Public perception of atrial fibrillation and treatment-related adverse events in the UK

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This study aimed to describe adverse events associated with atrial fibrillation (AF), and the medications used to treat it, and to estimate the importance of these adverse events from the perspective of the condition-naïve general public. Fourteen adverse event health state descriptions associated with paroxysmal/persistent and permanent AF were produced based on EQ-5D survey data, a literature review, and qualitative input from patients and clinicians. Further interviews with clinicians and AF patients confirmed the content of the health states as descriptions appropriate to AF. In total, 127 members of the general public valued the health states in a time trade-off interview and ranking task.

The study revealed how the public view the disutility of adverse health states associated with the treatment of AF. Each of the adverse events was associated with a perceived impairment from their respective base position. Interstitial lung disease showed the greatest perceived impact on quality of life (–0.17 paroxysmal/persistent base; –0.15 permanent base), whereas peripheral vasoconstriction had the least impact (–0.01 paroxysmal/persistent; –0.02 permanent).

In conclusion, this study provides insight into the importance of treatment-related adverse events in AF. The quality of life estimates collected in this study may prove useful in populating cost-effectiveness analyses and informing clinical treatment decisions.


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Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia affecting approximately six million patients in Europe and 2.3 million in the USA.[1] Estimates in the general population suggest a prevalence rate of 0.4–1.0%, with marked increase in prevalence with age, increasing to approximately 10% by the age of 80 years.[2] AF can precipitate heart failure, ventricular arrhythmias, and it is associated with a four- to five-fold increase in chance of stroke.[3,4] In addition, although AF is frequently asymptomatic, it can reduce quality of life causing fatigue, palpitations, anxiety and dizziness.[3]

AF is classified in three ways:[5]

- Paroxysmal: recurrent episodes that self-terminate in less than 7 days
- Persistent: recurrent episodes that last more than 7 days
- Permanent: an ongoing long-term episode.

Patients with AF should be assessed to quantify stroke risk and are usually offered thromboprophylaxis to prevent stroke. Rate control, usually using beta blockers, can improve symptoms. Rhythm control can maintain patients in sinus rhythm but is often ineffective and associated with side effects. Treatment associated adverse events can make physicians wary of prescribing some drug therapies particularly in patients experiencing few symptoms.[6,7]

The health-related quality of life (HRQL) impairments of AF are well known,[8-11] yet few studies explore the HRQL impact of treatment-related adverse events. This is important for two reasons. First, it would help clinicians to know how reductions in HRQL associated with AF adverse events are perceived by patients. Understanding this should allow for a better-informed decision-making process between patient and clinician, thereby improving adherence. Second, assessing the economic impact of AF therapy within a cost-utility framework is less valid without adverse event data.

The UK National Institute for Health and Clinical Excellence (NICE) makes treatment recommendations based on both clinical and economic evidence. One of the requirements of NICE approval is the demonstration of a specific type of cost-effectiveness known as cost-utility analysis. Typically, this is expressed as a cost per quality adjusted life year (QALY). QALYs are a product of increased length of life and quality of life (expressed as a health utility value). A therapy that can demonstrate an improvement in quality and/or length of life without adversely affecting the other will show a QALY improvement. Within a cost-utility analysis, preference-weighted values (as collected in this paper) provide a HRQL metric of disease symptoms or adverse events. This tells us the relative value that people place on the avoidance of those negatively perceived health states.

NICE prefers societal utility valuations collected from members of the general public rather than patients.[12] NICE has adopted this preference for societal values based on the justification that socialised medicine funded by the tax-payer should feature the preferences of those contributors. It has been further recommended that utility valuations should be made under a ‘veil of ignorance’ in which “a rational public decides what is the best course of action when blind to its own self-interest, aggregating the utilities of persons who have no vested interest in particular health states…”.[13,14]

In order to drive treatment decisions and possible economic analysis of future treatments, more information is needed about the general public’s perceived severity of treatment-related adverse events in atrial fibrillation therapy.

Study objectives

This study did not consider the serious clinical events associated with AF, such as thromboembolic stroke, but aimed to assess the value placed on the avoidance of AF treatment-related adverse events associated with pharmacotherapies for AF through collection of UK societal preferences.

