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EDITORIAL COMMENT

Cardiac Resynchronization Therapy

Are Modern Myths Preventing Appropriate Use?*

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Observational studies can help describe patient outcome, but only randomized controlled trials can assess the response to treatment. All too often, doctors confuse outcome with response, and nowhere is this better illustrated than with cardiac resynchronization therapy (CRT). If someone with little evidence of cardiac disease is implanted with a CRT device, he or she will almost certainly have an excellent outcome, but it would be wrong to attribute this to the device. A patient who was otherwise destined to die soon, who survived because he or she received CRT, but who had little improvement in symptoms may be considered to have had a poor outcome but, nevertheless, has responded to

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treatment. Differentiation between outcome and response is rendered even more difficult because most patients with heart failure experience episodes of acute deterioration and many experience a gradual decline in underlying cardiac function that may confound assessment of the benefits of treatment. Any patient with heart failure who has not deteriorated might be considered to have benefited from intervention. Indeed, this was a definition of treatment response used in the CARE-HF (Cardiac Resynchronisation in Heart Failure) trial (Table 1) (1–3). Prevention of sudden death in a patient who enjoys a reasonable quality of life is also generally regarded as a benefit even if the treatment does not improve symptoms and has some side effects. Observational studies are not very good at assessing the importance of the absence of such events.

However, observational studies can be useful. In this issue of the *Journal*, Mullens et al. (4) show, in an observational study, that patients who do not appear to have benefited from CRT often deteriorate when it is withdrawn (4). This suggests that in some patients, the benefit from CRT is "trumped" by deterioration in the underlying cardiac disease. This casts further doubt on the validity of observational trials that have attempted to predict who needs CRT using imaging or the electrocardiogram, as their results are highly dependent on the definition of response (5). Paradoxically, the observations made by Mullens et al. (4) undermine the notion that treatment response can be assessed reliably in an observational trial.

The mythological patron of medicine was Hermes (Greek) or Mercury (Roman), and many institutions use his wand (the caduceus) as a symbol. He was also the god of merchants, thieves, and gamblers. Maybe, as a profession, we are at risk of being as much doctors of "spin" as doctors of medicine. Doctors are very good at creating myths. Chronic aspirin therapy for coronary artery disease (6), antiarrhythmic drugs for ventricular arrhythmias (7,8), revascularization to improve the prognosis of patients with stable coronary disease (9) or for heart failure (10), and tight glucose regulation for diabetes (11) are but a few examples of recent or current management concepts, based on belief rather than on strong evidence, that have been challenged. Such beliefs, if wrong, may not be considered a large problem by a practicing physician, but from the point of view of generations of patients who may suffer the consequences of myth-based treatment this may be a disaster. The CAST (Cardiac Arrhythmia Suppression Trial) study saved millions of lives by exposing the delusion that suppressing ventricular arrhythmias with class I antiarrhythmic agents was an essential part of cardiology practice (7,8). We need more studies like it. Hopefully, some will show that the mythology was correct and the treatment really does work. However, treating people on the basis of inadequately tested hypotheses should be abhorrent to all good physicians, even if they are forced to practice this way until freed by science.

About 8 years ago, several groups of experts gathered to discuss the design of trials for CRT. No one had a strong rationale for which patients to select. Pioneers had developed the concept that QRS duration was a guide to ventricular dyssynchrony and used it as the basis to select patients for CRT (12,13). The sponsors of large trials have to balance innovation and wise investment. When the COMPANION (Comparison of Medical Therapy, Resynchronization, and Defibrillation Therapies in Heart Failure) (14) and CARE-HF trials (2,3,15,16) were conceived, there were only the results of the MUSTIC (Multisite Stimulation in Cardiomyopathies Study) trial to guide selection criteria

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Table 1 Various Definitions of Response Used in the CARE-HF Trial

