

Symptoms and Functional Status of Patients With Atrial Fibrillation

State of the Art and Future Research Opportunities

Michiel Rienstra, MD, PhD; Steven A. Lubitz, MD, MPH; Saagar Mahida, MB, ChB;

Jared W. Magnani, MD; João D. Fontes, MD, MPH; Moritz F. Sinner, MD, MPH;

Isabelle C. Van Gelder, MD, PhD; Patrick T. Ellinor, MD, PhD*; Emelia J. Benjamin, MD, ScM*

Atrial fibrillation (AF) is the most common arrhythmia and is associated with increased risks of stroke, heart failure, dementia, and death.^{1–8} Because the number of elderly individuals will increase over the years to come, the prevalence of AF is predicted to increase dramatically.⁹ Symptoms are a major reason that patients with AF seek medical attention. Approximately two thirds of all emergency department visits with a primary diagnosis of AF result in hospital admissions.¹⁰ AF and its related symptoms therefore represent a major therapeutic challenge and burden to health-care systems. The major goal of AF therapy is to reduce cardiovascular symptoms, morbidity, and mortality. Because the outcome of rate versus rhythm control therapies is similar,^{11,12} the degree of symptoms related to the arrhythmia is a major consideration during the selection of a treatment strategy. Given the cost and potential complications related to medications and ablation techniques used for rhythm control, an accurate evaluation of the symptoms and functional status of patients with AF is crucial.

Despite the fact that AF was described in humans in 1906,¹³ no standardized assessment of symptoms or functional status has been accepted as the gold standard. The management of AF stands in marked contrast to heart failure, for which there is a straightforward and widely used symptom scale. Although AF and heart failure often coexist and both may cause similar symptoms, the New York Heart Association functional class was not developed for use in AF per se. The lack of a standardized approach may result in part from the complex clinical decision-making process in patients with AF. Challenges arise because symptoms related to AF are highly variable, not only between patients but also in individual patients at different time points.

The most common symptoms include palpitations, chest pain, and a reduction in exercise tolerance. Yet, ≈15% to 30% of patients with AF are asymptomatic.^{14–16} The relation between symptoms or impaired functional status and the onset or recurrences of the arrhythmia is not always obvious. In addition, symptoms and impaired functional status may not be specific for AF because other cardiovascular conditions and risk factors for AF may cause similar symptoms. Furthermore, the magnitude of symptoms and functional status improvement attributable to specific AF therapies varies widely.

The aim of our review is to discuss the symptomatology and functional status of individuals with AF. We highlight current knowledge about the patient's experience of AF, as well as the pathophysiology and prognostic implications of symptoms related to AF. In addition, we provide an overview of the most frequently used tools to assess symptoms and functional status. Finally, we summarize current gaps in the literature on AF symptomatology and underscore important potential research directions.

Review Criteria

Our review was based on the authors' knowledge of the literature and a structured search of the PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed/>) using the terms "symptoms," "atrial fibrillation," "functional status," "functional capacity," "asymptomatic," "quality of life," "rate," "ablation," "rhythm," and "control," alone or in combination. Further selection was based on abstracts and clinical relevance. When available, we focused on randomized controlled trials; if unavailable, we presented important observational

From the Cardiovascular Research Center, Massachusetts General Hospital, Charlestown (M.R., S.A.L., S.M., M.F.S., P.T.E.); Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (M.R., I.C.V.G.); National Heart Lung and Blood Institute's and Boston University's Framingham Heart Study, Framingham, MA (M.R., J.W.M., J.D.F., M.F.S., E.J.B.); Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston (S.A.L., P.T.E.); Cardiology Section (J.W.M., J.D.F., E.J.B.) and Preventive Medicine Section (E.J.B.), Department of Medicine, Boston University School of Medicine, Boston, MA; Department of Medicine I, University Hospital Grosshadern, Ludwig-Maximilians University Munich, Munich, Germany (M.F.S.); Interuniversity Cardiology Institute of the Netherlands, Utrecht, the Netherlands (I.C.V.G.); and Epidemiology Department, Boston University School of Public Health, Boston, MA (E.J.B.).

*Drs Ellinor and Benjamin contributed equally to this article.

The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.111.069450/-DC1>.

Correspondence to Emelia J. Benjamin, MD, ScM, Framingham Heart Study, 73 Mount Wayte Ave, Ste 2, Framingham, MA 01702-5827. E-mail emelia@bu.edu

(*Circulation*. 2012;125:2933–2943.)

© 2012 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.111.069450

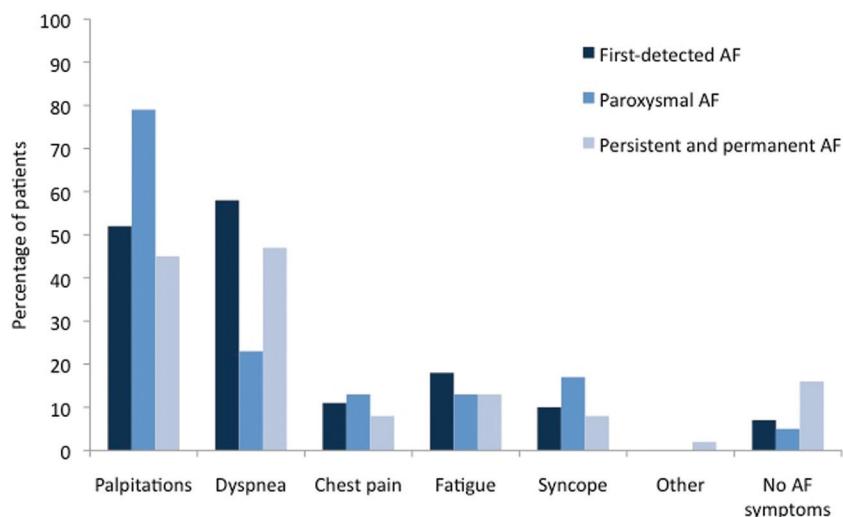


Figure 1. Symptoms according to type of atrial fibrillation (AF) in the French Etude en Activité Libérale de la Fibrillation Auriculaire (ALFA) study (data taken from Levy et al¹⁴).

studies. Our review is not intended to be all inclusive; rather, it represents the main studies published on this topic.

Symptoms Related to AF

AF symptomatology has been studied mainly in subjects referred for AF evaluation or treatment and therefore may be overestimated. The French Etude en Activité Libérale de la Fibrillation Auriculaire (ALFA) study reported that patients with paroxysmal AF are more symptomatic than patients with persistent and permanent AF (Figure 1).¹⁴

Patients may experience palpitations, dyspnea, chest pain, dizziness, and, less commonly, syncope or presyncope at some point during the life course of AF. Other, less specific symptoms reported in relation to AF include fatigue and anxiety. In the Euro Heart Survey on Atrial Fibrillation, 69% of AF patients had experienced symptoms related to the arrhythmia at some point since diagnosis. The majority of patients (54%) were asymptomatic at the time of the survey, and the lowest symptom burden was reported in patients with permanent AF (Table 1).¹⁷

There is substantial intraindividual and interindividual diversity in the type and severity of symptoms. Within an individual, symptoms may fluctuate widely over time. In addition, there is a wide heterogeneity in patterns of AF, precipitants of AF, and therapeutic approaches. There are major gaps in our knowledge about the relations of race and ethnicity, advancing age, sex, and socioeconomic status with AF-related symptoms and functional status.

Future Research

To determine whether AF therapies aimed at reducing symptoms are effective, it is imperative to know the natural history of AF-related symptoms. Research should focus on the incidence and prevalence of AF-related symptoms in different AF subsets, different age ranges, and other races and ethnicities, sexes, socioeconomic status, and hospital-based and community-based settings. The role of other cardiovascular diseases and different patterns of AF (paroxysmal, persistent and permanent AF) in generating symptoms needs to be determined. It is of great importance to know how AF-related symptoms change over time and whether AF therapies reduce AF-related symptoms. New imaging modalities (eg, magnetic resonance imaging, computer tomography, and positron emission tomography) and novel biomarkers (eg, natriuretic peptides) may facilitate the identification of specific AF endophenotypes related to particular AF symptoms. Emerging genomic, epigenomic, transcriptomic, proteomic, and metabolomic data also may increase the discovery of novel tissue-specific biomarkers or genomic markers that may correlate with distinct symptoms.

