Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 54, No. 5, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.04.051

What Is the Strength of Evidence for Heart Failure Disease-Management Programs?

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Heart failure (HF) disease-management programs are increasingly common. However, some large and recent trials of programs have not reported positive findings. There have also been parallel recent advances in reporting standards and theory around complex nonpharmacological interventions. These developments compel reconsideration in this Viewpoint of how research into HF-management programs should be evaluated, the quality, specificity, and usefulness of this evidence, and the recommendations for future research. Addressing the main determinants of intervention effectiveness by using the PICO (Patient, Intervention, Comparison, and Outcome) approach and the recent CONSORT (Consolidated Standards of Reporting Trials) statement on nonpharmacological trials, we will argue that in both current trials and meta-analyses, interventions and comparisons are not sufficiently well described; that complex programs have been excessively oversimplified; and that potentially salient differences in programs, populations, and settings are not incorporated into analyses. In preference to more general meta-analyses of programs, adequate descriptions are first needed of populations, interventions, comparisons, and outcomes in past and future trials. This could be achieved via a systematic survey of study authors based on the CONSORT statement. These more detailed data on studies should be incorporated into future meta-analyses of comparable trials and used with other techniques such as patient-based outcomes data and meta-regression. Although trials and meta-analyses continue to have potential to generate useful evidence, a more specific evidence base is needed to support the development of effective programs for different populations and settings. (J Am Coll Cardiol 2009;54:397–401) © 2009 by the American College of Cardiology Foundation

The development of disease-management programs for the large and vulnerable population with heart failure (HF) brought important multidisciplinary support to patients. However, a number of recent trials (1–6) have found no or limited benefits from programs. In the context of new CONSORT (Consolidated Standards of Reporting Trials) reporting requirements (7) and theoretical advances (8–10), it is timely to address how current research into HF-management programs should be evaluated; the quality, specificity, and usefulness of current evidence; and useful directions for future research.

How Should Program Trials Be Evaluated?

What are fair criteria with which to evaluate the quality of existing program trials? There is a strong case for drawing on the reporting requirements of the CONSORT statement (7) for nonpharmacological trials (Table 1). Published trials of programs predate these new reporting requirements but rather than introducing novel principles, the new CONSORT statement (7) codifies well-established principles of design and appraisal. As expressed in the acronym PICO (11), the effectiveness of any intervention is determined by the characteristics of the intervention (I) and the population receiving it (P). In trials, apparent effectiveness is also influenced by what the intervention is compared with (C), what outcomes are measured, and the quality and timing of these measurements (O) (11). As the 4 main determinants of treatment effectiveness, design weakness or vague reporting in any one of these aspects extensively impacts study quality.

The CONSORT statement (7) also recognizes that nonpharmacological trials are different than pharmacological trials. Recent theoretical work acknowledges the inherent complexity of health services interventions, for example, in systems (10) and contextual effects (12). These advances are evident in trial development frameworks (8,9), policy (13), and evaluation (14). For example, the American Heart Association (AHA) developed a taxonomy of HF-management programs that classified programs in structure and design around at least 8 parameters, each in at least 4 different ways (15).

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Manuscript received March 1, 2009; revised manuscript received April 6, 2009, accepted April 14, 2009.

JACC Vol. 54, No. 5, 2009
July 28, 2009:397–401

Abbreviations and Acronyms

AHA = American Heart Association

CONSORT = Consolidated Standards of Reporting Trials

HF = heart failure

PICO = Patient, Intervention, Comparison, Outcome

To improve knowledge translation, there is a growing realization that decision and policymakers need specific and context-responsive evidence (16). Knowledge is needed not only of whether there is a general likelihood that an entire genre of programs will work in any setting but the size of likely benefit in a particular setting from programs with specified components, delivery mechanisms, and personnel (10). Hence, rather than threatening the future existence of HF-management programs, considering evidence in the light of recent advances addresses essential elements of research design, theory, and knowledge translation.

Evidence From Current Trials

What is the quality of existing evidence from program trials? There are many complex issues to address in the design of a randomized trial (17), but both CONSORT (7) and PICO suggest some fundamental aspects require attention.

What interventions are studied? Interventions should be described comprehensively in terms of content, components, providers, and standardization procedures (7) because these dimensions could influence treatment effects (7,8,10). Concerns have been raised that, in current trials, programs are poorly described (18–22), and elements are seldom justified (15,23). There is a tendency to categorize programs based on a single or small number of macro characteristics (such as the main intervention setting or provider), although many other characteristics may be important (15,19,23). Wide diversity in trials exists around these potentially influential characteristics, including follow-up period, drug therapy optimization, intervention content, and mode(s) of provision (20,22). Other unknown or previously undocumented dimensions of interventions and their settings may also influence outcomes (8,10,24).

