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REVIEW

Quality of life in patients with atrial fibrillation: how to assess it and how to improve it

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Atrial fibrillation (AF) is the most frequent cardiac rhythm disorder and presents a considerable public health burden that is likely to increase in the next decades due to the ageing population. Current management strategies focus on the heart rate and rhythm control, thromboembolism prevention, and treatment of underlying diseases. The concept of quality of life (QoL) has gained significant importance in recent years as an outcome measure in AF studies evaluating therapeutic interventions and as a relevant component of a comprehensive treatment plan. Quality of life is impaired in the majority of patients with AF, and both rate and rhythm control strategies show significant improvement in QoL measures in highly symptomatic patients. This article reviews generic and specialized instruments for measuring QoL in the context of AF, discusses their applications and limitations to integration in clinical practice, and addresses the potential of early therapy for improving QoL outcomes. The development and validation of new QoL assessment tools will have a central role in the advancement of therapies and treatment guidelines for AF.

Keywords Atrial fibrillation (AF) • Quality of life (QoL) • Rhythm control • Rate control • Cardiac rhythm disorder • Management strategies

Introduction

Atrial fibrillation (AF), the most common arrhythmia resulting in hospital admission, has a significant impact on morbidity and mortality.[1,2] While AF is rarely life-threatening in itself, the distress caused by symptom onset can be severe and results in a major reduction in quality of life (QoL). This can be attributed to several factors. Typical arrhythmia-associated complaints include palpitations, chest pain, dizziness, and heart failure-like symptoms.[3] Underlying heart disease produces symptoms such as weakness, lightheadedness, and dyspnoea.[3] In addition, the consequences of treating AF, including side effects of drugs, interventions, and especially hospitalization, have a negative impact on QoL.

The World Health Organization defines health as not only the absence of disease and infirmity, but also as an aspect of well-being or QoL.[4] Nevertheless, there is currently no globally accepted definition for QoL in AF. The term is subjective and may be defined by one or many aspects, including symptoms, functional status, and patients' health perceptions, experiences, and expectations.[4,5] It is therefore important to consider the individual contribution of all these factors when assessing QoL,[6] as well as how intensely perceived AF-related symptoms affect QoL.

Most studies conducted to date have assessed health-related QoL (HRQoL) in symptomatic patients who are intolerant or refractory to antiarrhythmic therapy, or in those treated with ablation. The impact of AF on daily living in less severe or asymptomatic patients is therefore not well known or understood. Moreover, studies directly assessing HRQoL have been hampered by the small sample sizes and lack of control groups. A further confounding factor in the assessment of QoL in patients with AF is the presence of concomitant cardiovascular disease. Cardiovascular disease may dominate the patient's health preoccupations rather than the atrial dysrhythmia. It is therefore important in clinical studies to separate the impact of HRQoL on patients with AF from that of patients with other cardiac diseases. Studies have also been limited by bias introduced by questionnaires not self-administered by patients.[7,8]

At present, the management of AF aims to reduce symptoms and prevent severe AF-related complications.[3] It is important, however, that the management and treatment of AF take into account not only symptoms, but also individual patient factors such as psychological well-being.[9] Patients with AF are known to experience psychological distress, which may manifest as anxiety and/or depression, potentially leading to increased mortality, morbidity, and utilization of health-care resources.[10] One-third of patients with AF who

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do not have overt symptoms and are not aware of their condition will report a lower QoL than their peers in sinus rhythm.[9,11] It is estimated that more than half of the patients in selected populations have episodes of silent AF.[12]

Assessment of the benefits arising from therapeutic interventions in AF have included exercise tolerance and duration of rhythm after cardioversion as study endpoints. However, these endpoints do not correlate well with subjective assessment of the patients' symptoms. Measures of QoL take into consideration subjective improvements in well-being resulting from pain, psychological, emotional, and physical disturbances, as well as the potential burdens and side effects of therapeutic interventions that cause symptomatic improvement but lead to a reduction in well-being. As a result, QoL is becoming an increasingly important clinical outcome measure in AF,[9,13] although currently there are no specific guidelines for its assessment in AF patients.[14] Since multiple factors contribute to QoL (*Figure 1*), an assessment technique that is able to consider all its different aspects would be ideal. A large number of instruments are available for the assessment of QoL.[5,15–19] As a result, studies of QoL in AF rarely employ the same scores. This article will explore the various instruments that have been used to assess QoL in AF and their merits and drawbacks, as well as consider the impact of treatment on QoL.

Comparison of available quality-of-life instruments

There are several general limitations to the utility of QoL questionnaires in the context of AF. First, they can be highly subjective, both from the clinician's and the patient's perspective. Secondly, clinicians rarely use questionnaires as part of their clinical assessment. Thirdly, hospital boards are not convinced of their value; similarly, health insurance companies do not recognize their relevance. Fourthly, QoL questionnaires may vary dramatically, for example, in paroxysmal AF (PAF), rendering spontaneous variability in a patient's condition a relevant confounder. Finally, the relationship between symptoms and actual rhythm is elusive, and the establishment of an association between the two would be beneficial for the management of AF.[15] To maximize the clinical utility of QoL, it is important to choose the most appropriate instrument for its assessment. Quality-of-life instruments fall into two classes: generic and symptom scales. Generic QoL instruments are designed to be applicable across a wide range of populations and conditions. Symptom-based HRQoL measures are relevant to particular conditions.

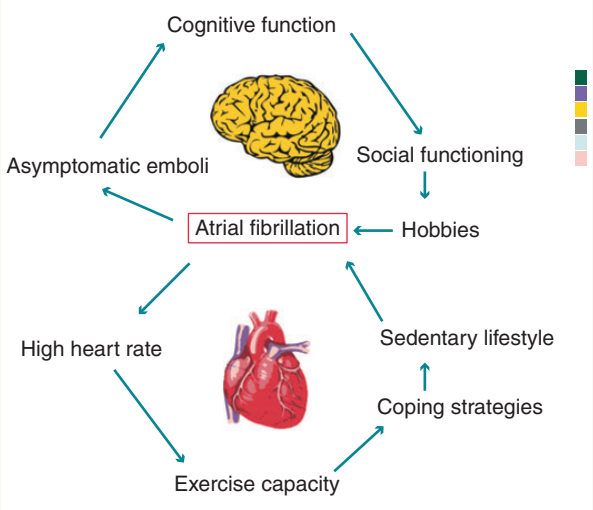

Figure 1 Quality of life in atrial fibrillation as a multidimensional construct.