Methods

Development of health states

A combination of techniques was used to provide the background for the creation of the AF ‘health states’. These ‘health states’ described AF and adverse event impacts in layperson language with a focus on everyday impairment terms easily understood by the UK public. A large multi-national survey collected EQ-5D responses from AF patients, which formed the basis for the paroxysmal/persistent and permanent AF health states (hereafter referred to as the ‘base’ health states).[15] Additional treatment-related adverse event descriptions and confirmation of the health states were produced through a review of AF literature and from qualitative interviews with AF patients (n=6) and specialist AF clinicians (n=5).

AF EQ-5D survey data

The base AF health states were created from EQ-5D descriptions collected in the multi-national Euro Heart Survey, which stratified patients by AF diagnosis (paroxysmal, persistent, and permanent).[15] The EQ-5D is a generic, preference-based questionnaire that assesses HRQL in five categories (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and can be transformed to a single index utility score.[16] The EQ-5D is the preferred source of utility values for use in cost analyses presented to NICE and so was selected for use as the descriptive source of the base health states used in this study.[12] We performed a subgroup analysis to calculate the EQ-5D response levels for Western and Northern European patients within the Euro Heart Survey and applied UK tariff values[17] (n=493 paroxysmal patients, n=233 persistent patients and n=380 permanent patients). The paroxysmal patients showed a mean EQ-5D utility score of 0.79 (standard deviation [SD]=0.23), persistent patients 0.80 (SD=0.21) and permanent patients 0.73 (SD=26). Utility is represented on a 0 to 1.0 scale where 0 represents death and 1.0 represents full health with no impairments, thereby reflecting that people with AF report suboptimal health. For comparison, stable non-small cell lung cancer with associated pain was shown to have a utility of 0.56,[18] moderate anaemia 0.64[19] and asthma 0.71.[20]

It was felt that persistent and paroxysmal patients should be combined as they demonstrated similar values within the survey and appeared to be associated with very similar HRQL detriments. This was confirmed in the subsequent qualitative interviews.

Literature review

A literature review was conducted in order to gain a better understanding of quality of life impairment in atrial fibrillation, as well as the impact of treatment-related adverse events on patient well-being. The literature search was used to inform the development of two interview discussion guides. A number of search terms (e.g. “Adverse Effects”[subheading]; “Atrial Fibrillation”[Majr]; “Quality of Life”[Majr]) were entered into the Medline database. In total, 214 abstracts were reviewed; 35 articles were deemed highly relevant and subjected to a full-text review.

The literature review was unsuccessful in locating relevant data on the quality of life impact of adverse events from AF therapies. The majority of studies identified simply reported HRQL changes within a clinical trial context. There were, however, a handful of studies identified which qualitatively described common adverse events (AEs) associated with AF drugs, particularly anti-arrhythmics and beta blockers.[21-24] Additional data were collected that described the manifestation of AEs, such as hyperthyroidism, outside of AF therapy.

Informative qualitative interviews

In order to confirm the EQ-5D base health state descriptions and build upon the findings of the literature review, a series of qualitative one-on-one interviews with AF patients and specialist clinicians were undertaken. Patients with current AF (n=6) were recruited from a commercial patient panel. The patients were also asked to describe their experiences with AF and AF medication(s), to elaborate on the day-to-day impact of AF, their condition symptoms, and how AF or treatment-related adverse events affected their perceived health status. They were also asked to complete the EQ-5D within the context of their AF and to explain their response choices. None of the patients included in the qualitative interviews had experienced anything beyond transient or minor AEs from their AF medications.

Interviews were also conducted with five physicians experienced in AF (n=4 cardiologists/electrophysiologists; n=1 GP with AF speciality), in order to capture information regarding the burden of specific AEs and AF itself. The clinicians were asked to describe the most common or debilitating symptoms of AF,

Table 1. Demographics (n=127 total interviews)

	Study sample	UK census 2001[29]
Mean age, years (SD)	41.45 (12.81)	38.2
Gender, n (% female)	76 (59.8%)	51% female
Ethnic group, n (%)		
White	122 (96.1%)	92.1%
Black	1 (0.8%)	2.0%
Asian	1 (0.8%)	4.0%
Other	3 (2.4%)	1.9%
Employment status, n (%)		
Full time	61 (48.0%)	48.6%
Part time	29 (22.8%)	11.7%
Home maker	8 (6.3%)	6.5%
Student	10 (7.9%)	7.3%
Retired	5 (3.9%)	13.6%
Disabled	0 (0.0%)	5.8%
Other	14 (11.0%)	6.5%
Education, n (%)		
No formal qualifications	5 (3.9%)	-
GCSE/O levels	26 (20.5%)	-
A levels	20 (15.7%)	-
Vocational or work based	14 (11.0%)	-
University degree	47 (37.0%)	-
Other	15 (11.8%)	-

Key: SD = standard deviation

how effectively they could be controlled by medication, and the general psychological, social, and physical impact of AF on patients. The major focus of the interviews was the clinician's descriptions of the AEs associated with AF pharmacotherapies from the perspective of the patient. As with the patients, the clinicians were asked to review the EQ-5D questionnaire and select the most appropriate responses for each AF health state. The clinicians felt that the EQ-5D response levels selected in the AF base health states were appropriate.