	Patients With Events (%)		
	Medical Therapy (n = 404)	CRT Group (n = 409)	OR or HR (95% CI; p Value)
Survived without unplanned hospitalization for a major cardiovascular event*	180 (44.6%)	250 (61.1%)	HR: 0.63 (0.51–0.77), <0.001
Survived (including extension phase)	249 (61.6%)	308 (75.3%)	HR: 0.60 (0.47–0.77), <0.0001
Survived free of hospitalization for heart failure	203 (52.7%)	291 (71.1%)	HR: 0.54 (0.43–0.68), <0.001
Absence of treatment failure at study end†	198 (49%)	264 (64.5%)	OR: 0.52 (0.32–0.70), <0.0001
Components of the Treatment Failure Definition at Study End (Survivors May Have Contributed to More Than 1 Component)			
Survived but worse NYHA functional class	22 (5.5%)	10 (2.4%)	OR: 0.44 (0.20–0.98), 0.044
Survived but requiring increase of furosemide or equivalent by ≤40 mg/day	89 (22.0%)	57 (13.9%)	OR: 0.56 (0.39–0.82), 0.003
Survived but required new use of loop and thiazide diuretics in combination	18 (4.5%)	13 (3.2%)	OR: 0.67 (0.31–1.44), 0.301
Death	120 (29.7%)	82 (20.0%)	OR: 0.59 (0.42–0.82), 0.002
Mechanistic or Post-Hoc Definitions of Response in the CARE-HF Trial			
Reduction in LV end-systolic volume by >40 ml by 18 months (24)‡	18.6%	49.2%	<0.001
Patient report of MLWHFQ score ≤35 at 18 months (1)‡	166 (41.1%)	213 (52.1%)	OR: 0.64 (0.48–0.86), 0.002
Investigator-assigned NYHA functional class I/II by 18 months (1)‡	151 (37.4%)	255 (62.3%)	OR: 0.36 (0.27–0.48), 0.0001

*Death or unplanned hospitalization for a major cardiovascular event expressed as proportion with event at main study end; †a prospectively defined secondary end point in the CARE-HF (Cardiac Resynchronisation in Heart Failure) trial (2,3); ‡by this time 52 deaths had occurred in those assigned to cardiac resynchronization therapy (CRT) versus 75 deaths in those assigned to the control group. CI = confidence interval; HR = hazard ratio; LV = left ventricular; MLWHFQ = Minnesota Living With Heart Failure Questionnaire; NYHA = New York Heart Association; OR = odds ratio.

(17). There was a healthy discussion between scientific groups, each anxious to provide a high-quality trial but each hoping for a positive result. These committees had to identify patients at substantial risk of cardiac events to justify implanting, at some risk, a device of unknown value. A best-guess set of entry criteria was evolved. Unfortunately, once clinical trial entry criteria are used to formulate recommendations, they can become a barrier to progress because the concepts of an absence of evidence of an effect and evidence of absence of an effect are often confused. Despite considerable efforts, analyses of the CARE-HF study has failed, as yet, to identify a particular set of patient characteristics that lead to clinically important differences in treatment effect (18,19). The effect of CRT in CARE-HF was large, suggesting that, by chance, the precise criteria for response had been chosen or, more likely, that the entry criteria had excluded many patients who would have responded. We need further randomized trials to find out which of the inclusion and exclusion criteria applied in trials should be adopted into clinical practice. It is important to know who CRT does and does not help, but only randomized trials can deliver a secure answer in most cases.

For potentially curable diseases, such as infections, it is sensible to talk about response rates. Heart failure is not generally curable—yet (20). It is naïve to think that patients with heart failure neatly divide into responders and nonresponders. There will be a spectrum of response. Some patients will be harmed by CRT, for instance those that get an infected system. Others may derive no benefit because they are too sick or too well and others will have a good response, which in some cases can appear miraculous. As with most interventions in clinical practice, there will also be a placebo response. Intercurrent events further complicate attempts to predict the course of the disease. However, response is also time dependent. Some patients do not appear to respond initially but may respond later, at a time when ventricular function and symptoms would have deteriorated had they not had the device. Cardiac dyssynchrony is unlikely to be a fixed entity and probably varies, either in response to stress or as a function of disease progression (5,21–23). The benefit of CRT may not be predictable before implantation because the substrate on which it will act in the future is not yet present (23). Perhaps it is best to abandon attempts to define narrowly who will or will not benefit from CRT and focus instead on optimizing outcomes (and response) after implantation in all those that might benefit.

There is, as yet, no evidence that QRS duration, dyssynchrony, or left ventricular ejection fraction is relevant for selecting patients for CRT. The appropriate trials to find out have not been done. We can identify patients who have good outcomes without CRT and, therefore, do not need it and perhaps a group of patients (e.g., cardiogenic shock) who will do badly despite CRT. Everything else is guess work, which should not be good enough for us or our patients.

