

# Cost-effectiveness of dronedarone and standard of care compared with standard of care alone: US results of an ATHENA lifetime model

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**Background:** The first antiarrhythmic drug to demonstrate a reduced rate of cardiovascular hospitalization in atrial fibrillation/flutter (AF/AFL) patients was dronedarone in a placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patients with Atrial fibrillation/atrial flutter (ATHENA trial). The potential cost-effectiveness of dronedarone in this patient population has not been reported in a US context. This study assesses the cost-effectiveness of dronedarone from a US health care payers' perspective.

**Methods and results:** ATHENA patient data were applied to a patient-level health state transition model. Probabilities of health state transitions were derived from ATHENA and published data. Associated costs used in the model (2010 values) were obtained from published sources when trial data were not available. The base-case model assumed that patients were treated with dronedarone for the duration of ATHENA (mean 21 months) and were followed over a lifetime. Cost-effectiveness, from the payers' perspective, was determined using a Monte Carlo microsimulation (1 million fictitious patients). Dronedarone plus standard care provided 0.13 life years gained (LYG), and 0.11 quality-adjusted life years (QALYs), over standard care alone; cost/QALY was \$19,520 and cost/LYG was \$16,930. Compared to lower risk patients, patients at higher risk of stroke (Congestive heart failure, history of Hypertension, Age  $\geq$  75 years, Diabetes mellitus, and past history of Stroke or transient ischemic attack (CHADS<sub>2</sub>) scores 3–6 versus 0) had a lower cost/QALY (\$9580–\$16,000 versus \$26,450). Cost/QALY was highest in scenarios assuming lifetime dronedarone therapy, no cardiovascular mortality benefit, no cost associated with AF/AFL recurrence on standard care, and when discounting of 5% was compared with 0%.

**Conclusions:** By extrapolating the results of a large, multicenter, randomized clinical trial (ATHENA), this model suggests that dronedarone is a cost-effective treatment option for approved indications (paroxysmal/persistent AF/AFL) in the US.

**Keywords:** cost-effectiveness, dronedarone, ATHENA

Atrial fibrillation (AF) is the most frequently occurring cardiac arrhythmia and collectively with atrial flutter (AFL) affects approximately 3.3 million patients in the US.<sup>1</sup> The prevalence of AF/AFL is highest in patients between 65 and 85 years of age,<sup>2,3</sup> and this is anticipated to rise as the proportion of those at risk of AF/AFL increases in an aging population.<sup>3</sup> Patients with AF/AFL often have high levels of cardiovascular comorbidities and are at increased risk of stroke and mortality.<sup>1,4–6</sup>

The health and cost burdens of AF are considerable.<sup>7–9</sup> The high cost burden of AF/AFL is driven largely by inpatient costs.<sup>7,8,10</sup> The development and use of beneficial and cost-effective treatments for AF/AFL is needed to reduce the burden of managing

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these conditions by reducing costs and improving patient quality of life.<sup>11</sup>

Dronedaron is an antiarrhythmic medication indicated to reduce the risk of AF hospitalization in patients with paroxysmal or persistent AF/AFL who are in sinus rhythm.<sup>12</sup> In the ATHENA trial (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENTs with Atrial fibrillation/atrial flutter), the antiarrhythmic drug dronedarone plus standard of care showed significant reductions in cardiovascular mortality (29%) and hospitalizations due to cardiovascular events (26%) and AF (37%) compared with placebo plus standard of care ( $P < 0.001$ ).<sup>13,14</sup> However, the potential lifetime cost-effectiveness of dronedarone has not been explored within the context of the US health care system. The objectives of this study were to estimate the lifetime cost-effectiveness of dronedarone in addition to standard of care for treatment of paroxysmal/persistent AF/AFL in the US from a health care payer's perspective and to compare this with standard of care alone.