Mechanisms of AF-Related Symptoms

There is a striking paucity of data on the mechanisms by which AF causes symptoms.¹⁸ The investigation of the mechanistic link between symptoms and AF is complicated by the fact that AF often occurs in the presence of heart failure and valve disease, conditions that may present with

Table 1. Presence of Symptoms According to Type of Atrial Fibrillation

AF-Related Symptoms*	First Detected AF (n=978), %	Paroxysmal AF (n=1517), %	Persistent AF (n=1167), %	Permanent AF (n=1541), %
Current	77	77	73	55
Previous	7	16	15	20
Never	16	6	10	21
Heart failure NYHA class III/IV	17	8	15	25

AF indicates atrial fibrillation; NYHA, New York Heart Association.

*Includes palpitations, syncope, dyspnea, chest pain, dizziness, fatigue, and nonspecified symptoms. Modified from Nieuwlaat et al¹⁷ with permission of the publisher. © 2005, The European Society of Cardiology.

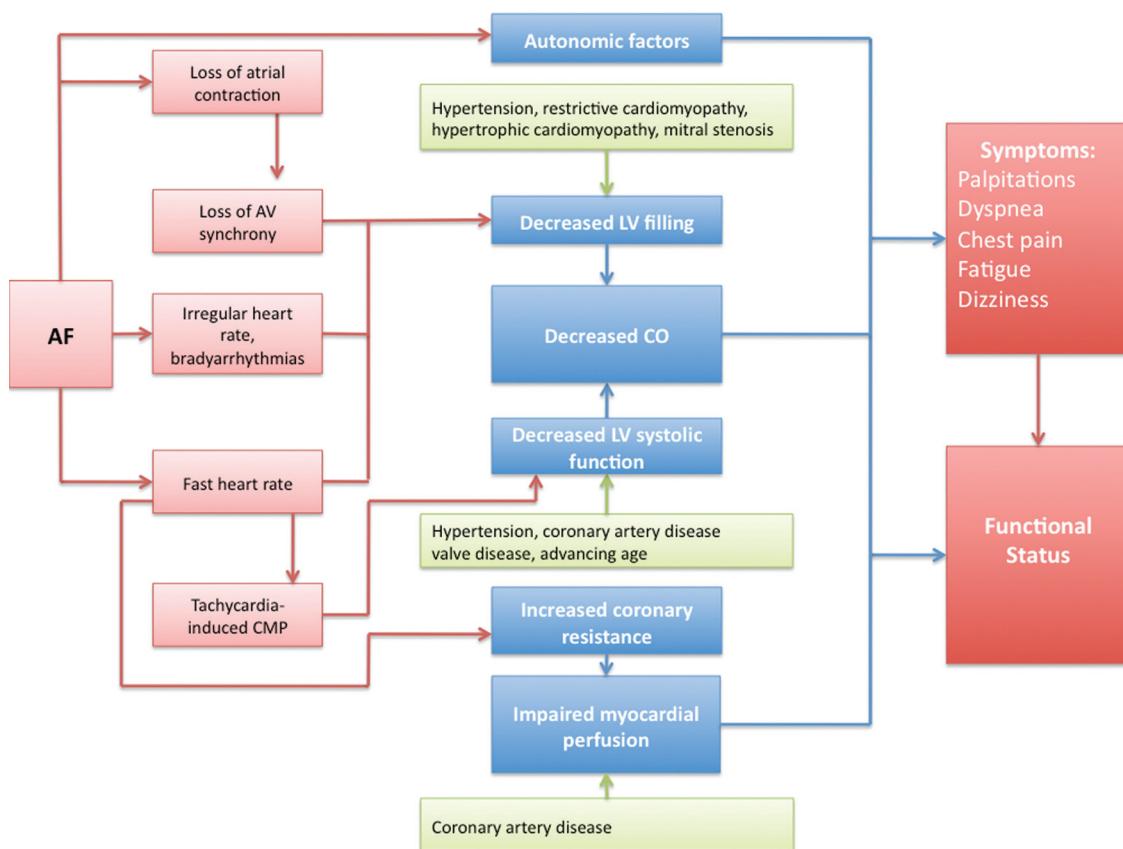


Figure 2. Conceptual model of pathophysiological mechanisms relating atrial fibrillation (AF) and symptoms. CO indicates cardiac output; CMP, cardiomyopathy.

similar symptoms. Heart failure is common in AF patients because both conditions share common risk factors such as hypertension, diabetes mellitus, valve disease, and myocardial infarction¹⁹ and because each disorder can predispose to the other condition. Furthermore, systolic and diastolic heart failure and valve disease not only may mimic AF symptoms but also may aggravate AF symptoms and functional status. Symptoms related to AF are likely to be multifactorial as a result of both direct and indirect effects of the arrhythmia (Figure 2). At the present time, it is unclear whether symptom patterns are heritable.

Palpitations

A significant proportion of AF patients experience palpitations, defined as an increased perception of the heartbeat. The sensory and mechanistic pathways underlying palpitations have yet to be defined.^{20,21} Interestingly, previous studies have reported that the neural stimuli for palpitations may not originate from the myocardium. Barsky et al²² demonstrated that despite the absence of cardiac innervation, one third of heart transplant recipients were accurately aware of their resting heartbeat. Further research is necessary to identify afferent neural pathways that transmit sensory information during palpitations.

Chest Pain

Chest pain often occurs during episodes of AF, even in the absence of overt structural heart diseases.²³ Although chest

pain may be a nonspecific sensation of abnormal cardiac motion, it may also relate to impaired myocardial perfusion.²⁴ It is unlikely that impaired myocardial perfusion is due solely to fast ventricular rates during AF because chest pain also is observed in AF patients with slow ventricular rates.²⁵ Previous studies have shown that coronary vascular resistance is elevated in patients with AF.^{26,27} Other factors such as an irregularity of the ventricular response and an alteration in the sympathetic nervous system activation and renin-angiotensin system also may contribute to the development of chest pain.^{24,26,27}

Reduced Exercise Capacity, Dyspnea, and Fatigue

More than half of all AF patients experience a reduction in exercise capacity measured by New York Heart Association class.¹¹ Reduced functional capacity may be a nonspecific symptom or may be due to symptoms such as dyspnea.²⁸ Exercise performance depends on a number of factors, including cardiac output and oxygen transport, which in turn depend on respiratory function. It has been proposed that during AF cardiac output may be compromised owing to impaired diastolic filling secondary to rapid ventricular rates.²⁹ Diastolic dysfunction in AF also may increase left-sided intracardiac pressures and predispose patients to episodes of subclinical pulmonary edema.³⁰ Interestingly, though, a hemodynamic study of patients in sinus rhythm or after the acute induction of AF demonstrated that the arrhyth-

mia was associated with normal or even low intracardiac pressures.³¹ Furthermore, structural heart diseases accompanying AF may be an important determinant of reduced exercise capacity. Finally, AF-related stroke may lead to disability and subsequently reduce exercise capacity.

