Effects of Pharmacologic Therapy on Health-Related Quality of Life in Elderly Patients with Atrial Fibrillation: A Systematic Review of Randomized and Nonrandomized Trials

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Abstract: This systematic review assessed the impact of atrial fibrillation (AF) and pharmacotherapy on health-related quality of life (HRQOL) in elderly patients. Highly prevalent in the elderly, AF is associated with morbidity and symptoms affecting HRQOL. A PubMed and EMBASE search (1999–2010) was conducted using the terms atrial fibrillation, elderly, quality of life, Medicare, and Medicaid. In all, 504 articles were identified and 15 were selected (studies examining pharmacotherapy [rate or rhythm control] and HRQOL in AF patients with a mean age ≥ 65 years). Information, including study design, cohort size, and HRQOL instruments utilized, was extracted. Five observational studies, 5 randomized trials comparing rate and rhythm control, 3 randomized trials investigating pharmacologic agents, and 2 trials examining HRQOL, depression, and anxiety were identified. Elderly AF patients had reduced HRQOL versus patients in normal sinus rhythm, particularly in domains related to physical functioning. HRQOL may be particularly affected in older AF patients. Although data do not indicate whether a pharmacologic intervention or single treatment strategy—namely rate versus rhythm control—is better at improving HRQOL, either of these strategies and many pharmacologic interventions may improve HRQOL in elderly AF patients. Based on reviewed data, an algorithm is suggested to optimize HRQOL among elderly patients.

Keywords: aged, antiarrhythmic agents, arrhythmia, atrial fibrillation, health-related quality of life
Introduction
Atrial fibrillation (AF) is the most common cardiac arrhythmia seen in clinical practice. Each year in the United States, AF contributes to approximately 5 million office visits, 500,000 outpatient and emergency department visits, and 350,000 hospitalizations. Atrial fibrillation predominantly affects the elderly population. Approximately 70% of AF patients are between 65 and 85 years of age, with a median age of 75 years. The high prevalence of AF in the elderly has been associated with age-related changes within the atrial myocardium and conducting tissues and with structural heart disease. The prevalence of AF increases with advancing age; approximately 5% of the population older than 65 years and almost 8% of the population older than 80 years are affected. Because of the aging of the US population and improved survival of patients with hypertension, diabetes, and heart failure, the projected prevalence of AF is about 8 million Americans by the year 2050.

Atrial fibrillation is associated with significant morbidity and mortality, resulting in an increased risk of stroke, thromboembolism, chronic heart failure (CHF), and sudden death. Older age is an independent risk factor for stroke and strokes attributable to AF tend to be associated with a higher mortality rate and level of disability. Furthermore, patients demonstrate a greater cognitive decline in the presence of AF compared with patients without arrhythmia. Stroke prevention is critical in patients with AF and has received prominent attention with the introduction of newer anticoagulants. Most elderly patients with chronic AF do not develop stroke even after 30 years of follow-up, yet all AF patients may have impaired health-related quality of life (HRQOL).

The negative effect that aging has on HRQOL is a highly relevant issue, in particular when considering management options because most patients consider HRQOL to be the most important outcome of therapy. Many patients experience considerable impairment from symptoms and report lower HRQOL levels, increased illness intrusiveness, less than total functional capacity, and lower global life satisfaction than do healthy individuals or asymptomatic patients. The 36-Item Short Form Health Survey (SF-36) is a health scale that measures HRQOL across numerous domains, including Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. Patients with AF report significantly below-average HRQOL scores on various SF-36 domains, falling between patients with CHF and myocardial infarction in terms of the level of HRQOL impairment.

Over the last 20 years, hospital admissions for AF have increased by 66%. This is attributable to several factors, including an aging population, the increased prevalence of chronic heart disease, and increased diagnosis rates owing to more frequent electrocardiogram monitoring. As health care utilization increases in AF patients, HRQOL is negatively affected.

The impact of AF on HRQOL has not been extensively evaluated and many studies that do assess HRQOL have significant limitations. The majority of studies examining HRQOL in patients with AF and following either rate or rhythm control strategies are conducted in highly symptomatic patients, highly selected patient populations, or subgroups of clinical trial patients, populations with the potential for bias and inadequate statistical power. Interventions studied have included ablation and pacing procedures, the Maze procedure, pulmonary vein isolation, internal or external cardioversion, different pacing modalities, and pharmacologic therapy. To date, most of the studies examined the impact of ablation procedures on HRQOL, with relatively few studies assessing the impact of pharmacologic therapies that are used in the majority of AF patients.

A previous systematic review found that HRQOL in the segment of the general population diagnosed with AF was inferior to that of healthy controls, the general population, and patients with coronary heart disease. The same study found that both rate and rhythm control strategies had a beneficial effect on HRQOL. As aging and its associated disorders (eg, hypertension, stroke) independently reduce HRQOL, the greater prevalence of AF in the elderly warrants a better understanding of the impact of AF on HRQOL for this specific patient population. Reductions in HRQOL seen in aging populations complicate any analysis of a potential relationship between an asymptomatic disorder such as hypertension and HRQOL in elderly patients. Generally, decreased HRQOL with age is seen in almost all areas, with older patients...
HRQOL in elderly AF patients with hypertension reporting more stress, worries about health, and difficulties with coping. To date, AF clinical trials examining HRQOL issues in the elderly versus younger patient populations are not available. This is further compounded by the lack of a generally accepted definition for the term elderly, either chronologically or physiologically. However, an age of 65 years or greater is generally accepted as a reasonable chronologic definition. A better understanding of the impact of AF on HRQOL in elderly patients and the influence of various pharmacotherapies on HRQOL may help physicians to better determine an individual patient’s optimal treatment plan.

**Methods**

**Objective**

This systematic review evaluated HRQOL in patients with AF and assessed the effects of pharmacologic interventions on HRQOL, with a focus on older patients (mean age $\geq 65$ years).

**Search strategy and study selection**

A literature search limited to studies conducted in humans and published in English between January 1, 1999, and September 27, 2010, was performed using PubMed and EMBASE. Both Medical Subject Heading (MeSH) terms and text word searches were used in the following search strategy (MeSH terms identified):

(Atrial Fibrillation [MeSH] OR paroxysmal atrial fibrillation OR persistent atrial fibrillation OR permanent atrial fibrillation OR chronic atrial fibrillation OR lone atrial fibrillation OR silent atrial fibrillation OR atrial fibrillation/drug therapy [MeSH]) AND (quality of life [MeSH] OR well being OR personal satisfaction [MeSH] OR palpitation) AND (rate control OR rhythm control OR intervention OR pharmacologic treatment OR non-pharmacological interventions) AND (elderly OR aged [MeSH] OR Medicare [MeSH] OR Medicaid [MeSH])

Once articles were identified as eligible for inclusion, the reference lists from those articles were reviewed to identify any additional studies meeting inclusion criteria.