Draft health state creation and validation

A set of draft health states associated with AF or the treatment of AF, were created based on the survey data, literature review, and clinician and patient interviews. The EQ-5D responses given by the qualitative patients and clinicians were in agreement with the Euro Heart Survey EQ-5D data. These EQ-5D states formed the two base AF health states for paroxysmal/persistent and permanent AF. AEs were described and added to the base health states. The AEs included: hyperthyroidism, hypothyroidism, liver deposits, pulmonary issues (interstitial lung disease), sleep disturbances, neuropathy, dermatological changes (photosensitivity and blotchy discolouration), optical issues (photosensitivity and corneal deposits), nausea, diarrhoea, circulatory issues, fatigue, mild skin rash, and dizziness.

In order to assess the content and face validity of the draft AF health states, a review was undertaken with additional cardiology experts (n=5). The clinicians were asked to review the draft health states and make recommendations to improve the clinical accuracy of the descriptions. In general, the clinicians concluded that the descriptions were accurate and appropriate **(see appendix)**.

Pilot study

The health states were piloted with five members of the general public in a time trade-off (TTO) interview where participants sacrifice length of life for improvements in health (see below). Following the completion of the TTO exercise, the participants were debriefed in order to identify any comprehension and language issues. No revisions were needed as a result of these pilot interviews.

Main study

Current residents of the UK were recruited to take part in the utility interviews. Participants were recruited via general public advertising (e.g. newspapers, websites) from the Oxfordshire, Bedfordshire, Warwickshire and Stirling areas. Prior to initiation of the interview, the purpose of the study was explained to the participants and written informed consent collected. All participants completed a socio-demographic questionnaire providing details of age, ethnicity, gender, education and employment status. Participants were also asked to complete the EQ-5D.

Participants then completed an ordinal ranking assessment of the health states, during which they placed the states, as they imagined them, in order from best to worst. This was followed by the TTO exercise.[25,26] In a TTO interview participants are asked to imagine that they have a health condition described by one of the hypothetical AF health states and will remain in that state for the final 10 years of their life beginning immediately. Next they are presented with two choices:

1. to remain in that AF condition, with the condition getting no better and no worse for those final 10 years
2. sacrifice a varying amount of those final 10 years but with the benefit that the remaining time is spent in full health without the AF condition.

The amount of time available in full health in option 2 was varied sequentially between 0–9.5 years of life remaining until the patient was indifferent about the choices. Health states that are not perceived as being very severe are less likely to result in the sacrifice of significant amounts of remaining life as people typically feel they can live with the condition and do not view it as a reasonable trade of remaining lifespan. Very severe conditions involving pain or major impairment are more likely to result

Table 2. Participants' ratings of their current health from the EQ-5D compared with data from a national survey reported by Kind *et al*. Table shows proportion of people reporting moderate or extreme problems on each dimension

	Present study		Kind *et al.*[28]	
Dimension	Moderate problem	Extreme problem	Moderate problem	Extreme problem
Mobility	6 (4.7%)	0 (0%)	18.3%	0.1%
Self-care	0 (0.0%)	0 (0%)	4.1%	0.1%
Usual activity	4 (3.1%)	0 (0%)	14.2%	2.1%
Pain/discomfort	24 (18.9%)	0 (0%)	29.2%	3.8%
Anxiety/depression	17 (13.4%)	2 (1.6%)	19.1%	1.8%

