NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Of

Multaq® (Dronedarone)

MANUFACTURER/SPONSOR SUBMISSION OF EVIDENCE

Contents

List of abbreviations and definition of terms

AAD	Antiarrythmic drugs
AE	Adverse event
AF	Atrial fibrillation
AFL	Atrial flutter
AV	Atrioventricular
Baseline therapy	Standard therapy for AF according to guidelines: e.g. anticoagulants and beta-blockers.
BID	Twice daily
CAD	Coronary artery disease
$CHADS_2$ score	Clinical prediction rule for estimating risk of stroke in patients with AF
CHF	Congestive heart failure
CI	Confidence interval
ECG	Electrocardiogram
EMEA	European Medicines Agency
FDA	US Food and Drug Administration
INR	International normalised ratio
IVRS	interactive voice response system
LVEF	left ventricular ejection fraction
LVF	Left ventricular function
MTC	Mixed treatment comparison
NICE	National Institute of Health and Clinical Excellence
NYHA	New York Heart Association
RCT	Randomised controlled trial
SAE	Serious adverse event
SHD	Structural heart disease
TEAE(s)	Treatment-emergent adverse event(s)
TIA	Transient ischaemic attack

Section A

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

Multaq®, dronedarone is an antiarrhythmic compound with activity in all 4 Vaughan Williams classes.

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Dronedarone does not yet have marketing authorisation but is currently under review by the EMEA with CHMP opinion anticipated in September 2009.

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

The anticipated indication which is under discussion with the EMEA:

Dronedarone is indicated for stable adult patients with either a recent history of, or current non-permanent atrial fibrillation (AF). Dronedarone has been shown to decrease the risk of AF-related hospitalisation.

This population is likely to exclude patients with NYHA Class IV CHF and also NYHA Class III CHF with a recent haemodynamic instability.

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

Dronedarone is not currently in use in the NHS and there are no ongoing clinical trials. It is anticipated to be available in the UK in December 2009.

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

Dronedarone was approved by the FDA in July 2009 as an anti-arrhythmic indicated to reduce the risk of cardiovascular hospitalisation in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors, who are in sinus rhythm or who will be cardioverted. Associated cardiovascular risk factors include age over 70 years, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥ 50mm or left ventricular ejection fraction (LVEF) < 40%, who are in sinus rhythm or who will be cardioverted.

Dronedarone has also been approved by Health Canada in August 2009 for the treatment of patients with a history of, or current atrial fibrillation to reduce their risk of cardiovascular hospitalisation due to this condition.

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

It is planned to submit dronedarone for an assessment to the Scottish Medicines Consortium (SMC) in November 2009, dependent upon product launch date. A Form A will also be submitted to AWMSG although it is anticipated that a Form B will not be requested.

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Dronedarone is available in 400mg tablets. For hospital use it is available in a pack size of 20 tablets representing 10 days of use, or for retail use in a pack size of 60 tablets (30 days).

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

Sanofi-aventis recommend that patients remain on dronedarone indefinitely unless persistence of a high level of AF symptoms or intolerability is deemed to require alternative therapy.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology

is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

A final price has not yet been confirmed, but is anticipated to be between £2.20 and £2.50 per day.

1.10 What is the setting for the use of the technology?

Dronedarone will typically be initiated by a specialist in an outpatient setting.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

7 days after initiation a creatinine test should be conducted by the GP. No further monitoring is required.

No other therapies are likely to be administered at the same time as dronedarone as part of a course of treatment, over standard baseline therapy.

2 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with either a recent history of, or current paroxysmal or persistent atrial fibrillation or atrial flutter, who are current receiving standard baseline treatment with or without beta blockers	*As per the anticipated licensed indication: for stable adult patients with a recent history of, or current non-permanent atrial fibrillation (AF).* *This population is likely to exclude patients with NYHA CHF Class IV and also NYHA Class III CHF with a recent haemodynamic instability.*
Intervention	Dronedarone	*Dronedarone*
Comparator(s)	As a first line treatment or as an adjunct to standard baseline therapy, dronedarone will be compared with • Standard baseline therapy with or without beta blockers As a second line therapy, dronedarone will be compared to the following drugs according to their indications • Class 1c anti arrhythmic agents (flecainide) • Sotalol amiodarone	*In patients with multiple CV risk factors (corresponding to a $CHADS_2 \geq 4$[i]) dronedarone should be given on top of baseline therapy. It will therefore be compared with:* • *Standard baseline therapy with or without beta blockers* *Dronedarone should also be considered as an alternative 1st line to current anti-arrhythmic agents when it is considered appropriate to introduce an AAD. Current AADs include:* • *Class 1c agents* • *Sotalol, and* • *Amiodarone*
Outcomes	The outcome measures	*The dronedarone clinical trial programme and*

[i] $CHADS_2$ is a stroke risk stratification scheme which is based on specific risk factors including congestive heart failure, hypertension, age >75, diabetes mellitus, and prior stroke or transient ischemic attack.

	to be considered include: • Time to recurrence of atrial fibrillation/atrial flutter • Symptoms related to atrial fibrillation/atrial flutter • Stroke • Mortality • Adverse effects of treatment • Health-related quality of life	*supportive registries provide evidence across the full range of surrogate and clinical endpoints relevant for AF. The outcome measures to be considered therefore include:* • *All-cause mortality* • *AF recurrence* • *Stroke* • *Cardiac events* • *Adverse events of treatment* • *Health-related quality of life*
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective	*The economic evaluation performed is a cost-utility analysis, based on a life-time discrete event, individual patient methodology. Patients are individually simulated and their progression through the disease model recorded, taking account of the events that they incur and the associated costs and quality of life detriments.* *Results are presented as incremental cost per quality-adjusted life years and costs are considered from an NHS and PSS perspective as per the required reference case*.
Subgroups to be considered	If data are available the following subgroups will be considered • Based on cardiovascular risk • People with atrial flutter	*As the model is based on UK guidelines[1], it already starts with identified sub-groups such as patients with paroxysmal or persistent AF.* *Additional subgroups are considered including:* • *$CHADS_2$ scores*

		Patients with AFL are not considered separately in the model as data was not available. Some AFL patients will likely be assumed to be clinically the same as AF and treated as such. Therefore the assumptions and outcomes of the economic model will apply for such patients.
Special considerations, including issues related to equity or equality	Details of components of best supportive care should be clearly described. Guidance will only be issued in accordance with the marketing authorisation.	

Section B

3 Executive summary

The UK approved name, brand name, marketing status and principal pharmacological action of the proposed drug.

Multaq ®, dronedarone is currently under review by the European Medicines Agency (EMEA) for an anticipated indication 'for stable adult patients with either a recent history of, or current non-permanent atrial fibrillation (AF). Dronedarone has been shown to decrease the risk of AF_related hospitalisation'. This population is likely to exclude patients with NYHA CHF Class IV and also NYHA Class III CHF with a recent haemodynamic instability (see Section 10 (Appendix 1) for the draft SPC).

Dronedarone demonstrates electrophysiological characteristics belonging to all 4 Vaughan Williams[2] classes of antiarrhythmic compounds: acting on transmembrane sodium, potassium, calcium and slow L-type calcium channels as well as adrenoceptors.

The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost (see Section 1.9) price.

Dronedarone is available in 400mg tablets. For hospital use it is available in a pack size of 20 tablets representing 10 days of use, or for retail use in a pack size of 60 tablets (30 days). The pack price to the NHS is anticipated to be between £22.00 and £25.00 for the 10 day pack or between £66.00 and £75.00 for the 30 day pack. Patients should take dronedarone tablets twice a day with morning and evening meals. It is not necessary to use a loading dose of dronedarone or to adjust the dose after initiation of a course of therapy. Sanofi-aventis recommend that patients remain on dronedarone indefinitely unless persistence of a high level of AF symptoms or intolerability is deemed to require alternative therapy.

The indication(s) and any restriction(s).

The indication for dronedarone is anticipated to be 'for stable adult patients with either a recent history of, or current non-permanent atrial fibrillation (AF). Dronedarone has been shown to decrease the risk of AF-related hospitalisation'. This population is likely to exclude patients with NYHA CHF Class IV and also NYHA Class III CHF with a recent haemodynamic instability.

A stable patient is defined as a patient with a stable haemodynamic condition i.e. without a recent acute decompensation of their heart failure. This implies that they have a sustained satisfactory clinical condition while on maintenance doses of their Congestive Heart Failure (CHF) treatments or that they do not have CHF at all. Unstable patients are patients with worsening symptoms of CHF or in whom maintenance doses of background treatments have not been achieved or in whom acute treatments, such as inotropes, have not yet been stopped.

While atrial flutter (AFL) is not at this time mentioned specifically within the proposed EMEA indication wording, it is anticipated that for patients where the AFL treatment is indistinguishable from AF that dronedarone will be an appropriate intervention.

The recommended course of treatment.
Neither a loading dose nor dose titration is required for dronedarone therefore the patient will receive 400mg twice daily indefinitely unless persistence of a high level of AF symptoms or intolerability is deemed to require alternative therapy.

The main comparator(s).
Treatment with current AADs to prevent recurrences of AF are often associated with severe adverse events such as proarrhythmias, cardiovascular death and/or serious non cardiac end-organ toxicity, thereby potentially leading to high discontinuation rates.[5] Dronedarone now offers a more balanced pharmacological therapy for AF due to its efficacy, safety and economic profile. It may also be considered appropriate for an atrial flutter patient (AFL) who is deemed by the clinician suitable to be treated as per an AF patient. It is expected that dronedarone will be used for patients with multiple CV risk factors (corresponding to a $CHADS_2 \geq 4$)[3] on top of standard baseline therapy (including anti-coagulation and beta-blockers as per the UK National Institute of Health and Clinical Excellent (NICE) guidelines.[1]. For these higher risk patients the comparator is baseline therapy alone.

Dronedarone will also be used as a first line antiarrhythmic alternative to current agents (amiodarone, sotalol and Class 1c agents - flecainide and propafenone) when it is appropriate to introduce an AAD.

Whether the key clinical evidence in the submission comes from head to head randomised trials (RCTs), from an indirect comparison of two sets of randomised trials involving a common comparator (for example, placebo or other active therapy), or from non-randomised studies.

The key clinical evidence comes from head to head RCTs, meta-analysis (direct and indirect comparisons) and data synthesis through mixed treatment comparison of RCTs.

A systematic search for dronedarone Phase III studies in patients with non-permanent AF (the anticipated licensed indication) identified 4 relevant trials: EURIDIS[4], ADONIS[4], ATHENA[5] and DIONYSOS.[6] These were all trials of dronedarone in patients with paroxysmal or persistent AF (non-permanent AF). Although DAFNE[7] enrolled subjects from the appropriate patient population it was excluded from the main clinical effectiveness review because it was a phase II study and therefore did not meet the inclusion criteria. Two other dronedarone studies were excluded because they did not meet the inclusion criteria for the review. These were ERATO which enrolled permanent AF patients[8] and ANDROMEDA which enrolled patients with severe heart failure. [9]

The EURIDIS and ADONIS trials were double-blind, randomised, placebo-controlled sister trials, identical in design, which were carried out to demonstrate the efficacy of dronedarone in the maintenance of sinus rhythm after cardioversion in 615 and 629 patients respectively, for one year.[4] ATHENA was a large (n=4628) randomised, double-blind, placebo-controlled trial to evaluate the long-term effect of dronedarone 400 mg twice daily (BID) versus placebo on top of baseline therapy on the combined risk of cardiovascular hospitalisation or all-cause mortality in patients with a recent or current history of AF/AFL. [10] This was the first and largest outcomes specific RCT for an antiarrhythmic drug (AAD). DIONYSOS was a double-blind RCT designed while ATHENA was ongoing, which compared the short-term efficacy (AF recurrence post cardioversion or drug discontinuation) and safety (occurrence of thyroid, hepatic, pulmonary, neurological, skin, eye, or gastrointestinal specific events or premature study drug discontinuation following any AE) of dronedarone versus amiodarone in 504 patients with persistent AF for electrical cardioversion, followed for at least 6 months.[6]

One Cochrane review, published in 2007 was included in the clinical review but due to its cut-off date, it had limited data on dronedarone. The only data available were the phase II RCT DAFNE, plus abstract data from EURIDIS and ADONIS RCT[11]. Consequently, a further systematic review, meta-analysis plus mixed treatment comparison (MTC) analysis was commissioned by sanofi-aventis to consider the full evidence base. This review was updated to April 2009 and included among other references efficacy and safety results from DAFNE, EURIDIS and ADONIS, and

additional dronedarone studies ATHENA and DIONYSOS. The meta-analysis used direct and indirect methods to compare the most frequently used drugs in the UK (amiodarone, flecainide, propafenone, sotalol) with dronedarone. Flecainide and propafenone are subsequently combined into a Class 1c agent group as noted in the UK guidelines. The key outcomes analysed were all-cause mortality, treatment discontinuations (discontinuation due to adverse events and any-cause), stroke, serious adverse events and AF recurrence.[12,13]

The main clinical results of the randomised trials and any relevant non RCTs.

For both the ADONIS and EURIDIS trials combined, the median times to a documented recurrence of AF were 116 days in the dronedarone group and 53 days in the placebo group. At 12 months, the rates of recurrence were 64.1% in the dronedarone group and 75.2% in the placebo group (hazard ratio, 0.75; 95% CI, 0.65 to 0.87; P<0.001). In the ATHENA trial the primary outcome (first hospitalisation due to cardiovascular events or death) occurred in 734 patients (31.9%) in the dronedarone group and in 917 patients (39.4%) in the placebo group, with a hazard ratio for dronedarone of 0.76 (95% confidence interval [CI], 0.69 to 0.84; P<0.001). There were 116 deaths (5.0%) in the dronedarone group and 139 (6.0%) in the placebo group (hazard ratio, 0.84; 95% CI, 0.66 to 1.08; P = 0.18). In the DIONYSOS study the incidence of the primary efficacy endpoint (recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy), was 73.9% and 55.3% in the dronedarone and the amiodarone groups respectively at Month 12 (hazard ratio=1.59, log-rank p-value<0.0001).

The safety profile of dronedarone 400 mg BID in patients with AF or AFL was evaluated on 5 pooled placebo-controlled studies (DAFNE, EURIDIS, ADONIS, ERATO, ATHENA), over a mean duration of 12 months. The incidence of serious adverse events (SAEs) was similar in the dronedarone 400 mg BID and placebo groups (18.0% and 19.7%, respectively). Furthermore, an evaluation of adverse events (AEs) known to be associated with amiodarone showed that, unlike amiodarone, dronedarone did not reveal endocrinological, neurological, or pulmonary toxicity. (See FDA briefing document March 2009).[14]

The newly commissioned meta-analysis and MTC analysis reinforced the findings from the dronedarone trials. In particular the evidence from the trials, from the direct and indirect meta-analysis and the MTC shows a trend for dronedarone to decrease the risk of all-cause mortality compared to placebo. It is important to note that in all

cases within the dronedarone RCT program the placebo arm represented baseline therapy including such treatments as beta-blockers and anti-coagulation.

In relation to the economic evaluation, details of:

- *the type of economic evaluation and justification for the approach used*
- *the pivotal assumptions underlying the model/analysis*
- *the mean costs, outcomes and incremental ratios from the evaluation.*

A cost-effectiveness analysis has been conducted in line with the reference case requirements of NICE and based on the UK guidelines for the management of AF as published in 2006. It is based on an individual patient life-time discrete event simulation (DES) methodology to allow for the complexity of AF to be reflected appropriately.

The pivotal assumptions underlying the analysis and therefore results are based around the all-cause mortality benefit related to dronedarone. Evidence from the mixed treatment comparison (MTC) suggests a significant all-cause mortality benefit in favour of dronedarone when compared to amiodarone and sotalol as an alternative 1st line AADs (when it is considered appropriate to introduce an AAD). In addition, a significant all-cause mortality benefit was found compared to baseline therapy for patients with a higher baseline risk as identified by $CHADS_2 \geq 4$ (indicated within ATHENA). These patients have a significantly higher morbidity and mortality risk such that adding dronedarone on top of baseline therapy offers considerable benefit.

Given the number of patient subgroups analysed (paroxysmal and persistent patients with different baseline characteristics) the range of results is summarised in Table 3.1.

Table 3.1: Summary Results across patients subgroups*

	Marginal Cost (£)	Marginal QALYs	ICER (£)
On top of baseline therapy (CHADS ≥ 4)	4215 - 4550	1.03 - 1.30	3254 - 4365
Alternative 1st line AAD	Marginal Cost (£)	Marginal QALYs	ICER (£)
versus amiodarone	3923 - 4509	1.75 - 1.86	2112 -2570
versus sotalol	3901 - 4307	2.07 – 2.24	1797 - 1927
versus Class 1c	2151 - 2421	0.11 – 0.13	18239 - 20143

* assumed base case price £2.30

Dronedarone is cost-effective in all scenarios for all comparators.

4 Context

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

Aetiology

Atrial fibrillation is a supraventricular tachyarrhythmia characterised by uncoordinated electrical activation of the atria with consequent deterioration of atrial mechanical function.[15] This can be seen on a echocardiogram (ECG) by the absence of consistent P-waves; instead there are rapid oscillations of fibrillatory waves that vary in size, shape and timing and are generally associated with an irregular ventricular response when atrioventricular (AV) conduction is intact.[1]

The causes of AF can be broadly categorised as cardiovascular and non-cardiovascular. Common cardiovascular causes include ischaemic heart disease, hypertension and congenital heart disease. Non-cardiovascular causes include hyperhyroidism, low potassium, penumonia, lung cancer, alcohol intake, and cardiothoracic surgery.

Patients diagnosed with AF may experience symptoms such as difficulty breathing, palpitations, chest pain, dizziness or in extreme cases loss of consciousness. However at the other extreme some patients may be asymptomatic. Symptomatic or not, AF is a contributing factor to, and an indicator of, progressive cardiovascular disease with all of the associated mortality and morbidity risks. Although AF is not generally considered to be a life-threatening arrhythmia it has been associated with a 1.5 – 2 fold increase in cardiovascular and total mortality in the Framingham Heart Study.[16] In addition, AF patients are associated with an increased risk of thromboembolism (ischaemic stroke and peripheral arterial embolism,[17] heart failure[4] and acute coronary syndromes[18]).

Stroke in particular, is a key clinical outcome associated with AF. One study noted that whilst coronary artery disease (CAD) doubles the age-adjusted risk of stroke, hypertension trebles it, congestive heart failure (CHF) quadruples it, and there is a 5-fold increase of stroke due to AF.[19] The incidence of stroke attributable to AF

increases from 1.5% at age 50–59 years to 23.5% at age 80–89 years.[20] In a study that tested the predictive accuracy of stroke risk stratification schemes in patients with AF, the $CHADS_2$ scheme (an acronym for Congestive heart failure, Hypertension, Age > 75, Diabetes mellitus, and prior Stroke or transient ischemic attack) successfully identified primary prevention patients who were at high risk of stroke (5.3 strokes per 100 patient-years) and low risk (0.8 strokes per 100 patient years).[3] In addition, a cohort study of over 100,000 patients in the Swedish Stroke Registry noted that the impact of each extra added risk factor comprised in the $CHADS_2$ score had a linear negative effect on the overall survival in patients with and without documented AF. Using $CHADS_2 = 0$ as a reference point for the risk of death (RR = 1), the risk of death associated with a $CHADS_2$ score of 4 was 4.25 (95% CI; 3.78 – 4.77) rising to 6.05 (95% CI; 5.26- 6.95) for AF patients with a $CHADS_2$ of 6.[21]

AF-related strokes tend to be more severe in that they are more likely to be fatal or incur longer hospital stays, and lead to greater disability and risk of recurrent strokes than non-AF related strokes.[22,23,24] One recent study of more than 1000 patients with ischemic strokes found that 41% of those with AF were bedridden compared with only 24% of those without AF.[25]

While such events as stroke account for much of the functional impairment associated with AF, the rhythm disturbance can also decrease quality of life directly.[26] It has been demonstrated that when compared to population norms for the SF-36 health survey, people with AF have significant impairment on all scales (physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health).[27]

Burden of Illness

AF is regarded as the most common arrhythmia seen in clinical practice. Previous research in the Framingham Heart Study suggested that the overall prevalence of AF is estimated as 3 per 1,000 person years in men and 2 per 1,000 person years in women aged between 55 and 64 years of age.[16] Moreover the prevalence doubled for every decade increment in age. It also reported a 0.1% annual incidence of AF. The life-time risk of developing AF was estimated to be 16-20%. A sample in England from the 'Heart of England' study found the overall prevalence of AF to be 1.7% of a random sample aged over 45, but to be 11.6% in the high risk groups.[28]

Other UK specific studies confirmed the increasing prevalence with age and in men. [29]

The clinical burden of illness is also reflected in the financial burden that has been recognised to be associated with AF. It has been found that among UK hospital admissions, AF is present in 3 – 6% of acute medical admissions.[30,31] An analysis by Stewart et al. examined trends in hospitalisations related to AF in Scotland during the period 1986-1996. The number of hospitalisations with a principal diagnosis of AF increased threefold from 1,869 in 1986 to 5,757 in 1996 and the number with a secondary diagnosis rose from 3,577 to 11,522. AF contributed to a growing proportion of cardiovascular-related bed-days utilised (from 18% to 37% with AF coded in any diagnostic position). [32]

Another study estimated the cost of AF in the UK by looking at 1995 figures and extrapolating to 2000.[33] Including hospital admissions, outpatient consultations, general practice consultations, and drug treatment (including the cost of monitoring anticoagulant treatment) the direct cost of health care was esimated at £244m or 0.62% of the NHS expenditure in 1995 (excluding secondary admissions and long-term nursing expenditure). Hospitalisations and drug prescriptions accounted for 50% and 20% of this expenditure, respectively. The direct costs of AF rose to £459 million in 2000, equivalent to 0.97% of total NHS expenditure based on 1995 figures. This figure represented the most conservative estimate of the cost burden attributable to AF in the UK.

In addition, there is an increased cost burden associated with AF patients because as mentioned previously, the condition is a major independent risk factor for stroke.[34] A recent US study found that severe strokes cost 11% to 71% more than minor strokes,[35] which, although not surprising, is pertinent because AF-related strokes tend to be more severe than non-AF strokes.[25]

Treatment Pathway and Treatment Options

Within the UK the NICE Clinical Guidelines provide guidance on treatment pathways for patients with AF and AFL when this treatment coincides with the treatment of AF.[1] Within the clinical guidelines AF is broadly categorised as shown in Table 4.1.

Table 4.1: Type of AF

Terminology	Clinical features	Pattern
Initial event (first detected episode)	Symptomatic Asymptomatic (first detected) Onset unknown (first detected)	May or may not reoccur
Paroxysmal	Spontaneous termination < 7 days and most often < 48 hrs	Recurrent
Persistent	Not-self-terminating Lasting > 7 days or prior cardioversion	Recurrent
Permanent	Not terminated Terminated but relapsed No cardioversion attempt	Established

Source: NICE AF guidelines, 2006.[1]

There are two main strategies for treating AF: rhythm and rate control. Rate control is described as the use of chronotropic drugs or electrophysiological/surgical interventions to reduce the rapid heart rate (ventricular rate) often found in AF patients. It improves symptoms and reduces the risk of associated morbidity. However the risk of stroke and thromboembolic events continues and requires the administration of antithrombotic drugs.[1] Rate control essentially lets AF evolve on its own but improves symptoms in some patients and is expected to reduce the risk of tachycardiomyopathy, although it is not proven.

Rhythm control involves the use of electrical or pharmacological cardioversion or electrophysiological/surgical interventions to convert the arrhythmia associated with AF to normal sinus rhythm. Patients who have been successfully cardioverted are generally administered anti-arrhythmic drugs long term to prevent the recurrence of AF. All patients should have a risk-benefit assessment performed to determine whether antithrombotic therapy is needed and over what period of time. The following is a summary of the pharmacological treatment options recommended within the guidelines for the different categories of AF.[1]

In patients with symptomatic paroxysms, with or without structural heart disease (SHD), a standard beta-blocker should be the initial treatment option (subsequently referred to in this document as baseline therapy). If symptom suppression is not achieved with baseline therapy and there is no SHD, either a Class 1c agent (flecanide or propafenone) or sotalol should be given and if these fail, amiodarone is prescribed or the patient is referred for non-pharmacological intervention. If the patient has CAD and baseline therapy does not achieve symptom suppression,

sotalol should be given followed by amiodarone or referral if symptom suppression is still not achieved. In patients with poor left ventricular function (LVF) amiodarone or referral should be considered if baseline therapy does not adequately suppress paroxysms.

Some persistent AF patients will satisfy the criteria for either rate or rhythm strategy therefore the indications are not mutally exclusive, but some baseline recommendations are suggested. A rate control strategy should be the preferred initial option for patients over 65 yrs old, with CAD, with contraindications to AADs, who are unsuitable for cardioversion or without CHF. A rhythm control approach should be the preferred initial option in symptomatic, younger patients, those presenting for the first time with lone AF, those with AF secondary to a treated/corrected precipitant and those with CHF. For persistent patients who require AADs and who have SHD a standard beta-blocker is recommended and if ineffective, contraindicated or not tolerated amiodarone should be used. For those with no SHD a standard beta-blocker should be the initial treatment (baseline therapy) and if ineffective, contraindicated or not tolerated, a Class 1c agent or sotalol should be given. When other drug classes are ineffective, contraindicated or not tolerated amiodarone should be administered.

Permanent AF patients needing rate control should start with beta-blockers or rate-limiting calcium antagonists as initial monotherapy. If monotherapy is inadequate digoxin can be added. Please note that dronedarone is not anticipated to be indicated for permanent patients at this time.

It is recognised within the clinical guidelines that an escalating approach to drug therapy has been recommended which is not totally in keeping with the evidence on efficacy. This evidence favours amiodarone, but due to concerns regarding adverse effects which may only become apparent after long-term use and include pulmonary, hepatic, ophthalmic and thyroid toxicity, amiodarone is generally kept to last-line. [1]

4.2 What was the rationale for the development of the new technology?

Treatment with current AADs to prevent recurrences of AF are often associated with severe adverse events such as proarrhythmias, cardiovascular death and/or serious non cardiac end-organ toxicity, thereby potentially leading to high discontinuation rates.[5] This created a need for an efficacious and safer treatment option. The development of dronedarone was therefore initiated with the intent of replicating the

effects of the AAD, amiodarone, while minimising its significant toxicity. Like amiodarone, dronedarone is a benzofuran derivative, but with different relative electrophysiological activities on individual ion channels. Specific structural modifications were introduced to minimise the non-cardiovascular adverse effects of amiodarone. A methane-sulfonamyl group was introduced to shorten half-life and decrease lipophilicity, and iodine substituents were eliminated to avoid the risk of thyroid side effects.

It is generally accepted that there are 2 main strategies to treating and managing patients with AF/AFL, i.e., by restoring and maintaining sinus rhythm (rhythm control) and by controlling ventricular rate with atrioventricular node blocking agents (rate control). The initial development of dronedarone therefore focused on its efficacy and safety for the control of rhythm and rate in patients with AF/AFL as per these strategies (ERATO[8], EURIDIS and ADONIS[4]).

During the development of the molecule, observations accumulated and helped to better understand dronedarone's properties and to delineate ways to manage its risks. The findings of the ANDROMEDA trial,[9] a trial conducted in patients with severe heart failure, helped to change the focus of the development programme from the symptomatic relief of arrhythmias to the long-term effects of drug therapy on the risk of cardiovascular death and hospitalisation, while a pooled analysis of two Phase III studies (EURIDIS and ADONIS) suggested that patients with paroxysmal or persistent AF who were randomised to dronedarone had a lower risk of hospitalisation or death than patients who were randomised to placebo (See FDA briefing document March 2009).[14] The clinical programme shifted emphasis to the management of cardiovascular risk in patients with AF/AFL. This was mainly achieved through the ATHENA study, the first RCT to focus on morbidity and mortality associated with a treatment for AF. This RCT included 4628 and the results demonstrated how dronedarone could be used in clinical practice in patients with AF or AFL (or with history of such events) and its exact associated therapeutic benefit. It demonstrated a significant 24% relative risk reduction in the composite endpoint of reduction in cardiovascular hospitalisation or death from any cause. This was in contrast to the previous AFFIRM study which demonstrated a significant increase in hospitalisation associated with rhythm control AADs compared to rate control agents, suggesting important cost implications with current AADs.[36] This important clinical benefit, is likely to be the result of several properties such as vasodilatory and blood pressure lowering features of the molecule probably related

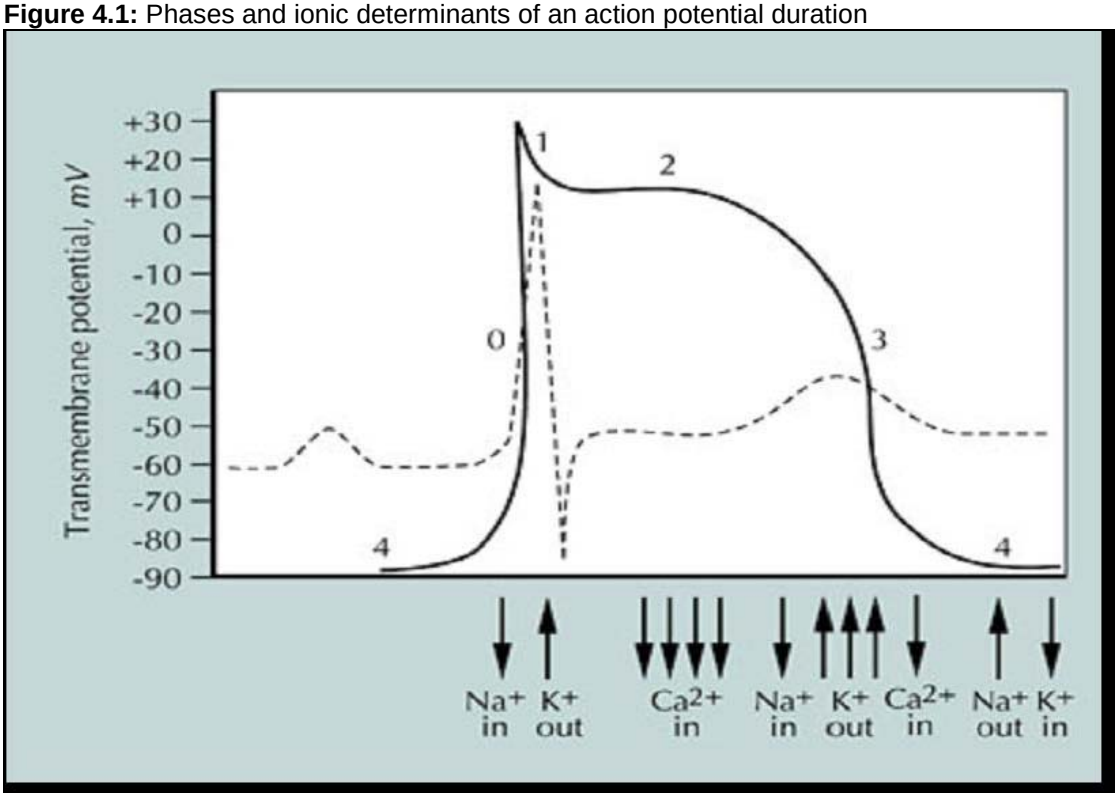
to, but not limited to, its demonstrated activity in maintaining cardiac sinus rhythm or/and in controlling ventricular rate.

4.3 What is the principal mechanism of action of the technology?

Dronedarone demonstrates electrophysiological characteristics belonging to all 4 Vaughan-Williams[2] classes of AAD:[37]

- To a limited extent it blocks sodium (INa) channels decreasing the slope of the depolarisation phase (phase 0) of the action potential (Class I effect) (Figure 4.1 - Phases and ionic determinants of an action potential duration)
- It has limited non-competitive α and β adrenoceptor antagonist properties (Class II effect)
- Its primary activity is to block the outward potassium currents involved in cardiac repolarisation at both the atrial [IK (ACh) and Ikur] and the ventricular (Ito, IK1, IKr, IKs and Isus) levels, thus prolonging action potential duration and the refractory period (Class III effect) (Figure 4.1 - Phases and ionic determinants of an action potential duration)
- Dronedarone weakly increases Ito, weakly decreases IK1, and reduces IKr, IKs, IK (ACh) and IKv1.5 in a concentration-dependent manner. With its highest affinity for IK (ACh), dronedarone's atrium level antiarrhythmic activity is expected to dominate over ventricular activity. Furthermore the concomitant inhibition of inward and outward currents may explain the decrease in the transmural dispersion of repolarisation that is thought to contribute to the low proarrhythmic potential of amiodarone and now dronedarone
- Finally, on a limited basis, it reduces L-type and T-type calcium current (ICa) inward currents (Class IV effect)
- The pharmacodynamic consequences of these various actions are mainly to
    - Increase cardiac refractoriness and slow down conduction velocity, corresponding to the main effects related to the antiarrhythmic action
    - Slow down AV node conduction resulting in the decrease of ventricular response of AF
    - Mild reduction of blood pressure
    - Coronary vasodilatation

Figure 4.1: Phases and ionic determinants of an action potential duration



The broad pharmacological action of dronedarone, including multiple ion channel blockade and β-adrenoceptor antagonism, leads to a variety of tissue response in patients with arrhythmias, including a reduction in heart rate, improved rhythm control, and haemodynamic effects such as lowering of blood pressure.

