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Effect of continuous versus episodic amiodarone treatment on quality of life in persistent atrial fibrillation

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Aims Amiodarone is associated with significant adverse effects. We hypothesized that episodic amiodarone treatment would be associated with better quality of life (QoL) compared with continuous treatment in the prevention of recurrent atrial fibrillation (AF).

Methods and results Quality of life was assessed in 158 patients from the Continuous vs. Episodic Prophylactic Treatment with Amiodarone for the Prevention of AF (CONVERT) study, using the Short Form (SF)-36 health survey and University of Toronto AF Severity Scale (AF severity scale) questionnaires at baseline and 1 year. The episodic group received amiodarone 1 month peri-cardioversion, the continuous group continued amiodarone. Patients were assessed for major adverse events and maintenance of sinus rhythm during follow-up (i.e. no AF recurrences at every follow-up visit). Quality of life (assessed by SF-36 and AF severity scale) was comparable between both treatment groups at baseline and 12 months, with similar incidence rates of major adverse events. Fewer patients in the episodic group had maintenance of sinus rhythm during follow-up [27 (36%) vs. 49 (59%), $P = 0.004$]. In the episodic group, maintenance of sinus rhythm was associated with a significant improvement on four SF-36 subscales and AF severity scale at 12 months. In contrast, in the continuous group no significant differences in QoL were seen between patients with continued maintenance of sinus rhythm compared with those with AF recurrence at the end of follow-up.

Conclusion Quality of life was comparable in the episodic and continuous treated group after 12 months of follow-up. Continued maintenance of sinus rhythm was associated with an improvement in QoL in the episodic but not the continuous treated group.

Keywords Atrial fibrillation • Amiodarone • Quality of life

Introduction

Atrial fibrillation (AF) is the most common occurring arrhythmia and is associated with complaints such as palpitations, dyspnoea, and fatigue. It may further lead to heart failure, stroke, and death.[1,2] Patients with symptomatic AF have been shown to have impaired quality of life (QoL) compared with the general population and even patients with other cardiac heart disease, such as ischaemic heart disease, including myocardial infarction.[3,4] The most widely used tool to assess general health-related quality of life (HRQL) is the Medical Outcomes Study Short Form (SF-36) questionnaire,[5] but more disease-specific measures of QoL for AF have been developed such as the University of Toronto Atrial Fibrillation Severity Scale to ascertain perceived AF severity.[6,7] We and others have shown that restoration and maintenance of sinus rhythm is associated with a significant increase in SF-36 subscales.[4,8,9] Furthermore, symptomatic patients at baseline were more likely to have improvement in SF-36 scores compared with asymptomatic patients.[9] Amiodarone is the most effective

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antiarrhythmic drug for achieving and maintaining sinus rhythm.[8,9] Amiodarone, however, can cause major (non-)cardiac adverse events, which might negate the positive benefit of maintaining sinus rhythm. In the present study, we analysed QoL, measuring general HRQL using the SF-36 and disease-specific measures of QoL using the AF severity scale, in patients randomized to either episodic or continuous amiodarone treatment for the prevention of AF. Our hypothesis was that episodic amiodarone treatment is associated with a lower major adverse event rate and a higher QoL compared with continuous amiodarone treatment, while AF is effectively suppressed although, at the cost of more electrical cardioversions (ECVs). We furthermore wanted to investigate the role of successful rhythm control on QoL in this population of patients with persistent AF.

