DQ = 11.8 ± 11.5 hours	Mean time to conversion Oral S = 10.2 ± 7.6 hours IV DQ = 4.0 ± 2.9 hours *3 hours* Oral S = 12% IV DQ = 36% *8 hours* Oral S = 24% IV DQ = 71%
Kumagai 2000[26]	Oral pilsicainide	IV disopyramide	Oral Pi = 40 IV Di = 32		*2 hours* Oral Pi = 73% IV Di = 56% Mean time to conversion Oral Pi = 60 ± 30 minutes IV Di = 23 ± 18 minutes
Madonia[a] 2000[27]	Oral propafenone	IV propafenone	Oral P = 48 IV P = 49		*12 hours* Overall = 83% *24 hours* Overall = 98.9% % of patients converted at 1 hour and 3 hours significantly greater for IV ($p < 0.001$ and $p = 0.001$) At 6, 12 and 24 hours, no significant difference

A, amiodarone; D, digoxin; Di, disopyramide; F, flecainide; IV, intravenous; P, propafenone; Pi, pilsicainide; Q, quinidine; S, sotalol.
a Although not a single oral dose the medication could still be taken as a pill-in-the-pocket strategy.

sotalol was not found to be as efficacious as intravenous digoxin–quinidine.[25]

As can be seen in *Table 28*, only one study[22] has specifically looked at the feasibility of a PiP therapy for the treatment of PAF and was the sole evidence for a PiP treatment available for consideration by the National Collaborating Centre for Chronic Conditions in 2006.[76] The 11 RCTs were all conducted in hospital and, as with the Alboni study,[22] were all conducted prior to publication of the full guideline in 2006.[76]

Ongoing trials

Seven databases of registered ongoing trials were searched and no relevant trials were found.

Systematic review evidence

The search strategy described in *Table 29* identified 10 reviews, and after application of the inclusion criteria (see *Table 26*), five relevant reviews were identified and are summarised in *Table 30*. Four of the five reviews focused solely on oral AADs and, of these, three[36,37,76] concluded that a single oral dose of propafenone was effective in converting PAF to NSR. One review[30] also considered flecainide and concluded that as flecainide had more favourable pharmacokinetics it was preferred over propafenone.

Four of the reviews[30,32,35,36] focused solely on oral AADs and of these three[30,35,36] concluded that a single oral dose of propafenone was effective in converting PAF to NSR. One review also considered flecainide and concluded that as flecainide had more favourable pharmacokinetics it was preferred over propafenone.[30] None of the five reviews were published after publication of the guidelines in 2006.[76]

Existing evidence base: scoping search for cost-effectiveness evidence

The search strategy described in *Table 31* identified nine cost-effectiveness papers, only one of which included PiP treatment in PAF as a comparator; this paper was predominantly a clinical paper that also included a comment on the possible economic impact of home-based administration of oral propafenone.[39] The paper was published in 1996 before the most recent guidelines[76] were released.

Conclusion

A scoping search of MEDLINE by LRiG at the end of 2008 did not identify any new clinical effectiveness or cost-effectiveness evidence post publication of the full guideline[76] by the National Collaborating Centre for Chronic Conditions in 2006.

TABLE 29 *Search strategy for clinical effectiveness: reviews*

Term		Hits
1	exp Atrial Fibrillation/	22,324
2	atrial fibrilation.mp.	30
3	atrial fibrillation.mp.	28,939
4	1 or 3 or 2	28,953
5	pill in the pocket.tw.	12
6	pill in the pocket.mp.	12
7	episodic treatment.mp.	76
8	single oral dose.mp.	6377
9	exp Administration, Oral/	93,316
10	oral.mp.	369,659
11	5 or 6 or 7 or 8 or 9 or 10	371,084
12	exp Anti-Arrhythmia Agents/	172,834
13	flecainide.mp. or exp Flecainide/	1670
14	flecanide.mp.	7
15	propafenone.mp. or exp Propafenone/	1434
16	Amiodarone.mp. or exp Amiodarone/	7212
17	exp Sotalol/or sotalol.mp.	2527
18	quinidine.mp. or exp Quinidine/	7635
19	digoxin.mp. or exp Digoxin/	13,335
20	exp Disopyramide/or disopyramide.mp.	1932
21	verapamil.mp. or exp Verapamil/	22,002
22	exp Procainamide/or procainamide.mp.	3965
23	dofetilide.mp.	550
24	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	185,177

continued

TABLE 29 *Search strategy for clinical effectiveness: reviews (continued)*

Term		Hits
25	4 and 11 and 24	671
26	("review" or "review academic" or "review tutorial").pt.	1,406,238
27	(medline or medlars or embase or pubmed).tw,sh.	33,326
28	(scisearch or psychinfo or psycinfo).tw,sh.	2454
29	(psychlit or psyclit).tw,sh.	749
30	cinahl.tw,sh.	3206
31	((hand adj2 search$) or (manual$adj2 search$)).tw,sh.	3500
32	(elecronic database$or bibliographic database$or computeri?ed database$or online database$).tw,sh.	2694
33	(pooling or pooled or mantzel haenszel).tw,sh.	28,342
34	(retraction of publication or retracted publication).pt.	2100
35	(peto or dersimonian or der simonian or fixed effecr).tw,sh.	732
36	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	65,053
37	26 or 36	27,178
38	meta-analysis.pt.	19,670
39	meta-analysis.sh.	34,346
40	(meta-analys$or meta analys$or metalanaly$).tw,sh.	18,529
41	(systematic$adj5 review$).tw,sh.	446
42	(systematic$adj5 overview$).tw,sh.	118
43	(quantitativ$adj5 overview$).tw,sh.	169
44	(methodologic$adj review$).tw,sh.	36
45	(methodologic$adj overview$).tw,sh.	58
46	(integrative research review$or research integration).tw.	2448
47	(quantitativ$adj5 review$).tw,sh.	870
48	(quantitativ$adj5 synthesis$).tw,sh.	50,025
49	38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48	66,849
50	37 or 49	10

TABLE 30 *Summary of review evidence*

Review	Focus of review	Oral or IV	Conclusion
Deneer 2004[30]	Oral antiarrhythmic drugs in converting recent-onset AF	Oral	Propafenone and flecainide are effective in converting recent-onset AF
Ferreira 1997[32]	Effectiveness of sotalol in converting AF to sinus rhythm	Oral	Published studies did not support sotalol for conversion of AF to sinus rhythm
Hughes 1997[35]	Oral propafenone for rapid conversion of recent-onset AF	Oral	A single 600-mg oral dose of propafenone is highly effective at restoring sinus rhythm in patients with AF with few adverse effects
Khan 2001[36]	Single oral dose of propafenone for pharmacological cardioversion of recent-onset AF	Oral	Single oral dose of propafenone highly effective
Slavik 2001[37]	Pharmacological conversion of AF	Oral or IV	For recent-onset AF, procainamide is preferred IV agent and propafenone the preferred oral agent

AF, atrial fibrillation; IV, intravenous.