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

The indication for dronedarone is anticipated to be 'for stable adult patients with either a recent history of, or current non-permanent atrial fibrillation (AF). Dronedarone has been shown to decrease the risk of AF-related hospitalisation'. This population is likely to exclude patients with NYHA CHF Class IV and also NYHA Class III CHF with a recent haemodynamic instability. As such dronedarone is expected to be used in two positions;

a. For patients with multiple CV risk factors (corresponding to a $CHADS_2 \geq 4$) on top of standard baseline therapy (including anti-coagulation and beta blockers as per the UK guidelines and referred to within the guidelines as 1st line treatment)
b. For patients when it is deemed appropriate to introduce an AAD, as a 1st line alternative to current AADs (referred to within the guidelines as 2nd line treatment).

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

NICE clinical guidelines note that their recommendations of an escalating approach to drug therapy is not totally in keeping with the evidence of efficacy as there is a concern with treatment-related adverse events (TEAEs). The evidence favours amiodarone, but due to concerns regarding adverse effects which may only become apparent after long-term use and include pulmonary, hepatic, ophthalmic and thyroid toxicity, amiodarone is generally kept to last-line. All of the current AADs are associated with potentially fatal AEs which means the clinician needs to balance efficacy with safety.

Furthermore increased hospitalisation due to AF (see Section 4.1 Burden of Illness) is becoming a big concern for current clinical practice. To date no current antiarrhythmic treatment has been shown to reduce the rate of hospitalisation due to cardiovascular events in patients with atrial fibrillation.[5]

4.6 Provide details of any relevant guidelines or protocols.

- UK NICE national clinical guideline for management of atrial fibrillation in primary and secondary care, 2006.[1]
- Scottish national clinical guideline for cardiac arrhythmias in coronary heart disease, 2007.[38]
- American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) guidelines for the treatment of atrial fibrillation, 2006.[39]

5 Equity and equality

5.1 Identification of equity and equalities issues

Are there any issues relating to equity or equalities (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

There are no issues relating to equity or equalities identified within the scope for the appraisal, currently.

How has the analysis addressed these issues?

Not applicable.

6 Clinical evidence

6.1 Identification of studies

Literature search

Strategy for finding dronedarone studies

To identify relevant studies, electronic databases were searched: Medline, EMBASE and the Cochrane Library were accessed in March 2009. There were no restrictions by date of publication. The search combined both MeSH and free-text terms for 'atrial fibrillation/flutter' with the interventions 'dronedarone', and publication type 'randomised clinical trial', or studies reporting quality of life outcomes. Cited references from included studies and previously published reviews were also searched. See Section 10 (Appendix 2) for the search strategies used.

Inclusion criteria

Only phase III RCTs of dronedarone were included if they enrolled patients with paroxysmal or persistent AF/AFL, and if they reported on any one of the following outcomes:

- time to recurrence of AF/AFL
- symptoms related to AF/AFL
- stroke
- mortality
- adverse effects of treatment
- health-related quality of life.

Literature search results

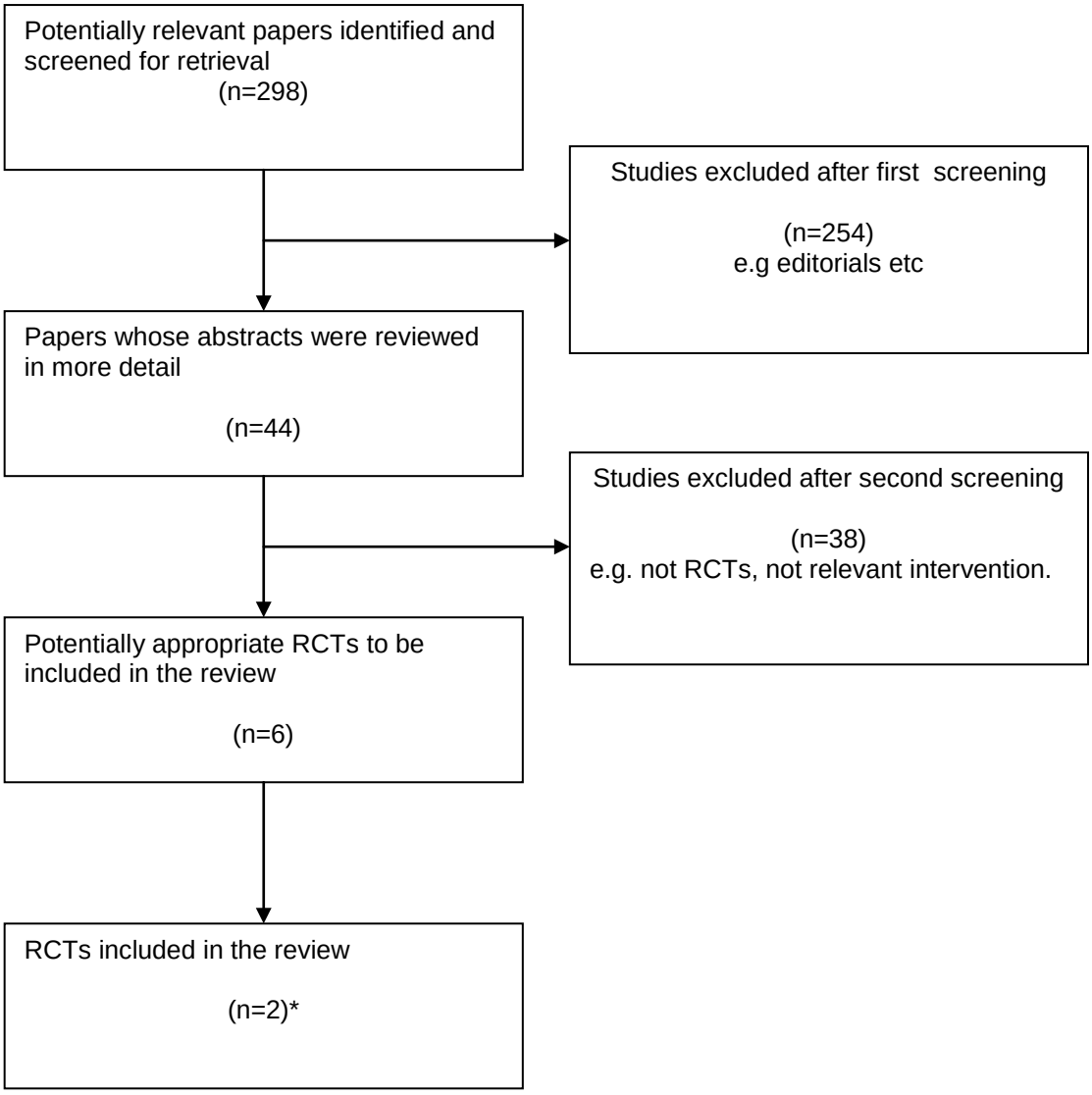
In total 298 studies were identified for dronedarone as a result of searches of MEDLINE (n=90), EMBASE (n=193) and Cochrane library (n=15) (Figure 6.1). Two publications met the inclusion criteria for this review. One publication (Singh et al, 2007) combined the results of two identical placebo-controlled phase III trials of dronedarone (ADONIS and EURIDIS) which included patients with paroxysmal and persistent AF (Table 6.1).[4] The second publication (Hohnloser et al) reported on

ATHENA, a large placebo-controlled trial of dronedarone in patients with paroxysmal and persistent AF with additional risk factors for death.[5] Three other dronedarone studies (DAFNE, ERATO and ANDROMEDA) were excluded from the effectiveness review because they did not meet the inclusion criteria. DAFNE was a phase II dose-ranging study.[7] ERATO enrolled patients with permanent AF[8] and ANDROMEDA enrolled patients with severe heart failure,[9] populations for which dronedarone is not indicated. [5] Sanofi-aventis provided a recently completed and as yet unpublished Clinical Study Report for DIONYSOS: a phase III RCT of dronedarone versus amiodarone for patients with persistent AF.[6] The main evidence for the clinical effectiveness section therefore comprises two published articles related to ADONIS/EURIDIS[4] and ATHENA,[5] as well as the clinical trial DIONYSOS (see Section 10 (Appendix 3)), in the form of an unpublished Clinical Study Report.[6]

One Cochrane systematic review (2007) was identified.[11] It assessed a number of antiarrhythmics, including dronedarone, for maintaining sinus rhythm after cardioversion of AF. However, only data from DAFNE and preliminary data from EURIDIS and ADONIS were available at the time of this review.

To update and expand on the Cochrane review, evidence from a newly commissioned meta-analysis is presented. The analyses assessed the efficacy and safety of dronedarone and other currently recommended AADs in the UK (Class 1c agents - flecainide and propafenone, sotalol and amiodarone) using direct and indirect meta-analysis as well as a mixed treatment comparison approach. See Section 6.5 for a summary of results. Please note that while some dronedarone studies were excluded from the clinical effectiveness review because they were not Phase III trials, they were included in the meta-analysis and MTC which considered the full evidence base for dronedarone in the target patient population.

Figure 6.1: Process of selecting studies related to dronedarone for inclusion in the review



* One study (Singh et al, 2007) reported results for the combined phase III trials of ADONIS and EURIDIS. One study reported the results of the ATHENA phase III trial (Hohnloser et al, 2009). One unpublished Clinical Study Report for the DIONYSOS phase III RCT was provided by sanofi-aventis.

Clinical study reports are available on request for all dronedarone studies included in the evidence review.

6.2 Study selection

6.2.1 Complete list of RCTs

Table 6.1 summarises the main characteristics of the clinical trials of dronedarone. Only those studies in the shaded rows met the inclusion criteria for the clinical effectiveness review. That is, they were phase III trials that enrolled patients with persistent AF/AFL or paroxysmal AF/AFL.

Table 6.1: Summary of all phase II and III trials of dronedarone

Study	Publications	Comparator	Follow-up	Population	N randomised	Primary outcome
DAFNE	Touboul, 2003[7]	Placebo	6months	Persistent/ paroxysmal AF	270	Time to recurrence of AF (for dose ranging)
EURIDIS [a]	Singh, 2007[4]	Placebo	12 months	Persistent/ paroxysmal AF	612	Time to recurrence of AF
ADONIS[a]	Singh, 2007[4]	Placebo	12 months	Persistent/ paroxysmal AF	625	Time to recurrence of AF
ATHENA	Hohnloser, 2009[5]	Placebo	12 months	Persistent/paroxysmal AF with additional risk factors for death	4628	Hospitalisation for CV event or death
ERATO	Davy, 2008[8]	Placebo	6 months	Permanent AF	174	Change in mean ventricular rate (baseline to day 14)
ANDROMEDA	Køber, 2008[9]	Placebo	Median = 2 months	Severe heart failure	627	All cause death or hospitalisation for heart failure
DIONYSOS	Clinical Study Report, 2009	Amiodarone	6 months	Persistent/paroxysmal AF	504	AF recurrence+drug discontinuation

Notes a. EURIDIS and ADONIS trials are identical in design. They were conducted in different parts of the world.
ADONIS= American–Australian–African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm, EURIDIS=European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm, ATHENA=**A** placebo-controlled, double-blind, parallel arm **T**rial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular **H**ospitalisation or death from any cause in pati**EN**ts with **A**trial fibrillation/atrial flutter, ERATO=The Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation.

6.2.2 Inclusion and exclusion criteria

See Section 6.1 for full description of inclusion criteria.

6.2.3 List of relevant RCTs

The appropriate comparators to dronedarone, as specified in the decision problem, are standard baseline therapy (e.g. anticoagulants and beta-blockers) and currently used AADs in the UK (class 1c agents, sotalol and amiodarone). Therefore, the evidence review includes three phase III RCTs that compare dronedarone to placebo which is representative of standard baseline therapy in the UK (EURIDIS, ADONIS and ATHENA) [4,5] as well as one phase III RCT that directly compares the technology with the AAD amiodarone (DIONYSOS)[6].

ATHENA was a largest placebo-controlled trial (n=4628) to evaluate the long-term effect of dronedarone versus placebo on top of baseline therapy (e.g. anticoagulation and beta-blockers) on the combined risk of cardiovascular hospitalisation or all-cause

mortality in patients with a recent or current history of AF/AFL. The objectives of the ATHENA trial were: (1) to determine if dronedarone's favourable effects in patients with AF/AFL (demonstrated in earlier trials: DAFNE[7], EURIDIS, ADONIS[4] and ERATO[8]) could result in a long-term reduction in the risk of major adverse cardiovascular events; and (2) to clarify and further elucidate the effect of dronedarone on the risk of death in patients likely to receive the drug in clinical practice. This was the first outcomes trial in AF for an AAD. The trial included patients with stable heart failure but excluded patients who were clinically decompensated (who had comprised the patients studied in the ANDROMEDA trial). Treatment with dronedarone was associated with a statistically significant reduction of the combined risk of cardiovascular hospitalisation or all cause-death when compared with placebo. This reduction was due to both a lower number of cardiovascular hospitalisations and cardiovascular deaths and was consistent across all subgroups evaluated. [5]

Additional studies that have been included in the effectiveness review (ADONIS and EURIDIS) focused more on efficacy for the control of rhythm and rate in patients with AF/AFL as they were designed earlier in the clinical trial program. EURIDIS and ADONIS showed that dronedarone was significantly more effective than placebo in maintaining sinus rhythm and in reducing the ventricular rate during recurrence of arrhythmia.[4] A post-hoc analysis showed that dronedarone was associated with a lower risk of the combined endpoint of first cardiovascular hospitalisation or death.[4]

It is important to note that in these placebo-controlled studies both dronedarone and placebo were given on top of baseline therapy similar to that recommended in the UK guidelines (e.g. anticoagulation and beta-blockers). In a recent pooled analysis of 5 of the dronedarone clinical trials (EURIDIS, ADONIS, DAFNE, ATHENA and ERATO) the baseline demographics suggested that 66% of the pooled placebo arm of the trials received beta-blockers and 62% anticoagulation versus 64% and 63% of the dronedarone pooled trial data. [40]

DAFNE, ERATO and ANDROMEDA do not form part of this effectiveness review as they did not meet the inclusion criteria (see Section 6.1), but their results are summarised for completeness. The DAFNE trial was a phase II dose-ranging study whose results led to 400 mg BID being the selected therapeutic dose for future studies.[7] ERATO demonstrated that dronedarone decreased the ventricular rate, both at rest and during exercise (digoxin is not effective during exercise), in patients

with permanent AF, thus (together with the results of the other placebo-controlled trials) establishing that the drug has the ability to control both rate and rhythm in patients with AF.[8]

The US FDA was cognisant of the fact that many anti-arrhythmic drugs reduce the risk of an arrhythmia but at the same time have been shown to increase the risk of CV death in vulnerable populations (e.g. patients with significant SHD or heart failure). Consequently, the FDA recommended that the company carry out a trial to exclude the possibility that dronedarone increased the risk of death.

The ANDROMEDA trial therefore enrolled patients hospitalised for decompensated heart failure, to evaluate the effect of dronedarone on the risk of hospitalisations for worsening heart failure or death in this high risk CHF population. The trial was prematurely terminated upon the recommendation of the trial's Data and Safety Monitoring Board (DSMB) after the enrollment of 627 patients, when it was noted that dronedarone was associated with 25 deaths vs. 12 in the placebo group; this imbalance was largely related to an increased risk of death from worsening heart failure.[9] This is expected to be reflected in the contra-indication section of the EU labelling.

The DIONYSOS trial was a short term study, comparing the efficacy (in terms of AF recurrence) and safety of dronedarone versus amiodarone in patients with persistent AF eligible for electrical cardioversion, followed for at least 6 months. The primary endpoint was defined as recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy. As expected, recurrences of AF were more frequent in the dronedarone group when compared with the amiodarone group, whereas, premature study drug discontinuations due to intolerance were more frequent in the amiodarone group when compared to the dronedarone group. The DIONYSOS 2009 RCT is not yet published and is in the form of a Clinical Study Report.[6]

The full clinical trial programme for dronedarone has been the largest for an AAD with more than 8000 patients. The safety programme within AF/AFL includes more than 6000 patients (ATHENA, EURIDIS, ADONIS, ERATO and DAFNE) with a mean follow-up period of 12 months and in some cases up to 30 months.

6.2.4 List of relevant non-randomised controlled trials

No non-randomised controlled trials were included in the effectiveness review.

6.2.5 Ongoing studies

There are currently no ongoing studies of dronedarone.

6.3 Summary of methodology of relevant RCTs

This section presents a description of the methods and results from each of the four phase III trials which met the inclusion criteria for the evidence review of dronedarone (Table 6.2).

Table 6.2: Summary of dronedarone trials which met the inclusion criteria for the clinical effectiveness review

Study	ADONIS/EURIDIS	ATHENA	DIONYSOS	Note
Publications	Singh, 2007[4]	Hohnloser, 2009[5]	Clinical study report, 2009	CSRs available on request
Comparator	Placebo	Placebo	Amiodarone	Patients in placebo controlled studies were also on baseline therapy e.g. beta-blockers and anticoagulants.
Number randomised	625/612	4628	504	
Follow-up period	12 months	12 months	6 months	
Population	Persistent/paroxysmal AF	Persistent/paroxysmal AF with additional risk factors for death	Persistent AF	
Primary outcome	Time to recurrence of AF/AFL	Hospitalisation for CV event or death	AF recurrence + drug discontinuation	
Secondary outcomes	1. AF related symptoms 2. Ventricular rate control 3. AF recurrence after blood drug plasma level reached 4. Tolerability 5. Pharmacokinetics of selected dose	1. Death from any cause 2. First CV hospitalisation 3. CV death	1. Main safety endpoint (MSE)[a] 2. Adverse events 3. Laboratory parameters 4. Vital signs 5. ECGs	DIONYSOS secondary analysis pre-specified: 1. time to first MSE 2. time to first MSE exc. GI events, 3. time to MSE
Safety measures	TEAEs, serious TEAEs, and TEAEs leading to drug discontinuation	TEAEs, serious TEAEs, and TEAEs leading to drug discontinuation	TEAEs, serious TEAEs, and TEAEs leading to drug discontinuation	Pooled analysis of safety data from ADONIS/EURIDIS, ERATO, DAFNE and ATHENA published in abstract form.[40]

a. MSE= the occurrence of thyroid, hepatic, pulmonary, neurological, skin, eye, or gastrointestinal specific events or premature study drug discontinuation following any adverse event (AE).
Note: GI=gastrointestinal, TEAEs = treatment emergent adverse events

EURIDIS and ADONIS Trials

Study design and methods

The EURIDIS and ADONIS trials were sister studies, identical in design, which were carried out as pivotal trials to demonstrate the 1-year efficacy of dronedarone (400 mg BID) in the maintenance of normal sinus rhythm after electrical, pharmacological, or spontaneous conversion of AF/AFL. EURIDIS and ADONIS differed only in the location where the studies were conducted: EURIDIS was conducted in European countries and ADONIS conducted in the US, Canada, Australia, South Africa and Argentina. Results for both studies were combined and reported in 2007 by Singh et al.[4] The following summary is taken from that publication.

Patients were included if they had at least one episode of AF (as seen on ECG) in the preceding 3 months, and were in sinus rhythm for at least 1 hour before randomisation. The study excluded patients with permanent AF and those with NYHA class III or IV CHF. In total, 828 patients received 400 mg of dronedarone twice daily and 409 patients received placebo. Both the dronedarone and placebo arms were given on top of baseline therapy which included between 55 - 58% of patients receiving beta-blockers and approx. 70% of patients receiving anti-coagulation. The primary end point was the time to the first recurrence of AF or AFL.

Results

In the European trial, 680 patients were screened, and 612 were randomly assigned to study groups to receive treatment (411 to the dronedarone group and 201 to the placebo group). In the non-European trial, 731 patients were screened, and 625 were randomly assigned to receive treatment (417 to the dronedarone group and 208 to the placebo group). Three patients in the European trial and four in the non-European trial did not receive a study drug.

The mean age of all patients was 63 years, and 69% were men; 41% had structural heart disease. There were 60 patients (10%) with AFL in the European trial and 71 (11%) in the non-European trial. In the European trial, 67(16.3%) patients in the dronedarone group and 25(12.4%) in the placebo group discontinued the study prematurely; in the non-European trial, the corresponding numbers were 81(19.4%) and 36(17.3%).

For the two trials combined, the median times to a documented recurrence of AF were 116 days in the dronedarone group and 53 days in the placebo group. At 12

months, the rates of recurrence were 64.1% in the dronedarone group and 75.2% in the placebo group (hazard ratio, 0.75; 95% CI, 0.65 to 0.87; P<0.001) (Table 6.3). The time to first recurrence to AF/AFL was consistent across all of the subgroups identified in baseline characteristics.

Table 6.3: Study endpoints for EURIDIS and ADONIS

Variable	European Trial				Non-European Trial				Combined Trials			
	Placebo	Dronedarone	Hazard Ratio (95% CI)	P Value	Placebo	Dronedarone	Hazard Ratio (95% CI)	P Value	Placebo	Dronedarone	Hazard Ratio (95% CI)	P Value
Time to first recurrence of atrial fibrillation												
No. of patients	201	411			208	417			409	828		
Median (days)	41	96			59	158			53	116		
Recurrence rate at 12 mo (%)	77.5	67.1	0.78 (0.64–0.96)	0.01	72.8	61.1	0.73 (0.59–0.89)	0.002	75.2	64.1	0.75 (0.65–0.87)	<0.001
Recurrence rate at treatment analysis (%)	76.5	65.5	0.78 (0.64–0.95)	0.01	72.7	58.8	0.71 (0.57–0.88)	0.002	74.7	62.3	0.74 (0.64–0.86)	<0.001
Recurrence at 12 mo												
No. of patients	148	307			146	327			294	634		
Analysis excluding drug exposure of <5 days (%)	69.5	56.4	0.71 (0.56–0.91)	0.006	62.6	51.3	0.74 (0.57–0.96)	0.02	66.2	53.8	0.72 (0.60–0.86)	<0.001
First symptomatic atrial fibrillation	47.5	37.1	0.70 (0.54–0.90)	0.006	44.5	38.3	0.74 (0.57–0.96)	0.02	46.0	37.7	0.71 (0.60–0.86)	<0.001
Ventricular rate at first recurrence (with TTM)												<0.001
No. of patients	117	199			102	188			219	387		
Mean rate (bpm)	117.5±29.1	102.3±24.7		<0.001	116.6±31.9	104.6±27.1		<0.001	117.1±30.4	103.4±25.9		<0.001
Hospitalization or death (%)	32.0	21.2	0.66 (0.47–0.93)	0.02	29.8	24.5	0.80 (0.56–1.14)	0.22	30.9	22.8	0.73 (0.57–0.93)	0.01

* Plus–minus values are means ±SD. TTM denotes transtelephonic monitoring.

In the European trial, the mean (±SD) ventricular rate during the first adjudicated recurrence was 102.3±24.7 beats per minute in the dronedarone group and 117.5±29.1 beats per minute in the placebo group (P<0.001). The corresponding numbers for the non-European trial were 104.6±27.1 beats per minute in the dronedarone group and 116.6±31.9 beats per minute in the placebo group (P<0.001) (Table 6.3).

The rate of TEAEs and deaths was similar between the dronedarone and placebo groups. There was a slightly higher rate of serious TEAEs in the placebo groups and a slightly higher rate of treatment discontinuations in the dronedarone groups.

Table 6.4 shows the incidence of selected AEs in the two study groups. Most of these specific AEs are shown because they include many of the known side effects of amiodarone. In addition, there was a higher incidence of elevated serum creatinine levels in the dronedarone group than in the placebo group (2.4% vs. 0.2%, P =

0.004). This was shown to be related to inhibition of creatinine secretion at kidney tubular level without decrease in glomerular filtration rate.[41] It has been observed that the increase in serum creatinine occurs early after treatment initiation and reaches a plateau after 7 days. If an increase in creatininemia is observed this value should be used as the new reference baseline taking into account that this may be expected with dronedarone.

Table 6.4: Selected AEs and laboratory anomalies*

Event	Treatment Group		P Value†
	Dronedarone (N=828)	Placebo (N=409)	
Death — no. (%)			
Any cause	8 (1.0)	3 (0.7)	1.00
Sudden death	4 (0.5)	1 (0.2)	1.00
Stroke — no. (%)‡	4 (0.5)	3 (0.7)	0.69
Pulmonary event — no. (%)§			
Cough	19 (2.3)	7 (1.7)	0.67
Dyspnea	27 (3.3)	15 (3.7)	0.74
Endocrine event — no./total no. (%)¶			
Hyperthyroidism	67/801 (8.4)	56/396 (14.1)	0.002
Hypothyroidism	44/801 (5.5)	14/396 (3.5)	0.15
Cardiac event — no. (%)			
Bradycardia or conduction block‖			
Any event	22 (2.7)	8 (2.0)	0.56
Serious event	8 (1.0)	3 (0.7)	1.00
Heart failure or shock**			
Any event	20 (2.4)	4 (1.0)	0.12
Serious event	13 (1.6)	3 (0.7)	0.29
Ventricular arrhythmia††	6 (0.7)	2 (0.5)	1.00
Neurologic event — no. (%)			
Insomnia or other sleep disorder	12 (1.4)	6 (1.5)	1.00
Memory impairment	1 (0.1)	0	1.00
Peripheral neuropathy	0	1 (0.2)	0.33
Paresthesia	11 (1.3)	4 (1.0)	0.78
Tremor	6 (0.7)	2 (0.5)	1.00
Gastrointestinal or hepatic event			
Diarrhea — no. (%)	59 (7.1)	20 (4.9)	0.14
Nausea — no. (%)	36 (4.3)	14 (3.4)	0.54
Abnormality of liver function — no./total no. (%)‡‡	100/822 (12.2)	55/405 (13.6)	0.52
Dermatologic event — no. (%)			
Photosensitivity or skin discoloration§§	6 (0.7)	1 (0.2)	0.44
Other			
Elevation of serum creatinine — no. (%)	20 (2.4)	1 (0.2)	0.004

* Adverse events were defined as those occurring between the first administration of a study drug and the last administration plus 10 days.
† P values were calculated with the use of Fisher's exact test.
‡ Stroke includes cerebral-artery embolism, cerebrovascular accident, cerebral infarction, and transient ischemic attack.
§ Dyspnea includes exacerbated, exertional, and nocturnal dyspnea.
¶ Hyperthyroidism was defined as a free triiodothyronine or free thyroxine level above the normal range or a thyrotropin level below the normal range. Hypothyroidism was defined as a free triiodothyronine or free thyroxine level below the normal range or a thyrotropin level above the normal range. Patients with inconsistent changes in these measures were excluded from the analysis.
‖ Bradycardia or conduction block includes complete atrioventricular block. Serious adverse events include complete atrioventricular block, sinus bradycardia, first-degree atrioventricular block, and nodal arrhythmia.
** Heart failure or shock includes congestive cardiac failure, cardiac failure, left ventricular failure, and right ventricular failure. Serious adverse events include congestive cardiac failure, cardiac failure, left ventricular failure, cardiogenic shock, and ventricular dysfunction.
†† Ventricular arrhythmia includes ventricular tachycardia, ventricular extrasystoles, and ventricular fibrillation.
‡‡ An abnormality of liver function was defined as a level of alanine aminotransferase or aspartate aminotransferase of more than 2 times the upper limit of the normal range, an alkaline phosphatase level of more than 1.5 times the upper limit of the normal range, a γ-glutamyltransferase level of 3 times the upper limit of the normal range or more, or a total bilirubin level of 2 mg per deciliter (34 μmol per liter) or more. Patients with no abnormality and with at least one missing measurement of liver function were excluded.
§§ Photosensitivity or skin discoloration includes photosensitive rash and photosensitivity reaction.

In the European Trial, a post hoc analysis revealed that 21.2% of patients in the dronedarone group had been hospitalised or had died at 12 months, as compared with 32.0% of those in the placebo group (hazard ratio, 0.66; 95% CI, 0.47 to 0.93; P = 0.02). In the non-European trial, 24.5% of patients in the dronedarone group had been hospitalised or had died, as compared with 29.8% of those in the placebo group (hazard ratio, 0.80; 95% CI, 0.56 to 1.14; P = 0.22). The corresponding numbers in the combined analysis were 22.8% and 30.9% (hazard ratio, 0.73; 95% CI, 0.57 to 0.93; P = 0.01) (Table 6.4).

Conclusion

When considered individually or as pooled data, the findings of the two identical trials, demonstrated that relative to placebo one-year's treatment with dronedarone (400 mg BID) significantly decreased the risk of first recurrence of AF/AFL; more than doubled the median time from randomisation to the first recurrence of AF/AFL; reduced the risk of first recurrence of symptomatic episodes of these arrhythmias; slowed the ventricular response in patients whose atrial arrhythmia recurred; and was associated with a lower risk of hospitalisation for cardiovascular reasons. This consistent pattern of efficacy over a prolonged period suggests that dronedarone might have favourable effects on important cardiovascular outcomes in patients who present with a current or recent history of AF/AFL. These results were obtained with a good level of safety with no report of proarrhythmic event nor signs of organ toxicity. The overall incidence of AEs was similar in the dronedarone and placebo groups. Although neither of the trials directly compared dronedarone with amiodarone, on the basis of experience with amiodarone in other trials, these results suggest that the rate of AEs might be significantly lower with dronedarone compared to amiodarone.

ATHENA Clinical Trial

Study design and methods

This was a large (n=4628) multicentre, double-blind, randomised placebo-controlled trial evaluating the effects of dronedarone in patients with AF/AFL who had additional risk factors for death for a minimum of 12 months.[5] Both the dronedarone and placebo arms were given on top of baseline therapy which included 70% of patients receiving beta-blockers and 60% patients receiving anti-coagulation. The study had two main aims. The first was to determine if dronedarone's favourable effects in patients with AF/AFL (demonstrated in the DAFNE, EURIDIS, ADONIS and ERATO

trials) could result in a long-term reduction in the risk of major adverse cardiovascular events, including death. The second was to more extensively evaluate its safety profile in patients likely to receive the drug in clinical practice.

The intent of the ATHENA trial was to enrol a wide spectrum of patients with AF/AFL, similar to that seen in clinical practice. However, in order to achieve the number of events needed to test the primary hypothesis of the study, the inclusion criteria were similar to those of the AFFIRM study.[42] Specifically, patients were randomised into the study if they had had AF/AFL and sinus rhythm within the previous 6 months. All patients were to be treated according to baseline therapy for their cardiac condition, according to published guidelines (e.g. beta-blockers and oral anticoagulants).

In addition to the requirement for AF/AFL, patients were also required to have at least one additional risk factor for the occurrence of a major cardiovascular event. In the original protocol, this could be achieved (1) if patients were at least 70 years old and had no additional risk factors; or (2) if patients were less than 70 years old and had one of the following:

- Hypertension (taking antihypertensive drugs of at least 2 different classes)
- Diabetes
- Prior cerebrovascular accident (stroke or transient ischaemic attack) or systemic embolism
- Left atrium diameter greater than or equal to 50 mm by M-Mode echocardiography
- LVEF less than 0.40 by 2D-echocardiography.

Patients were excluded if they had permanent AF, an unstable haemodynamic condition, NYHA class IV congestive heart failure or an acute myocardial infarction.
The primary outcome was first hospitalisation due to cardiovascular event or death from any cause. Secondary outcomes included death from any cause, first cardiovascular hospitalisation and cardiovascular death.

During the course of the trial, overall mortality figures were lower than expected so the protocol was amended. Patients 75 years or older were eligible whether or not they had any previously specified risk factors, but patients 70 years or older were eligible only if they had 1 or more other risk factors. Patients younger than 70 years were no longer eligible.