Dyspnea and reduced functional capacity also may be an indirect consequence of AF. Multiple studies have shown that long-term AF may induce left ventricular dysfunction or a tachycardiomyopathy. The loss of atrioventricular synchrony and a rapid ventricular rate are the primary mechanisms thought to adversely affect ventricular function and overall hemodynamic status.^{32,33} However, AF can also predispose to left ventricular dysfunction and tachycardiomyopathy at normal heart rates, presumably as a result of the irregularity of RR intervals.³²⁻³⁵ Left ventricular dysfunction and heart failure may cause dyspnea and a reduction in exercise capacity. Conversion to sinus rhythm may improve left ventricular systolic function and reverse tachycardiomyopathy.^{36,37} Adequate rate control, however, may also improve left ventricular systolic dysfunction and AF-related symptoms.^{38,39}

Dizziness

Dizziness, syncope, and presyncope are relatively uncommon symptoms related to AF. Sympathovagal imbalance may play a role in patients with AF and dizziness.⁴⁰ Increased sympathetic and parasympathetic impulses can result in adverse hemodynamic effects; thus, predicting the specific effects of these impulses during AF is challenging.¹⁸ Other potential mechanisms of dizziness or syncope include sinus node dysfunction with pauses on conversion of AF to sinus rhythm or rapid ventricular rates in patients with underlying conditions such as hypertrophic cardiomyopathy, valvular stenosis, or an accessory pathway.⁴¹ In the absence of underlying cardiac conditions or a bypass tract, AF is unlikely to cause significant adverse hemodynamic effects.³¹

Future Research

An in-depth understanding of pathophysiological mechanisms underlying AF symptomatology is likely to enhance our ability to define more clearly the relation between symptoms and arrhythmia. Although it is difficult to dissect whether symptoms are caused by AF itself or by other cardiac diseases, well-designed studies including individuals with various types of AF that are stratified or adjusted for age, sex, race, socioeconomic status, pattern of AF, and medication use are warranted. The role of other cardiovascular diseases and different patterns of AF (paroxysmal, persistent and permanent AF) in generating symptoms needs to be determined. Emerging research in the fields of atrial imaging, biomarkers, and genomics of AF may elucidate pathophysiological mechanisms underlying AF-related symptoms.

Symptoms and Documentation of AF

In patients with AF, it often remains unclear why some patients are asymptomatic and others are severely symptomatic. Both somatic and psychological factors²⁰ are likely to contribute to the complex relation between symptoms and arrhythmia.⁴²⁻⁴⁴ A subanalysis of the Atrial Fibrillation

Follow-Up Investigation of Rhythm Management (AFFIRM) trial reported that patients with asymptomatic AF have less severe cardiac disease.¹⁵

Approximately 15% to 30% of patients with AF are asymptomatic.¹⁴⁻¹⁶ Asymptomatic AF is often discovered incidentally, eg, during population surveys or when patients undergo routine physical examinations. In ≈15% to 25% of patients with AF, stroke is the initial presenting sign of AF.^{45,46} Similarly, data from patients with implantable pacemakers or defibrillators revealed that high percentages (up to 70%) of paroxysms of AF are asymptomatic.^{26,47-50} Thus, the simple awareness of symptoms is not a good discriminator of the presence or absence or of the severity of the arrhythmia.

In patients with persistent AF, particularly elderly patients, symptoms decrease or may even disappear with longer durations of the arrhythmia, and AF may become permanent.^{14,15,41} Conversely, the presence of symptoms may prompt the clinician to interrupt the progression from persistent to permanent AF by more vigorous pursuit of rhythm control strategies. Symptoms also may abate when patients are started on pharmacological therapy, in some cases despite the persistence of arrhythmia.^{51,52} For instance, the Suppression of Paroxysmal Atrial Tachyarrhythmias (SOPAT) trial reported an inverse correlation between symptoms and use of antiarrhythmics and a direct correlation between symptoms and high ventricular rates.⁵³

The discordance between symptoms and the presence of AF is of particular relevance because, as mentioned previously, recurrence of symptomatic AF is currently used to evaluate the success of pulmonary vein ablation therapy.⁵⁴⁻⁵⁹ Not surprisingly, several reports demonstrated an underestimation of the recurrence rate of the arrhythmia and an overestimation of the success rate of pulmonary vein ablation because a high proportion of recurrences of AF are asymptomatic.^{60,61}

Future Research

Although it is known that there is a weak association between AF-related symptoms and the actual rhythm, little is known about influencing factors. Taking advantage of the implantable cardiac rhythm recorders such as implantable pacemakers, defibrillators, and loop recorders, we can study the longitudinal history of symptoms in the same individual and determine why some episodes of AF are symptomatic and others are asymptomatic. Information on the influence of AF therapies or daily activities on specific symptoms on the transition from symptomatic to asymptomatic AF is within reach. Furthermore, current interest in the heritability and genetics of AF offers an opportunity to study whether the presence or absence of AF-related symptoms is heritable.

AF-Related Symptoms Systematic Measures

In an attempt to provide a more objective assessment of symptoms and a more accurate measure of response to therapy, a number of questionnaires have been developed for patients with AF (summarized in Table 2). The majority of such questionnaires have been developed for research purposes. The most widely used symptom-scoring systems are

Table 2. Selected Scoring Systems for Symptoms Related to Atrial Fibrillation

Measure, Year Described	Description	Scores	Design/Validation Cohort	Comments/Limitations
Symptom Checklist–Frequency and Severity Scale, ^{62–65} 1989	Score based on severity and frequency of symptoms (palpitations, dyspnea, dizziness, exercise intolerance, chest discomfort, and syncope)	0–64 for frequency, 0–48 for severity	Validated in multiple cohorts (pacemaker, atrioventricular node ablation for AF, radiofrequency catheter ablation for supraventricular arrhythmias, and pulmonary vein ablation for AF)	Advantages: most extensively validated; reproducible Limitations: relatively time-consuming; uncertain generalizability
University of Toronto Atrial Fibrillation Severity Scale, ^{66–69} 1998	14-item disease-specific scale—subjective and objective ratings of AF disease burden, including frequency, duration, and patient-perceived severity of episodes, and healthcare use	3–30	Validated in patients with paroxysmal and persistent AF included in the Canadian Trial of Atrial Fibrillation	Advantages: validated and reproducible Limitations: relatively time-consuming; uncertain generalizability
Canadian Cardiovascular Society Severity of Atrial Fibrillation Scale, ^{70,71} 2009	Score determined in 3 steps: identification of the major AF-related symptoms (palpitations, dyspnea, dizziness/syncope, chest pain, weakness/fatigue), determination of symptom-rhythm correlation, and assessment of symptom impact on daily activities and quality of life	0–4	Designed by members of the Primary Panel of the Canadian Cardiovascular Society Consensus Conference on Atrial Fibrillation; validated in a large cohort of paroxysmal, persistent, and permanent AF	Advantages: simple; correlates with SF-36 quality-of-life scores and University of Toronto Atrial Fibrillation Severity Scale Limitations: rather poor correlation with subjective AF burden; uncertain generalizability
Atrial Fibrillation 6 Scale, ⁷² 2009	6 Questions focusing on dyspnea at rest, exertion, limitations in daily life, and feeling of discomfort, fatigue and worry/anxiety	0–60 (1–10 on a Likert scale for each question)	Designed for patients at the AF clinic; validated in AF patients pericardioversion	Advantages: items based on patient interviews; satisfactory reliability and validity Limitations: relatively time-consuming; uncertain generalizability
EHRA classification, ⁷³ 2007	Classification based exclusively on patient-reported symptoms and impact on normal daily activities	EHRA class I–IV	Proposed by panel of experts of the European Heart Rhythm Association; no validation	Proposed advantage: simple Limitations: not used in studies yet; unknown validity, generalizability, and reproducibility

AF indicates atrial fibrillation; SF-36, Short-Form 36; and EHRA, European Heart Rhythm Association.

the Symptom Checklist–Frequency and Severity Scale (developed specifically for cardiac arrhythmias by Bubien et al and modified by Jenkins)⁶⁵ and the University of Toronto Atrial Fibrillation Severity Scale.^{66,67} Published validation data for the AF specific scales are sparse. Whether the reproducibility of the symptoms measures is sufficient and whether the symptom measures are generalizable to all AF subjects are unknown.