TABLE 31 *Search strategy for cost-effectiveness*

Term		Hits
1	exp Atrial Fibrillation/	22,324
2	atrial fibrilation.mp.	30
3	atrial fibrillation.mp.	28,939
4	1 or 3 or 2	28,953
5	pill in the pocket.tw.	12
6	pill in the pocket.mp.	12
7	episodic treatment.mp.	76
8	single oral dose.mp.	6377
9	exp Administration, Oral/	93,316
10	oral.mp.	369,659
11	5 or 6 or 7 or 8 or 9 or 10	371,084
2	exp Anti-Arrhythmia Agents/	172,834
13	flecainide.mp. or exp Flecainide/	1670
14	flecanide.mp.	7
15	propafenone.mp. or exp Propafenone/	1434
16	Amiodarone.mp. or exp Amiodarone/	7212
17	exp Sotalol/or sotalol.mp.	2527
18	quinidine.mp. or exp Quinidine/	7635
19	digoxin.mp. or exp Digoxin/	13,335
20	exp Disopyramide/or disopyramide.mp.	1932
21	verapamil.mp. or exp Verapamil/	22,002
22	exp Procainamide/or procainamide.mp.	3965
23	dofetilide.mp.	550
24	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	185,177
25	4 and 11 and 24	671
26	cost minimisation analysis.mp.	67
27	cost effectiveness analysis.mp.	3303
28	exp Cost-Benefit Analysis/	43,978
29	exp "Costs and Cost Analysis"/	138,930
30	cost utility analysis.mp.	623
31	cost benefit analysis.mp.	44,556
32	26 or 27 or 28 or 29 or 30 31	139,632
33	23 and 32	9

Appendix 2
Drug information

TABLE 32 *Indications of drugs used in PAF treatment*

Drug	Indications
Flecainide	AV nodal reciprocating tachycardia, arrhythmias associated with accessory conducting pathways (e.g. Wolff–Parkinson–White syndrome), disabling symptoms of paroxysmal atrial fibrillation in patients without left ventricular dysfunction (arrhythmias of recent onset will respond more readily)[17]
Propafenone	Ventricular arrhythmias; paroxysmal supraventricular tachyarrhythmias which include paroxysmal atrial flutter or fibrillation and paroxysmal re-entrant tachycardia involving the AV node or accessory pathway, where standard therapy is ineffective or contraindicated[17]
Sotalol	Tablets and injection: life-threatening arrhythmias including ventricular tachyarrhythmias, symptomatic non-sustained ventricular tachyarrhythmias
	Tablets only: prophylaxis of paroxysmal atrial tachycardia or fibrillation, paroxysmal AV re-entrant tachycardia (both nodal and involving accessory pathways), paroxysmal supraventricular tachycardia after cardiac surgery, maintenance of sinus rhythm following cardioversion of atrial fibrillation or flutter
	Injection only: electrophysiological study of inducible ventricular and supraventricular arrhythmias; temporary substitution for tablets[17]
Atenolol	By mouth: hypertension (25–50 mg daily, higher doses rarely necessary), angina (100 mg daily in one or two doses) and arrhythmias (50–100 mg daily)
	By intravenous injection: arrhythmias (2.5 mg at a rate of 1 mg/minute, repeated at 5-minute intervals to a maximum of 10 mg)
	By intravenous infusion: arrhythmias (150 µm/kg over 20 minutes, repeated every 12 hours if required)
Diltiazem LA	Prophylaxis and treatment of angina; hypertension
Amiodarone	Amiodarone is licensed in the UK for treatment of:
	Paroxysmal supraventricular, nodal and ventricular tachycardia
	Atrial fibrillation and flutter
	Ventricular fibrillation
	Tachyarrhythmias associated with Wolff–Parkinson–White syndrome

AV, atrioventricular.

TABLE 33 *Costs of drugs used in PAF treatment*

Drug	Costs and presentation
Flecainide	Flecainide (non-proprietary): tablets, flecainide acetate 50 mg, net price 60-tablet pack = £9.81; 100 mg, 60-tablet pack = £15.04[17] (prices November 2008)
	Flecainide Tambocor® (3M): Tablets, flecainide acetate 50 mg, net price 60-tablet pack = £14.46; 100 mg (scored), 60-tablet pack = £20.66
	Injection, flecainide acetate 10 mg/ml, net price 15-ml amp = £4.40[17] (prices November 2008)
Propafenone	Propafenone Arythmol® (Abbot): tablets, f/c, propafenone hydrochloride 150 mg, net price 90-tablet pack = £7.37; 300 mg, 60-tablet pack = £9.34[17] (prices November 2008)
Sotalol	Sotalol (non-proprietary): tablets, sotalol hydrochloride 40 mg, net price 56-tablet pack = £1.34; 80 mg, 56-tablet pack = £1.99; 160 mg, 28-tablet pack = £2.21[17]
	Sotalol Beta-Cardon® (UCB Pharma): tablets, scored, sotalol hydrochloride 40 mg (green), net price 56-tablet pack = £1.34; 80 mg (pink), 56-tablet pack = £1.99; 200 mg, 28-tablet pack = £2.50[17]
	Sotalol Sotacor® (Bristol–Myers Squibb): tablets, scored, sotalol hydrochloride 80 mg, net price 28-tablet pack = £3.25; 160 mg, 28-tablet pack = £6.41. Injection, sotalol hydrochloride 10 mg/ml, net price 4-ml amp = £1.76[17] (all prices November 2008)
Atenolol	Atenolol: 50 mg, 28-tablet pack = £0.85[17]
Diltiazem LA	Tildiam LA® (Sanofi-Synthelabo): capsules, m/r, diltiazem hydrochloride 200 mg (pink/grey, containing white pellets), net price 28-capsule pack = £6.66[17] (this is the only presentation containing 200 mg or fractions)
Amiodarone	Amiodarone: tablets, amiodarone hydrochloride 100 mg, net price 28-tablet pack = £1.39; 200 mg, 28-tablet pack = £1.42

amp, ampule; f/c, film-coated; m/r, modified release.

Appendix 3
Search strategies

TABLE 34 *Search strategy for clinical effectiveness: RCTs (run on 20 July 2009)*

Term		Hits
1	exp Atrial Fibrillation/	23,833
2	atrial fibrilation.mp.	32
3	atrial fibrillation.mp.	30,975
4	1 or 3 or 2	30,990
5	pill in the pocket.tw.	13
6	pill in the pocket.mp.	13
7	episodic treatment.mp.	80
8	single oral dose.mp.	6548
9	exp Administration, Oral/	96,704
10	oral.mp.	382,790
11	5 or 6 or 7 or 8 or 9 or 10	384,318
12	exp Anti-Arrhythmia Agents/	176,685
13	flecainide.mp. or exp Flecainide/	1742
14	flecanide.mp.	7
15	propafenone.mp. or exp Propafenone/	1478
16	Amiodarone.mp. or exp Amiodarone/	7581
17	exp Sotalol/or sotalol.mp.	2613
18	quinidine.mp. or exp Quinidine/	7614
19	digoxin.mp. or exp Digoxin/	13,564
20	exp Disopyramide/or disopyramide.mp.	1975
21	verapamil.mp. or exp Verapamil/	22,577
22	exp Procainamide/or procainamide.mp.	3986
23	dofetilide.mp.	567
24	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	189,354
25	4 and 11 and 24	717
26	exp Randomized Controlled Trial/	275,701
27	"Randomized controlled trial".pt.	275,701
28	"controlled clinical trial".pt.	79,912
29	(random$or placebo$).ti,ab,sh.	636,559
30	((singl$or double$or triple$or treble$) and (blind$or mask$)).tw,sh.	112,964
31	(retraction of publication or retracted publication).pt.	2380
32	30 or 27 or 31 or 26 or 29 or 28	702,976
33	25 and 32	239
34	limit 33 to (english language and humans)	203

TABLE 35 *Search strategy for clinical effectiveness evidence: reviews (run on 20 July 2009)*