Results

A total of 4628 patients were enrolled, of whom 2301 were randomly assigned to receive dronedarone and 2327 to receive placebo. The two groups were well matched with respect to baseline characteristics. Overall, the mean age was 71.6 years, and 46.9% of participants were female. Twenty-five percent of patients had AF at randomisation. The predominant underlying cardiovascular disease was hypertension (86%), and there was evidence of structural heart disease in the majority of patients (59.6%). The LVEF was quantified in 4544 patients, of whom 179 (3.9%) and 540 (11.9%) had an ejection fraction of less than 35% and less than 45%, respectively. There was a history of NYHA heart failure in 979 patients (21.2%): class II failure in 779 (17.1%) and class III in 200 (4.4%).

Primary endpoint (composite of hospitalisation for CV event or death)

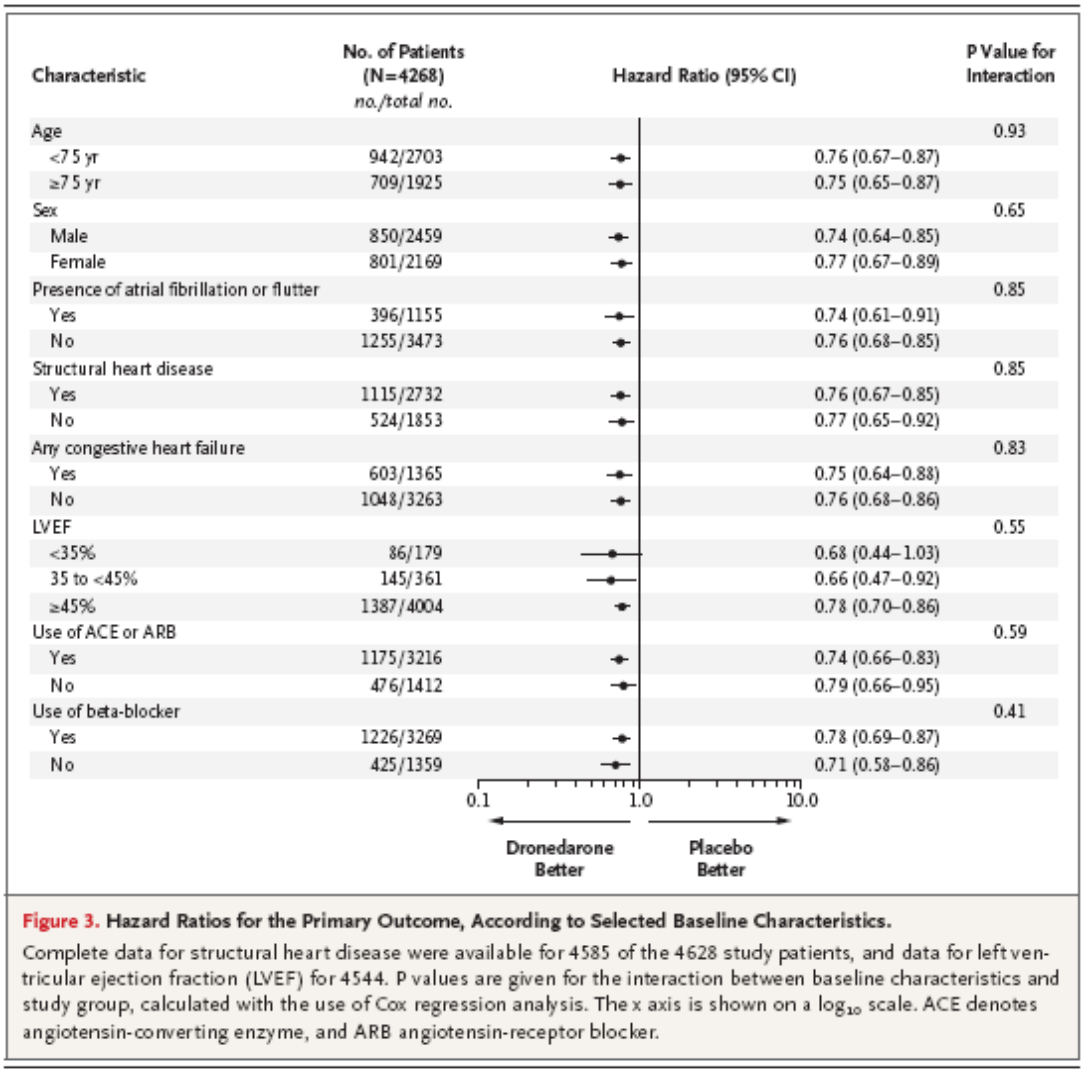
The primary outcome was the first hospitalisation due to cardiovascular events or death, whichever occurred first. Among patients assigned to receive dronedarone, 734 (31.9%) had a primary outcome event, including 675 (29.3%) with a hospitalisation due to cardiovascular events and 59 (2.6%) who died. In the placebo group, 917 patients (39.4%) had a primary outcome event. These included 859 (36.9%) with a first hospitalisation due to cardiovascular events and 58 (2.5%) who died before hospitalisation. The hazard ratio for the primary outcome in the dronedarone group was 0.76 (95% confidence interval [CI], 0.69 to 0.84; P<0.001) (Table 6.5 and Figure 6.2a).

Table 6.5: Study outcomes ATHENA

Outcome	Dronedarone (N=2301)	Placebo (N=2327)	Hazard Ratio for Dronedarone (95% CI)	P Value
	number (percent)			
Primary outcome	734 (31.9)	917 (39.4)	0.76 (0.69–0.84)	<0.001
First hospitalization due to cardiovascular events	675 (29.3)	859 (36.9)	0.74 (0.67–0.82)	<0.001
First hospitalization				
For atrial fibrillation	335 (14.6)	510 (21.9)	0.63 (0.55–0.72)	<0.001
For congestive heart failure	112 (4.9)	132 (5.7)	0.86 (0.67–1.10)	0.22
For acute coronary syndrome	62 (2.7)	89 (3.8)	0.70 (0.51–0.97)	0.03
For syncope	27 (1.2)	32 (1.4)	0.85 (0.51–1.42)	0.54
For ventricular arrhythmia or nonfatal cardiac arrest	13 (0.6)	12 (0.5)	1.09 (0.50–2.39)	0.83
Death from any cause	116 (5.0)	139 (6.0)	0.84 (0.66–1.08)	0.18
From noncardiovascular causes	53 (2.3)	49 (2.1)	1.10 (0.74–1.62)	0.65
From cardiovascular causes	63 (2.7)	90 (3.9)	0.71 (0.51–0.98)	0.03
From nonarrhythmic cardiac causes	17 (0.7)	18 (0.8)	0.95 (0.49–1.85)	0.89
From cardiac arrhythmia	26 (1.1)	48 (2.1)	0.55 (0.34–0.88)	0.01
From noncardiac vascular causes (including stroke)	20 (0.9)	24 (1.0)	0.84 (0.47–1.52)	0.57
Any hospitalization due to any cardiovascular event or death from any cause	1253 (54.5)	1668 (71.7)	0.76 (0.68–0.84)	<0.001

The effect of dronedarone on the primary outcome was consistent across a variety of important sub-groups (not pre-specified). Figure 6.1 shows the hazard ratios according to selected baseline characteristics.

Figure 6.1: Hazard Ratio for the Primary Outcome, according to baseline characteristics



Characteristic	No. of Patients (N=4268) *no./total no.*	Hazard Ratio (95% CI)	P Value for Interaction
Age			0.93
<75 yr	942/2703	0.76 (0.67–0.87)	
≥75 yr	709/1925	0.75 (0.65–0.87)	
Sex			0.65
Male	850/2459	0.74 (0.64–0.85)	
Female	801/2169	0.77 (0.67–0.89)	
Presence of atrial fibrillation or flutter			0.85
Yes	396/1155	0.74 (0.61–0.91)	
No	1255/3473	0.76 (0.68–0.85)	
Structural heart disease			0.85
Yes	1115/2732	0.76 (0.67–0.85)	
No	524/1853	0.77 (0.65–0.92)	
Any congestive heart failure			0.83
Yes	603/1365	0.75 (0.64–0.88)	
No	1048/3263	0.76 (0.68–0.86)	
LVEF			0.55
<35%	86/179	0.68 (0.44–1.03)	
35 to <45%	145/361	0.66 (0.47–0.92)	
≥45%	1387/4004	0.78 (0.70–0.86)	
Use of ACE or ARB			0.59
Yes	1175/3216	0.74 (0.66–0.83)	
No	476/1412	0.79 (0.66–0.95)	
Use of beta-blocker			0.41
Yes	1226/3269	0.78 (0.69–0.87)	
No	425/1359	0.71 (0.58–0.86)	

Figure 3. Hazard Ratios for the Primary Outcome, According to Selected Baseline Characteristics.
Complete data for structural heart disease were available for 4585 of the 4628 study patients, and data for left ventricular ejection fraction (LVEF) for 4544. P values are given for the interaction between baseline characteristics and study group, calculated with the use of Cox regression analysis. The x axis is shown on a $\log_{10}$ scale. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

Death from any cause and cardiovascular events

Over the course of the study there were 116 deaths (in 5.0% of patients) in the dronedarone group and 139 (in 6.0%) in the placebo group (hazard ratio, 0.84; 95% CI, 0.66 to 1.08; P = 0.18) (Table 6.5 and Figure 6.2b). Death was classified, on the basis of blinded adjudication, as being cardiovascular in origin in 63 patients (2.7%) in the dronedarone group and 90 (3.9%) in the placebo group (hazard ratio, 0.71; 95% CI, 0.51 to 0.98; P = 0.03) (Table 6.5 and Figure 6.2c). There were 26 deaths from cardiac arrhythmia (in 1.1% of patients) in the dronedarone group and 48 (in 2.1%) in the placebo group (hazard ratio, 0.55; 95% CI, 0.34 to 0.88; P = 0.01) (Table 6.5).

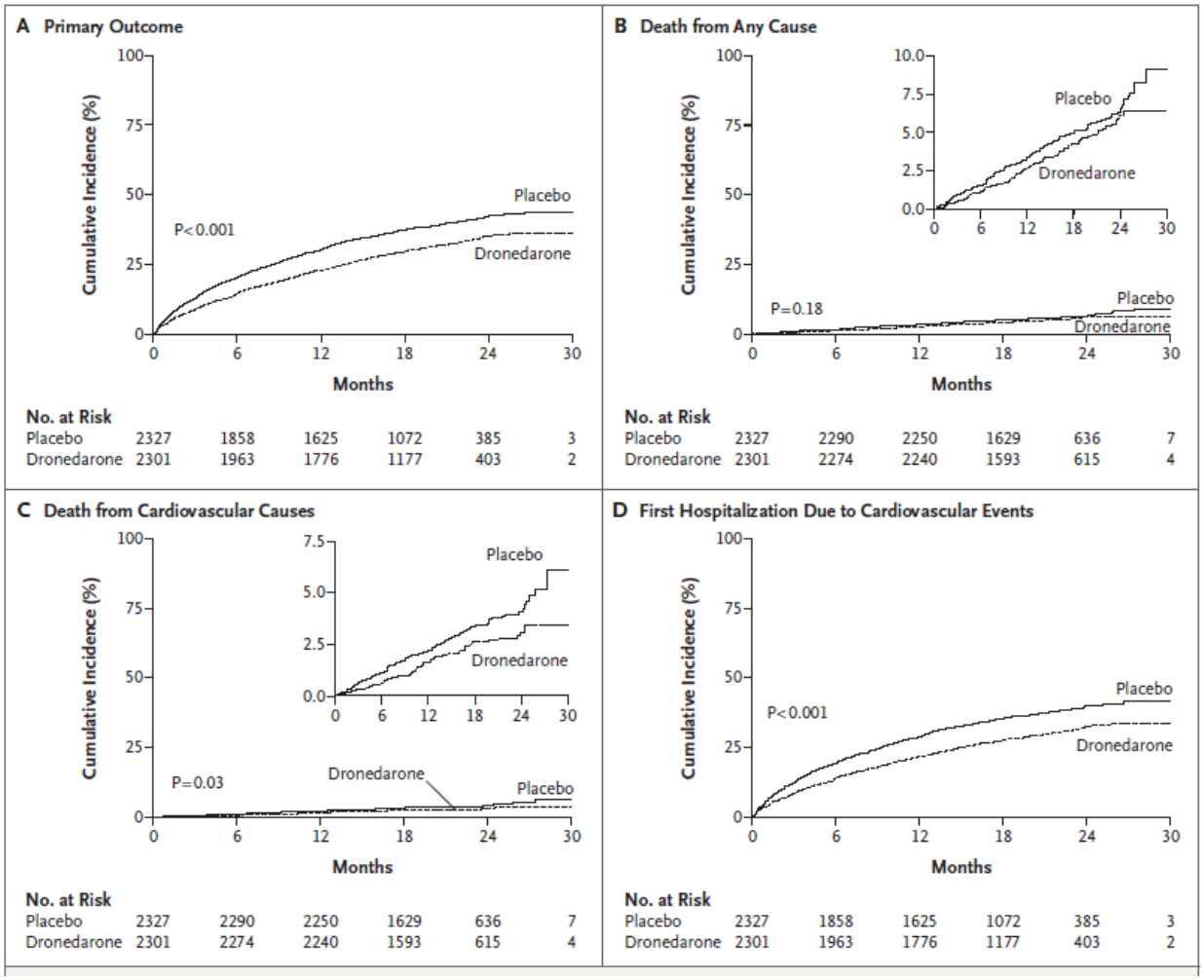
Hospitalisation due to cardiovascular events

In the dronedarone group, 675 patients (29.3%) had a first hospitalisation due to cardiovascular events, as compared with 859 patients (36.9%) in the placebo group (hazard ratio, 0.74; 95% CI, 0.67 to 0.82; P<0.001) (Table 6.5 and Figure 6.2d). This reduction in the rate of hospitalisation due to cardiovascular events was driven mainly by a reduction in the number of hospitalisations for AF.

Study Discontinuation and AEs

The study drug was prematurely discontinued in 696 (30.2%) of patients receiving dronedarone, as compared with 716 (30.8%) of those receiving placebo. The main reasons were AEs (in 12.7% of patients in the dronedarone group vs. 8.1% in the placebo group), subject's request (7.5% in each group), and other reasons (9.4% in the dronedarone group vs. 14.4% in the placebo group). The imbalance in the "other reasons" category was mainly due to the more-frequent investigator initiation of study-disallowed antiarrhythmic medication or recurrent AF in the placebo group. Analysis of important treatment-emergent AEs and laboratory abnormalities (see Table 6.6) shows that bradycardia, QT-interval prolongation, diarrhoea, nausea, rash, and an increase in the serum creatinine level were significantly more common in the dronedarone group than in the placebo group. Pulmonary symptoms, interstitial lung disease, and abnormalities of thyroid function were not significantly more common with dronedarone than with placebo.

Figure 6.2: Kaplan–Meier Cumulative Incidences of the Primary and Secondary Outcomes in ATHENA



Cumulative incidences are shown for the primary study outcome (composite of first hospitalisation due to cardiovascular events or
death from any cause) (Panel A) and for secondary study outcomes: death from any cause (Panel B), death from cardiovascular causes (Panel C), and first hospitalisation due to cardiovascular events (Panel D). The number of patients is the number for whom the variable was assessed. The hazard ratios for the dronedarone group as compared with the placebo group were 0.76 (95% confidence interval [CI], 0.69 to 0.84; P<0.001) for the primary outcome, 0.84 (95% CI, 0.66 to 1.08; P = 0.18) for death from any cause, 0.71 (95% CI, 0.51 to 0.98; P = 0.03) for death from cardiovascular causes, and 0.74 (95% CI, 0.67 to 0.82; P<0.001) for first hospitalisation due to cardiovascular events.

Table 6.3: Selected AEs and Laboratory Abnormalities in Patients Who Received the Study Drug

Event*	Dronedarone (N=2291)	Placebo (N=2313)	P Value†
	number (percent)		
Any TEAE	1649 (72.0)	1603 (69.3)	0.048
Cardiac events			
Any	260 (11.3)	221 (9.6)	0.048
Bradycardia	81 (3.5)	28 (1.2)	<0.001
QT-interval prolongation	40 (1.7)	14 (0.6)	<0.001
Respiratory events	332 (14.5)	337 (14.6)	0.97
Cough	83 (3.6)	83 (3.6)	1.00
Dyspnea	120 (5.2)	97 (4.2)	0.10
Interstitial lung disease‡	5 (0.2)	5 (0.2)	1.00
Gastrointestinal events	600 (26.2)	508 (22.0)	<0.001
Diarrhea	223 (9.7)	144 (6.2)	<0.001
Nausea	122 (5.3)	72 (3.1)	<0.001
Abnormal liver-function test§	12 (0.5)	14 (0.6)	0.84
Endocrine events	25 (1.1)	25 (1.1)	1.00
Hypothyroidism	11 (0.5)	6 (0.3)	0.23
Hyperthyroidism	6 (0.3)	7 (0.3)	1.00
Neurologic events	373 (16.3)	381 (16.5)	0.87
Dizziness	169 (7.4)	152 (6.6)	0.30
Headache	70 (3.1)	87 (3.8)	0.19
Skin-related events	237 (10.3)	176 (7.6)	0.001
Rash	77 (3.4)	47 (2.0)	0.006
Urticaria	11 (0.5)	9 (0.4)	0.66
Serum creatinine increase	108 (4.7)	31 (1.3)	<0.001
Any serious TEAE	456 (19.9)	489 (21.1)	0.31
Cardiac events	15 (0.7)	15 (0.6)	1.00
Respiratory events	41 (1.8)	45 (1.9)	0.74
Gastrointestinal events	81 (3.5)	68 (2.9)	0.28
Endocrine events	4 (0.2)	5 (0.2)	1.00
Neurologic events	21 (0.9)	27 (1.2)	0.47
Skin-related events	7 (0.3)	6 (0.3)	0.79
Increase in serum creatinine	5 (0.2)	1 (<0.1)	0.12
Premature discontinuation of study drug because of an adverse event	290 (12.7)	187 (8.1)	<0.001

* A treatment-emergent adverse event (TEAE) was defined as an adverse event occurring between first dose of the study drug and 10 days after the last dose. A serious TEAE was one that resulted in death; was life-threatening; required or prolonged hospitalization; was a medically important event; resulted in persistent, clinically significant disability or incapacity; or was a congenital anomaly or birth defect. Any adverse event was an adverse event occurring before 10 days after the last dose of the study drug.

† P values were calculated with the use of Fisher's exact test.

‡ Interstitial lung disease includes the following preferred terms according to the *Medical Dictionary for Regulatory Activities*: interstitial lung disease, pneumonitis, pulmonary fibrosis, lung infiltration, and pulmonary toxicity.

§ Results of liver-function tests were coded with the use of hepatobiliary-investigation high-level group terms in the adverse-event database. No scheduled liver-function tests were performed in this study.

Post Hoc Analyses

Two post hoc analyses of note have been conducted on the ATHENA trial. One considered the outcome of stroke and found that dronedarone was associated with a 34% reduction (p = 0.027) in adjusted risk of stroke compared with placebo over a follow-up averaging 21 months. This reduction was in patients who were generally receiving appropriate antithrombotic therapy (approximately 60% of patients were receiving oral anticoagulation – 15% of which were on OAC and anti-platelet, and over 30% were receiving anti-platelet agents alone). In addition, the results were consistent in higher-risk patients with different risk factors.[43]

A further post hoc analysis of subgroups of patients in the ATHENA trial categorised by risk of stroke was undertaken. $CHADS_2$ score (C=CHF=1 point, H=hypertension=1 point, A=age=1 point, D=diabetes=1 point, S_2=prior stroke or TIA= 2 points) is a clinical prediction rule for estimating the risk of stroke in patients with AF.[3] It is used to determine the degree of anticoagulation therapy required. The stroke risk algorithm developed for a UK population and used in the 2006 NICE guidelines incorporates similar risk factors but addresses the cumulative nature of risk from multiple risk factors. A high $CHADS_2$ score corresponds to a greater risk of stroke, and vice-versa. According to the findings of the $CHADS_2$ validation study[44], the risk of stroke as a percentage per year is: Score 0=1.9%; 1=2.8%; 2=4.0%; 3=5.9%; 4=8.5%; 5=12.5%; and 6=18.2%.

[redacted] It should be noted that this post-hoc analysis must be treated with caution as the study was not set up to directly collect, examine or answer any questions relating to $CHADS_2$ subgroups. However, this analysis was undertaken because of its clinical relevance to this patient group: that is, due to the well documented increased risk of stroke in AF patients[45] and also the increased risk of death associated with higher $CHADS_2$ scores. [21]

Further subgroup analyses are being considered from the ATHENA trial including CHD and AF hospitalisation which are planned to be presented at the European Society of Cardiology later in 2009.

Conclusion

The ATHENA trial demonstrated that long-term treatment of patients with AF/AFL with dronedarone on top of baseline therapy was associated with a highly significant 24% reduction in the combined risk of all-cause mortality or cardiovascular hospitalisation. The reduction in risk was related to a significant reduction in the risk of cardiovascular death and a significant reduction in the risk of cardiovascular hospitalisation. Results from post hoc analyses suggest a significant reduction in the risk of stroke. Furthermore, subgroup analysis by stroke risk category indicated that the odds of all-cause mortality were statistically significantly lower in patients with a $CHADS_2$ score ≥4: that is, with a higher risk of stroke and death. The findings of the ATHENA trial (which focused on patients with AF/AFL and excluded patients with decompensated heart failure) indicated with a high degree of confidence that dronedarone did not increase the risk of death. They also indicated that dronedarone, on top of baseline therapy mainly based on rate control and antithrombotic management provides a significant added benefit that appears early and continues to develop over time.

DIONYSOS Clinical Trial

Study design and methods

This study was initiated during the conduct of the ATHENA study to meet a request from the EMEA for a study with an active comparator. The analysis of the DIONYSOS trial has recently been completed.[6]

The DIONYSOS trial was a multicentre, randomised, double-blind, parallel-arm study to compare the efficacy and safety of dronedarone (400 mg BID) versus amiodarone (600 mg daily for 28 days, then 200 mg daily thereafter) for at least 6 months for the maintenance of sinus rhythm in patients with an episode of persistent AF eligible for electrical cardioversion. The trial was carried out in 112 centres in 23 countries. Patient enrolment began in June 2007 and the last patient completed in October 2008.

Patients included those aged 21 years or more with documented AF for more than 72 hours for whom cardioversion and antiarrhythmic treatment were indicated in the opinion of the Investigators, and receiving anticoagulant. The primary efficacy endpoint was defined as recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy. The main safety endpoint (MSE) was the

occurrence of thyroid, hepatic, pulmonary, neurological, skin, eye, or gastrointestinal specific events or premature study drug discontinuation following any AE.

Results

Patient disposition

A total of 618 patients were screened for the study and 504 were randomised to treatment: 249 patients in the dronedarone group and 255 in the amiodarone group. [redacted] In both groups the median duration of treatment was 7 months.

Baseline characteristics

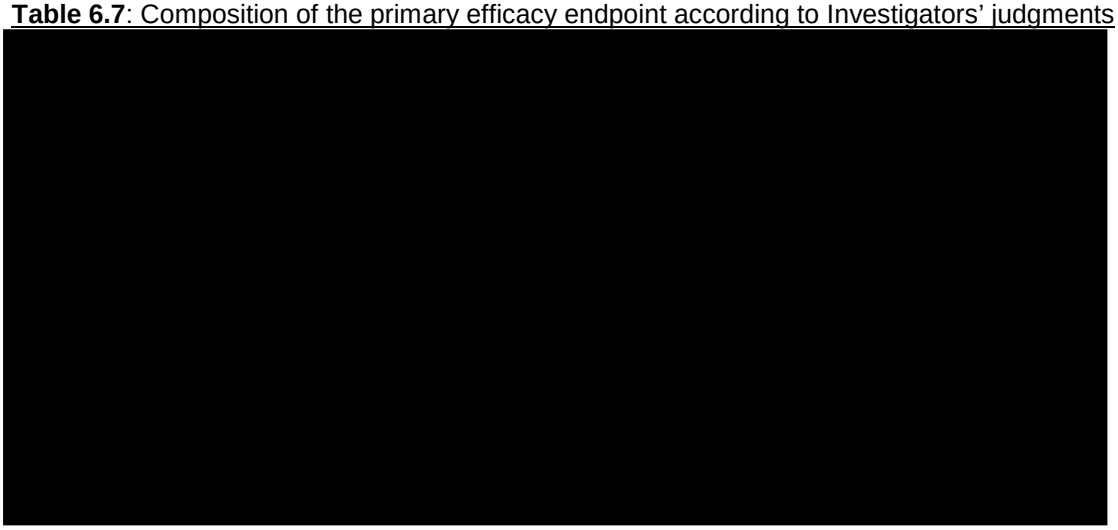
The 2 treatment groups were well balanced for demographic characteristics. The mean age of the patients was 64.0 ± 10.7 years (mean± SD). The overall proportion of patients aged≥75 years was about 20%. One third of patients were females in both treatment groups. The majority of patients (62.9%) had a history of persistent AF. For 21.6% of patients, it was the first episode of AF. The mean duration of the AF episode motivating inclusion in the study was 77.4 days.

Primary efficacy endpoint

The incidence of the primary efficacy endpoint, defined as recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy, was 73.9% and 55.3% in the dronedarone and the amiodarone groups respectively at Month 12 (hazard ratio=1.59, log-rank p-value<0.0001).

The analysis of the components of the primary efficacy endpoint showed that there were fewer AF recurrences (including absence of conversion) in the amiodarone group than in the dronedarone group, whereas there were less premature study drug discontinuations due to intolerance in the dronedarone group (Table 6.7).

Table 6.7: Composition of the primary efficacy endpoint according to Investigators' judgments



The disparity between the results for premature study discontinuation in Table 6.7 (n=26 for dronedarone and n=34 for amiodarone) and in data related to Patient Disposition [redacted] relates to differences in how the data are reported within each analysis. The data in the Patient Disposition description relate to the total number of patients who prematurely discontinued the study drug due to lack of efficacy or due to an AE. Within this total there will be patients who had AF recurrence. To avoid double counting Table 6.7 reports for each patient only the first component of "treatment failure". Therefore, if a patient discontinued the study drug prematurely because of AF recurrence they will not be included again within the "Premature study drug discontinuation" numbers in Table 6.7.

Main safety endpoint

The main safety endpoint was defined as the time to first occurrence of thyroid, hepatic, pulmonary, neurological, skin, eye or GI specific events or premature study drug discontinuation following any AE. The following analyses were pre-specified:

- Time to first component of the MSE
- Time to first component of the MSE excluding gastrointestinal events
- Time to first event for each component of the MSE taken independently.

The incidence for the first pre-specified endpoint was 39.3% and 44.5% in the dronedarone and the amiodarone groups, respectively, after 12 months of treatment (HR=0.80, 95% CI=0.60; 1.07, log-rank p-value=0.13).

The analysis of GI AEs confirmed that these were driven by diarrhoea (dronedarone 400 mg BID: [redacted] none of which was serious. [redacted]

The reduction in the incidence of the main safety endpoint was driven by a reduction of thyroid, neurological, skin, and ocular effects. When analysed individually as predefined, the following was shown:

- For thyroid disorders, an [redacted] was observed in the dronedarone group compared to amiodarone. The majority of cases were hypothyroidisms: [redacted]
- For neurological events, an 87.6% relative reduction ($p<0.0001$) in sleep disorders and tremor was observed in the dronedarone group (n=3 [1.2%]) compared to amiodarone (n=17 [6.7%]).
- [redacted]

No pulmonary events, such as interstitial lung disease, hypersensitivity pneumonitis, or interstitial/alveolar pneumonitis, were reported during this short-term study.

[redacted] The number of deaths during the on-treatment period was 2 (0.8%) in the dronedarone group [redacted] and 5 (2.0%) in the amiodarone group [redacted]

[redacted]

No torsades de pointes were observed during the study. [redacted]

[redacted]

Conclusion

This study, performed in patients with persistent fibrillation and an indication for electrical cardioversion, and with a median duration of treatment of 7 months, showed higher activity of amiodarone than dronedarone in controlling cardiac rhythm. [redacted]. Amiodarone was associated with higher incidences of adverse drug reactions mainly related to thyroid dysfunction, significant bradycardia and effects on the central nervous system. [redacted]

6.3.1 Methods

See Section 6.3 for full description of study design, methods and results.

6.3.2 Participants

6.3.3 Patient numbers

6.3.4 Outcomes

6.3.5 Statistical analysis and definition of study groups

6.3.6 Critical appraisal of relevant RCTs

All of the four relevant studies ADONIS, EURIDIS, ATHENA and DIONYSOS were international, multi-centre, double blind trials and treatment was assigned by central randomisation using interactive voice response system (IVRS). Blinding procedures for patients and members of the steering committed were described in detail. Each study provided a sample size calculation and justified the number of patients enrolled. Primary and secondary outcomes were clearly defined. The flow of participants through each stage was provided for each study and they reported the numbers of patients randomly assigned, receiving intended treatment, completing the study protocol and analysed for the primary outcome. Reasons for discontinuing study drug were documented. An intention to treat analysis was undertaken in all studies and study groups' baseline characteristics were similar, in general. In the DIONYSOS study in order to document safety, follow-up was prolonged up to 12 months.

If the RCT was not conducted in the UK, is clinical practice likely to differ from UK practice?

How do the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.

The relevant RCTs for dronedarone were global in design although they did include some UK centres. There is no evidence to suggest that clinical practice within these studies differs significantly from UK practice. In EURIDIS, ADONIS and ATHENA all patients received baseline therapy similar to the baseline therapy recommended by UK guidelines.[1] In a pooled meta-analysis of 5 of the dronedarone RCTs (EURIDIS, ADONIS, DAFNE, ATHENA and ERATO) it was noted that the placebo arms of the trials actually included 66% and 62% of patients receiving beta-blockers and anti-coagulation (64% and 63% respectively for the pooled dronedarone arms).[40] UK guidelines recommend that beta-blockers are considered to be an appropriate baseline therapy for most AF patients, while within the associated UK guideline costing report it has been noted that up to 75% of patients should be receiving anti-coagulation.

6.4 Results of the relevant comparative RCTs

All relevant comparative RCTs have been included in the meta-analysis and MTC. See Section 6.5.

6.5 Meta-analysis and mixed treatment comparison

Background and aims

As part of the earlier literature search for dronedarone studies (Section 6.1), a Cochrane systematic review and meta-analysis of AADs was identified (Lafuente-Lafuente et al 2007)[11]. The aim of the Cochrane review was to determine, in patients who recovered sinus rhythm after AF, the effect of long-term treatment with AADs on death, stroke and embolism, adverse effects, pro-arrhythmia and recurrence of AF. It assessed a number of drugs which are considered comparators to dronedarone and included specific data on dronedarone from DAFNE, EURIDIS and ADONIS.

More recently, in 2009 sanofi-aventis commissioned further analyses aimed at updating and extending the Cochrane review. The aim of the analyses was to compare the efficacy and safety of dronedarone with four other AADs commonly used in the UK (flecainide, propafenone – combined into Class 1c agents, sotalol and amiodarone).

A systematic review indicated that there were few studies that compare different AADs directly against each other. Therefore, the commissioned work took the form of three types of analysis to help answer questions regarding the relative efficacy and safety of dronedarone and other commonly used AADs. Specifically, the analyses comprised three kinds of data synthesis:

- A direct meta-analysis using pooled study data to compare each of the drugs head-to-head when relevant data were available;
- An indirect meta-analysis which allows comparisons between the different drugs using pooled data from placebo/controls used in the studies;
- A mixed treatment comparison (MTC) which combines direct and indirect information from clinical trials in order to compare outcomes between drugs.

Methods

The literature search was conducted in March 2009 thereby incorporating dronedarone trial data from the ATHENA and DIONYSOS studies. Details on search criteria, data extraction and analysis are available in Section 10 (Appendix 4).

The main aim of the meta-analysis and MTC was to compare dronedarone with current relevant AAD therapies for the UK (amiodarone, sotalol, and Class 1c agents) as well as with controls. It should be noted that the control arm in some trials may include baseline therapy (e.g. anticoagulants and beta blockers) so the "control" does not always represent an untreated state. Furthermore the treated arm in these trials may be 'drug plus baseline therapy' as opposed to the drug alone. In addition, events for flecainide and propafenone were combined and labelled Class 1c. The aim was to strengthen the analysis because of small numbers of outcome events within such studies, and also because the UK guidelines refer to Class 1c agents as a whole when making recommendations regarding treatment.[1]

Outcomes reported were AF recurrence, all-cause mortality, treatment discontinuations, and stroke. Serious adverse events (SAEs) were also considered and results are presented in Section 6.7. Further details on studies included and results for each outcome are provided in Appendices 5 (AF recurrence), 6 (all-cause mortality), 7 (treatment discontinuation), 8 (stroke) and 9 (SAEs).

