Europace (2010) **12**, 634–642
doi:10.1093/europace/euq007

Impact of the control of symptomatic paroxysmal atrial fibrillation on health-related quality of life

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Received 23 September 2009; accepted after revision 4 January 2010; online publish-ahead-of-print 13 February 2010

Aims Patients with atrial fibrillation (AF) consider the related symptoms disruptive to their quality of life (QoL). This study aimed to evaluate the impact of the control of symptomatic paroxysmal AF (PAF) on QoL.

Methods and results Patients with symptomatic PAF were treated for 48 weeks with open-label flecainide acetate controlled release (Flec CR). Quality of life was assessed by SF-36 and Atrial Fibrillation Severity Scale scores at baseline, Week 12 (W12), W24, and W48. Of the 229 treated patients, 217 were analysed for QoL (123 with controlled and 94 with uncontrolled symptomatic PAF at inclusion). The controlled group had a similar or better QoL (SF-36) at baseline compared with a reference population (significantly better for: *physical functioning*, *bodily pain*, and *physical component*). The uncontrolled group had an inferior QoL (significantly worse for: *role physical*, *general health*, *vitality*, *role emotional*, *social functioning*, *mental health*, and *mental component*). When treated with Flec CR, the controlled group baseline QoL scores were maintained and the uncontrolled group scores were improved to a level comparable to the controlled group scores. Safety findings reflect the known clinical safety profile of flecainide acetate.

Conclusion In this study, patients with uncontrolled symptomatic PAF at baseline had an inferior QoL to those with controlled symptomatic PAF. Following treatment with controlled-release flecainide acetate, their QoL improved to a level comparable to controlled patients.

Keywords Paroxysmal atrial fibrillation • Quality of life • Reference population • Antiarrhythmic drug

Introduction

Atrial fibrillation (AF), whether paroxysmal (PAF) or persistent, is a chronic disorder, and recurrence is likely at some point in most patients with AF.[1] Stroke as well as functional impairments and cardiac failure are the well-known consequences of AF.[1] However, interventions such as antiarrhythmic drugs, electrical cardioversion, or catheter ablation for terminating or suppressing AF have not been shown to prevent stroke or reduce mortality.[2–4] On the other hand, patients with AF also experience a broad range of symptoms which adversely affect their quality of life (QoL).[5]

The impact of AF on QoL is strongly influenced by the segment of the population that is concerned, as some patients are entirely asymptomatic.[6] One study[7] shows that the majority of patients with PAF consider the dysrhythmia disruptive to their life; however, QoL literature specific to PAF patients is sparse.

In patients with recurrent arrhythmias, radiofrequency catheter ablation of the atrioventricular (AV) node and pacemaker insertion improved QoL[8] as determined by the SF-36 health status questionnaire[9] and the disease-specific Symptom Checklist Frequency and Severity Scale.[10] However, the relative impact of AF among patients who have received little prior treatment to restore or maintain sinus rhythm is not clear.[11] In a study of patients with symptomatic AF,[12] QoL improved after pharmacological treatment of their ailment, and patients in whom therapy prevented AF recurrence experienced the greatest benefit. The latter study also suggests that measures of

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subjective well-being are important adjunct measures, in addition to objective measures of disease severity (e.g. frequency or duration of AF attacks). Other studies have confirmed a meaningful improvement of QoL after both pharmacological and non-pharmacological AF therapies.[12–15] Thus, one of the primary goals of rhythm control interventions should be to control symptoms and improve QoL.[6,16]

Flecainide acetate, a Class IC antiarrhythmic used as a preventive treatment, has been shown to significantly decrease the incidence of PAF episodes, with a good safety profile.[17–25] Two marketed formulations of flecainide acetate exist. The first is an immediate-release formulation (Flec IR) to be taken twice a day, the second is a once-a-day controlled-release formulation (Flec CR).[26]

The primary objective of the present study was to evaluate the impact of the control of symptomatic PAF on QoL. A composite efficacy and safety criterion of 'clinical success' was also evaluated as a secondary endpoint.

Methods

Ethics

This study was conducted in compliance with the ethical principles of the revised Declaration of Helsinki (Somerset West, Republic of South Africa, 1996). Local independent Ethics Committees approved the study protocol and the patients provided informed consent prior to study entry.

