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Review

What is the methodological and reporting quality of health related quality of life in chronic heart failure clinical trials?

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ABSTRACT

Background: Although the number of clinical trials assessing health related quality of life (HRQoL) in chronic heart failure (CHF) has increased exponentially over the last decade, little is known about the quality of reporting. The purpose of this review was to assess the methodological and reporting rigor of HRQoL in RCTs of pharmacological therapy in CHF.
Methods: The electronic data bases, Medline and EMBASE were searched from 1990 to 2009 using the key search terms 'heart failure' combined with 'quality of life', 'pharmacological therapy' and 'randomized controlled trials'. A total of 136 articles were identified and evaluated according to the "Minimum Standard Checklist (MSC) for Evaluating HRQoL Outcomes".
Results: According to the MSC criteria, 26 (19.1%) studies were considered 'very limited', 91 (66.9%) were 'limited' and only 19 (14.0%) studies were considered to be of a 'probably robust' in terms of methodological and reporting rigor. In fact, the quality of HRQoL reporting has not improved over time.
Conclusion: HRQoL is a critical consideration in CHF management, yet reporting is highly variable. There is a need to develop a standardized method for measuring and reporting HRQoL measures in clinical trials to aid in the interpretation and application of findings.

1. Introduction

Chronic heart failure (CHF) is a common, costly and resource intensive syndrome with a poor prognosis. Patients with CHF experience poor outcomes including severely impaired health related quality of life (HRQoL) [1]. Some studies have shown that patients with CHF experienced a poorer quality of life compared to individuals with other chronic conditions [2,3]. Many patients with advanced CHF also ascribe greater importance to the quality rather than the length of their life [4].

The number of clinical trials incorporating HRQoL assessment as an endpoint has increased in recent decades [5]. Increasingly CHF clinical trials focus on the benefit of "add-on" therapy for which the cumulative benefits may be an incremental gain in HRQoL, in spite of a limited impact on survival [6]. This increased focus on incremental benefit means that methods of assessment and reporting of endpoints such as HRQoL need to be rigorous and robust.

Although the purpose of measuring HRQoL in randomized control trials (RCTs) may have been to guide future patient care and treatment decisions, there is evidence of the limited influence of this approach on individual clinical decision making and/or treatment policies [7]. This may be attributed to inadequate reporting, low compliance with completing study measures, underpowered studies and variable quality in studies assessing HRQoL [8–10]. Furthermore, most clinical trials using HRQoL as an endpoint solely report psychometric properties and do not extend to the issue of relevance of the measure nor to the rigor in measuring and reporting [11]. In spite of mushrooming of HRQoL assessment and as a consequence numerous reviews and meta-analyses on HRQoL in patients with CHF [5,12–14] the methodological and reporting rigor of the HRQoL assessment in RCTs has not been described.

The purpose of this review was to assess the methodological and reporting of HRQoL in RCTs of pharmacological therapy in CHF, either as a primary or secondary endpoint using the "Minimum Standard Checklist (MSC) for Evaluating HRQoL Outcomes" [9] (Table 1). RCTs of pharmacological therapy were chosen for a number of reasons; for its potential for incremental therapeutic benefit [15]; of additive therapies [16]; and the fact that regulatory bodies such as

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Table 1
Level of reporting[a] according to the Minimum Standard Checklist for evaluating Health related quality of life outcomes in pharmacological trials in CHF.

HRQoL issue	Description
Conceptual	
A priori hypothesis stated	Assessed whether authors had a predefined HRQOL end point and/or stated expected changes because of the specific treatment.
Rationale for instrument reported	Assessed whether authors gave a rationale for using a specific HRQOL measure.
Measurement	
Psychometric properties reported[b]	Assessed whether a previously validated measure was used or psychometric properties were reported or referenced in the article.
Cultural validity verified	Assessed whether the measure was validated for the specific study population.
Adequacy of domains covered	Assessed whether the measure covered, at least, the main HRQOL dimensions relevant for a generic HF population and/or according to the specific research question.
Methodology	
Instrument administration reported	Assessed whether authors specified who and/or in which clinical setting the HRQOL instrument was administered.
Baseline compliance reported[b]	Assessed whether authors reported the number of patients providing an HRQOL assessment before the start of treatment.
Timing of assessment documented	Assessed whether authors specified the HRQOL timing of assessment during the trial.
Missing data documented[b]	Assessed whether authors gave some details on HRQOL missing data during the trial.
Interpretation	
Clinical significance addressed	This refers to the discussion of HRQOL data being clinically significant from a patient's perspective and not simply statistically significant.
Presentation of results in general	Assessed whether authors discussed the HRQOL outcomes, giving any comments regardless of the results (either expected or not).