A panel of experts of the European Heart Rhythm Association proposed a novel AF-related classification based exclusively on patient-reported symptoms and impact on normal daily activities.⁷³ Although not yet validated, it has been recommended in the recent European Society of Cardiology guidelines.⁷⁴

The development and clinical use of scoring systems for AF-related symptoms is challenging for a number of reasons. First, there is a weak correlation between symptoms and arrhythmia. Second, systematic measures of both symptoms and functional capacity are strongly influenced by age, sex, race, socioeconomic situation, and concomitant cardiovascular conditions.^{75,76} Finally, the relations of

symptoms to meaningful outcomes and prognosis have not been well examined.⁷⁶ A number of potential solutions have been suggested, including combining existing AF-related symptoms measures with more generalized quality-of-life measures^{76,77} and developing shorter, more specific scales that focus on symptoms related to AF.^{57,78–80}

Recently, a novel questionnaire (Atrial Fibrillation Effect on Quality-of-Life) has been developed and validated by a broad range of researchers involved in the development of the previous symptom measures.⁸¹ The 20-item Atrial Fibrillation Effect on Quality-of-Life measure consists of a 4-item symptoms score, an 8-item daily activities score, a 6-item treatment concerns score, and a 2-item treatment satisfaction scale. The Atrial Fibrillation Effect on Quality-of-Life score combines symptoms, functional status, and quality of life in 1 measure. The score has been shown to be valid, reliable, and responsive to clinical change. It represents an important step forward, although the tool will require further testing to assess whether it overcomes the limitations of the other AF-related symptom measures.

Future Research

As Coyne et al⁸⁰ suggested in 2005, for health-outcome quality-of-life measures in AF, more research is warranted to increase the validity, reproducibility, test-retest reliability, accuracy of day-to-day variability, and generalizability of the AF symptom measures. Most measures were developed and tested in specific hospital-based cohorts or randomized trials; the validity in other settings is unknown and needs more study. Furthermore, most measures have not been widely validated in different age groups, races, and ethnicities or in socioeconomic backgrounds. Whether these symptom scores have specificity for AF-related symptoms versus symptoms caused by other cardiac diseases is largely unknown. To increase the comparability of trials using symptoms as outcome measures, a consensus will need to emerge among investigators and clinicians on which measures to use rather than new measures being developed for each specific purpose. Finally, integrating these measures into the management of AF will be critical.

Functional Status Systematic Measures

As discussed previously, in a significant proportion of AF patients, a reduction in exercise tolerance is the major presenting symptom. Previous studies have reported that in many AF patients, the reduction in exercise tolerance is on the order of 15% to 20%.²⁸ It is therefore of clinical interest to measure functional status in patients with AF both as a means of measuring symptom burden and as an outcome measure for therapeutic interventions.⁸²

Similar to measures of AF-related symptoms, multiple tests are available for measuring functional status in AF, each of which has specific limitations (summarized in Table I in the online-only Data Supplement).⁸³ The most commonly used subjective measures are the New York Heart Association classification, Canadian Cardiovascular Society classification, Duke Activity Scale Index, and Goldman Specific Activity Scale. More objective measures include the 6-minute walk test or an exercise stress test.⁸³ Importantly, the published measures have not been specifically designed or validated in patients with AF.

A review of the literature indicates that different studies have variably used terms such as functional performance, functional capacity, level of impairment, quality-of-life health status, physical functioning, and activities of daily living to describe an individual's functional status.⁸³ Although many times these measures are used interchangeably, there are some subtle differences between the terminologies used to describe functional status. For instance, functional performance refers to the ability to perform day-to-day activities, specifically "to meet basic needs, fulfill usual roles, and maintain the health and well-being."⁸³ In contrast, functional capacity refers to an individual's maximum potential to carry out activities of daily living or self-care. Whereas the New York Heart Association classification, Canadian Cardiovascular Society Classification, and Goldman Specific Activity Scale are measures of functional performance, the Duke Activity Scale Index, the 6-minute walk, and exercise stress testing are measures of functional capacity.

The use of a variety of measures makes comparison of outcomes from different studies describing relations between functional status and AF difficult. Each of the functional status measures has specific characteristics in terms of sensitivity, discrimination, scaling, reliability, validity, and applicability. The lack of consistency between studies has led to challenges in interpreting study results and making comparisons between studies.

Although functional status measures have been of value for research purposes to quantify the functional limitation in patients with AF, they are associated with some major drawbacks. There is no clearly defined relation between AF and functional capacity. Plus, not much is known about confounding by age, sex, race, socioeconomic background, other cardiac diseases, and medication use.⁸³ As a result, the use of functional capacity as the sole outcome measure of AF therapies may be insufficient. In addition, some functional measures are associated with specific limitations; eg, exercise tests and walk tests may not be possible in elderly patients or patients with disabilities.

Future Research

Considerations on the validity, reproducibility, and generalizability of the instruments also are applicable to the functional status assessments in AF. Most measures were not developed specifically for AF, so investigating the value of functional measures in AF patients will be essential.

Impact of Therapies on AF-Related Symptoms

Trials that have investigated the relation of therapeutic interventions with symptom burden and functional status are summarized in Table II in the online-only Data Supplement.

Pharmacological Rate and Rhythm Control Therapies

Large randomized trials have demonstrated that a rate control strategy was noninferior to a rhythm control strategy in terms of cardiovascular morbidity and mortality. In the majority of trials that directly compared the 2 treatment strategies, neither strategy was superior for improving AF-related symptoms.^{11,12,78,84–86} It should be noted that severely symptomatic patients were not included in the large rate versus rhythm control trials. The effect of the treatment strategy on functional status in these trials was less clear and in some cases depended on the specific tool used to measure functional capacity. For instance, whereas improvements in exercise tolerance were reported in the rhythm control arm using objective measures such as a 6-minute walk test and treadmill exercise test,^{78,85,87} the results were not consistent when qualitative measures such as New York Heart Association and Canadian Cardiovascular Society classifications were used.^{78,84,85,87} Of note, the reported improvements in functional class were relatively modest. Interestingly, the presence of other cardiovascular conditions appeared to have a greater impact than AF per se in these trials.^{87,88} A number of substudies of rate versus rhythm control trials and a recently published randomized trial also investigated the relations between the achieved heart rate and symptoms in the rate

control arm.⁸⁹⁻⁹¹ The rate control studies reported no relation between heart rate and symptoms or functional status.

Multiple small, nonrandomized studies have shown that rhythm control therapy with cardioversion results in an improvement in exercise capacity, typically within the range of 10% to 20%.^{28,37,92,93} Two trials compared different pharmacological rhythm control agents and found that restoration and maintenance of sinus rhythm were associated with improvements in both symptoms and functional status.^{94,95} However, once again, the magnitude of difference in these studies was modest; 15% to 20% relative changes in Symptom Checklist scores were seen.⁷⁶ Another trial compared different amiodarone regimes and found no improvement in symptoms with either treatment strategy.⁹⁶ Not surprisingly, the greatest improvement in symptom reduction and functional status, if any, was seen in those with the most severe symptoms and worst functional status at baseline.