Patients

Patients presenting with documented symptomatic PAF (arrhythmia terminating spontaneously) either controlled (defined a priori in the protocol as no more than one symptomatic PAF episode per 6 months) or uncontrolled (two or more symptomatic PAF episodes per 6 months) were considered for study eligibility. During the study, an issue with the above definition was identified: patients undergoing a treatment modification within a few months of inclusion and experiencing no symptomatic PAF episodes since the modification were being classified as uncontrolled at inclusion based on symptomatic PAF episodes in the last 6 months but prior to the treatment modification. The definition was therefore revised to more appropriately classify such patients. In particular, patients having undergone a PAF treatment modification in the last 1–6 months prior to inclusion were defined as controlled if they had no symptomatic PAF episodes occurring under the last therapeutic strategy or uncontrolled if they had at least one symptomatic PAF episode.

Since it was considered that sites would more easily recruit controlled patients and in order to ensure more than one-third of recruited patients were uncontrolled at inclusion, each investigator was encouraged to recruit one uncontrolled patient for one controlled patient. Patients of either sex were included in the study if they met the following criteria: aged 18 to <80 years; in sinus rhythm at the time of inclusion; who had experienced symptomatic AF episodes of 1 min to 72 h, based on the history of at least two symptomatic PAF episodes, at least one of which was documented by electrocardiography (ECG) and/or Holter; requiring antiarrhythmic therapy in the investigator's judgement; with left ventricular ejection fraction (LVEF) of at least 40% documented by ultrasonography; and women of childbearing potential had to use a reliable method of contraception. Those patients exhibiting the following criteria were not included: intolerance and/or failure of previous therapy with Flec IR; severe symptoms (syncope and ischaemic angina) during episodes of arrhythmia; coronary heart disease and/or history of myocardial infarction; congestive heart failure [New York Heart Association classes II, III, and IV]; history of arrhythmia other than PAF; paroxysmal supraventricular tachycardia or atrial flutter unless ablated; sinus dysfunction or atrial disease (bradytachycardia syndrome); heart rate <45 b.p.m.; second- or third-degree AV block; right bundle branch block associated with left hemiblock or complete left bundle branch block; implanted pacemaker; renal failure; decompensated cirrhosis; significant extracardiac or systemic disease susceptible of interfering with assessment of QoL.

Design

This international, open-label study was conducted from September 2003 until September 2005 by 49 cardiologists from 47 cardiology practices (8 hospitals, 4 private hospitals, 1 cardiology centre, and 34 private practices) in France, Belgium, and Italy.

All patients were to be treated with Flec CR over a 48-week period. Patients were classified as having either controlled or uncontrolled symptomatic PAF at inclusion. Depending on their previous antiarrhythmic treatment, patients were managed as follows: (i) patients not exposed to Flec IR at inclusion entered a 2-week titration period starting with Flec CR 100 mg once a day that was increased to 200 mg from Day 8 onwards provided that the QRS duration was <140 ms and had not increased by $\geq 25\%$ from baseline and that there were no tolerability issues; (ii) patients under Flec IR at inclusion were switched to the equivalent daily dose of Flec CR for 48 weeks without titration. Follow-up visits were scheduled for all patients at Week 12 (W12), W24, and W48. Study data were reported in paper case report forms designed according to the study protocol.

On the basis of pre-defined safety and efficacy criteria, doses of Flec CR could be increased to a maximum of 200 mg per day or reduced by 50 mg per day to a minimum of 100 mg per day, where applicable.

All Classes I–III antiarrhythmics were washed out before starting Flec CR. Amiodarone as a preventive treatment of PAF had to have been interrupted for at least 4.5 months before inclusion in the study. Previous use of amiodarone for the purpose of cardioversion was allowed, provided treatment duration was limited to a maximum of 8 days. The ongoing use of beta-blockers, digoxin, or calcium antagonists was permitted, provided daily doses used before the start of Flec CR were kept constant throughout study treatment.

Quality of life

A generic and a disease-specific self-administered QoL questionnaires were filled in by the patients in their own language (French for France, French or Dutch for Belgium, and Italian for Italy) at baseline, W12, W24, and W48.

To assess the primary endpoint of QoL, the generic Medical Outcomes Study 36-Item Short-Form Health Survey (MOS SF-36)[9] was used. The MOS SF-36 provides eight subscale measures of QoL based on 35 of the 36 items in the survey: physical functioning (10 items scored 1–3), role limitations due to physical problems (role physical, 4 items scored 1–2), bodily pain (2 items scored 1–5 and 1–6, respectively), general health (5 items scored 1–5), vitality (4 items scored 1–6), role limitations due to emotional problems (role emotional, 3 items scored 1–2), social functioning (2 items scored 1–5), and mental health (5 items scored 1–5). Two summary scores, mental component scale and physical component scale, were computed by linear combinations of the eight subscale measures.