Generic instruments

Generic QoL instruments employed in AF include the Medical Outcome Study Short-Form Health Survey (MOS-SF 36, known as SF-36),[19] the 12-item Short Form Health Survey (SF-12, derived from SF-36),[20] and the Euro-QoL 5-Dimensional questionnaire (EuroQoL/EQ-5D)[16] (*Table 1*). Both the SF-12 and the EuroQoL are validated for measuring QoL in general across different spectra of diseases. The Karnofsky Performance Status Scale,[21,22] which has been applied to describe global functional status of patients for >50 years in other therapeutic areas such as cancer, has also been utilized in AF.[23]

Generic instruments have the advantages of having been extensively validated and the most commonly used (SF-36) are available in many languages. They tend to be easy to use, and have been used in a large number of clinical investigations of QoL in AF patients. Their main disadvantage is the fact that they measure general health and functioning, rather than symptoms specific to AF, and therefore scores on these questionnaires are influenced by patient demographics and comorbidities, which are prevalent in older patients with AF. The FRACTAL (Fibrillation Registry Assessing Costs, Therapies, Adverse events, and Lifestyle) study concluded that generic tools are not ideal for measuring AF-specific QoL.[24] There is a need for a comprehensive, validated AF-specific questionnaire to measure the spectrum of QoL domains affected by AF.

The German Competence Network on Atrial Fibrillation (AFNET) has developed a dedicated QoL instrument that makes use of domains covered in generic instruments, such as the SF-12 and EuroQoL, and supplements these with elements from validated depression scales. The usefulness of this generic instrument is currently being assessed in ongoing trials. Both the AFNET and the European Heart Rhythm Association (EHRA) recommend the design, validation, and further use of AF-specific instruments to assess AF-related QoL, particularly when improvement of symptoms and QoL are the desired primary outcomes of a trial.[15]

Specific atrial fibrillation quality-of-life instruments and atrial fibrillation symptom scales

The main advantage of developing AF-specific HRQoL questionnaires is their specificity: they enable assessment of domains that are relevant and exclusive to AF and increase the sensitivity to changes in patients' health status. In clinical trials, they have greater statistical power than generic instruments regarding discrimination between patients with AF recurrence and arrhythmia-free patients.[25]

Table 1 Generic QoL instruments most commonly used in AF

QoL instrument	QoL domains measured	Scoring	Advantages	Disadvantages
SF-12[20]	Limitations in physical activities due to health problems Bodily pain General mental health (psychological distress and well-being) Limitations in usual role activities due to emotional problems Vitality (energy and fatigue) General health perceptions	Summary scores for physical health and mental health, standardized to population norms with the mean score set at 50 (SD = 10)	Extensively validated Generalizability Extensive data on AF already collected using this method	By design, reflects general health and functioning Scores among AF patients strongly influenced by patient demographics and comorbid conditions Less sensitive to change in older AF patients with multiple health problems
EuroQoL[16]	Self-care Usual activities Pain/discomfort Anxiety/depression Complemented by visual aid score	Rated on three levels Range from 'no problems' to 'severe problems'	Extensively validated Ease of use Validated for most languages Long track record of use in a variety of medical conditions Has a well-accepted method for transforming raw scores to preference-based utility weights Generalizability Extensive data on AF already collected using this method	May not be sensitive to HRQoL-related aspects of AF not covered by the five generic dimensions By design, reflects general health and functioning Scores among AF patients strongly influenced by patient demographics and comorbid conditions Less sensitive to change in older AF patients with multiple health problems
SF-36[19]	Limitations in physical activities due to health problems Bodily pain General mental health (psychological distress and well-being) Limitations in usual role activities due to emotional problems Vitality (energy and fatigue) General health perceptions	0–100 scoring system	Most widely validated generic instrument Has been used to study a great variety of cardiac diseases Validated for most languages Extensive data on AF already collected using this method	By design, reflects general health and functioning Scores among AF patients strongly influenced by patient demographics and comorbid conditions Less sensitive to change in older AF patients with multiple health problems

SF-12, 12-item Short Form Health Survey; SF-36, Medical Outcome Study Short-Form Health Survey (MOS-SF 36); QoL, quality of life; SD, standard deviation.

Several AF-specific QoL instruments have been validated in the last few decades. The Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) questionnaire assesses the QoL based on the four parameters: symptoms (four items), daily activities (eight items), treatment concerns (six items), and treatment satisfaction (two items).[8,26] This questionnaire combines symptoms, functional status, and QoL in a single measure and has found to be reliable and sensitive to clinical changes.[27] Other AF-specific QoL questionnaires include the Atrial Fibrillation Quality of Life (AF-QoL) questionnaire,[28] the QoL in AF (QLAF) questionnaire,[29] and the Quality of Life of Atrial Fibrillation (AFQLQ) questionnaire,[30,31] details of which are summarized in *Table 2*.

To provide a more accurate assessment of changes to QoL in response to therapeutic interventions, symptom scales have been devised (*Table 3*). The Specific Activity Scale is frequently used in AF studies but covers cardiovascular disease as a whole.[37] The most commonly employed symptom scales for AF are the Arrhythmia Symptom Checklist, Frequency, and severity (SCL),[5] and the University of Toronto Atrial Fibrillation severity Scale (AFSS).[32,33] The SCL is straightforward and sensitive and has been employed in many clinical studies. However, several of the symptoms are non-specific, for example, 'trouble concentrating', and there is no assessment of functional status or patient satisfaction. The AFSS and SCL have been used with a similar frequency in trials of AF therapy, although generally they did not detect between-group differences related to treatment. The evidence of responsiveness for these measures is limited, and the results are mixed.