**Inclusion and exclusion criteria**

Observational HRQOL studies, non-interventional HRQOL studies, and randomized clinical trials examining pharmacotherapy (rate or rhythm control) and HRQOL in AF patients with a mean age of 65 years or greater were included. To be all-inclusive, studies assessing HRQOL through any HRQOL measurement instruments were eligible for inclusion, as were studies with any duration of follow-up. Studies that did not examine HRQOL were excluded, as were studies examining the effects of radiofrequency ablation and pacing therapy, internal or external direct current cardioversion, implantable defibrillators on HRQOL, or arrhythmia surgery.

**Quality assessment and data abstraction**

Each study eligible for inclusion was then reviewed to record the duration of the study, size of cohort, study sample representation of overall patient population, study design, and HRQOL instruments utilized. Limitations of each study were assessed based on information included in each article’s discussion section.

**Results**

The literature search identified 504 English-language citations (Fig. 1) published between January 1999 and September 2010. Removal of duplicate records left 379 citations. After reviewing the titles and abstracts of the 379 citations based on the inclusion and exclusion criteria, 357 were excluded. Thereafter, 22 full-text articles were assessed for eligibility, 6 were added based on review of the full-text article bibliographies, and 13 were excluded because HRQOL was not measured.

![Figure 1. Literature search flow diagram.](image-url)
A total of 15 studies remained and were included in this review: 5 observational studies, 5 randomized trials comparing effects of rate versus rhythm management strategies on HRQOL, and 3 randomized trials investigating the effects of specific pharmacologic agents on HRQOL. Additionally, 2 clinical trials examining HRQOL, depression, and anxiety in patients with AF, as well as the relationship between depression/anxiety and HRQOL, were included. The most common instrument utilized for HRQOL assessment in these 15 studies was the SF-36, including the physical component summary (PCS) and mental component summary (MCS) scales. The SF-36 measures health status in 8 domains: Physical Functioning, Role-Physical (limitations due to physical problems), Vitality, Mental Health, Role-Emotional (limitations due to emotional problems), Social Functioning, Bodily Pain, and General Health. A description of all the HRQOL instruments used in these studies is provided in Table 1 and summary data from the 15 studies are presented in Table 2.

**Observational quality-of-life studies in elderly patients with AF**

A cross-sectional study (part of the CliniQualVie Program) compared HRQOL in elderly inpatients with AF aged 65 years or older ($n = 41$) with that of age-matched controls ($n = 123$). Two HRQOL tools were utilized: the SF-36 and the Duke Health Profile questionnaire. The Duke Health Profile questionnaire measures HRQOL through 6 health measures—physical, mental, social, general, perceived health, and self-esteem—and 4 dysfunctions: anxiety, depression, pain, and disability. After adjustment for coronary artery disease or chronic respiratory failure, patients with AF had lower scores than matched controls in more than 70% of dimensions, namely 8 of 10 Duke Health Profile subscales and 6 of 8 SF-36 domains. Differences reached statistical significance for the Mental ($P = 0.01$), Anxiety ($P = 0.03$), and Depression ($P = 0.003$) subscales in the Duke Health Profile. No significant differences were observed between the 2 groups in the PCS or MCS of the SF-36. Limitations of this study include the small sample size, a cross-sectional design which did not allow conclusions to be made regarding causal relationship, and the cohort of hospitalized patients because hospitalization itself may have had negatively impacted HRQOL.

In another study, patients with AF ($n = 52$) reported overall HRQOL scores similar to those of population controls in normal sinus rhythm (SR) ($n = 48$). The PCS and MCS scores revealed a trend toward lower scores in patients with AF compared with controls, but differences did not achieve statistical significance (PCS, 43.0 versus 45.9, $P = 0.24$; MCS, 52.5 versus 55.3, $P = 0.07$). However, significantly lower scores were reported in AF patients for the Social Functioning (77.16 versus 89.32, $P = 0.01$) and Role-Emotional (82.05 versus 94.44, $P = 0.01$) domains. There was no difference in scores in the Physical Functioning domain, as assessed by the Yale Physical Activity Survey, which estimates the amount of time an individual spends performing physical activities and equivalent kilocalorie expenditures. This study was limited by reduced power due to a small cohort size and the fact that sicker AF patients (ie, those who were recently hospitalized) were excluded. Patients in this study had a mean age of 77 years; these patients are generally less active and could perhaps have fewer cardiovascular demands than younger patients.

Another study observed lower physical and mental scores in patients with newly diagnosed AF ($n = 81$) compared with the general US population (physical health, 38.53 versus 50.0; mental health, 48.74 versus 50.00). The frequency and severity of symptoms (as reported on the Symptom Checklist: Frequency and Severity scale) were inversely related ($P < 0.01$) to HRQOL for both physical and mental health, although causality could not be determined. This study had a relatively focused population of newly diagnosed elderly patients; however, it had reduced power due to small sample size and lack of follow-up.

The **Canadian Trial of Atrial Fibrillation** (CTAF) was a double-blind, randomized, multicenter study evaluating the effect of amiodarone versus sotalol or propafenone in preventing AF recurrence in patients with a history of paroxysmal or persistent AF. Patients with AF who participated in the CTAF completed validated HRQOL questionnaires at baseline, 3 months, and 12 months after antiarrhythmic drug treatment. Patients with AF were compared with controls age-matched to men and women with AF from a published database of population survey data. Both men ($n = 108$) and women ($n = 62$) from the CTAF had significantly worse HRQOL than gender-matched and age-matched controls for the vast majority of all...
### Table 1. Health-related quality of life (HRQOL) instrument descriptions.

