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Tackling patient-reported outcomes in AF & HF: identifying disease-specific symptoms?

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SYNOPSIS

Atrial fibrillation (AF) and heart failure (HF) both significantly impact morbidity and mortality, and also account for high symptom burden and impaired health-related quality of life (hrQoL). Several well-designed and broadly-implemented patient-reported outcome (PRO) instruments are available for both AF and HF, and can easily measure hrQoL in each disease process. Disease-specific interventions for AF and HF, separately, have been demonstrated to improve both clinical outcomes and PROs, and emerging data support aggressive treatments for patients with both AF and HF. A better understanding of the diverse phenotypes of AF and HF, as well as the heterogeneous treatment effects of disease-specific interventions, are necessary to further disentangle the complex relationship between symptoms of AF and HF.

Keywords

Atrial fibrillation; heart failure; patient reported outcomes; health-related quality of life

Among patients with heart failure (HF), atrial fibrillation (AF) occurs in more than one third, including up to half of those with *severe* HF.(1–3) While both diseases are well known to significantly impact morbidity and mortality, they also account for high symptom burden and significantly impair health-related quality of life (hrQoL). While improving quality of

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life remains a primary goal in the care of patients with AF and HF, measurement and improvement of hrQoL outcomes remains a major challenge. This review will discuss the measurement of hrQoL in AF and HF, including its importance, tools for such measurement and discrimination, and implications for disease management to improve hrQoL in these high-risk patients.

Importance of hrQoL

Separately, AF and HF each reduce hrQoL due to impaired functional status and high symptom burden. For patients with AF *without* HF, hrQoL has been found to be comparable to that of patients with an acute myocardial infarction.(4) Among patients with HF *without* AF, hrQoL is very poor for more than 20% of patients with HF, and is associated with increased healthcare utilization, increased costs, and worse clinical prognosis.(5–7) These patients are less likely to report good outlook, more likely to be depressed, and subsequently limit their engagement in care.(8)

However, clinical outcomes among patients with concomitant HF and AF are dramatically worse than either disease alone,(3,9) and there is reason to believe the impact on hrQoL is also compounded.(3) Patients with AF and CHF in the Atrial Fibrillation and Congestive Heart Failure trial demonstrated Short Form 36 Physical Component Summary scores 1.3 standard deviations below the national average. Normal rhythm was associated with improved hrQoL, supporting some independent effects of AF, and the implementation of arrhythmia interventions for these patients (see below).(10,11)

However, the routine and/or systematic measurement of hrQoL in clinical care of patients with AF and HF remains challenging, despite the availability of numerous tools to assess symptoms and hrQoL in these patients.

Measurement of hrQoL in AF and in HF

Patient reported outcomes (PROs) are best defined as “...any report of the status of a patient’s health condition that comes directly from the patient...”(12); they represent the most direct measurement of hrQoL, without influence of interpretation by the clinician or other healthcare personnel. The formal measurement of hrQoL can best be ascertained via structured, validated PROs. Additionally, when performed using well-validated and well-calibrated tools, PROs can provide the well-controlled, quantitative evidence to support interventions to improve hrQoL. For each disease, AF and HF, several PRO tools have been developed to assess symptom status and hrQoL, some of which have been extensively validated and implemented (Table 1).

AF PROs

Care of patients with AF is multi-dimensional, including the treatment of comorbidities, management of symptoms, and prevention of sequelae, principally stroke. Therefore, AF-specific PROs may target different aspects of the disease, such as: (1) overall health status and impact of the disease (e.g. AFEQT); (2) detailed burden of specific, AF-related symptoms (e.g. the symptom checklist, MAFSI); and (3) the impact of oral anticoagulation

on hrQoL (e.g., ACTS). Due to the overlap of AF and HF symptoms, the present review will focus on the first two categories of AF-related PROs.

Several AF-specific PRO instruments have been developed, and they are validated to a varying degree. These PROs have been derived primarily to assess symptom burden in the setting of interventions, such as catheter ablation. Nevertheless, they have been deployed in a variety of clinical and research settings, to assess hrQoL in patients with AF.

