Literature Review of Patient-Reported Outcome Measures Assessing Anticoagulant Therapy

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BACKGROUND

- Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with an overall prevalence of 1% and a prevalence of approximately 10% in patients aged 80 years and older.[1]
- Significant increased morbidity and mortality are observed in patients with AF, including elevated risk of thromboembolic events.
- There are a variety of treatment regimens for preventing thromboembolism in patients with nonvalvular AF, including traditional oral anticoagulants (most commonly, the vitamin K antagonist [VKA] warfarin) and novel oral anticoagulants (NOACs), including dabigatran, rivaroxaban, and apixaban.
- There are a number of characteristics of anticoagulation with VKAs that may impair patient health-related quality of life (HRQOL) and treatment satisfaction, including the need for regular blood testing, complex dosing regimens, potential interactions with food or other drugs, and activity limitation and worry related to bleeding and bruising, as well as experiencing minor and major bleeds.[2,3]
- NOACs are able to overcome some of the shortcomings of VKA therapy, such as its slow onset of action, variable pharmacologic effects, food-drug interactions, and the need for frequent blood testing; however, the potential for minor and major bleeds remains.[4]
- Anticoagulant therapy noncompliance and discontinuation are common and are associated with a higher stroke risk in patients with AF.[5]
- Assessment of patient-reported outcomes (PROs) related to oral anticoagulants in clinical trials of thromboprophylaxis presents multiple challenges. The drugs do not treat the patient's primary cardiovascular condition (e.g., AF); rather, they prevent thromboembolism related to the condition. Anticoagulants also do not relieve symptoms; rather, they add potentially bothersome side effects, including the tendency to bruise and the potential for minor and major bleeds.

OBJECTIVE

- To identify and summarize the key characteristics, strengths, and weaknesses of available PRO measures, including measures assessing anticoagulation-specific HRQOL, treatment satisfaction, or other patient-reported domains related to treatment benefit or burden in adult patients with AF using long-term anticoagulant therapy, with a focus on how well the measures meet current regulatory guidance requirements.

METHODS

Phase 1

- A comprehensive review of multiple sources (PubMed, ClinicalTrials.org[6]; Patient-Reported Outcome and Quality of Life Instruments Database [PROQOLID][7]) was conducted to identify candidate PRO measures.
- The PubMed search was limited to studies published in English since January 2004 and describing research in humans. The initial searches to identify candidate measures were not limited to AF, because patients receiving thromboprophylaxis for other conditions (e.g., deep vein thrombosis [DVT], pulmonary embolism [PE]) may have relevant experience with anticoagulants.
- Those measures assessing relevant concepts, with use in observational or clinical studies or with a promising development and validation history, were selected to be explored further during the second phase of the instrument review.

Phase 2

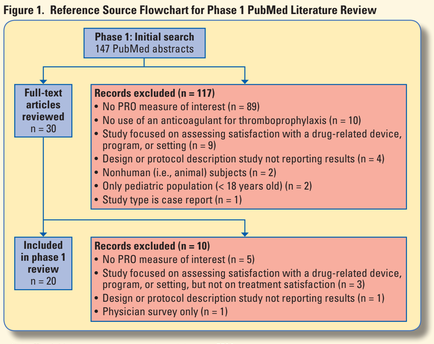
- Development process and psychometric or clinical study data related to the PRO measures selected in Phase 1 were extracted and compared across the measures. These data were gathered through additional PubMed and Internet searches and information provided by the instrument developers, either online or upon request.
- Shortcomings in the documented development processes and psychometric evaluation of the measures were identified using the standards set forth in the United States Food and Drug Administration (FDA) guidance for PRO measures that are used to support regulatory approval or promotional claims.[8] 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 thoroughly validated in the target population.

RESULTS

Phase 1

- The results of the phase 1 review included the following:
  - PubMed: 147 abstracts were identified; 30 full-text articles were reviewed; and 20 studies were included in the review (Figure 1).
  - ClinicalTrials.gov: 47 clinical studies were identified; 22 appeared to include PROs; however, in most of these trials, the concept assessed (e.g., HRQOL) was given, but the instrument was not identified by name. No unique PRO measures were identified through the ClinicalTrials.gov search.
  - PROQOLID: 2 PRO measures related to anticoagulant treatment satisfaction in AF or PE were identified.
- In total, 13 PRO measures related to assessing anticoagulation therapy were identified. Of the 13 measures, 7 were anticoagulation-specific or contained an anticoagulation-specific subscale, 5 were generic HRQOL measures, and 1 was a measure of anxiety. Two of the anticoagulation-specific PRO measures were visual analog scales assessing satisfaction and HRQOL and were not further evaluated.
- Five PRO measures were selected for further review (Table 1).

