Editorial

Cardiac Resynchronization Therapy for Heart Failure
A Hammer in Search of Nails

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A number of randomized clinical trials have clearly established that cardiac resynchronization therapy (CRT) improves ventricular function and symptom status while reducing hospitalizations and mortality in heart failure patients with left ventricular ejection fraction (LVEF) ≤35% who have New York Heart Association class III or IV symptoms despite optimal medical management, are in sinus rhythm, and have evidence of ventricular electromechanical dyssynchrony.1 Because the outcomes for patients with heart failure remain poor despite maximal pharmacotherapy and because the magnitude of the benefits from CRT is similar to that reported for angiotensin-converting enzyme inhibitors and β-blockers, the rapid increase in CRT device implants in patients with heart failure over the past few years is not surprising.2 Although ongoing trials continue to test the efficacy and safety of CRT in patient groups who were underrepresented or excluded from prior trials, the CRT evidence base is evolving and following the well-established pattern of investigation for technological advances in which health services researchers follow the clinical trialists into an area to evaluate the uptake, effectiveness, and safety of new technologies when deployed in routine clinical practice. As a first step in this process, the study by Piccini and colleagues3 in this week’s Circulation examines who is, and who is not, receiving CRT in routine clinical practice.

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In their prospective cohort study of patients hospitalized for heart failure between 2005 and 2007 in 228 US hospitals participating in the American Heart Association’s Get With the Guidelines—Heart Failure Program, Piccini et al3 had access to detailed clinical information that permitted them to explore the predictors of CRT use. It should be noted that these patients (median age, 73 years; median LVEF, 35%) were well cared for: 87% of those with left ventricular systolic dysfunction were prescribed an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and 89% were prescribed a β-blocker, and 91% of smokers received smoking cessation counseling. Furthermore, patients receiving CRT in this cohort were more likely to receive evidence-based therapies such as β-blockers, aldosterone antagonists, and lipid-lowering therapy than those who did not receive CRT. After excluding patients with new-onset heart failure and those without LVEF assessments, Piccini et al3 found that 12% of 33,898 heart failure patients were discharged with a CRT in situ and that patients were less likely to have a CRT device implanted if they were black (odds ratio [OR], 0.45; 95% CI, 0.36 to 0.57), were from the Northeast (OR, 0.40; 95% CI, 0.30 to 0.53, compared with the West), were older (OR, 0.56; 95% CI, 0.48 to 0.65, for patients >70 years of age), or had comorbidities such as chronic renal disease, diabetes, pulmonary disease, or cerebrovascular disease (OR, 0.33 to 0.73).

It would not surprise any reader of health services literature to learn that CRT use varied widely between hospitals, across geographic regions, and between patient subgroups.4 Nor would readers be surprised by the finding that CRT recipients in clinical practice are older and have more comorbidities than the participants in the CRT trials.2,5 Moreover, the finding by Piccini et al3 that higher-risk patients (ie, older patients or those with comorbidities) were less likely to receive CRT is a theme that often emerges in health outcomes research.6 However, in this case, it could be argued whether this truly is another example of the frequently quoted “risk-treatment mismatch” or merely a case of physicians appropriately reserving an expensive therapy like CRT for patients who are less likely to die of competing noncardiac risks.

Although only 12% of the patients with chronic heart failure had CRT, it is impossible to judge the appropriateness of CRT use in their cohort because Piccini and colleagues did not have access to their patients’ ECGs (to measure QRS duration), echocardiograms (to evaluate for echocardiographic parameters of mechanical dyssynchrony), or New York Heart Association functional class. In addition, because this study was limited to therapy at hospital discharge, we do not know how many patients subsequently received CRT during outpatient follow-up. Moreover, we do not have any idea how many patients were offered CRT but declined the invasive procedure to implant the device.7 Without these 5 crucial pieces of information, we cannot determine whether CRT is being underused in this cohort of heart failure patients, nor can we draw any firm conclusions from the observed differences in CRT usage rates between blacks and whites, men and women, or patients from different regions of the country. The question of how many heart failure patients are eligible for CRT thus remains unresolved, with estimates still ranging between 1% and 14%.8,9 This important question needs to be addressed for those charged with cardiovascular healthcare planning and should be a research priority.
Piccini and colleagues’ finding that 10% of patients with a new CRT had an LVEF $>35\%$ before implantation (and 6% had an LVEF $\geq 40\%$) draws attention to the potential overuse of CRT in some patient groups because this therapy is currently recommended only for patients with LVEF $\leq 35\%$ as a result of a lack of randomized trial data in patients with preserved systolic function. Although it is possible that some of the CRT implants in patients with less severe systolic dysfunction were done prophylactically (to avoid worsening systolic function in patients who required a right ventricular pacemaker for bradyarrhythmias), the 10% proportion is sufficiently high to raise the specter of “indication creep” for CRT.