Symptom checklists are a major component of AF PROs, and comprise at least a component of the 16-item AF Symptom Checklist (SCL) tool, the Toronto AF Symptom Severity Scale (AFSS), the Mayo AF-specific Symptom Inventory (MAFSI), and the AF Effect on Quality of Life (AFEQT; Table 2).(13–18) Some are more closely tied to AF-specific symptoms than others, and may include additional domains, such as psychological function or sexual activity, in addition to physical function or symptoms. For example, the MAFSI functions as a very specific symptom survey and includes the most common physical symptoms associated with AF, such as palpitations, dizziness, exertional intolerance, sense of low heart rate, and syncope or pre-syncope.(16) Others, such as AF-QoL, are structured more broadly across domains of Psychological, Physical, and Sexual Activity impacts, with many questions that are less specific for AF.(13) As AF clearly affects hrQoL via multiple avenues (e.g., symptoms, anxiety of disease, restriction of activity), different measurement tools for different interventions may be required to demonstrate impact across a variety of domains.

HF PROs

Similarly, PRO instruments have been developed to capture physical symptom burden, psychological and emotional domains, and overall quality of life among patients with HF. Furthermore, there is robust evidence supporting the use of HF PROs as intermediate endpoints via the FDA's Expedited Access for Premarket Approval pathway.(19) The most common HF PROs are summarized in Table 1, with the earliest being the Minnesota Living with Heart Failure (MLHF) questionnaire.(20–22) This 21-item instrument is summarized as a single score, without specifically-targeted domains, and assesses the impact of HF on physical, emotional, social, and mental components of quality of life.(23)

The most well-validated, and the only HF PRO that is now qualified as a medical device development tool by the FDA, is the Kansas City Cardiomyopathy Questionnaire (KCCQ). (24,25) The KCCQ includes PRO assessment of HF across 7 domains: Physical Limitation, Symptom Stability, Symptom Frequency, Symptom Burden, Self-Efficacy, Quality of Life, and Social Limitations. A shorter version, the KCCQ-12, has also been developed and validated to target specific domains, but maintain the reliability, responsiveness, and interpretability of the full length-version.(26) Therefore, the KCCQ-12 focuses primarily on domains most related to HF health status (physical limitation, symptom frequency, quality of life, and social limitation), and has been successfully deployed as a routine HF PRO measurement in busy clinical settings.(27) In clinical trials, the KCCQ has been found to be independently predictive of subsequent resource utilization and mortality among HF patients.(5,7,28–30)

Disease-Specific Interventions & Outcomes

Improvement of hrQoL in AF

In studies of AF interventions, PROs often track with clinical and arrhythmia outcomes. For example, in the AFFIRM study testing strategies of rate versus rhythm control, consistent maintenance of sinus rhythm was suboptimal, and clinical outcomes were not significantly different.(31) The PROs and hrQoL among a subset of patients in the two arms were not different.(17). Similarly, the CTAF trial tested several different antiarrhythmic drugs in rhythm control of AF;(32) there was improvement in hrQoL across agents tested, with some of the effect attenuated by recurrence of AF during follow-up.(33,34) In addition, there have been numerous studies comparing catheter ablation of AF to medical therapy (i.e., antiarrhythmic drugs), which have demonstrated favorable results of ablation, with respect to maintaining sinus rhythm and hrQoL.(35,36) Furthermore, many of these studies have included much more aggressive monitoring for arrhythmia, and thus more detailed data on recurrence rates and AF burden. Contemporary data from the CABANA trial have also shown very favorable effects of catheter ablation on hrQoL in a broad population of patients with AF.(37) And in studies with longer follow-up, the effect of ablation on hrQoL appears sustained at 2 years, even among patients with recurrent AF.(16)

It is important to acknowledge that many studies used a variety of PROs, including both disease-specific for AF, as well as more generic hrQoL tools that operate independent of disease state. However, there is robust evidence in support of the specificity of disease-specific PROs, which may better-discriminate improvement targeted at specific disease states and pathophysiology. In a study of 54 patients undergoing ablation, the six-item AF6 questionnaire was found to be more responsive to hrQoL improvement following ablation, compared to the more generic, but longer, standard, SF-36 tool.(38)