Methods

Patients

The present study was a predefined sub-study of the CONVERT study. The methods and results have previously been described in detail.[10] The study was approved by the institutional review boards of all participating centres and patients gave written informed consent. In total 209 patients were included, 106 in the episodic amiodarone treatment arm, and 103 in the continuous amiodarone treatment arm. In short, patients were included in the presence of symptomatic AF recurrence and were loaded with 600 mg oral amiodarone for 4 weeks prior to a planned ECV and received a maintenance dose of 200 mg after achieving sinus rhythm. Patients were subsequently randomly assigned to receive either episodic or continuous amiodarone treatment. In the episodic treated group, patients continued amiodarone only 1 month post-ECV, while patients in the continuous treated group continued amiodarone throughout. In case of a recurrence of AF, patients were re-loaded with amiodarone if it occurred under inadequate (desethyl)amiodarone serum levels. AF was accepted in case of adequate (desethyl)amiodarone levels of more than 2 mg/L at the moment of a relapse. Patients were evaluated at the outpatient department for rhythm control outcome and occurrence of the composite primary endpoint (amiodarone- and underlying heart disease-related major adverse events) throughout follow-up. For the purpose of the present study, we defined patients to have maintenance of sinus rhythm during follow-up if they did not have a recurrence of AF at every follow-up visit.

Endpoints

The primary endpoint of the CONVERT study was a composite of amiodarone-related (cardiovascular effects, hyper- and hypothyroidism, pulmonary and hepatic toxicity, dermatological, ophthalmologic, neurological, and gastrointestinal effects) and underlying heart disease-related major events (hospital admission for heart failure, thromboembolic complications, bleeding, myocardial ischaemia or infarction, and death). In the parent study, no significant difference in incidence rate of the primary endpoint was encountered between both treatment strategies. For the present analysis, we included 158 patients who had completed at least 1 year of follow-up and completed the questionnaires at baseline and 12 months follow-up, 75 in the episodic group and 83 in the continuous treated group, respectively. Another 51 patients (31 episodic and 20 continuous treated patients) either did not complete the questionnaires at either baseline or 1 year or died during follow-up ($n = 9$) and were excluded from the present analysis. All the excluded patients did not differ significantly from included patients at baseline and follow-up.

Quality of life questionnaire

Patients were asked to complete questionnaires at baseline (i.e. inclusion visit and ~4 weeks prior to ECV) and at 12 months follow-up. Health-related quality of life was assessed using the Medical Outcomes Study Short-Form health survey (SF-36) questionnaire. The SF-36 is a standardized, validated, generic health survey that has been frequently used in arrhythmia studies. The SF-36 has been translated and validated in the Netherlands.[5] It contains eight subscales. The subscales for assessing physical health are general health perception, physical functioning, role limitations due to physical problems, and bodily pain. Mental health is assessed with the subscales social functioning, role limitations due to emotional problems, mental health, and vitality. Scores are transformed to a scale ranging from 1 to 100, with lower scores representing a lower HRQL. Severity of AF-related symptoms was assessed using Part C of the University of Toronto AF Severity Scale (AF severity scale). This was developed as a disease-specific instrument intended to measure the patient's perception of severity of arrhythmia-related symptoms[6] and represents an AF-specific measurement of QoL. This is a seven-item checklist that includes common AF symptoms (e.g. palpitations and dyspnoea). Items are rated on a six-point scale. Scores range from 0 to 35, with higher scores indicating greater AF symptom severity.

Statistical analysis

Baseline descriptive statistics are presented as the mean ± standard deviation (SD) or median (range) for continuous variables and numbers with percentages for categorical variables. At each measurement point all subscales of the SF-36 and AF severity scale were compared between the episodic and continuous treatment groups. Within each treatment strategy, all subscales of the SF-36 and AF severity scale were compared at baseline and 12 months between patients who maintained sinus rhythm during follow-up and patients with AF recurrence. For a comparison of scores between groups, Student *t*-test was used for independent variables. For all analyses of differences in scores at baseline and 12 months paired samples Student *t*-tests were used. Effect size was calculated according to Cohen[11] by dividing the difference within the assigned treatment strategies in the mean changes in SF-36 scores from baseline divided by the pooled standard deviation to assess the clinical importance of differences in SF-36 measures. *P*-value of <0.05 was deemed statistically significant. All analyses were performed on an intention-to-treat basis. The statistical analyses were carried out using the statistical program SPSS, version 16.0.