Nonpharmacological Rate Control Therapies

In selected patients with severely symptomatic AF and uncontrollable heart rates despite antiarrhythmic drug therapy, atrioventricular node ablation with permanent pacemaker implantation may be an effective alternative. Many, mostly nonrandomized, studies have addressed the impact of this treatment strategy on symptoms related to AF and quality of life.⁹⁷ In 2 studies, atrioventricular node ablation and pacemaker implantation were associated with a reduction in symptom scores of 18% to 30%.^{98,99} Functional capacity was measured in one of the trials and did not significantly improve in the treatment arm. In a meta-analysis including 21 studies with a total of 1181 patients, both symptoms and functional status (measured with a variety of scales and scores) improved after ablation and pacing therapy.⁹⁷

An alternative rate control approach, which has been used only in research settings, is to implant a permanent pacemaker with ventricular response pacing algorithms in patients with intact atrioventricular node conduction.¹⁰⁰ The ventricular response pacing algorithm is designed to promote regularity of the ventricular rate while ensuring that the mean ventricular rate does not increase. However, in a small crossover study of 45 patients, ventricular response pacing reduced the severity of AF-related symptoms but did not improve functional status (Duke Activity Status Index and 6-minute walk test).¹⁰⁰

Nonpharmacological Rhythm Control Therapies

Alternatives for pharmacological rhythm control for the treatment of AF include maze surgery and pulmonary vein isolation (PVI) for AF. The use of maze surgery to treat isolated AF has decreased dramatically, mainly because of the emergence of less invasive alternatives. Several small series have shown the efficacy of the maze procedure; however, data on symptom reduction and functional status improvement are sparse.^{101,102} Multiple, mostly nonrandomized, PVI studies have reported an improvement in symptoms (measured with the Symptom Checklist or a derived score based on the Symptom Checklist).⁷⁶ A few small randomized controlled trials have compared PVI with other treatment

strategies.¹⁰³ In 2 randomized multicenter studies (n=112 and n=167, respectively) of patients with paroxysmal AF who failed on 1 antiarrhythmic drug,^{59,104} PVI was reported to be superior to antiarrhythmic drugs in terms of both short and intermediate maintenance of sinus rhythm and improvement in symptoms and functional status (as measured by the Symptom Checklist and an exercise test, respectively). In a trial of heart failure patients comparing PVI with atrioventricular node ablation and biventricular pacemaker implantation, PVI was reported to be superior in terms of functional status measured by 6-minute walk distance after 6 months.¹⁰⁵

It is difficult to compare results of PVI studies and results of pharmacological rhythm control studies because of differences in patient characteristics. However, it is likely that in the subset of patients with paroxysmal AF with a high symptom burden, PVI is more effective than pharmacological rhythm control in terms of short- to intermediate-term symptom alleviation,⁵⁹ even allowing for ascertainment bias from blended evaluation.¹⁰⁶

Exercise Training and Impact on AF-Related Symptoms

Interestingly, in a few studies, an exercise-training program improved the symptoms (Symptom Checklist) and functional status (exercise test) of AF patients.¹⁰⁷⁻¹⁰⁹ A specific exercise training program might be an interesting treatment approach for AF, although more research is needed to support this therapy.

Future Research

A more uniform and standardized approach to measure AF-related symptoms and functional status is of vital importance to the field. Another important area of inquiry involves the relation of symptom and functional status scores to study end points and prognosis. Randomized clinical trials specifically aiming to reduce AF-related symptoms and functional status are needed. In addition, prospective evaluation of AF-related symptoms and functional status and the use of specific therapies to reduce symptom burden are essential. Finally, the effects of AF-related symptoms and functional status on healthcare use and costs require further study.

Future Research Opportunities

In Table 3, we summarize potential future research topics detailed after each section to clarify the relation between AF and symptoms. To address these needs, we advocate a multipronged cross-disciplinary and translational research program capitalizing on experimental, observational databases and randomized controlled trials. The main opportunities for future research are (1) to determine the variation in AF-related symptoms by patient demographics, comorbid conditions, therapies, and AF subtype; (2) to determine pathophysiological mechanisms underlying AF-related symptoms; (3) to describe the temporal relations between the presence and absence of AF-related symptoms; (4) to enhance the validity, reproducibility, and generalizability of the AF-related symptoms and functional status measures; (5) to standardize the methods of measuring AF-related symptoms

Table 3. Future Directions

Field	Goals
Symptoms related to AF	Incidence and prevalence of AF symptoms in different AF subsets in terms of age, race/ethnicity, sex, socioeconomic status, and setting (hospital-based or community-based)*
Concomitant cardiovascular conditions related to AF-related symptoms	Relation of specific AF therapies to variation in AF-related symptoms
Longitudinal change in AF-related symptoms over time	Patterns of AF (paroxysmal, persistent, and permanent AF) related to AF-related symptoms
Pathophysiology of AF-related symptoms	Utility of imaging and biomarkers to define specific endophenotypes of AF in relation to symptoms
	Pathophysiological mechanisms underlying AF-related symptoms in lone AF and in AF in the setting of concomitant cardiovascular conditions
	Pathophysiological mechanisms underlying the absence of AF-related symptoms
Temporal relation between AF and symptoms	Utility of imaging to (CT, MRI, PET) to increase our understanding of mechanisms underlying AF-related symptoms
	Relation of genomic markers and biomarkers to specific symptoms
Systematic AF-related symptom and functional status measures	Temporal relation of actual AF episodes and symptoms
	Factors related to absence of AF-related symptoms
AF symptoms as an outcome measure of AF therapies	Heritability of absence, presence, and severity AF-related symptoms
	Increase in the validity, reproducibility and generalizability of the AF-related symptoms and functional status measures specifically in patients with AF, accounting for setting and type of AF*
	Relation of test performance to clinical characteristics such as age, sex, race/ethnicity, socioeconomic status, and comorbidities
	Uniform and standardized measurements of AF-related symptoms in clinical trials (and clinical practice) to enhance the interpretability and comparability of AF trials*
	Relation of AF-related symptom and functional status measures to health outcomes including heart failure, stroke, and death*
	Relation of AF-related symptom and functional status measures to healthcare use and costs*
	Specific therapies or training to reduce or control AF-related symptoms and to improve prognosis*

AF indicates atrial fibrillation; CT, computed tomography; MRI, magnetic resonance imaging; and PET, positron emission tomography.

*Key recommendations.

in both clinical trials and clinical practice to enhance the interpretability and comparability of AF trials; and (6) to determine whether AF-related symptom and functional status measures are related to meaningful health outcomes, healthcare use, and costs of care.

Conclusions

Although there are still multiple unanswered questions about the mechanisms of symptoms and functional status in AF and the impact of other cardiac diseases and AF therapies, the symptom burden associated with AF is a major consideration when deciding on the treatment strategy. According to the available literature, AF therapies are only moderately effective in relieving symptoms and improving functional status. With the emergence of ablation techniques as a treatment for AF, more accurate assessment of symptom burden and functional status is increasingly important. More systematic research is urgently warranted to answer the many unresolved questions concerning the relation between symptoms and AF.

Sources of Funding

Dr Rienstra is supported by a grant from the Netherlands Organization for Scientific Research (Rubicon grant 825.09.020). This work was supported by grants from the National Institutes of Health to Drs Benjamin and Ellinor (1RO1HL092577), Dr Benjamin (RO1AG028321, RC1-HL01056, 1R01HL102214), Drs Magnani (R21) and Benjamin (Evans Center for Interdisciplinary Biomedical Research ARC on Atrial Fibrillation at Boston University [<http://www.bumc.bu.edu/evanscenteribr/>]), Dr Ellinor (5R21DA027021, 1RO1HL104156, 1K24HL105780), 6R01-NS 17950, and N01-HC 25195. Dr Magnani is supported by American Heart Association Award 09FTF219028. Dr Sinner is supported by the German Heart Foundation. Dr Van Gelder is supported by the Netherlands Heart Foundation, Interuniversity Cardiology Institute The Netherlands, AstraZeneca, Biotronik, Medtronic, Sanofi-aventis, Boehringer Ingelheim, St. Jude Medical, and Boston Scientific.

Disclosures

Dr Van Gelder receives honoraria from Medtronic, MSD, Sanofi-aventis, Boehringer Ingelheim, and AGA Medical. The other authors report no conflicts.