Improvement of hrQoL in HF

Across HF studies, several successful interventions for morbidity and mortality have also been shown to improve PROs. In fact, the KCCQ has been found to reliably reflect clinical changes in HF status, and statistically out-performed both the New York Heart Association (NYHA) classification and the 6-minute walk test.(39) Non-pharmacological, non-invasive interventions, such as exercise training, have been shown to improve hrQoL among HF patients.(40) And in the recent PARADIGM-HF study comparing sacubitril/valsartan versus enalapril, the KCCQ was collected in more than 90% of patients.(41) Sacubitril/valsartan was shown not only to improve clinical HF markers and mortality, but there was substantial improvement in nearly all KCCQ physical and social activities. Even more aggressive and invasive HF treatments have also improved hrQoL – patients undergoing implantation of left-ventricular assist devices (LVADs) for end-stage HF again improved mortality, and demonstrated dramatic improvements in hrQoL, despite the morbidity of a major surgical procedure.(42)

Interventions for AF & HF

However, most of these studies did not specifically target patients with concomitant AF and HF – prevalence of AF often hovered around one-third of those enrolled in major HF trials.

(43–45) Given the unique risks and challenges of patients with concomitant AF and HF, several studies have specifically targeted these patients, and have reported hrQoL outcomes.

The AF-CHF trial compared strategies of rate-only versus rhythm control among 1,376 patients with AF and HF, and found no differences in the rates of cardiovascular death (the primary endpoint).(46) And while hrQoL also did not differ between the 2 groups overall, maintenance of sinus rhythm was associated with improved NYHA class and hrQoL.(10) In fact, there is mounting evidence that targeted treatment of AF (i.e., restoring and/or maintaining sinus rhythm), dramatically improves PROs among HF patients. Even short-term interventions, such as cardioversion, appear to improve exercise capacity for those who maintain sinus rhythm.(11)

More recently, trials of more definitive interventions for AF, in the setting of HF, have demonstrated favorable long-term results in this high-risk population. Several studies of catheter ablation, specifically in patients with AF and concomitant HF, have shown improvements in clinical outcomes.(47–49) In fact, the first study demonstrating a mortality benefit of ablation in AF, the CASTLE-AF trial, specifically targeted patients with AF and concomitant HF.(50) Subsequent meta-analyses of AF ablation in patients with HF (compared with medical therapy) have shown not only consistent clinical benefits, but improvements in functional status and hrQoL.(51,52)

Discriminating AF vs. HF hrQoL

A major unmet clinical challenge remains the discrimination of effects of AF versus HF in patients with both disease processes, with respect to both adverse clinical events and PROs. Atrial fibrillation may manifest before or after the development of HF, and the temporal relationship may indicate distinct clinical phenotypes and subsequent outcomes. For example, the sequelae of persistent tachycardia, often due to AF, have been well-described to lead to left-ventricular dysfunction and HF;(53,54) rhythm control interventions for AF in these specific patients appear to demonstrate significant benefits, compared with patients manifesting cardiomyopathy due to other causes.(55) Yet, AF may develop later in the HF process, and these patients likely represent different clinical phenotypes. While there remains a role for rhythm control interventions such as ablation, clinical response is often more heterogeneous in this broader group of HF patients.(48)

This variability in disease states limits our ability to identify the relative contributions of AF versus HF to poor hrQoL, across the population of patients with AF & HF. Disentangling the complex relationship between AF & HF is also limited by the significant overlap in symptomatology between the two – each can account for relatively vague symptoms of dyspnea, exertional limitation, and fatigue, to name a few (Figure 1). Therapeutic interventions specifically targeted to either AF or HF (as discussed above) may still provide mechanistic insight through understanding *which* patients are most likely to respond to specific interventions.

Patient Reported Outcomes and Clinician Reported Outcomes

A major concern in the treatment of AF and HF symptoms is the distinction between PROs and clinician reported outcomes (CROs). Several CROs are frequently used in these patients, such as the NYHA classification (for HF) and the European Heart Rhythm Association classification (EHRA; for AF). These scales have been adopted and widely used as a way of classifying disease burden and/or functional status on a simple I-IV scale, *as assessed and interpreted by the clinician*. They frequently reflect the clinician's general impression of disease status or burden, and provide little to no detail regarding the patient's experience and symptoms. While there appears to be general concordance that higher worse status by CROs translates to higher symptom burden by PROs,(15,24) detailed, disease-specific PROs appear to be more sensitive and relevant outcomes for patients, particularly following interventions.(56) In both research and clinical settings, they can provide complementary information on individual patients, and across patient cohorts.