	Term	Hits
1	exp Atrial Fibrillation/	23,833
2	atrial fibrilation.mp.	32
3	atrial fibrillation.mp.	30,975
4	1 or 3 or 2	30,990
5	pill in the pocket.tw.	13
6	pill in the pocket.mp.	13
7	episodic treatment.mp.	80
8	single oral dose.mp.	6548
9	exp Administration, Oral/	96,704
10	oral.mp.	382,790
11	5 or 6 or 7 or 8 or 9 or 10	384,318
12	exp Anti-Arrhythmia Agents/	176,685
13	flecainide.mp. or exp Flecainide/	1742
14	flecanide.mp.	7
15	propafenone.mp. or exp Propafenone/	1478
16	Amiodarone.mp. or exp Amiodarone/	7581
17	exp Sotalol/or sotalol.mp.	2613
18	quinidine.mp. or exp Quinidine/	7614
19	digoxin.mp. or exp Digoxin/	13,564
20	exp Disopyramide/or disopyramide.mp.	1975
21	verapamil.mp. or exp Verapamil/	2257
22	exp Procainamide/or procainamide.mp.	3986
23	dofetilide.mp.	567
24	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	189,354
25	4 and 11 and 24	717
26	(“review” or “review academic” or “review tutorial”).pt.	1,468,120
27	(medline or medlars or embase or pubmed).tw,sh.	36,947
28	(scisearch or psychinfo or psycinfo).tw,sh.	2938
29	(psychlit or psyclit).tw,sh.	782
30	cinahl.tw,sh.	3673
31	((hand adj2 search$) or (manual$adj2 search$)).tw,sh.	3822
32	(elecronic database$or bibliographic database$or computeri?ed database$or online database$).tw,sh.	2908
33	(pooling or pooled or mantzel haenszel).tw,sh.	30,206
34	(retraction of publication or retracted publication).pt.	2380
35	(peto or dersimonian or der simonian or fixed effecr).tw,sh.	794
36	31 or 29 or 32 or 30 or 28 or 34 or 27 or 35 or 33	70,936
37	26 and 36	30,331
38	meta-analysis.pt.	21,924
39	meta-analysis.sh.	21,924
40	(meta-analys$or meta analys$or metalanaly$).tw,sh.	37,989
41	(systematic$adj5 review$).tw,sh.	21,227
42	(systematic$adj5 overview$).tw,sh.	509
43	(quantitativ$adj5 overview$).tw,sh	125
44	(methodologic$adj review$).tw,sh.	178
45	(methodologic$adj overview$).tw,sh.	40
46	(integrative research review$or research integration).tw.	62
47	(quantitativ$adj5 review$).tw,sh.	2634
48	(quantitativ$adj5 synthesis$).tw,sh.	913
49	38 or 42 or 43 or 39 or 44 or 41 or 45 or 48 or 40 or 46 or 47	55,558
50	37 or 49	73,874
51	25 and 50 (11)	11

TABLE 36 *Search strategy for cost-effectiveness evidence (run on 27 July 2009)*

Term		Hits
1	exp Atrial Fibrillation/	23,861
2	atrial fibrilation.mp.	32
3	atrial fibrillation.mp.	31,017
4	1 or 3 or 2	31,032
5	pill in the pocket.tw.	13
6	pill in the pocket.mp.	13
7	episodic treatment.mp.	80
8	single oral dose.mp.	6557
9	exp Administration, Oral/	96,796
10	oral.mp.	383,134
11	5 or 6 or 7 or 8 or 9 or 10	384,664
12	exp Anti-Arrhythmia Agents/	176,750
13	flecainide.mp. or exp Flecainide/	1742
14	flecanide.mp.	7
15	propafenone.mp. or exp Propafenone/	1479
16	Amiodarone.mp. or exp Amiodarone/	7586
17	exp Sotalol/or sotalol.mp.	2615
18	quinidine.mp. or exp Quinidine/	7617
19	digoxin.mp. or exp Digoxin/	13,569
20	exp Disopyramide/or disopyramide.mp.	1975
21	verapamil.mp. or exp Verapamil/	22,588
22	exp Procainamide/or procainamide.mp.	3986
23	dofetilide.mp.	568
24	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	189,430
25	4 and 11 and 24	718
26	cost minimisation analysis.mp.	75
27	cost effectiveness analysis.mp.	3526
28	exp Cost-Benefit Analysis/	46,187
29	exp "Costs and Cost Analysis"/	144,556
30	cost utility analysis.mp.	673
31	cost benefit analysis.mp.	46,793
32	30 or 29 or 26 or 31 or 27 or 28	145,282
33	25 and 32	12

Appendix 4

Summary of evidence

TABLE 37 *Summary of RCT evidence*

Study	Treatment	Comparator	*n*	Duration of atrial fibrillation prior to treatment
Alp 2000[24]	Oral flecainide	IV flecainide	Oral F = 40 IV F = 39	Oral F = 10.8 hours IV F = 11.0 hours
Blanc 1999[10]	Oral propafenone	Oral amiodarone	Oral P = 43 Oral A = 43	1 day
Boriani 1995[12]	Oral propafenone	IV propafenone	Oral P = 29 IV P = 29	Oral P = 9 ± 10 hours IV P = 8 ± 7 hours
Boriani 1998[11]	Oral flecainide	IV amiodarone IV propafenone Oral propafenone Oral flecainide	Oral F = 69 IV A = 51 IV P = 57 Oral P = 119	28–31 hours
Botto 1998[13]	Oral propafenone	IV propafenone	Oral P = 41 IV P = 40	Oral P = 17 ± 20 hours IV P = 11 ± 19 hours
Capucci 1994[14]	Oral quinidine	Oral propafenone	Oral Q = 29 Oral P = 29	Oral P = 19 ± 8 hours Oral Q = 22 ± 8 hours
Capucci[a] 1999[16]	Oral propafenone	IV digoxin + oral quinidine IV digoxin + oral Propafenone	Oral P = 66 ID D + oral Q = 70 IV D + oral P = 70	Oral P = 17.8 ± 21.1 hours IV D + oral Q = 14.7 ± 17.7 hours IV D + oral P = 16.0 ± 18.2 hours
Capucci 1992[15]	Oral flecainide	IV amiodarone followed by oral amiodarone	Oral F = 22 IV A + oral A = 19	Oral F = 28 ± 29.4 hours IV A + Oral A = 29.8 ± 30.2 hours
Crijns 1988[23]	Oral flecainide	IV flecainide	Oral F = 14 IV F = 13	68% < 24 hours
Halinen[a] 1995[25]	Oral sotalol	IV digoxin–quinidine	Oral S = 33 IV DQ = 28	Oral S = 12.4 ± 10.8 hours IV DQ = 11.8 ± 11.5 hours
Kumagai 2000[26]	Oral pilsicainide	IV disopyramide	Oral Pi = 40 IV Di = 32	
Madonia[a] 2000[27]	Oral Propafenone	IV propafenone	Oral P = 48 IV P = 49	

A, amiodarone; D, digoxin; Di, disopyramide; F, flecainide; IV, intravenous; P, propafenone; Pi, pilsicainide; Q, quinidine; S, sotalol.
a Although not a single oral dose, the medication could still be taken as a pill-in-the-pocket strategy.