The Atrial Fibrillation Severity Scale (AFSS, Parts A, B, and C)[10] was also used to assess QoL. At baseline, W12, W24, and W48, patients completed the disease-specific self-administered questionnaire to assess well-being and bothering symptom frequency via Question 4

of AFSS Part A and Questions 1–7 of AFSS Part C. At baseline, patients were also asked AFSS Part A Questions 5–8 pertaining to AF burden. AFSS Part B was completed by the investigator at baseline to further characterize PAF history.

The 'clinical success' composite safety and efficacy criterion was defined as follows: patient alive; without pharmacological or electrical cardioversion; with sinus rhythm maintained (not more than one documented AF per 24-week period); still receiving Flec CR; with QRS duration <140 ms and change from baseline <25%; and with LVEF of at least 35%. Patients not fulfilling all of these criteria for 'clinical success' were considered as clinical failures. Other efficacy endpoints were the time to first PAF recurrence objectively documented by ECG or subjectively documented by inquiry and comments recorded on the patient's diary.

Cardiac safety was assessed based on the incidence of proarrhythmic effects (worsening PAF and/or occurrence of atrial flutter or of paroxysmal supraventricular tachycardia not previously diagnosed and/or occurrence of a clinically significant ventricular arrhythmia in the absence of the known history of ventricular arrhythmia), ECG changes (mostly QRS and QTc changes), and signs of cardiac failure (clinical examination and left ventricular function by ultrasonography).

Statistical analyses

Study analysis data sets were defined as follows. The safety data set included all patients who took at least one capsule of controlled-release flecainide acetate after study inclusion. The intention-to-treat (ITT) efficacy data set included all patients from the safety data set except for those treated with Flec IR who were not controlled at inclusion (exclusion criterion). The QoL baseline and post-baseline data sets excluded patients with missing baseline SF-36 or control status data. Any missing post-baseline QoL data for patients in the QoL post-baseline data set were extrapolated using the last observation carried forward (LOCF) method for analysis purposes.

The score of each subscale of the SF-36 was calculated as the mean of the items, except in the case where more than half of the items were missing, in which case, the subscore was considered as missing. The physical component and mental component summary scores were calculated as the linear combination of the eight standardized [mean = 0, standard deviation (SD) = 1] subscores. Each summary score was then transformed by multiplying by 10 and adding 50 in order to be compared with scores issued from a reference population with mean 50 and SD 10. The reference population was derived from national surveys representative in terms of age and gender.[16,27] The process matched each treated study patient with a random sample of country/language-, gender-, and age-matched subjects from a general reference population.

Controlled and uncontrolled patients were compared with the reference population for SF-36 scores at baseline, W24, and W48 by paired *t*-tests. Complementary analyses were stratified by country/language, with age and gender as covariates. Adjustments were made for the multiplicity of comparisons. The robustness of the results was assessed using a non-parametric analysis of covariance (ANCOVA). AFSS scores [Part A (4) and Part C (1–7)] were analysed and compared between the pre-defined analysis subgroups using a Wilcoxon test.

Clinical failure was analysed globally and in terms of time to clinical failure using the Kaplan–Meier time-to-event method. Time to first PAF recurrence was also analysed. Cox's proportional hazards models were used to assess the relationship between the difference from baseline to end of study for each QoL score and (i) clinical failure and (ii) first PAF recurrence.

It was considered necessary to enrol 240 patients (assuming 15% of the patients would be non-evaluable) in order to achieve 95% power at a two-sided type I error rate of 5% for comparisons of SF-36 physical and mental health summary measures between patient subgroups and the reference population. It was considered that half of the SD of the reference population (SD = 10) would be a perceptible variation (medium effect size[28]).

Results

Of the 230 patients enrolled in the study, 229 were treated (the patient excluded from the safety data set had no treatment data and no adverse reactions reported). The baseline control status of five patients was missing and five other patients had missing SF-36 data at baseline; these patients were excluded from the QoL baseline data set (219 patients: 155 French, 22 French-speaking Belgians, 20 Dutch-speaking Belgians, and 22 Italians).

Two patients were excluded from post-baseline analyses due to their failure to satisfy the major entry criterion of control under Flec IR at inclusion. In particular, the ITT efficacy data set was comprised of 227 patients: 126 controlled (100 of whom were switched from Flec IR at inclusion); 96 uncontrolled; and 5 unknown status (1 of whom was switched from Flec IR at inclusion). The QoL post-baseline data set was comprised of 217 patients: 123 controlled and 94 uncontrolled.

Patient characteristics at baseline

Demographic and main baseline characteristics of the safety data set according to symptomatic PAF control at inclusion are summarized in *Table 1*. Of the five patients with missing control status, three were male and two were female. They had a median time since PAF diagnosis of 0.1 months and four of the patients had a median time since first symptomatic PAF episode of 1.7 months. One was exposed to FLEC IR at inclusion; four were not.