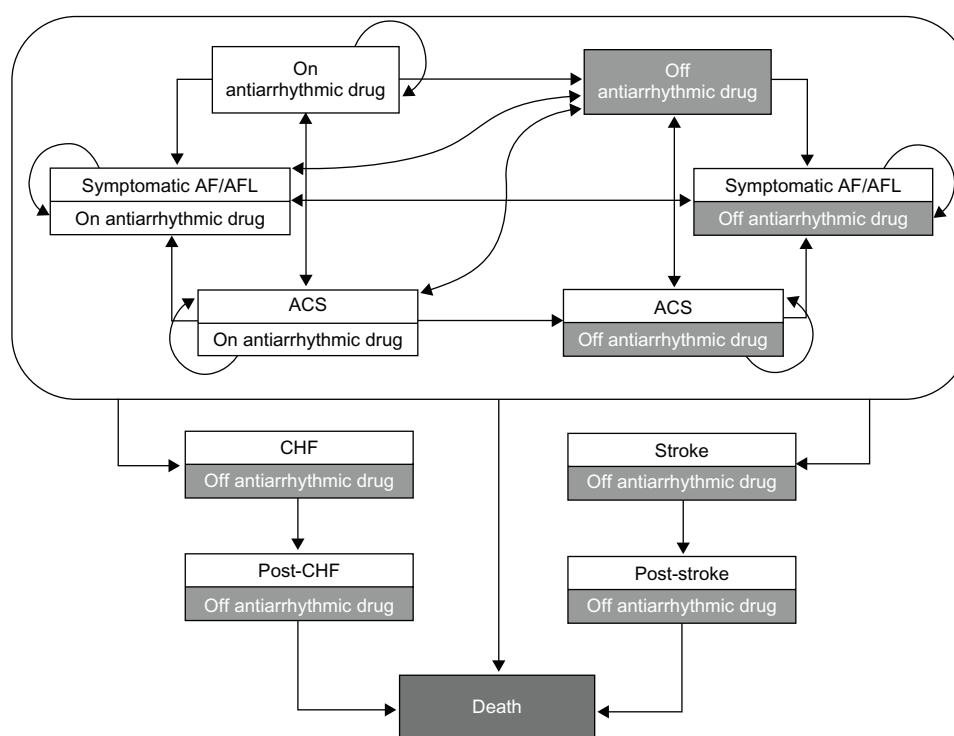
## Methods

The cost-effectiveness of dronedarone was determined using a patient-level health state transition model based on the

ATHENA trial and published US cost and mortality data. The model included a Monte Carlo microsimulation of 1 million fictitious patients able to transition at a constant rate between a variety of health states (on/off antiarrhythmic drug, symptomatic AF/AFL recurrence, acute coronary syndrome, congestive heart failure, stroke, and death) at monthly intervals (one-cycle length) (Figure 1; Table 1). A team of clinical and health economic experts selected the health states and patient characteristics that influenced health state transitions on the basis of relevance to AF/AFL patient subgroups. Probabilities of health state transitions were based on patient-level data derived from the baseline event rates for stroke, congestive heart failure, acute coronary syndrome, and symptomatic AF/AFL in the ATHENA trial. Survival analyses (Weibull regressions using STATA® software and formulas described by Briggs et al)<sup>15</sup> were used to transform the trial results into health state transition probabilities.<sup>16</sup> The total cost for an individual moving through the health states was calculated and multiplied by the proportion of a hypothetical cohort in a given health state during all cycles of the model.

## Patient characteristics and the ATHENA trial

The patient characteristics used in the model were selected to be most relevant to the US population, and because of slight



**Figure 1** Structure of the model.

**Abbreviations:** AF/AFL, atrial fibrillation/flutter; ACS, acute coronary syndrome; CHF, congestive heart failure.

**Table 1** Health states and possible transitions

Health state	Patient details	Time in health state and transition potential
On antiarrhythmic drug	ATHENA patients treated with dronedarone plus standard of care	Patients start in this health state and remain in it until discontinuation of the last line of treatment (when they will move to the off-antiarrhythmic drug state) or until experiencing an event.
Off antiarrhythmic drug	ATHENA patients on standard of care only	Patients will remain in this health state until experiencing an event or death.
Symptomatic AF (on and off antiarrhythmic drug)	Patients with current AF/AFL symptoms	These patients are subject to lower utility weightings and higher costs. A patient stays in this health state for one cycle at a time. Patients with symptomatic AF/AFL are at risk of developing permanent AF/AFL – no state cost is applied to permanent AF/AFL patients, but the utility reduction continues until death.
Acute coronary syndrome (on and off antiarrhythmic drug)	Patients with acute coronary syndrome	A patient stays in this health state for one cycle at a time but repeat visits to this state are allowed and the increased risk of suffering subsequent acute coronary syndrome events is included.
Congestive heart failure (off antiarrhythmic drug)	Patients with congestive heart failure	A patient will remain in the congestive heart failure state for one cycle and then move to either the post-congestive heart failure or the death state. All patients having experienced congestive heart failure are assumed to have discontinued treatment as no further treatment effect is modeled following congestive heart failure and adding a treatment cost without effects would introduce bias. Patients with a history of congestive heart failure at baseline have treatment costs and a utility reduction applied when moving to the congestive heart failure state.
Post-congestive heart failure (off antiarrhythmic drug)	Patients with prior congestive heart failure	The only possible move from the post-congestive heart failure state is to death. Patients with a history of congestive heart failure at baseline have treatment costs and a utility reduction applied when moving to the post-congestive heart failure transition state.
Stroke (off antiarrhythmic drug)	Patients suffering a stroke	Patients remain in the stroke state for one cycle and then move to post-stroke or death state. All patients are assumed to have discontinued treatment after a stroke as no further treatment effect is modeled post-stroke and adding a treatment cost without effects would introduce a bias. Patients with a history of stroke at baseline have treatment costs and utility decrements added when moving to the stroke state.
Post-stroke (off antiarrhythmic drug)	Patients with a prior stroke	The only possible move from the post-stroke state is to death, as the limited number of strokes in the ATHENA trial prevents modeling recurrent stroke. Patients with a history of stroke at baseline get treatment cost and utility reduction deducted when in the post-stroke state.
Death	Patient death	No further transitions.