Results

The baseline characteristics of the patients in both treatment groups were comparable with similar co-morbidity, except for more chronic obstructive pulmonary disease in the episodic group (*Table 1*). At baseline, the mean heart rate was comparable between both treatment strategies (92 ± 19 vs. 90 ± 19 beats per minute, $P = 0.5$). Baseline SF-36 scores were compared with sex and age matched controls. The controls scored significantly higher on all but two subscales (mental health and bodily pain) indicating that our study population represents a typical persistent AF population (*Figure 1A*).

Table 1 Patient characteristics

	Episodic amiodarone treatment ($n = 75$)	Continuous amiodarone treatment ($n = 83$)	*P*-value
Age (years)	68 ± 9	65 ± 9	0.1
Male, *n* (%)	43 (57%)	55 (67%)	0.3
AF/AFL, *n* (%)	74/1 (99/1%)	79/4 (95/5%)	0.3
Heart rate at baseline (beats per minute)	92 ± 19	90 ± 19	0.5
Total AF duration (days)	525 (55–11 750)	402 (48–9857)	0.8
Duration present episode of AF (days)	33 (0–255)	37 (0–917)	0.9
Complaints of AF, *n* (%)	71 (95%)	75 (90%)	0.4
Palpitations, *n* (%)	29 (39%)	33 (40%)	0.7
Dyspnoea, *n* (%)	52 (69%)	53 (64%)	0.9
Fatigue, *n* (%)	38 (51%)	42 (51%)	0.9
Underlying diseases			
Coronary artery disease, *n* (%)	10 (13%)	13 (16%)	0.8
Valve disease, *n* (%)	5 (7%)	4 (5%)	0.7
Cardiomyopathy, *n* (%)	3 (4%)	2 (2%)	0.7
Hypertension, *n* (%)	33 (44%)	40 (48%)	0.6
History of chronic obstructive pulmonary disease, *n* (%)	13 (17%)	4 (5%)	0.01*
History of diabetes mellitus, *n* (%)	9 (12%)	9 (11%)	1.0
History of heart failure hospitalization, *n* (%)	2 (3%)	7 (8%)	0.2
NYHA class I for heart failure, *n* (%)	23 (31%)	30 (36%)	0.6
NYHA class II for heart failure, *n* (%)	52 (69%)	53 (64%)	
Systolic blood pressure (mmHg)	136 ± 17	137 ± 18	0.6
Diastolic blood pressure (mmHg)	84 ± 11	85 ± 10	0.9
Left atrial size, long axis (mm)	47 ± 6	45 ± 5	0.04*
Left ventricular end diastolic diameter (mm)	50 ± 8	51 ± 7	0.7
Left ventricular end systolic diameter (mm)	35 ± 10	35 ± 7	0.7
Fractional shortening (%)	31 ± 12	31 ± 9	0.9
Medication at screening			
Acenocoumarol, *n* (%)	72 (96%)	83 (100%)	0.2
Beta blocker, *n* (%)	45 (60%)	62 (75%)	0.1
Diuretics, *n* (%)	26 (35%)	30 (36%)	1.0
Angiotensin converting enzyme inhibitor, *n* (%)	35 (47%)	32 (39%)	0.3
Angiotensin II receptor blocker, *n* (%)	9 (12%)	10 (12%)	1.0
Digoxin, *n* (%)	22 (29%)	20 (24%)	0.5
Verapamil or diltiazem, *n* (%)	11 (15%)	14 (17%)	0.6
Statin, *n* (%)	10 (13%)	13 (16%)	0.8

AF, atrial fibrillation; AFL, atrial flutter; MI, myocardial infarction; NYHA, New York Heart Association; *statistically significant.