Table 3. Ranking task – ordered best to worst

Rank	Health state	Mean ordinal rank
1*	Paroxysmal/persistent (PX) AF	1.84
2	PX peripheral vasoconstriction	4.25
3*	Permanent (PE) AF	4.92
4	PX rash	5.40
5	PE peripheral vasoconstriction	5.95
6	PX sleep disturbances	6.35
7	PX dizziness	6.47
8	PX fatigue	6.63
9	PE rash	7.71
10	PX nausea	7.97
11	PE dizziness	8.14
12	PX liver deposits	8.42
13	PX neuropathy	8.48
14	PX dermatological changes	8.77
15	PE sleep disturbances	9.08
16	PE liver deposits	9.16
17	PE fatigue	9.23
18	PX diarrhoea	9.50
19	PX hyperthyroidism	9.58
20	PE nausea	9.97
21	PX optical issues	10.19
22	PX hypothyroidism	10.94
23	PE dermatological issues	11.02
24	PE diarrhoea	11.09
25	PE hyperthyroidism	11.29
26	PE neuropathy	11.46
27	PE optical issues	12.05
28	PE hypothyroidism	12.57
29	PX interstitial lung disease	12.87
30	PE interstitial lung disease	13.85

*base AF states
Key: AF = atrial fibrillation

in bigger sacrifices in life expectancy in return for removal of that symptom.[27]

Statistical analysis

A descriptive analysis was undertaken to explore the demographic and HRQL characteristics of the sample. In addition, the EQ-5D data were analysed to determine how closely the sample matched a previous national survey.[28]

Results

All recruited participants attended and completed the TTO interview (n=127). The sample population was a good match to UK census population sets, but with higher employment and female representation (**table 1**).[29] The study sample also reported less moderate and extreme problems on the EQ-5D than those described in the Kind *et al.* study[28] (**table 2**). This is not unexpected given that the Kind *et al.* study was a postal survey and our study was conducted in person, which may have prevented more disabled participants from attending.

The ordinal ranking task served as a check against the valuation results from the TTO interviews. The results from the ranking task confirmed the ordering of the health states in the TTO (**table 3**).

Each of the AE values was associated with a quality of life impairment or 'disutility'. Disutility of each AE was very similar whether the AE was added to the paroxysmal/persistent AF base state or the permanent AF base state. Interstitial lung disease was associated with the greatest perceived disutility (–0.17 paroxysmal/persistent base; –0.15 permanent base) and peripheral vasoconstriction had the least impact (–0.01 paroxysmal/persistent; –0.02 permanent) (**table 4**).

Discussion

To our knowledge, this is the first study that focuses on the utility impact of AEs associated with treatments of AF. This is of particular importance as real or perceived AEs are likely to influence treatment decisions in a condition that is often asymptomatic. We believe that this data could be usefully applied to inform both clinical treatment choices and cost-utility assessments for AF.

Data from the study showed the significance that the general public place on avoiding treatment-related AEs. Each AE led to a minimal decline of –0.01, with participants considering hypothyroidism and pulmonary issues to be the worst events. What this means is that people on average stated that they would be willing to sacrifice 12–18 months of life for the avoidance of the worst AEs associated with typical AF therapies. It is worth pointing out, however, that these valuations are from the viewpoint of the general public who are likely to be largely unfamiliar with AF outside of their participation in this study. It may be that AF patients would view potential treatment-related AEs in the perspective of their overall condition.

The study had some limitations that may limit its extrapolation into clinical care, including small qualitative sample sizes and the lack of an exhaustive literature search. Given more time and resources, it would have been preferable to conduct further qualitative interviews with both

Table 4. Disutility of treatment-related adverse events from base state

	Paroxysmal	Permanent
Peripheral vasoconstriction	–0.01	–0.02
Dizziness	–0.01	–0.03
Rash	–0.03	–0.03
Liver deposits	–0.03	–0.03
Sleep disturbances	–0.04	–0.04
Fatigue	–0.04	–0.05
Nausea	–0.06	–0.05
Dermatological changes	–0.06	–0.09
Hyperthyroidism	–0.08	–0.06
Neuropathy	–0.08	–0.07
Diarrhoea	–0.08	–0.08
Optical issues	–0.08	–0.08
Hypothyroidism	–0.10	–0.10
Interstitial lung disease	–0.17	–0.15

clinicians and AF patients in order to establish a stronger consensus on the AE descriptions and base EQ-5D health states. A formal saturation grid would have allowed us to be more confident that certain clinical experiences were not missed and strengthened the validity of our AEs descriptions.

There are concerns from certain regulatory bodies about the collection of utility values using descriptive approaches such as in this study.[12] However, the collection of adverse event data using large, patient-derived generic instruments such as the EQ-5D can be problematic for a number of reasons. This study represents a compromise in that the AF health states, which serve as the main driver of cost-utility models, are collected from patient-derived survey data and are supplemented with AE utilities collected in a public preference valuation.