**Abbreviations:** ATHENA, A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patients with Atrial fibrillation/atrial flutter; AF/AFL, atrial fibrillation/flutter.

**Table 2** Baseline patient characteristics used in the US cost-effectiveness model based on US ATHENA patients and compared with the entire ATHENA study population

Baseline characteristic	US patients in ATHENA (n = 1255)	Mean value across the entire ATHENA study population (n = 4628)
Age at start (years)	73	72
Female (%)	41	47
SHD (%)	64	60
Coronary artery disease (%)	44	30
Stroke (%)	15	13
Congestive heart failure	23	29
CHADS <sub>2</sub> index		
0	2.9	3.0
1	29.9	32.4
2	38.6	36.0
3	16.1	18.0
4	9.1	7.5
5	2.8	2.6
6	0.7	0.5

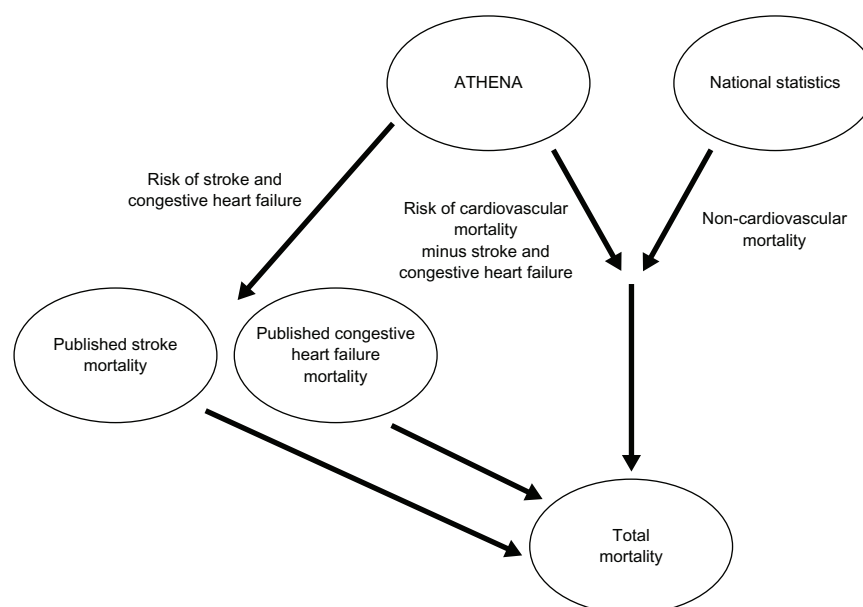
**Abbreviations:** US, United States; ATHENA, A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter; SHD, structural heart disease; CHADS<sub>2</sub>, Congestive heart failure, history of Hypertension, Age  $\geq$  75 years, Diabetes mellitus, and past history of Stroke or transient ischemic attack.

differences between the ATHENA population as a whole and ATHENA patients from the US, these were based on the average characteristics of US patients from the ATHENA trial (Table 2). The details and findings of this trial have been reported elsewhere.<sup>13,14</sup> Briefly, patients in the ATHENA trial

had a history of paroxysmal/persistent AF/AFL and were aged  $\geq$  70 years with  $\geq$  1 additional cardiovascular risk factor and were randomized (1:1) to receive either dronedarone plus standard of care (n = 2301) or placebo and standard of care (n = 2327). Those  $>$  75-years old were not required to have an additional cardiovascular risk factor. Standard of care may have included: rate control agents, antithrombotic therapy, or other cardiovascular agents (eg, angiotensin-converting enzyme inhibitors or statins).<sup>13,14</sup> The base-case model in the current study assumes that patients were treated with dronedarone for 21 months (the mean duration of follow-up in the ATHENA trial).<sup>13</sup>