References

1. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol*. 1998;82:2N-9N.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke*. 1991;22:983-988.
3. 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;98:946-952.
4. Wolf PA, Benjamin EJ, Belanger AJ, Kannel WB, Levy D, D'Agostino RB. Secular trends in the prevalence of atrial fibrillation: the Framingham study. *Am Heart J*. 1996;131:790-795.
5. Hannon N, Sheehan O, Kelly L, Marnane M, Merwick A, Moore A, Kyne L, Duggan J, Moroney J, McCormack PM, Daly L, Fitz-Simon N, Harris D, Horgan G, Williams EB, Furie KL, Kelly PJ. Stroke associated with atrial fibrillation: incidence and early outcomes in the North Dublin Population Stroke Study. *Cerebrovasc Dis*. 2010;29:43-49.
6. Bunch TJ, Weiss JP, Crandall BG, May HT, Bair TL, Osborn JS, Anderson JL, Muhlestein JB, Horne BD, Lappe DL, Day JD. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm*. 2010;7:433-437.
7. Dublin S, Anderson ML, Haneuse SJ, Heckbert SR, Crane PK, Breitner JC, McCormick W, Bowen JD, Teri L, McCurry SM, Larson EB. Atrial fibrillation and risk of dementia: a prospective cohort study. *J Am Geriatr Soc*. 2011;59:1369-1375.
8. Miyasaka Y, Barnes ME, Bailey KR, Cha SS, Gersh BJ, Seward JB, Tsang TS. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. *J Am Coll Cardiol*. 2007;49:986-992.
9. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119-125.

10. Zimetbaum P, Reynolds MR, Ho KK, Gaziano T, McDonald MJ, McClenen S, Berezin R, Josephson ME, Cohen DJ. Impact of a practice guideline for patients with atrial fibrillation on medical resource utilization and costs. *Am J Cardiol*. 2003;92:677–681.
11. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347:1834–1840.
12. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–1833.
13. Einthoven W. Le telecardiogramme. *Arch Int Physiol*. 1906;4:132–164.
14. Levy S, Maarek M, Coumel P, Guize L, Lekieffre J, Medvedowsky JL, Sebaoun A. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study: the College of French Cardiologists. *Circulation*. 1999;99:3028–3035.
15. Flaker GC, Belew K, Beckman K, Vidaillet H, Kron J, Safford R, Mickel M, Barrell P. Asymptomatic atrial fibrillation: demographic features and prognostic information from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J*. 2005;149:657–663.
16. Kerr C, Boone J, Connolly S, Greene M, Klein G, Sheldon R, Talajic M. Follow-up of atrial fibrillation: the initial experience of the Canadian Registry of Atrial Fibrillation. *Eur Heart J*. 1996;17(suppl C):48–51.
17. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, Cobbe S, Breithardt G, Le Heuzey JY, Prins MH, Levy S, Crijns HJ. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart survey on atrial fibrillation. *Eur Heart J*. 2005;26:2422–2434.
18. MacRae CA. Symptoms in atrial fibrillation: why keep score? *Circ Arrhythm Electrophysiol*. 2009;2:215–217.
19. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol*. 2003;91:2D–8D.
20. Sears SF, Serber ER, Alvarez LG, Schwartzman DS, Hoyt RH, Ujhelyi MR. Understanding atrial symptom reports: objective versus subjective predictors. *Pacing Clin Electrophysiol*. 2005;28:801–807.
21. Bhandari AK, Anderson JL, Gilbert EM, Alpert BL, Henthorn RW, Waldo AL, Cullen MT Jr, Hawkinson RW, Pritchett EL. Correlation of symptoms with occurrence of paroxysmal supraventricular tachycardia or atrial fibrillation: a transtelephonic monitoring study: the Flecainide Supraventricular Tachycardia Study Group. *Am Heart J*. 1992;124:381–386.
22. Barsky AJ, Ahern DK, Brener J, Surman OS, Ring C, Dec GW. Palpitations and cardiac awareness after heart transplantation. *Psychosom Med*. 1998;60:557–562.
23. Brown AM, Sease KL, Robey JL, Shofer FS, Hollander JE. The risk for acute coronary syndrome associated with atrial fibrillation among ED patients with chest pain syndromes. *Am J Emerg Med*. 2007;25:523–528.
24. Goette A, Bukowska A, Dobrev D, Pfeiffenberger J, Morawietz H, Strugala D, Wiswedel I, Rohl FW, Wolke C, Bergmann S, Bramlage P, Ravens U, Lendeckel U. Acute atrial tachyarrhythmia induces angiotensin II type 1 receptor-mediated oxidative stress and microvascular flow abnormalities in the ventricles. *Eur Heart J*. 2009;30:1411–1420.
25. Connolly SJ, Schnell DJ, Page RL, Wilkinson WE, Marcello SR, Pritchett EL. Symptoms at the time of arrhythmia recurrence in patients receiving azimilide for control of atrial fibrillation or flutter: results from randomized trials. *Am Heart J*. 2003;146:489–493.
26. Kochiadakis GE, Skalidis EI, Kaleebas MD, Igoumenidis NE, Chrysostomakis SI, Kanoupidis EM, Simantirakis EN, Vardas PE. Effect of acute atrial fibrillation on phasic coronary blood flow pattern and flow reserve in humans. *Eur Heart J*. 2002;23:734–741.
27. Range FT, Schafers M, Acil T, Schafers KP, Kies P, Paul M, Hermann S, Brisse B, Breithardt G, Schober O, Wichter T. Impaired myocardial perfusion and perfusion reserve associated with increased coronary resistance in persistent idiopathic atrial fibrillation. *Eur Heart J*. 2007;28:2223–2230.
28. Ueshima K, Myers J, Graettinger WF, Atwood JE, Morris CK, Kawaguchi T, Froelicher VF. Exercise and morphologic comparison of chronic atrial fibrillation and normal sinus rhythm. *Am Heart J*. 1993;126:260–261.
29. Skinner NS Jr, Mitchell JH, Wallace AG, Sarnoff SJ. Hemodynamic consequences of atrial fibrillation at constant ventricular rates. *Am J Med*. 1964;36:342–350.
30. Lau CP, Leung WH, Wong CK, Cheng CH. Haemodynamics of induced atrial fibrillation: a comparative assessment with sinus rhythm, atrial and ventricular pacing. *Eur Heart J*. 1990;11:219–224.
31. Alboni P, Scarfo S, Fuca G, Paparella N, Yannacopulu P. Hemodynamics of idiopathic paroxysmal atrial fibrillation. *Pacing Clin Electrophysiol*. 1995;18:980–985.
32. Clark DM, Plumb VJ, Epstein AE, Kay GN. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. *J Am Coll Cardiol*. 1997;30:1039–1045.
33. Daoud EG, Weiss R, Bahu M, Knight BP, Bogun F, Goyal R, Harvey M, Strickberger SA, Man KC, Morady F. Effect of an irregular ventricular rhythm on cardiac output. *Am J Cardiol*. 1996;78:1433–1436.
34. Natale A, Zimmerman L, Tomassoni G, Kearney M, Kent V, Brandon MJ, Newby K. Impact on ventricular function and quality of life of trans-catheter ablation of the atrioventricular junction in chronic atrial fibrillation with a normal ventricular response. *Am J Cardiol*. 1996;78:1431–1433.
35. Farshi R, Kistner D, Sarma JS, Longmate JA, Singh BN. Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. *J Am Coll Cardiol*. 1999;33:304–310.
36. Peters KG, Kienzle MG. Severe cardiomyopathy due to chronic rapidly conducted atrial fibrillation: complete recovery after restoration of sinus rhythm. *Am J Med*. 1988;85:242–244.
37. Van Gelder IC, Crijns HJ, Blanksma PK, Landsman ML, Posma JL, Van Den Berg MP, Meijler FL, Lie KI. Time course of hemodynamic changes and improvement of exercise tolerance after cardioversion of chronic atrial fibrillation unassociated with cardiac valve disease. *Am J Cardiol*. 1993;72:560–566.
38. Grogan M, Smith HC, Gersh BJ, Wood DL. Left ventricular dysfunction due to atrial fibrillation in patients initially believed to have idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1992;69:1570–1573.
39. Lazzari JO, Gonzalez J. Reversible high rate atrial fibrillation dilated cardiomyopathy. *Heart*. 1997;77:486.
40. van den Berg MP, Hassink RJ, Tuinenburg AE, Lefrandt JD, de Kam PJ, Crijns HJ. Impaired autonomic function predicts dizziness at onset of paroxysmal atrial fibrillation. *Int J Cardiol*. 2001;81:175–180.
41. Fuster V, Ryden LE, Cannon DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: 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. *Circulation*. 2006;114:e257–e354.
42. Barsky AJ, Cleary PD, Barnett MC, Christiansen CL, Ruskin JN. The accuracy of symptom reporting by patients complaining of palpitations. *Am J Med*. 1994;97:214–221.
43. Zeldis SM, Levine BJ, Michelson EL, Morganroth J. Cardiovascular complaints: correlation with cardiac arrhythmias on 24-hour electrocardiographic monitoring. *Chest*. 1980;78:456–461.
44. Clark PI, Glasser SP, Spoto E Jr. Arrhythmias detected by ambulatory monitoring: lack of correlation with symptoms of dizziness and syncope. *Chest*. 1980;77:722–725.
45. Lin HJ, Wolf PA, Benjamin EJ, Belanger AJ, D'Agostino RB. Newly diagnosed atrial fibrillation and acute stroke: the Framingham study. *Stroke*. 1995;26:1527–1530.
46. Asberg S, Henriksson KM, Farahmand B, Asplund K, Norrving B, Appelros P, Stegmayer B, Asberg KH, Terent A. Ischemic stroke and secondary prevention in clinical practice: a cohort study of 14,529 patients in the Swedish stroke register. *Stroke*. 2010;41:1338–1342.
47. Fetsch T, Bauer P, Engberding R, Koch HP, Lukl J, Meinertz T, Oeff M, Seipel L, Trappe HJ, Treese N, Breithardt G. Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial. *Eur Heart J*. 2004;25:1385–1394.