Table 2 Atrial fibrillation-specific QoL symptom scales

QoL instrument[a]	QoL domains measured	Scales/scoring	Advantages	Disadvantages
AFEQT/ AF-QoL-18[26]	Initially developed as a 42-item questionnaire to assess the impact of AF and its treatment on patients' symptoms, functioning, and daily activities through six domains: symptoms, social functioning, physical functioning, emotional functioning, treatment concerns, and treatment satisfaction Later refined and renamed AF-QoL-18 questionnaire comprising two parts: (i) AF-QoL-7, comprising seven items which deal with the psychological domain; (ii) AF-QoL-11, comprising 11 items which deal with physical activity	*Five-point Likert scale* Totally agree Sufficiently agree Neither agree nor disagree Sufficiently disagree Totally disagree	Applicable to all types of AF (paroxysmal and permanent)	Limited clinical data; unknown validity, and reproducibility
AF-QoL[28]	Psychological Physical Sexual activity	*Five-point Likert scale* Totally agree Sufficiently agree Neither agree nor disagree Sufficiently disagree Totally disagree *Scoring* 0–100 0 = worst HRQoL 100 = best HRQoL	Able to capture changes over time in patients' HRQoL	Uncertain generalizability. Scores among AF patients may be influenced by patient demographics
QLAF[30]	Palpitation Breathlessness Chest pain Dizziness Drug Direct-current cardioversion Ablation	Domains numbered sequentially (I–VII) Questions containing items to be scored sequentially numbered 1–22 'Yes/no' questions leading into domains not numbered or scored Higher numbers indicate worse QoL	Simple Practical Rapidly administered (useful in the outpatient setting) Internally consistent Responsive	Relatively time-consuming Uncertain generalizability
AFQLQ[30,31]	Variety and frequency of symptoms (Questions 1–6) Severity of symptoms (Questions 7–12) Limitations of daily and special activities and mental anxiety (Questions 13–26)	*Scales* Physical functioning Role functional-physical Role functional-emotional Bodily pain General health perceptions Vitality Social functioning Mental health Subscales transformed to create Physical and Mental Component Summary scores (PCS and MCS, respectively), range 0–100 points Higher scores indicate a well health status *Scoring* Questions 1–6: 0–24 points Questions 7–12: 0–18 points Questions 13–26: 0–56 points Higher scores for each subscale indicate a well health status as with SF-36	Practical Internally consistent Responsive	Relatively time-consuming; uncertain generalizability

[a]This list is not exhaustive.

AF, atrial fibrillation; HRQoL, health-related quality of life; AFEQT, Atrial Fibrillation Effect on QualiTy-of-Life questionnaire; AF-QoL-18, Atrial Fibrillation Quality of Life 18; AF-QoL, Atrial Fibrillation Quality of Life questionnaire; AF AWARE, Atrial Fibrillation AWareness And Risk Education group; QLAF, Quality of Life in Atrial Fibrillation; QoLAF, Quality of Life and Atrial Fibrillation study; AFQLQ, Atrial Fibrillation Quality of Life Questionnaire; SF-36, Medical Outcome Study Short-form Health Survey.

The EHRA recently proposed an AF symptom scale based exclusively on patient-reported symptoms and their impact on daily activities.[34] The EHRA instrument relates specifically to the time when the patient feels to be in the arrhythmia and its classification scales are summarized in *Table 4*. Latest guidelines for AF suggest that the EHRA score should be used in the clinical evaluation of patients to guide decisions on rhythm control therapy.[15,34] However, validation of the EHRA score has not yet been

Table 3 Symptom scales for AF

AF instrument	Domains measured	Scales/scoring	Advantages	Disadvantages
Arrhythmia symptom checklist, Frequency, and Severity[5]	16 items (symptoms associated with AF)	Frequency (from 0 to 4) Severity (from 1 to 3) of each symptom Frequency and severity scores are not combined	Straightforward to use, sensitive to change, had been used in many AF studies	Relatively time-consuming Uncertain generalizability
University of Toronto Atrial Fibrillation Severity Scale AFSS[32,33]	9 items: Total AF burden = AF frequency + AF Duration + AF severity Global well-being AF symptoms healthcare utilization Demographic data Current AF status	Individual symptoms attributable to AF are scored on a five-point Likert scale, such that the total AFSS severity score ranges from 0 to 35, with higher scores indicating increased AFSS	Able to capture changes over time in patients' HRQoL	Relatively time-consuming Uncertain generalizability
EHRA AF symptom scale[34]	Symptoms that are attributable to AF and reverse or reduce upon restoration of sinus rhythm or with effective rate control	EHRA 1–IV (see *Table 4*)	Clinical relevance simplicity	Limited clinical data; unknown validity, generalizability, and reproducibility
Canadian cardiovascular Society Severity in Atrial Fibrillation Scale (CCS-SA)[35,36]	AF-related symptoms (palpitations, dyspnoea, dizziness/syncope, chest pain, weakness/fatigue); determination of symptom-rhythm correlation; assessment of the effect of these symptoms on patient daily function, and QoL	4-point scale 0 (asymptomatic) to 4 (severe)	Achieves a balance of simplicity, precision, and comprehensiveness Ease of use at the bedside	Poor correlation with subjective AF burden Uncertain generalizability

AF, atrial fibrillation; QoL, quality of life.

Table 4 European Heart Rhythm Association score of AF-related symptoms

Classification of AF-related symptoms (EHRA score)	
EHRA class	Explanation
EHRA I	'No symptoms'
EHRA II	'Mild symptoms'; normal daily activity not affected
EHRA III	'Severe symptoms'; normal daily activity affected
EHRA IV	'Disabling symptoms'; normal daily activity discontinued

AF, atrial fibrillation; EHRA, European Heart Rhythm Association. Printed with permission from Camm *et al.*[3]

completed. A similar score, the Canadian Cardiovascular Society Severity in Atrial Fibrillation (CCS-SAF) scale, which aims to achieve a balance of simplicity, precision, and comprehensiveness and can be used at the bedside, has recently been validated.[35,36] These novel symptom scales may help target specific HRQoL problems in individual patients.

Although many of the disease-specific instruments currently under clinical evaluation may prove to be superior tools to evaluate QoL and AF symptoms, there is a paucity of data validating their use. It is still not known whether these symptom scales are applicable to all AF subjects; they have not yet been applied in major trials or been validated for use in the clinic.[34] Furthermore, questionnaires based entirely on symptoms have limitations, being influenced by patient demographics and comorbid conditions. More research is needed to validate and assess the generalizability of these measures in different clinical settings as well as in different age, ethnic, and socioeconomic groups.[27]

Impact of atrial fibrillation therapies on quality of life

Clinical studies employing the QoL instruments detailed above have found that patients with AF have a marked impairment of HRQoL compared with population norms,[38–40] healthy controls,[41–43] and other patients with coronary heart disease (CHD).[33] However, most of the published QoL literature in AF is derived from studies of rate and/or rhythm control interventions and is therefore biased towards selection of highly symptomatic patients or subgroups of clinical trial patients. Such populations are likely to be biased and have inadequate statistical power. Unsurprisingly, baseline scores on QoL instruments tend to be lower than the general population in these studies.[41,43,44]

