BACKGROUND

Atrial Fibrillation
• Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with an estimated prevalence of 1% and a prevalence of approximately 10% in patients aged 80 years and older.
• Significant increased morbidity and mortality are observed in patients with AF. Symptoms associated with AF are primarily caused by rapid and irregular heartbeat and include palpitations, shortness of breath, dizziness, anxiety, and reduced physical capacity, which may result in impaired health-related quality of life (HRQOL)2. Sequence of AF include thromboembolic events and precipitation or worsening of heart failure.
• Multiple treatment options, including pharmacotherapy and ablation strategies, must be carefully evaluated on a patient-by-patient basis, because treatment options exist and may have limited efficacy depending on the subtype of AF.

• Because few interventions have been shown to reduce mortality and serious morbidity, the assessment of patient-reported outcomes (PROs), including HRQOL, symptom severity, and frequency, is crucial in the treatment of AF and in the study of new therapies for AF. Furthermore, in clinical trials of antithrombotic therapies, endpoints focused on the maintenance of heart rhythm may not accurately reflect the degree to which patients’ AF symptoms improve. Moreover, limited information is available to determine which instruments (if any) are available for assessing PROs in patients treated with antithrombotic therapy.

• The FDA Guidance for PRO Measures for Patient-Centered Outcomes Research (2011) recommends the development of PRO instruments and, if appropriate, existing instruments in the target population.

• The United States Food and Drug Administration (FDA) has issued detailed guidance on the requirements for PRO measures that are to be used to support regulatory approval or promotional claims.

• The guidance, developed with input from the FDA’s Study Endpoints and Label Development (SEAD) group, describes both the recommended development of a PRO measure and the psychometric properties for which evidence must be presented.

• This guidance clearly stipulates that any PRO measure used to support labeling or promotional claims must be developed with extensive input from patients to establish content validity and be thoroughly validated in the target population.

OBJECTIVE

• To identify and evaluate the key characteristics, strengths, and weaknesses of existing AF-specific PRO measures, focusing on how well the measures meet the regulatory guidance requirements set out by the FDA in its PRO Guidance for Industry.

METHODS

This review was conducted in two phases.

• In phase 1, a comprehensive review of multiple sources (PubMed, Embase, Patient Reported Outcomes and Quality of Life Instruments Database (PRODIDOLX), ClinicalTrials.gov) was conducted to identify potential PRO measures, including measures assessing HRQOL, symptom burden, and treatment satisfaction (as per patient-reported domains). One measure, the Canadian Cardiovascular Society Severity of Atrial Fibrillation (CCS-SAF) Scale, was determined to be a chimeric instrument and was subsequently excluded.

• In phase 2, data related to the development and psychometric properties of the instruments meeting the prespecified instrument criteria were reviewed and compared. These data were sought through additional searches of PubMed and information provided by the instrument developers, either online or upon request.

RESULTS

The results of the phase 1 review of multiple sources included the following:
• PubMed: N = 625 abstracts identified; 138 full-text articles reviewed and 40 included (Figure 1).
• ClinicalTrials.gov: 55 antithrombotic AF trials identified, 13 approved to include AF-specific PROs.
• PRODIDOL: 4 PRO measures related to AF or atrial fibrillation identified.

• In total, 25 PRO measures with use in AF were identified, including 7 AF-specific measures, 5 generic HRQOL measures, 2 measures of functional status in cardiology conditions, and 11 measures developed for use in other conditions (e.g., measures assessing mood or fitness intrusiveness).

• Phase 1 included a comprehensive review of multiple sources (PubMed, ClinicalTrials.gov, PRODIDOL). This review served to identify potential PRO measures, including measures assessing HRQOL, symptom burden, and treatment satisfaction.

• Phase 2 focused on review of patient-reported outcome instruments for assessing atrial fibrillation.

DISCUSSION

• The two symptom measures, the SCL and AFSS, were developed in the late 1990s, before the introduction of the current PRO guidance. The SCL and AFSS have the least available evidence in support of their psychometric properties.

• The HRQLD measures were all developed since the draft PRO guidance was published in 2006.

• The level of patient involvement for the AFEQT appears to meet the standards set forth to establish content validity in the FDA PRO guidance. The AFEQT included patients in the initial generation of items, which is an important step and provides a basis of evidence for content validity.

• The AFEQT has demonstrated achievement in the greatest number of the evaluated psychometric properties, although to date it has not been included in a clinical trial in AF to evaluate its responsiveness in that setting.

AF-Specific HRQOL

It is unlikely that the HRQOL instruments reviewed in their current form, would be acceptable to the FDA to support a PRO promotional label claim. All of the measures likely would face challenges relating to relatively long recall periods and multidimensional assessment of a complex measurement concept (HRQOL).

• Additional studies confirming the AFEQT’s measurement properties are needed, given that currently only one study has demonstrated the instrument’s content validity and responsiveness, and an instrument’s properties ideally are demonstrated during repeated use and evaluation.

CONCLUSIONS

• Use of a PRO measure that meets the standards of the FDA PRO guidance is a clinical standard that may need to be considered in the potential for a PRO label claim. If included in a drug product label, an AF-specific PRO measure may be used to support promotional materials.

• Additional studies confirming the AFEQT’s properties may be required to support the label.

• The AFEQT appears to be the strongest available instrument for measuring HRQOL in AF, with the most rigorous and well-established development and breadth of demonstration of measurement properties, including reliability, criterion-related validity, and responsiveness.

REFERENCES

Please see handout.

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Structured Review of Patient-Reported Outcome Instruments for Assessing Atrial Fibrillation

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