48. 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;89:224–227.
49. Page RL, Tilsch TW, Connolly SJ, Schnell DJ, Marcello SR, Wilkinson WE, Pritchett EL. Asymptomatic or “silent” atrial fibrillation: frequency in untreated patients and patients receiving azimilide. *Circulation*. 2003;107:1141–1145.
50. Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinach R, Cook J, Paraschos A, Love J, Radoslovich G, Lee KL, Lamas GA. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the atrial diagnostics ancillary study of the Mode Selection Trial (MOST). *Circulation*. 2003;107:1614–1619.
51. Wolk R, Kulakowski P, Karczmarewicz S, Karpinski G, Makowska E, Czepiel A, Ceremuzynski L. The incidence of asymptomatic paroxysmal atrial fibrillation in patients treated with propranolol or propafenone. *Int J Cardiol*. 1996;54:207–211.
52. Savelieva I, Camm AJ. Clinical relevance of silent atrial fibrillation: prevalence, prognosis, quality of life, and management. *J Interv Card Electrophysiol*. 2000;4:369–382.
53. Patten M, Maas R, Karim A, Muller HW, Simonovsky R, Meinertz T. Event-recorder monitoring in the diagnosis of atrial fibrillation in symptomatic patients: subanalysis of the SOPAT trial. *J Cardiovasc Electrophysiol*. 2006;17:1216–1220.
54. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339:659–666.
55. Pappone C, Rosanio S, Oreti G, Tocchi M, Gugliotta F, Vicedomini G, Salvati A, Dicandia C, Mazzone P, Santinelli V, Gullette S, Chierchia S. Circumferential radiofrequency ablation of pulmonary vein ostia: a new anatomic approach for curing atrial fibrillation. *Circulation*. 2000;102:2619–2628.
56. Pappone C, Rosanio S, Augello G, Gallus G, Vicedomini G, Mazzone P, Gullette S, Gugliotta F, Pappone A, Santinelli V, Tortoriello V, Sala S, Zangrillo A, Crescenzi G, Benussi S, Alfieri O. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. *J Am Coll Cardiol*. 2003;42:185–197.
57. Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi F Jr, Bates ER, Lehmann MH, Vicedomini G, Augello G, Agricola E, Sala S, Santinelli V, Morady F. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med*. 2006;354:934–941.
58. Hsu LF, Jais P, Sanders P, Garrigue S, Hocini M, Sacher F, Takahashi Y, Rotter M, Pasquie JL, Scavee C, Bordachar P, Clementy J, Haissaguerre M. Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med*. 2004;351:2373–2383.
59. Jais P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clementy J, Haissaguerre M. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation*. 2008;118:2498–2505.
60. Hindricks G, Piorkowski C, Tanner H, Kobza R, Gerds-Li JH, Carabucicchio C, Kottkamp H. Perception of atrial fibrillation before and after radiofrequency catheter ablation: relevance of asymptomatic arrhythmia recurrence. *Circulation*. 2005;112:307–313.
61. Senatore G, Stabile G, Bertaglia E, Donnici G, De Simone A, Zoppo F, Turco P, Pascotto P, Fazzari M. Role of transtelephonic electrocardiographic monitoring in detecting short-term arrhythmia recurrences after radiofrequency ablation in patients with atrial fibrillation. *J Am Coll Cardiol*. 2005;45:873–876.
62. Bubien R, Packa D, Karst G, Kay G. Does activity sensing rate adaptive pacing improve quality of life? *Pacing Clin Electrophysiol*. 1989;12:688.
63. Kay G, Bubien R, Karst G. Metabolic versus activity sensors for rate-adaptive pacing: a prospective comparison utilizing quality of life measurements. *Pacing Clin Electrophysiol*. 1989;12:641.
64. Bubien R, Kay G. A randomized comparison of quality of life and exercise capacity with DDD and VVIR pacing modes. *Pacing Clin Electrophysiol*. 1990;13:524.
65. 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;94:1585–1591.
66. Maglio C, Sra J, Paquette M, Dorian P, Bygrave A, Wood K, Ayers G. Measuring quality of life and symptom severity in patients with atrial fibrillation [abstract]. *Pacing Clin Electrophysiol*. 1998;21:839.
67. Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, Camm J, Akhtar M, Luderitz B. 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;36:1303–1309.
68. Paquette M, Roy D, Talajic M, Newman D, Couturier A, Yang C, Dorian P. Role of gender and personality on quality-of-life impairment in intermittent atrial fibrillation. *Am J Cardiol*. 2000;86:764–768.
69. Dorian P, Paquette M, Newman D, Green M, Connolly SJ, Talajic M, Roy D. Quality of life improves with treatment in the Canadian Trial of Atrial Fibrillation. *Am Heart J*. 2002;143:984–990.
70. Dorian P, Cvitkovic SS, Kerr CR, Crystal E, Gillis AM, Guerra PG, Mitchell LB, Roy D, Skanes AC, Wyse DG. A novel, simple scale for assessing the symptom severity of atrial fibrillation at the bedside: the CCS-SAF scale. *Can J Cardiol*. 2006;22:383–386.
71. Dorian P, Guerra PG, Kerr CR, O'Donnell SS, Crystal E, Gillis AM, Mitchell LB, Roy D, Skanes AC, Rose MS, Wyse DG. 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;2:218–224.
72. Harden M, Nystrom B, Kulich K, Carlsson J, Bengtson A, Edvardsson N. Validity and reliability of a new, short symptom rating scale in patients with persistent atrial fibrillation. *Health Qual Life Outcomes*. 2009;7:65–75.
73. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener HC, Goette A, Hindricks G, Hohnloser S, Kappenberger L, Kuck KH, Lip GY, Olsson B, Meinertz T, Priori S, Ravens U, Steinbeck G, Svernhaug E, Tijssen J, Vincent A, Breithardt G. 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;9:1006–1023.
74. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenk B, Heldal M, Hohloser SH, Kohl P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369–2429.
75. 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;152:1097–1103.
76. Reynolds MR, Ellis E, Zimetbaum P. Quality of life in atrial fibrillation: measurement tools and impact of interventions. *J Cardiovasc Electrophysiol*. 2008;19:762–768.
77. 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.e1–448.e19.
78. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation: Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet*. 2000;356:1789–1794.
79. Brignole M, Gianfranchi L, Menozzi C, Alboni P, Musso G, Bongiorni MG, Gasparini M, Raviele A, Lolli G, Paparella N, Acquarone S. Assessment of atrioventricular junction ablation and DDDR mode-switching pacemaker versus pharmacological treatment in patients with severely symptomatic paroxysmal atrial fibrillation: a randomized controlled study. *Circulation*. 1997;96:2617–2624.
80. Coyne K, Margolis MK, Grandy S, Zimetbaum P. The state of patient-reported outcomes in atrial fibrillation: a review of current measures. *Pharmacoconomics*. 2005;23:687–708.
81. Spertus J, Dorian P, Bubien R, Lewis S, Godejohn D, Reynolds MR, Lakkireddy DR, Wimmer AP, Bhandari A, Burk C. 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.
82. Atwood JE, Myers JN, Tang XC, Reda DJ, Singh SN, Singh BN. Exercise capacity in atrial fibrillation: a substudy of the Sotalol-Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T). *Am Heart J*. 2007;153:566–572.