## Mortality

Model inputs on the risk of death were taken from a combination of sources (Figure 2). All health states included a risk of non-cardiovascular death, estimated as the age- and gender-adjusted overall mortality risk (from US life tables)<sup>17</sup> after excluding deaths for cardiovascular causes. For all but the stroke and congestive heart failure health states, the risk of cardiovascular death was based on ATHENA data.<sup>13</sup> External sources were used for congestive heart failure (Table 3)<sup>16,18</sup> and non-cardiovascular mortality rates,<sup>17</sup> as fatal events due to these causes were uncommon in ATHENA and lacked long-term observation. Stroke mortality rates were obtained from published non-US sources: stroke mortality within the first month post-stroke was based on data from a recent systematic literature review,<sup>19</sup> while stroke mortality beyond 1 month was based on the findings of a randomized controlled clinical trial.<sup>20</sup>



**Figure 2** Sources of mortality data.

**Table 3** Mortality after congestive heart failure

Age (years)	Probability of death at specific time intervals after a congestive heart failure event					
	30 days <sup>18,a</sup>		1 year <sup>18,a</sup>		3 years <sup>16,b</sup>	
	Male	Female	Male	Female	Male	Female
45–54	0.04	0.04	0.09	0.08	–	–
55–64	0.05	0.06	0.15	0.16	–	–
65–74	0.07	0.08	0.22	0.22	–	–
>75	0.14	0.12	0.35	0.30	–	–
35–64	–	–	–	–	0.17	0.19
65–84	–	–	–	–	0.41	0.36

Notes: <sup>a</sup>Data for the year 2000; <sup>b</sup>data from 1999–2001.

## Costs

The costs used in the model (2010 values) were obtained from published sources (Table 4). Non-US data were used only in the absence of relevant US data. The model included only a single hospitalization for congestive heart failure and stroke, so the costs applied to these health states do not include rehospitalization. To estimate hospitalization costs for symptomatic AF/AFL, it was assumed that 27% of patients on dronedarone plus standard of care and 31% of patients on standard of care alone were hospitalized, based on results for the overall ATHENA population.<sup>13</sup> Costs based on the average readmission for symptomatic AF/AFL (\$9061) were applied per 1-month

**Table 4** Costs in US\$ (2010 values)

Health state costs	Cost \$ (SD)
Symptomatic AF/AFL – on antiarrhythmic drug	2523 (1262) <sup>21,43</sup>
Symptomatic AF/AFL – standard of care	2886 (1443) <sup>23,43</sup>
Acute coronary syndrome (first month)	18,566 (9283) <sup>44</sup>
Acute coronary syndrome (subsequent months)	1980 (990) <sup>44</sup>
Congestive heart failure (first month)	7333 (3667) <sup>45</sup>
Congestive heart failure (subsequent months)	1155 (577) <sup>45</sup>
Stroke (first month)	9859 (4930) <sup>46</sup>
Post-stroke (subsequent months)	922 (461) <sup>46</sup>
Applied costs	
Daily dronedarone cost	7.56
Cardioversion	767 <sup>43</sup>
Hospitalization	9061 <sup>21</sup>
3-monthly ECG monitoring cost	115 <sup>22</sup>
Adverse skin events	283
Adverse gastrointestinal events	345
Adverse cardiac events	503

Notes: The cost of symptomatic AF treated with the antiarrhythmic drug dronedarone was calculated as [(percentage of patients on dronedarone × average cost per readmission] + [proportion of patients with cardioversion × cardioversion cost] = (0.27 × \$9061) + (0.10 × \$767), where the proportions of patients with symptomatic AF on antiarrhythmic drug, standard of care, and undergoing cardioversion are those obtained in the ATHENA trial (0.27, 0.31, and 0.10, respectively).

Abbreviations: US, United States; SD, standard deviation; AF/AFL, atrial fibrillation/flutter; ECG, electrocardiogram; ATHENA, A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patients with Atrial fibrillation/atrial flutter.

cycle and were reapplied on re-entry to this health state.<sup>21</sup> In the ATHENA trial, 10% of patients were treated for arrhythmia with cardioversion, so this was used to guide cost application in this model (Table 4). The cost of 3-monthly electrocardiogram (ECG) monitoring was estimated for assessment of the impact of this safety requirement on the cost-effectiveness of dronedarone in a sensitivity analysis (Table 4).<sup>22</sup>

Adverse events (AEs) were applied as a one-off cost, where the occurrence was based on the difference between the dronedarone and standard of care alone arms of the ATHENA trial (where incidences of skin events, gastrointestinal events, and bradycardia were 2.7%, 4.2%, and 2.3% higher, respectively, with dronedarone versus standard of care alone) (Table 4).<sup>13</sup>