TABLE 38 *Summary of key paper*

Study	Treatment	Comparator	*n*	Duration of atrial fibrillation prior to treatment
Alboni 2004[22]	Flecainide pill-in-pocket	Propafenone pill-in-pocket	Flecanide = 74 Propafenone = 136	280 ± 368 minutes

TABLE 39 *Summary of evidence from the key paper and RCTs*

Study	Setting	Follow-up	Mean time to conversion	Conversion rate	Frequency of hospital visits	Frequency of reoccurrence	Health-related quality of life	Progression to persistent
Alboni 2004[22]	Out of hospital treatment	15 ± 5 months	113 ± 84 minutes	534/569 in < 6 hours	Per person 31/210 Per episode 31/618	618/210	NS	7/210 required prophylactic treatment
Alp 2000[24]	Cardiac care unit	2 hours and 8 hours	Oral F = 110 ± 82.3 minutes IV F = 52 ± 54.5 minutes	*2 hours* Oral F = 27/40, 68% IV F = 25/39, 64% *8 hours* Oral F = 30/40, 75% IV F = 28/39, 72%	NA	NA	NA	NS
Blanc 1999[10]	Hospital	24 hours	Oral P = median 2.4 hours, 0.25–20.45 Oral A = median 6.9 hours, 0.05–19.5	*By 48 hours* Oral P = 25/43, 58% Oral A = 27/43, 63%	NA	NA	NS	NS
Boriani 1995[12]	Hospital	89 hours	Oral P = 138 ± 140 minutes IV P = 163 ± 114 minutes	*8 hours* Oral P = 20/29, 69% IV P = 19/29, 66%	NA	NA	NS	NS
Boriani 1998[11]	Hospital	8 hours	Up to 8 hours IV A = 225 ± 142 minutes IV P = 137 ± 139 minutes Oral P = 181 ± 118 minutes Oral F = 161 ± 110 minutes	*Up to 8 hours* IV A = 29/51, 57% IV P = 43/57, 75% Oral P = 91/119, 76% Oral F = 52/69, 75%	NA	NA	NS	NS
Botto 1998[13]	Emergency medicine	8 hours	Within 4 hours	*1 hour* IV P = 19/40, 48% Oral P = 6/41, 15% *4 hours* IV P = 20/40, 50% Oral P = 29/41, 71% *8 hours* IV P = 21/40, 53% Oral P = 32/41, 78%	NA	NA	NS	0

Study	Setting	Follow-up	Mean time to conversion	Conversion rate	Frequency of hospital visits	Frequency of reoccurrence	Health-related quality of life	Progression to persistent
Capucci 1994[14]	Hospital	48 hours	Within 48 hours Oral Q = 648 ± 631 minutes Oral P = 267 ± 238 minutes Placebo = 893 ± 622 minutes	*6 hours* Oral Q = 11/29, 38% Oral P = 18/29, 62% Placebo = 6/29, 17% *12 hours* Oral Q = 14/29, 48% Oral P = 24/29, 83% Placebo = 10/29, 34% *24 hours* Oral Q = 22/29, 76% Oral P = 25/29, 86% Placebo = 16/29, 55% *48 hours* Oral Q = 23/29, 79% Oral P = 25/29, 86% Placebo = 22/29, 76%	NS	NS	NS	NS
Capucci[a] 1999[16]	Cardiac centre	24 hours	Oral P = 4.0 ± 4.1 hours IV D + oral Q = 5.4 ± 4.5 hours IV D + oral P = 5.0 ± 8.6 hours	NS	NS	NS	NS	NS
Capucci 1992[15]	Hospital	24 hours	Within 24 hours Oral F = 190 ± 147 minutes IV A + oral A = 705 ± 418 minutes	*Within 24 hours* Oral F = 21/22, 95% IV A + oral A = 17/19, 89%	NS	NS	NS	NS
Crijns 1988[23]	Outpatient department	24 hours	Oral F = 104 ± 86 minutes IV F = 14.1 ± 8 hours	Oral F within 5 hours = 10/14, 71% IV F within 30 minutes = 10/13, 77%	NS	NS	NS	NS

continued

TABLE 39 *Summary of evidence from the key paper and RCTs (continued)*

Study	Setting	Follow-up	Mean time to conversion	Conversion rate	Frequency of hospital visits	Frequency of reoccurrence	Health-related quality of life	Progression to persistent
Halinen[a] 1995[25]	Accident and emergency	24 hours	Oral S = 10.2 ± 7.6 hours IV DQ = 4.0 ± 2.9 hours	Oral S = 17/33, 52% IV DQ = 24/28, 86%	NS	NS	NS	Oral S = 13/33, 39.4 IV DQ = 4/28, 14.3%
Kumagai 2000[26]	NS	2 hours	Oral Pi = 60 ± 30 minutes IV Di = 23 ± 18 minutes	*2 hours* Oral Pi = 73% IV Di = 56%	NS	NS	NS	NS
Madonia[a] 2000[27]	Emergency medicine	48 hours	NS	*12 hours* Overall = 83% *24 hours* Overall = 98.9%	NS	NS	NS	NS

A, amiodarone; D, digoxin; Di, disopyramide; F, flecainide; IV, intravenous; NA, not applicable; NS, not stated; P, propafenone; Pi, pilsicainide; Q, quinidine; S, sotalol.
a Although not a single oral dose, the medication could still be taken as a pill-in-the-pocket strategy.

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TABLE 40 *Summary of evidence from the key paper and RCTs*

Study	Conversion to atrial flutter	Proarrhythmia	Thromboembolic events	Death	Other adverse events, e.g. nausea, asthenia, vertigo	All adverse events	Notes
Alboni 2004[22]	1	1 patient/165 patients	NS	NS	11	12	569/618 episodes were treated
Alp 2000[24]	Oral F = 0 IV F = 1 = 2.6%	Oral F = 1 asymptomatic ventricular tachycardia IV F = 0	NS	0	0	Oral F = 1 IV F = 1	
Blanc 1999[10]	Oral P = 2/43, 4.7% 2 to 1 atrial flutter Oral A = 0	Oral P = 0 Oral A = 1/43, 2.3% supraventricular tachycardia	0	0	Oral P = 4 digestive discomfort,1 non-sustained tachycardia Oral A = 4 digestive discomfort, 1 non-sustained tachycardia	Oral P = 7 Oral A = 6	
Boriani 1995[12]	Oral P = 2 IV P = 1	NS	NS	NS	Oral P = 1 sig QRS widening, 1 transient hypotension IV P = 1 hypotension, 1 phlebitis	Oral P = 4 IV P = 3	
Boriani 1998[11]	Oral F = 2	0	0	0	10–16% of active treatment patients reported minor adverse events (slight hypotension, transient bradychardia, asymptomatic pauses on Holter, dizziness, phlebitis) IV P = 1 hypotension and pulmonary oedema in the presence of mildly dilated cardiomyopathy Oral F = 2 left ventricular decomposition		
Botto 1998[13]	0	IV P = 2 regular tachycardia 2:1 and 3:1 AV conduction	0	NS	Oral P = 1 junctional rhythm	IV P = 2 Oral P = 1	
Capucci 1994[14]	Oral Q = 1 Oral P = 4	NS	NS	NS	Oral Q = 1 asymptomatic pause > 2 seconds, 1 gastrointestinal side effect Oral P = 1 asymptomatic pause > 2 seconds, 1 hypotension, excessive QRS widening, 1 mild hypotension with bradycardia	Oral Q = 3 Oral P = 7	