A summary of the results of the meta-analysis and MTC are presented here. Because the only active head to head trial data available for dronedarone is from the DIONYSOS study where the comparator is amiodarone, comparisons between dronedarone and other active agents are reliant on indirect evidence.

It should be noted that due to the different inclusion criteria used by the meta-analysis and the MTC analysis, each type of analysis comprised a different set of studies for each outcome analysed. For example, in the meta-analysis where inclusion criteria were very broad, data from 43 studies were available for the all-cause mortality. Whereas, in the MTC analysis in order to achieve convergence, trials were restricted to those comparing target pharmaceutical therapy either with an untreated control condition or an alternative target pharmaceutical, with at least 100 subjects per randomised group and at least 1 event in either group. This resulted in only 7 trials meeting the inclusion criteria. Full reports on the methods for the meta-analysis and the MTC are available on request as is the raw data for the MTC.

Results

The previous Cochrane review identified 45 studies which fulfilled inclusion criteria and had useable data compared with 84 studies for dronedarone and the four commonly used AADs identified by the commissioned review. The difference in numbers is explained by differences in the inclusion criteria applied in the two reviews (Table 6.8).

Table 6.8: Inclusion criteria applied in commissioned review vs. previous Cochrane review

	Commissioned review	**Cochrane Review**
Types of studies	• RCTs and controlled trials • Cross-over or parallel design • Follow-up ≥3 months	• RCTs • Follow-up ≥6 months
Participants	• Adults with any type of AF • Cardiac surgery >3 months	• Adults with any type of AF • Restoration of NSR • Prior cardiac surgery excluded
Intervention	• Intervention: dronedarone, amiodarone, sotalol, propafenone, flecainide • Control: placebo, rate control, other AAD	• Intervention: Any AAD • Control: placebo, rate control, AAD
Outcomes	• Mortality • Stroke • AF recurrence • Treatment withdrawals • SAEs	• Mortality • AF recurrence • Treatment withdrawals due to AE • proarrhythmia

AF recurrence

In the meta-analysis this is defined as the reported number of patients failing to maintain sinus rhythm at any point within the study timeframe, or the reported number of patients with a recurrence of AF within the timeframe of the study. A total of 42 studies were included. In the MTC studies were restricted to trials comparing target pharmaceutical therapy either with an untreated control condition or an alternative target pharmaceutical (n=25). Dronedarone studies included were DAFNE, ADONIS, EURIDIS and DIONYSOS.

The meta-analysis of all data on AF recurrence indicates that for all of the AADs analysed, the odds of an AF recurrence is significantly lower with active treatment compared with control (Table 6.9).

Using direct head-to-head data from DIONYSOS, the odds of AF recurrence are significantly lower for amiodarone versus dronedarone [Direct Peto OR amiodarone versus dronedarone= 0.42 (0.30, 0.60)].

Table 6.9: Meta-analysis summary of comparison between treatments: Odds ratio (OR) for AF recurrence

[redacted]

In the absence of direct comparisons, the interpretation of the other results comparing dronedarone to sotalol and Class 1c agents is subject to caution. For example, differences in protocol, and therefore baseline patient populations (e.g. those with paroxysmal vs. persistent AF, or those who were successfully cardioverted vs. those who were not), may mean that it is difficult to ascertain whether delayed AF recurrence is a real treatment effect or is in fact due to a different patient population. In addition, measurement of the end-point can vary considerably from study to study. In older studies, AF recurrences are only captured by ECG made at scheduled visits or when patients come to hospital with symptoms. In more recent studies such as EURIDIS and ADONIS, portable monitors are given to patients to record ECG when they experience symptoms, but also during totally silent periods so that asymptomatic episodes are also captured. In this regard, the definition of treatment failure can be dramatically different.

All-cause mortality

In the meta-analysis all-cause mortality is defined as the reported number of deaths from any cause within the timeframe of the study. A total of 43 studies were included.

Dronedarone studies included were DAFNE, ADONIS, EURIDIS, ERATO, ATHENA and DIONYSOS. In the MTC analysis trials were restricted to those comparing target pharmaceutical therapy either with an untreated control condition or an alternative target pharmaceutical, with at least 100 subjects per randomised group and at least 1 event in either group (n=7). No studies of either Class 1c agents, flecainide or propafenone, met these inclusion criteria.

The meta-analysis indicates that all cause mortality events are rare within the timeframe of the clinical trials and the estimates of the treatment effect are subject to a high degree of uncertainty. Therefore the results of the meta-analysis on all cause mortality do not show conclusively a trend towards increased mortality on active treatment.

The odds of death were lower for dronedarone compared to control, though the difference was not significant (Table 6.10). While the MTC included a much smaller number of studies the results were similar.

Table 6.10: Summary of comparison between treatments: Odds ratio for all-cause mortality

	Peto OR (95% CI)	**Peto OR (95% CI)**
Non-active control	**Direct analysis**	**Indirect analysis**
Class 1c v control**	0.68 (0.20, 2.31)	NA
Dronedarone v control	0.85 (0.66, 1.09)	NA
Amiodarone v control	2.02 (0.70, 5.80)	NA
Sotalol v control	2.72 (1.16, 6.38)	NA
Head to head		
Amiodarone v dronedarone	2.32 (0.52, 10.32)	2.38 (0.80, 7.07)
Class 1c v dronedarone**	NA	0.8 (0.23, 2.49)
Sotalol v dronedarone	NA	3.20 (1.32, 7.78)
Mixed treatment comparison*		
	OR (95% CI)	**P value**
Amiodarone v dronedarone	3.19 (1.16, 8.76)	0.032
Sotalol v dronedarone	5.05 (1.84, 13.87)	0.009
Control v dronedarone	1.17 (0.91, 1.50)	0.165

Odds ratio greater than 1 indicates a higher risk of mortality for the comparator
**Class 1c includes flecainide and propafenone combined. Individual results are available on request

[redacted]

Treatment discontinuation

To facilitate the health economics model an outcome of treatment discontinuation was defined as the reported number of treatment discontinuations of any cause within the timeframe of the study.

Meta-analysis results indicate a trend towards an increase in discontinuations for active treatment compared with control (Table 6.11). For dronedarone the odds of treatment discontinuation are similar to control (OR ~1; and 95% confidence interval is small) (Table 6.11).

Table 6.11: Meta-analysis summary of comparison between treatments: Odds ratio for treatment discontinuations

The direct and indirect estimates for amiodarone versus dronedarone are not consistent. The direct estimate, based on DIONYSOS, indicates the odds of treatment discontinuation are significantly lower for amiodarone compared with dronedarone. The indirect estimate indicates the odds of treatment discontinuation are higher for amiodarone compared with dronedarone. An explanation for this is the variation in the definition of treatment discontinuation that is often not fully explained when reported in RCTs. Within DIONYSOS more patients in the dronedarone group discontinued treatment due to lack of efficacy while more patients in the amiodarone group discontinued due to adverse . Within the indirect comparison some studies reported any-cause treatment discontinuation while others reported it specifically due to AEs.

An additional analysis considering only discontinuation due to AEs found a consistent and more expected result; dronedarone was associated with less discontinuation due to AEs than amiodarone (see Table 6.12).

Table 6.12: Meta-analysis summary of comparison between treatments: Odds ratio for treatment discontinuations due to AEs

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]

[redacted]

The MTC analysis reports that there is no statistically significant difference in any-cause treatment discontinuation or discontinuation due specifically to AEs between dronedarone and other AADs. However, it is worth noting that while the odds ratio for discontinuation due to AEs for amiodarone versus dronedarone was not statistically significantly different [redacted] it could be considered clinically relevant given the concern associated with current AAD adverse events. In addition, due to the known cumulative effect of amiodarone the difference might have become significant if the DIONYSOS study had been continued for a longer period. For example, pulmonary adverse events most frequently emerge during the first 1-2 years of therapy and dermatological adverse events have a peak frequency between 6 months and 2 years.

Please note it was not possible to analyse discontinuation due to reasons other than AEs (e.g. lack of efficacy due to recurrence or persistent symptoms, etc) due to inconsistency in the definitions and reporting of identified studies.

Stroke

Limited evidence was available on stroke (n = 4; dronedarone v control x 2, dronedarone v amiodarone x 1, and sotalol v control). All four studies had some data on stroke events but none actually included stroke as a study outcome. Therefore, stroke events were not included in the meta-analysis as results were mainly limited to

dronedarone. However, in order to help populate the health economics model a MTC analysis on stroke data was performed to allow us to consider the relative differences between products.

In the MTC analysis trials were restricted to those comparing target pharmaceutical therapy either with an untreated control condition or an alternative target pharmaceutical, in which there were at least 50 patients randomised in each group and at least one event. No studies of Class 1c agents met these inclusion criteria. In total 4 trials were included, in which 7034 subjects were randomised and 138 subjects experienced stroke. Trials included 261 patients randomised to sotalol, 3378 patients randomised to dronedarone, 522 patients randomised to amiodarone, and 2873 patients randomised to placebo.

Table 6.13: MTC odds ratio for stroke

Mixed treatment comparison*		
	OR (95% CI)	**P value**
Control v dronedarone	1.44 (1.19, 1.76)	0.015
Amiodarone v dronedarone	1.29 (0.69, 2.41)	0.221
Sotalol v dronedarone	1.15 (0.56, 2.39)	0.495

*Odds ratio higher than 1 describes a higher rate of SAE for the comparator treatment

As shown in Table 6.13 dronedarone was associated with a statistically significant reduction in stroke compared with control. Neither amiodarone, nor sotalol achieved statistically significant reductions compared to control.

Conclusion

All of the active treatments reviewed are effective in maintaining sinus rhythm compared to controls. Direct evidence from one trial (DIONYSOS) indicates that amiodarone is superior to dronedarone in preventing AF recurrences, while indirect evidence suggests that other active comparators are also superior to dronedarone but such results need to be interpreted with caution: differing levels of disease severity among patients in different studies, different protocols etc.

The data indicate that all cause mortality events are rare within the timeframe of the clinical trials and the estimates of the treatment effect are subject to a degree of uncertainty. While the results of the meta-analysis on all cause mortality were not conclusive they showed a trend towards increased mortality on active treatments with the exception of dronedarone and Class 1c agents. There was insufficient evidence to draw a robust conclusion for Class 1c agents as previously found in the Cochrane

review. The mortality results from the direct and indirect meta-analysis show a trend for dronedarone to decrease the risk of all-cause mortality. Within the MTC analysis the odds ratio for a reduction in all-cause mortality for dronedarone compared to amiodarone and sotalol reached statistical significance [redacted] respectively). There was insufficient robust evidence on the Class 1c agents to allow a MTC analysis to be conducted.

The analysis points to a trend towards an increase in discontinuation for active treatment compared with control. When compared directly to amiodarone, treatment with dronedarone is significantly more likely to lead to treatment discontinuation however this is driven by a lack of efficacy rather than due to AEs. When specifically considering AEs, amiodarone is consistently more likely to lead to treatment discontinuation.

6.6 Mixed treatment comparisons (MTC)

MTC results are included in Section 6.5.

6.7 Safety

Safety analyses

There are two analyses of safety data reported in this section. The first is a safety profile of dronedarone 400 mg BID in patients with AF or AFL that was conducted on 5 pooled phase II and III placebo-controlled published studies, ATHENA, EURIDIS, ADONIS, ERATO and DAFNE. (Please see FDA briefing document, March 2009).[14] In this section this will be referred to as the pooled analysis. Please note this does not include DIONYSOS as it is not currently published nor is it a placebo control trial.

The second analysis presented is a summary of results of the meta-analysis and MTC analysis of SAEs taken from studies of dronedarone and appropriate AAD comparators (sotalol, Class 1c and amiodarone). A summary of the methods of these analyses has been reported in Section 10 (Appendix 9).

Pooled analysis

In the studies included in the pooled analysis (ATHENA, EURIDIS, ADONIS, ERATO and DAFNE), a total of 6285 patients were randomised and treated. Of these, 3282 patients were treated with dronedarone 400 mg twice daily, and 2875 received placebo. The mean exposure across studies was 12 months.

The main AEs identified with dronedarone were diarrhoea, nausea or vomiting, serum creatinine increase (shown to be related to inhibition of creatinine secretion at kidney tubular level without decrease in glomerular filtration), rash, and cardiac effects consistent with the pharmacodynamic profile of dronedarone (bradycardia, QT prolongation). There was no evidence of a proarrhythmic effect of dronedarone; one case of torsades de pointes (TdP) was identified during the overall clinical development program. Assessment of intrinsic factors on the incidence of any treatment emergent AEs (TEAEs) did not suggest any excess of AEs in a particular sub-group.

The incidence of SAEs was similar in the dronedarone 400 mg BID and placebo groups (18.0% and 19.7%, respectively). Those were mainly related to system organ classes (SOCs) of infections and infestations, GI disorders, and cardiac disorders.

Premature discontinuation due to AEs occurred in 11.8% of the dronedarone-treated and in 7.7% in the placebo-treated groups, respectively. The most common reasons for discontinuation of therapy with dronedarone were GI disorders (3.2 % of patients versus 1.8% in the placebo group) mainly due to diarrhoea. The incidence of patients who permanently discontinued treatment due to TEAEs of the "Investigations" class was 2.3% on dronedarone 400 mg BID vs. 0.8% on placebo, mostly due to ECG investigations, and in particular, prolonged QT-interval consistently with the pharmacodynamic effects of dronedarone.

Regarding drug-drug interactions, drugs potentially interacting with dronedarone from a pharmacokinetic or pharmacodynamic point of view were allowed in the AF/AFL clinical program. The potential impact of these interactions on patients' safety was evaluated by reviewing specific AEs that could be induced by these interactions. These safety analyses provided assurance that recommendations given in clinical studies for the use of beta-blockers, calcium channel inhibitors, digitalis, and statins were adequate for the clinical management of the documented interactions.

An evaluation of AEs known to be associated with amiodarone showed that, unlike amiodarone, dronedarone did not reveal endocrinological, neurological, or pulmonary toxicity in the pooled AF/AFL studies. In addition, in the recently completed

DIONYSOS trial that compared dronedarone with amiodarone, the following was shown:

- For thyroid disorders, dronedarone decreased the risk of events by [redacted] compared to amiodarone. The majority of cases were hypothyroidisms, but [redacted].

- For neurological events, dronedarone decreased the risk of events (sleep disorders and tremor) by 87.6% (HR [95%CI] 0.124 [0.037 – 0.413]) compared to amiodarone. That is, n=3 (1.2%) events in the dronedarone group vs. n=17 (6.7%) in the amiodarone group.

- For bleeding events [redacted].

In addition to the contraindication in patients with worsening CHF or hospitalised for CHF within the last month, dronedarone labelling will also include instructions on the management of interacting drugs as well as interpretation of the serum creatinine increase (see Section 10 (Appendix 1) draft SPC)

Meta-analysis and MTC analysis of serious adverse events

For the purposes of this analysis, SAEs are defined as the total reported number of AEs within the timeframe of the study where it was stated in the citation explicitly that the AE was considered to be serious.

The meta-analysis indicates that for amiodarone, sotalol and Class 1c agents the odds of an SAE are significantly higher with active treatment compared with control (Table 6.14). Amongst the UK recommended AADs, dronedarone and sotalol have the lowest odds of [redacted]

Using data from the DIONYSOS trial, odds of a SAE is higher for amiodarone versus dronedarone though the difference is not significant. The indirect estimate is consistent with this result and becomes statistically significant [Peto OR amiodarone

versus dronedarone = [redacted] Indirect OR amiodarone versus dronedarone = [redacted]

Table 6.14: Meta-analysis summary of comparison between treatments: Odds ratio for SAEs

	Peto OR (95% CI)	**Peto OR (95% CI)**
Non-active control	**Direct analysis**	**Indirect analysis**
Dronedarone v control	0.96 (0.84, 1.11)	NA
Sotalol v control	1.38 (1.06, 1.81)	NA
Class 1c v control**	2.77 (1.78 – 4.30)	NA
Amiodarone v control	8.10 (2.36, 27.81)	NA
Head to head		
Amiodarone v dronedarone	1.45 (0.89, 2.35)	8.44 (2.44, 29.17)
Sotalol v dronedarone	NA	1.44 (1.07, 1.93)
Class 1c v dronedarone**	NA	2.89 (1.82 4.58)
Mixed treatment comparison*		
	OR (95% CI)	**P value**
Control v dronedarone	1.02 (0.77, 1.35)	0.886
Amiodarone v dronedarone	1.86 (0.76, 4.55)	0.160
Sotalol v dronedarone	1.35 (0.72, 2.51)	0.324
Class 1c v dronedarone**	3.06 (0.82, 11.46)	0.091

NA=not available
*Odds ratio higher than 1 describes a higher rate of SAE for the comparator treatment
**Class 1c includes flecainide and propafenone combined

In conclusion, results from both the meta-analysis and MTC analysis, indicates that amongst the UK recommended drugs, dronedarone has one of the lowest odds of an SAE. All analyses suggest that amiodarone increases the risk of an SAE compared to dronedarone but the difference is only statistically significant for the indirect comparison. The risk of SAE also appears to be higher with sotalol and Class 1c agents compared to dronedarone within the indirect and MTC results but again these are only significant in the indirect analysis.

6.8 Non-RCT evidence

The evidence considered in this clinical effectiveness chapter is based on RCT data.

6.8.1 Details of how the relevant non-RCTs have been identified and selected

6.8.2 Summary of methodology of relevant non-RCTs

6.8.3 Critical appraisal of relevant non-RCTs

6.8.4 Results of the relevant non- RCTs

6.9 Interpretation of clinical evidence

6.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes

assessed in clinical trials to the clinical benefits experienced by patients in practice.

Relevance to the decision problem

The evidence base for dronedarone is very relevant to the decision problem. Specifically for dronedarone, 4 key RCTs: ADONIS, EURIDIS, ATHENA and DIONYSOS provide a comprehensive picture of the treatment effect across all of the outcomes identified as relevant to the AF patient. This allows us to evaluate the treatment effect on AF recurrence, all-cause mortality, treatment discontinuation, stroke and SAEs. The meta-analysis and MTC then facilitate comparisons with identified comparators within the decision problem. Since none of the existing AADs have ever demonstrated efficacy on morbidity/mortality outcomes to this level, dronedarone represents a new advance in the management of patients with AF/AFL, addressing an important unmet clinical need for patients and physicians.

Relevance of study outcomes to clinical benefits to patients

Most trials of AADs, as well as guidelines for AF focus on restoring sinus rhythm while balancing the AEs associated with AAD use. Consequently AF recurrence is often the main study endpoint in trials. However, there is a lack of direct correlation between AF recurrences and long-term CV outcomes. This was highlighted in the AFFIRM trial in which management of AF with a rhythm-control strategy offered no survival advantage over the rate-control strategy. The initial development of dronedarone focused on its efficacy for the control of rhythm and rate in patients with AF/AFL and later the focus of the development programme changed from the symptomatic relief of arrhythmias to the long-term effects of drug therapy on the risk of cardiovascular death and hospitalisation. ATHENA is the first RCT which studied the long-term morbid-mortality rather than pure AF recurrence only.

From a patient perspective the dronedarone evidence base demonstrates potential outcomes beyond simply maintenance of sinus rhythm, specifically a decrease in CV hospitalisation and death and an AE profile not significantly different to baseline therapy.

6.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted.

What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

The study results for dronedarone are applicable to patients in routine clinical practice in the UK for a number of reasons.

- The UK guidelines require clinicians to identify patient subgroups to determine appropriate treatment pathways. The treatment effect in the dronedarone RCTs (EURIDIS, ADONIS and ATHENA) is consistent across these subgroups (patients with SHD, LVD, CAD, etc) and therefore the results are applicable across the subgroups in the guidelines.
- The population in the RCTs are receiving baseline therapy which reflects the baseline therapy recommended by the UK guidelines as described in Section 6.3.6 (primarily beta-blockers and anti-coagulation).
- Subsequent to the DAFNE study, all RCTs were conducted using the 400mg BID dose. The total number of patients with AF and treated with dronedarone in the clinical program was 3410; of these a total of 3282 were treated with the 400mg dose BID as specified in the SPC (96% of patients receiving dronedarone).

Within DIONYSOS, the loading dose of amiodarone is higher than would be recommended in the UK. This dose (600mg loading dose daily for 28 days, then 200mg daily thereafter) was selected based on the scheme that was used in the SAFE-T study, the most recent comparative study done with amiodarone. It is felt that this does not impact on the relevance of the study from a UK perspective.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

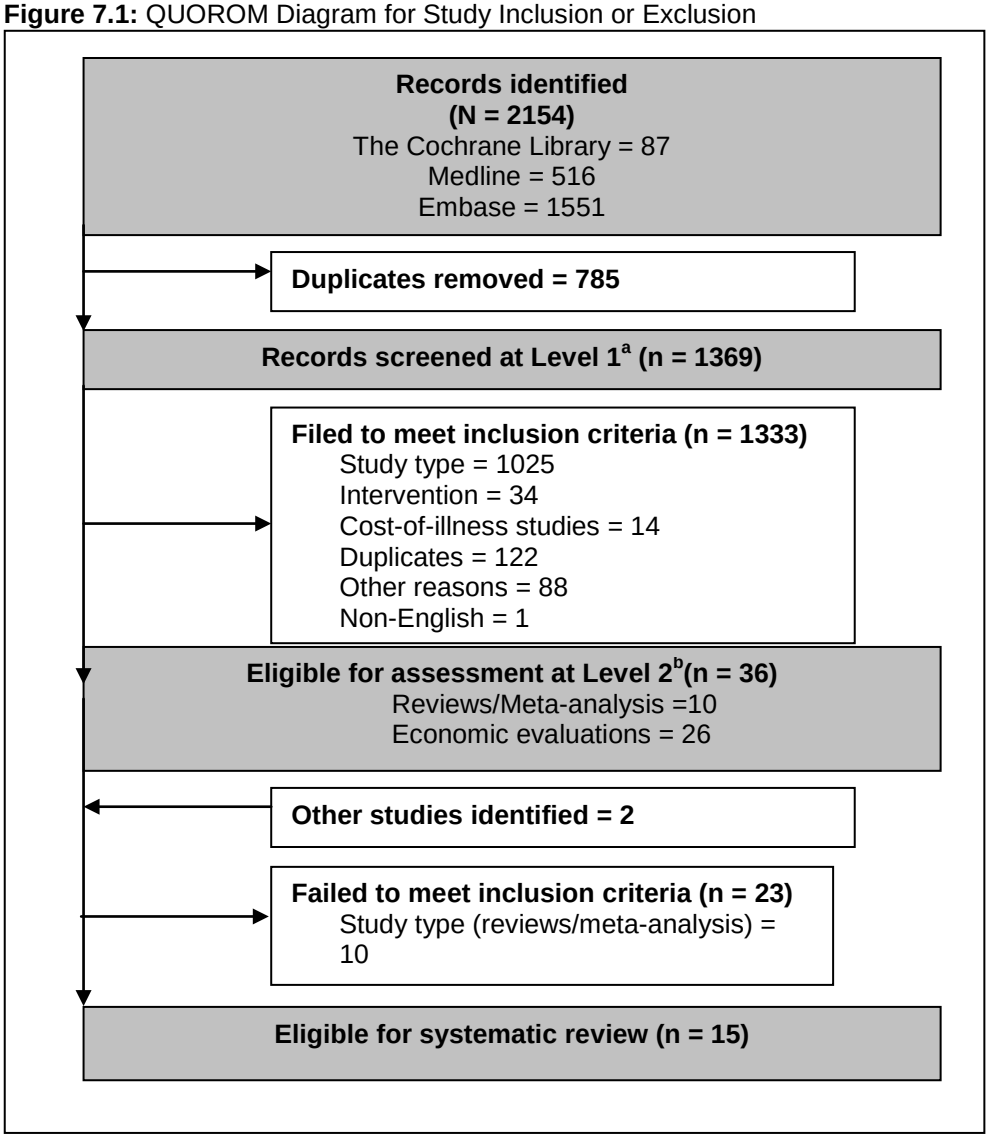
7.1.1 Identification of studies

Searches were conducted for cost-effectiveness and cost-utility studies for dronedarone and comparators (amiodarone, sotalol, class 1c). Electronic databases searched included Medline, Embase, Medline (R) In-Process, Health Economic Evaluation Database, NHS Economic Evaluation Database (NHS EED). The search strategy used to identify any published cost-effectiveness literature is shown in Section 10 (Appendix 10).

Inclusion criteria consisted of economic evaluation studies, including studies based on models, cost analyses performed alongside clinical trials, and budget-impact analyses. Also included were clinical studies of dronedarone that reported any cost or resource use data. Clinical studies investigating dronedarone that reported resource use or cost data were included in the systematic review report if identified during the searches, particularly when conducting internet searches of conference abstracts. These studies were also expected to be identified either from reviews of dronedarone or other anti-arrhythmia agents of interest.

Publications were excluded if they were reviews, letters, comment articles and other sources that discussed costs but which did not conduct a formal economic analysis.
Also excluded were general cost-of-illness or economic burden studies that do not estimate incremental cost-effectiveness or cost-utility ratios and also excluded were clinical studies investigating amiodarone, sotalol, flecainide, or other AAD or beta-blockers that reported some resource use and/or costs but where no formal or comprehensive economic analysis had been undertaken.

Figure 7.1: QUOROM Diagram for Study Inclusion or Exclusion



7.1.2 Description of identified studies

No cost effectiveness studies of dronedarone were identified. Those studies eligible for review were all based on comparators and were not relevant for this decision problem (full report available on request).

7.2 De novo economic evaluation(s)

7.2.1 Technology

7.2.1.1 *How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.*

Dronedarone is assumed to be used in the model as per the licence, i.e. 400mg bid for stable adult patients with either a recent history of, or current non-permanent AF. The duration of treatment is anticipated to be for the remainder of the patient's life unless the patient suffers intolerable adverse events or persistence of a high level of AF symptoms which is deemed to require alternative therapy. This population is likely to exclude patients with NYHA CHF Class IV and also NYHA Class III CHF with a recent haemodynamic instability. As such dronedarone is expected to be used in two positions;

a. For patients with multiple CV risk factors (corresponding to a $CHADS_2 \geq 4$) on top of standard baseline therapy (including anti-coagulation and beta blockers as per the UK guidelines and referred to within the guidelines as 1st line treatment)
b. For patients when it is deemed appropriate to introduce an AAD, as a 1st line alternative to current AADs (referred to within the UK guidelines as 2nd line treatment).

7.2.1.2 *Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.*

- *the costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required)*
- *the robustness and plausibility of the endpoint on which the rule is based*
- *whether the 'response' criteria defined in the rule can be reasonably achieved*
- *the appropriateness and robustness of the time at which response is measured*
- *whether the rule can be incorporated into routine clinical practice*
- *whether the rule is likely to predict those patients for whom the technology is particularly cost effective*
- *issues with respect to withdrawal of treatment from non-responders and other equity considerations.*

Treatment discontinuation in the model is based on the placebo treatment discontinuation rate observed in the ATHENA trial and adjusted for each intervention

using the odds ratio reported for discontinuation rates for any-cause from the MTC. In ATHENA, patients remain on treatment until their symptoms become uncontrolled or they incur an intolerable adverse event. Therefore if a patient suffers an AF recurrence and are able to revert back to NSR they remain on treatment. Uncontrolled AF symptoms or intolerable adverse events are easily implementable as stopping rules and are part of current clinical practice. Monitoring requirements and associated costs for each treatment are based on the treatment profile and are discussed in Section 7.2.9.1.

The model is constructed using a discrete event methodology. With regards to treatment discontinuation there is a lack of data that links discontinuation from treatment to specific modelled events. The model therefore considers treatment discontinuation as an independent event from any event in the model. Patients therefore remain on treatment until they reach their sampled treatment discontinuation time regardless of whether they have incurred symptomatic AF recurrence, an AF-related event (defined to be either ACS, stroke or CHF), or an adverse events. Whilst at an individual level this may not fully reflect clinical practice, the overall outcome at a population level reflects the defined stopping rules.

7.2.2 Patients

7.2.2.1 *What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?*

The patient population considered in the economic evaluation matches that of the licensed indication.

Patients are stratified depending on their clinical AF type and baseline risk factors in line with the UK guidelines[1]. The patient groups considered are therefore:

- Paroxysmal AF patients with no structural heart disease
- Paroxysmal AF patients with coronary heart disease
- Paroxysmal AF patients with LV dysfunction
- Persistent AF patients with no structural heart disease
- Persistent AF patients with structural heart disease.

7.2.2.2 *Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?*

The base case analysis starts with the subgroups identified in 7.2.2.1 as dictated in the UK guidelines. Each identified subgroup in the guidelines requires a different treatment pathway dependent on patient baseline characteristics and are considered for treatment with dronedarone as a 1st line anti-arrhythmic.

A subgroup of patients based on a $CHADS_2$ score $\geq$ 4 has been identified with a higher baseline risk of stroke (Gage 2004),[3] mortality (Henriksson 2009)[21] and AF recurrence (as predicted from ATHENA risk equations (see Section 7.2.7.1)). These patients may benefit from earlier treatment with dronedarone. Results from a post hoc analysis of ATHENA data by $CHADS_2$ score categories (see Section 6.3: ATHENA clinical trial) shows that the hazard ratio of death (all cause mortality) are statistically significantly lower with dronedarone compared to placebo in these patients [redacted]. These patients are considered for treatment with dronedarone as a baseline standard therapy on top of beta-blockers and anti-coagulation.

Subgroup analysis has also been performed on the following populations to determine if there are any groups of patients that would benefit more from treatment with dronedarone. These are all considered within the position of dronedarone as an alternative 1st line AAD to current AADs:

- Patients aged 65 to provide a threshold analysis of the effect in younger patients
- $CHADS_2$ scores from 0 to 6
- Gender.

These subgroups were deemed by clinical experts to be the most clinically relevant as they are the clearest way of looking at different baseline risks. The different $CHADS_2$ scores are a proxy for the risk of stroke and mortality. The age and sex subgroups are associated with differing all-cause mortality. Clinicians also noted that they would be less likely to give a younger patient the AAD amiodarone due to the associated adverse events AEs and the tendency for escalated AEs over time. Hence age was a subgroup of additional interest. Whilst the absolute risk values of mortality and cardiovascular events will be different in these subgroups, the relative risks of treatment effect are assumed to remain constant (see Section 7.2.7.2).

Statistical analysis on data from the ATHENA clinical trial was performed using survival analysis techniques to determine time to event. Age, sex, $CHADS_2$ score and CV status were included in the equations as explanatory variables used to estimate the absolute risk for placebo treatment patients in the subgroup (see Section 7.2.7.2).

7.2.2.3 *Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.*

AFL patients could be considered a subgroup that warrants separate consideration. AFL patients were included but not identified nor analysed as a subgroup within the dronedarone trial programme and therefore there is no data available to model these separately. The submission reflects NICE guidelines and includes those patients with atrial flutter that is indistinguishable from AF. These patients are assumed to have the same baseline risks and treatment effects as AF patients.

7.2.2.4 *At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?*

All patients enter the model having recently returned to sinus rhythm. As such patients will enter the model in one of two positions

a. at baseline therapy (refer to Section 4.1) for those with a $CHADS_2 \geq 4$; and
b. when it is appropriate for an AAD therapy to be introduced (amiodarone, sotalol or class 1c) as noted in the UK guidelines, as detailed in Section 4.1.

Patients exit the model on death. There is no assumed difference in 'enter' and 'exit' points between treatment sequences.

7.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

The economic evaluation has been developed as a treatment sequence model based on the UK guidelines[1], to reflect routine standard care in the UK. The sequence used is dependent on the patient's baseline characteristics as defined in the guidelines. For patient groups which are considered for treatment with dronedarone as an alternative 1st line AAD to current AADs we do not include baseline therapy with standard care as this period is assumed to be the same in all treatment arms and so cancels out. If patients fail on all available active therapies in the pathway, they then revert to end of line therapy (rate control agents), for which the comparator arm of the ATHENA trial is used as a proxy. Figure 7.2a and 7.2b below shown where dronedarone is considered in the patient pathway for each patient type.

Figure 7.2a: Comparator treatment pathway and considered dronedarone positions. Paroxysmal AF patients.