To what are interventions compared? Both PICO and CONSORT require that the care that comparison groups receive should be described comprehensively (7). Systematic review has identified that trials of programs currently do not detail sufficiently what "usual" or "routine" care comparison groups received (20,22,25,26). This lack of detail creates bias because pharmacological care for HF varies widely over place, time, and sector (27,28). Prescription rates of key pharmacotherapies have differed historically and are influenced by geographic location (28), the availability of specialists (29,30), and the aggressiveness of management (31,32). These differences are crucial because any apparent effect (or lack thereof) in a trial could be attributed equally to variations in usual care as to the intervention (7).

What is measured and how? More research is needed into the long-term effects of programs. Some trials with long-term follow-up show sustained benefits (33,34), but others do not (35). Most trials follow patients up for 9 to 12 months (27,36), but this duration may be insufficient to demonstrate impact on mortality (37), or patients may be readmitted before receiving the full effect of a program (1).

What should be concluded from current trials? Taking account of the trends in design and reporting described, there remains uncertainty regarding the direction and size of short- and long-term benefits likely to arise from different types of programs in different populations and settings. This is not to say that such benefits do not exist. However, to conclude that all or any types of programs will be as effective in all settings assumes a similarity or irrelevance of population, intervention, comparison, and context that is not substantiated by current data or theory.

Table 1 Reporting Standards for Intervention Components From CONSORT and Modified CONSORT for Nonpharmacological Treatments

Recommendations for Reporting	Standard CONSORT	CONSORT for Nonpharmacological Trials
Item 4	Precise details of the interventions intended for each group and how and when they were actually administered	Precise details of both the experimental treatment and comparator
Item 4A		Description of the different components of the interventions and, where applicable, description of the procedure for tailoring to individual participants
Item 4B		Details of how interventions were standardized
Item 4C		Details of how adherence of care providers with the protocol was assessed or enhanced

CONSORT = Consolidated Standards of Reporting Trial.

Building a Better Trial Evidence Base

More randomized trials of well-described interventions with longer-term follow-up periods are needed. To evaluate the effects of different types of programs in particular populations and settings, precise details should be provided of care for both the intervention and comparison groups, how the intervention was standardized across settings and personnel, and the degree and assessment of adherence of the providers of the intervention to the protocol (7). To identify the multiple dimensions of a complex intervention and the ways it is intended to improve outcomes, future trials should be developed by the use of frameworks designed to support the design and evaluation of complex interventions (8,9). The CONSORT standards (7) and AHA taxonomy (15) should be used to incorporate reporting standards into design, data collection, and other trial documentation. Adjunct qualita-

tive studies should be used to better understand "what works for whom, when and why" (19,24) via exploration of the mechanisms of effect of interventions and the moderating effects of population and context (8,10,19).

Evidence From Current Meta-Analyses

Trials of programs form complex, diverse, and often poorly described evidence, but this has not deterred frequent meta-analysis (20,22,26,36–46).

Populations: sample composition, size, and study weighting. Reflecting the trials themselves, the sample size in the majority of systematic reviews is comparatively small (22,42), with total sample sizes rarely reaching 5,000 (36,37) and most being around 2,000 (22,37–39,42,44,46). Size is likely to be related to the degree of focus of the review, but smaller sample size can lead to false conclusions due to random error (47). Also, because few reviews include >15 trials (22,42,46,48), pooled estimates in meta-analysis are then heavily influenced by a small number of large single trials (Table 2) (49).

No existing reviews pool data on outcomes by sex or age, and many do not identify the sex of the population that pooling is based on (22,37,38,40,42,44). This reflects incomplete reporting in the trials, but treatment and outcomes do vary by sex (50,51). This omission also prevents subanalysis to determine whether variation occurs in programs (52), an important step when studies have diverse populations (53).

Interventions: comparisons and heterogeneity. In meta-analysis, a lack of comprehensive descriptions of interventions and usual care makes it problematic to decide if and when trial findings should be pooled or to pinpoint the source of variations (54) because there must be sufficient similarity between trials for data to be pooled (55). Those (20,22,25,26) undertaking meta-analysis of programs have acknowledged a shortage of information about interventions in trial reports. However, few (22) have fully recognized the constraining implications this has on the ability to pool data.