| Acronym | Full name | Scale | Description |
|---------|-----------|-------|-------------|
| Cantril Ladder of Life | Higher score = more favorable HRQOL | Vertical boxed “ladder” with numbers within boxes ranging from 1 (“worst possible life”) to 10 (“best possible life”); patients write the number of the step on which they feel they currently stand, previously stood, and would stand at 3 points in time (present, 5 years previously, and 5 years hence). |
| QLI | Quality of Life Index (Cardiac Version) | Higher scores = greater satisfaction with HRQOL domains important to the patient | Assesses patient satisfaction and importance of 4 HRQOL factors: health and functioning, socioeconomic, psychological/spiritual, and family. |
| AFQLQ | Japanese Society of Electrocardiology’s Atrial Fibrillation QoL Questionnaire | Higher score = well health status | Contains 3 subscales, one of which assesses anxiety and limitation of daily activities related to AF and its treatment. |
| BDI | Beck Depression Inventory | Higher score = greater depression | Measures behavioral manifestations of depression using an inventory of 21 categories of symptoms and attitudes; 13-item short version is derived from the BDI. |
| BDI-SF-13 | Beck Depression Inventory Short Form-13 | | Questionnaire based on 16 statements regarding beliefs about specific medications prescribed for the patient (BMQ-specific) and 18 statements regarding beliefs about medicine in general (BMQ-general). The BMQ-specific includes two 5-item factors: specific necessity (present and future need for prescribed medication for health) and specific concern (concern for potential long-term dependence and toxicity); the BMQ-general includes two 4-item factors: general harm (harmfulness, addictiveness, and poisonousness) and general overuse (over-prescribed and over-relied upon by physicians). |
| BMQ | Beliefs About Medicines Questionnaire | Higher scores = stronger beliefs | Questionnaire based on 16 statements regarding beliefs about specific medications prescribed for the patient (BMQ-specific) and 18 statements regarding beliefs about medicine in general (BMQ-general). The BMQ-specific includes two 5-item factors: specific necessity (present and future need for prescribed medication for health) and specific concern (concern for potential long-term dependence and toxicity); the BMQ-general includes two 4-item factors: general harm (harmfulness, addictiveness, and poisonousness) and general overuse (over-prescribed and over-relied upon by physicians). |
| COOP | Dartmouth Primary Care Cooperative Information Project Chart | Higher scores = less favorable HRQOL | Assesses physical fitness, social activities, daily activities, feelings, overall health, pain, change in health, social support, and quality of life. |
| DASI | Duke Activity Status Index | Calculated score used to estimate peak oxygen capacity | Weighted 12-question survey of activities of daily living including personal care, ambulation, household tasks, sexual function, and recreational activities. |
| DUKE | Duke Health Profile | High scores = good health for health measures, poor health for dysfunction measures | Includes 10 measures: 6 health (physical, mental, social, general, perceived, and self-esteem) and 4 dysfunctions (anxiety, depression, pain, and disability). |
| IPQ | Illness Perception Questionnaire | Each scale summed and ordered separately; cause-of-illness scale not summed | Includes 5 scales that assess the components of illness: symptoms (12 items), consequences (physical, social, or economic; 7 items), cause (internal or external; 10 items), time-line (short, long, or permanent; 3 items), and control or cure (6 items). |
| MLWHF | Minnesota Living with Heart Failure Questionnaire | Higher scores = poorer HRQOL | Measures effects of heart failure and its treatment on patient HRQOL. |
| PSS | Perceived Stress Scale | Higher scores = greater perceived stress | Includes 14 items regarding global measure of perceived stress. |
Table 1. (Continued)

| Acronym | Full name | Scale | Description |
|---------|-----------|-------|-------------|
| SAS     | Specific Activity Scale<sup>6</sup> | Higher classification = poorer activity level | Questions assess the patient’s ability to perform activities of daily living; answers to questions dictate the functional classification (I through IV) of the patient according to the Canadian Cardiovascular Society. The SF-36 includes 36 questions assessing health status in 8 domains: PCS (physical component summary); Physical Functioning, Role-Physical, Bodily Pain, and General Health Perceptions; MCS (mental component summary); Social Functioning, General Mental Health, Role-Emotional, and Vitality. The SF-12 includes 12 questions derived from the SF-36, yielding PCS and MCS scale results. Includes 2 self-report scales comprising 20 questions each. The State Anxiety scale includes questions regarding how the patient currently feels, and the Trait Anxiety scale includes questions regarding how the patient generally feels. Assessment of total time, energy expenditure, frequency, and duration of activities (eg, work, yard work, caretaking, exercise, recreation). |
| SF-36 and SF-12 | Medical Outcomes Study 36-Item Short-Form Health Survey<sup>2,43,45</sup> | Medical Outcomes Study 12-Item Short Form Health Survey<sup>46</sup> | Higher scores = better HRQOL | The SF-36 includes 36 questions assessing health status in 8 domains: PCS (physical component summary); Physical Functioning, Role-Physical, Bodily Pain, and General Health Perceptions; MCS (mental component summary); Social Functioning, General Mental Health, Role-Emotional, and Vitality. The SF-12 includes 12 questions derived from the SF-36, yielding PCS and MCS scale results. Includes 2 self-report scales comprising 20 questions each. The State Anxiety scale includes questions regarding how the patient currently feels, and the Trait Anxiety scale includes questions regarding how the patient generally feels. Assessment of total time, energy expenditure, frequency, and duration of activities (eg, work, yard work, caretaking, exercise, recreation). |
| STAI   | State-Trait Anxiety Inventory<sup>46</sup> | Higher scores = higher state of anxiety | Includes 2 self-report scales comprising 20 questions each. The State Anxiety scale includes questions regarding how the patient currently feels, and the Trait Anxiety scale includes questions regarding how the patient generally feels. |
| YPAS   | Yale Physical Activity Survey<sup>47</sup> | Activities gauged by hours/week and kilocalories/week; higher values = more favorable activity level | Assessment of total time, energy expenditure, frequency, and duration of activities (eg, work, yard work, caretaking, exercise, recreation). |

Randomized clinical trials studying rate versus rhythm control and HRQOL in elderly patients with atrial fibrillation reported greater impairment versus controls than versus controls plus disease-specific impairment in Physical Functioning domain. A strength of this study was the gender comparison groups, which were from the same cohort of patients and focused on elderly patients with newly diagnosed AF. Although the mean age was significantly higher among women compared with men (62 years, P < 0.05), this may not have been a limitation because women generally manifest cardiovascular disease at an older age than men.
the occurrence frequency of 6 symptoms (palpitations, dizziness, shortness of breath, chest discomfort, irregular pulse, and pulse deficit), the severity of these symptoms, and anxiety and limitation of daily activities related to AF and AF treatment. Frequency of Symptoms subset scores were better in the rhythm control group \( (P = 0.0027) \), whereas Severity of Symptoms, AF-Related Anxiety, and Limitation of Daily Activities subset scores improved with both treatment strategies and were not significantly different between groups. In this study, therapeutic strategies were not blinded to physicians and patients, which could have led to bias. As Japanese patients may differ physiologically and/or culturally compared with patients in other countries, the results of this study may not be generalized to other patient populations.

A substudy of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) demonstrated significant improvements in HRQOL from baseline in patients treated with both rate and rhythm strategies \( (n = 716) \). There were, however, no differences in HRQOL measurements between the rate and rhythm control groups, regardless of instrument or time point. At 4 years, Physical Functioning \( (51.8 \text{ versus } 58.1; \ P < 0.0001) \) and General Health \( (54.0 \text{ versus } 59.1; \ P < 0.0001) \) domain scores remained significantly improved from baseline. Furthermore, a secondary analysis showed that achieving SR was not associated with an improvement in HRQOL when compared with the presence of fibrillation. Although this study utilized multiple HRQOL assessment tools and reported data over 4 years, the HRQOL subgroup was not a randomly selected cohort, had some significant differences from the original study population, and was too small to determine equivalence between treatment groups.