To date, there are limited data assessing QoL in a general AF patient population.[33,40,44–46] Most studies have examined the impact of specific interventions, including ablation and pacemaker implantation,[47–58] different pacing modalities,[56,58] cardioversion,[59–62] the Maze operation,[39,63,64] percutaneous closure of the left atrial appendage,[65] pharmacological therapies,[53–55,66,67] and pulmonary vein isolation (PVI).[68,69] Furthermore, the open-label nature of studies

investigating PVI may introduce a bias towards the intervention and may therefore influence QoL scores. A recent systematic review of randomized and non-randomized trials on QoL in elderly patients (mean age ≥65 years) with AF concluded that many pharmacological interventions may improve QoL in this patient population and recommended an algorithm to optimize QoL.[67]

The interpretation of data also presents a challenge. In a study investigating the impact of the control of symptomatic PAF on QoL, patients with uncontrolled symptomatic PAF at baseline had an inferior QoL compared with those with controlled symptomatic PAF. The QoL improved to a comparable level in controlled patients following treatment with controlled-release flecainide acetate.[70] However, a discrepancy was found between patient-reported AF symptoms and physical functioning in the uncontrolled PAF group.[71] While other studies have shown that symptoms in AF are inversely correlated to physical functioning, these results imply that uncontrolled PAF patients were not as physically impaired by their symptoms as predicted.[72]

Rate vs. rhythm control strategies

A number of randomized, controlled studies have investigated the effect of 'rate vs. rhythm' control strategies on QoL in patients with AF: the Strategies of Treatment of Atrial Fibrillation (STAF) study,[41] the Pharmacological Intervention in Atrial Fibrillation (PIAF) study,[42] the RAte Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) study,[43] the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study,[70] and the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) study.[72]

Improvement in QoL during follow-up was observed in most of these studies, but with no difference between the rate vs. rhythm strategies.[41–43] Similar improvements in QoL were observed between the rate and rhythm control arms of the AFFIRM and AF-CHF studies.[73,74] Results from these studies indicate that a strategy of rate control can be at least as effective as efforts to control rhythm with respect to several specific outcomes.[71] Assessment of QoL was a secondary goal of most of the rate vs. rhythm studies. However, these studies suffer from a number of methodological weaknesses, including lack of control groups, short follow-up periods (<6 months), and the utilization of non-validated instruments for QoL assessment. With the exception of AFFIRM and AF-CHF, these studies were not powered to detect QoL differences between the two strategies. The patient cohorts were not highly symptomatic in terms of arrhythmia. Nevertheless, in general, rhythm did not perform better than rate control concerning changes in HRQoL.

Relationship between quality of life and disease states in atrial fibrillation

The relationships between QoL and different disease states in clinical AF are largely unexplored. In idiopathic AF, patients may not have symptoms between attacks, although the memory of the arrhythmia may have a negative impact on the patient's activities and ambitions. The arrhythmia may be almost clinically silent in a large proportion of patients with persistent or permanent AF.[75] Such types of arrhythmia may only be detected when a serious and often difficult-to-reverse condition occurs (e.g. stroke, decompensated heart failure), significantly reducing the patient's QoL.

A recent study evaluated QoL in patients with persistent, paroxysmal, or permanent AF using the AF-QoL questionnaire.[76] The HRQoL was influenced by clinical parameters but seemingly not affected by the type of AF, except in the psychological dimension. Patients with a long history of disease, specifically those with permanent AF, tended to have stable AF with fewer symptomatic episodes over the course of time. Therefore, they had better HRQoL in terms of psychological symptoms, due to a lessening of the anxiety associated with their condition.[77] There is a correlation between the number of visits to the emergency department and the deterioration in HRQoL.[78] Hence, it can be deduced that the greater the number of symptomatic episodes, as in patients with PAF, the greater the impact of the episodes on the patient. A high frequency of episodes will have a negative impact on the patient's HRQoL, particularly in terms of psychological aspects of the AF-QoL scale.[76]

Relationship between achievement of sinus rhythm and quality of life

Despite the large number of studies conducted to date, there remains a lack of evidence of the relationship between achievement of sinus rhythm (SR) and QoL. In the SAFE-T study ($n = 1180$), patients with persistent AF, restoration, and maintenance of SR was associated with improvements in QoL measures.[78] In the AF-CHF study, which is the largest study conducted to date ($n = 1376$), a higher proportion of time spent in SR was associated with a modestly greater improvement in QoL scores.[72] Establishing such relationships presents a number of challenges. It is difficult to relate rhythm directly to complaints or formal assessment of QoL in clinical practice. Even if a relationship is established between rhythm and QoL, it may not be linear, i.e. an expected high QoL with chronic SR may be offset by the side effects of an antiarrhythmic drug such as amiodarone.[79] Timing of assessment of QoL relative to the occurrence of the arrhythmia also seems to be important.[11] Although this may be less important in patients with severe symptoms, QoL may be influenced by the memory of the symptoms, as well as anxiety about its recurrence.

Assessment of quality of life in asymptomatic patients

The assessment of QoL in patients who are largely asymptomatic presents a challenge. It is universally accepted that the reduced QoL associated with AF extends to patients with asymptomatic AF.[11] Conversely, a significant proportion of 'asymptomatic' patients improve following restoration of SR, which suggests that they have been symptomatic without knowledge of the fact. In addition, these patients may benefit from the management of their underlying hypertension, angina, or heart failure. Nevertheless, the impact of rate or rhythm interventions on asymptomatic patients is not easily measurable. The EHRA score is not sensitive enough to measure QoL in this patient population, and the clinical usefulness of formal QoL measurement in asymptomatic patients needs to be investigated.

Unanswered questions in quality-of-life outcomes in atrial fibrillation

One of the least understood aspects of AF is the association between the disease and cognitive impairment; in particular, whether there is evidence of a causal link. Cognitive status in patients with AF has been assessed with the Mini Mental State Examination (MMSE) in several studies to date. A literature review showed that these data were somewhat unreliable, and a causal link between AF and cognitive impairment could not be established.[80] However, in a recent study of subjects aged >65 years with either SR or permanent AF, cognitive status was found to be significantly lower in the AF group ($P < 0.05$), as reflected by lower MMSE scores.[81] Although cognitive impairment in older patients is multifactorial, permanent AF appeared to be one of the causes of low cognitive function in this study. Future prospective clinical trials may further elucidate the deterioration of cognitive function in AF patients.