continued

TABLE 40 *Summary of evidence from the key paper and RCTs*

Study	Conversion to atrial flutter	Proarrhythmia	Thromboembolic events	Death	Other adverse events, e.g. nausea, asthenia, vertigo	All adverse events	Notes
Capucci[a] 1999[16]	Oral P = 9 IV D + oral Q = 13 IV D + oral P = 12	Oral P = 3 complete left bundle branch block, 2 reversible asymptomatic Wenckebach II Degree sinus atrial block pauses < 3 seconds observed at the time of resinusalisation IV D + oral Q = 1 asymptomatic ventricular runs of 3–4 ventricular ectopic beats, 2 complete left bundle branch block, 2 reversible asymptomatic Wenckebach II Degree sinus atrial block pauses < 3 seconds observed at the time of reinusalisation IV D + oral P = 4 asymptomatic ventricular runs of 3–4 ventricular ectopic beats, 2 complete left bundle branch block	NS	NS	Oral P = 5 transient mild arterial hypotension IV D + oral Q = 1 transient mild arterial hypotension IV D + oral P = 1 transient mild arterial hypotension	Oral P = 19 IV D + oral Q = 19 IV D + oral P = 19	
Capucci 1992[15]	0	0	0	0	Oral F = 1 mild light headedness IV A + Oral A = 2 superficial phlebitis	Oral F = 1 IV A + Oral A = 2	
Crijns 1988[23]	0	0	0	0	Oral F = 2 development of mild congestive heart failure IV F = 2 development of mild congestive heart failure	Oral F = 2 IV F = 2	
Halinen[a] 1995[25]	NS	Oral S = 13% asymptomatic wide complex tachycardia (QRS > 0.12 seconds) IV DQ = 27% asymptomatic wide complex tachycardia (QRS > 0.12 seconds)	NS	NS	Oral S = 16 asymptomatic bradycardia or hypotension		
Kumagai 2000[26]	NS	NS	NS	NS	NS	NS	
Madonia[a] 2000[27]	NS	NS	NS	NS	NS	None resulting in treatment suspension	Non-valvular paroxysmal atrial fibrillation

A, amiodarone; AV, atrioventricular; D, digoxin; Di, disopyramide; F, flecainide; IV, intravenous; NS, not stated; P, propafenone; Pi, pilsicainide; Q, quinidine; S, sotalol.
a Although not a single oral dose, the medication could still be taken as a pill-in-the-pocket strategy.

Appendix 5
Quality assessment

TABLE 41 *Classification of studies*

Study	Description
Ruigomez 2005[4]	Case–control study
Kerr 2005[9]	Cohort study
Alboni 2004[22]	Non-randomised clinical trial
SPAF 1998[57]	Cohort study
Wardlaw 1998[58]	Cohort study
Birman-Deych 2006[59]	Cohort study
SPAF 1991[60]	Randomised clinical trial
Rodgers 2008[53]	HTA report
Pappone 2006[61]	Randomised clinical trial
Wallerstedt 2009[62]	Cohort study
Kaufman 2004[66]	Randomised clinical trial

HTA, *Health Technology Assessment* journal; SPAF, Stroke Prevention in Atrial Fibrillation study.

TABLE 42 *Cohort studies quality assessment*

Screening questions	SPAF 1998[57]	Wardlaw 1998[58]	Birman-Deych 2006[59]	Wallerstedt 2009[62]	Kerr 2005[9]
1. Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes
2. Did the authors use an appropriate method to answer their question?	Yes	Yes	Yes	Yes	Yes
3. Was the cohort recruited in an acceptable way?	Yes	Yes	Yes	Yes	Yes
4. Was the exposure accurately measured to minimise bias?	Yes	No	Yes	Yes	Yes
5. Was the outcome accurately measured to minimise bias?	Yes	Yes	Yes	Yes	Yes
6a. Have the authors identified all important confounding factors?	Yes	Yes	Yes	Yes	Yes
6b. Have they taken account of the confounding factors in the design and/or analysis?	Yes	Yes	Yes	Yes	Yes
7a. Was the follow-up of subjects complete enough?	Yes	Yes	NS	NS	Yes
7b. Was the follow-up of subjects long enough?	Yes	No	NS	NS	Yes

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Screening questions	SPAF 1998[57]	Wardlaw 1998[58]	Birman-Deych 2006[59]	Wallerstedt 2009[62]	Kerr 2005[9]
8. What are the results of this study?	The rate of primary events was 2.2% per year (95% CI 1.6% to 3.0%). Those with a history of hypertension had a higher rate of primary events (3.6% per year) than those with no history of hypertension (1.1% per year) ($p < 0.001$)	In 993 patients in the stroke registry, visible infarction increased the risk of being dead or dependent at 6 months (OR 2.5; 95% CI 1.9 to 3.3) or dead (OR 4.5; 95% CI 2.7 to 7.5), both on its own and after adjustment for time from stroke to CT, stroke symptoms, and other important clinical prognostic variables (OR for death or dependence in the predictive model 1.5; 95% CI 1.0 to 2.0; OR for death 2.4; 95% CI 1.4 to 4.1)	After adjusting for comorbid conditions, warfarin prescription was more frequent and monitoring more regular in white Medicare beneficiaries than in black or Hispanic beneficiaries ($p < 0.0001$). Warfarin use was associated with 35% fewer ischaemic strokes (HR 0.65; 95% CI 0.55 to 0.76) than no antithrombotic therapy but was less effective in black and Hispanic beneficiaries (p for interaction = 0.048)	The total incidences of bleedings per 1000 treatment-years were 51.4 (25.7–92.0) and 23.9 (13.1–40.1), respectively, and the unadjusted incidence rate ratio 2.15 (0.88 to 5.11). Cox regression analysis including first bleedings revealed an adjusted HR of 3.49 (1.37 to 8.91) for bleeding during treatment with a combination of SSRI and warfarin compared with treatment with warfarin only	The probability of progression to CAF by 1 year was 8.6% and thereafter there was a slow but steady progression to 24.7% by 5 years. By 5 years, the probability of documented recurrence of any AF (chronic or paroxysmal) was 63.2%. Increasing age, significant aortic stenosis or mitral regurgitation, left atrial enlargement, and diagnosis of cardiomyopathy were independently associated with progression to CAF. A more rapid heart rate during AF was associated with decreased risk of progression
9. How precise are the results? How precise is the estimate of the risk?	All results are reported with a 95% CI and the p-values were lower than 0.05	All results are reported with a 95% CI but p-values were not reported	All results are reported with a 95% CI and the p-values were lower than 0.05	All results are reported with a 95% CI and the p-values were lower than 0.05	All results are reported with a 95% CI and the p-values were lower than 0.05
10. Do you believe the results?	Yes	Yes	Yes	Yes	Yes
11. Can the results be applied to the local population?	Yes	No	Yes	No	Yes
12. Do the results of this study fit with other available evidence?	Yes	Yes	Yes	Yes	Yes

AF, atrial fibrillation; CAF, chronic atrial fibrillation; CI, confidence interval; CT, computerised tomography; HR, hazard ratio; NS, not stated; OR, odds ratio; SPAF, Stroke Prevention in Atrial Fibrillation study; SSRI, selective serotonin reuptake inhibitors.