The mean average heart rate during follow-up, irrespective of rhythm, was significantly higher in the episodic compared with the continuous group (72 ± 11 vs. 66 ± 12 beats per minute, $P = 0.003$). At 12 months, mean heart rate was also higher in the episodic group (76 ± 17 vs. 69 ± 18 beats per minute, $P = 0.01$) with fewer patients on amiodarone therapy in the episodic group [12 (16%) vs. 49 (59%), $P < 0.001$]. Patients who maintained sinus rhythm during follow-up had a significant lower mean average heart rate during follow-up (63 ± 8 vs. 74 ± 13 beats per minute, $P < 0.001$) and mean heart rate at 12 months (64 ± 11 vs. 81 ± 19 beats per minute, $P < 0.001$). No difference was observed in mean average heart rate in patients with AF recurrence during follow-up in both treatment strategies (75 ± 12 vs. 73 ± 13 beats per minute, in the episodic and continuous group, respectively, $P = 0.5$).

At 12 months of follow-up, a comparable number of patients were on rate control medication [52 (70%) vs. 53 (64%) in the episodic vs. continuous group, $P = 0.4$]. The majority of patients were on continuous beta blocker medication from baseline [40 (53%) vs. 48 (58%) patients, $P = 0.6$]. The mean duration of beta blocker use was comparable (11.8 ± 3.8 months vs. 10.7 ± 5.4 months, $P = 0.2$). At 12 months of follow-up, only six patients remained on digoxin from baseline. Digoxin was mostly discontinued early during follow-up [1.2 (0.4–14.2) months in the episodic and 2.2 (0.7–13.1) months in the continuous group, $P = 0.9$].