The question of how early treatment intervention affects QoL outcomes should also be addressed. The administration of oral antiarrhythmic agents at the time of symptom onset has been shown to be safe and reduces the number of emergency room visits and hospital admissions.[82] Therefore, it seems obvious that the earlier the AF can be treated, the higher the impact of treatment on QoL. However, asymptomatic AF can preclude its timely detection and early initiation of therapy: 30–45% of patients had an incidental diagnosis of AF after undergoing electrocardiogram for unrelated reasons.[83,84] Asymptomatic AF may be more common than symptomatic AF in patients with PAF.[85] Early treatment in addition to identification of patients at risk may help improve the impact of treatments on QoL.

It is well known that time-dependent atrial remodelling renders the arrhythmia unmanageable, leading to a decrease in QoL. The changes in atrial properties that cause AF result in contractile dysfunction and counter-regulatory processes, a cellular survival mechanism that attempts to prevent the death of myocardial cells due to cytosolic calcium overload.[86] Although irreversible AF-induced atrial damage can occur within days of arrhythmia,[87] this could be prevented by early restoration and maintenance of SR; clinical observations support this concept.[88] Importantly, antiarrhythmic drugs are relatively effective in converting AF to SR when AF duration is short,[89] but almost never effective when AF persists for >2 weeks.[90] Similarly, catheter ablation has a higher success rate in patients with PAF compared with patients with sustained forms of the arrhythmia.[91] Therefore, rhythm control therapy may be more effective when it is initiated early.[92]

Antiarrhythmic drug treatment is recommended only in patients with recurrent AF; current guidelines do not recommend treatment at the time of diagnosis.[3,14] Although this strategy could be advantageous for delaying any potentially harmful effects of antiarrhythmic drugs until the second episode, it does not concur with the observation that AF is an arrhythmia that progresses chronically in most patients.[93–96] Only a highly selected subgroup of patients will experience short, sporadic episodes of PAF over several decades.[97] In fact, it is likely that many of the events contributing to AF occur before the first episode and before the disease is diagnosed. Delaying treatment may prevent effective prevention of AF recurrences.[92]

The working group of the second AFNET/EHRA consensus meeting suggested that an early intervention with pharmacological rhythm control therapy and/or ablation should be tested in controlled trials in patients with a first documented episode.[86] The pathophysiology of AF alludes to the idea that an early treatment strategy would be more successful, with fewer harmful effects than current practice.[98] However, long-term follow-up would be required to detect any delay in AF progression, including long-term effects on left atrial mechanical function and the incidence of very late recurrence.[86] Some of these issues will be addressed in the ongoing Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA),[99] Early Treatment of Atrial Fibrillation for Stroke Prevention (EAST)[100] trials, as well as in the Routine versus Aggressive upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) study.[101]

The impact of age on QoL in AF also merits discussion. The majority of older individuals with AF have comorbid conditions, such as CHD and diabetes, which affect treatment outcomes. However, this population may still benefit from interventions, such as electrical cardioversion and AF ablation therapy.[102,103] One study compared 52 'elderly' (mean age 77) patients with chronic AF with 48 age-matched controls in sinus rhythm. No differences were found in QoL, as assessed by the SF-36, between these groups.[45] Older patients may have a lesser symptom burden specifically from AF than younger patients.[24] Conversely, targeting the younger patient population for rhythm interventions is much more likely to result in positive outcomes for QoL, and the benefits of treatment are therefore likely to be much greater. This was observed in the RACE trial; age <69 years was associated with a greater likelihood of QoL improving over time.[43]

Conclusions

The management of AF is overshadowed by controversy and contradiction, and trials to date have failed to establish the ideal treatment strategy. Although medical advances will undoubtedly continue to reduce mortality rate, variations in QoL could be the most reliable way to differentiate between treatment regimens, given the currently available outcome measures. The assessment of QoL is still not standardized, and many assessment tools have shortcomings. However, the advent of new QoL scales with a greater focus on symptoms has increased the clinical utility of these instruments. The CCS-SAF and EHRA score could be valuable in the future, both for assessing the impact of symptoms on QoL and for assisting in the selection of appropriate treatment.

Rate and rhythm control studies have demonstrated a significant improvement in QoL among highly symptomatic patients. Future studies on AF should be conducted using large, randomized cohorts of a more 'general' population. The field would also benefit from studies measuring explicitly a range of QoL-specific endpoints in very symptomatic AF patients. Finally, the interventions tested should be comprehensive, including all aspects of AF. 'Newer' rhythm control strategies should be tested in conjunction with more traditional ones, as well as with rate control strategies, so that the best treatment option may be identified, not only in

terms of morbidity and mortality, but also in the context of QoL. Until all of these analyses are performed, there will be no change in treatment strategy.

Outcomes of future studies may support the development of new guidelines in favour of earlier intervention in the treatment of patients with AF. Future recommendations for AF should make provisions for the management of AF in terms of QoL in older as well as younger patients, in whom the QoL benefits may be much greater.