The open, randomized, pilot Strategies of Treatment of Atrial Fibrillation (STAF) study \( (n = 200; 100 \text{ patients each in the rhythm and rate control groups}) \) assessed HRQOL using the SF-36 over 36 months as a prespecified secondary measure of interest. This study found that 2 HRQOL domains were significantly improved from baseline in the rhythm control group \( (\text{Role-Physical } [P < 0.05] \text{ and Mental Health } [P < 0.01]) \) compared with 5 measures that significantly improved in the rate control group \( (\text{Physical Functioning, Role-Physical, Social Functioning [all } P < 0.05], \text{ Bodily Pain, and Mental Health [both } P < 0.01]) \). There were no significant changes in AF-related symptoms during the study and no significant differences between the rhythm and rate control groups; however, there was a trend toward lower HRQOL scores in the rate control group at baseline.

Although the prospective design of this study was a strength, the STAF study included a relatively small study group that was negatively selected based on risk of recurrence. For example, in the AFFIRM study, patients could be cardioverted before randomization and were excluded if they could not maintain SR for at least 24 hours. At randomization, 54% of patients in the AFFIRM study were in SR compared with none in the STAF study. The STAF study also excluded patients with paroxysmal AF who were non-systematically treated.

In the Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study, patients with AF \( (n = 352) \) in both treatment groups reported lower HRQOL scores at baseline compared with healthy, age-matched controls. HRQOL was assessed using the SF-36 scale. The largest impairments were found in the Physical Functioning \( (47.0 \text{ versus } 67.0, \text{ respectively}) \) and Role-Emotional \( (71.0 \text{ versus } 84.0) \) domains \( (P < 0.05 \text{ for both}) \). At study end, HRQOL was significantly improved from baseline in 3 domains in those assigned rate control \( (\text{Mental Health, Role-Physical, and Social Functioning; all } P < 0.05) \), while the Physical Functioning domain scores significantly decreased over time \( (59.0 \text{ versus } 62.0; \ P < 0.05 \text{ versus baseline and 12-month scores}) \). No significant improvements or decrements occurred in those assigned rhythm control or between assigned treatment strategies \( (\text{rate versus cardioversion}) \) in HRQOL absolute scores. In regression analysis, SR at study end was associated with HRQOL improvements \( (P = 0.003) \); however, the number of patients in each treatment group was small and, overall, only 10% of patients demonstrated clinically relevant HRQOL improvements in at least 5 subscales. The similar comparison groups and methodology contributed to this study’s strengths, but approximately 80% of patients had comorbid heart disease \( (\text{representative of elderly patients with AF}) \), potentially contributing to the impaired HRQOL observed in this study.

A randomized, controlled study of rate versus rhythm control in patients with chronic AF and CHF \( (\text{CAFÉ-II study}) \) found HRQOL to be significantly
Aged Physical health summary improved significantly from baseline AF: Overall: 67 (74.1%)

Frequency of Symptoms scores were better in rhythm control patient AF likely to be Lower physical and mental scores reported in patients with newly diagnosed AF

Randomized clinical trials studying rate vs. rhythm control and HRQOL in patients with AF Ogawa et al\textsuperscript{53} Overall: 823
Rate: 404 Rate vs. rhythm control

Patients with paroxysmal AF (PAF); PAF was defined as AF expected to convert spontaneously to SR within 48 hours of onset

Japanese Society of Electrocardiology
Atrial Fibrillation
Quality of Life Questionnaire (AFQLQ)

Jenkins et al\textsuperscript{28} 70 ± 9 716 Rate vs. rhythm control; AF vs. SR

AF likely to be recurrent or cause illness or death, including those aged ≥65 y or with risk factors for stroke or death\textsuperscript{76} Perceived health; Cantril Ladder of Life; SF-36; QOL Index; SCL

Table 2. Description of studies.

| Study | Mean age, y | N | Patient characteristics | Comparator population | HRQOL, symptom, and severity instruments |
|-------|-------------|---|-------------------------|-----------------------|-----------------------------------------|
| Perret Guillaume et al\textsuperscript{48} | AF: 72.3 ± 3.9 Control: 72 ± 4.0 | Total: 164 | Inpatients aged ≥65 y presenting with AF at admission | 3 controls per patient; inpatients without cardiac arrhythmia | SF-36, including PCS and MCS; Duke Health Profile |
| Howes et al\textsuperscript{49} | AF: 77 ± 7.2 Control: 76 ± 6.4 | Total: 100 | Aged ≥60 y; persistent AF for ≥6 mo | Aged ≥60 y; documented SR for previous 6 mo; no history of AF or symptomatic arrhythmia | SF-36, including PCS and MCS; Yale Physical Activity Survey |
| Kang et al\textsuperscript{50} | 67 (74.1%, ≥60 y) | 81 | Aged ≥18 y; newly diagnosed (≤6 mo) AF | General US population | SF-36, including PCS and MCS; SCL |
| Paquette et al\textsuperscript{51} | Women: 68 ± 9 Men: 62 ± 11 | Total: 170 | Aged >18 y; symptomatic paroxysmal or persistent AF without long-term (>4 wk) treatment | Population survey data; men vs. women | SF-36, including PCS and MCS; DASI; SCL; AFSS |
| Reynolds et al\textsuperscript{52} | Women: 69 ± 13 Men: 64 ± 15 | Total: 963 | Aged ≥65 y; new-onset AF | Aged ≤65 years; new-onset AF | SF-12; SCL; AFSS |

"DASI" is not a standard abbreviation. It might be a typographical error or a specific term used in the context of the study. If it is meant to represent the Duke Activity Status Index, a well-known measure of physical activity, it's advisable to verify its correct spelling or provide a clarification.
HRQOL in elderly AF patients