Figure 1. Reference Source Flowchart for Phase 1 PubMed Literature Review



Note: The initial searches were conducted January 2014.

Table 1. Overview of PRO Measures of Interest (N = 5)

Questionnaire/Objective	Content/Recall Period
Anti-Clot Treatment Scale (ACTS)[9] • Anticoagulation-specific questionnaire assessing treatment satisfaction • Based on the DASS (modified to be more applicable to a wider range of conditions and languages) • Not limited to specific conditions or anticoagulant administration routes	15 items in 2 domains: • ACTS Burdens scale (12 items) • ACTS Benefits scale (3 items) 2 global items: • Negative impact of treatment on a patient's life • Positive impact of treatment on a patient's life **Recall period:** During the past 4 weeks
Duke Anticoagulation Satisfaction Scale (DASS)[3] • Anticoagulation-specific questionnaire assessing treatment satisfaction • Not limited to specific conditions or anticoagulant administration routes	25 items in 2 domains: • Negative impacts of anticoagulation (potentially further divided into limitations, hassles, and burdens) • Positive impacts of anticoagulation **Recall period:** None specified
Perception of Anticoagulant Treatment Questionnaire (PACT-Q)[10] • Anticoagulation-specific questionnaire assessing patient expectations and satisfaction with treatment • Not limited to specific conditions or anticoagulant administration routes	27 items, originally hypothesized as 4 domains: • Treatment Expectations (7 items) • Convenience (11 items) • Burden of Disease and Treatment (2 items) • Anticoagulant Treatment Satisfaction (7 items) Domains supported by principle component analysis (PCA): • PACT-Q1, originally composed of the Treatment Expectations dimension (7 items), was not found to be unidimensional, so each item should be analyzed separately • PACT-Q2, to be administered to patients once treatment is underway; originally composed of Convenience, Burden, Anticoagulant Treatment Satisfaction; Convenience and Anticoagulant Treatment Satisfaction were retained **Recall period:** None specified
Sawicki questionnaire[11] • Anticoagulation-specific questionnaire developed in Germany to compare home- and clinic-managed anticoagulation	32 items (reduced from 40 items but no description of how or why items were deleted[12]), including 5 "topics": • General treatment satisfaction • Self-efficacy • Strained social network • Daily hassles • Distress **Recall period:** None specified
Deep Venous Thrombosis Quality of Life (DVTQOL)[13] • DVT-specific questionnaire assessing HRQOL outcomes (including the practical and psychological demands of oral anticoagulant therapy) in connection with a primary event of DVT	29 items with 6 dimensions: • Emotional distress • Symptoms (e.g., pain, swollen ankles, cramp, bruising) • Limitation in physical activity • Hassle with coagulation monitoring • Sleep disturbance • Dietary problems **Recall period:** None specified

Phase 2

- Phase 2 searches were conducted to gather data to evaluate and compare the five measures meeting the inclusion criteria in phase 1.
  - The instrument-specific PubMed searches identified 62 abstracts.
  - Of these 62 abstracts, 17 had been identified in the phase 1 searches, 37 were not relevant and were excluded, and 8 were selected for full-text review and were included in the final review.
- Table 2 provides a summary of the types of documented patient involvement during the development processes of the instruments.
- Table 3 presents a summary of the evaluated measurement properties of each of the instruments of interest.

Table 2. Summary of Target Population Involvement During Instrument Development

Development Step	ACTS[d]	DASS[d]	PACT-Q[d]	Sawicki[e]	DVTQOL[f]
Item generation/modification[a]	✓	✓	✓	✓	✓
Evaluation of item completeness and acceptability[b]	✓	✓	✓	—	✓
Item-reduction process[c]	✓	✓	✓	—	✓

✓ = Yes; — = No (not reported or not adequately documented).
[a] Individual interviews or focus groups were conducted with target population.
[b] Through pilot testing, feasibility testing, or cognitive debriefing with individual interviews, the target population evaluated the completeness of item coverage and performed an initial assessment of clarity and readability.
[c] Item reduction was based on content analysis of feedback from members of the target population.
[d] The development and validation populations included people with AF, DVT, and PE taking anticoagulants.
[e] Input was received from patients taking oral anticoagulants (conditions not specified).
[f] The development and validation populations consisted of patients with DVT taking warfarin.