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References

1. Bialy D, Lehmann MH, Schumacher DN, Steinman RT, Meissner MD. Hospitalization for arrhythmias in the United States: importance of atrial fibrillation. *J Am Coll Cardiol* 1992;**19**:41A.
2. Santini M, De Ferrari GM, Pandozi C, Alboni P, Capucci A, Disertori M *et al.* Atrial fibrillation requiring urgent medical care. Approach and outcome in the various departments of admission. Data from the atrial Fibrillation/flutter Italian REgistry (FIRE). *Ital Heart J* 2004;**5**:205–13.
3. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S *et al.* Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 2010;**12**:1360–420.
4. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. *N Engl J Med* 1996;**334**:835–40.
5. Bubien RS, Knotts-Dolson SM, Plumb VJ, Kay GN. Effect of radiofrequency catheter ablation on health-related quality of life and activities of daily living in patients with recurrent arrhythmias. *Circulation* 1996;**94**:1585–91.
6. Reynolds MR, Ellis E, Zimetbaum P. Quality of life in atrial fibrillation: measurement tools and impact of interventions. *J Cardiovasc Electrophysiol* 2008;**19**:762–8.
7. Luderitz B, Jung W. Quality of life in patients with atrial fibrillation. *Arch Intern Med* 2000;**160**:1749–57.
8. Badia X, Arribas F, Ormaetxe JM, Peinado R, de Los Terreros MS. Development of a questionnaire to measure health-related quality of life (HRQoL) in patients with atrial fibrillation (AF-QoL). *Health Qual Life Outcomes* 2007;**5**:37.
9. Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med* 2006;**119**:448 e1–19.
10. McCabe PJ. Psychological distress in patients diagnosed with atrial fibrillation: the state of the science. *J Cardiovasc Nurs* 2009;**25**:40–51.
11. Savelieva I, Paquette M, Dorian P, Luderitz B, Camm AJ. Quality of life in patients with silent atrial fibrillation. *Heart* 2001;**85**:216–7.
12. Defaye P, Dournaux F, Mouton E. Prevalence of supraventricular arrhythmias from the automated analysis of data stored in the DDD pacemakers of 617 patients: the AIDA study. The AIDA Multicenter Study Group. Automatic interpretation for diagnosis assistance. *Pacing Clin Electrophysiol* 1998;**21**:250–5.
13. Grönefeld GC, Hohnloser SH. Quality of life in atrial fibrillation: an increasingly important issue. *Eur Heart J Suppl* 2003;**5**:H25–33.
14. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NA III *et al.* 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011;**123**:104–23.
15. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener HC *et al.* Outcome parameters for trials in atrial fibrillation: recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association. *Europace* 2007;**9**:1006–23.
16. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;**37**:53–72.
17. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation* 1981;**64**:1227–34.
18. Devins GM. Illness intrusiveness and the psychosocial impact of lifestyle disruptions in chronic life-threatening disease. *Adv Ren Replace Ther* 1994;**1**:251–63.
19. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;**30**:473–83.
20. Ware J Jr, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;**34**:220–33.
21. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. *J Clin Oncol* 1984;**2**:187–93.
22. Grieco A, Long CJ. Investigation of the Karnofsky performance status as a measure of quality of life. *Health Psychol* 1984;**3**:129–42.
23. Kirchhof P, Fetsch T, Hanrath P, Meinertz T, Steinbeck G, Lehmacher W *et al.* Targeted pharmacological reversal of electrical remodeling after cardioversion—rationale and design of the Flecainide Short-Long (Flec-SL) trial. *Am Heart J* 2005;**150**:899.
24. Reynolds MR, Lavelle T, Essebag V, Cohen DJ, Zimetbaum P. Influence of age, sex, and atrial fibrillation recurrence on quality of life outcomes in a population of patients with new-onset atrial fibrillation: the Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) study. *Am Heart J* 2006;**152**:1097–103.
25. Berkowitsch A, Neumann T, Kurzidim K, Reiner C, Kuniss M, Siemon G *et al.* Comparison of generic health survey SF-36 and arrhythmia related symptom severity check list in relation to post-therapy AF recurrence. *Europace* 2003;**5**:351–5.
26. Spertus J, Dorian P, Bubien R, Lewis S, Godejohn D, Reynolds MR *et al.* Development and validation of the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) Questionnaire in patients with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011;**4**:15–25.
27. Rienstra M, Lubitz SA, Mahida S. Symptoms and functional status of patients with atrial fibrillation: state-of-the-art and future research opportunities. *Circulation* 2012;**125**:2933–43.
28. Arribas F, Ormaetxe JM, Peinado R, Perulero N, Ramirez P, Badia X. Validation of the AF-QoL, a disease-specific quality of life questionnaire for patients with atrial fibrillation. *Europace* 2010;**12**:364–70.
29. Braganca EO, Filho BL, Maria VH, Levy D, de Paola AA. Validating a new quality of life questionnaire for atrial fibrillation patients. *Int J Cardiol* 2009;**143**:391–8.
30. Yamashita T, Komatsu T, Kumagai K, Uno K, Niwano S, Fijiki A. Internal consistency and reproducibility of Atrial fibrillation Quality of Life Questionnaire (AFQLQ). *Jpn J Electrocardiol* 2005;**25**:488–94.
31. Yamashita T, Kumagai K, Koretsune Y, Mitamura H, Okamura K, Ogawa S. A new method for evaluating quality of life specific to patients with atrial fibrillation: Atrial Fibrillation Quality of Life Questionnaire (AFQLQ). *Jpn J Electrocardiol* 2003;**23**:332–43.
32. Dorian P, Paquette M, Newman D, Green M, Connolly SJ, Talajic M *et al.* Quality of life improves with treatment in the Canadian Trial of atrial fibrillation. *Am Heart J* 2002;**143**:984–90.
33. Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM *et al.* The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *J Am Coll Cardiol* 2000;**36**:1303–9.
34. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S *et al.* Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 2010;**12**:1360–420.
35. Dorian P, Cvitkovic SS, Kerr CR, Crystal E, Gillis AM, Guerra PG *et al.* A novel, simple scale for assessing the symptom severity of atrial fibrillation at the bedside: the CCS-SAF scale. *Can J Cardiol* 2006;**22**:383–6.
36. Dorian P, Guerra PG, Kerr CR, O'Donnell SS, Crystal E, Gillis AM *et al.* Validation of a new simple scale to measure symptoms in atrial fibrillation: the Canadian Cardiovascular Society Severity in Atrial Fibrillation scale. *Circ Arrhythm Electrophysiol* 2009;**2**:218–24.
37. Goldman L, Hashimoto B, Cook EF, Loscaizo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation* 1981;**64**:1227–34.
38. Erdogan A, Carlsson J, Neumann T, Berkowitsch A, Neuzner J, Hamm CW *et al.* Quality-of-life in patients with paroxysmal atrial fibrillation after catheter ablation: results of long-term follow-up. *Pacing Clin Electrophysiol* 2003;**26**:678–84.
39. Lonnerholm S, Blomstrom P, Nilsson L, Oxelbark S, Jideus L, Blomstrom-Lundqvist C. Effects of the maze operation on health-related quality of life in patients with atrial fibrillation. *Circulation* 2000;**101**:2607–11.
40. Kang Y, Bahler R. Health related quality of life in patients newly diagnosed with atrial fibrillation. *Eur J Cardiovasc Nurs* 2003;**3**:71–6.

41. Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S *et al.* Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol* 2003;**41**:1690–6.
42. Gronefeld GC, Lilienthal J, Kuck KH, Hohnloser SH. Impact of rate versus rhythm control on quality of life in patients with persistent atrial fibrillation. Results from a prospective randomized study. *Eur Heart J* 2003;**24**:1430–6.
43. Hagens VE, Ranchor AV, Van Sonderen E, Bosker HA, Kamp O, Tijssen JG *et al.* Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) Study. *J Am Coll Cardiol* 2004;**43**:241–7.
44. Paquette M, Roy D, Talajic M, Newman D, Couturier A, Yang C *et al.* Role of gender and personality on quality-of-life impairment in intermittent atrial fibrillation. *Am J Cardiol* 2000;**86**:764–8.
45. Howes CJ, Reid MC, Brandt C, Ruo B, Yerkey MW, Prasad B *et al.* Exercise tolerance and quality of life in elderly patients with chronic atrial fibrillation. *J Cardiovasc Pharmacol Ther* 2001;**6**:23–9.
46. van den Berg MP, Hassink RJ, Tuinenburg AE, van Sonderen EF, Lefrandt JD, de Kam PJ *et al.* Quality of life in patients with paroxysmal atrial fibrillation and its predictors: importance of the autonomic nervous system. *Eur Heart J* 2001;**22**:247–53.
47. Kay GN, Ellenbogen KA, Giudici M, Redfield MM, Jenkins LS, Mianulli M *et al.* The Ablate and Pace Trial: a prospective study of catheter ablation of the AV conduction system and permanent pacemaker implantation for treatment of atrial fibrillation. APT Investigators. *J Interv Card Electrophysiol* 1998;**2**:121–35.
48. Marshall HJ, Harris ZI, Griffith MJ, Gammage MD. Atrioventricular nodal ablation and implantation of mode switching dual chamber pacemakers: effective treatment for drug refractory paroxysmal atrial fibrillation. *Heart* 1998;**79**:543–7.
49. Levy T, Walker S, Rex S, Paul V. Ablate and pace for drug refractory paroxysmal atrial fibrillation. Is ablation necessary? *Int J Cardiol* 2000;**75**:187–95.
50. Takahashi Y, Yoshito I, Takahashi A, Harada T, Mitsuhashi T, Shirota K *et al.* AV nodal ablation and pacemaker implantation improves hemodynamic function in atrial fibrillation. *Pacing Clin Electrophysiol* 2003;**26**:1212–7.
51. Lee SH, Chen SA, Tai CT, Chiang CE, Wen ZC, Cheng JJ *et al.* Comparisons of quality of life and cardiac performance after complete atrioventricular junction ablation and atrioventricular junction modification in patients with medically refractory atrial fibrillation. *J Am Coll Cardiol* 1998;**31**:637–44.
52. Twidale N, McDonald T, Nave K, Seal A. Comparison of the effects of AV nodal ablation versus AV nodal modification in patients with congestive heart failure and uncontrolled atrial fibrillation. *Pacing Clin Electrophysiol* 1998;**21**:641–51.
53. Natale A, Zimerman L, Tomassoni G, Newby K, Leonelli F, Fanelli R *et al.* AV node ablation and pacemaker implantation after withdrawal of effective rate-control medications for chronic atrial fibrillation: effect on quality of life and exercise performance. *Pacing Clin Electrophysiol* 1999;**22**:1634–9.
54. Levy T, Walker S, Mason M, Spurrell P, Rex S, Brant S *et al.* Importance of rate control or rate regulation for improving exercise capacity and quality of life in patients with permanent atrial fibrillation and normal left ventricular function: a randomised controlled study. *Heart* 2001;**85**:171–8.
55. Brignole M, Menozzi C, Gasparini M, Bongiorni MG, Botto GL, Ometto R *et al.* An evaluation of the strategy of maintenance of sinus rhythm by antiarrhythmic drug therapy after ablation and pacing therapy in patients with paroxysmal atrial fibrillation. *Eur Heart J* 2002;**23**:892–900.
56. Duff HJ, Raj SR, Exner DV, Sheldon RS, Roach D, Mitchell LB *et al.* Randomized controlled trial of fixed rate versus rate responsive pacing after radiofrequency atrioventricular junction ablation: quality of life, ventricular refractoriness, and paced QT dispersion. *J Cardiovasc Electrophysiol* 2003;**14**:1163–70.
57. Weerasooriya R, Davis M, Powell A, Szili-Torok T, Shah C, Whalley D *et al.* The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT). *J Am Coll Cardiol* 2003;**41**:1697–702.
58. Tse HF, Newman D, Ellenbogen KA, Buhr T, Markowitz T, Lau CP. Effects of ventricular rate regularization pacing on quality of life and symptoms in patients with atrial fibrillation (Atrial fibrillation symptoms mediated by pacing to mean rates [AF SYMPTOMS study]). *Am J Cardiol* 2004;**94**:938–41.
59. Fiala M, Wichterle D, Bulková V, Sknouril L, Nevralová R, Toman O *et al.* A prospective evaluation of haemodynamics, functional status, and quality of life after radiofrequency catheter ablation of long-standing persistent atrial fibrillation. *Europace* 2014;**16**:15–25.
60. Newman DM, Dorian P, Paquette M, Sulke N, Gold MR, Schwartzman DS *et al.* Effect of an implantable cardioverter defibrillator with atrial detection and shock therapies on patient-perceived, health-related quality of life. *Am Heart J* 2003;**145**:841–6.
61. Berry C, Stewart S, Payne EM, McArthur JD, McMurray JJ. Electrical cardioversion for atrial fibrillation: outcomes in 'real-life' clinical practice. *Int J Cardiol* 2001;**81**:29–35.
62. Kale M, Bennett DH. Atrial septal pacing in the prevention of paroxysmal atrial fibrillation refractory to antiarrhythmic drugs. *Int J Cardiol* 2002;**82**:167–75.
63. Jessurun ER, van Hemel NM, Defauw JA, Stofmeel MA, Kelder JC, de la Riviere AB *et al.* Results of maze surgery for lone paroxysmal atrial fibrillation. *Circulation* 2000; **101**:1559–67.
64. Jessurun ER, van Hemel NM, Defauw JJ, Brutel De La Riviere A, Stofmeel MA, Kelder JC *et al.* A randomized study of combining maze surgery for atrial fibrillation with mitral valve surgery. *J Cardiovasc Surg (Torino)* 2003;**44**:9–18.
65. Alli O, Doshi S, Kar S, Reddy V, Sievert H, Mullin C *et al.* Quality of life assessment in the randomized PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial of patients at risk for stroke with nonvalvular atrial fibrillation. *J Am Coll Cardiol* 2013;**61**:1790–8.
66. Tse HF, Lam YM, Lau CP, Cheung BM, Kumana CR. Comparison of digoxin versus low-dose amiodarone for ventricular rate control in patients with chronic atrial fibrillation. *Clin Exp Pharmacol Physiol* 2001;**28**:446–50.
67. Pepine CJ. Effects of pharmacologic therapy on health-related quality of life in elderly patients with atrial fibrillation: a systematic review of randomized and nonrandomized trials. *Clin Med Insights Cardiol* 2013;**7**:1–20. Epub 22 January 2013.
68. Chen MS, Marrouche NF, Khaykin Y, Gillinov AM, Wazni O, Martin DO *et al.* Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. *J Am Coll Cardiol* 2004;**43**:1004–9.
69. Purerfellner H, Martinek M, Aichinger J, Nesser HJ, Kempen K, Janssen JP. Quality of life restored to normal in patients with atrial fibrillation after pulmonary vein ostial isolation. *Am Heart J* 2004;**148**:318–25.
70. Guedon-Moreau L, Capucci A, Denjoy I, Morgan CC, Perier A, Leplege A *et al.* Impact of the control of symptomatic paroxysmal atrial fibrillation on health-related quality of life. *Europace* 2010;**12**:634–42.
71. Crijns HJ. Rate versus rhythm control in patients with atrial fibrillation: what the trials really say. *Drugs* 2005;**65**:1651–67.
72. Aves T, Dorian P. Paroxysmal atrial fibrillation and health-related quality of life: the importance of keeping score. *Europace* 2010;**12**:606–7.
73. Jenkins LS, Brodsky M, Schron E, Chung M, Rocco T Jr, Lader E *et al.* Quality of life in atrial fibrillation: the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J* 2005;**149**:112–20.
74. Suman-Horduna I, Roy D, Frasure-Smith N, Talajic M, Lespérance F, Blondeau L *et al.* Quality of life and functional capacity in patients with atrial fibrillation and congestive heart failure. *J Am Coll Cardiol* 2013;**61**:455–60.
75. Savelieva I, Camm AJ. Clinical relevance of silent atrial fibrillation: prevalence, prognosis, quality of life, and management. *J Interv Card Electrophysiol* 2000;**4**:369–82.
76. Peinado R, Arribas F, Ormaetxe JM, Badia X. Variation in quality of life with type of atrial fibrillation. *Rev Esp Cardiol* 2010;**63**:1402–9.
77. Thrall G, Lip GY, Carroll D, Lane D. Depression, anxiety, and quality of life in patients with atrial fibrillation. *Chest* 2007;**132**:1259–64.
78. Singh SN, Tang XC, Singh BN, Dorian P, Reda DJ, Harris CL *et al.* Quality of life and exercise performance in patients in sinus rhythm versus persistent atrial fibrillation: a Veterans Affairs Cooperative Studies Program Substudy. *J Am Coll Cardiol* 2006;**48**: 721–30.
79. Zimetbaum P. Amiodarone for atrial fibrillation. *N Engl J Med* 2007;**356**:935–41.
80. Mead GE, Keir S. Association between cognitive impairment and atrial fibrillation: a systematic review. *J Stroke Cerebrovasc Dis* 2001;**10**:35–43.
81. Wozakowska-Kaplon B, Opolski G, Kosior D, Jaskulska-Niedziela E, Maroszynska-Dmoch E, Wlosowicz M. Cognitive disorders in elderly patients with permanent atrial fibrillation. *Kardiol Pol* 2009;**67**:487–93.
82. Alboni P, Botto GL, Baldi N, Luzi M, Russo V, Gianfranchi L *et al.* Outpatient treatment of recent-onset atrial fibrillation with the 'pill-in-the-pocket' approach. *N Engl J Med* 2004;**351**:2384–91.
83. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol* 1994;**74**:236–41.
84. Blackshear JL, Kopecky SL, Litin SC, Safford RE, Hammill SC. Management of atrial fibrillation in adults: prevention of thromboembolism and symptomatic treatment. *Mayo Clin Proc* 1996;**71**:150–60.
85. Page RL, Wilkinson WE, Clair WK, McCarthy EA, Pritchett EL. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. *Circulation* 1994;**89**:224–7.
86. Kirchhof P, Bax J, Blomstrom-Lundquist C, Calkins H, Camm AJ, Cappato R *et al.* Early and comprehensive management of atrial fibrillation: proceedings from the 2nd AFNET/EHRA consensus conference on atrial fibrillation entitled 'research perspectives in atrial fibrillation'. *Europace* 2009;**11**:860–85.
87. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiol Rev* 2010;**91**:265–325.
88. Kirchhof P. Can we improve outcomes in AF patients by early therapy? *BMC Med* 2009;**7**:72.
89. Roy D, Pratt CM, Torp-Pedersen C, Wyse DG, Toft E, Juul-Moller S *et al.* Vernakalant hydrochloride for rapid conversion of atrial fibrillation: a phase 3, randomized, placebo-controlled trial. *Circulation* 2008;**117**:1518–25.
90. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA *et al.* ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart

Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace* 2006;**8**:651–745.
91. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A *et al.* Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol* 2009;**2**:349–61.
92. Cosio FG, Aliot E, Botto GL, Heidbuchel H, Geller CJ, Kirchhof P *et al.* Delayed rhythm control of atrial fibrillation may be a cause of failure to prevent recurrences: reasons for change to active antiarrhythmic treatment at the time of the first detected episode. *Europace* 2008;**10**:21–7.
93. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;**113**:359–64.
94. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;**98**:946–52.
95. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener HC *et al.* Outcome parameters for trials in atrial fibrillation: recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association. *Europace* 2007;**9**:1006–23.
96. Kerr CR, Boone J, Connolly SJ, Dorian P, Green M, Klein G *et al.* The Canadian Registry of Atrial Fibrillation: a noninterventional follow-up of patients after the first diagnosis of atrial fibrillation. *Am J Cardiol* 1998;**82**:82N–5N.
97. Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO, Kopecky SL *et al.* Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. *Circulation* 2007;**115**:3050–6.
98. Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. *Circ Arrhythm Electrophysiol* 2008;**1**:62–73.
99. http://clinicaltrials.gov/ct2/show/NCT00911508 Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA) (24 July 2013, date last accessed).
100. http://clinicaltrials.gov/show/NCT01288352 Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST) (date last accessed July 24, 2013).
101. http://clinicaltrials.gov/ct2/show/NCT00911508 Routine Versus Aggressive Upstream Rhythm Control for Prevention of Early Atrial Fibrillation in Heart Failure (RACE 3) (24 July 2013, date last accessed).
102. Fumagalli S, Boncinelli L, Bondi E, Caleri V, Gatto S, Di Bari M *et al.* Does advanced age affect the immediate and long-term results of direct-current external cardioversion of atrial fibrillation? *J Am Geriatr Soc* 2002;**50**:1192–7.
103. Zado E, Callans DJ, Riley M, Hutchinson M, Garcia F, Bala R *et al.* Long-term clinical efficacy and risk of catheter ablation for atrial fibrillation in the elderly. *J Cardiovasc Electrophysiol* 2008;**19**:621–6.