Indication creep refers to the use of an intervention for off-label indications. In the case of CRT, implantation in patients with preserved systolic function does not meet current guideline recommendations. The off-label rates for CRT reported by Piccini and colleagues are consistent with studies of other cardiovascular technologies (such as percutaneous transluminal coronary angioplasty or coronary artery bypass surgery), which reported that up to 14% of such procedures conducted in the United States were “inappropriate” (ie, not congruent with guideline indications). 

Indication creep is not unique to devices or technological interventions. A study of the IMS Health National Disease and Therapeutic Index found that 21% of all prescriptions (and 46% of prescriptions for antianginals, antiarrhythmics, and anticoagulants) were for off-label indications, with only 27% of these off-label prescriptions supported by any published evidence. 

Of course, such utilization is not necessarily inappropriate. Skilled clinicians frequently (and often quite appropriately) use clinical judgment in extrapolating beyond the limits of the published clinical trial data for individual patients. However, it should be acknowledged that off-label use for any intervention is not without potential risk. For example, although spironolactone was proved to reduce mortality by almost one third in patients with symptomatic, advanced systolic dysfunction in the Randomized Aldactone Evaluation Study (RALES) and was well tolerated by trial participants (1% excess risk of hyperkalemia), the rapid upswing in spironolactone prescribing after RALES was associated with a marked increase in hospitalizations and deaths from hyperkalemia. An exploration of spironolactone prescriptions in Medicare beneficiaries demonstrated that spironolactone prescribing increased after RALES by similar degrees in a wide variety of heart failure patients, regardless of their baseline renal function. As a result, 31% of all spironolactone prescriptions in 2001 (after publication of RALES) were for patients who would have been excluded from RALES because of their renal dysfunction or elevated potassium levels at baseline.

Of course, Piccini et al are not the first to document indication creep for a new technology or that the uptake of a new technology sometimes precedes the evidence for its efficacy and safety in some patient subgroups. For example, an analysis of coronary angiography after acute myocardial infarction in the Canadian province of Ontario found that the use of this technology began increasing nearly 1 year before the first positive randomized trial was published, and the subsequent rate of increase in the use of this technology in the 1990s mirrored the increases in catheterization laboratory capacity rather than changes in population demographics, prevalence, or severity of coronary disease or the evidence base. Similar data from the United States have confirmed the marked growth in the use of many cardiac technologies over the past decade and have shown that these temporal trends often appear to be driven largely by supply issues. In the words of those investigators, “areas that have higher rates . . . give more procedures to everyone, not just ideal candidates.” Although Piccini et al attempted to adjust for supply issues in their sensitivity analyses by using cardioverter-defibrillator implants as a proxy for the availability of implanting physicians at that site (and found that regional and interhospital differences persisted), future studies of CRT use should examine whether geographic variations in use are driven by variations in the availability of electrophysiology services (for both initial implant and subsequent follow-up).

If evidence and capacity are not the only factors driving the uptake of new technologies, what else is important? Leff and Finucane identified 7 aspects of human nature that encourage the use of new technologies and emphasized the common-sense appeal of many of these technologies, the “human love of bells and whistles,” and the fact that “surgical exploits are valued more highly than . . . diligent bedside care.” The influence of these factors should not be underestimated; the popularity of some technologies has increased even after negative trial evidence accumulated. For example, the use of directional coronary atherectomy increased after the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT) had demonstrated increased complications (including deaths and nonfatal myocardial infarctions), higher costs, and no clinical benefits, even in hospitals that had participated in CAVEAT.

In closing, the report by Piccini and colleagues from the Get With the Guidelines—Heart Failure Program demonstrating variations between geographic regions, hospitals, and patient groups in CRT use is a first step in examining the impact and implications of CRT in routine clinical practice. The key question that the Piccini et al study raises that remains unanswered is whether differences in rates of CRT use actually translate into differences in clinical and/or functional outcomes for our patients. Indeed, this question is really a proxy for the question that arises for any novel therapy after its efficacy and safety have been established in randomized trials: Will the benefit-to-safety ratio be preserved outside the confines of a clinical trial (ie, in a wider spectrum of patients, usually older and with a higher burden of comorbidities, cared for by less experienced providers working in lower-volume hospitals)? Piccini et al have drawn attention to potential indication creep in CRT use, and because CRT use in patients less likely to derive benefit will almost assuredly erode its benefit-to-safety ratio and undermine its cost-effectiveness, this is an important issue. Mark Twain cautioned that “to a man with a hammer, everything looks like a nail.” Although CRT may be the newest hammer added to our therapy toolkits, we should strive to remember that not all of our patients with heart failure are nails.
Sources of Funding
Dr McAlister is supported by salary awards from the Alberta Heritage Foundation for Medical Research, the Canadian Institutes of Health Research, and the Merck Frosst/Aventis Patient Health Management Chair at the University of Alberta. None of these organizations had input into the writing of this editorial.

Disclosures
None.

References

**Key Words:** Editorials  heart failure  pacemakers
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Circulation. 2008;118:901-903
doi: 10.1161/CIRCULATIONAHA.108.800722
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/118/9/901

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