Conclusions

Health-related quality of life is best measured using disease-specific, validated PROs, and patients with AF and HF have significantly impaired hrQoL. Several well-designed and broadly-implemented PRO instruments are available for both AF and HF, and can easily measure hrQoL burden for each disease process. Disease-specific interventions for AF and HF, separately, have demonstrated improvements in both clinical outcomes and PROs, and emerging data support aggressive treatments for patients with both AF and HF. A better understanding of the diverse phenotypes of AF and HF, as well as the heterogeneous treatment effects of disease-specific interventions, are necessary to further disentangle the complex relationship between AF and HF.

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KEY POINTS

- AF and HF each represent disease process with significant impacts on health-related quality of life (hrQoL)
- hrQoL is best ascertained through the use of structured, well-validated patient reported outcomes (PROs)
- Several PRO instruments have been developed and validated for measurement of disease-specific hrQoL domains in AF and in HF.
- Some PRO instruments focus on overall AF disease -specific hrQoL, others on symptoms, and others on anticoagulation satisfaction.
- Interventions for AF and for HF have demonstrated improvement in hrQoL, as measured by PROs

Figure 1.
Overlap in symptoms specific for AF versus HF.

Table 1.

Summary of Instruments for PRO Measurement in AF and in HF

PRO Tools	Structure	Sample Clinical Study Implementation
AF		
AFEQT(14)	4 Domains: (1) symptoms, (2) daily activities, (3) treatment concerns, (4) treatment satisfaction	ORBIT-AF registry(57), CABANA trial(37)
AFSS(4)	4 Domains: (1) AF burden, (2) global well-being, (3) AF symptom score, (4) healthcare utilization	RACE II trial(58,59), CTAF trial(34)
AF-QoL(13)	3 Domains: (1) Psychological, (2) Physical, (3) Sexual	SARA trial(60)
MAFSI(16)	Single inventory of AF symptoms	CABANA trial(37)
SCL(61)	Single inventory of AF symptom frequency and severity	AFFIRM trial(17)
ASTA(62)	Single inventory of arrhythmia symptoms	SMURF study(63)
HF		
KCCQ / KCCQ-12(24,26)	7 Domains: (1) Physical limitation, (2) symptoms frequency, (3) symptom severity, (4) symptom stability, (5) self-efficacy, (6) limitations to lifestyle, (7) quality of life; KCCQ-12 includes only #1,2,6,7	STICH(64), PARADIGM-HF(44), TOPCAT(65) trials FDA cleared(25)
MLWHF	Cumulative Domains: HF symptoms, physical functioning, sleep, role function, sex, recreation, appetite, psychological/emotional, adverse effects of medication, hospitalization, medical costs	SOLVD(66), A-HeFT(67)
CHQ	3 Domains: (1) Dyspnea, (2) Fatigue, (3) Emotional function	

PROs: patient reported outcomes; AF: atrial fibrillation; HF: heart failure; AFEQT: AF Effect on Quality of Life; AFSS: University of Toronto AF Severity Scale; AF-QoL: AF Quality of Life scale; MAFSI: Mayo AF-specific Symptom Inventory; SCL: Symptom Checklist; ASTA: Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHF, Minnesota Living with Heart Failure; CHQ: chronic heart failure questionnaire.

Patient reported outcome tools developed specifically for HF, and the symptoms they target. Adapted from Mark DB. Assessing quality-of-life outcomes in cardiovascular clinical research. *Nat Rev Cardiol* 2016;13:286–308 with permission.

Table 2.
Potential AF-Related Symptoms Included in the Most Common AF-Specific PROs

✓ Palpitations	✓ Anxiety about:	✓ Weakness
✓ Irregular heart beat	○ Impending episodes	✓ Fatigue at rest
✓ Pause in heart activity	○ AF-related sequelae	✓ Exercise intolerance
✓ Sense of low heart rate	○ Procedures	✓ Dyspnea at rest
✓ Chest pain/pressure	○ Medication effects, including bleeding	✓ Dyspnea with exertion
✓ Lightheadedness/dizziness	○ Limitations of daily living	✓ Treatment satisfaction
✓ Flushing	✓ Lack of appetite	○ Control of AF
✓ Swelling	✓ Difficulty with concentration	○ Relief of AF symptoms
✓ Syncope/Pre-Syncope	✓ Sleep disturbance	

AF: atrial fibrillation; PROs: patient reported outcomes.