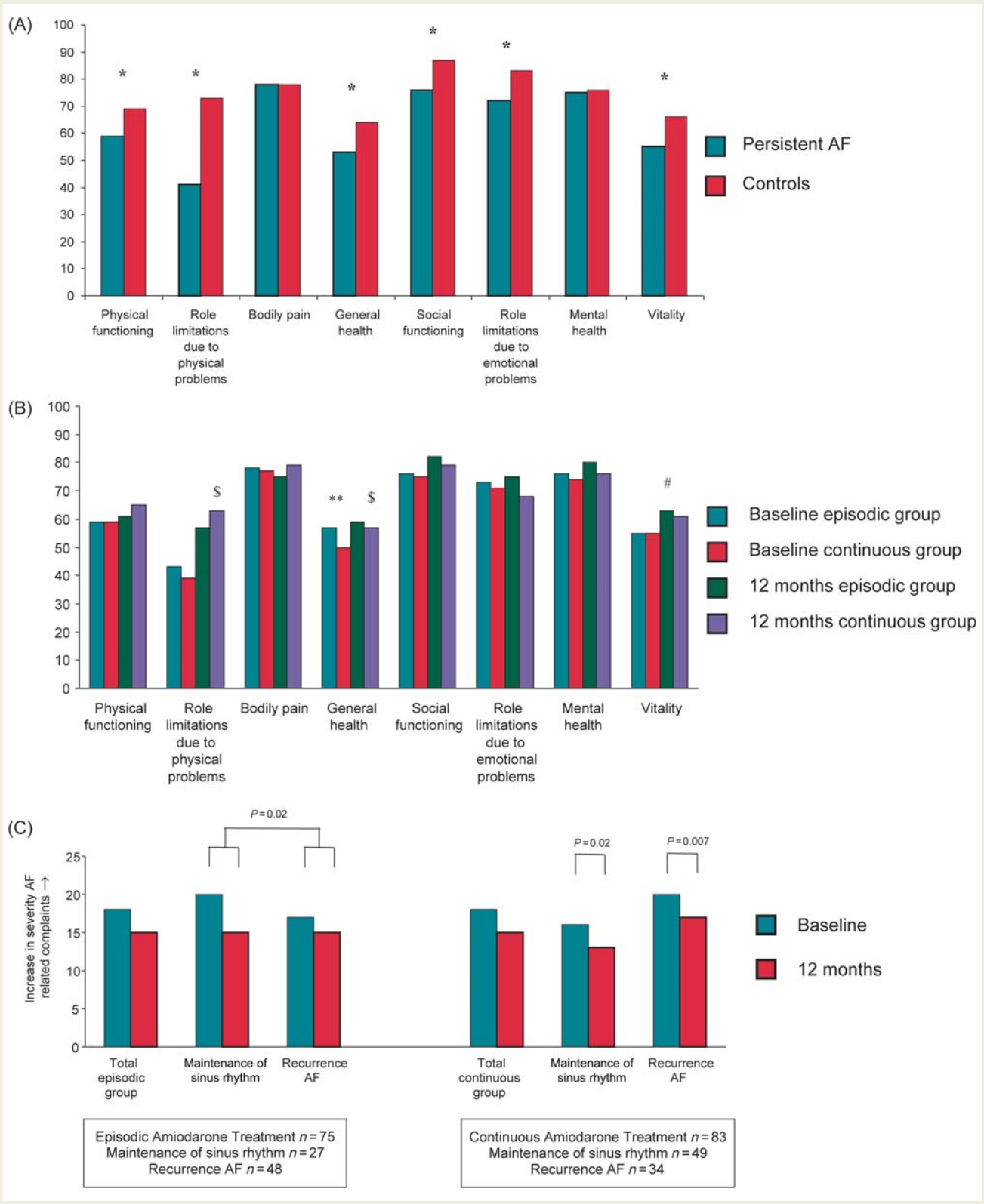

Figure 1 SF-36 scores of persistent AF study patients at baseline compared with healthy gender and age matched controls (*A*); SF-36 scores at baseline and 12 months follow-up in episodic and continuous treated groups (*B*); Atrial fibrillation severity scale scores at baseline and 12 months (*C*). AF, atrial fibrillation; SF-36, Short Form-36 health survey. $^{*}P < 0.05$ study patients vs. healthy controls; $^{**}P < 0.05$ episodic vs. continuous group; $^{\#}P < 0.05$ episodic group: baseline vs. 12 months; $^{\$}P < 0.05$ continuous group: baseline vs. 12 months.

Quality of life in episodic vs. continuous treated group

Short Form-36 scores were comparable between the episodic and continuous treated groups at baseline and 12 months (*Figure 1B*). The only difference between treatment strategies was seen at baseline on the subscale general health with a higher score in the episodic group (57 vs. 50, $P < 0.05$, *Figure 1B*). In the episodic group, an improvement after 12 months was seen on the subscale vitality (+8, $P = 0.03$, *Figure 1B*). In the continuous group, an improvement was seen on the subscales role limitations due to physical problems and general health after 12 months (+24, $P = 0.001$ and +7, $P = 0.02$, respectively, *Figure 1B*). The effect sizes of changes (i.e. the measurement of the magnitude of a treatment effect) in SF-36 scores within the treatment strategies were, however, small and below 0.25 (i.e. one-fourth standard deviation). Scores on the AF severity scale, indicating perceived severity of AF-related complaints, were comparable at baseline and after 12 months in both treatment groups (*Figure 1C*).

The incidence of major adverse events was comparable between the episodic and continuous treated groups during 12 months of follow-up [19 (25%) vs. 20 (24%), $P = 0.9$]. In 26 (16%) patients an amiodarone-related major adverse event occurred [9 (12%) vs. 17 (20%), $P = 0.1$, in the episodic and continuous treated group, respectively], with thyroid dysfunction being the most prevalent. After 12 months, improvement on all SF-36 scales was seen independent of the occurrence of an amiodarone-related adverse event (data not shown). In total 13 (8%) patients encountered an underlying heart disease-related adverse event during 12 months of follow-up. Significantly more underlying heart disease-related adverse events occurred in the episodic compared with the continuous treated group [10 (13%) vs. 3 (4%), $P = 0.03$]. Significant impairment was seen on the subscale bodily pain in patients with an underlying heart disease-related major adverse event compared with those without ($P = 0.04$).