TABLE 43 *Randomised and non-randomised studies assessment*

Checklist item	SPAF 1991[60]	Pappone 2006[61]	Kaufman 2004[66]	Alboni 2004[22]
Randomisation				
Was the randomisation method adequate?	Yes	Yes	Yes	NA
Was the allocation of treatment adequately concealed?	Yes	Yes	Yes	NA
Was the number of participants randomised stated?	Yes	Yes	Yes	NA
Baseline comparability				
Were details of baseline comparability presented?[a]	Yes	Yes	Yes	No
Were the groups similar for prognostic factors?	Yes	Yes	Yes	NS
Eligibility criteria and co-interventions				
Were the eligibility criteria for study entry specified?	Yes	Yes	Yes	Yes
Were any co-interventions identified?	No	Yes	Yes	No
Blinding				
Were outcome assessors blinded to treatment allocation?	No	No	NS	No
Were administrators blinded to the treatment allocation?	NS	No	No	No
Were patients blinded to the treatment allocation?	Yes	No	No	No
Was the method of the blinding procedure assessed?	No	No	No	No
Withdrawals				
Any unexpected imbalances in dropouts between groups? Were they explained or adjusted for?	No/NA	No/NA	No/NA	No/NA
Were ≥80% patients included in the final analysis?	Yes	Yes	NS	Yes
Were reasons for withdrawals stated?	Yes	No	NS	Yes
Was an intention-to-treat analysis included? Was this appropriate? Were appropriate methods used to account for missing data?	Yes	Yes	Yes	No
Outcomes				
Evidence of more outcomes measured than reported?	No	No	No	No

NA, not applicable; NS, not stated; SPAF, Stroke Prevention in Atrial Fibrillation Study.

TABLE 44 *Case–control studies assessment*

Screening questions	**Ruigomez 2005[4]**
1. Did the study address a clearly focused issue?	Yes
2. Did the authors use an appropriate method to answer their question?	Yes
3. Were the cases recruited in an acceptable way?	Yes
4. Were the controls recruited in an acceptable way?	Yes
5. Was the exposure accurately measured to minimise bias?	Yes
6a. What confounding factors have the authors accounted for?	Unspecific codes of supra-ventricular and sinus arrhythmias
6b. Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Yes
7. What are the results of this study?	During a mean follow-up of 2.7 years, 70 of 418 paroxysmal AF patients with complete information progressed to chronic AF. Risk factors associated with progression were valvular heart disease (OR 2.7, 95% CI 1.2 to 6.0) and moderate to high alcohol consumption (OR 3.0, 95% CI 1.1 to 8.0)
8a. How precise are the results?	CIs were wide (see question 7)
8b. How precise is the estimate of risk?	*p*-values were not reported
9. Do you believe the results?	Yes
10. Can the results be applied to the local population?	The results were taken from a GP registry
11. Do the results of this study fit with other available evidence?	Yes

AF, atrial fibrillation; CI, confidence interval; GP, general practitioner; OR, odds ratio.

