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Composite outcome measures in a pragmatic clinical trial of chronic heart failure management: A comparative assessment☆

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ABSTRACT

Background: A number of composite outcomes have been developed to capture the perspective of the patient, clinician and objective measures of health in assessing heart failure outcomes. To date there has been a limited examination in the composition of these outcomes.

Methods and results: Three commonly used scoring systems in heart failure trials: Packer's composite, Patient Journey and the African American Heart Failure Trial (A-HeFT) scores were compared in assessing outcomes from the Which heart failure intervention is most cost-effective & consumer friendly in reducing hospital care (WHICH(?)) Trial. Comparability and interpretability of these outcomes and the influence of each component to the final outcome were examined. Despite all three composite outcomes incorporating mortality, hospitalisation and quality of life (QoL), the contribution of each individual component to the final outcomes differed. The component with the most influence in deteriorating condition for the Packer's composite was hospitalisation (67.7%), while in Patient Journey it was QoL (61.5%) and for A-HeFT composite score it was mortality (45.4%).

Conclusions: The contribution made by each component varied in subtle, but important ways. This study emphasises the importance of understanding the value system of the composite outcomes to enable meaningful interpretation of results.

1. Introduction

Chronic heart failure (CHF) is a common, complex and multifaceted syndrome [1]. Evaluating interventions in progressive, life limiting conditions challenge traditional approaches of outcome assessment, such as mortality and morbidity. Increasingly, CHF patients and clinicians alike are concerned not only with survival but also the quality of that survival [2]. Currently, there is a lack of consensus on appropriate measures to assess outcomes in clinical trials [3–7], while there is an increasing recognition that treatment efficacy needs to be measured by multiple outcomes, especially where management or the outcomes of interventions have various components [8,9]. As reproducibility is challenged in clinical trials, understanding the reliability, validity and value of outcome assessments is important.

A composite outcome in a clinical trial is where clinically relevant measures are combined into a single outcome that can characterise clinically meaningful benefits of a treatment [10]. The benefits of composite outcomes include a reduced sample size as a consequence of increasing the event rate and hence lower costs of undertaking a trial, and the ability to capture the net benefits of the multiple dimensions into a single summary measure [9,11]. Using a composite outcome will circumvent the need to make an allocation for multiple hypotheses testing, as one is essentially dealing with a single outcome [10]. In addition, the problem of competing risks can be avoided especially if a clinical outcome such as mortality is combined with morbidity [10]. A

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rationale for using composite outcome is well described in Neaton [10]. But more importantly, conceptually and theoretically composite outcomes seek to obtain the perspective of the patient, clinician as well as objective biomedical measures.

Composite outcomes are difficult to interpret when the treatment effects vary considerably across the components of the measure [12]. The most extreme case would be when the components are moving in different directions such as an increase in mortality and an improvement in QoL. The problem of interpretation is compounded when components are dissimilar in patient importance [11]. For example, it is useful to consider whether admission to the emergency room is comparable to a catastrophic stroke. Many of these problems may be resolved by choosing clinically relevant components of the composite and applying appropriate weightings of these components [5,11].

Using a composite outcome requires considerations, such as the selection of the number and type of clinically relevant components as well as their relative weightings or derivation methods which have important implications in the interpretation of the composite outcome [5]. Although the clinical and statistical challenges to using and interpreting composite outcomes have been discussed [13–16], there is limited discussion on the derivation method of composite outcomes or in establishing the standards for weighting components of a composite outcome.

This paper seeks to provide a better understanding of conceptual and measurement issues in composite outcome assessment by comparing and contrasting Packer's composite, [13] Cleland's Patient Journey [14] and the composite outcome used in the African American Heart Failure Trial (A-HeFT) [15], in a secondary analysis of a prospective, multi-centred randomised controlled trial. These composite outcomes have been chosen because they are commonly known composite outcome models in HF clinical trials and they capture the patient-centred components, namely mortality, hospitalisation and QoL from the perspective of the patient, clinician as well as including objective measures of health. The main objective of this paper was to compare and contrast these three composite outcomes to increase our understanding of the numerous pathways components influence the final outcome in CHF patients. Specifically, this paper does not aim to assess which composite outcome is 'best' or to assess the validity of these composite outcomes but rather to gain insight into the relationship amongst composite outcomes that measure similar patient-centred components. In addition, we sought to examine the methodological consequence of each component on the final outcomes.