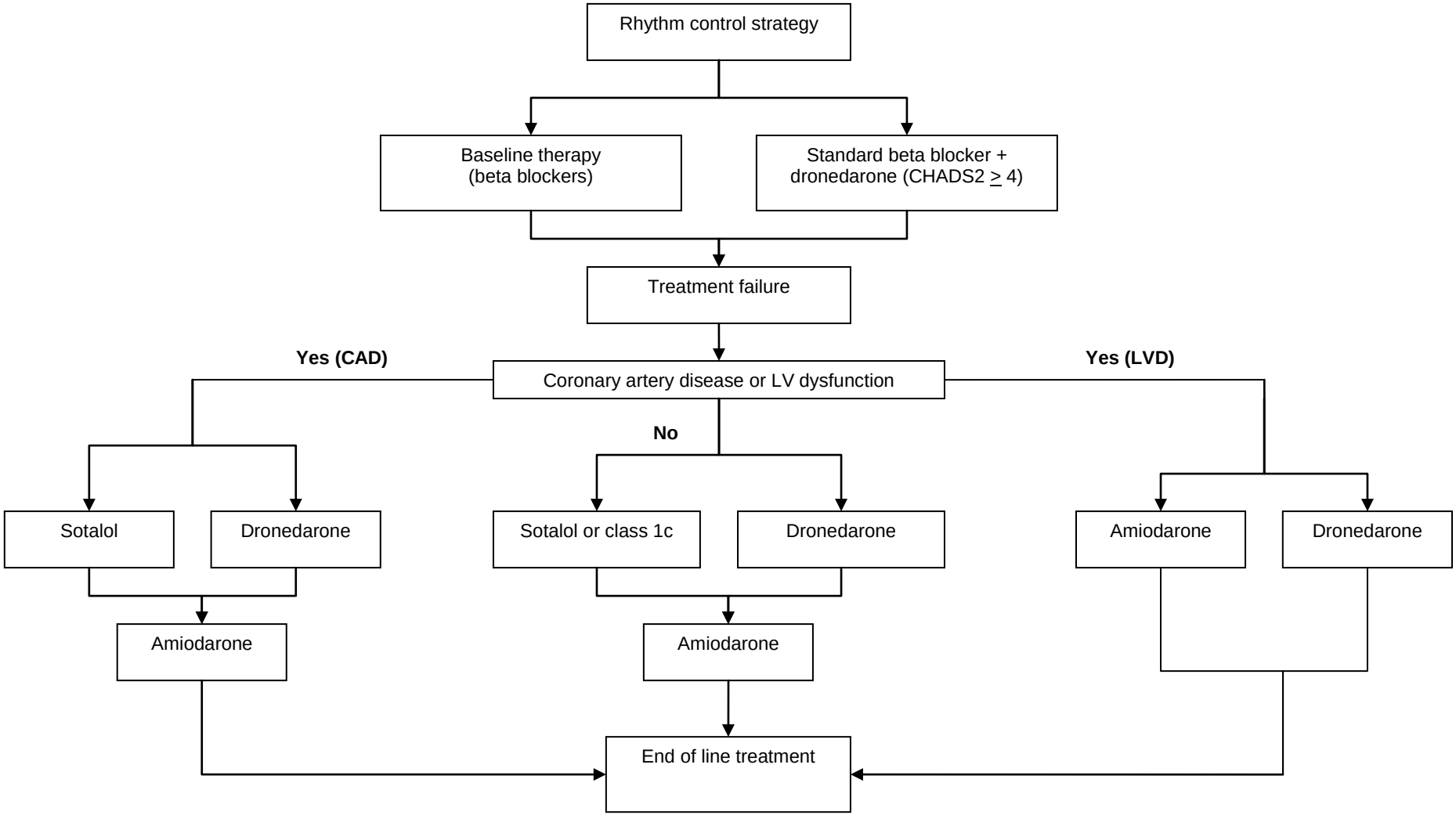
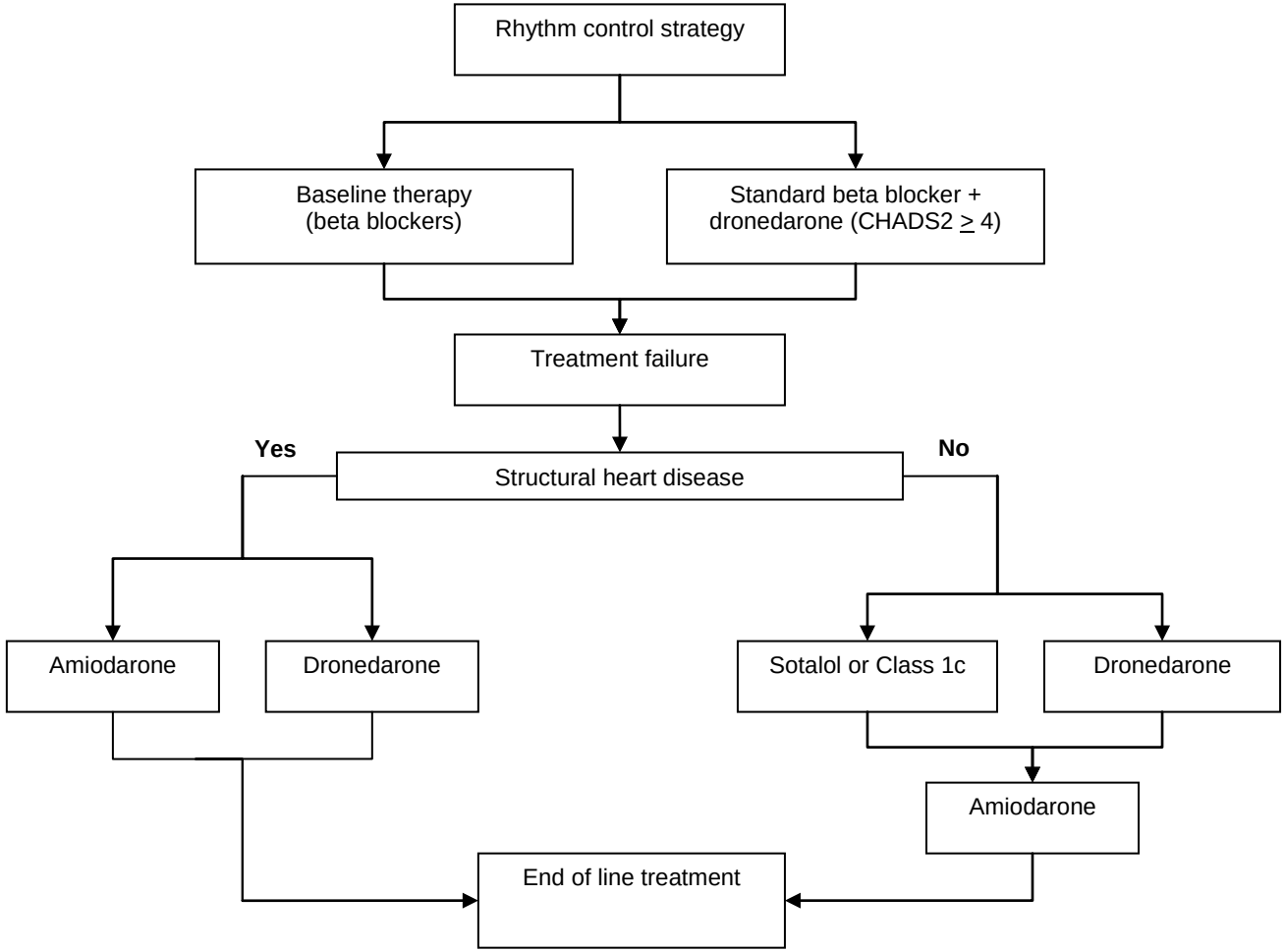


Figure 7.2b: Comparator treatment pathway and considered dronedarone positions. Persistent AF patients.



7.2.4 Study perspective

The perspective of the economic evaluation is that of the NHS and PSS in England and Wales, as per the NICE reference case.

7.2.5 Time horizon

The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.

A life-time horizon was adopted for the base case analysis. AF is a life time disease with an increased risk of long term morbidity including stroke, CHF and ACS. To fully capture the long term cost and benefits associated with treatment, a life-time model was deemed appropriate.

A year on year analysis is presented in sensitivity analysis which shows the effect on the incremental cost-effectiveness ratio (ICER) of increasing the model timeframe 1 year at a time (see Section 10 (Appendix 20)).

7.2.6 Framework

a) Model-based evaluations

7.2.6.1 *Please provide the following.*

- *A description of the model type.*
- *A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.*
- *A list of all variables that includes their value, range (distribution) and source.*
- *A separate list of all assumptions and a justification for each assumption.*

Description of the model type

The evaluation performed is a cost-utility analysis, using an individual patient life-time discrete event simulation (DES) methodology. The model predicts a patient's course for a treatment pathway that includes treatment with dronedarone, and compares this to the predicted course with treatment pathways based on current guidelines. Although cohort Markov models are the most commonly used technique for such

analyses today[46], that approach does not have the flexibility required to address time and event dependant changes in disease progression and event risk, which are central in the management of AF.

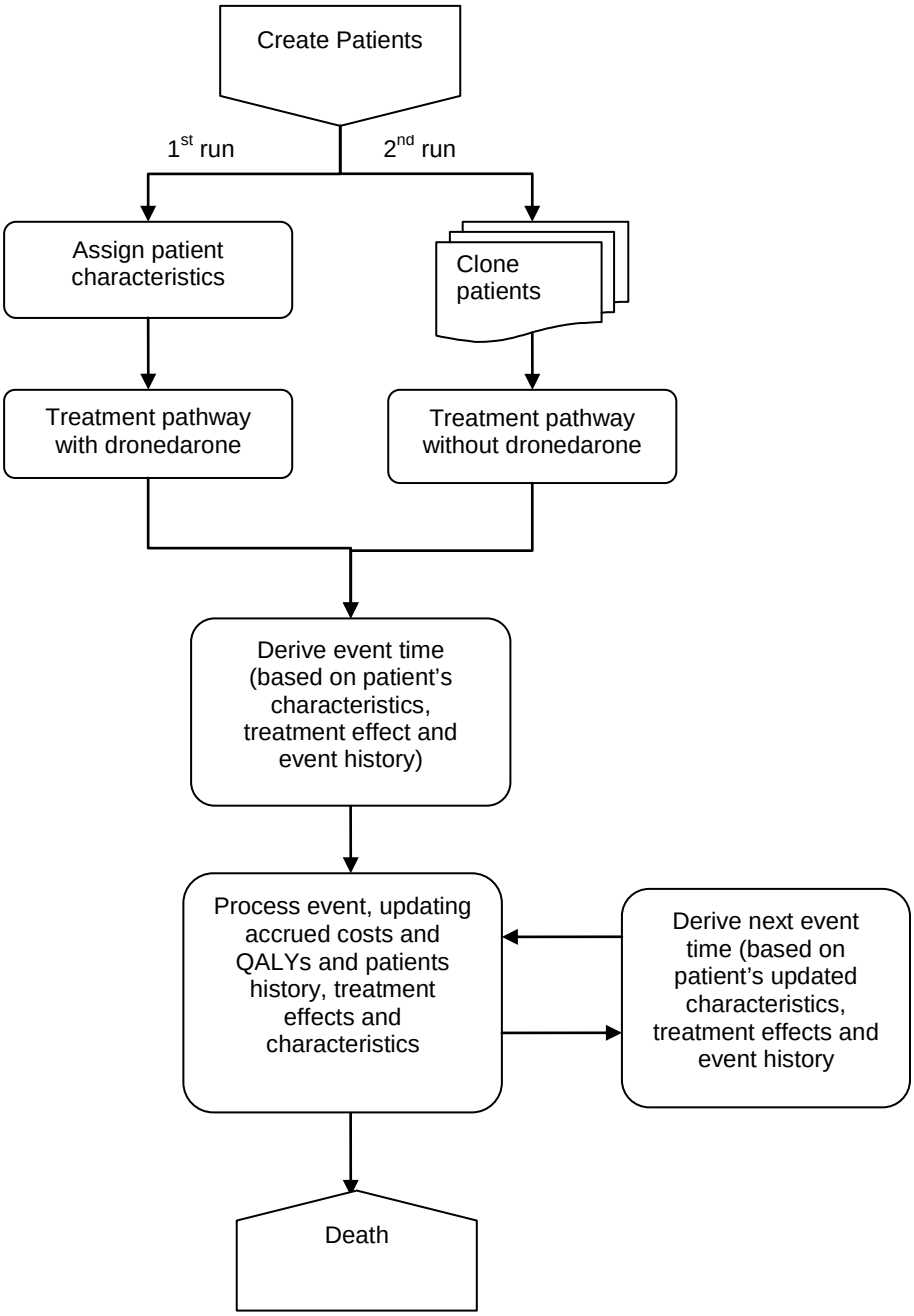
DES is a modelling technique that conceptualises the course of a disease and its management in terms of events that occur and the impact these events have on patients and other components of the system. A major benefit of this technique is that it can represent the management and the course of the disease with higher accuracy by handling the events of interest (e.g. milestones of the disease course and their immediate and future consequences) exactly at the predicted times of these events. Therefore the appropriate effects of the events can be implemented at the time of the event, avoiding any artificial assumptions about timing and consequences. DES is a well established approach to modelling complex processes over time.[47] Although it has been used relatively little in medicine, it was chosen because it permits the development of very realistic models that avoid the typical over-simplification of techniques that are popular today, such as using the model parameters at mean values rather than using observed distributions, and ignoring the clinical histories of individuals which may have an effect on the future course of the disease. The simulation is performed in Simul8® which takes input and returns results to an Excel® front end.

The model is an individual patient simulation. It considers the experience of a large hypothetical population consisting of specific individuals generated with characteristics that reflect the AF population of interest. The course of each patient is considered under various treatment options. Patients are individually simulated and their progression through the disease model recorded, taking account of the events that they incur and the associated costs and quality of life detriments. This means that the model is event driven; the time to the next event is simulated with the patient remaining in their current health state until the next event occurs. The current event determines which health state the patient remains in until the next event. The patients are then regenerated (so that a clone population has been created) and the simulation rerun using the comparator treatment pathway. Cloning ensures that factors other than treatment do not create nuisance variance and is analogous to carrying out an identical twin study. When identical copies of patients are made, the random numbers used to generate the events are the same in both treatment arms to ensure that, in the absence of treatment, the course in the model is the same. For example, the time of stroke and the time of death are estimated for each individual at

this point. Any changes in these event times later in the model are therefore a result of treatment rather than a product of random variation. An overview of the logical structure of the model is shown in Figure 7.3 below.

The model encompasses outcome measures for costs, health outcomes and incremental cost-effectiveness. Outcomes for costs include those relating to drugs and medications, monitoring, routine follow-up, hospitalisation due to AF recurrence or AF related event and AE management. Health effects are expressed in terms of life years (LYs) and quality adjusted life years (QALYs). The model outcomes are expressed in terms of cost per LY and per QALY gained. Univariate and probabilistic sensitivity analysis (PSA) is performed to examine the overall effect of the uncertainty in the model.

Figure 7.3: Overview of the structural flow of the model



Health states and events

The model is divided into 4 health states in which the patient remains between events. These are:

Normal sinus rhythm*:* The patient has a normal pattern of electrical activity (and subsequent muscular contraction) of the heart or asymptomatic AF that does not require any additional treatment beyond their current treatment option.

Permanent AF with uncontrolled symptoms: The patient has permanent AF and is suffering AF symptoms that are sufficiently worse than those they are used to living with and require either a GP visit or hospitalisation.

Permanent AF with controlled symptoms: The patient has permanent AF and their symptoms sufficiently controlled at a level that they are used to living with and managing using rate control.

Death: The patient has died.

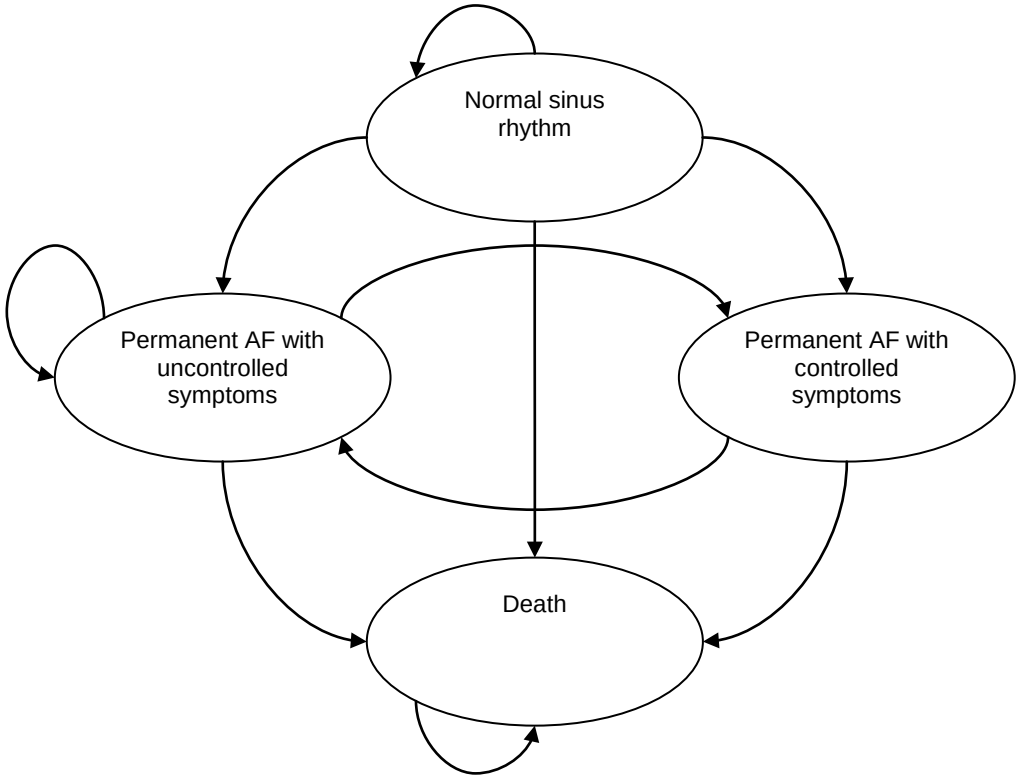
The possible movements between these states are shown in Figure 7.4.

Movements between the health states are driven by events. There are 7 events that are modelled:

- AF recurrence
- ACS
- Stroke
- CHF
- Treatment discontinuation (any cause)
- AF symptoms change for permanent patients
- Death.

Within each event there are numerous probabilities of different outcomes (except death), in the form of within-event decision trees (see Section 10 (Appendix 11) for examples). These decision trees dictate the probabilities of which health state the patient remains in until the next event, and the cost and quality of life outcomes that are associated with each event.

Figure 7.4: The modelled health states and the allowed movement between states due to events



List of all variables in the model

A list of all the variables in the model is shown in Section 10 (Appendix 12).

Assumptions (A) and justifications (J)

(A) It was assumed that the placebo treatment arm of ATHENA was representative of baseline therapy in the UK and could therefore be used as the base case for time to events and is subsequently referred to as the reference arm in the model. The mean follow-up trial period of 21 months is extrapolated to predict patient life-time events.

(J) Section 6.3 and Section 6.3.6 provide detail of the similarity of the placebo arm of ATHENA to baseline therapy as recommended in the UK guidelines (primarily beta blockers and anti-coagulation). There is no available data that examines the life-time effect of treatment on AF patients. ATHENA is the longest RCT that specifically examines an AAD (other trials such as AFFIRM[36] are longer but are designed to investigate rate versus rhythm control) and therefore provides the best available proxy to model life-time AF events.

(A) We assume that the treatment effect is consistent across all relevant subgroups as defined by UK guidelines.

(J) It has been demonstrated in ATHENA, EURIDIS and ADONIS that the treatment effect on the primary endpoint is consistent in all identified subgroups (see Section 6.3).

(A) It is assumed that discontinuation from treatment is an event independent from any other event in the model (i.e. is not associated with AF recurrence, AF related event or intolerable AE).

(J) Whilst clinically it is probably the case that treatment discontinuation is associated with clinical events, the evidence does not support disaggregation of the discontinuation rate as per the events required for the model. The discontinuation rates for any cause are presented in the MTC in Section 6.5, Table 6.8. This means that on an individual patient basis the model may not fully reflect real life, however the overall population treatment discontinuation rate from a full run of the model will mirror that observed in the trials and literature.

(A) Asymptomatic AF recurrences are not included in the model.

(J) Many patients incur asymptomatic AF recurrences and do not present to medical care [1]. Data on these incidences are scarce as asymptomatic episodes are difficult to quantify and monitor outside clinical trials. It is assumed that these recurrences have no effect on quality of life and incur zero costs.

(A) Although AF recurrence was not an outcome measure in ATHENA, the placebo treatment arm is used in the model as the reference arm for time to first symptomatic AF recurrence. The relative treatment results from the MTC can then be applied to this reference arm.

(J) ATHENA is the largest AAD AF trial conducted to date (n=4628) and provides the data for all the other reference outcomes in the model. For consistency we also use ATHENA for time to AF recurrence. AF recurrence is estimated using appropriate outcome measures in ATHENA identified a posteriori by recurrence on ECG, cardioversion or hospitalisation for AF. It was recognised that ECG identification of recurrence may be asymptomatic therefore it was considered appropriate to include 70% of the AF recurrence at ECG as a proxy of symptomatic recurrence.

(A) It is assumed that only a proportion of symptomatic recurrences result in hospitalisation. Those patients who are not hospitalised are assumed to incur a GP and an outpatient visit.

(J) There is evidence from ATHENA that only approximately 29.4% of all AF recurrences require hospitalisation (a pooled dronedarone and placebo treatment rate). This figure is used to determine the percentage of AF recurrences within the model which incur a hospitalisation cost. This percentage is assumed to be the same no matter what AAD treatment is being administered and whatever the type of AF. There was no information from DIONYSOS (amiodarone versus dronedarone) on AF recurrence hospitalisation that could help with this conservative assumption.

(A) Whenever a paroxysmal AF patient suffers a symptomatic recurrence, there is a probability that they will not spontaneously return to normal sinus rhythm and so will require manual cardioversion. When this happens they are then classed as a persistent patient if they are then successfully cardioverted or permanent patient if normal sinus rhythm is not achieved.

(J) Patients can move from paroxysmal to persistent or permanent AF[2]. The Euro Heart Survey in AF [Nieuwlaat 2008][48] reported that at the end of year 1, approximately 15% of paroxysmal patients moved to either persistent or permanent AF. From ATHENA it is estimated that non-permanent patients suffer approximately 0.5 symptomatic recurrences per year [data on file]. We therefore estimate that in 10% of paroxysmal AF recurrences in the model the patient does not spontaneously return to normal sinus rhythm and moves to either persistent or permanent AF depending on whether they are successfully manually cardioverted.

(A) There is no distinction made between paroxysmal and persistent AF patients in terms of AAD efficacy. The only difference between the two AF types will be the NICE defined treatment sequences and the pathway post AF recurrence where paroxysmal patient can spontaneously return to sinus rhythm.

(J) The data from the literature and the clinical trials does not differentiate paroxysmal and persistent patients in terms of efficacy and so this assumption has to be made.

(A) It is assumed that when suffering a symptomatic AF recurrence, paroxysmal patients do not require hospitalisation.

(J) Paroxysmal patients by definition quickly spontaneously return to normal sinus rhythm (usually within 48 hours) and so do not require hospitalisation. If a

paroxysmal patient suffers an AF recurrence and does not spontaneously return to normal sinus rhythm, they then are considered a persistent or permanent patient and can be hospitalised during the current and subsequent AF recurrences.

(A) Persistent patients that have an AF recurrence can receive up to a maximum of 2 cardioversion attempts per recurrence. It is assumed that the proportion of patients receiving electrical vs pharmacological is 9:1 in favour of electrical cardioversion.
(J) This figure was elicited from expert clinician opinion (see Section 10 (Appendix 13); Expert opinion list).

(A) A proportion of persistent patients that incur symptomatic AF recurrence or uncontrolled symptoms will receive an ablation attempt either as a result of failed cardioversion attempts or as an alternative to cardioversion.
(J) Expert clinician opinion indicated that a small proportion of patients would receive an ablation. This is further supported by evidence from the Euro Heart Survey [Nieuwlaat 2008] which indicates that in the first year of the survey 4% of persistent patients and 6% of paroxysmal patients received an ablation.[48]

(A) Patients that are successfully ablated are assumed to remain in normal sinus rhythm until death. They incur no other events.
(J) Successful ablation is generally curative and patients are no longer at risk from the effects of AF. There is some evidence of recurrence after ablation, however there is a lack of usable data and so a simplifying assumption is made to assume that all patients remain cured.

(A) It is assumed that a cardioversion or ablation attempt is not attempted until 48 hours after the AF recurrence or 7 days after a failed cardioversion attempt.
(J) UK guidelines suggest that a patient should be given at least 48 hours to determine if spontaneous return to NSR is achieved and to allow underlying precipitants (e.g. thyrotoxicosis, infections) to be successfully treated. A period of 1 day to 2 weeks is recommended before reattempting a cardioversion after a failed attempt.[1] We assume a midpoint of 7 days.

(A) The data from the literature on the relative performance of each AAD in the reduction of AF recurrence relative to the pooled placebo controlled arms from the included trials are synthesised within the MTC. It is assumed that this relative risk

can be applied to the reference arm of the model (see Section 6.5 for definition of AF recurrence).

(J) It is difficult to clearly define and capture all AF recurrences, and whilst we acknowledge that the MTC and ATHENA results may have some weaknesses, they are the best, most robust data available and so are used in the model.

(A) It is assumed that when persistent or paroxysmal patients in AF fail to revert back to NSR that they become permanent patients. Permanent patients remain on the treatment on which they entered the permanent state until their sampled discontinuation time at which point they move to end of line treatment. For example if a patient has a discontinuation from dronedarone time of 2 years, but during an AF recurrence in year 1, they fail to revert back to NSR and become a permanent patient, then they still remain on dronedarone as a rate control patient until year 2.

(J) This assumption is required so that the simulated discontinuation rates for each treatment match the rate reported in the MTC. If we assumed that patients discontinue from treatment once moving to a permanent AF status then the modelled discontinuation rates would be overestimated. Furthermore expert clinician opinion suggested that wherever possible patients would continue on treatment as permanent patients until symptoms became uncontrolled or the patient suffered intolerable adverse events causing them to withdraw. The UK guidelines suggest that permanent patients are treated with beta-blockers, anti coagulation and rate limiting calcium antagonists [1].

(A) It has been assumed that permanent patients have episodes of increased symptoms which we have described as uncontrolled symptoms (Section 7.2.6). The rate of uncontrolled symptoms is assumed to be the same as the proxy rate of AF recurrence from ATHENA. The rate of hospitalisation for uncontrolled symptoms is also assumed to be the same as the rate of hospitalisation for AF recurrence. It is assumed that uncontrolled symptoms last for 7 days with associated utility decrements and costs – for those not hospitalised all with have a GP visit.

(J) Uncontrolled symptoms are difficult to define in permanent patients as by definition permanent patients are living with symptoms of AF and the degree of manageability of disease varies from patient to patient. Given the lack of usable data, this assumption attempts to best reflect the experience of permanent patient.

(A) We assume an increased risk of ACS, CHF and stroke in post stroke patients by increasing the $CHADS_2$ score by 2 points (the score increase associated with a

prior stroke or TIA in the $CHADS_2$ index). Patients that are identified at base line as having previously suffered a stroke do not have their CHADS score increased post subsequent stroke. There is no increased ACS, CHF or stroke risk associated with post CHF or ACS.

(J) The risk equations for CHF, ACS and stroke from ATHENA include $CHADS_2$ score which is positively correlated with an increased risk of AF related event. A patients $CHADS_2$ score is increased by 2 points after a stroke and so this is the best available proxy for increased risk post stroke. There is no such measure post CHF or ACS, due to the lack of comparator data for these events.

(A) It is assumed that there is an increased risk of mortality post stroke and CHF events. All cause mortality is adjusted to account for increased CHF and stroke risk.

(J) Clinical evidence supports this assumption[21].

(A) Baseline all-cause mortality for AF patients is adjusted to reflect the increased mortality rate in AF patients compared to the general population. Male patients have an odds ratio for all-cause mortality of 1.5 compared to the general population female patients have an odds ratio of 1.9 [Bengamin 1998].[49] An all-cause mortality risk equation is generated based on UK life tables [Interim life tables 2005-07 http://www.gad.gov.uk].[50,21] Details of this adjustment are discussed in Section 7.2.7.1.

(J) There is good evidence that suggests that AF patients have a worsened mortality compared to the general population [1].

(A) It is assumed that there is no difference in all-cause mortality associated with Class 1c agents and dronedarone.

(J) Due to the lack of data around the Class 1c agents it was not possible to conduct any analyses to assess any treatment differences between Class 1c agents and placebo and subsequently dronedarone. The assumption of no all-cause mortality difference is considered to be very conservative.

(A) Where a treatment has either a positive or a negative treatment effect, this benefit or detriment is removed as soon as the patient discontinues treatment. The patient immediately acquires the mortality effect of the next treatment regimen.

(J) Whilst there is likely to be some time dependent relationship between cessation of treatment and discontinuation of treatment effect on clinical outcomes such as mortality and stroke prevention, this is impossible to quantify given the

available data. The assumption of immediate cessation of effect is likely to be conservative, biasing against dronedarone, particularly in relation to all-cause mortality for which dronedarone has a trend towards a preventive effect compared to baseline therapy, whereas based on evidence from the MTC all the comparators in the evaluation have a detrimental effect on mortality.

(A) AEs are not modelled as individual events and are assumed to have a combined background rate with associated costs and QALY detriments.
(J) There are no AEs that affect a patient's risk of other events in the model or that would lead to a health state change (since treatment discontinuation is modelled as an independent event). Therefore to improve processing time in the model the costs and QALY detriments associated with the treatment are applied to each patient based on the reported annualised rate of each event.

(A) It is assumed that the cost of short term adverse events is applied as a one off cost on treatment initiation and life-time AE costs are applied every 6 months.
(J) Short term adverse events are assumed to last only for 1 month and the costs of treatment are easy to capture in a one off cost and this assumption is made for modelling simplicity. This may be very slightly overestimated by being applied on treatment initiation due to discounting.

(A) Utility decrements as a result of AEs are defined as either short term on life-time. Those categorised as short term have a 1 month utility decrement, life-time AEs have continuous utility decrement
(J) There are some adverse events that have been identified by clinicians as having life-time effects (interstitial lung disease, hyperthyroidism and hypothyroidism) and so the quality of life detriments should be modeled as having a life-time impact. Whilst the short term adverse events will each have a different time periods over which utility detriment will occur. Clinical advice was a one month period would reflect the average patient experience.

(A) We assume that there is a treatment effect with stroke for some interventions, but assumed same treatment effect for ACS and CHF as there was no data available to show otherwise.
(J) There was sufficient evidence for MTC for stroke for amiodarone and sotalol, but no evidence on comparators for ACS or CHF therefore it had to be assumed that the treatment effect was the same. There is a small indirect treatment effect in the model

between treatments for ACS and CHF as history of previous stroke increases the risk of these events.

(A) It was assumed that Class 1c agents would have no effect on stroke.
(J) Within the systematic review and meta-analysis there was no evidence specific to Class 1c agents to allow an analysis of the treatment effect on stroke. The MTC noted no significant treatment effect for amiodarone or sotalol on stroke compared to placebo therefore it was deemed reasonable to assume no treatment effect on stroke for Class 1c agents.

7.2.6.2 *Why was this particular type of model used?*

The treatment pathways and outcomes associated with AF are complex. Furthermore the morbidities associated with AF include various outcomes that have a changing effect on long term risks which require the model to have a memory of previous events incurred by a patient. The number of health states required in a Markov cohort model to keep track of the patient's events would be so great that assumptions would need to be made to reduce the number of health states, thus reducing the ability of the model to appropriately reflect the disease. An individual patient model has an inherent capability to record patient disease history thereby accurately and effectively modelling the increased risk associated with incurred events. It was felt that this would be the most appropriate way to model AF.

7.2.6.3 *What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.*

The structure of the model was chosen as it best represents the patient pathways defined in the UK guidelines which have been assumed to represent routine care in the UK[2]. The structure has also been validated with UK clinicians who approved the structure as being representative of their practice. No other structures were considered as they would then deviate from the UK guidelines and not be representative of UK best practice.

7.2.6.4 *What were the sources of information used to develop and inform the structure of the model?*

The UK guidelines and expert clinician advice were the main sources used to develop the structure of the model.

7.2.6.5 *Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?*

All relevant features of the condition are considered.

7.2.6.6 *For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?*

The model is constructed with a daily time cycle which fully enables the model to reflect the pathology and symptom changes of the disease.