Table 3. Summary of Psychometric Properties Reported in the Literature for Anticoagulation PRO Instruments of Interest

Psychometric Property	Published After the Draft FDA PRO Guidance		Published Before the Draft FDA PRO Guidance		
	ACTS (2009)[9]	PACT-Q (2009)[10]	DASS (2004)[3]	Sawicki (1999)[11]	DVTQOL (2004)[13]
Internal consistency[a]	✓	✓	✓	✓	✓
Test-retest reliability[b]	✓	NR	✓	NR	NR
Content validity[c]	✓	✓	✓	✓	✓
Construct validity, convergent[d]	✓	NR	✓	NR	✓
Construct validity, divergent[d]	✓	NR	NR	NR	NR
Known-groups validity[e]	✓	✓	✓	NR	NR
Responsiveness, longitudinal validation study[f]	✓	—	NR	NR	NR
Responsiveness, randomized clinical trial[g]	✓	—	✓	✓	NR

✓ = Instrument achieved or exceeded the established psychometric standard or the standard set by the authors of this review (see notes for the specific standard for each property).
— = Instrument did not meet the established psychometric standard or the standard set by the authors of this review (see notes for the specific standard for each property).
[a] Range for acceptable Cronbach's alpha: above 0.70 but not higher than 0.95.[14]
[b] Threshold for acceptable test-retest reliability: interclass correlation coefficient of 0.75 or greater.[15]
[c] Target population (patients using anticoagulation therapy) participated in initial item generation (focus groups or interviews) or subsequent refinement of item content ("face-to-face" or cognitive debriefing interviews).
[d] At least one Pearson's correlation coefficient (r) value was categorized as moderate (0.10-0.50) or strong (> 0.50).[16]
[e] Discriminant validity demonstrated by statistically significant ($P < 0.05$) difference in at least one comparison of patient subgroups with differing clinical features.
[f] Responsiveness demonstrated by statistically significant ($P < 0.05$) results in at least one longitudinal validation study.
[g] Responsiveness demonstrated by statistically significant ($P < 0.05$) results in at least one randomized controlled trial.

DISCUSSION

- Based on qualitative studies with patients using VKAs (primarily warfarin), the burden of VKA therapy is significant. Patients noted the negative impact of bleeding and bruising, frequent blood testing, and dietary and alcohol restrictions, as well as the psychological and social impact of VKA therapy. Many patients seemed to adjust to and accept this burden over time because of lack of alternative treatments.[17]
- The ACTS, DASS, and PACT-Q focus primarily on treatment satisfaction and include one or two items assessing the HRQOL impact of treatment. The Sawicki questionnaire and the DVTQOL, on the other hand, primarily assess HRQOL, with treatment satisfaction or burden being one dimension of HRQOL.
- Among the five measures reviewed, the ACTS is the measure with the most rigorous and well-documented development and most successful demonstration of measurement properties, including reliability, validity, and responsiveness.
- The ACTS has been included in two studies comparing VKA-centered therapies to NOACs or other non-VKA treatment: one clinical trial in acute symptomatic DVT[18] and one observational study in AF.[2] In both studies, the ACTS Burdens scale found significant between-group differences that met the authors' proposed standards of clinically important difference, but the ACTS Benefits scale was less responsive.
- Additional studies confirming the ACTS's measurement properties in AF populations are needed, given that currently only one clinical study in DVT[18] is the source of the measure's validation data, and an instrument's properties ideally are demonstrated during repeated use and evaluation in the target population.
- Despite its relatively rigorous development and overall strong psychometric properties, the ACTS is unlikely to support an FDA PRO label claim. The ACTS (or any of the reviewed measures) likely would not be deemed "fit for purpose" by the FDA, because of the difficulty in establishing that the complex measurement concept matches the targeted claim (e.g., improvement in treatment satisfaction). The ACTS also has a relatively long recall period (4 weeks).

CONCLUSIONS

- Use in a clinical trial of a PRO measure that meets the standards of the FDA PRO guidance may result in a PRO label claim. If included in a drug product label, results from PRO measures and related PRO claims may be used in promotional materials to support promotional activities.
- There does not appear to be an anticoagulation-specific HRQOL or treatment satisfaction measure that would be likely to support an FDA PRO label claim in its current form. In general, the European Medicines Agency (EMA) is more receptive than the FDA to complex patient-reported concepts such as HRQOL or treatment satisfaction for label claims. However, we found no precedent for a treatment satisfaction or HRQOL EMA label claim related to anticoagulation therapy.

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