| Time point at which HRQOL was assessed | Results | Limitations |
|--------------------------------------|---------|-------------|
| N/A                                  | AF patients had lower scores than matched controls in >70% of dimensions (8/10 Duke subscales and 6/8 SF-36 domains); SF-36 PCS and MCS showed no significant difference between AF patients and controls; in Duke Health Profile, statistical significance was reached in the Mental ($P = 0.01$), Anxiety ($P = 0.03$), and Depression ($P = 0.003$) subscales. | Study had a small sample size. Cross-sectional design did not allow conclusions on causal relationships. Hospitalization could have negatively affected HRQOL. |
| N/A                                  | SF-36 PCS and MCS did not show a significant difference between groups. PCS (43.0 vs. 45.9, $P = 0.24$), MCS (52.5 vs. 55.7, $P = 0.07$), physical activity (22.0 vs. 21.6 h/wk, $P = 0.92$), estimated energy expenditure (5010.2 vs. 5335.0 kcal/min, $P = 0.72$), and specific activity indexes revealed no significant differences between groups. | Only 1 HRQOL measurement was used. Study used a small cohort of patients. It is likely that sicker AF patients (ie, patients recently hospitalized) were excluded from study. |
| N/A                                  | Lower physical and mental scores reported in patients with newly diagnosed AF vs. general US population (physical health, 38.53 vs. 50.0; mental health, 48.74 vs. 50.00). Frequency and severity of symptoms per the SCL were significantly ($P < 0.01$) and inversely related to HRQOL for both physical and mental health. | No major study limitations were noted. |
| 3 mo, 12 mo                          | Physical health summary improved significantly from baseline to 3-mo visit for women (36.5 ± 9.0 to 39.5 ± 8.0), but less improvement was observed in men (45.2 ± 7.9 to 46.4 ± 9.0) ($P < 0.001$ for overall time effect, $P = 0.086$ for interaction between time and gender). Mental health improved significantly over time for men (47.1 ± 10.9 to 49.3 ± 9.7, $P = 0.007$) but not for women (48.1 ± 9.8 to 48.5 ± 10.1, $P = 0.707$). Cardiac symptom frequency and severity improved for women and men, but measures of global well-being and functional capacity did not improve significantly over time for men or women. No significant changes in HRQOL outcomes from 3–12 mo for men or women. | Women were significantly older than men. Significant baseline differences were noted for men vs. women. |
| 12 mo: up to 30 mo follow-up         | Patients aged >65 y reported lower HRQOL scores for general health and physical functioning but higher scores for mental health (regression coefficients: PCS, $-1.4$ [$P < 0.05$]; MCS, $+1.4$ [$P < 0.01$]). Older patients reported less prominent disease-specific impairment, indicated by lower mean symptom frequency ($-2.3$; $P < 0.001$) and severity ($-1.8$; $P < 0.001$) scores. | Surveillance methods for AF recurrence, which relied on symptoms and patient self-reports, probably underestimated AF episodes. |
| ~19 months                           | Frequency of Symptoms scores were better in rhythm control group than in rate control group ($P = 0.0027$). Severity of Symptoms, AF-Related Anxiety, and Limitation of Daily Activities scores improved with both strategies but were not significantly different. | Therapeutic strategies were not blinded to physicians and patients. |
| 48 mo                                | Ratings of perceived health deemed “excellent” or “very good” did not differ from baseline over time. Patient HRQOL ratings of present life satisfaction were significantly improved from baseline at all time points ($P < 0.01$ at 2 mo, 1 y, 2 y, and 4 y; $P < 0.05$ at 3 y). For health status SF-36 scores, no between-group differences were noted. Mean physical summary scores increased significantly from baseline at 2 mo and 1 y, and were significantly decreased at 4 y. Mental summary scores improved significantly at all time points. Symptom frequency and severity decreased significantly at all time points vs. baseline. | Not all data sets were complete for each patient at each time point, mainly due to patient refusal to complete forms. Differences between the 2 study groups in terms of unmeasured variables may have existed. Results can only be generalized to the specific patient profiles in the AFFIRM trial. |

(Continued)
AF vs. SR
Total:
At end of study, no significant differences were found between the
Rate:
Limitations
SF-36; SCL; SAS;
Two HRQOL measures, assessed by SF-36, significantly improved
No significant between-group differences were found regarding
36 mo
SF-36 including
12 mo
36 mo

Table 2. (Continued)

| Study               | Mean age, y | N        | Patient characteristics                                      | Comparator population          | HRQOL, symptom, and severity instruments |
|---------------------|-------------|----------|--------------------------------------------------------------|-------------------------------|-----------------------------------------|
| Carlsson et al[54]  | Rate: 66    | Total: 200 | ≥18 y; persistent AF with moderate to high risk of recurrence | Rate vs. rhythm control       | SF-36                                   |
|                     | Rhythm: 65  | Rate: 100 |                                                               |                               |                                         |
|                     | (44.5% of  | Rhythm: 100 |                                                               |                               |                                         |
|                     | patients, 60–69 y; 34.5%, |                       |                                                               |                               |                                         |
|                     | ≥70 y)      |                       |                                                               |                               |                                         |
| Hagens et al[56]    | Rate: 69 ± 9| Total: 352 | Recurrent, persistent AF                                      | Rate vs. rhythm control       | SF-36                                   |
|                     | Rhythm: 69 ± 8 |                       |                                                               |                               |                                         |
| Shelton et al[57]   | Total: 72 ± 7| Total: 61  | Aged ≥18 y; persistent AF and CHF (NYHA symptom class ≥II) with evidence of LVD | Rate vs. rhythm control; AF vs. SR | SF-36; MLWHF                               |
|                     | Rate: 73 ± 8 | Rate: 31   |                                                               |                               |                                         |
|                     | Rhythm: 72 ± 5 |                       |                                                               |                               |                                         |
|                     |             |                       |                                                               |                               |                                         |
| Randomized clinical trials: pharmacologic agents and HRQOL |
| Dorian et al[58]    | Overall: 65 ± 10 | Total: 264 | Symptomatic AF; naive to long-term (>4-wk) antiarrhythmic therapy | Amiodarone, sotalol, propafenone; AF recurrence vs. no recurrence | SF-36, including PCS and MCS; DASI; SCL; AFSS |
|                     | AF recurrence: 64 ± 11 |                       |                                                               |                               |                                         |
|                     | No recurrence: 65 ± 9 |                       |                                                               |                               |                                         |
|                     | AF: 66 ± 10 | Total: 624 | Persistent AF                                               | AF vs. SR                     | SF-36; SCL; SAS; AFSS; EP                |
|                     | SR: 67 ± 9  |                       |                                                               |                               |                                         |
|                     | BB group: 305 |                       |                                                               |                               |                                         |
|                     | AF group: 319 |                       |                                                               |                               |                                         |
| Tsuneda et al[59]   | Overall: 67 ± 8 | Total: 29  | Permanent AF with resting heart rate of 60–80 bpm with digitalis >6 mo | Digitalis, BB, CA             | SF-36 including PCS and MCS; AFQLQ    |
|                     | BB: 69 ± 8   |                       |                                                               |                               |                                         |
|                     | CA: 66 ± 7   |                       |                                                               |                               |                                         |
Two HRQOL measures, assessed by SF-36, significantly improved vs. baseline in rhythm control group vs. 5 measures in rate control group ($P < 0.05$, for each measure except Mental Health [$P < 0.01$] in both groups and Bodily Pain [$P < 0.01$] in the rate control group).