Adapted from Efficace et.al. [9].
HRQoL, health related quality of life; CHF, chronic heart failure.
[a] When multiple instruments were used in a single study only one instrument had to satisfy the item in a checklist to have deemed to have met the health related quality of life issue for that study.
[b] High priority concerns that need to be satisfied.

the Food and Drug Administration (FDA) in the United States (US) request HRQoL data when making drug approval decisions [17]. Including non-pharmacological therapy and devices trials in this review would require additional methodological and reporting issues to be considered [18,19]. This review also sought to investigate whether the methodological and reporting quality of HRQoL outcomes in RCTs have improved over time and as how HRQoL outcome is used in the study (primary vs. secondary outcomes).

2. Methods

A search of the electronic data bases Medline and EMBASE was undertaken with the assistance of a health librarian. The search strategy used relevant keywords and Medical Subject Heading (MeSH) terms including 'heart failure' combined with 'health related quality of life', 'pharmacological therapy' and 'randomized controlled trials' restricted to articles in English (Supplementary material 1). The search was restricted to 1990–2009 as it is in the last 20 years HRQoL has become a research area of interest. RCTs were considered to be eligible if HRQoL was explicitly designated as either primary or secondary endpoint. No restriction was set on type or number of HRQoL assessments in the study. Case reports, editorials, letters, commentaries, reviews, overviews and conference presentations were excluded along with cases where HRQoL assessment was included as a part of a composite endpoint. Studies with insufficient information regarding HRQoL assessment were also excluded. Potentially relevant articles were initially retrieved and if it was deemed appropriate the full text article were sought. Additional relevant studies were identified through a manual search of reference lists from previous review articles [5,14].

The following information was extracted from included studies: Authors, main objective and study interventions, diagnosis, duration of the study, sample size, HRQoL used as primary/secondary outcome, description and type of the HRQoLs used and whether a power calculation was undertaken. When the primary outcome was not explicitly stated by the authors, it was defined as the one that was given prominence in the report or the outcome used for the sample size calculation.

Each RCT was evaluated according to the MSC [9] (Table 1). This checklist facilitates a critical review and interpretation of HRQoL outcomes by addressing the basic and essential issues that a given trial should possess to have sound and reliable HRQoL outcomes in clinical trials [9]. This checklist consists of 11 items grouped into categories addressing basic and essential methodological and reporting issues related to HRQoL assessment in clinical trials: conceptual, measurement, methodology, and interpretation. The items were originally selected from the literature by consensus of HRQoL researchers and further refined by an additional independent panel of 30 experts in the field of HRQoL including clinicians, psychologists and statisticians [9]. Summative scores of eight and over, including three mandatory items (baseline compliance, reporting psychometric properties or referencing validation article and missing data documentation) on this checklist were considered as 'probably robust'. Scores between five and seven or not including all three mandatory items were classified as 'limited' and all other studies were classified as 'very limited'. If more than one HRQoL instrument was used, the study was credited for fulfilling a particular criterion/checklist if it was satisfied by any one of the instruments employed.

To examine the effect of time on the MSC total score for HRQoL outcome, a linear regression model was used with the MSC total score as the dependent variable and the time of publication as the continuous independent variable. Prior to linear regression modeling, correlation analysis was used between MSC total scores, the year of publication, the usage of HRQoL outcome (primary vs. secondary), sample size and the duration of the study in weeks to identify any confounding variables. In addition, the publication year was classified as before and after 2005 to further examine any changes between these two time periods.

3. Results

A total of 392 studies were retrieved. After excluding 256 articles (Fig. 1) not meeting the inclusion criteria 136 studies were included in the review. Of the 136 studies (Supplementary material 2), 73 (53.7%) studies were published from 2000 to 2009. Most studies (n = 112; 82.4.4%) used the New York Heart Association (NYHA) class to identify the patient group studied, with the most common grouping being NYHA II–III (46/112; 41.1%) followed by NHHA II–IV (30/112; 26.8%). The reported duration of the study ranged from 1 week to 235 weeks with 54 (40.0%) studies reporting 12 weeks or less. In some studies, this may include a run-in period (Table 2).

HRQoL assessment was described as either a primary or co-primary endpoint in 19 (14.0%) studies (Table 3). However in only 4 of these 19 studies (4/19; 21.1%) the sample size was calculated based on a HRQoL hypothesis or the adequacy of calculated sample size to detect clinically significant HRQoL changes was considered. In more than half of these studies (10/19; 52.6%) a sample size calculation was not reported at all and in five studies (5/19; 26.3%) the sample size calculation was based on the other endpoints. Six of these studies (6/19; 31.6%) were sub-studies of larger RCTs [20–24]. For studies where HRQoL assessment was a secondary endpoint, only four studies (4/117; 3.4%) considered the adequacy of a calculated sample size on HRQoL assessment [25–27] while 64 studies (64/117; 54.7%) did not report on the sample size calculation at all. Of all 136 studies reviewed, 69 (50.7%) studies had a sample size less than 100 patients with the median sample size of 81.5.