Differences in age and gender were not statistically different between the two subgroups. Time since first symptomatic PAF episode was much shorter in uncontrolled compared with controlled patients, as shown in particular by the percentages of patients with a time shorter than 6 months (54.2 vs. 5.8%, respectively) and conversely by the percentages of patients with time between 12 and 60 months (17.7 vs. 46.7%) or at least 60 months (18.8 vs. 35.0%).

Sixteen patients in the controlled group were diagnosed with PAF (according to the study requirement of two symptomatic PAFs with at least one documented by ECG and/or Holter) in the last 6 months prior to inclusion. However, only seven of them had experienced their first symptomatic PAF episode within the last 6 months. These seven patients were included in the controlled group because they had started treatment for PAF following several symptomatic PAF episodes at least 1 month prior to inclusion and had experienced no symptomatic PAF episodes since treatment instauration.

Overall, the most frequent symptoms accompanying PAF were palpitations (85.2% of patients), fatigue (31.0%), respiratory disorders (20.5%), and chest pain (11.8%). Dizziness, lipothymia, and weakness were reported by <10% of the patients.

Table 1 Demographic and other baseline characteristics of the patients (safety data set)

Parameter	Total (n = 229)[a]	Controlled (n = 126)	Uncontrolled (n = 98)
Age (years)			
Mean (SD)	64.6 (12.0)	65.6 (11.3)	63.2 (13.0)
Range	21.0–87.0	26.0–84.0	21.0–87.0
Gender, *n* (%)			
Male	142 (62.0)	81 (64.3)	58 (59.2)
Female	87 (38.0)	45 (35.7)	40 (40.8)
Weight (kg)			
Mean (SD)	78.4 (16.1)	79.3 (17.0)	77.1 (15.3)
Range	46.0–199.0	46.0–199.0	47.0–120.0
BMI (kg/m^2)			
Mean (SD)	27.1 (4.7)	27.2 (4.6)	26.8 (4.9)
Range	18.0–52.3	18.0–52.3	18.3–48.1
Time since first symptomatic PAF (months)			
Missing	9	6	2
Mean (SD)	46.8 (60.6)	56.0 (53.5)	37.1 (67.8)
Range	0.0–303.6	1.1–303.6	0.0–275.1
<1 month, *n* (%)	36 (16.4%)	0 (0.0%)	34 (35.4%)
1–3 months, *n* (%)	15 (6.8%)	3 (2.5%)	12 (12.5%)
3–6 months, *n* (%)	11 (5.0%)	4 (3.3%)	6 (6.3%)
6–12 months, *n* (%)	24 (10.9%)	15 (12.5%)	9 (9.4%)
12–60 months, *n* (%)	74 (33.6%)	56 (46.7%)	17 (17.7%)
≥60 months, *n* (%)	60 (27.3%)	42 (35.0%)	18 (18.8%)
Time since PAF diagnosis (months)			
Mean (SD)	40.6 (57.6)	51.4 (53.4)	28.7 (61.3)
Range	0.0–303.6	0.1–303.6	0.0–275.1
<1 month, *n* (%)	61 (26.6)	5 (4.0)	53 (54.1)
1–3 months, *n* (%)	10 (4.4)	6 (4.8)	4 (4.1)
3–6 months, *n* (%)	10 (4.4)	5 (4.0)	4 (4.1)
6–12 months, *n* (%)	24 (10.5)	16 (12.7)	8 (8.2)
12–60 months, *n* (%)	71 (31.0)	54 (42.9)	16 (16.3)
≥60 months, *n* (%)	53 (23.1)	40 (31.7)	13 (13.3)
Mean duration (h:min/year)			
Missing	26	17	6
Mean (SD)	17:22 (37:32)	16:40 (24:52)	18:32 (48:51)
Range	0:01–336	0:01–120	0:01–336
Left ventricular ejection fraction (%)			
Missing	5	3	2
Mean (SD)	67.3 (8.4)	67.5 (8.6)	66.7 (8.0)
Range	40.0–90.0	40.0–90.0	47.0–86.0
Diabetes, *n* (%)	16 (7.0)	10 (8.0)	6 (6.1)
Hypertension, *n* (%) (SBP ≥ 140 and/or DBP ≥ 90 mmHg)	96 (41.9)	52 (41.3)	41 (41.8)
Treated for PAF in last 6 months, *n* (%)	166 (72.5)	119 (94.4)	46 (46.9)
Flec IR exposure at inclusion, *n* (%)	103 (45.0)	100 (79.4)	2 (2.0)
Electrical cardioversion, *n* (%)	38 (16.6)	28 (22.2)	9 (9.2)
Pharmacological cardioversion, *n* (%)	121 (52.8)	69 (54.8)	52 (53.1)
Country/language, *n* (%)			
France/French	163 (71.2)	90 (71.4)	70 (71.4)
Belgium/French	22 (9.6)	12 (9.5)	10 (10.2)
Belgium/Dutch	21 (9.2)	12 (9.5)	8 (8.2)
Italy/Italian	23 (10.0)	12 (9.5)	10 (10.2)

[a]Five unknown control status; SD, standard deviation; PAF, paroxysmal atrial fibrillation.