At end of study, no significant differences were found between the 2 groups for any of the 8 subscales on the SF-36. At 12 mo, HRQOL improved significantly from baseline ($P < 0.05$) on 4 and 3 subscales in the rate and rhythm control groups, respectively.

HRQOL improvement may have been an artifact of changes from symptomatic events to asymptomatic events.

Groups (AF, SR) compared were not constructed by randomization.

Selection bias may have been introduced through specific patient inclusion criteria (maintained on digitalis for $>6$ mo). Only monotherapy with study drug was analyzed, although combination therapy is commonly utilized. Study duration utilized was short, included too few women, and examined a small total number of patients.
improved in the rhythm control group (n = 30) versus the rate control group (n = 31) after 1 year, as assessed by overall (P = 0.020), MCS (P = 0.050), and PCS (P = 0.029) scores on the SF-36 scale. The greatest improvements occurred when SR was maintained, leading to the conclusion that restoring SR in patients with CHF may improve HRQOL compared with a rate control strategy. Post hoc analyses of patients achieving adequate treatment response (defined as SR and adequate rate control) with their respective treatment strategies found significant differences using both measurements. This study contributed prospective as well as post hoc data on a specific patient population—those with AF patients and comorbid CHF. However, the study was limited by its small sample size and unblinded study design.

Randomized clinical trials: pharmacologic agents and HRQOL in elderly patients
In the CTAF study (n = 264), significant improvements in both physical and mental health HRQOL occurred over the first 3 months of therapy regardless of whether patients were assigned to amiodarone, sotalol, or propafenone (PCS: 41.9–43.7, P = 0.001; MCS: 47.5–49.0, P = 0.023), but no differences in HRQOL improvements were observed between treatment groups. However, AF burden was improved to a greater extent in patients treated with amiodarone compared with sotalol or propafenone (P = 0.001, interaction between time and treatment). No significant differences in HRQOL scores were noted at 3 and 12 months between treatment groups. Patients had relatively new AF without exposure to long-term antiarrhythmic therapies; therefore, the investigators were able to study a population without the bias of drug resistance or nonresponse. However, the small sample size diminished the power to compare HRQOL assessments over time or between treatment groups.

Another study examined HRQOL and exercise performance in patients with persistent AF converted to SR (n = 305) compared with patients remaining in or reverting to AF (n = 319). Patients were randomized to receive amiodarone, sotalol, or placebo as part of the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T). Patients not achieving SR after

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**Table 2. (Continued)**

| Study                                      | Mean age, y | N   | Patient characteristics                      | Comparator population                        | HRQOL, symptom, and severity instruments |
|--------------------------------------------|-------------|-----|---------------------------------------------|---------------------------------------------|------------------------------------------|
| Clinical trials examining anxiety and depression in patients with AF | 71 ± 9      | 70  | Aged ≥18 y; newly referred lone AF (≤4 wk) | Age-matched general population norms; baseline vs. time points assessed | BDI-SF-13; STAI; PSS; SF-36; IPQ; BMQ |
| Lane et al<sup>26</sup>                    |             |     |                                             |                                             |                                          |
| Thrall et al<sup>31</sup>                 |             |     | Aged ≥18 y; AF; naive to previous electrical cardioversion | Age- and sex-matched patients in SR with essential HTN | BDI; STAI; Dartmouth COOP charts |
|                             | AF: 66 ± 11 | Total: 198 |                                             |                                             |                                          |
|                             | HTN: 68 ± 7 | AF: 101 |                                             |                                             |                                          |
|                             |             | HTN: 97 |                                             |                                             |                                          |
4 weeks of therapy underwent electrical cardioversion; if SR was not achieved after a second cardioversion, patients were placed in an open-label arm. According to SR status at 8 week and 1 year visits, patients were classified into SR or AF groups. General HRQOL was evaluated using the SF-36 scale. The Symptom Checklist, Specific Activity Scale (which measures subjective functional capacity), AF Severity Scale, and Exercise Performance scale were also used. Compared with patients in the AF group, patients in the SR group had significant improvements in HRQOL at 8 weeks that persisted at 1 year, independent of treatment group or whether cardioversion was utilized. Additionally, exercise tolerance was improved to a greater degree in patients in SR versus those in AF at 8 weeks (81.5 versus 33.5 seconds, \( P = 0.01 \)) and at 1 year (74.6 versus 15.2 seconds, \( P = 0.02 \)). Interestingly, there was a strong correlation between HRQOL and exercise performance in patients in SR at both 8 weeks and 1 year; however, exercise performance did not significantly correlate with HRQOL scores in AF patients for any measurements at 1 year. Overall, the study had an adequate sample size, with multiple instruments utilized to determine HRQOL. The study was, however, limited by a few factors. Firstly, it did not utilize randomization because classification of patients into SR or AF groups was determined by the investigators. Secondly, because AF patients were less likely to complete exercise performance testing, the benefits of SR on exercise performance may have been underestimated. Lastly, adequate rate control in AF patients may not have been achieved, potentially having an effect on the results of the study.

In a crossover study, AF patients treated with digitalis who had a resting heart rate between 60 and 80 beats per minute (bpm) for more than 6 months \((n = 29)\) were randomized to monotherapy with either a beta blocker or a calcium antagonist (CA). \(^{40}\) Patients consenting to continue \((n = 12)\) were switched to the other therapy; efficacy was determined once adequate heart rate was achieved for at least 1 month. Patients received beta blocker therapy for a mean duration of \(79.3 \pm 34.5\) days and CA therapy for a mean duration of \(72.8 \pm 27.4\) days. Calcium antagonists, but not beta blockers, showed improvement over digitalis baseline therapy in the Role-Physical domain.
of the SF-36 scale (48.6 versus 54.1, \( P < 0.05 \)), as well as in the Frequency and Severity of Symptoms domain of the AF HRQOL Questionnaire (15.1 versus 17.0, \( P < 0.05 \)). The authors concluded that CA, rather than beta blocker monotherapy, may be preferable to digitalis to improve HRQOL in permanent AF patients. However, this study was limited by a small, predominantly male \((n = 25/29)\) sample and a brief study duration. In addition, the narrow selection of patients treated with digitalis may limit generalizability of the findings. The study of monotherapy rather than combination therapy may also have influenced the results.

### Clinical trials examining anxiety and depression in patients with atrial fibrillation

HRQOL, depression, and anxiety during the first 12 months following a diagnosis of lone persistent or permanent AF \((N = 70)\) were examined in a study.\(^{26}\) Low levels of depression were reported by patients, and although SF-36 domain scores were lower in AF patients compared with age-matched population controls (with the exception of Mental Health over time), no significant differences in HRQOL (with the exception of General Health) were reported over 12 months. Anxiety was more prevalent than depression—it was reported by 38.5%, 30.9%, and 35.7% of patients at baseline, 6 months, and 12 months, respectively, with no significant differences between time points. This was one of the few studies evaluating the effects of AF on anxiety and depression in addition to HRQOL; however, the study population comprised patients from a single center, all of whom were Caucasian, had AF, and were without comorbid conditions.