7.2.6.7 *Was a half-cycle correction used in the model? If not, why not?*

A half-cycle correction is not relevant in a discrete event individual patient simulation.

7.2.6.8 *Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?*

The presented economic model is a life-time model and so cost and clinical outcomes are extrapolated. The key source of data is the ATHENA model with a median follow-up period of 21 months for all events. The model uses the placebo treatment arm of the ATHENA study as the base line risk of event. ATHENA is the longest available RCT of an AAD and therefore provides the best available proxy to model life-time AF events. The placebo treatment arm provides a way of being able

to compare the different treatment options analysed in the MTC which presents event odds ratios for each treatment option versus control.

The risk of AF recurrence, CHF, ACS, stroke and treatment discontinuation are all extrapolated from risk equations derived from ATHENA and extrapolated to a life-time risk of event. These risks are then adjusted for the current treatment using the odds ratio reported in the MTC. There was only sufficient data on AF recurrence; stroke and treatment discontinuation for inclusion in the MTC. Further details on these equations are presented in Section 7.2.7.1.

b) Non-model-based economic evaluations

7.2.6.9 *Was the evaluation based on patient-level economic data from a clinical trial or trials?*

Not applicable.

7.2.6.10 *Provide details of the clinical trial, including the rationale for its selection.*

Not applicable.

7.2.6.11 *Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?*

Not applicable.

7.2.6.12 *Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?*

Not applicable.

7.2.6.13 *Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?*

Not applicable.

7.2.7 Clinical evidence

7.2.7.1 *How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.*

Baseline disease progression is based on the reference arm event risk equations described in Section 7.2.6.8. This analysis extrapolates the ATHENA trial based event risks to patient's life-time risk of event. Survival analysis has been performed on the time to event for each of the modelled events. These analyses generate risk equations which include the covariates, age, gender, and baseline characteristics of SHD, CAD and $CHADS_2$ score. These characteristics reflect the different subgroups identified by NICE in their clinical guidelines ($CHADS_2$ is very similar to the stroke algorithm used by NICE therefore relevant in this instance) and can be used to determine the change in risk of event as patients incur events in the model (i.e. patients that incur a stroke have an increased $CHADS_2$ score). These covariates were kept in the models irrespective if they reached significance or not.

Various curve fits have been examined and the most appropriate fit chosen based on the Akaike's information criterion (AIC) and the Bayesian information criterion (BIC). The AIC and BIC are measures of the goodness of fit of an estimated statistical model. In the general case,

the AIC is defined as; $$AIC = 2k - 2\ln(L)$$

and the BIC is defined as; $$-2 \cdot \ln p(x|k) \approx \mathrm{BIC} = -2 \cdot \ln L + k \ln(n).$$

When estimating model parameters using maximum likelihood estimation, it is possible to increase the likelihood by adding additional parameters, which may result in overfitting. The BIC resolves this problem by introducing a penalty term for the number of parameters in the model. This penalty for additional parameters is stronger than that of the AIC.

Table 7.2 shows the chosen curve fit for each modeled clinical outcome. A breakdown of the AIC and BIC scores for each of the examined curves is presented in Section 10 (Appendix 14).

Table 7.2: Curve choice for the modelled clinical outcomes based on the AIC.

Clinical outcome	**Chosen curve**
AF recurrences	Exponential
Treatment discontinuation	Gamma
CHF	Weibull
ACS	Exponential
Stroke	Exponential

These curves are used to generate time to event distributions which extrapolate beyond the end of the trial follow-up period.

The risk of event for each treatment type is adjusted based on the results of the MTC, described in Section 7.2.7.2. The adjustment is made to the risk equations by assuming that the shape parameter of the curve remains fixed and the scale parameter is adjusted so that the hazard is adjusted by the relative risk.

The risk equations described above are dependent on the patient's baseline $CHADS_2$ score. The model base case assumes the same $CHADS_2$ distribution as observed in the ATHENA trial. A sensitivity analysis is performed which uses a distribution based on the RECORD-AF study (European data only), which is more likely to represent 'real world' data and not a trial population (data on file). The RECORD-AF study is an international observational prospective survey assessing the control of AF and recruiting more than 5,600 patients across 21 countries. The distribution of $CHADS_2$ is also available from a GPRD data set on a UK AF population (data on file). This also offers a good representation of the distribution of scores from a 'real-life' UK population and is used in a sensitivity analysis (Section 10, Appendix 20). These score distributions are presented in Table 7.3

Table 7.3: Baseline $CHADS_2$ score distributions used in the model

CHADS-2 Score	% of population		
	ATHENA (base case) n=4628	RECORD-AF European scores (sensitivity analysis) [redacted]	GPRD [redacted]
0	3%	[redacted]	[redacted]
1	32%	[redacted]	[redacted]
2	36%	[redacted]	[redacted]
3	18%	[redacted]	[redacted]
4	8%	[redacted]	[redacted]
5	3%	[redacted]	[redacted]
6	1%	[redacted]	[redacted]

Due to the relatively low number of deaths occurring during the trial, use of a Weibull regression model to predict survival after the end of the trial would overestimate the number of remaining life-years. This would mean that patients would be predicted to survive longer than the actual average life expectancy for their respective age group, an effect that can often be observed in clinical trials with relatively low mortality during the study. All-cause mortality is instead estimated using UK all-cause mortality life tables produced by the government actuarial department. These tables estimate mortality for males and females by age. Patients with AF are often at risk of mortality from other risk factors reflected by their $CHADS_2$ score. The relationship between all-cause mortality and $CHADS_2$ score in patients with and without AF has been investigated by Henriksson et al (2009)[21]. The risk of all-cause mortality is adjusted for the $CHADS_2$ score based on Table 7.4 below. It is acknowledged that the general life tables include patients with AF and some double counting of effect will occur, however this is expected to be minimal and the results give a good proxy of survival in patients with AF and increasing $CHADS_2$ score.

Table 7.4: Increased risk of mortality based on $CHADS_2$ score

$CHADS_2$	RR of mortality
0	1.00(reference)
1	2.52
2	3.14
3	3.99
4	4.25
5	5.13
6	6.05

To estimate curves for time to mortality, a simulation was performed in which a cohort of patients were generated and their mortality times probabilistically sampled by sampling a random number and determining if it is less then the annual risk of all-cause mortality, adjusted using the AF OR for males or females. This sampled cohort of patients was then analysed in STATA and a risk equation generated based on age and sex. The coefficients for these equations are presented in Section 10 (Appendix 14).

As there were too few strokes in ATHENA to reliably model survival following a stroke, we relied on external sources. Two sources were used: Feigin and colleagues have recently reported the fatality rates after 21 days to one month based on a systematic review of 56 population based studies [Feigin 2009].[51] For studies published between 2000 and 2008, the most frequently reported fatality rates were in the range of 20 – 30%. We conservatively used the lower figure for mortality immediately post stroke. For following years, we used data published by Lekander et al [Lekander 2008] based on data on females from Swedish National Registries.[52] Conservatively, we applied the data for patient's life-time after stroke. This data is presented in Section 10 (Appendix 15). As patients age in the model, their all-cause risk of death (adjusted for AF patients) becomes higher than their risk of mortality post stroke. We assume therefore that the all-cause mortality risk is applied. This anomaly is likely to be due to the baseline characteristics of the patients in the Lekander study who are not as high risk of stoke or all-cause mortality as AF patients. This assumption is likely to underestimate the mortality associated with stroke in the model and bias against dronedarone which has the greatest reduction in risk of stroke.

Due to sample size considerations, mortality following CHF was also based on published data. [Shafazand 2009] [53] This data is also presented in Section 10 (Appendix 15).

The patient's treatment pathway is dependent on the patient's baseline characteristics, including their clinical AF type, which is used by the UK guidelines to determine the treatment sequence for the patient. Full details of the baseline treatment pathways are given in Table 7.1 in Section 7.2.3.

7.2.7.2 *How were the relative risks of disease progression estimated?*

We assume here that disease progression is represented by an event occurring, i.e. an incidence of stroke, CHF, ACS, AF recurrence or treatment discontinuation. The relative risks of disease progression were estimated using a MTC to synthesise the results of the formal systematic review (see Section 6.5).

A MTC model was estimated for the experimental treatments of dronedarone, amiodarone, sotalol, class 1c in comparison with control with data from all available relevant trials in AF. Randomised trials were included which compared the target treatments with control or with each other.

Summary details and results from the MTC as used in the economic evaluation are presented in Section 6.6 with further detail presented Section 10 (Appendices 5 to 8). A summary of these results is shown in Table 7.5 below.

Table 7.5: Odds ratios (95% CI) relative to control treatment reported in the MTC.

Treatment	**Parameter**			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

7.2.7.3 *Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?*

No intermediate outcome measures were modelled.

7.2.7.4 *Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?*

Individual AEs associated with each treatment are included in the economic model. Individual data was not available from the meta analysis or MTC therefore various sources have been used to populate the model. AE data for dronedarone was taken from pooled data from the clinical trials (DAFNE ADONIS, ERATO, EURIDIS, ATHENA) and DIONYSOS. Amiodarone data was taken from DIONYSOS. There was scarce data available for sotalol and the class 1c drugs and so the US summary of product characteristics (SPC) has been used to estimate the rate of adverse events. As flecainide represents nearly 90% of the class 1c UK market, we have utilised the individual adverse event rates from the flecainide SPC for class 1c in the model. The US SPC was used as this contained incidence rates for specific adverse events which were not included in the UK SPC. Adverse events included in the model are:

- Cardiac events (bradycardia, tachycardia, proarrhythmia)
- Eye events (photophobia, blurred vision)
- Fatigue
- Gastrointestinal (diarrhoea, nausea, vomiting)
- Hepatic events
- Hyperthyroidism
- Hypothyroidism
- Neurological events (tremor, sleep disorder)
- Pulmonary (dyspnea)
- Skin events (photosensitivity, rash etc).

As described in Section 7.2.6.1, adverse events are considered either short term where patients are assumed to incur a one off cost of treatment and utility decrement or life-time where they incur continuous costs and utility decrements for their remaining time in the model.

The adverse event rates used in the model are shown in Table 7.6 below and include the DIONYSOS results as this is a direct head-to-head RCT of dronedarone versus amiodarone. It is likely that the rates used in the model are underestimated for

amiodarone. Expert clinical opinion would suggest much higher adverse event rates in practice than is observed in clinical studies. The high rate of AEs is not reflected in the clinical trial data as clinicians chose patients carefully for inclusion in a study and as a result it is possible that the study does not reflect the AE profile reported by clinicians. Clinicians have stated that over the modelled treatment period the cumulative effect of AEs would increase over time, but again there is a lack of data to model this.

Table 7.6: Adverse event rates.

	Incidence rate			
Adverse event	[redacted]	[redacted]	**Sotalol[&]**	**Class 1c[&]**
Cardiac events (bradycardia, tachycardia, proarrhythmia)	[redacted]	[redacted]	15.00%	7.00%
Eye events (photophobia, blurred vision)	[redacted]	[redacted]	2.60%	15.90%
Gastrointestinal (diarrhoea, nausea, vomiting)	[redacted]	[redacted]	13.00%	8.90%
Fatigue	[redacted]	[redacted]	19.60%	7.70%
Hepatic events	[redacted]	[redacted]	0.00%	0.00%
Hyperthyroidism	[redacted]	[redacted]	2.60%	0.00%
Hypothyroidism	[redacted]	[redacted]	0.00%	0.00%
Neurological events (tremor, sleep disorder)	[redacted]	[redacted]	0.00%	4.70%
Pulmonary (interstitial lung disease)	[redacted]	[redacted]	0.00%	10.00%
Skin events (photosensitivity, rash etc)	[redacted]	[redacted]	0.00%	0.00%

** Source: Pooled data from DRI/3350/DAFNE (Dronedarone 400mg bid only), EFC3153/EURIDIS, FC4788/ADONIS, EFC4508/ERATO, EFC5555/ATHENA and DIONYSOS*
 # Source: DIONYSOS
& Source: SmPC

7.2.7.5 *Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?*

There was no requirement for the estimation of clinical parameters by expert opinion.

7.2.7.6 *What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?*

Expert opinion was required to estimate the proportion of patients that receive electrical and pharmacological cardioversion, percentage of ablation in the UK and whether patients remain on treatment when moving to permanent. Various UK clinicians were interviewed and all concurred with the assumptions (see Section 10 (Appendix 13)).

7.2.8 Measurement and valuation of health effects

7.2.8.1 *If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?*

Health effects are expressed in terms of life years and quality adjusted life years gained.

7.2.8.2 *Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.*

Health effects were measured for the patient's demographic characteristics (age and sex) and the patient's current health state (with or without symptomatic AF, post stroke, post CHF and post ACS). Utility scores were also measured for the effects of AEs. This encompasses those that will have a positive impact and a negative impact as a result of treatment.

7.2.8.3 *How were health effects measured and valued? Consideration should be given to all of the following:*

- *State whether the EQ-5D was used to measure HRQL or provide a description of the instrument/s used.*
- *Provide details of the population in which health effects were measured. Include information on recruitment of sample, sample size, patient characteristics and response rates.*
- *Were the data collected as part of a RCT? Refer to Section 5.3 as necessary and provide details of respondents.*
- *How were health effects valued? If taken from the published literature, state the source and describe how and why these values were selected. What other values could have been used instead?*
- *Was a mapping mechanism (or 'cross-walk') generated to estimate health-related utilities of patients in the trials? Provide details of the rationale for the analysis, the instruments used, the sample from which the data were derived and the statistical properties of the mapping mechanism.*

- *Were health states directly valued? If so, provide details of the rationale for the analysis, the HRQL measures that were valued, the population who produced the values and full details of the methods used. Explain the rationale for the analysis and the choice of instruments used.*

There was no quality of life data collected in any of the dronedarone clinical trials. Therefore utility weights for the different health states were based on data from the AFTER cohort (part of the Euro Heart Survey on AF undertaken by the European Society of Cardiology). To derive quality adjusted survival, utility weights were applied to patients' survival.[Berg 2008].[54] At baseline, 5050 patients enrolled in the Euro Heart Survey on AF had completed all five dimensions of the EQ-5D. After one year, survival status was known for 4192 patients, of which 95% patients were alive. Of these, 3045 had completed the EQ-5D. Patients' answers to the EQ-5D were translated into utilities via an algorithm developed for general population preferences in the UK, which is based on decision-analytic methods.

Utility scores are calculated based on the coefficients presented in Table 7.7 with example utility scores calculated and presented in Table 7.8.

Utility reductions are applied for the period of the disease in question. That is patients suffering a stroke or CHF have the utility reduction applied until death. Patients suffering from ACS are assumed to have their utility reduced during one year. These assumptions are supported by findings in non-AF populations, where stroke patients have no improvement over time, while patients with ACS move back to their initial values after a year [Lindgren 2006], [Lindgren 2008]. [55,56]

Table 7.7: Health state and event utility weights use in the model.

Factor	Coefficient	SD
[redacted]	[redacted]	[redacted]

Table 7.8: Example utility scores for different combinations of age, sex and AF related events.

Age	70	70	75	70	70	70	70
Sex	Male	Female	Male	Male	Male	Male	Male
AF symptoms	No	No	Yes	No	No	No	Yes
With Stroke	No	No	No	Yes	No	No	Yes
With CHF	No	No	No	No	Yes	No	Yes
With ACS	No	No	No	No	No	Yes	Yes
Utility	0.918	0.851	0.819	0.623	0.728	0.773	0.204

A literature review of quality of life data did not identify any utility specific AF treatment AE data (see Section 10 (Appendix 16)). Therefore a study was undertaken to describe common adverse events associated with atrial fibrillation treatments. This study utilised a survey to estimate societal utility values as no AF treatment specific utility data was available related to adverse events from the literature. AF base health state descriptions were produced based on EQ-5D Euro Heart Survey, with input from patients and clinicians. AE descriptions were added to the base health states so that associated disutility could be described. The health states described paroxysmal/persistent and permanent AF along with 14 adverse events. Interviews with five AF experienced clinicians and six AF patients were carried out to inform and assess the content and face validity of the health states as descriptions appropriate to AF. The final health states were then piloted for any difficulties in interpretation or comprehension, of which none emerged. In total, 127 members of the general public valued the health states in a time trade-off (TTO) interview and ranking task. The disutility of adverse events from the base atrial fibrillation states grouped by the event type from the clinical trials are shown in Table 7.9 [ISPOR poster accepted]. [57] Full details of this study are presented in Section 10 (Appendix 17).

Table 7.9: Utility decrements for treatment related adverse events

Adverse event type	**Paroxysmal**	**Permanent**
Cardiac events (bradycardia, tachycardia, proarrhythmia)	0.020	0.033
Eye events (photophobia, blurred vision)	0.080	0.080
Gastrointestinal (diarrhoea, nausea, vomiting)	0.070	0.065
Fatigue	0.040	0.050
Hepatic events	0.030	0.030
Neurological events (tremor, sleep disorder)	0.060	0.055
Skin events (photosensitivity, rash etc)	0.045	0.060

The AEs described in Section 7.2.7.4 are assigned one of the AE types from Table 7.8 and the rate of incidence presented in Table 7.6 used to apply a utility loss whilst on treatment. We assume that pulmonary, hyperthyroidism and hypothyroidism are permanent life-time illnesses and will incur continuous costs and utility loss. All other events are assumed to have a 28 day utility detriment and one-off cost. The weighted utility loss for each treatment type is shown in Table 7.10. For AEs that have more than one utility category, we assume the mean utility score across the categories. Where patients suffer multiple AEs it is assumed that utility decrements are independent and additive.

Table 7.10: Weighted utility loss for treatment related adverse events

Adverse event	Utility category	Weighted utility detriment			
		Dronedarone	**Amiodarone**	**Sotalol**	**Class 1c**
Permanent utility loss (applied to daily to all patients for life-time)					
Hyperthyroidism	Hyperthyroidism	0.0002	0.0013	0.0021	0.0000
Hypothyroidism	Hypothyroidism	0.0007	0.0039	0.0000	0.0000
Pulmonary (dyspnoea)	Pulmonary issues	0.0003	0.0000	0.0000	0.0170
Total*		**0.0012**	**0.0052**	**0.0021**	**0.00170**
One off utility loss (applied to all patients on treatment initiation)					
Cardiac events (bradycardia, tachycardia, proarrhythmia)	Fatigue, circulatory issues and dizziness	0.0001	0.0002	0.0004	0.0002
Eye events (photophobia, blurred vision)	Optical issues	0.0000	0.0001	0.0002	0.0010
Gastrointestinal (diarrhoea, nausea, vomiting)	Nausea and diarrhoea	0.0007	0.0004	0.0006	0.0004
Fatigue	Fatigue	0.0002	0.0001	0.0008	0.0003
Hepatic events	Liver deposits	0.0001	0.0001	0.0000	0.0000
Neurological events (tremor, sleep disorder)	Sleep disturbances and neuropathy	0.0000	0.0004	0.0000	0.0002
Skin events (photosensitivity, rash etc)	Rash and Dermatological changes	0.0001	0.0001	0.0000	0.0000
Total*		**0.0014**	**0.0014**	**0.0018**	**0.0021**

* Totals have been rounded up to 4 decimal points

7.2.8.4 *Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 6.2.11).*

There were no other generic or condition specific preference based measures used in the clinical trials.

7.2.8.5 *Were any health effects excluded from the analysis? If so, why were they excluded?*

No health effects were excluded from the analysis.

7.2.9 Resource identification, measurement and valuation

7.2.9.1 *What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)*

Drug costs

Daily costs of drugs were based on the British National Formulary 57 and are shown in Table 7.11 [www.bnf.org.uk].[58] Doses are based on the recommended dose stated in the intervention SPCs.

Table 7.11: Drug doses and costs used in the economic model.

Treatment	Dose (mg)	Pack cost	Tablets per pack	Tablet size (mg)	Daily cost
Dronedarone	400 b.i.d	£66.00	60 (30 day)	400	£2.30
Amiodarone	200	£1.42	28	200	£0.05
Sotalol	320	£2.21	28	160	£0.16
Class 1c*	n/a	n/a	n/a	n/a	£0.25

+ This is the assumed basecase cost. The final cost will be confirmed before launch.
* Although different doses and pack sizes are used for Flecainide and Propafenone, the daily cost work out the same.

Treatment initialisation

Dronedarone can be initiated by a specialist during an outpatient visit hence the price of an outpatient visit to the cardiologist has been assumed (National schedule of reference costs: TCLFASFF, Speciality code 320) [NHS reference costs].[59] After this, dronedarone requires a creatinine test 7 days after treatment initiation assumed to be completed within a routine GP visit. It is assumed that amiodarone, sotalol and class 1c all require hospitalisation for initiation [Sheffield formulary, 2008].[60] There is potentially an issue of double counting the cost of initialisation as patients are likely to change treatment as a result of an AF recurrence or an adverse event and may already be hospitalised. Clinician advice however, is that a patient would have any existing health issues resolved before instigating a change in treatment and thus the initialisation hospitalisation is independent of any other event.

Initialisation costs are summarised in Table 7.12

Table 7.12: Treatment initialisation costs used in the model*

Treatment	Initialisation cost*	Source
Dronedarone	£202.47#	UK reference cost: Consultant Led First Attendance Outpatient Face to Face code 320. plus GP visit
Amiodarone	£249	UK reference cost: Observation Wards - Not Leading to Admitted. Code: VEB07I
Sotalol	£249	UK reference cost: Observation Wards - Not Leading to Admitted. Code: VEB07I
Class 1c	£249	UK reference cost: Observation Wards - Not Leading to Admitted. Code: VEB07I

 # additional costs include GP visit and creatinine test.
**Costs inflated to 2008 prices using PSSRU inflator of 0.0454 [Curtis 2007]*

Monitoring costs

There are no requirements for monitoring with dronedarone outside of initiation follow-up (see draft SPC in Section 10 (Appendix 1)). Amiodarone requires that every 6 months a patient visits a GP for a thyroid function test (TFT), a Liver function test (LFT), a digoxin level test and an electrolyte test. Sotalol and class 1c's require an electrolyte test and an ECG every 6 months, also performed at the GP surgery. The unit cost of these test are shown in Table 7.13 and the total monitoring costs and assumptions for each treatment summarised in Table 7.14.

Table 7.13: Unit costs for monitoring requirements

Test	Cost	Source
Liver function test	£1.48	UK reference costs : DAP841 (TDAPS) – Biochemistry
Thyroid function test	£1.48	UK reference costs : DAP841 (TDAPS) – Biochemistry
Digoxin level test	£1.48	UK reference costs : DAP841 (TDAPS) – Biochemistry
Electrolyte test	£1.48	UK reference costs : DAP841 (TDAPS) – Biochemistry
ECG	£28.23	UK reference costs : DA01 ECG [12 Lead]
X-Ray	£5.64	UK reference costs : DAP840 (TDAPS) – Other
GP visit	£46	PSSRU 2007

Table 7.14: The cost of regular monitoring for each treatment in the model*

Treatment	Monitoring cost	Time applied	Monitoring requirements
Dronedarone	£0	n/a	n/a
Amiodarone	£57.56	Every 6 months on treatment	GP visit + LFT, TFT,DLT,electrolyte test + Xray
Sotalol	£75.71	Every 6 months on treatment	GP visit + ECG, electrolyte test
Class 1c	£75.71	Every 6 months on treatment	GP visit + ECG, electrolyte test

**Costs inflated to 2008 prices using PSSRU inflator of 0.0454 [Curtis 2007]*

Event costs

The cost of events occurring in the model are mostly taken from the literature. The costs incurred for a patient suffering a stroke are based on a publication by Youman et al [Youman 2003].[61] The study reports the 5-year cost of a stroke. We have allocated the acute care cost for the initial admission, £9,019 (inflating to 2008 prices using PSSRU inflation index [Curtis 2007])[62] and converted the remaining costs into a daily cost (£10 per day). This is likely to be a conservative estimate as there is evidence that the severity of stroke is greater in AF patients.

CHF costs are estimated from investigations by Stewart and colleagues, which estimate the total cost of CHF to the health care system [Stewart 2002].[63] The study includes both initial acute care cost, which are applied in the model on incidence of CHF, as well as post-discharge costs, secondary admissions and long-term nursing costs which are assumed as ongoing costs in the model. The costs are split for male

and female patients and show that the incidence is more than three fold for male patients than female patients, but the male ongoing cost is less.

Palmer and colleagues estimate the costs associated with ACS as part of a cost-effectiveness analysis of glycoprotein IIb/IIIa inhibitors. This cost is assumed to be incurred on incidence of ACS in the model [Palmer 2005].[64]

To estimate the cost of recurrent AF, we assumed that a proportion of patients will incur a recurrence severe enough to require hospitalisation. We assume this to be the same proportion of patients that have an AF hospitalisation in ATHENA (29.4% see Section 7.2.6 assumptions and justifications). The non-hospitalised AF patients are assumed to require only a GP visit and an outpatient cardiologist visit to receive a cardioversion attempt. The cost of an AF hospitalisation is based on the NHS reference cost for arrhythmia (HRG code: EB07I - arrhythmia or conduction disorders without CCs) [NHS reference costs 2006/7]. [59]

The assumed costs for clinical events in the model are summarised in Table 7.15 below.

Table 7.15: Incidence and ongoing costs incurred as the result of an event in the economic model.

Event	One off or daily cost	Cost	Source
Ablation	One off	£3,137	UK reference costs (HRG: EA29z)[59]
ACS	One off	£4,568	Palmer et al.[64]
AF hospitalisation	One off	£1,154	UK reference costs (HRG: EB07h and EB07i: weighted by number of FCE's)[59]
CHF incidence (females)	One off	£4,765	Stewart et al. EJHF 2002[63]
CHF ongoing (females)	Daily	£5	Stewart et al. EJHF 2002
CHF incidence (males)	One off	£3,938	Stewart et al. EJHF 2002
CHF ongoing (males)	Daily	£4	Stewart et al. EJHF 2002
Cardioversion	One off	£373	Boodhoo et al, 2004 [65]
Stroke incidence	One off	£8,803	Youman et al. Pharmacoeconomics 2003[61]
Stroke ongoing	Daily	£10	Youman et al. Pharmacoeconomics 2003

* Inflated to 2008 prices where appropriate using PSSRU inflation index of 0.04537

Adverse events

A proportion of AEs are serious enough to require hospitalisation. The rates of hospitalisation for each AE have been estimated by UK clinicians and are shown in Table 7.16. Costs for hospitalised patients are taken from UK NHS reference costs. For patients who are not hospitalised an outpatient consultant visit is assumed. The costs of management of short term AEs are applied as a one off cost on treatment initiation. AEs with life-time effects (pulmonary, hyperthyroidism and hypothyroidism) are assumed to require a GP visit every 6 months. The treatment related AE costs are summarised in Table 7.16 and the cost per treatment based on the incidence rate of adverse events from Table 7.6 are shown in Table 7.17.

Table 7.16: Total cost of treatment for adverse events included in the economic model.

Adverse Event	**Cost**
Hypothyroidism	£542.30
Hyperthyroidism	£552.00
Neurological events (tremor, sleep disorder)	£440.60
Skin events (photosensitivity)	£177.55
Eye events (photophobia, blurred vision)	£154.00
Gastrointestinal (diarrhea, nausea, vomiting)	£217.00
Hepatic events	£919.00
Cardiac events (bradychardia, tachycardia, proarrythmia)	£316.00
Pulmonary (interstitial lung disease)	£1010.80
Fatigue	£158.00

Table 7.17: One off treatment adverse event cost, applied on treatment initiation

Adverse Event	**Dronedarone**	**Amiodarone**	**Sotalol**	**Class 1c**
Cardiac events (bradycardia, tachycardia, proarrhythmia)	£12.01	£19.91	£47.40	£22.12
Eye events (photophobia, blurred vision)	£0.00	£3.08	£4.00	£24.49
Fatigue	£23.70	£11.69	£20.54	£14.06
Gastrointestinal (diarrhea, nausea, vomiting)	£5.21	£5.21	£42.53	£16.71
Hepatic events	£0.00	£11.03	£0.00	£0.00
Hyperthyroidism	£0.00	£8.83	£14.35	£0.00
Hypothyroidism	£0.00	£21.15	£0.00	£0.00
Neurological events (tremor, sleep disorder)	£0.00	£44.94	£0.00	£20.71
Pulmonary (dyspnea)	£54.58	£20.22	£30.32	£101.08
Skin events (photosensitivity, rash etc)	£6.39	£5.68	£0.00	£0.00
Total	**£101.89**	**£151.74**	**£159.15**	**£199.17**

7.2.9.2 *How were the resources measured?*

Health resource use is based on reported usage from the literature, clinician opinion and the rate of events observed in the clinical trials.

7.2.9.3 *Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?*

No. Disease progression is based on the results from ATHENA and evidence from the MTC. Health resource use was not available from the clinical trials and so is estimated from separate studies identified in the literature and clinician advice and applied to the clinical outcomes estimated from the trial data.

7.2.9.4 *Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).*

Treatment costs were included for patient's life-time and so include all relevant years.

7.2.9.5 *What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.*

Health resource use was not available from the clinical trials and so is estimated from separate studies identified in the literature and applied to the clinical outcomes estimated from the trial data. The sources used to values the resources are described in Section 7.2.9.1

7.2.9.6 *What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations*

with which the discount has been agreed for the whole of the NHS in England and Wales.

The unit cost for dronedarone used in the analysis is £2.30 per day of treatment. No price discounting has been included. The base case assumption is a price point in a range of prices being considered. Final confirmation of price will be confirmed in October 2009 after CHMP opinion.

7.2.9.7 *Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.*

No additional infrastructure is required for drug administration. It is anticipated that dronedarone will be administrated within the current outpatient setting.

7.2.9.8 *Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?*

Yes, resources were measured using UK published studies and valued using published NHS reference costs whenever possible.

7.2.9.9 *Were resource values indexed to the current price year?*

All resource use sources we inflated to 2008 prices where appropriate using the PSSRU pay and price index[62].

7.2.10 Time preferences

Yes. An annual discount rate of 3.5% was used for costs and for health benefits.

7.2.11 Sensitivity analysis

7.2.11.1 *Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.*

There were no alternative structural assumption investigated.

7.2.11.2 *Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.*

A full PSA analysis was undertaken. The distributions and their sources are presented in Section 10 (Appendix 19), with the results of the PSA presented in the Section 7.3.1.1.

7.3 Results

7.3.1 Base-case analysis

7.3.1.1 *What were the results of the base-case analysis?*

The base-case analysis consists of a comparison with the 5 possible treatment sequences defined by UK guidelines for patients recommended for a rhythm control strategy. In each scenario two positions are presented; dronedarone on top of standard baseline therapy for patients with multiple CV risk factors (corresponding to $CHADS_2$ ≥4) and dronedarone as a 1st line alternative AAD for all patients deemed appropriate for the introduction of an AAD. The treatment pathways are dependent on the patient's baseline characteristics.

The results show that dronedarone is cost effective at conventional threshold levels in all comparison. The one comparator that stands out across the subgroups due to a higher ICER, although still cost-effective, is the Class 1c agent group. This is largely due to a lack of evidence for the class 1c agents and the necessity to assume that all-cause mortality for these agents is the same as dronedarone. This assumption is conservative and examined in sensitivity analysis (see Section 10, Appendix 21).

Paroxysmal patient with no structural heart disease

The treatment pathway for these patients is for baseline therapy followed by either sotalol or class 1c 1st line anti-arrhythmic when an AAD is deemed needed and then amiodarone as 2nd line anti-arrhythmic.

Table 7.18: Cost effectiveness results for paroxysmal patients with no structural heart disease (dronedarone priced at £2.30 per day)

Pathway	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs	Cost per QALY gained
Position 1: – on top of standard baseline therapy ($CHADS_2 \geq 4$)					
Without Dronedarone	£2,484	4.00	£4,550	1.12	£4,070
With Dronedarone	£7,034	5.12			
Position 2: – Replacing Sotalol as 1st line AAD					
Without Dronedarone	£2,090	2.49	£3,901	2.17	£1,797
With Dronedarone	£5,992	4.66			
Position 3: – Replacing Class 1c as 1st line AAD					
Without Dronedarone	£3,448	4.25	£2,151	0.11	£20,143
With Dronedarone	£5,599	4.36			

Paroxysmal patient with coronary artery disease

The treatment pathway for these patients is for baseline therapy followed by either sotalol when an AAD is deemed needed and then amiodarone as 2nd line anti-arrhythmic.