Quality of life

A comparison of the baseline SF-36 scores of controlled patients to their matched reference population showed that their QoL scores were significantly better for the physical functioning subscale, the bodily pain subscale, and the physical component score. The other SF-36 scores showed non-statistically significant differences that favoured the controlled group for all scores except for the role emotional and mental health scores, and consequently the global mental component score, which favoured the reference population. For the uncontrolled group, all of the 10 QoL scores were worse compared with the matched reference population, of which 7 differences were statistically significant. The relationship between uncontrolled symptomatic PAF and inferior QoL impacted the mental scores (significantly worse for role emotional, social functioning, mental health, and mental component) more than the physical scores, although the role physical score, which reflects work and daily activities, and the mixed general health and vitality scores were also significantly worse for uncontrolled patients compared with the reference population. The difference of 4.82 for the global mental component score in the uncontrolled group corresponds to an influence of non-control of AF on QoL close to half the SD (4.82/10.91 = 0.44), which can be considered as a medium effect size.[28] Mean differences in baseline SF-36 scores are presented by control group in *Table 2*.

The analysis of the differences between the controlled and the uncontrolled groups in baseline SF-36 scores and changes from baseline at W12, W24, and W48 are presented in *Table 3*. The differences were mostly positive at baseline (indicating worse QoL in the uncontrolled group, and reaching statistical significance for the general health and vitality scores and for the mental component score), then mostly negative for changes from baseline at the subsequent time points, indicating a greater improvement of QoL under Flec CR treatment in the uncontrolled group. The most significant results were obtained at W24, and the effect was maintained at W48. Patients entering the trial under Flec IR, who represented 80% of the controlled patients, had their QoL maintained when switched to Flec CR.

The mean well-being score (SD) at baseline as assessed from Question 4 of AFSS Part A was 6.7 (2.0) in the uncontrolled group compared with 7.2 (1.5) in the controlled group. This score did not change significantly throughout the study. The total AFSS score, calculated as the sum of scores for Questions 1–7 of AFSS Part C was assessed at baseline, W12, W24, W48, and at end of study. As expected, the mean score at baseline was higher for uncontrolled patients compared with controlled patients. Still higher in the uncontrolled group at W12, it then became similar to that of the controlled group at W24 and was maintained at the same level in both groups thereafter (*Table 4*). These results are consistent with those obtained with the SF-36 questionnaire.

Table 2 Mean differences (reference − study subgroup) in baseline SF-36 scores for controlled and uncontrolled patients (QoL baseline data set)

Variable	*n*	Mean (95% CI)	SD	*P*-value
Controlled ($N = 123$)				
Physical functioning*	122	−4.71 (−9.15, −0.27)	24.76	0.0378
Role physical	121	−0.23 (−7.09, 6.63)	38.10	0.9473
Bodily pain*	121	−4.75 (−8.89, −0.60)	23.01	0.0251
General health	119	−1.48 (−4.92, 1.96)	18.93	0.3957
Vitality	120	−0.77 (−4.01, 2.46)	17.89	0.6373
Role emotional	119	0.91 (−5.54, 7.37)	35.57	0.7797
Social functioning	121	−0.28 (−3.97, 3.41)	20.52	0.8812
Mental health	120	2.51 (−0.58, 5.59)	17.05	0.1099
Mental component	115	1.21 (−0.41, 2.83)	8.76	0.1414
Physical component*	115	−2.01 (−3.87, −0.15)	10.06	0.0346
Uncontrolled ($N = 96$)				
Physical functioning	96	2.65 (−2.34, 7.65)	24.65	0.2947
Role physical*	93	12.89 (4.49, 21.29)	40.78	0.0030
Bodily pain	96	0.43 (−5.15, 6.02)	27.56	0.8784
General health*	96	6.43 (2.13, 10.72)	21.20	0.0038
Vitality*	96	8.19 (4.12, 12.27)	20.12	0.0001
Role emotional*	96	12.75 (4.60, 20.90)	40.23	0.0025
Social functioning*	96	6.71 (1.84, 11.58)	24.03	0.0074
Mental health*	96	7.27 (3.40, 11.15)	19.12	0.0003
Mental component*	93	4.82 (2.58, 7.07)	10.91	<0.0001
Physical component	93	1.41 (−0.89, 3.70)	11.15	0.2267

Higher subscale scores indicated better QoL. *N*, total number of patients; CI, confidence interval; SD, standard deviation.
*Statistically significant at the 0.05 level.