Another study found that patients with AF \((n = 101)\) and hypertension \((n = 97)\) reported similar levels of depression and HRQOL; however, AF patients exhibited significantly higher anxiety scores (37.4 versus 33.3, \( P = 0.02 \)).\(^{61}\) Quality of life, depression, and anxiety scores were unchanged at 6 months. Overall, approximately one third of AF patients had elevated levels of depression and anxiety that persisted at 6 months. Depression and anxiety were both significantly associated with a patient’s perceived HRQOL \((P < 0.001)\), and improvement in depression symptoms was a significant predictor of HRQOL scores at 6 months \((P < 0.001)\). Although this study was the first to examine the association between the affective status of AF patients and HRQOL, it was limited by its small sample of AF patients recruited from a single cardiology clinic.

### Discussion

The data examined in this systematic review suggest that HRQOL may be particularly affected in older patients. An algorithm drawn from these data to aid in decision-making is provided to optimize HRQOL among elderly patients with AF (Fig. 2). The algorithm describes the HRQOL parameters that should be assessed in all patients with AF. The 2010 Canadian Cardiovascular Society AF Guidelines also recommend that assessment of patient quality of life be part of the evaluation of every patient with AF.\(^{62}\)

![Figure 2. An algorithm designed to optimize HRQOL among elderly patients with AF.](image-url)
Five observational studies with a predominantly elderly population were reviewed. In one study, no statistically significant difference between patients with AF and controls in overall HRQOL was observed. However, based on several methodological weaknesses, the relevance of this study is low. Interestingly, this was the only study with a population aged greater than 75 years. Three other studies reported decreased HRQOL in the elderly with AF compared with age-matched \( n = 28,54,56,57 \) and general population \( n = 28,54 \) controls. The FRACTAL subanalysis \( n = 52 \) indicated slightly lower HRQOL scores (General Health and Physical Functioning domains) in patients older than 65 years compared with those aged 65 years or less.

Two clinical trials \( n = 26,61 \) examined anxiety and depression in addition to HRQOL. Both studies were substantially limited by their designs, primarily the small, single-center patient populations. While they yielded interesting data on anxiety and depression and correlations with HRQOL, changes in HRQOL scores were not significantly different from those of controls.

Several clinical trials (AFFIRM, STAF, RACE, J-RHYTHM, and others \( n = 28,53,54,56,57 \)) examined the effects of 2 different treatment strategies—rate control and rhythm control—on HRQOL in patients with AF. While the AFFIRM and STAF trials reported significant improvements from baseline in patients treated with both rhythm and rate control strategies, these trials reported no significant changes in HRQOL between treatment groups. \( n = 28,54 \)

Results in the RACE trial revealed significant improvements in several components of HRQOL in the rate control group, but not in the rhythm control group, when compared with baseline scores. \( n = 56 \) Conversely, investigators reported significant improvement in HRQOL in the rhythm control group versus the rate control group, but only in a specific patient population with comorbid CHF. \( n = 57 \)

In the J-RHYTHM study, only the Frequency of Symptoms subset scores were better in the rhythm control group than in the rate control group; Severity of Symptoms, AF-Related Anxiety, and Limitation of Daily Activities improved with both strategies and were not significantly different between groups. \( n = 53 \)

The effects of various pharmacologic agents to positively influence HRQOL in patients with AF was explored in 3 randomized clinical trials. Agents included amiodarone, sotalol, propafenone, digitalis, beta blockers, and CAs. In the CTAF trial, amiodarone was not significantly different from sotalol in measures of HRQOL; however, AF burden was improved to a greater extent in patients treated with amiodarone than those treated with sotalol or propafenone. This is in contrast to results of the SAFE-T trial, where patients in SR showed significant improvement in HRQOL regardless of treatment group (amiodarone or sotalol). Several domains of the HRQOL questionnaire improved following use of CAs—but not beta blockers—when compared with digitalis therapy. \( n = 60 \) This study, however, was limited by its small sample size and biased patient selection and is therefore of limited relevance.

Other recent randomized clinical trials and registries add important data for the management of patients with AF. The J-RHYTHM study was designed to determine the optimal strategic approach for AF patients (rate or rhythm control) and emphasized patient-reported experience and perception of AF-specific disability. This study showed that in patients with paroxysmal AF, the primary outcome—first occurrence of all-cause mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, heart failure hospitalization, or physical/psychological disability requiring alteration of treatment strategy—was significantly reduced with a rhythm control strategy compared with a rate control strategy \( P = 0.0128 \). \( n = 53 \)

Results from a substudy of the RACE II trial \( n = 63 \) suggest that the method of rate control (strict \( n = 207 \) or lenient \( n = 230 \)) has no difference on HRQOL in patients with permanent AF. Strict rate control was defined by a resting heart rate of less than 80 bpm and heart rate during moderate exercise of less than 110 bpm. Lenient rate control was defined as a resting heart rate of less than 110 bpm. Lenient rate control was defined as a resting heart rate of less than 110 bpm. \( n = 64 \) HRQOL was assessed using the SF-36 scale, the AF severity scale, the Minnesota Living with Heart Failure (MLHF) questionnaire, and the Multidimensional Fatigue Inventory-20 (MFI-20) at baseline, 1 year, and study conclusion. Over a median follow-up of 3 years, results of the MLHF questionnaire and AF severity scale did not differ between lenient and strict rate control groups from the baseline to the end of study. In the SF-36 scale, Physical Functioning domain scores decreased in both the lenient \( P = 0.01 \) and
strict control groups (P = 0.04) by study completion. A history of heart failure and an age older than 75, but not strict or lenient rate control, were associated with decreased HRQOL. These data show that changes in HRQOL appear to be influenced by age, symptoms, gender, and underlying heart disease rather than a strict or lenient rate control strategy. Registry data are valuable since they represent real-life situations. Two large registries containing HRQOL data—RECORD-AF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation) and AFFECTS (The Atrial Fibrillation: Focus on Effective Clinical Treatment Strategies)—document that the initial treatment strategy assigned by cardiologists to the majority of AF patients is rhythm control. This preference decreased with age in both registries. When compared with patients assigned a rate control strategy, patients managed with a rhythm control strategy were more frequently symptomatic and more likely to have recently diagnosed AF. In the RECORD-AF registry, a rate control strategy was more frequently chosen for heart failure, valve disease, or persistent AF, and in the AFFECTS registry, patients in the rate control group tended to be older, had a longer mean duration of AF, and were more likely to have a family history of AF. At 1 year, 81% of RECORD-AF patients treated with a rhythm control strategy were in SR compared with only 33% treated with a rate control strategy. Additionally, only 13% of rhythm control patients progressed to permanent AF compared with 54% of rate control patients. Therapeutic success—defined as SR for patients receiving a rhythm control strategy or a resting heart rate lower than or equal to 80 bpm with a rate control strategy, no crossover of treatment strategy, and no incidence of clinical outcomes—was significantly different between patients assigned a rhythm control (60%) and a rate control strategy (47%). Rhythm control patients were more likely to be hospitalized for arrhythmias and rate control patients were more likely to be hospitalized for heart failure, but the difference in total number of clinical events between these patients did not reach statistical significance at 1-year follow-up in RECORD-AF. In the AFFECTS registry, there were too few deaths and cardiovascular-related events for a meaningful comparison between rhythm control and rate control strategies. Data obtained from RECORD-AF and AFFECTS provide a “real-world” look at a physician’s choice of treatment for the management of patients with AF. Registry data are valuable because randomized controlled trials often do not completely represent real-life situations. RECORD-AF data demonstrate that when physicians are able to select a treatment strategy, they are successful at meeting the goals of that strategy 81% of the time. Results from registries such as these can provide important insight to physician-based management strategies, particularly treatment strategies for AF patients with decreased HRQOL.

