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EDITORIAL

Beyond the *P*-value and the sound bite: learning from 'negative' clinical trials

Akshay S. Desai and Marc A. Pfeffer*

Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, USA

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This editorial refers to 'Standard vs. intensified management of heart failure to reduce healthcare costs: results of a multicentre, randomized controlled trial'[†], by P.A. Scuffham *et al.*, on page 2340.

Happy is the one who finds wisdom, the one who gains understanding;
For its value is greater than silver, it yield than fine gold.
It is more precious than rubies, no treasure can match it.'

Proverbs 3:13

Physicians have the privilege and responsibility to use and incorporate the best available data in their shared decision-making with their patients. Fortunately, in well-studied conditions such as heart failure, multiple therapeutic interventions have been rigorously tested in randomized controlled clinical trials demonstrating meaningful improvements in clinical outcomes. These trials also generate much needed information regarding the safety profile of these therapies. Based largely on the results of these trials, professional societies have developed practice guidelines to provide some weighted consideration for evidence-based therapeutic options.

The heavy reliance of treatment guidelines in cardiology on the results of randomized controlled treatment trials has fuelled a somewhat reductionist view of clinical trial evidence in practice. Trials are commonly viewed as 'positive', 'neutral', or, even worse, 'negative', with the implication that neutral results are largely uninformative, while the positive trials may be practice changing. However, this emphasis on the *P*-value for the primary trial result as the only meaningful sound bite from a large, multicentre randomized trial often fails to do justice to the tremendous effort expended by patients and investigators. There is a wealth of clinical information in even 'negative' trials that is belied by this one-word characterization, and clinicians should take note of what can be learned even when the *P*-value is < 0.05.

Moreover, the management of patients with heart failure is not 'plug and play' since responses vary and the therapies need to be frequently adjusted by treating physicians and other caregivers. With the accompanying age-related co-morbidities and frailty of many patients with heart failure, the capacity of these efficacious therapies, especially in combinations, to produce untoward effects is particularly problematic. This challenge to assist the individual patient in optimizing their benefits while minimizing the risks, the art of medicine, is a common thread that attracts compassionate physicians to be caregivers for patients with the healthcare burdens associated with heart failure, and is a central focus of chronic heart failure disease management programmes.

In this issue of the journal, Schuffman *et al.* present the principal results of the (Which Heart failure Intervention is most Cost-Effective in reducing Hospital stay) WHICH? II trial.[1] The Stewart team from Australia conducted a rigorous randomized clinical trial comparing two strategies of delivering post-discharge multidisciplinary heart failure care. This experienced group has already set the bar high with their existing, well-established heart failure disease management programme and was testing whether an even more intensive heart failure management strategy incorporating more home-based intervention supplemented with structured telephone support would further reduce total healthcare costs during 12 months of follow-up. The principal findings were that compared with their existing programme, the intensive strategy was associated with higher costs, but did not produce improvements in survival, hospital admissions, and most indices of patient-reported quality-of-life. The extra support provided to the subjects in the intervention arm was substantial, including additional home visits to remote sites, telephone contacts, and laboratory tests over standard management. In this way, the findings confirm those of the COACH study,[2] in which more intensive heart failure management strategies also did not appear to influence the rate of death or hospitalization for heart failure over 18 months. With an adequate number of events and no hint of a difference between groups for all hospital events reported (Schuffman *et al.* table 2), this should be considered a definitively neutral study, meaning that other attempts to evaluate these two strategies will not be likely to yield a difference. These results challenge the conventional assumption that more

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* Corresponding author. Division of Cardiovascular Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02445, USA. Tel: +1 617 732 5681, Fax: +1 617 732 5291, Email: mpfeffer@rics.bwh.harvard.edu

patient contact necessarily translates into better clinical outcomes for heart failure patients, and argues that augmenting a strong clinic/home-based disease management approach with more frequent in-home care or telephone support (even for higher risk patients) may not add significant value.

Despite the neutral topline result, this well-conducted trial offers a number of important insights into the management that may be valuable to clinicians who treat patients with heart failure. Importantly, the study provides a granular description of a year in the life of a cohort of elderly heart failure patients (one-third with heart failure with preserved ejection fraction) with a high burden of co-morbidities managed in the context of a high-quality, nurse-led disease management framework with a large component of home-based care (particularly for metropolitan area residents). High rates of recurrent hospitalization (>50%) and death (18%) for the cohort as a whole during the 12-month follow-up period may reflect the current best-case scenario of heart failure outcomes. Beyond the *P*-value, this study highlights the substantial residual risk of morbidity and mortality of modernly managed patient with heart failure. Further, the study provides validation of the GARDIAN-HF algorithm for pre-discharge profiling of risk for subsequent hospitalization and death.[3] In particular, patients in the lowest risk ('Green') category had very low rates of death (1%) and low cumulative burden of all-cause hospitalization, compared with those in the higher risk ('Amber' and 'Red') categories. This ability to identify a cohort at very low risk for subsequent adverse events may point the way to a tiered approach to heart failure care that focuses limited disease management resources on the patients who stand to benefit the most. Finally, this neutral trial also offers valuable information concerning the costs associated with high-quality heart failure care. For this cohort of 787 subjects, comprehensive costs were estimated at > A$20 million (~€13 million/US$15 million), reflecting a substantial per-patient expenditure, with the majority of these costs related to hospitalization. These numbers are likely to be an underestimate of the total aggregate costs of caring for heart failure patients, as they do not account for the costs of medications, lost wages, and the burden on caregivers.