Efficacy

The clinical success rate was similar in the controlled and uncontrolled groups with, respectively, 89 of 126 (70.6%) and 66 of 96 (68.8%) patients classified as successes. The other 67 patients failed for one or more of the following reasons: 'pharmacological/electrical cardioversion', 7 of 37 and 4 of 30 for the controlled and uncontrolled groups, respectively; 'two or more documented PAF per 24-week period', 1 of 37 and 2 of 30; 'withdrawn for treatment inefficacy/safety reasons, for non-compliance or for death', 24 of 37 and 22 of 30; and finally 'withdrawn due to delta QRS ≥25 or duration ≥140', 11 of 37 and 12 of 30, respectively. No patients failed for 'LVEF <35%'.

Of the 158 patients (69.8%) who were clinical successes, 153 (67.4%) completed the study and 5 (2.2%) were withdrawn from the study for reasons not related to efficacy, safety, or non-compliance. The latter five patients were right censored at the end of treatment (or end of study if end of treatment was missing) for time-to-event analyses. Time to event was similar in the controlled and uncontrolled groups. The Cox proportional hazards analysis of the relationship between clinical failure and each SF-36 score difference from baseline to end of study

Table 3 Summary of controlled and uncontrolled subgroup scores for baseline, W12, W24, and W48 in SF-36 scores (QoL post-baseline data set)

Variable	Baseline															
	Day 0			Week 12			Week 24			Week 48						
	Controlled LS mean	Uncontrolled LS mean	*P*-value	Controlled LS mean	Uncontrolled LS mean	*P*-value	Controlled LS mean	Uncontrolled LS mean	*P*-value	Controlled LS mean	Uncontrolled LS mean	*P*-value	Controlled LS mean	Uncontrolled LS mean	*P*-value	
Physical Functioning	79.4	75.1	0.13	0.1	2.3	0.29	−1.3	3.4	0.08	0.2	4.9	0.08				
Role Physical	71.3	61.4	0.06	3.2	8.4	0.26	1.3	15.5	0.02*	2.0	10.4	0.23				
Bodily Pain	72.0	68.2	0.23	−0.1	3.2	0.49	−2.6	0.5	0.49	−0.4	2.9	0.49				
General Health	64.1	57.6	0.01*	−0.5	4.0	0.03*	−1.5	5.8	0.002*	−1.7	5.2	0.003*				
Vitality	58.8	50.8	0.001*	0.0	3.7	0.08	−1.1	5.5	0.004*	−0.1	4.5	0.07				
Social Functioning	78.7	73.3	0.08	3.3	3.6	0.90	1.5	5.2	0.34	2.1	6.0	0.33				
Role Emotional	73.6	66.5	0.16	2.6	9.4	0.14	−0.5	12.5	0.02*	−0.5	10.2	0.09				
Mental Health	65.6	61.7	0.08	1.1	3.5	0.22	1.5	5.1	0.10	1.1	3.5	0.19				
Mental Component scale	48.9	46.0	0.029*	0.8	2.3	0.16	0.7	3.3	0.04*	0.3	2.8	0.09				
Physical Component scale	47.7	45.6	0.10	0.1	1.4	0.22	−1.1	1.8	0.03*	−0.1	2.0	0.10				

Results are expressed in least square means (*P*-value) adjusted for age, country, and language in country. Missing post-baseline data were extrapolated using the LOCF method. *P*-values for post-baseline differences are adjusted for multiplicity using a step-down permutation procedure taking into account correlations among hypothesis tests.
*Statistically significant at the 0.05 level.

Table 4 Evolution of total AFSS [Part C (1–7)] (QoL baseline data set)