## Assumptions made for the cost-effectiveness model

As with other cost-effectiveness models, this model makes a number of assumptions. Firstly, the model extrapolates ATHENA data beyond the trial period and in doing so assumes that there is no change in the effect of dronedarone over this period, which was further tested by sensitivity analyses. Secondly, considering the transition states, it was assumed that after 21 months (the mean duration of the ATHENA trial) the probabilities of health state transitions would revert to those in the standard of care arm. Symptomatic patients developing permanent AF/AFL in ATHENA (15.2% of patients) were assumed to have discontinued dronedarone and were not included in the model, which only provides an assessment of dronedarone's cost-effectiveness in paroxysmal/persistent AF/AFL. Thirdly, because of the limited number of strokes and congestive heart failure recurrences in the ATHENA trial, only first occurrences of stroke and congestive heart failure were included in the model. Fourthly, it was assumed that AF-related costs applied to patients with symptomatic AF/AFL and that these were driven solely by hospitalization. When applying the utility reduction, based on patient-level data from ATHENA, it was assumed that 70% of patients with AF/AFL detected by ECG were symptomatic. Finally, it was assumed that acute coronary syndrome-related monitoring costs were incorporated into the costs of treating and monitoring AF/AFL.

## Utility weights

In the absence of US data, EuroHeart Survey data on the quality of life of patients with AF<sup>23</sup> were converted to utility values<sup>24</sup> as detailed in an assessment of dronedarone's cost-effectiveness in Canada, Italy, Sweden, and Switzerland.<sup>25</sup>



Utility reductions, based on non-AF patient data,<sup>26,27</sup> were applied until death for stroke and congestive heart failure and for 1 year in patients with acute coronary syndrome.<sup>28,29</sup> If stroke or congestive heart failure was present at baseline, the utility reduction was made once at the start of the model. Based on a previous study of utility values for AF/AFL, AEs were also given a one-off utility reduction, applied over a 1-month cycle. One-off utility reductions of 0.1 were applied for skin, gastrointestinal, and cardiac AEs.

## Sensitivity and subgroup analyses

One-way sensitivity analyses were used to evaluate the robustness of the cost-effectiveness estimates. The sensitivity analyses were used to assess the impacts of: discounting, the proportion of patients in the health states ( $\pm 20\%$ ), changes in the utility of health states, lifetime treatment on dronedarone, and the risk of developing permanent AF/AFL (10%–20%). The impacts of age, gender, and risk of stroke (indicated by the CHADS<sub>2</sub> score<sup>30</sup> [Congestive heart failure, history of Hypertension, Age  $\geq 75$  years, Diabetes mellitus, and past history of Stroke or transient ischemic attack]) were assessed by subgroup analysis. The model allowed for probabilistic sensitivity analysis with the following distributional assumptions: risk of developing permanent AF =  $\beta$ , health state specific costs = normal, health state specific utility reductions = normal, and transition probabilities = empirical.

An additional sensitivity analysis was undertaken to investigate the impact of 3-monthly ECG monitoring costs on the cost-effectiveness of dronedarone.

## Results

### Base-case

The base-case model compared dronedarone added to standard of care with standard of care alone. Total treatment costs for dronedarone (at \$7.56 per day) were estimated at \$3270 based on the average in-trial treatment duration of 21 months. These costs were partially offset by a reduction in other health care costs (for congestive heart failure, stroke, acute coronary syndrome, and symptomatic AF/AFL, as observed in the ATHENA trial), resulting in an incremental lifetime cost of \$2200 for dronedarone plus standard of care versus standard of care alone (Table 5).

The addition of dronedarone also provided 0.13 life years gained (LYG) and 0.11 quality-adjusted life years (QALY) gained over standard of care alone. This gain was derived from a reduction in the probability of events associated with both short- and long-term mortality risks. The lifetime cost-effectiveness of dronedarone was \$16,930/LYG, and \$19,520/QALY gained. Subgroup analysis demonstrated that patients

**Table 5** Base-case lifetime results for dronedarone versus standard of care (US\$)

Item	Dronedarone [D]	Standard of care [S]	Difference [D – S]
Dronedarone cost* (\$)	3270	0	3270
Direct costs (\$)	33,880	34,950	–1070
Total cost (\$)	37,150	34,950	2200
Survival (years)	10.16	10.03	0.13
QALY (years)	7.31	7.19	0.11
Cost per LYG (\$)	–	–	16,930
Cost per QALY (\$)	–	–	19,520

**Note:** \*Including initiation treatment.

**Abbreviations:** US, United States; QALY, quality-adjusted life year; LYG, life year gained.

at higher risk of stroke (CHADS<sub>2</sub> score of 6) had lower costs/QALY gained (\$9580) than patients at lower risk (CHADS<sub>2</sub> scores of 0 and 3 costing \$26,450 and \$16,000, respectively). Costs/QALY gained were also marginally lower in males than females (\$17,280 versus \$18,270, respectively).