Interestingly, the participants in this study rated the quality of life described by the EQ-5D health states higher than the same EQ-5D states rated by UK tariff sample.[17] The UK tariff dataset collected EQ-5D utility values with TTO interviews from a large UK general public sample (n >3,000). This means that our sample rated the impairments in quality of life to be less than those in the dataset typically applied in cost-utility analysis. The paroxysmal/persistent AF health state and permanent AF health state are valued at 0.78 for paroxysmal/persistent and 0.74 for permanent when applying the UK tariffs values. Within our TTO interviews the same states were valued at 0.93 and 0.91, respectively. This means that our sample was less willing to sacrifice remaining length of life for avoidance of AF impairments. It is not entirely clear why our participants would be more conservative in their willingness to trade quantity versus quality of life when compared against the UK tariff participants. It may be that our participants were valuing the base states in the context of the AE descriptions. Alternatively, there is some concern that the rescaling of health states perceived to be worse than dead in the UK tariff tends to pull down all valuations.[30] Our higher values may reflect this trend.

Given that the intention of this study was to value the disutility associated with AEs common to AF pharmacotherapies, we recommend that researchers using this study to inform cost-utility analysis continue to use the UK tariff values for the AF base states and the disutility values of AF treatments reported here for AE utility scores as recommended by NICE.[12]

Conclusion

Our study provides AE disutilities common to AF pharmacotherapies. The methods of vignette development and testing described allow for the societal valuation of AF AEs that would be very difficult to capture otherwise. The study shows clear quality of life impairments associated with treatment-related AEs as demonstrated by the choices of a representative sample of the UK general public. The results demonstrate the importance of AEs on HRQL from a clinical and economic perspective ●

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Conflict of interest

None declared.

Key messages

- The study describes the perceived quality of life impact of atrial fibrillation and atrial fibrillation treatment adverse events
- Quality of life impairments of adverse events ranged from mild (–0.01 to –0.03 for peripheral vasoconstriction and dizziness) to moderate (–0.10 to –0.17 for hypothyroidism and interstitial lung disease)
- Results demonstrate the importance of adverse events in a clinical and economic framework

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Appendix: Atrial fibrillation (AF) base and adverse event health states

Paroxysmal/persistent AF (EQ-5D base state)	Permanent AF (EQ-5D base state)
● You have some problems in walking about	● You have some problems in walking about
● You have no problems with washing or dressing yourself	● You have no problems with washing or dressing yourself
● You have no problems performing your usual activities (e.g. work, study, housework, family or leisure activities)	● You have some problems performing your usual activities (e.g. work, study, housework, family or leisure activities)
● You have no pain or discomfort	● You have no pain or discomfort
● You are moderately anxious or depressed	● You are moderately anxious or depressed
Adverse events	
● **Hyperthyroidism:** You have an overactive thyroid gland, which causes your metabolism to speed up. You have lost weight and experience hot flushes. You need to take medication and regularly have blood tests done.	● **Optic issues:** Your eyes are sensitive to bright light, particularly sunlight. Your vision can be slightly blurry in places and you see halos around objects in dim lighting or darkness.
● **Hypothyroidism:** You have an underactive thyroid gland, which causes your metabolism to slow down. You have gained weight and often feel cold. You need to take medication and regularly have blood tests done.	● **Neuropathy:** You have an uncomfortable 'pins and needles' sensation in your hands and feet. Sometimes it can be a painful tingling that can be sensitive to touch. Other times you may have trouble feeling with your fingertips.
● **Liver deposits:** You have developed problems with your liver. This is not likely to be serious and should get better in time, but it means you need to have regular blood tests done.	● **Interstitial lung disease:** You have developed problems with your lungs that affect your breathing and can leave you feeling breathless or tired.
● **Diarrhoea:** You have mild diarrhoea and need to go to the bathroom several times per day.	● **Peripheral vasoconstriction:** You have poor circulation, which often leads to cold hands and feet.
● **Sleep disturbance:** You have trouble falling asleep or staying asleep.	● **Fatigue:** You feel fatigued and tire easily.
● **Nausea:** You have mild nausea and occasional vomiting.	● **Dermatological issues:** You are sensitive to sunlight and sunburn easily. Your skin has taken on a blotchy, slightly bluish-grey tinge.
● **Rash:** You have a mild rash that is red and itchy.	● **Dizziness:** You occasionally experience spells of dizziness.