	Controlled	Uncontrolled
Score at Day 0		
n	121	95
Mean (SD)	11.8 (4.1)	16.1 (5.7)
Median	11.0	15.0
Min–max	6.0–26.0	7.0–30.0
Score at Week 12		
n	107	79
Mean (SD)	11.7 (4.8)	12.5 (4.0)
Median	11.0	12.0
Min–max	4.0–33.0	7.0–22.0
Score at Week 24		
n	96	72
Mean (SD)	11.5 (4.3)	10.8 (3.5)
Median	11.0	10.0
Min–max	7.0–28.0	6.0–21.0
Score at Week 48		
n	98	68
Mean (SD)	11.2 (4.2)	11.0 (4.2)
Median	10.0	10.0
Min–max	6.0–23.0	7.0–26.0
Score at EOS		
n	108	76
Mean (SD)	11.8 (4.7)	11.8 (5.2)
Median	10.0	10.0
Min–max	6.0–27.0	7.0–32.0

showed that physical functioning [$P = 0.01$, hazard ratio (HR) = 0.981 (0.966, 0.996)], bodily pain [$P = 0.001$, HR = 0.981 (0.970, 0.993)], and physical component [$P = 0.0003$, HR = 0.946 (0.917, 0.974)] scores were strongly related to clinical failure. (An HR of <1 means there is a lower risk of clinical failure for every one point reduction in the SF-36 component score.)

Of the 227 patients in the ITT data set, 87 (38.3%) experienced at least one PAF episode on study treatment [41 (32.5%) controlled and 45 (46.9%) uncontrolled patients]. Twenty-three (10.1%) patients experienced at least one documented PAF episode on study treatment. Three (1.3%) patients experienced two or more documented PAF episodes per 24-week period. Time to first PAF episode after the start of study treatment was significantly shorter (log-rank test, $P = 0.015$; Wilcoxon test, $P = 0.003$) in the uncontrolled group [mean (SD) time of 42.0 (63.0) days; median of 7.0 days] compared with the controlled group [mean time (SD) of 94.2 (93.6) days; median of 81.0 days]. The analysis of the relationship between first PAF recurrence and each QoL score difference from baseline to end of study showed that physical functioning [$P = 0.005$, HR = 0.981 (0.969, 0.994)] and physical component [$P = 0.02$, HR = 0.967 (0.942, 0.994)] scores were strongly related to first PAF recurrence. (An HR of <1 means there is a lower risk of clinical failure for every one point reduction in the SF-36 component score.)

Similar trends were seen in the 23 patients (12 controlled, 10 uncontrolled, and 1 unknown) who experienced at least one documented PAF recurrence.

Cardiac safety

Fifteen events related to proarrhythmic effects were observed in 14 of 229 (6.1%) patients. They included atrial flutter (six patients), bradycardia (three patients), right bundle branch block (two patients), and sudden death (one patient). The other three events were not reported by the investigator but were documented as adverse events related to proarrhythmic effects by the sponsor after a post-study review of the ECG data. The sudden death of a 77-year-old male with uncontrolled symptomatic PAF at inclusion, who had a 10-year history of high blood pressure and venous insufficiency and a recent aortic regurgitation, was considered probably not related to the study drug by the investigator. In the absence of sufficient information to definitely exclude a proarrhythmic effect of Flec CR, the serious adverse event was documented by the sponsor as possibly related to the study drug.

A QRS duration $\geq$140 ms or an increase in QRS by 25% or more was noted for 2 of 109 (1.8%) patients by W12 in the controlled group vs. 7 of 83 (8.4%) in the uncontrolled group. The mean (SD, median) QRS change at the end of the study was 1.1% (17.9, 0.0%) for the controlled group compared with 4.7% (15.1, 2.6%) for the uncontrolled group. At the end of the study, QTc was prolonged to over 440 ms in 15 of 106 (14.2%) controlled patients with a baseline QTc interval of no more than 440 ms compared with 15 of 80 (18.8%) uncontrolled patients. Comparing patients based on Flec IR status at inclusion (Flec IR vs. no Flec IR), at the end of the study, QTc was prolonged to over 440 ms in 10 of 88 (11.4%) Flec IR patients with a baseline QTc interval of no more than 440 ms compared with 20 of 101 (19.8%) no Flec IR patients.

General safety

A total of 146 of 229 (63.8%) patients experienced at least one treatment emergent adverse event during the study and 23 serious adverse events were reported in 20 (8.7%) patients (including one death described earlier). Gastrointestinal disorders (20.5% of the patients), nervous system disorders (19.7%), musculoskeletal disorders (18.8%), infections and infestations (16.2%), general disorders (13.1%), cardiac disorders (12.7%), and vascular disorders (11.4%) were the most common system organ classes (MedDRA) of adverse events in the study. Thirty-five (15.3%) patients experienced events which were thought by the investigator to be possibly or probably related to study treatment and 7.9% of the patients were withdrawn from the study due to the occurrence of an adverse event.