Overall, then, while the authors have not clearly identified a more cost-effective system to implement medical care for heart failure

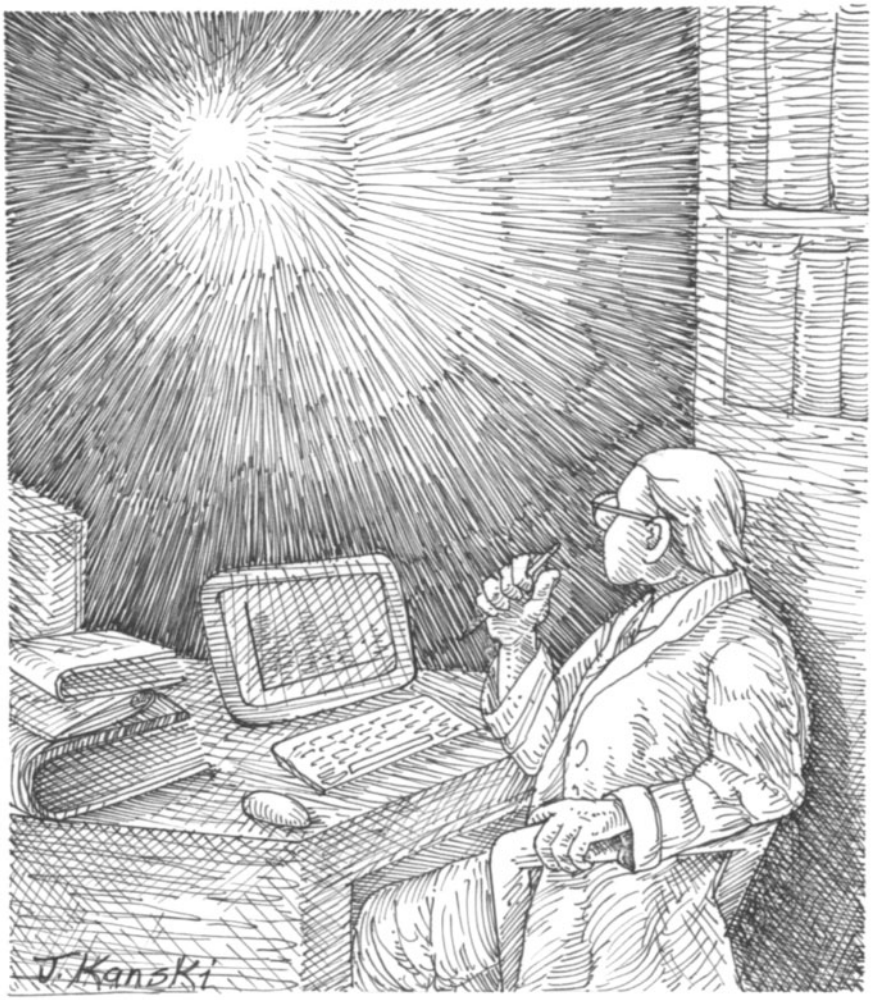

Figure 1 Finding light in darkness. Original illustration by Jean Kanski.

patients, the neutral trial does shed more light on the problem (*Figure 1*), taking us a bit further towards an understanding of the shape of the enemy. As we look to novel approaches to heart failure disease management that leverage new technologies for remote monitoring of filling pressures, device-derived diagnostics, and other biomarkers,[4] the WHICH? Infrastructure provides a useful background of care in which to test the incremental value of these approaches on top of 'best' heart failure nursing care.

Not having a significant difference in the primary objective of a major clinical trial can be harshly considered by some as a 'negative' trial. Even the less callous designation of a 'neutral' trial ignores the many lessons beyond the *P*-value or the initial sound bite. In addition to answering the question that the specific additional resources, over and above an existing quality comprehensive heart failure management programme did not reduce costs or improve outcomes, this investigative team has provided us with a wealth of information and understanding of the path of patients with symptomatic heart failure. The pearls of information hidden within this neutral trial provide a striking example of the silliness of attempting to reduce information generated from a quality trial to one word. The impressive co-operation between those involved in this effort to improve the well-being of their patients by optimizing information already generated from other therapeutic trials is laudatory and provides a strong foundation for future studies.

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