Rhythm control outcome and quality of life

At the end of follow-up, in total 76 (48%) patients had maintained sinus rhythm, i.e. had no recurrence of AF at every follow-up visit. Episodic treatment was significantly less successful in achieving maintenance of sinus rhythm after 12 months of follow-up [27 (36%) vs. 49 (59%) patients, $P = 0.004$]. Median number of AF recurrences during 12 months of follow-up was comparable between both treatment groups [1 (1–2) in the episodic vs. 1 (1–3) in the continuous treated group, $P = 0.7$]. Mean time to first AF recurrence was also comparable between both treatment groups and occurred relatively late (after 244 ± 192 days in the episodic vs. 320 ± 157 days in the continuous treated group, $P = 0.1$). Within the treatment strategies there were significant differences in QoL, assessed by SF-36 and AF severity scale. In the episodic treated group, after 12 months of follow-up significant improvement in QoL was seen in patients who maintained sinus rhythm during follow-up compared with patients with AF recurrence. Improvement occurred on four SF-36 subscales [two subscales assessing physical (physical functioning and role limitations due to physical problems) and two assessing mental health (social functioning and vitality)] (*Figure 2*). Furthermore, a significantly larger decrease in severity of AF-related complaints as assessed by the AF severity scale was observed in the episodic group (*Figure 1C*). In contrast, in the continuous treated group no significant differences in QoL were seen between patients who maintained sinus rhythm during follow-up after 12 months of follow-up compared with those with AF recurrence. Similar scores on the SF-36 subscales (*Figure 2*) and comparable decrease in severity of AF-related complaints were observed (*Figure 1C*). Patients who maintained sinus rhythm throughout follow-up seemed to show larger improvements in SF-36 scores in the episodic compared with the continuous treated group, though it did not reach statistical significance (*Figure 2*). Role limitations due to physical problems showed a significant larger improvement in case of recurrent AF if patients were randomized to continuous amiodarone therapy (*Figure 2*). In both treatment groups, patients with recurrence of AF showed a trend to worsening of role limitations due to emotional problems (*Figure 2*).

Discussion

Our study shows that the assigned treatment strategy, episodic or continuous amiodarone therapy, does not influence QoL, assessed by SF-36 and AF severity scale, during 12 months of follow-up. Successful rhythm control outcome, though, seems to influence QoL positively, but only in the episodic group. Episodic amiodarone treatment, however, was less effective in successful rhythm control. In the present analysis, in continuously treated patients, improvement in QoL between successfully and not successfully treated patients was comparable.

Quality of life and amiodarone

Our persistent AF patients have lower SF-36 scores, compared with healthy controls, which has consistently been shown in previous reports.[4,6] Quality of life improved in both our amiodarone rhythm control strategies, as assessed by SF-36 and the AF severity scale, without significant differences between the episodic [amiodarone 2 month peri-(re-) cardioversion] and continuous amiodarone treated groups. This may suggest that amiodarone itself does not influence QoL. In line with our findings, Dorian *et al.*[6] have shown that amiodarone treatment improves SF-36 scores after 3 months of follow-up in a comparable study population. In that study similar improvements in SF-36 scores were seen in the sotalol and propafenone randomized treatment groups. In the same study, scores on the AF severity scale also decreased as well in the amiodarone, as in the sotalol and the propafenone randomized patients.[12] Another study comparing placebo, short-term and long-term amiodarone treatment for the prevention of persistent AF showed no differences in SF-36 scores between the three groups during follow-up.[13] Recently, Mark *et al.* compared SF-36 scores in heart failure patients, though mostly without AF, treated with defibrillator or amiodarone therapy. Defibrillator therapy improved SF-36 scores at 3 and 12 months, while amiodarone therapy did not show any impact on SF-36 scores.[14] These studies all highlight that amiodarone therapy did not worsen HRQL as assessed by SF-36. Whether this was achieved, however, through a direct effect of amiodarone, either by