2. Method

2.1. Composite outcome measures

Three commonly known composite outcome models were selected for the purpose of this comparative analysis. These were Packer's composite [17], Cleland's Patient Journey [18] and the composite outcome used in the African American Heart Failure Trial (A-HeFT) [19]. Although these composite outcomes incorporate similar components, each uses a different derivation method and/or different weighting of the components likely reflecting priorities. All components in the composite were examined separately to estimate their relative effect on respective composite outcome.

The Packer's composite outcome measure [17] is perhaps the most widely used in clinical trials [20]. This score combines mortality, heart failure (HF) hospitalisation, change in New York Heart Association (NYHA) classification and a change in patient's global self-assessment of well-being measured in five discrete classes to classify patients as improved, unchanged, or worsened (Table 1).

The Patient Journey [18] is another composite outcome in CHF incorporating information on mortality, hospitalisation and QoL/well-being. Furthermore, this measure incorporates the change in therapy in the scoring scheme [18]. Essentially this measure is a refinement of days alive and out of hospital (DAOH). It incorporates longevity and out of hospital into a single measure in days, and assign for each DAOH score of 100% if the patient reported feeling very good ('well-being' score 1). This score is subsequently reduced by 20% for each decrement in the patient-reported score down to a lowest potential score of 20% ('well-being' score 5). The intensification of diuretic therapy to control symptoms is also integrated by considering patients to be worse in the patient QoL/well-being than actually expressed [18]. However, a reduction in diuretic therapy does not necessarily lead to increase in the QoL/well-being.

The A-HeFT composite outcome [19] includes all-cause mortality, a first HF hospitalisation, and a change in QoL using Minnesota Living with Heart Failure questionnaire (MLWHFQ). A weight given to each component to generate the composite is shown in Table 1. Initial score of 0 is assigned to all patients, which will change depending on patient's experience [19].

2.2. Weighting algorithms for composite scores

The weighting algorithms for each of the components for the composite outcomes are summarised in Table 1. Despite measuring similar concepts, each composite outcome captures and weighs each component differently. In addition, the measurements of the final outcomes were different. The Patient's Journey [18] is well-being weighted DAOH, where the final outcome is expressed in days whereas the final outcome for the Packer's is a qualitative measure and the A-HeFT composite is a numeric score between −6 and 2.

The extent of differences in measuring and weighting for each component is apparent even in the hospitalisation. In the Packer's [17] and the A-HeFT scores [19], the incident of first HF hospitalisation is used whereas the Patient Journey [18] uses total hospitalisation days for all-causes. For the QoL component, not all composite outcomes use the same instruments and in some cases more than one instrument/measure are used. In the Packer's composite, changes in the NYHA functional class is combined with the changes in patient assessed global well-being, while in the Patient's Journey, increased use in diuretic adjusts QoL/well-being weights which is then applied to DAOH. For the A-HeFT score, greater weight is assigned to a change in QoL than for an incidence of first HF hospitalisation.

Discrete and comparative analysis of the three aforementioned composite outcomes were carried out using the data from Which heart failure intervention is most cost-effective & consumer friendly in reducing hospital care (WHICH(?)), a multicentre randomised controlled study [21]. The main focus of the study was to compare the multidisciplinary CHF management delivered via an outreach, home-based intervention (HBI) with an outpatient or a specialised CHF clinic-based intervention (CBI), in patients with moderate to severe symptoms of HF with at least one admission for acute HF. A detailed description of the rationale and design, baseline findings and primary results for this trial has been published elsewhere [21,22].

2.3. The WHICH Trial

A total of 280 patients were recruited from three tertiary referral hospitals in three different states in Australia. Of these, 143 patients were randomised to the home-based and 137 to clinic-based post-discharge management. As previously described [21], baseline characteristics were similar in the two arms. All hospitalisations were adjudicated on the type (elective/unplanned) and the cause, and all deaths were reviewed by a blinded outcome committee. The intervention was found to be not significant on the primary outcome of all-cause mortality or all-cause unplanned hospitalisation [22] during 12–18 months of follow-up.

For the purpose of the current study, the patients with a follow-up greater than 12 months were censored at the date of contact at 12 months to ensure that all patients had an equal follow-up duration.