Limitations
This analysis is limited by several factors. The study duration varied considerably in the studies analyzed, ranging from 6 months to 4 years. Many of the studies assessing HRQOL were subanalyses of larger clinical trials and, with the exception of the AFFIRM substudy, may not have had adequate statistical power. Many of these studies used generic HRQOL questionnaires, most commonly the SF-36 scale, which may not detect subtle but significant HRQOL changes in patients with AF. In addition, statistically significant changes in HRQOL may have gone unobserved between treatment groups using non-disease-specific questionnaires, as elderly populations are likely to have comorbidities. Importantly, no studies have specifically examined HRQOL in an exclusively elderly population; therefore, this review focused on trials wherein the mean population age was 65 years.

Future Directions
Both aging and AF are associated with impaired HRQOL and more data are needed on HRQOL in the elderly AF population. Since few interventions have shown decreased morbidity and mortality rates, the treatment of AF in clinical trials remains focused on controlling symptoms and improving HRQOL. Thus, HRQOL is a critical issue in the treatment of AF as well as in the study of new therapies for AF.

New treatment strategies may improve HRQOL in patients with AF. Dronedarone is an antiarrhythmic agent approved by the US FDA for the management of patients with AF. Dronedarone is indicated in the US to reduce the risk of hospitalization for AF in patients in SR with a history of paroxysmal or persistent AF. In the post-marketing setting,
cases of hepatocellular liver injury and hepatic failure in patients receiving dronedarone have been reported, including 2 reports of acute hepatic failure requiring transplantation and new-onset or worsening heart failure.70,71 The revised prescribing information recommends obtaining periodic hepatic serum enzymes, especially during the first 6 months of treatment.69 Cases of increased international normalized ratio with or without bleeding events have also been reported in patients on warfarin and dronedarone.69,72 Dronedarone is contraindicated in patients with symptomatic heart failure showing recent decompensation requiring hospitalization or NYHA class IV heart failure, as well as in patients with AF who will not or cannot be cardioverted into normal SR.69

Vernakalant (intravenous formulation) has been approved in the European Union, Iceland, and Norway for the rapid conversion of recent-onset AF to SR in nonsurgical adult patients with AF of 7 days or less and for postcardiac-surgery adult patients with AF of 3 days or less.73 In the AVRO study (A Phase III Superiority Study of Vernakalant vs. Amiodarone in Subjects With Recent Onset Atrial Fibrillation), treatment with vernakalant resulted in a significantly greater improvement in patient perception of state of health (as measured by the EQ-5D QOL assessment visual analog scale) at hour 2 compared with amiodarone (mean adjusted increase from baseline of 10.9 points vs. 5.6 points; \( P = 0.0006 \), respectively).74 Further studies are needed to compare these treatment options with currently available agents as well as to assess any potential effects on HRQOL. Additionally, the impact of AF type on HRQOL has not been well studied as it is confounded by comorbidities and type of treatment.

A validated, AF-specific HRQOL questionnaire would be ideal in enabling clinicians to make well-informed decisions regarding treatment strategies for patients with AF (ie, rate or rhythm control). Recently, the 20-item long Atrial Fibrillation Effect of Quality-of-Life (AFEQT) questionnaire was developed and validated in a prospective observational study.75 This instrument provides a 4-item symptoms score, an 8-item daily activities score, a 6-item treatment concerns score, and a 2-item treatment satisfaction score. In contrast to generic HRQOL instruments, disease-specific instruments allow patients to quantify the extent to which their limitations are attributable to a specific disease. In this study, AFEQT was shown to be reliable as indicated by the high Cronbach \( \alpha \) coefficients, valid by demonstrating adequate convergent and divergent correlations, and sensitive in discriminating the severity of patients’ AF. These preliminary findings support its use in following patients with AF; however, future studies with this instrument will provide an understanding of how to best evaluate the efficacy of AF therapy and the quality of care for AF patients.75 HRQOL information from large registries also provides a representation of real-world AF management. The data in this review indicate that HRQOL should be strongly considered when designing AF treatment strategies for individual patients, especially the elderly.

**Conclusions**

Atrial fibrillation (AF) is a chronic illness disproportionately affecting the elderly population. An increase in prevalence is anticipated over the next several decades. Because of the broad range of symptoms and sequelae associated with AF, health-related quality of life (HRQOL) is of increased interest to clinicians caring for this patient population. The articles selected for this systematic review demonstrate that HRQOL is impaired to some degree in all patients with AF and may particularly affect older patients. Although the data do not demonstrate a particular pharmacologic intervention to be superior over others at improving HRQOL, many pharmacologic interventions have been shown to improve HRQOL in the elderly patient with AF. More research is warranted to address the limitations of the available data. HRQOL-specific registry data will also be important to provide real-world information. As new therapies become available, further research regarding effect on patient HRQOL is warranted to allow clinicians to select therapies that take into account the physical, emotional, and social well-being of patients.

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**Author Contributions**

Conceived and designed the experiments: CJP. Analyzed the data: CJP. Wrote the first draft of the manuscript: VM. Contributed to the writing of the manuscript: CJP. Agree with manuscript results and conclusions: CJP.
Jointly developed the structure and arguments for the paper: CJP. Made critical revisions and approved final version: CJP. The author reviewed and approved the final manuscript.

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Disclosures and Ethics
As a requirement of publication, the author has provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The author has read and confirmed his agreement with the ICMJE authorship and conflict of interest criteria. The author has also confirmed that this article is unique and not under consideration or published in any other publication, and that he has permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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