Table 7.19: Cost effectiveness results for paroxysmal patients with coronary artery disease (dronedarone priced at £2.30 per day)

Pathway	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs	Cost per QALY gained
Position 1: – on top of standard baseline therapy ($CHADS_2 \geq 4$)					
Without Dronedarone	£2,867	3.91	£4,493	1.03	£4,365
With Dronedarone	£7,360	4.94			
Position 2: – Replacing Sotalol as 1st line AAD					
Without Dronedarone	£2,446	2.51	£3,906	2.07	£1,888
With Dronedarone	£6,352	4.58			

Paroxysmal patients with Left Ventricular Dysfunction.

The treatment pathway for these patients is for baseline therapy followed by amiodarone when an AAD is deemed needed. Patients in this scenario have better overall survival that the previous scenarios because they do not receive sotalol.

Table 7.20: Cost effectiveness results for paroxysmal patients with LVD (dronedarone priced at £2.30 per day)

Pathway	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs	Cost per QALY gained
Position 1: – on top of standard baseline therapy ($CHADS_2 \geq 4$)					
Without Dronedarone	£2,554	4.29	£4,545	1.23	£3,699
With Dronedarone	£7,099	5.52			
Position 2: – Replacing Amiodarone as 1st line AAD					
Without Dronedarone	£2,266	3.39	£3,923	1.86	£2,112
With Dronedarone	£6,188	5.25			

Persistent patient with no structural heart disease.

The treatment pathway for these patients is for baseline therapy followed by sotalol or class 1c when AAD is deemed needed and then amiodarone as 2nd line anti-arrhythmic.

Table 7.20: Cost effectiveness results for persistent patients without SHD – (dronedarone priced at £2.30 per day)

Pathway	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs	Cost per QALY gained
Position 1: –on top of standard baseline therapy ($CHADS_2 \geq 4$)					
Without Dronedarone	£3,569	4.04	£4,397	1.28	£3,424
With Dronedarone	£7,965	5.32			
Position 2: – Replacing sotalol as 1st line AAD					
Without Dronedarone	£2,473	2.50	£4,307	2.24	£1,927
With Dronedarone	£6,781	4.74			
Position 3: – Replacing class 1c as 1st line AAD					
Without Dronedarone	£3,924	4.29	£2,421	0.13	£18,239
With Dronedarone	£6,344	4.42			

Persistent patients with structural heart disease.

The treatment pathway for these patients is for baseline therapy followed by amiodarone when an AAD is deemed needed.

Table 7.22: Cost effectiveness results for persistent patients with SHD (dronedarone priced at £2.30 per day)

Pathway	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs	Cost per QALY gained
Position 1: – on top of standard baseline therapy ($CHADS_2 \geq 4$)					
Without Dronedarone	£4,033	4.19	£4,215	1.30	£3,254
With Dronedarone	£8,248	5.48			
Position 2: – Replacing amiodarone as 1st line AAD					
Without Dronedarone	£3,040	3.43	£4,509	1.75	£2,570
With Dronedarone	£7,549	5.18			

Detailed breakdown of clinical outcomes

The clinical outcomes for each scenario are summarised in Section 10 (Appendix 18). These show that dronedarone benefits from an increase in survival, a reduction in the costs of monitoring and treatment initialisation and reduced costs due to a reduced number of strokes. There are cost increases incurred however due to the higher number of AF recurrences incurred and the increased cost of drug acquisition. Patients on average are treated with dronedarone for 4.5 years.

7.3.2 Sensitivity analyses

Probabilistic Sensitivity Analysis (PSA)

A PSA has been run for each of the scenarios above to estimate the overall effect of the uncertainty surrounding each of the input parameters and to capture any interactions between parameter uncertainties. A table of all the parameters included in the PSA and the chosen distributions is presented in Section 10 (Appendix 19). The main uncertainty in the model is the curve fits to extrapolate clinical outputs of AF recurrence, stroke, CHF, ACS and treatment withdrawal. We assume that the covariance relationship between the parameters is non-linear and so sample curves using a Cholesky decomposition to handle the covariance. We assume that all other

parameters in the PSA are independent and are sampled by drawing a random number for each parameter.

Each PSA analysis consists of 1,000 runs of the model, each run with a sampled set of input variables from the input parameter distributions. The results of the PSA are summarised in Table 7.23. Scatter plots and CEACs from the analysis are provided in Section 10 (Appendix 19). The analysis shows that in nearly all scenarios, there is a good level of certainty that the ICER is below £20,000.

Table 7.23: Summary results from Probabilistic Sensitivity Analysis

	Probability cost effective at threshold	
Scenario	**£20,000 threshold**	**£30,000 threshold**
Paroxysmal patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	72%	84%
Paroxysmal patients No structural heart disease 1st line AAD (replacing Sotalol)	96%	98%
Paroxysmal patients No structural heart disease 1st line AAD (replacing class 1c)	50%	82%
Paroxysmal patients Coronary artery disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	74%	86%
Paroxysmal patients Coronary artery disease 1st line AAD (replacing sotalol)	95%	98%
Paroxysmal patients Left ventricle dysfunction, $CHADS_2 \geq 4$ (add on to baseline therapy)	74%	85%
Paroxysmal patients Left ventricle dysfunction 1st line AAD (replacing amiodarone)	94%	97%
Persistent patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	74%	84%
Persistent patients No structural heart disease 1st line AAD (replacing sotalol)	94%	98%
Persistent patients No structural heart disease 1st line AAD (replacing class 1c)	52%	84%
Persistent patients Structural heart disease, $CHADS_2 > 4$ (add on to baseline therapy)	74%	85%
Persistent patients Structural heart disease 1st line AAD (replacing amiodarone)	94%	97%

One-way sensitivity analysis

One way sensitivity analysis has been performed on the main variables in the model and demonstrate that the model is most sensitive to assumptions of mortality benefit for dronedarone and the cost of drug acquisition. The results of this analysis are shown in Section 10 (Appendix 20).

Mortality Benefit Sensitivity Analysis

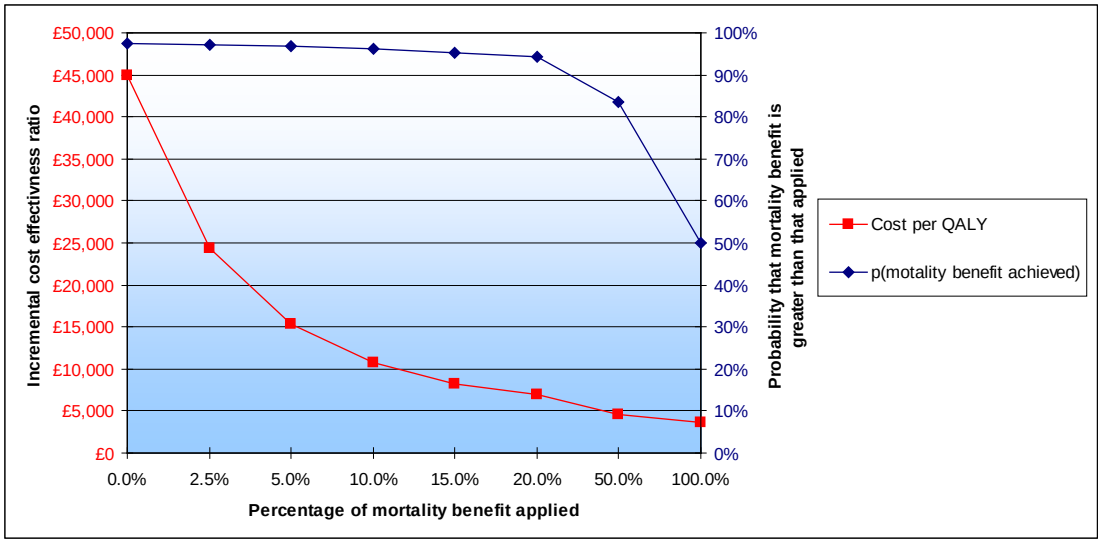
The main driver of cost effectiveness in the analysis is the all-cause mortality benefit demonstrated with dronedarone compared to the alternate anti-arrhythmic therapies. The presented sensitivity analysis shows the effect of varying the percentage of the mortality benefit incurred (on the logarithmic scale). The analysis also includes from the MTC the probability that the percentage of the mortality benefit is achieved. An example of the results of this analysis are shown in Figure 7.5 below. The graph shows that for persistent patients with structural heart disease, if no mortality benefit is assumed then the ICER increases to £45,000. However assuming that only 5% of the reported MTC mortality benefit is achieved results in an ICER that is below £15,000. This is associated with a 96% probability that a least 5% of the mortality benefit is achieved.

The full results of this analysis are shown in Section 10 (Appendix 21) and show that in all scenarios where dronedarone replaces either amiodarone, sotalol or base line therapy ($CHADS_2 \geq 4$), if at least 10% of the mortality benefit (and in most cases 5%) is assumed then the deterministic ICER is below £20,000.

This analysis shows the sensitivity of the results to mortality benefit, but provides confidence that only small amounts of benefit are required for dronedarone to be cost effective.

This sensitivity analysis includes an assumption that dronedarone has a mortality benefit over class 1c agents. There is a lack of usable evidence to assume mortality benefit, however if only 5% of the potential mortality benefit associated with amiodarone is given to class 1c agents, then dronedarone is shown to be cost effective.

Figure 7.5: Analysis of the effect on applying a proportion of the dronedarone mortality benefit and the probability of at least achieving the benefit.



Effect of applying different curve fits to data extrapolations

Section 10 (Appendix 14) shows the AIC and BIC for the potential distribution to model the extrapolation of clinical outcome data in the model. The base case assumption is that the curve with the lowest AIC is chosen. The effect of the curve choice is demonstrated in Section 10 (Appendix 13), which shows the effect on the ICER of choosing the curve with the 2nd lowest AIC.

Table 7.24: Curve fits for extrapolation of clinical outcome data

Clinical outcome	Best Fit Curve	2nd Best Curve Fit
AF recurrences	Exponential	Log-Normal
Treatment discontinuation	Gamma	Log-Normal
CHF	Weibull	Log-logistic
ACS	Exponential	Weibull
Stroke	Exponential	Weibull

7.3.3 Interpretation of economic evidence

7.3.3.1 *Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?*

There is little published economic evidence on the treatment in the UK of AF when it comes to anti-arrhythmic agents. This is largely due to the complexity of such analysis. The presented analysis has been validated by the manufacturer with UK

and international clinicians, whom have given support to the assumptions used. The model has also been validated against the largest dronedarone trial, ATHENA and so has face validity and credence. Results of this analysis are available on request.

7.3.3.2 *Is the economic evaluation relevant to all groups of patients who could potentially use the technology?*

Dronedarone could potentially be used by patients with a $CHADS_2 < 4$ in the on top of baseline therapy position that we have presented for patients with a $CHADS_2 \geq 4$. However there is has been no significant all-cause mortality benefit demonstrated in these patients and thus no analysis is presented.

8 Assessment of factors relevant to the NHS and other parties

See Section 10 (Appendix 22)

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10 Appendices (see separate document)

1 Appendices

1.1 Appendix 1: Draft Summary of Product Characteristics

1.2 Appendix 2: Search strategy for section 6, clinical effectiveness

1.3 Appendix 3: DIONYSOS Clinical Study Report (Highly Confidential)

1.4 Appendix 4: Search strategy for meta-analysis and MTC

1.5 Appendix 5: Summary of meta-analysis and MTC results and references for AF recurrence

1.6 Appendix 6: Summary of meta-analysis and MTC results and references for all-cause mortality

1.7 Appendix 7: Summary of meta-analysis and MTC results and references for treatment discontinuation

1.8 Appendix 8: Summary of meta-analysis and MTC results and references for Stroke

1.9 Appendix 9: Summary of meta-analysis and MTC results and references for SAEs

1.10 Appendix 10: Search strategy for health economic evaluations of dronedarone

1.11 Appendix 11: Within model decision trees

Appendix 20: Sensitivity analysis

This appendix presents the results of various sensitivity analyses that are detailed in the main submission. The analyses considered are:

- Varying the acquisition price of dronedarone across the expected price range (£2.20 - £2.50)
- Running subgroup analysis based on $CHADS_2$ scores for cohorts of patients with the $CHADS_2$ scores 0 to 6.
- Using different sources for the distribution of $CHADS_2$ score
- Effect on the cost effectiveness of varying the model time horizon
- Running a subgroup analysis for patients aged 65 to show the cost effectiveness in a younger cohort of patients
- Running subgroup analysis examining the effect of gender on the cost effectiveness.

Full univariate analysis has not been feasible given the long run time of the model. Therefore an analysis has been performed that groups variables together to demonstrate which have the greatest impact on the sensitivity. In each analysis the lower end of confidence interval for all the variables is run and then for the upper confidence interval. The variable groups that are considered are:

- Mortality treatment effect
- Stroke treatment effect
- Treatment discontinuation treatment effect
- Adverse event rates (varied by +/- 20%)
- Costs excluding dronedarone acquisition price (where no range available, varied by +/- 20%).
- Cost of dronedarone acquisition
- Utilities (where no range available, varied by +/- 20%)

The analyses have been run and the results presented in tornado diagrams at the end of the appendix.

Analysis 1: Impact of varying the acquisition price of dronedarone

It is anticipated that dronedarone will be priced between £2.20 and £2.50. This range is examined for each of the scenarios in the model.

Scenario	ICER at dronedarone price	
	£2.20	**£2.50**
Paroxysmal patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,922	£4,365
Paroxysmal patients No structural heart disease 1st line AAD (replacing Sotalol)	£1,730	£1,931
Paroxysmal patients No structural heart disease 1st line AAD (replacing class 1c)	£18,849	£22,729
Paroxysmal patients Coronary artery disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£4,213	£4,671
Paroxysmal patients Coronary artery disease 1st line AAD (replacing sotalol)	£1,821	£2,023
Paroxysmal patients Left ventricle dysfunction, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,487	£3,865
Paroxysmal patients Left ventricle dysfunction 1st line AAD (replacing amiodarone)	£2,034	£2,268
Persistent patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,565	£3,966
Persistent patients No structural heart disease 1st line AAD (replacing Sotalol)	£1,862	£2,057
Persistent patients No structural heart disease 1st line AAD (replacing class 1c)	£17,021	£20,313
Persistent patients Structural heart disease, $CHADS_2 > 4$ (add on to baseline therapy)	£3,137	£3,487
Persistent patients Structural heart disease 1st line AAD (replacing amiodarone)	£2,493	£2,723

Analysis 2: Effect of varying CHADS score

The model is run for cohorts of patients all with the same $CHADS_2$ ranging from 0 to 6. Patients with higher $CHADS_2$ scores are at risk of increased mortality and morbidity.

Scenario	Base case	$CHADS_2$ score						
		0	1	2	3	4	5	6
Paroxysmal patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£4,070	£5,174	£4,986	£4,767	£4,555	£4,348	£4,155	£3,928
Paroxysmal patients No structural heart disease 1st line AAD (replacing Sotalol)	£1,797	£1,770	£1,894	£2,013	£2,128	£2,248	£2,365	£2,480
Paroxysmal patients No structural heart disease 1st line AAD (replacing class 1c)	£20,143	£17,554	£18,309	£19,055	£19,810	£20,550	£21,301	£22,046
Paroxysmal patients Coronary artery disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£4,365	£5,549	£5,331	£5,112	£4,889	£4,668	£4,442	£4,213
Paroxysmal patients Coronary artery disease 1st line AAD (replacing sotalol)	£1,888	£1,860	£2,065	£2,261	£2,454	£2,662	£2,856	£3,048
Paroxysmal patients Left ventricle dysfunction, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,699	£4,702	£4,524	£4,330	£4,152	£3,951	£3,771	£3,570
Paroxysmal patients Left ventricle dysfunction 1st line AAD (replacing amiodarone)	£2,112	£1,415	£1,684	£1,943	£2,191	£2,464	£2,715	£2,961
Persistent patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,424	£4,353	£4,185	£4,008	£3,832	£3,664	£3,489	£3,305
Persistent patients No structural heart disease 1st line AAD (replacing Sotalol)	£1,927	£1,870	£2,013	£2,140	£2,267	£2,396	£2,521	£2,645
Persistent patients No structural heart disease 1st line AAD (replacing class 1c)	£18,239	£16,045	£16,811	£17,591	£18,360	£19,120	£19,880	£20,643
Persistent patients Structural heart disease, $CHADS_2 > 4$ (add on to baseline therapy)	£3,254	£4,137	£3,983	£3,819	£3,650	£3,484	£3,321	£3,140
Persistent patients Structural heart disease 1st line AAD (replacing amiodarone)	£2,570	£1,722	£2,046	£2,352	£2,675	£2,995	£3,309	£3,603

Analysis 3: Different sources for the distribution of $CHADS_2$ scores.

There are three potential sources for the distribution of $CHADS_2$ score. These are ATHENA which is used in the base case, RECORD-AF and the GPRD (see section 7.2.7). These are examined in the sensitivity analysis below.

Scenario	$CHADS_2$ distribution source		
	ATHENA	**RECORD AF**	**GPRD**
Paroxysmal patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£4,070	£3,680	£3,883
Paroxysmal patients No structural heart disease 1st line AAD (replacing Sotalol)	£1,797	£1,591	£1,743
Paroxysmal patients No structural heart disease 1st line AAD (replacing class 1c)	£20,143	£17,960	£19,215
Paroxysmal patients Coronary artery disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£4,365	£3,897	£4,169
Paroxysmal patients Coronary artery disease 1st line AAD (replacing sotalol)	£1,888	£1,677	£1,818
Paroxysmal patients Left ventricle dysfunction, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,699	£3,333	£3,526
Paroxysmal patients Left ventricle dysfunction 1st line AAD (replacing amiodarone)	£2,112	£1,903	£2,018
Persistent patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,424	£3,078	£3,253
Persistent patients No structural heart disease 1st line AAD (replacing Sotalol)	£1,927	£1,701	£1,857
Persistent patients No structural heart disease 1st line AAD (replacing class 1c)	£18,239	£16,297	£17,348
Persistent patients Structural heart disease, $CHADS_2 > 4$ (add on to baseline therapy)	£3,254	£2,891	£3,083
Persistent patients Structural heart disease 1st line AAD (replacing amiodarone)	£2,570	£2,288	£2,465

Analysis 4: Effect of fitting the second choice curve based on the AIC criteria

Scenario	Curve choice	
	Best fit	**2nd best fit**
Paroxysmal patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£4,070	£4,356
Paroxysmal patients No structural heart disease 1st line AAD (replacing Sotalol)	£1,797	£1,974
Paroxysmal patients No structural heart disease 1st line AAD (replacing class 1c)	£20,143	£19,761
Paroxysmal patients Coronary artery disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£4,365	£4,754
Paroxysmal patients Coronary artery disease 1st line AAD (replacing sotalol)	£1,888	£1,973
Paroxysmal patients Left ventricle dysfunction, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,699	£3,144
Paroxysmal patients Left ventricle dysfunction 1st line AAD (replacing amiodarone)	£2,112	£2,346
Persistent patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,424	£3,541
Persistent patients No structural heart disease 1st line AAD (replacing Sotalol)	£1,927	£2,342
Persistent patients No structural heart disease 1st line AAD (replacing class 1c)	£18,239	£20,456
Persistent patients Structural heart disease, $CHADS_2 > 4$ (add on to baseline therapy)	£3,254	£3,645
Persistent patients Structural heart disease 1st line AAD (replacing amiodarone)	£2,570	£2,633

Analysis 5: Effect on the cost effectiveness of varying the model time horizon

The model is run for 1 year up to lifetime to determine the effect of shorter time horizons.

Scenario	Model years				
	1	**3**	**5**	**7**	**10**
Paroxysmal patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£86,627	£11,862	£6,000	£4,580	£4,070
Paroxysmal patients No structural heart disease 1st line AAD (replacing Sotalol)	£6,966	£4,549	£2,301	£2,022	£1,797
Paroxysmal patients No structural heart disease 1st line AAD (replacing class 1c)	£40,937	£32,045	£26,997	£22,667	£20,143
Paroxysmal patients Coronary artery disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£92,906	£12,722	£6,435	£4,912	£4,365
Paroxysmal patients Coronary artery disease 1st line AAD (replacing sotalol)	£7,319	£4,779	£2,418	£2,125	£1,888
Paroxysmal patients Left ventricle dysfunction, $CHADS_2 \geq 4$ (add on to baseline therapy)	£78,731	£10,781	£5,453	£4,163	£3,699
Paroxysmal patients Left ventricle dysfunction 1st line AAD (replacing amiodarone)	£16,237	£3,774	£2,611	£2,326	£2,112
Persistent patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£72,877	£9,979	£5,048	£3,853	£3,424
Persistent patients No structural heart disease 1st line AAD (replacing Sotalol)	£7,470	£4,549	£2,467	£2,168	£1,927
Persistent patients No structural heart disease 1st line AAD (replacing class 1c)	£37,067	£29,785	£24,445	£20,524	£18,239
Persistent patients Structural heart disease, $CHADS_2 > 4$ (add on to baseline therapy)	£69,259	£9,484	£4,797	£3,662	£3,254
Persistent patients Structural heart disease 1st line AAD (replacing amiodarone)	£19,758	£4,592	£3,177	£2,897	£2,570

Analysis 6: Varying the Mortality benefit

The model is run varying the mortality benefit from the lower 95% confidence interval of the comparators vs the upper CI of dronedarone (minimum benefit) to the upper 95% confidence interval of the comparators vs. the minimum 95% confidence interval of dronedarone (maximum benefit)

	ICER based on Mortality benefit	
Scenario	**Upper 95% CI (Maximum benefit)**	**Lower 95% CI (Minimum benefit)**
Paroxysmal patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,699	£16,985
Paroxysmal patients No structural heart disease 1st line AAD (replacing Sotalol)	£1,434	£2,413
Paroxysmal patients No structural heart disease 1st line AAD (replacing class 1c)	£20,143	£20,143
Paroxysmal patients Coronary artery disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,528	£15,286
Paroxysmal patients Coronary artery disease 1st line AAD (replacing sotalol)	£1,556	£2,581
Paroxysmal patients Left ventricle dysfunction, $CHADS_2 \geq 4$ (add on to baseline therapy)	£2.981	£14,297
Paroxysmal patients Left ventricle dysfunction 1st line AAD (replacing amiodarone)	£1,235	Dominated
Persistent patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£2,785	£14352
Persistent patients No structural heart disease 1st line AAD (replacing Sotalol)	£1,574	£2,974
Persistent patients No structural heart disease 1st line AAD (replacing class 1c)	£18,239	£18,239
Persistent patients Structural heart disease, $CHADS_2 > 4$ (add on to baseline therapy)	£2,446	£14,046
Persistent patients Structural heart disease 1st line AAD (replacing amiodarone)	£1,248	Dominated

Analysis 7: Varying the starting age of patient

A sensitivity analysis has been run for a younger cohort of patients, all with an age of 65.

Scenario	ICER varying starting age	
	Age = 72	**Age = 65**
Paroxysmal patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£4,070	£3,665
Paroxysmal patients No structural heart disease 1st line AAD (replacing Sotalol)	£1,797	£1,625
Paroxysmal patients No structural heart disease 1st line AAD (replacing class 1c)	£20,143	£18,215
Paroxysmal patients Coronary artery disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£4,365	£3,943
Paroxysmal patients Coronary artery disease 1st line AAD (replacing sotalol)	£1,888	£1,703
Paroxysmal patients Left ventricle dysfunction, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,699	£3,342
Paroxysmal patients Left ventricle dysfunction 1st line AAD (replacing amiodarone)	£2,112	£1,897
Persistent patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,424	£3,050
Persistent patients No structural heart disease 1st line AAD (replacing Sotalol)	£1,927	£1,731
Persistent patients No structural heart disease 1st line AAD (replacing class 1c)	£18,239	£16,394
Persistent patients Structural heart disease, $CHADS_2 > 4$ (add on to baseline therapy)	£3,254	£2,935
Persistent patients Structural heart disease 1st line AAD (replacing amiodarone)	£2,570	£2,313

Analysis 8: The effect of gender

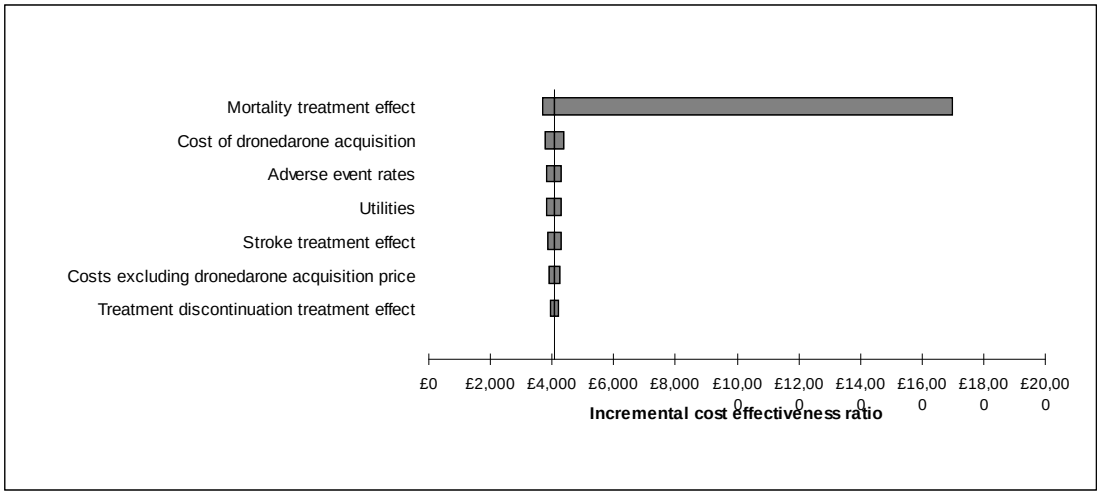
A sensitivity analysis has been run for a cohort of all male patients and all female patients.

Scenario	ICER varying gender	
	Males	**Females**
Paroxysmal patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,868	£4,170
Paroxysmal patients No structural heart disease 1st line AAD (replacing Sotalol)	£1,708	£1,841
Paroxysmal patients No structural heart disease 1st line AAD (replacing class 1c)	£19,143	£20,638
Paroxysmal patients Coronary artery disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£4,148	£4,472
Paroxysmal patients Coronary artery disease 1st line AAD (replacing sotalol)	£1,794	£1,934
Paroxysmal patients Left ventricle dysfunction, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,515	£3,790
Paroxysmal patients Left ventricle dysfunction 1st line AAD (replacing amiodarone)	£2,007	£2,164
Persistent patients No structural heart disease, $CHADS_2 \geq 4$ (add on to baseline therapy)	£3,254	£3,508
Persistent patients No structural heart disease 1st line AAD (replacing Sotalol)	£1,831	£1,974
Persistent patients No structural heart disease 1st line AAD (replacing class 1c)	£17,334	£18,687
Persistent patients Structural heart disease, $CHADS_2 > 4$ (add on to baseline therapy)	£3,092	£3,334
Persistent patients Structural heart disease 1st line AAD (replacing amiodarone)	£2,442	£2,633

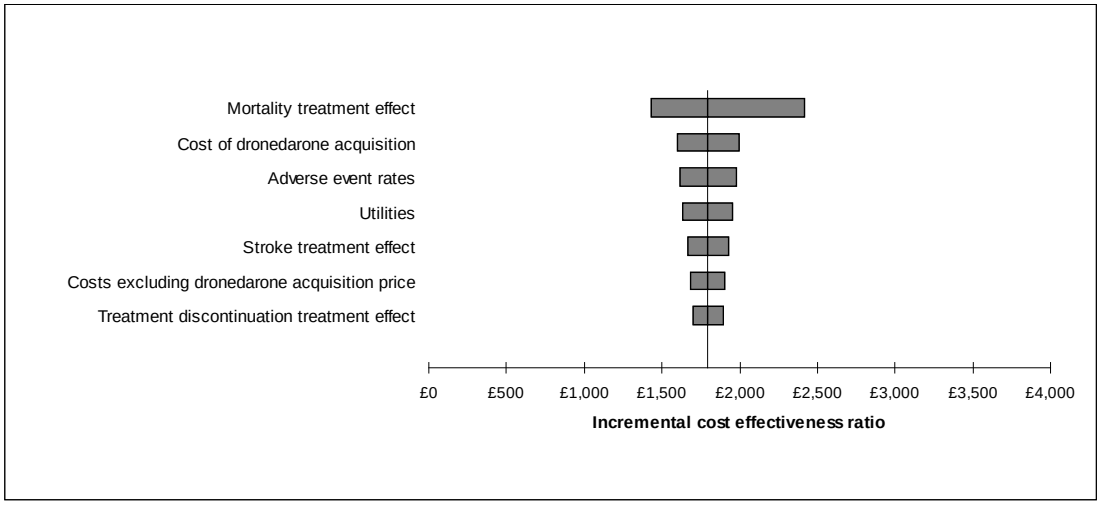
Tornado diagrams showing univariate analyses.