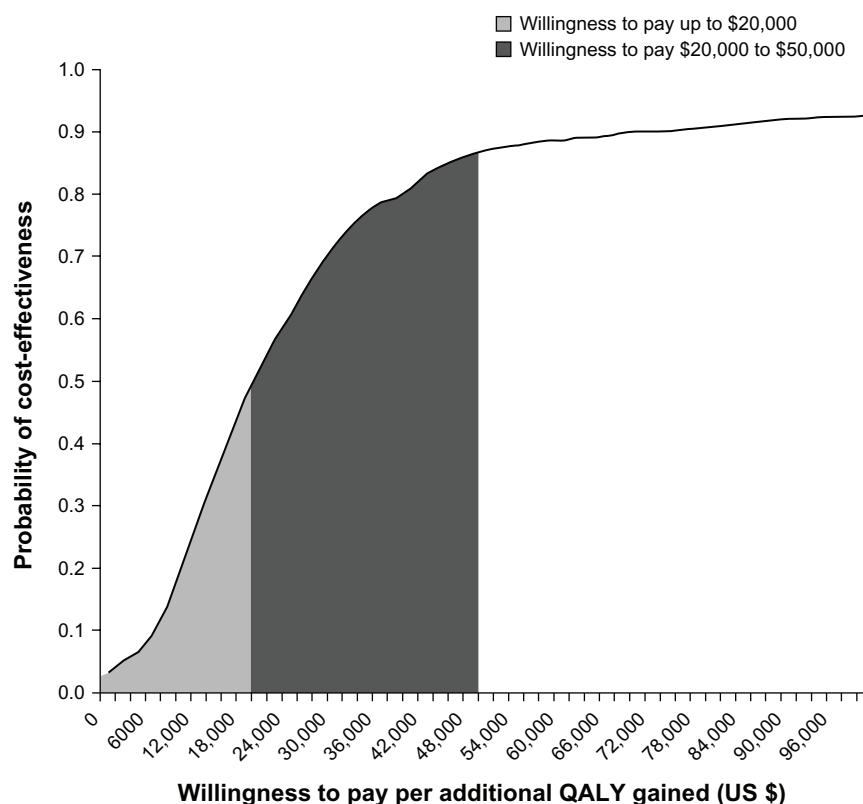
## Sensitivity analysis

The model estimates were analyzed to assess how the costs per QALY gained compared with widely used thresholds. Probabilistic sensitivity analysis, based on 1000 second-order simulations of 10,000 patients each, showed that 50% of the simulations fell below a willingness-to-pay threshold of \$20,000/QALY and 85% fell below \$50,000/QALY (Figure 3).

The base-case results (<\$30,000 per QALY gained) were found to be generally stable across the scenarios evaluated in the one-way sensitivity analysis. This analysis also demonstrated that the cost/QALY was highest in scenarios assuming lifetime therapy with dronedarone, no cardiovascular mortality benefit, no cost associated with AF recurrence on standard of care, and when discounting of 5% was compared with 0% (Figure 4). The analyses also indicated that cost-effectiveness was not sensitive to changes in the risk of developing permanent AF/AFL within the tested range, with costs/QALY of \$17,640 at 10% and \$19,310 at 20% risk. Furthermore, the costs/QALY were not greatly altered by the addition of 3-monthly ECG monitoring costs (\$115, that were increased by 20% in the sensitivity analysis to \$138), being \$21,950 and \$23,310 respectively in comparison to the base-case cost/QALY of \$19,520. However, the cost-effectiveness estimate was sensitive to whether or not dronedarone reduced cardiovascular mortality (Figure 4).