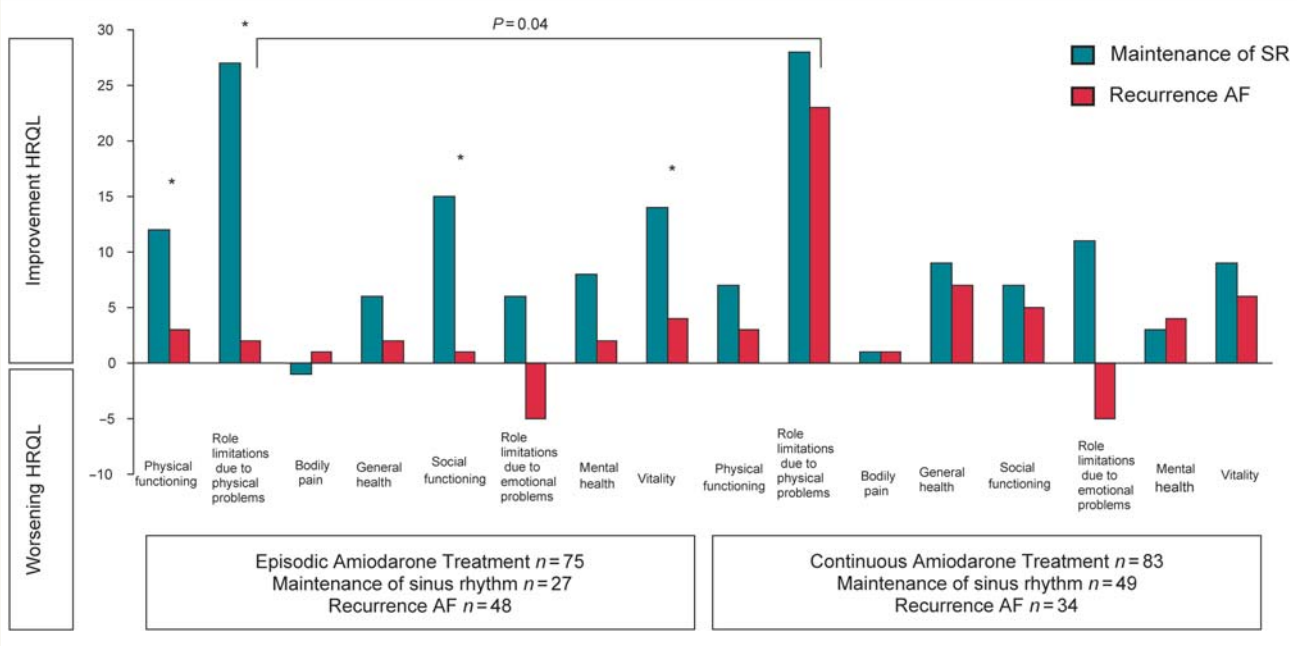

Figure 2 Mean changes in SF-36 scores at 12 months from baseline in both treatment strategies according to rhythm control outcome. AF, atrial fibrillation; HRQL, health-related quality of life; SF-36, Short Form-36 health survey; SR, sinus rhythm. *$P < 0.05$ maintenance of sinus rhythm during follow-up vs. recurrence atrial fibrillation.

maintaining sinus rhythm or its rate controlling properties during AF, on HRQL and/or through sinus rhythm maintenance remains difficult to ascertain. In this respect, it is important to state that drugs that possess rate controlling properties in addition to anti-arrhythmic effects may have important advantages. The new anti-arrhythmic drug, dronedarone, also contains this beneficial combination of drug actions.[15,16]

The impact of major adverse events due to amiodarone therapy on HRQL has, however, not been investigated before. Our results showed a similar incidence rate of major adverse events after 12 months of follow-up in both treatment strategies [19 (25%) vs. 20 (24%), in the episodic and continuous group, respectively]. This may, in part, account for the comparable SF-36 scores after 12 months of follow-up found in both groups. In addition, even though the episodic group had more patients with AF recurrence the median number of recurrences per patient during 12 months of follow-up was one in both treatment groups, resulting in similar SF-36 scores.