Paroxysmal patient with no structural heart disease

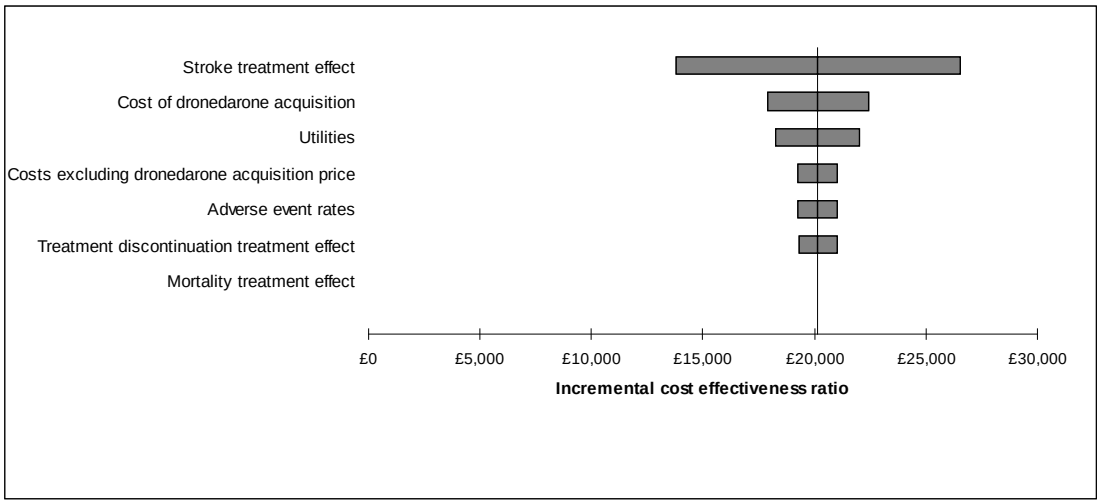
Position 1: – In addition to baseline therapy (CHADS2 ≥ 4)



Position 2: – Replacing Sotalol as 1st line AAD

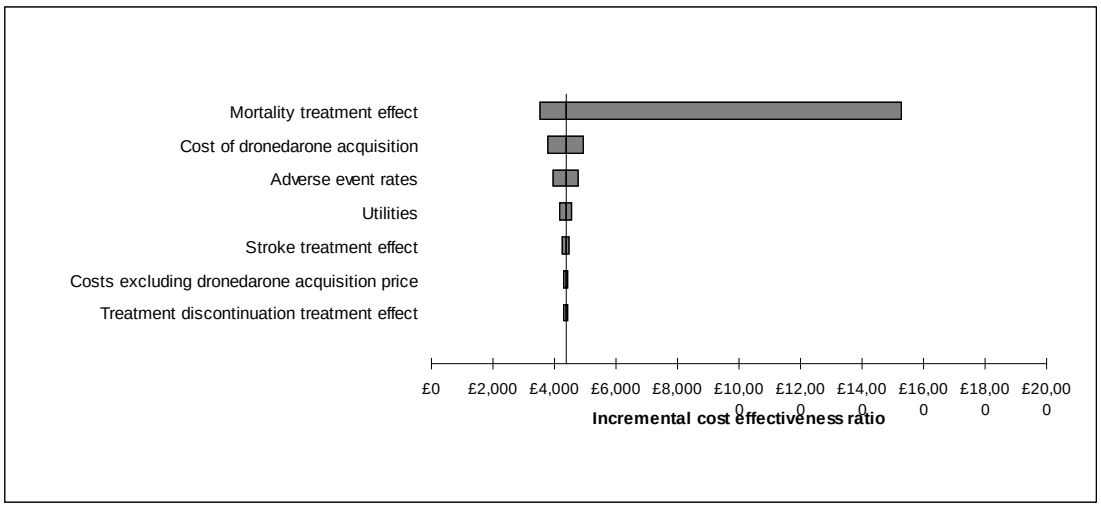


Position 3: – Replacing Class 1c as 1st line AAD

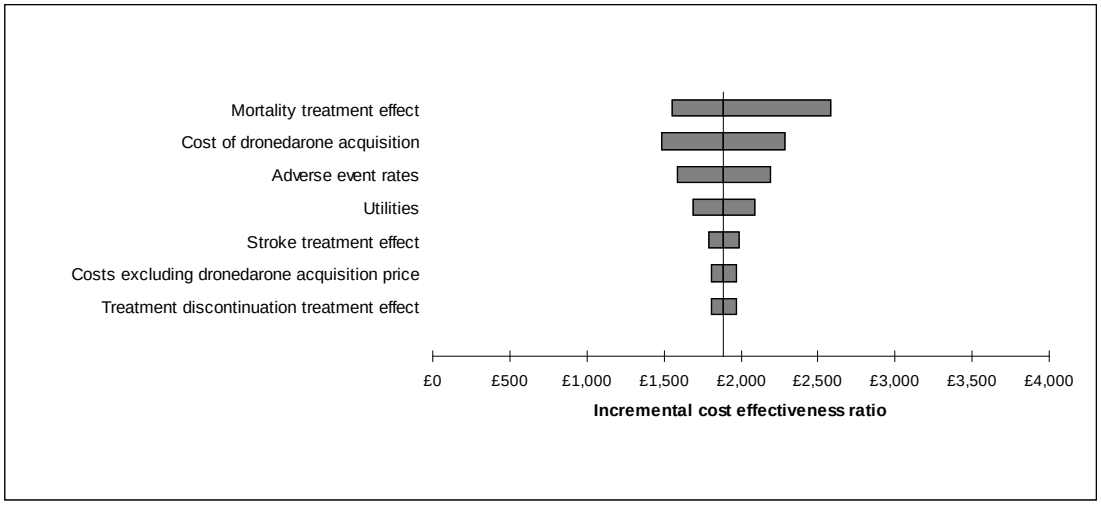


Paroxysmal patient with coronary artery disease

Position 1: – In addition to baseline therapy (CHADS2 ≥ 4)

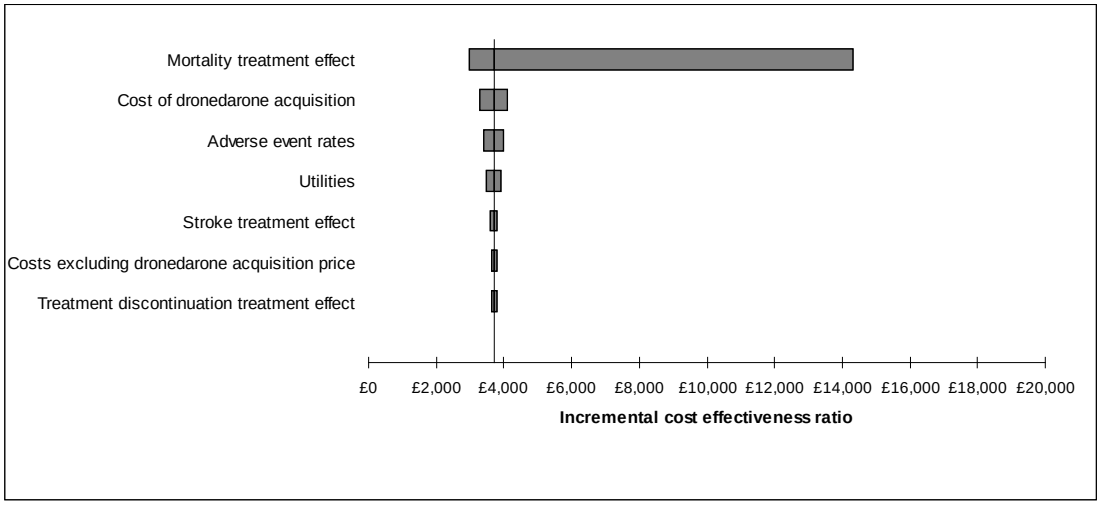


Position 2: – Replacing Sotalol as 1st line AAD

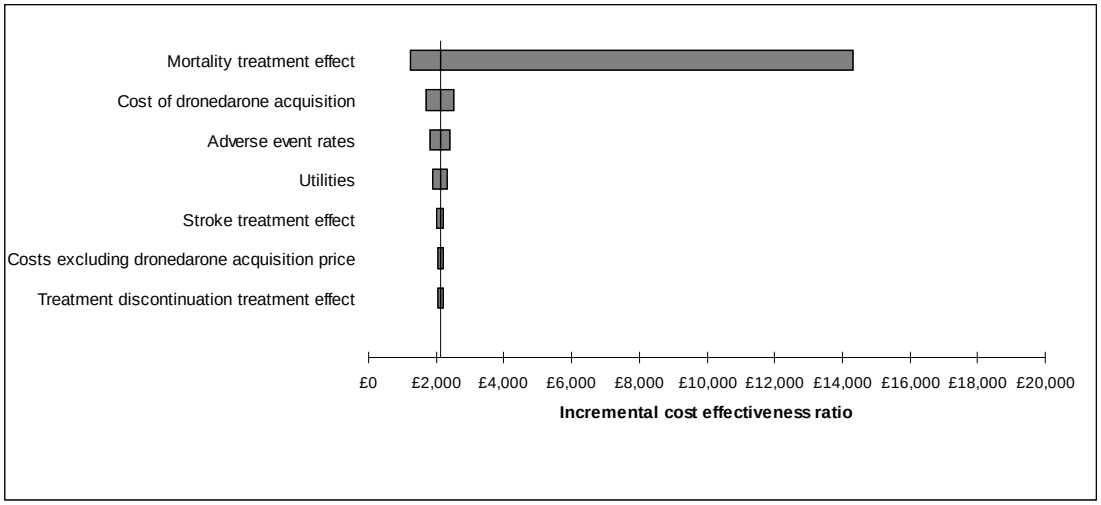


Paroxysmal patients with Left Ventricular Dysfunction.

Position 1: – In addition to baseline therapy (CHADS2 ≥ 4)

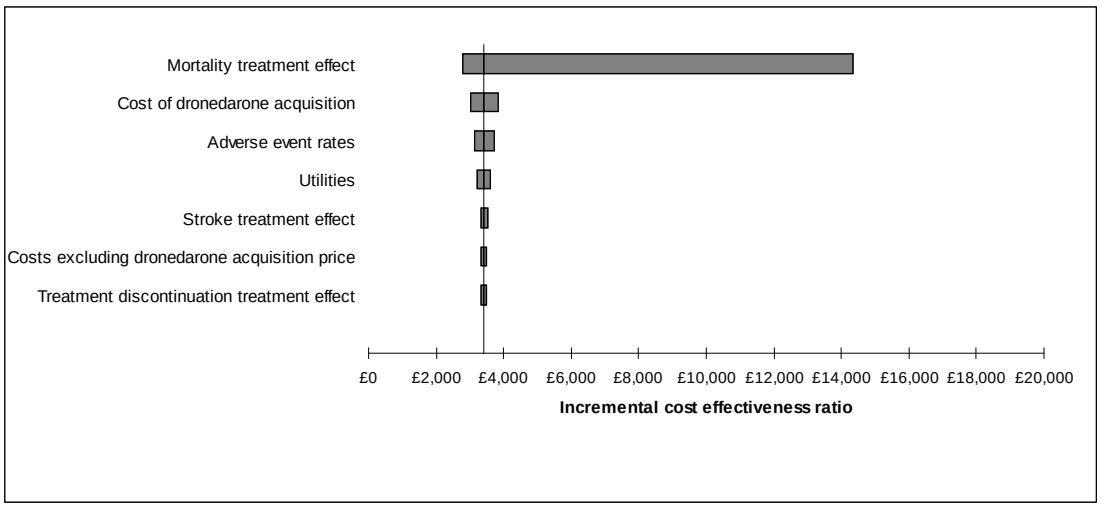


Position 2: – Replacing Amiodarone as 1st line AAD

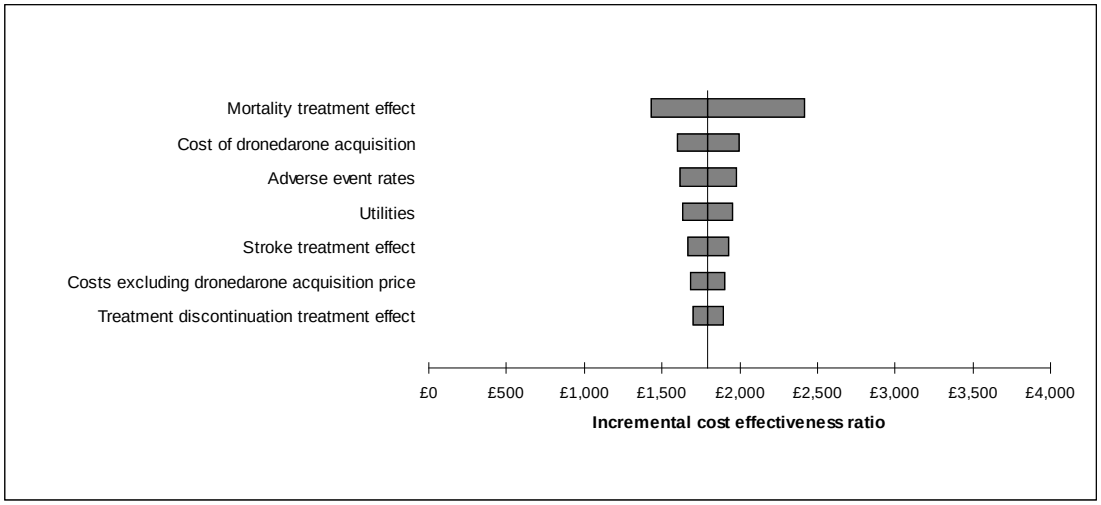


Persistent patient with no structural heart disease.

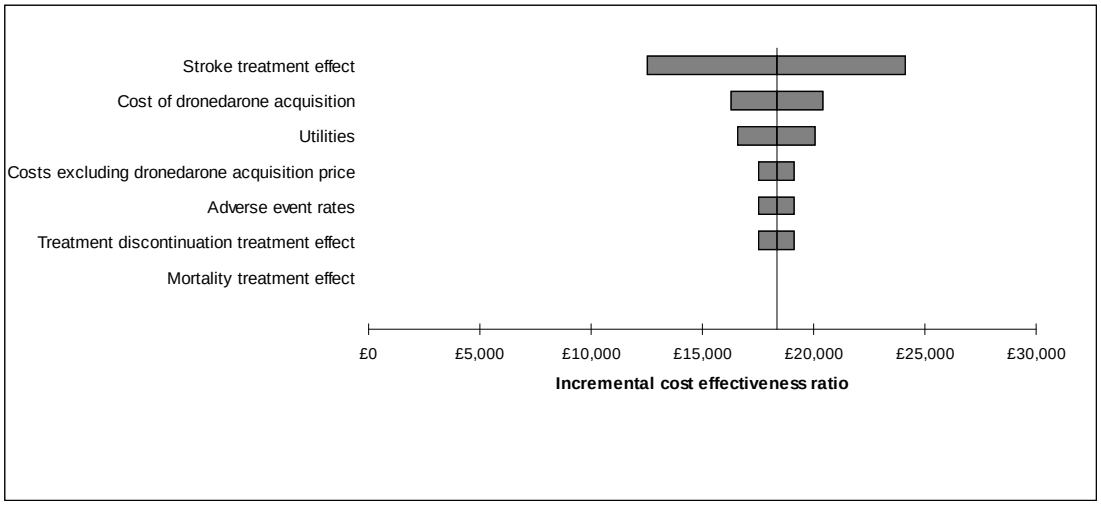
Position 1: – In addition to baseline therapy (CHADS2 ≥ 4)



Position 2: – Replacing sotalol as 1st line AAD

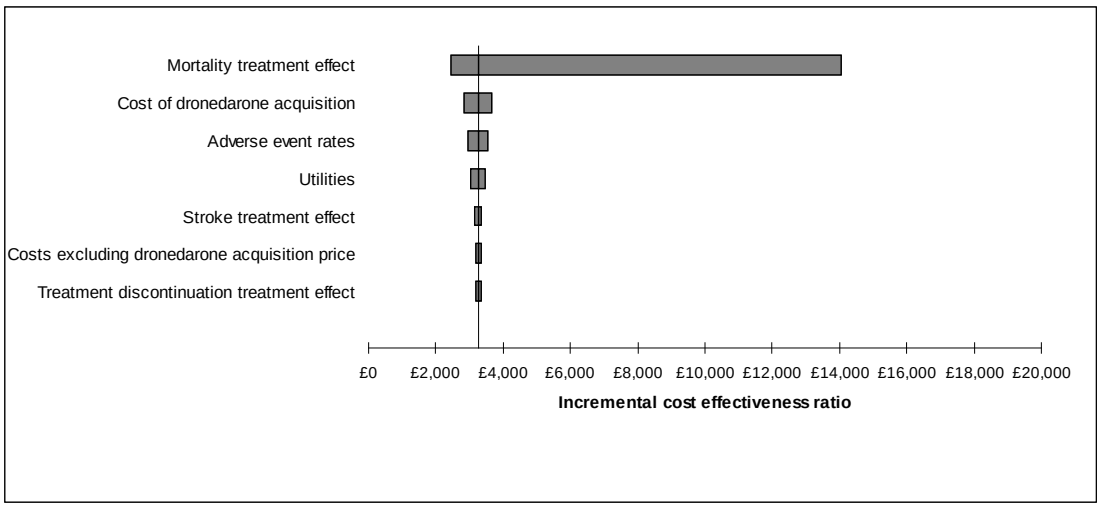


Position 3: – Replacing Class 1c as 1st line AAD

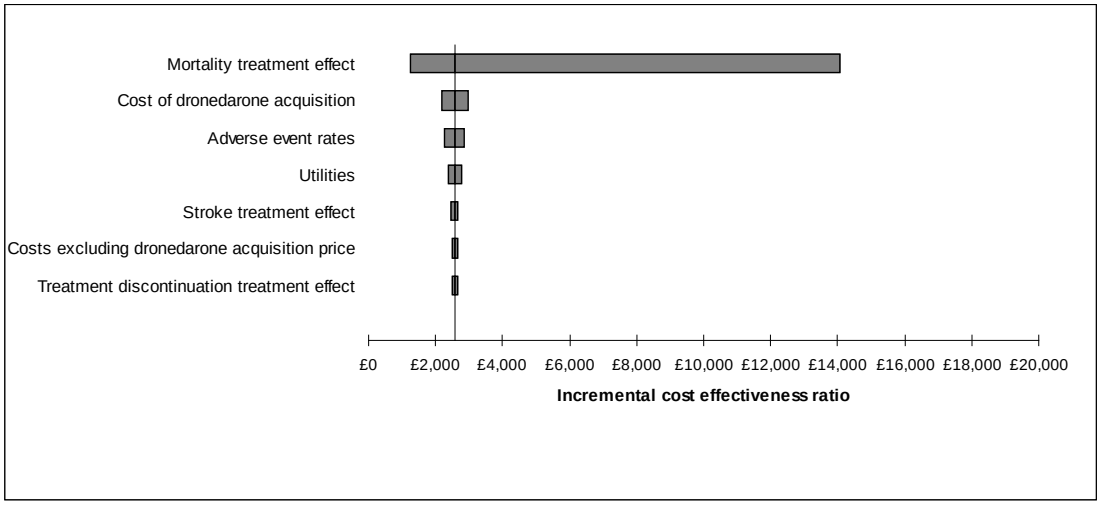


Persistent patients with structural heart disease.

Position 1: – In addition to baseline therapy (CHADS2 ≥ 4)



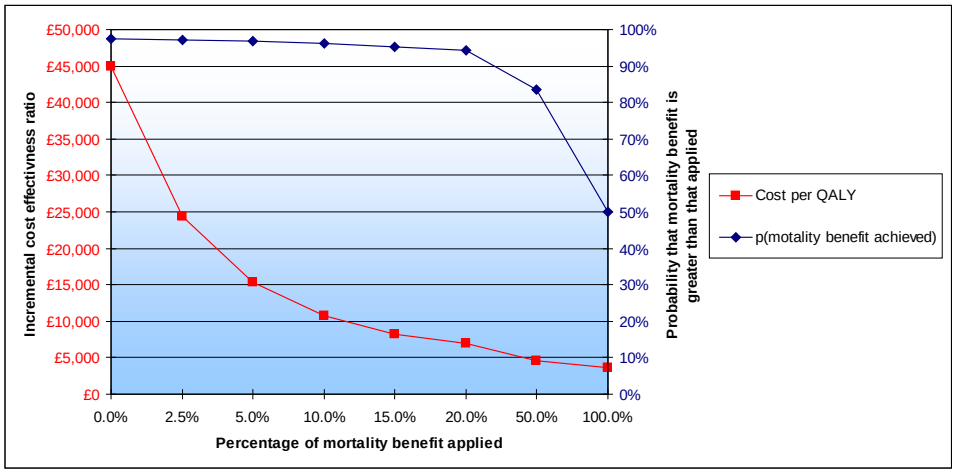
Position 2: – Replacing amiodarone as 1st line AAD



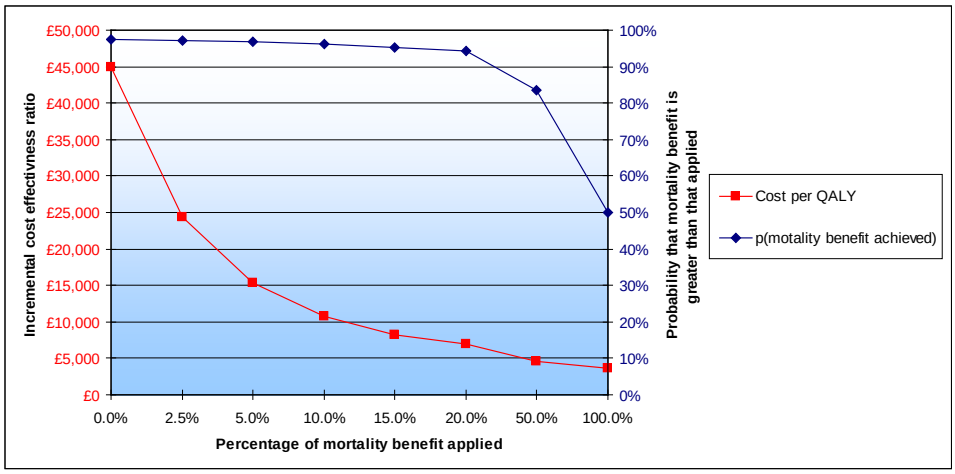
Appendix 21 – Mortality benefit results

Paroxysmal patient with no structural heart disease

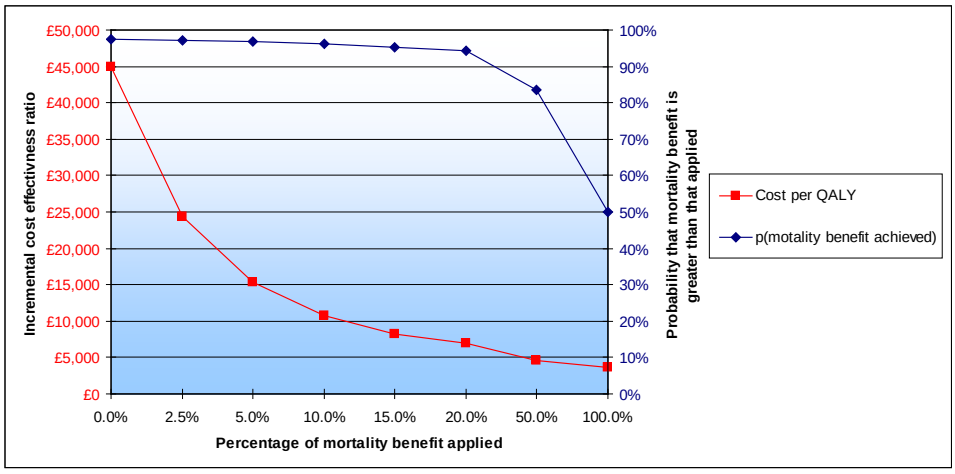
Position 1: – In addition to baseline therapy (CHADS2 ≥ 4)



Position 2: – Replacing Sotalol as 1st line AAD

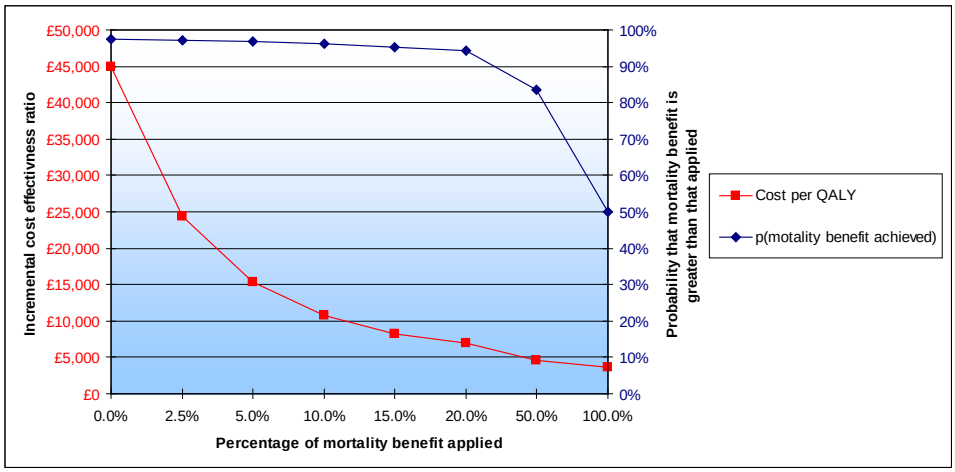


Position 3: – Replacing Class 1c as 1st line AAD

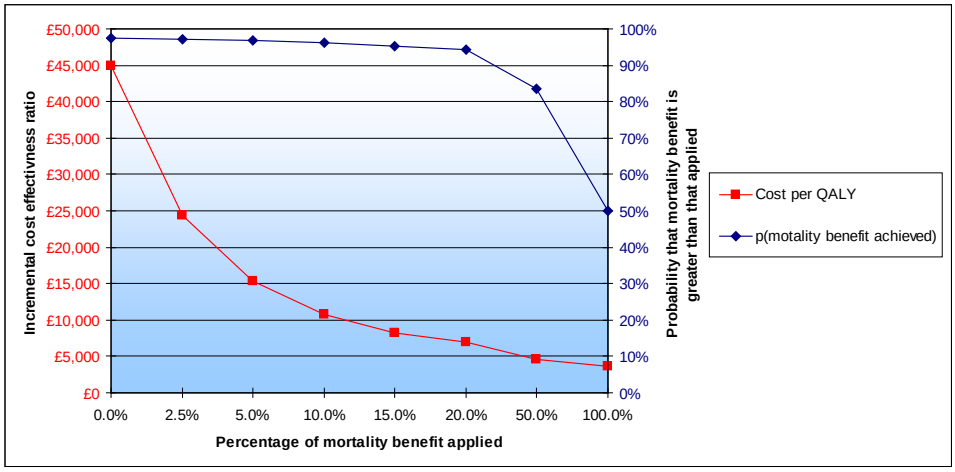


Paroxysmal patient with coronary artery disease

Position 1: – In addition to baseline therapy (CHADS2 ≥ 4)

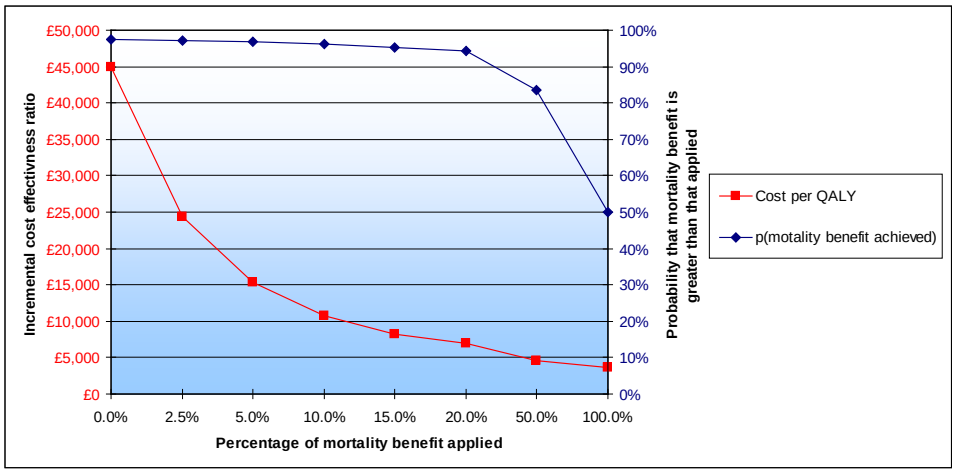


Position 2: – Replacing Sotalol as 1st line AAD

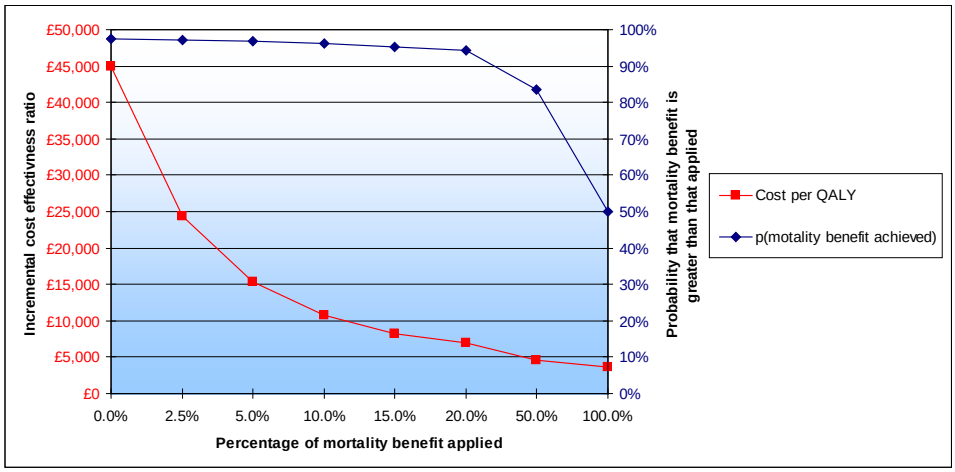


Paroxysmal patients with Left Ventricular Dysfunction.

Position 1: – In addition to baseline therapy (CHADS2 ≥ 4)

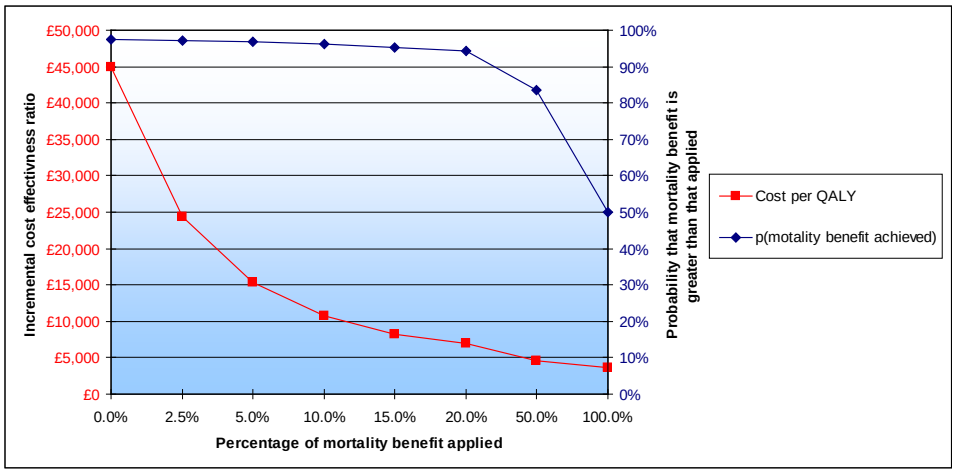


Position 2: – Replacing Amiodarone as 1st line AAD

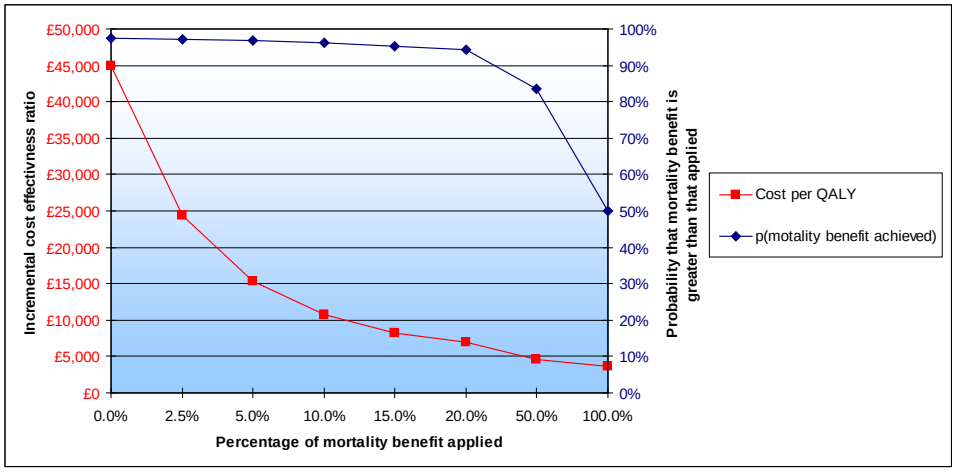


Persistent patient with no structural heart disease.

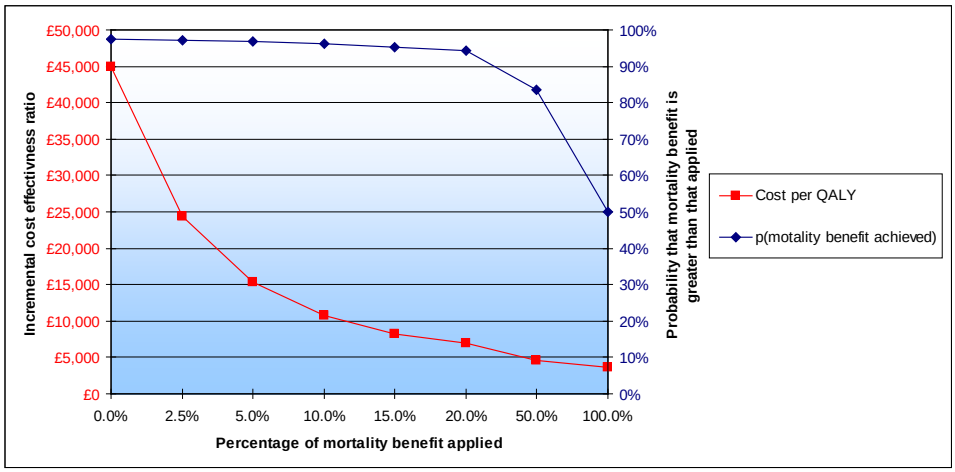
Position 1: – In addition to baseline therapy (CHADS2 ≥ 4)



Position 2: – Replacing sotalol as 1st line AAD

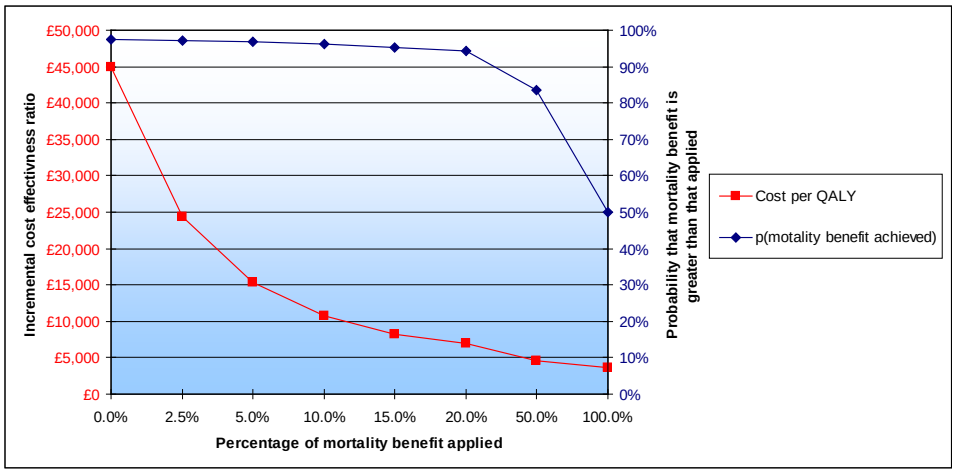


Position 3: – Replacing class 1c as 1st line AAD



Persistent patients with structural heart disease.

Position 1: – In addition to baseline therapy (CHADS2 ≥ 4)



Position 2: – Replacing amiodarone as 1st line AAD