## Discussion

The US lifetime model used in this study indicates that, from a health care payer's perspective, dronedarone is a



**Figure 3** Cost-effectiveness acceptability of dronedarone plus standard of care compared with standard of care alone.

**Note:** All values in US\$, 2010 values.

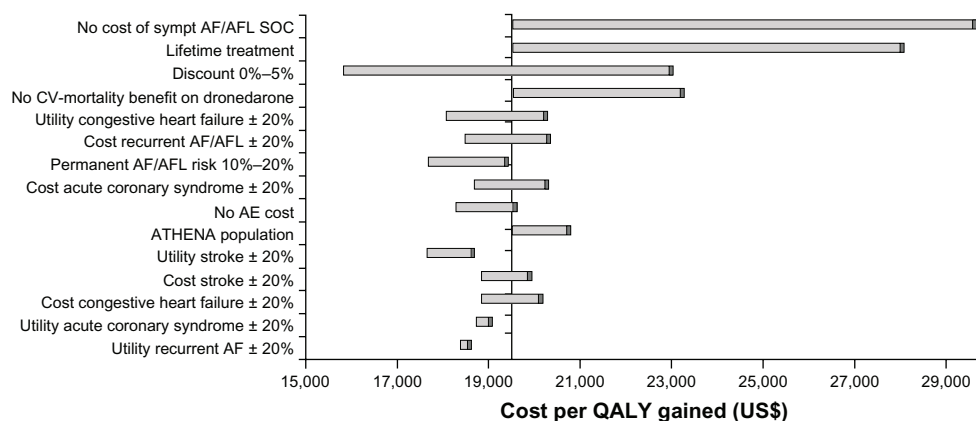
**Abbreviation:** QALY, quality-adjusted life year.

cost-effective treatment option to manage paroxysmal/persistent AF/AFL in the US. The base-case scenario cost/QALY was \$19,520, and 85% of the probabilistic sensitivity analysis simulations fell well below the commonly used threshold of \$50,000/QALY.<sup>31</sup>

A feature of this cost-effectiveness model is that it was sensitive to the reduction in cardiovascular mortality associated with dronedarone therapy. The relatively minor cost for

3-monthly ECG monitoring did not change the results of the model in any appreciable way, and the monitoring cost used was most likely an overestimation for current US practice costs.

The finding that cost-effectiveness is below current thresholds is consistent with the conclusions of a similar assessment of dronedarone in Canada, Italy, Sweden, and Switzerland, where the costs/QALY gained were €5828, €5873, €14,970, and €8554, respectively.<sup>25</sup> Variation across



**Figure 4** Sensitivity analysis of dronedarone plus standard of care compared with standard of care alone.

**Notes:** Discount 0%–5%, discounting at 0% and 5% are compared; all values in US\$, 2010 values.

**Abbreviations:** AF/AFL, atrial fibrillation/flutter; AE, adverse event; QALY, quality-adjusted life year; no cost of sympt AF/AFL SOC, no cost of symptomatic atrial fibrillation in standard of care alone; CV, cardiovascular.

countries is largely attributed to differences in treatment costs, which were markedly higher in the US and Sweden. The cost-effectiveness results from the current model were also stable across the examined subgroups, and the incremental cost-effectiveness ratios were lower in patients with a higher risk of cardiovascular events, as anticipated.

We believe that the cost-effectiveness estimates provided by this model are of relevance to patient care, given the long-term control of arrhythmia that may be required by AF/AFL patients. This study used robust clinical trial data from one of the largest datasets on patients with paroxysmal/persistent AF/AFL (ATHENA),<sup>13</sup> to provide the assessment of cost-effectiveness over the patients' lifetime.

The conclusions of this study are consistent with those of an evaluation of dronedarone in non-permanent AF conducted by the National Institute for Health and Clinical Excellence (NICE). Based on several evaluations, including a United Kingdom lifetime model, NICE concluded that dronedarone was a cost-effective treatment option in patients with similar characteristics to those of the ATHENA population.<sup>32</sup> However, following a review of its benefit–risk balance conducted in light of the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) trial results,<sup>26</sup> the European Medicines Agency has recommended that use of dronedarone should be restricted to patients with paroxysmal/persistent AF who are in sinus rhythm and only after other antiarrhythmic drugs have been tried.<sup>27</sup> Similarly, the US Food and Drug Administration now recommends that dronedarone should be initiated only in nonpermanent AF patients who are in sinus rhythm and that it should be discontinued in patients whose AF becomes permanent (ie, cannot or will not be cardioverted).<sup>33</sup> It is acknowledged that the US lifetime model assumes that there is no change in effect of treatment when extrapolating beyond the ATHENA trial data. The use of data from this large trial permits greater precision than the use of data from either a smaller study or the collection of data from multiple published studies. Also, the approach of extrapolating to consider cost-effectiveness over a lifetime is considered a requirement to assist health care decision makers in identifying appropriate and cost-effective treatments for cardiovascular disease.<sup>34</sup>

The current model assesses the cost-effectiveness of dronedarone in its currently approved indications of paroxysmal and persistent AF/AFL. While a moderate proportion of patients with paroxysmal and persistent AF/AFL eventually progress to permanent AF/AFL,<sup>35–37</sup> within the base case of this model, symptomatic patients who developed permanent AF/AFL (15.2% of patients) were assumed to have

discontinued dronedarone. This differentiates this study from the recent investigation of the use of dronedarone in patients aged  $\geq 65$  years with permanent AF (the PALLAS trial), which was stopped after unexpected findings of an increase in cardiovascular events with dronedarone in comparison with placebo.<sup>26</sup> We conclude that the findings of this study are relevant to patients with paroxysmal or persistent AF/AFL.