Appendix 6

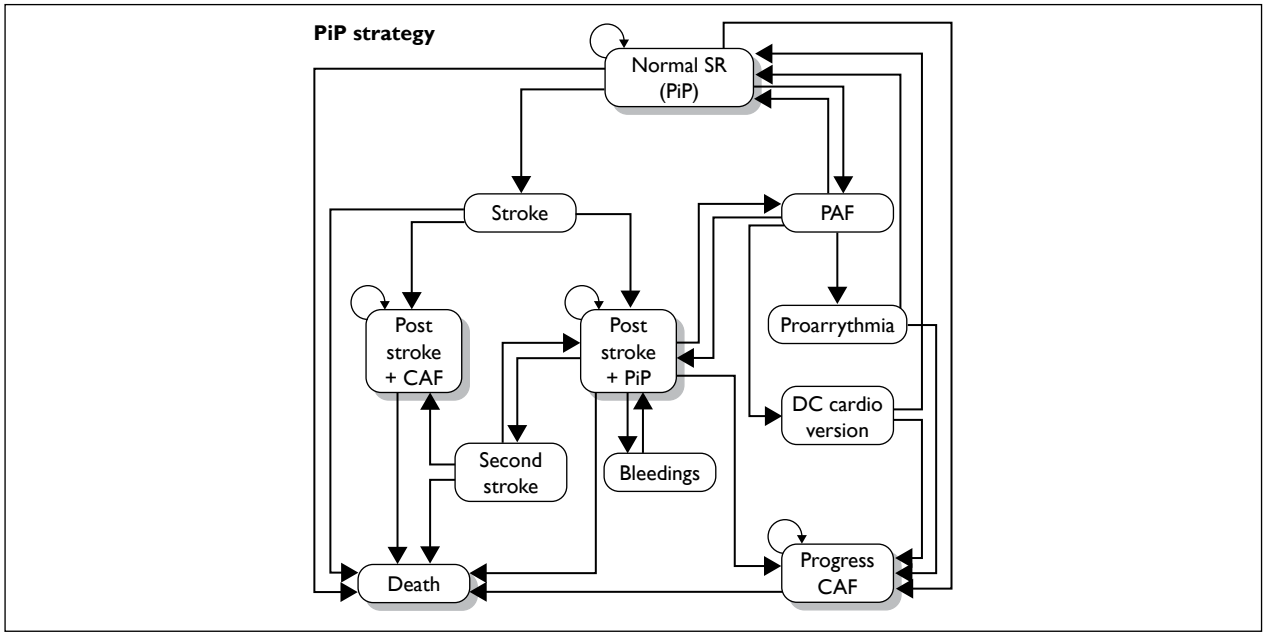

FIGURE 4 *Strategy of the PiP strategy in the model. SR, sinus rhythm.*

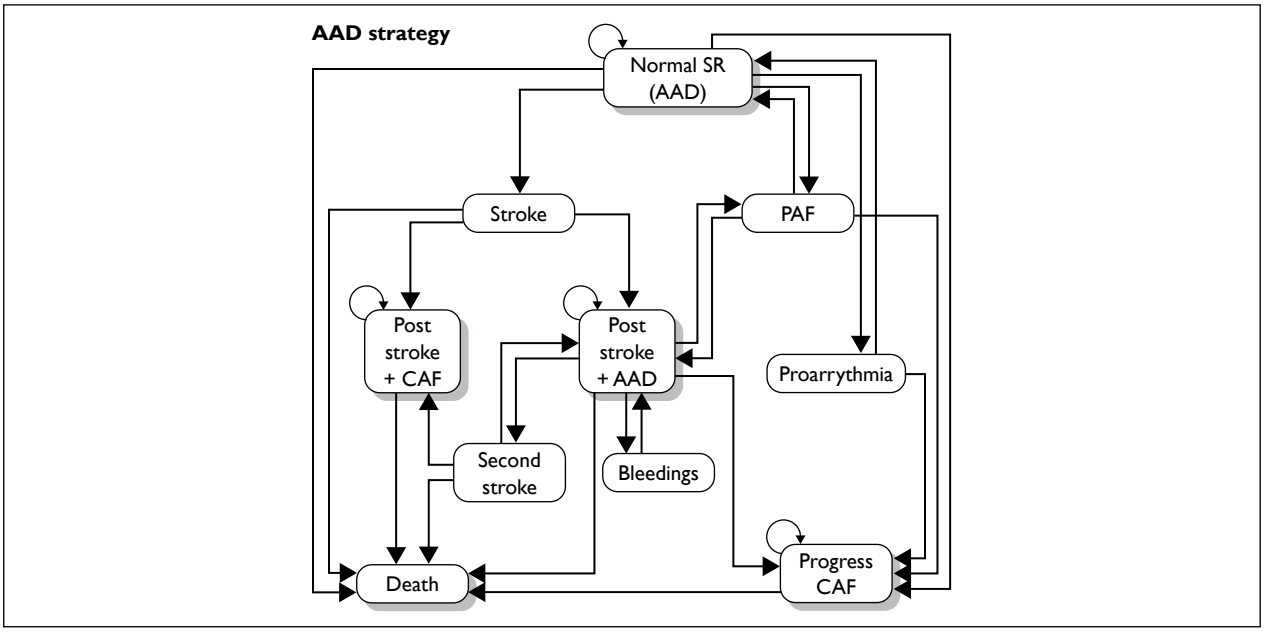

FIGURE 5 *Structure of the AAD strategy in the model. SR, sinus rhythm.*

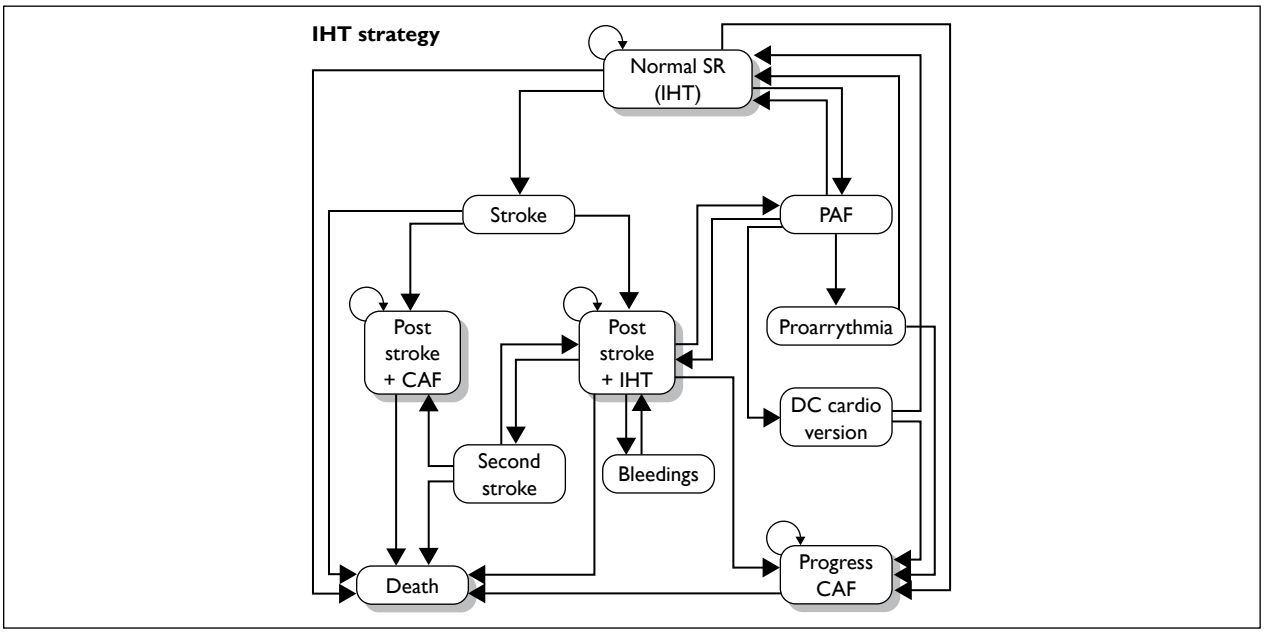

FIGURE 6 *Structure of the IHT strategy in the model. SR, sinus rhythm.*

Appendix 7

TABLE 45 *Probabilistic values of probability parameters in all strategies*

Parameter	Distribution (parameter)	Source
Probability of keeping an NSR in IHT and PiP	Beta (41,169)	Alboni 2004[22]
Probability of dying from post-stroke state in all strategies	Beta (248,745)	Wardlaw 1998[58]
Probability of progressing after a (moderate and severe) stroke all strategies	Beta (16,26)	SPAF 1991[60]
Probability of first stroke in all strategies	Beta (20,872)	SPAF 1998[57]
Probability of dying after being in post-stroke + CAF in all strategies	1.5 × [Beta (248,745)]	Wardlaw 1998,[58] Ruigomez 2005[4]
Probability of return to NSR after a stroke in all strategies	Beta (24,18)	SPAF 1991[60]
Probability of death from NSR in all strategies (all-cause death)	Death risk (life tables)	Mortality rates[63]
Probability of death from CAF (RR = 1.5 risk of death) in all strategies	RR × life tables	Ruigomez 2005[4]
Probability of progressing to CAF from NSR in all strategies	Mean_progression	Kerr 2005,[9] Ruigomez 2005[4]
Probability of progressing to CAF from post-stroke in all strategies	Mean_progression	Kerr 2005,[9] Ruigomez 2005[4]
Probability of suffering a second stroke from post-stroke in all strategies	Beta (1,19)	Wardlaw 1998,[58] Birman-Deych 2006[59]
Probability of keeping post-stroke state in IHT and PiP (after the first stroke)	Beta (41,169)	Alboni 2004[22]
Risk of a bleeding event in all strategies	Beta (39,363)	Wallerstedt 2009[62]
Probability of dying after the first stroke in all strategies	Beta (2,40)	SPAF 1991[60]
Probability of progress post-CAF after the second stroke	Beta (12,30)	SPAF 1998[57]
Probability of dying after the second stroke	Beta (5,15)	Wardlaw 1998[58]
Probability of return to post-stroke no CAF after the second stroke in all strategies	1 – [Beta (5,15)] – [Beta (12,30)]	Author assumption

CAF, chronic atrial fibrillation; IHT, in-hospital treatment; NSR, normal sinus rhythm; PiP, pill-in-the-pocket; RR, relative risk; SPAF, Stroke Prevention in Atrial Fibrillation study.

TABLE 46 *Probabilistic values of probability parameters in PiP strategy*

Parameter	Distribution (parameter)	Source
Probability of efficacy of the PAF treatment	Beta (538,31)	Alboni 2004[22]
Probability of proarrhythmia	Beta (1,164)	Alboni 2004[22]
Probability of return to NSR after proarrhythmia event	Beta (9,1)	Alboni 2004[22]
Probability of progressing to CAF after proarrhythmia event	1 – [Beta (9,1)]	Alboni 2004[22]
Probability of PAF treatment fail	1 – [Beta (2,40)] – [Beta (538,31)]	Author assumption
Probability of return to NSR after DC cardioversion	Beta (69,16)	Dankner 2009[65]
Probability of progressing to CAF after DC electrical cardioversion	1 – [Beta (69,16)]	Dankner 2009[65]
Probability of recurrences	1 – probability of keeping NSR Probability of a stroke Mean_progression Mortality risk	Author assumption
Probability of keeping CAF state	1 – relative risk × life table mortality risk	Author assumption
Probability of being in post-CAF	1 – 1.5 × [Beta (5,15)]	Author assumption
Probability of recurrences after post-stroke	1 – probability of keeping post + PiP Probability of suffering a new stroke in post + PiP Risk of bleeding event Probability of dying post + PiP Mean_progression risk	Author assumption

CAF, chronic atrial fibrillation; DC, direct current; NSR, normal sinus rhythm; PAF, paroxysmal atrial fibrillation; PiP, pill-in-the-pocket.