Analyses of CARE-HF, which is much larger than any observational trial, have struggled to identify anything that predicts the effects of CRT on morbidity, mortality, or quality of life. Indeed, dyssynchrony predicted a better prognosis regardless of assigned treatment possibly because such patients are more likely to have dilated cardiomyopathy and more viable myocardium, both of which are associated with a better prognosis (18,19). In observational studies of CRT implantation, patients with dyssynchrony will have a better outcome because they have a better intrinsic prognosis. Whether CRT has an additional benefit remains uncertain. Improvement in cardiac function 3 months after implantation of a CRT device is a good sign associated with a better outcome but explains very little of the long-term

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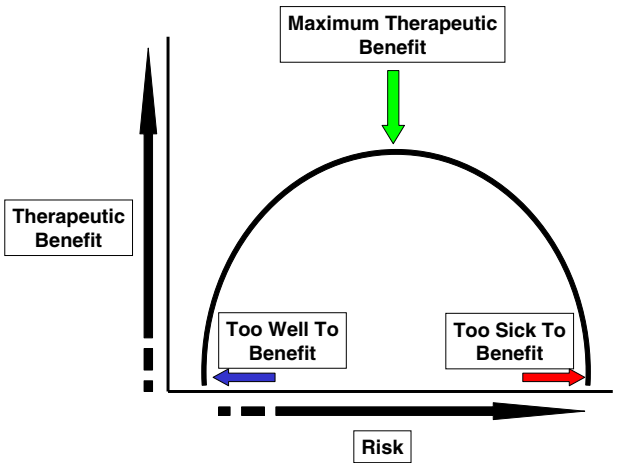

Figure 1 The Goldilocks Effect

When considering treatment for many diseases there will be some patients who are too well to benefit and will thrive without treatment and others who are too sick who will die despite intensive management. In between, there will be a group that obtains the maximum benefit from treatment. This may be likened to the story of Goldilocks, who found that 1 bowl of porridge was too hot, 1 was too cold, but another was just right. In more scientific terms, it might be called the risk–benefit parabola or optimal treatment window.

response to CRT (19). Patients with ischemic heart disease had less improvement in ventricular function than patients with dilated cardiomyopathy with CRT and they had a worse prognosis, but the change in prognosis caused by CRT was similar in patients with or without ischemic heart disease (24,25).

Of all the variables studied so far in CARE-HF, amino-terminal pro-brain natriuretic peptide (NT-proBNP) was the best baseline predictor of outcome (19), bettered only by NT-proBNP measured 3 months after randomization, but neither value predicted the long-term response to CRT. The absolute improvement in prognosis with CRT was similar in patients with values above and below the median NT-proBNP (26). Patients with relatively normal values of NT-proBNP have an excellent prognosis, and treatment with CRT may be deferred. On the other hand, patients who have extreme elevations of NT-proBNP have a poor prognosis. Although they may have a large response to CRT, the outcome is likely still to be poor, unless they are suitable for a heart transplant. The optimal response to treatment, that is, change in outcome, is to be expected among patients at intermediate risk with moderately elevated increases in NT-proBNP. Clinical trialists should restrain their instinct to enroll populations with high event rates in whom treatment response is often small. Far better to design trials that exclude patients at either extreme of risk who cannot benefit and find the "sweet-spot" associated with large treatment effects (Fig. 1).

In conclusion, the report of Mullens et al. (4) indicates that we should be very wary indeed in asserting whether or not a patient has responded to CRT. Observational data are usually hard to interpret and translate into clinical practice. For the time being, stick to the guidelines when selecting patients for CRT and optimize programming, particularly atrioventricular delay, for those patients who remain symptomatic after implantation. We must also ensure that we do not confuse outcome *with* treatment and *response to* treatment.