Published information on the cost-effectiveness of treatments for AF/AFL is limited. The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study concluded that rhythm control was more costly and less effective than rate control, with an incremental cost difference of \$5077 between the two treatment classes.<sup>38</sup> The probability of rhythm control being more cost-effective than rate control was reportedly  $<0.01$ , even at a value of \$100,000/QALY gained.<sup>38</sup> This evaluation was for a 3.5-year follow-up period rather than being a lifetime model.

A major difference between AFFIRM and ATHENA is in the direction of survival trends. In AFFIRM, all-cause mortality was numerically higher in the rhythm control arm than in the rate control arm (23.8% versus 21.3% at 5 years,  $P = 0.08$ ).<sup>38,39</sup> Thus, in the AFFIRM health economic analysis there was a low probability that rhythm control was more effective in terms of LYG.<sup>38,40</sup> In ATHENA, the dronedarone treatment arm had numerically lower all-cause mortality than the control group (5.0% versus 6.0%;  $P = 0.18$ ) and a statistically significantly lower cardiovascular mortality rate (2.7% versus 3.9%;  $P = 0.03$ ).<sup>13</sup> As expected, our model projected higher LYG with dronedarone therapy, consistent with the ATHENA results, but the model results are sensitive to assumptions about the magnitude of the survival benefit.

## Limitations

The findings of this study should be considered in the context of certain limitations that are consequential of basing the cost-effectiveness model on clinical trial data. It is well recognized that discontinuation rates are higher in routine clinical practice than in clinical trials. Also, given that dronedarone is relatively new to the market, it is not possible to accurately assess how trial-based efficacy data compare with the effectiveness of dronedarone in the real-world setting. Another possible limitation of using trial data is that the inclusion and exclusion criteria used in these trials provide a restriction not present in clinical practice. For example, to be included in the ATHENA trial patients were required to be over 75-years old or over 70-years old with one or more additional cardiovascular risk factor. Also, the ATHENA trial excluded patients with unstable hemodynamic conditions;



New York Heart Association class IV congestive heart failure; acute myocarditis; bradycardia with a heart rate of <50 beats per minute or a PR interval of >0.28 seconds; previous clinically significant sinus-node disease (if not currently treated with a pacemaker); planned major surgery; any (non-cardiac) severe illness that limited life expectancy; limited kidney function; or who were in need of prohibited concomitant medication (other class I or III antiarrhythmic drugs). For this reason, external sources of mortality data were used as model parameters.

The multinational nature of the ATHENA trial may also impact the applicability of some of the results of this trial to the US population. For example, approximately 20% of the patients enrolled in ATHENA were from Russia, and mortality rates in these patients may differ considerably from those in the US. To compensate for this limitation, US-specific data were used for noncardiac mortality data, and the characteristics of the subgroup of ATHENA patients from the US (27% of the ATHENA cohort) were used in this study rather than data from all of the patients enrolled in ATHENA.

This model did not include hospital readmissions or additional costs for subsequent events after baseline, for stroke, or congestive heart failure in the assessment of cost-effectiveness. Our estimates of cost-efficiency can therefore be considered conservative, as rehospitalization of USAF/AFL patients occurs frequently.<sup>9,41</sup> There is also some evidence that AF readmissions are more costly than the initial admission.<sup>42</sup> Additionally, the model also used the lower range of commonly reported 1-month stroke fatality rates.

Certain assumptions made in the model may not be representative of clinical practice; for example, that there is no change in health state transition probability over the 21-month period of dronedarone treatment. It should also be noted that cardiovascular mortality was only one of several mortality risks in the cost-effectiveness model and the model's sensitivity to the assumed reduction in all-cause mortality with dronedarone is uncertain.

## Conclusion

Based on the results of a large, multicenter, randomized clinical trial (ATHENA), this lifetime cost-effectiveness model demonstrates that dronedarone is a cost-effective treatment option to manage paroxysmal/persistent AF/AFL in US patients with similar characteristics.

## Disclosure

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