TABLE 47 *Probabilistic values of probability parameters in AAD strategy*

Parameter	Distribution (parameter)	Source
Probability of efficacy of the PAF treatment	Beta (34,22)	Dankner 2009[65]
Probability of proarrhythmia	Beta (12,2021)	Kaufman 2009[66]
Probability of return to NSR after proarrhythmia	Beta (9,1)	Alboni 2004[22]
Probability of progressing to CAF after proarrhythmia	1 – [Beta (9,1)]	Alboni 2004[22]
Probability of PAF treatment fail	1 – [Beta (12,2021)] – [Beta (34,22)]	Author assumption
Probability of return to NSR after DC electrical cardioversion	Beta (69,16)	Dankner 2009[65]
Probability of progressing to CAF after DC electrical cardioversion	1 – [Beta (69,16)]	Dankner 2009[65]
Probability of recurrences	1 – Mean_progression	Author assumption
	Mortality risk	
	Probability of keeping NSR	
	Probability of a stroke	
Probability of keeping CAF state	1 – relative risk × life table mortality risk	Author assumption
Probability of being in post-CAF	1 – 1.5 × [Beta (5,15)]	Author assumption
Probability of recurrences after post-stroke	1 – probability of keeping post + IHT	Author assumption
	Probability of suffering a new stroke in post + IHT	
	Risk of bleeding event	
	Probability of dying post + IHT	
	Mean_progression risk	

CAF, chronic atrial fibrillation; DC, direct current; IHT, in-hospital treatment; NSR, normal sinus rhythm; PAF, paroxysmal atrial fibrillation.

TABLE 48 *Probabilistic values of probability parameters in IHT strategy*

Parameter	Distribution (parameter)	Source
Probability of efficacy of PAF treatment (DC electrical cardioversion)	Beta (69,16)	Dankner 2009[65]
Probability of keeping an NSR	Beta (35,64)	Pappone 2006[61]
Probability of proarrhythmia	Beta (12,2021)	Kaufman 2009[66]
Probability of returning to NSR after proarrhythmia	Beta (9,1)	Rodgers 2008[53]
Probability of progressing to CAF after proarrhythmia	1 – [Beta (9,1)]	Rodgers 2008[53]
Probability of recurrences	1 – Mean_progression Mortality risk Probability of keeping NSR Probability of a stroke Probability of proarrhythmia	Author assumption
Probability of keeping CAF state	1 – relative risk × life table mortality risk	Author assumption
Probability of being in post-CAF	1 – 1.5 × [Beta (5,15)]	Author assumption
Probability of recurrences after post-stroke	1 – probability of keeping post + AAD Probability of suffering a new stroke in post + AAD Risk of bleeding event Probability of dying post + AAD Mean_progression risk	Author assumption
Probability of progression after DC cardioversion due to PAF event	1 – [Beta (69,16)]	Dankner 2009[63]

AAD, antiarrhythmic drug; CAF, chronic atrial fibrillation; DC, direct current; NSR, normal sinus rhythm; PAF, paroxysmal atrial fibrillation.

TABLE 49 *Probabilistic values of utility parameters*

Parameter	Data	Distribution (parameter)	Source
Utility value of being in CAF state	0.71	Beta (43.195,14.398)	Dorian 2000[67]
Utility of being dependent after a stroke	0.38	Beta (41.930,68.412)	LSR-Dorman 2000[64]
Utility of being independent after a stroke	0.74	Beta (209.875,73.740)	LSR-Dorman 2000[64]
Utility during AF event	0.71	Beta (43.195,14.398)	Dorian 2000,[67] Lamotte 2007[75]
Utility in NSR	0.89	Beta (26.482,4.858)	Rienstra 2006[72]
Utility of death	0.005	Gamma (0.500,0.005)	Author assumption
Loss of utility for suffer an PAF event (7 days: maximum number of days in the definition of PAF in the national clinical guideline[3])	0.0035	Gamma ($2.000, 3.125 \times 10^{-6}$)	Author assumption
Loss of utility for suffer a proarrhythmia event (1 day more with AF utility)	0.0005	Gamma (2.000,0.001)	Author assumption
Loss of utility for suffer a bleeding (5 days with a 15% reduction in previous utility)	0.0015	Gamma ($18, 18 \times 10^{-8}$)	Eckman 2009[63]
Loss of utility due to the fail of the PAF treatment	0.0005	Gamma (2.000,0.001)	Author assumption

AF, atrial fibrillation; CAF, chronic atrial fibrillation; DC, direct current; NSR, normal sinus rhythm; PAF, paroxysmal atrial fibrillation.

TABLE 50 *Probabilistic values of costs parameters*

Parameter (all strategies)	Distribution (parameter)	Source
Annual cost of long-term care in post-stroke CAF (dependent)	Gamma (3.39,1987.22)	Chambers model,[73] Saka 2009[71]
Annual cost of long-term care in post-stroke (independent)	Gamma (3.39,154.46)	Chambers model,[73] Saka 2009[71]
Cost of a stroke dependent event (51 days inpatient stay)	Gamma (24.57,388.43)	Wardlaw 1998,[58] Saka 2009[71]
Cost of a stroke independent event (14 days inpatient stay)	Gamma (4.97,662.52)	Wardlaw 1998,[58] Saka 2009[71]
Cost of a stroke event followed by death (33 days inpatient stay)	Gamma (172.59,29.11)	Wardlaw 1998,[58] Saka 2009[71]
Annual cost of being in CAF (rate control drug sotalol 240 mg daily)	Gamma (1.432,31.665)	*British National Formulary*[17]
Annual cost of warfarin treatment	Gamma (3.64,1.08)	Abdelhafiz 2003[74]
Cost of bleeding events prices 2009	Gamma (4.14,24.88)	Abdelhafiz 2003[74]
Parameter (PiP strategy)		
Cost of PAF event in PiP (cost of flecainide based on a 100-mg 60-tablet pack = £15.04) (2009)	Gamma (2.9,0.18)	*British National Formulary*[17]
Cost of proarrhythmia event (electrical cardioversion plus warfarin)	Gamma (2.08,357.22)	*NHS reference costs 2008/09: collection guidance*[56]
Cost of PAF treatment fail (electrical cardioversion plus warfarin)	Gamma (2.08,357.22)	*NHS reference costs 2008/09: collection guidance*[56]
Annual cost of being in NSR in PiP	0	Author assumption
Parameter (AAD strategy)		
Cost of PAF event in AAD (90% patients electrical cardioversion plus warfarin and 10% pharmacological cardioversion)	Gamma (1.00,363.15)	*NHS reference costs 2008/09: collection guidance*[56]
Cost of proarrhythmia event in AAD (electrical cardioversion plus warfarin)	Gamma (2.08,357.22)	*NHS reference costs 2008/09: collection guidance*[56]
Annual cost of being in NSR in AAD (200 mg daily of flecainide)	Gamma (9.146,16215)	*British National Formulary*[17]
Parameter (IHT strategy)		
Cost of PAF event in IHT returning to NSR (cost of an IV infusion in A&E room)	Gamma (1.00,363.15)	*NHS reference costs 2008/09: collection guidance*[56]
Cost of proarrhythmia event (electrical cardioversion plus warfarin)	Gamma (2.08,357.22)	*NHS reference costs 2008/09: collection guidance*[56]
Cost of PAF treatment fail (electrical cardioversion plus warfarin)	Gamma (2.08,357.22)	*NHS reference costs 2008/09: collection guidance*[56]
Annual cost of being in NSR in IHT	0	Author assumption

AAD, antiarrhythmic drug; A&E, accident and emergency; CAF, chronic atrial fibrillation; IHT, in-hospital treatment; IV, intravenous; NSR, normal sinus rhythm; PAF, paroxysmal atrial fibrillation; PiP, pill-in-the-pocket.

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We look forward to hearing from you.

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