Discussion

In this study, patients with uncontrolled symptomatic PAF, unlike patients with controlled symptomatic PAF, had an inferior perceived health-related QoL when compared with a country/language-, gender-, and age-matched general reference population. These patients showed an inferior QoL in all eight SF-36 subscales, with significantly worse scores for role physical, general health, vitality, role emotional, social functioning, and mental health and a significantly worse summary score for mental health. The SF-36 is the most widely validated generic instrument available to measure perceived health-related QoL and has been used in a number of studies. The present results are in agreement with several published studies including an international study of 152 patients with PAF (60.5%) or persistent (39.5%) AF[5] and a large inspection cohort of 963 newly diagnosed patients in North America with PAF (4.0%) or persistent (96.0%) AF.[16] The distinctive feature of the present study is the focus on PAF which may disable QoL in a different way to persistent or permanent AF. Indeed PAF can concern a different population regarding associated cardiac disease and can be perceived differently due to the paroxysms. In this study, extracardiac co-morbidity could have impacted the SF-36 result[6] as it is a generic instrument; however, the AF-specific scale confirms the difference at baseline between controlled and uncontrolled patients. Furthermore, the study population had few co-morbid health conditions.

Following treatment with controlled-release flecainide acetate, SF-36 scores showed an improvement in the QoL of uncontrolled patients, with maximum effect obtained at W24 and maintenance of improvement at W48. Baseline QoL levels were maintained for controlled patients. Results of a sensitivity analysis using a country/language-, gender- and age-adjusted non-parametric ANCOVA on SF-36 scores validate these findings. Previous studies have shown that QoL improves with a variety of AF control therapies, whether pharmacological for rate or rhythm control in persistent AF[29] and for rhythm control in studies investigating amiodarone, propafenone, or sotalol in persistent AF,[12,15] or non-pharmacological, such as catheter ablation.[7]

Total AFSS scores illustrated a marked improvement of symptoms in the uncontrolled group at W12. Scores then continued to improve between W12 and W24 and were maintained at this level between W24 and W48. Flecainide acetate is known to significantly decrease the incidence of PAF episodes and the relationship between AFSS improvement and decrease/disappearance of AF recurrence has been previously reported in the CTAF.[30]

Clinical success, based on a composite safety and efficacy endpoint, was observed in ~70% of the patients with no difference between the uncontrolled and the controlled groups. There was a significant relationship between clinical failure and the SF-36 scores physical functioning ($P = 0.01$), bodily pain ($P = 0.001$), and physical component ($P = 0.0003$).

The HRs presented above indicate a 1.9% reduction in risk is associated with a decrease of one point in both the bodily pain and physical functioning subscales of the SF-36; and a 5.4% reduction in risk per single point in the physical component score.

Physical functioning and physical component scores were also significantly related to the time to first PAF recurrence ($P = 0.005$ and $P = 0.02$, respectively).

The time-to-first-PAF-recurrence HRs presented above indicate a 1.9% reduction in risk is associated with a decrease of one point in the physical functioning subscale; and a 3.3% reduction in risk per single point in the physical component score.

Since one of the main goals of maintenance therapy is suppression of symptoms and the most beneficial therapies for patients prevent AF recurrence, this study was designed to investigate

the impact of the control of symptomatic PAF on QoL. Post-baseline analyses investigating the relationship between AF burden and QoL are beyond the scope of this study.

Caution should be taken when interpreting study results due to the fact that patient control status is defined based on symptoms reported by the patient. Furthermore, there is a significant difference between the two control status subgroups in the duration of illness at inclusion (54.2% of uncontrolled patients experienced their first symptomatic PAF episode <6 months prior to inclusion compared with 5.8% of controlled patients). As such, improvements in QoL in the uncontrolled group may be related to patients adjusting to their AF. It is beyond the scope of this study to directly attribute improvements in QoL to a specific drug effect.

Another key limitation of the study is the inability to assess all symptomatic PAF episodes objectively (ECG). In an attempt to collect information on all symptomatic PAF episodes, inquiry and patient diaries were also used to record symptomatic PAF based on subjective evaluations without the objective confirmation of an ECG. Some analyses combined objective and subjective assessments (as indicated in the description of the analyses) and this should be taken into consideration when interpreting results.

Conclusion

In this study, patients with uncontrolled symptomatic PAF at baseline had an inferior QoL to patients with controlled symptomatic PAF. Following treatment with controlled-release flecainide acetate, their QoL improved to a level comparable to controlled patients. The use of QoL questionnaires to assist with therapeutic decision-making and follow-up evaluation for patients with symptomatic PAF could prove valuable.

Acknowledgements

We thank the study investigators, the health staff, and the patients who participated in this study. We also thank the providers of the reference populations (France: Emmanuel Ecosse; Belgium: Martin Muller; and Italy: Paola Mosconi).

Conflict of interest: none declared.

Funding

This study was sponsored by 3M Santé and then MEDA Pharma. Funding to pay the Open Access publication charges for this article was provided by MEDA Pharma SAS.

Appendix

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