83. Coyne KS, Allen JK. Assessment of functional status in patients with cardiac disease. *Heart Lung*. 1998;27:263–273.

84. Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, Walter S, Tebbe U. 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;41:1690–1696.

85. Opolski G, Torbicki A, Kosior DA, Szulc M, Wozakowska-Kaplon B, Kolodziej P, Achremczyk P. Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) study. *Chest*. 2004;126:476–486.

86. Jenkins LS, Brodsky M, Schron E, Chung M, Rocco T Jr, Lader E, Constantine M, Sheppard R, Holmes D, Mateski D, Floden L, Prasun M, Greene HL, Shemanski L. Quality of life in atrial fibrillation: the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J*. 2005;149:112–120.

87. Chung MK, Shemanski L, Sherman DG, Greene HL, Hogan DB, Kellen JC, Kim SG, Martin LW, Rosenberg Y, Wyse DG. Functional status in rate- versus rhythm-control strategies for atrial fibrillation: results of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) functional status substudy. *J Am Coll Cardiol*. 2005;46:1891–1899.

88. Rienstra M, van Gelder IC, Hagens VE, Veeger NJ, van Veldhuisen DJ, Crijns HJ. Mending the rhythm does not improve prognosis in patients with persistent atrial fibrillation: a subanalysis of the RACE study. *Eur Heart J*. 2006;27:357–364.

89. Cooper HA, Bloomfield DA, Bush DE, Katcher MS, Rawlins M, Sacco JD, Chandler M. Relation between achieved heart rate and outcomes in patients with atrial fibrillation (from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management [AFFIRM] study). *Am J Cardiol*. 2004;93:1247–1253.

90. Groenveld HF, Crijns HJ, Rienstra M, Van den Berg MP, Van Veldhuisen DJ, Van Gelder IC. Does intensity of rate control influence outcome in persistent atrial fibrillation? Data of the RACE study. *Am Heart J*. 2009;158:785–791.

91. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, Tukkie R, Bosker HA, Van Veldhuisen DJ, Van den Berg MP. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010;362:1363–1373.

92. Ueshima K, Myers J, Morris CK, Atwood JE, Kawaguchi T, Froelicher VF. The effect of cardioversion on exercise capacity in patients with atrial fibrillation. *Am Heart J*. 1993;126:1021–1024.

93. Atwood JE, Myers J, Sullivan M, Forbes S, Sandhu S, Callaham P, Froelicher V. The effect of cardioversion on maximal exercise capacity in patients with chronic atrial fibrillation. *Am Heart J*. 1989;118:913–918.

94. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagne P, Nattel S, Thibault B. Amiodarone to prevent recurrence of atrial fibrillation: Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med*. 2000;342:913–920.

95. Singh SN, Tang XC, Singh BN, Dorian P, Reda DJ, Harris CL, Fletcher RD, Sharma SC, Atwood JE, Jacobson AK, Lewis HD Jr, Lopez B, Raisch DW, Ezekowitz MD. 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;48:721–730.

96. Ahmed S, Ranchor AV, Crijns HJ, Van Veldhuisen DJ, Van Gelder IC. Effect of continuous versus episodic amiodarone treatment on quality of life in persistent atrial fibrillation. *Europace*. 2010;12:785–791.

97. Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clinical outcomes after ablation and pacing therapy for atrial fibrillation: a meta-analysis. *Circulation*. 2000;101:1138–1144.

98. Kay GN, Ellenbogen KA, Giudici M, Redfield MM, Jenkins LS, Mianulli M, Wilkoff B. 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;2:121–135.

99. Weerasooriya R, Davis M, Powell A, Szili-Torok T, Shah C, Whalley D, Kanagaratnam L, Heddle W, Leitch J, Perks A, Ferguson L, Bulsara M. The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT). *J Am Coll Cardiol*. 2003;41:1697–1702.

100. 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;94:938–941.

101. Jessurun ER, van Hemel NM, Defauw JA, Stofmeel MA, Kelder JC, de la Riviere AB, Ernst JM. Results of maze surgery for lone paroxysmal atrial fibrillation. *Circulation*. 2000;101:1559–1567.

102. Hemels ME, Gu YL, Tuinenburg AE, Boonstra PW, Wiesfeld AC, Van Den Berg MP, van Veldhuisen DJ, van Gelder IC. Favorable long-term outcome of maze surgery in patients with lone atrial fibrillation. *Ann Thorac Surg*. 2006;81:1773–1779.

103. Bonanno C, Paccanaro M, La Vecchia L, Ometto R, Fontanelli A. Efficacy and safety of catheter ablation versus antiarrhythmic drugs for atrial fibrillation: a meta-analysis of randomized trials. *J Cardiovasc Med*. 2010;11:408–418.

104. Reynolds MR, Walczak J, White SA, Cohen DJ, Wilber DJ. Improvements in symptoms and quality of life in patients with paroxysmal atrial fibrillation treated with radiofrequency catheter ablation versus antiarrhythmic drugs. *Circ Cardiovasc Qual Outcomes*. 2010;3:615–623.

105. Khan MN, Jais P, Cummings J, Di Biase L, Sanders P, Martin DO, Kautzner J, Hao S, Themistoclakis S, Fanelli R, Potenza D, Massaro R, Wazni O, Schweikert R, Saliba W, Wang P, Al-Ahmad A, Beheiry S, Santarelli P, Starling RC, Dello Russo A, Pelargonio G, Brachmann J, Schibilla V, Bonsu A, Casella M, Raviele A, Haissaguerre M, Natale A. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med*. 2008;359:1778–1785.

106. Wyse DG, Anter E, Callans DJ. Cardioversion of atrial fibrillation for maintenance of sinus rhythm: a road to nowhere. *Circulation*. 2009;120:1444–1452.

107. Mertens DJ, Kavanagh T. Exercise training for patients with chronic atrial fibrillation. *J Cardiopulm Rehabil*. 1996;16:193–196.

108. Vanhees L, Schepers D, Defoor J, Brusselle S, Tchursh N, Fagard R. Exercise performance and training in cardiac patients with atrial fibrillation. *J Cardiopulm Rehabil*. 2000;20:346–352.

109. Hegbom F, Stavem K, Sire S, Heldal M, Orning OM, Gjesdal K. Effects of short-term exercise training on symptoms and quality of life in patients with chronic atrial fibrillation. *Int J Cardiol*. 2007;116:86–92.

KEY WORDS: arrhythmia ■ atrial fibrillation ■ review ■ signs and symptoms ■ exercise