That said, when viewed as complex, differences between health services interventions abound (56). Heterogeneity resulting from these differences is detectable not only via statistical testing but also by examining the characteristics of populations, interventions, and outcomes (57). Current reviews focus overwhelmingly on statistical heterogeneity with notable exceptions (22,40). Clinical and methodological heterogeneity arising from differences in population, programs, and methods remain comparatively ignored (58). This is unfortunate because exploring sources of clinical and methodological heterogeneity is arguably more important than testing for statistical heterogeneity (57,58).

Reflecting the diversity of trials included in reviews, many meta-analyses (20,26,36–38,40,41,44–46) report high statistical heterogeneity. Rather than merely commenting on the existence of statistical heterogeneity, it is more important to take it into account in the Methods and Conclusions sections (57,58) and explain or investigate why differences occur (56). This is hampered by the lack of comprehensive and detailed descriptions of trials and control groups. Even with strong evidence of statistical heterogeneity, some reviews (41,59) nevertheless pool data to produce summative estimates and make conclusions thereon.

Measurements: duration and follow-up. Duration of intervention and length of follow-up are not consistently reported in reviews and few reviews report data in both areas (36,37,40,45,46), which again raises the possibility that studies with short-term follow-up will not identify actual changes in mortality and morbidity.

How should future programs be evaluated? Given the complex nature of programs and the need for specific evidence, how should programs be evaluated in the future by the use of systematic review? Meta-analysis has had success in allowing the benefits of cardiovascular therapies to emerge from inconsistent results from trials and reviews (60). However, when used simplistically, inappropriately or with a biased sample of studies, meta-analysis can be a misplaced attempt to create certainty where none such can exist (61).

New trial findings of programs should not be incorporated de facto into additional general meta-analyses of programs to calculate amended overall effect sizes (62). Meta-analysis is dependent on comprehensive and accurate information on past trials. There is an urgent need for a comprehensive and systematic survey of the authors of existing trials, drawing on CONSORT (7) and the AHA taxonomy (15), around the key population, intervention, comparison, and outcomes characteristics missing from existing published trials. Although most published trials of health services interventions do not describe interventions adequately (63), trial authors often record many details on interventions beyond those included in publications (63). This would support future meta-analyses by adding important and rigorous descriptive detail of past trials.

Meta-analyses can be too occupied with seeking "headline" summative effect sizes (61,64) by pooling data from incomparable trials to increase sample size and the likelihood of a significant effect (61,64). This assumes similar

Table 2 Highest Trial Weightings in Selected Meta-Analyses of Heart Failure Disease-Management Programs

Review (Ref. #)	Highest Weighting of Individual Trial, %
Clark et al. (42)	39.73
Gonseth et al. (38)	68.18 21.55
Gwadry-Sridhar et al. (39)	19.6 25.7
Holland et al. (5)	9.49 10
Roccaforte et al. (45)	10.61
Taylor et al. (22)	17.2 40.9 34.5 (Various subanalyses)

effect sizes in different types of programs, populations, and settings (24); does not explain inconsistent trial results (24); and provides findings that are too general to be useful for practice and policy (12). Recognizing the complexity of programs (15), it is inappropriate to focus new meta-analyses on whether programs en masse work or do not work for all populations and settings (19). As has occurred in drug-eluting stents, strenuous efforts are needed to specify benefits and costs of programs of different types in different settings and subpopulations (64), including women, different health systems, patients >80 years of age, and patients in rural settings. It should be a priority to perform meta-analyses based on patient-based data rather than published results; this may allow more rapid understanding of the effects of comparable programs on different subpopulations (65).

Meta-analysis of any complex health services intervention faces the challenge of determining at which point a trial becomes sufficiently incomparable to pool with other studies. The multitude of known and unknown differences in a complex intervention means that differences and heterogeneity are inevitable (66). Findings should only be pooled in future meta-analyses when programs share similar features that are likely to have an impact on outcomes. This accepts the inevitability of heterogeneity but accepts this providing it occurs around features that are unlikely to be associated with the treatment effects or program costs (66).

To inform this, more evidence is needed regarding what program characteristics are most likely to determine program effects. A number of existing reviews have attempted to do this in relation to effectiveness (22,26,27), but these attempts are constrained by inadequate reporting in trials. The potential for bias arising from the effects of a small number of trials could also be addressed in pooling by weighting trials by quality (49). With improved data on existing trials, knowledge of which characteristics are most influential should accrue. Meta-regression offers a promising means to identify which characteristics of programs predict better outcomes (27) and could inform subanalyses and sensitivity analyses.

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Key Words: chronic ■ health promotion ■ self care ■ disease management ■ CHF.