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REFERENCES

1. Cleland JGF, Freemantle N, Daubert J-C, Toff W, Leisch F, Tavazzi L. Long-term effect of cardiac resynchronisation in patients reporting mild symptoms of heart failure: a report from the CARE-HF Study. Heart 2008;94:278–83.
2. Cleland JGF, Daubert JC, Erdmann E, et al. Design and methodology of the CARE-HF trial. A randomised trial of cardiac resynchronisation in patients with heart failure and ventricular dyssynchrony. Eur J Heart Fail 2001;3:481–9.
3. Cleland JGF, Daubert J-C, Erdmann E, et al., for the Cardiac Resynchronisation–Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49.
4. Mullens W, Verga T, Grimm RA, Starling RC, Wilkoff BL, Tang WHW. Persistent hemodynamic benefits of cardiac resynchronization therapy with disease progression in advanced heart failure. J Am Coll Cardiol 2009;53:600–7.
5. Cleland JG, Cullington D, Khaleva O, Tageldien A. Cardiac resynchronisation therapy: dyssynchrony imaging from a heart failure perspective. Curr Opinion Cardiol 2008;23:634–45.
6. Cleland JGF. Is aspirin 'the weakest link' in cardiovascular prophylaxis. The surprising lack of evidence supporting the use of aspirin for cardiovascular disease. Prog Cardiovasc Dis 2002;44:275–92.
7. Greenberg HM, Dwyer EM Jr., Hochman JS, Steinberg JS, Echt DS, Peters RW. Interaction of ischaemia and encainide/flecainide treatment: a proposed mechanism for the increased mortality in CAST I. Br Heart J 1995;74:631–5.
8. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo—the Cardiac Arrhythmia Suppression trial. New Engl J Med 1991;324:781–8.
9. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;365:1503–16.
10. Coletta AP, Cleland JGF, Cullington D, Clark AL. Clinical trials update from Heart Rhythm 2008 and Heart Failure 2008: ATHENA, URGENT, INH study, HEART and CK-1827452. Eur J Heart Fail 2008;10:917–20.
11. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–59.
12. Auricchio A, Klein H. Multiple chambered pacing for treatment of congestive heart failure. Pacing Clin Electrophysiol 1995;18:750–1.
13. Daubert JP, Ritter P, Le Breton H, et al. Permanent left ventricular pacing with transvenous leads inserted into the coronary veins. Pacing Clin Electrophysiol 1998;21 Suppl:239–45.
14. Bristow MR, Saxon LA, Boehmer J, et al., for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50.
15. Cleland JG, Daubert J-C, Erdmann E, et al., CARE-HF Study Steering Committee and Investigators. Baseline characteristics of patients recruited into the CARE-HF study. Eur J Heart Fail 2005;7:205–14.
16. Cleland JGF, Daubert J-C, Erdmann E, et al., on behalf of the CARE-HF Study Investigators. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure {the Cardiac

Resynchronization—Heart Failure (CARE-HF) trial extension phase}. Eur Heart J 2006;27:1928–32.
17. Cazeau S, Leclerc C, Lavergne T, et al., Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873–80.
18. Richardson M, Freemantle N, Calvert MJ, Cleland JGF, Tavazzi L. Predictors and treatment response with cardiac resynchronisation therapy in patients with heart failure characterised by dyssynchrony: a predefined analysis from the CARE-HF trial. Eur Heart J 2007;28:1827–34.
19. Cleland JG, Freemantle N, Ghio S, et al. Predicting the long-term effects of cardiac resynchronisation therapy on mortality from baseline variables and the early response: a report from CARE-HF (Cardiac Resynchronisation in Heart Failure). J Am Coll Cardiol 2008;52:438–45.
20. Cleland JGF, Coletta A, Freemantle N, Velavan P, Tin L, Clark AL. Clinical trials update from the American College of Cardiology Meeting: CARE-HF and the Remission of Heart Failure, Women's Health Study, TNT, COMPASS-HF, VERITAS, CANPAP, PEECH and PREMIER. Eur J Heart Fail 2005;7:931–6.
21. Cleland JGF, Nasir M, Tageldien A. Cardiac resynchronization therapy or atriobiventricular pacing—what should it be called? Nat Clin Pract Cardiovasc Med 2007;4:90–101.
22. Chattopadhyay S, Alamgir F, Nikitin NP, Fraser AG, Clark AL, Cleland JG. The effect of pharmacological stress on intraventricular dyssynchrony in left ventricular systolic dysfunction. Eur J Heart Fail 2008;10:412–20.
23. Clark AL, Goode K, Cleland JGF. The prevalence and incidence of left bundle branch block in ambulant patients with chronic heart failure. Eur J Heart Fail 2008;10:696–702.
24. Ghio S, Freemantle N, Serio A, et al. Long term left ventricular reverse remodelling with cardiac resynchronization therapy. Results from the CARE-HF trial. Eur J Heart Fail 2009. In press.
25. Wikstrom GB, Lundqvist CB, Andren B, et al. The effects of aetiology on outcome in patients treated with cardiac resynchronization therapy in the CARE HF trial. Eur Heart J 2009. In press.
26. Fruhwald FM, Fahrleitner-Pammer A, Berger R, et al. Early and sustained effects of cardiac resynchronization therapy on N-terminal pro-B-type natriuretic peptide in patients with moderate to severe heart failure and cardiac dyssynchrony. Eur Heart J 2007;28:1592–7.

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