Quality of life and sinus rhythm

In our study population QoL, assessed by SF-36 and AF severity scale, improved significantly if sinus rhythm could be maintained, but only in the episodic treated group. Significant QoL improvements were seen on four subscales, with lower severity of AF-related complaints in those who maintained sinus rhythm at 12 months of follow-up, indicating that sinus rhythm indeed improves AF-related complaints. The positive benefit of sinus rhythm maintenance in the episodic group may, however, have been influenced by the timing of AF recurrence. AF recurrence occurred relatively late (after a mean of 244 days) and close to completion of the questionnaires and could therefore have had a more substantial influence on outcome. Fewer patients in the episodic group, however, maintained sinus rhythm throughout follow-up compared with patients treated with continuous amiodarone. This was influenced by the fact that significantly fewer patients in the episodic group were on amiodarone therapy at 12 months of follow-up. In line with these findings, Singh *et al.*[17] also found significant improvements on various SF-36 subscales in patients who maintained sinus rhythm compared with patients in AF, with significant reduction in perceived AF severity. These patients were all continuously treated with amiodarone. Dorian *et al.*[12] showed that scores on the AF severity scale decreased more in the amiodarone group compared with the propafenone and sotalol groups, probably due to the superiority of amiodarone in sinus rhythm maintenance. We have also previously shown that improvement in HRQL, assessed by SF-36 is associated with the presence of sinus rhythm at the end of follow-up.[4]

Interestingly, patients in the continuous group, on the other hand, had similar QoL improvement, both on the SF-36 scores and the AF severity scale, independent of rhythm control outcome. Even though continuous amiodarone treatment was superior to episodic treatment for maintaining sinus rhythm, it did not lead to vaster improvement in QoL. The positive benefit of sinus rhythm maintenance on QoL may therefore have been counterbalanced by daily amiodarone use. Alternatively, the lower heart rate during recurrent AF in the continuous group, due to the rate controlling property of amiodarone, may have had favourable effects on QoL, as AF recurrences may have been asymptomatic. We did not monitor for AF recurrences between follow-up visits to systematically detect asymptomatic

recurrences. This is also reflected by the larger improvement on the subscale role limitations due to physical problems in patients with AF recurrence on continuous amiodarone therapy. These results suggest that substantial improvement in QoL is not achieved by sinus rhythm maintenance alone, but especially by sinus rhythm maintenance without the need for antiarrhythmic drug use. This poses an interesting question for whom episodic amiodarone treatment may be a viable therapy option for successful rhythm control.

Study limitations

We studied QoL, using SF-36 and AF severity scale in a small study population. The study was, however, a predefined sub-study of the CONVERT study. Due to the small number of patients in this study the power to detect differences between the two treatment strategies and their effect on QoL is low. This was also further confounded by the exclusion of nearly a quarter of the cohort (51 out of 209 patients), though they had comparable baseline characteristics to the included patients. The results may have been different with the inclusion of these patients. Our results regarding rhythm control outcome and QoL are also based on a small number of patients and are an analysis of a subset of patients. The conclusions that have been drawn should, therefore, be interpreted with caution and seen as hypothesis-generating. It cannot be generally applied to all patients with persistent AF. We used the SF-36, which is a validated questionnaire, but is a tool to measure general HRQL. It may also measure complaints due to non-cardiac diseases, and not only cardiac disease specific complaints. Questionnaires were not filled out at the time of a recurrence of AF or at the time of an amiodarone- or underlying heart disease-related major adverse event, but at baseline and after 12 months. In addition, patients might have had asymptomatic AF recurrences between follow-up visits, which were not detected. The causal relationship between SF-36 and AF severity scale scores and a recurrence of AF or occurrence of a major averse event can therefore not be clearly established. Longer follow-up may yield different results as the proportion of patients maintaining sinus rhythm and the incidence of adverse events may be significantly different.

Conclusions

In patients with persistent AF episodic amiodarone treatment is not associated with higher QoL, assessed by SF-36 and AF severity scale, compared with continuous amiodarone treatment. Successful rhythm control outcome influenced QoL positively, but only in the episodic treated group.

Conflicts of interest: I.C.V.G. reports receiving research grants from Sanofi-Aventis, AstraZeneca, Boehringer Ingelheim, and Medtronic.

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