Cardiac resynchronization therapy (CRT) has been shown to consistently improve cardiac performance and exercise capacity, leading to reversal of cardiac remodeling and improvement in survival in patients with advanced heart failure and a significant ventricular conduction delay. The strategy of CRT for the treatment of advanced heart failure was secured in 2005 by the landmark Cardiac Resynchronization Therapy in Heart Failure (CARE-HF) study.1 Recently, 2 studies have extended these observed benefits of CRT to patients with less advanced (New York Heart Association [NYHA] class I/II) signs and symptoms who still fulfilled standard indications for resynchronization therapy. The recently published Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) study demonstrated 34% relative risk reduction in death or heart failure events with CRT and defibrillator (CRT-D) compared with implantable cardioverter-defibrillator alone in 1820 subjects with left ventricular (LV) ejection fraction ≤30% and QRS duration ≥130 ms, which was largely driven by reduction in heart failure events and associated with reverse remodeling.2 Although the primary end point of a heart failure clinical composite response was not met in the Resynchronization Reverse Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial, observed improvement in the prospectively powered secondary end point of LV end-systolic volume index in the presence of CRT suggests that early implementation of CRT is feasible in mild heart failure (NYHA class I/II, LV ejection fraction ≤40% and LV end-diastolic dimension ≥55 mm by echocardiography, QRS duration ≥120 ms) may be considered a beneficial strategy.3 The article by St John Sutton and colleagues4 extends the concept of reverse remodeling of CRT by carefully examining the time course of reverse remodeling and identifying the subgroups that may have a particularly favorable response. The investigators now provide a more expansive analysis of the remodeling data, which is internally consistent and highly favorable. The authors go on to conclude that progressive LV remodeling can be prevented or even reversed by CRT in patients with mild heart failure with the use of resynchronization criteria to the same extent as in those with advanced heart failure, particularly in those with nonischemic etiology.

These findings are potentially very important and may have far-reaching implications for both patient care and healthcare costs. In particular, one has to consider that implantation of CRT is an invasive procedure with rare but sometimes serious periprocedural complications. Although some may argue that the present study population already in some cases fulfilled criteria for implantable cardioverter-defibrillator implantation, adding 1 or even 2 leads may extend procedural time and risks, as well as increase technical demands and the potential for inappropriate pacing. Currently, the CRT-D device has a retail price of $20 000 to $25 000. Meanwhile, sustained benefit in patients with advanced heart failure has been reported to be ≥70%, and patients’ disease may still progress despite effective CRT-D.5 This beneficial impact may likely diminish in less symptomatic patients with lower disease burden, particularly when it is considered that such devices have a measurable battery life. The overall lack of harm in the CRT group for both large studies is therefore reassuring, although a complete economic analysis may provide a stronger argument for adoption of such a strategy.

What kind of patient entered this trial? Investigators used the NYHA classification to determine who was in class I and class II. Although the NYHA classification is a revered and certainly time-honored system, it is notoriously qualitative and highly subjective. Distinguishing NYHA class II from class III patients is not so easy. On the other hand, few patients with such advanced degrees of cardiac dysfunction and dys synchrony may truly lack signs and symptoms when their functional capacities are assessed objectively. One also needs to understand that investigators are always under some pressure to find patients who meet study enrollment criteria. We also do not know how long these patients had experienced heart failure symptoms before enrollment. Nevertheless, there was robust blinding of patients and end point adjudication in REVERSE, and the ability to examine both CRT-ON and CRT-OFF settings provides the opportunity to distinguish acute hemodynamic augmentation versus long-term reverse remodeling effects.

Two findings in this echocardiographic analysis may have broader implications. First, the magnitude of LV reverse remodeling in the cohort of nonischemic patients appears to be larger than in their ischemic counterparts. This is in

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Cardiovascular Division, University of Minnesota, Minneapolis (G.S.F.), and Cleveland Clinic, Cleveland, Ohio (W.H.W.T.).

Correspondence to Gary S. Francis, MD, University of Minnesota Cardiovascular Division, 420 Delaware St SE, MMC 508, Minneapolis, MN 55455-0341. E-mail franc354@umn.edu
(Circulation. 2009;120:1845-1846.)
© 2009 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.109.902205
contrast to the observations from CARE-HF, in which there were no discernible differences in degree of reverse remodeling after 3 months of CRT versus no CRT, but is consistent with other prior studies with up to 12 months of follow-up. Although the extent of viable or scarred myocardium can be postulated as a contributor, one should not forget that ventricular conduction delay itself can be the primary etiology of cardiac dysfunction, and hence an intervention that directly corrects such conduction abnormality may negate the root cause of cardiomyopathy. Second, the graded increase in degree of improvement in LV volumes with increasing interventricular mechanical delays (particularly in those >40 ms) as well as increasing QRS duration (>140 to 160 ms) illustrates the larger impact of LV reverse remodeling, which is the primary benefit for CRT in this population, in those with more electric or mechanical dys synchrony. Taken together, one can even speculate that patients who present with an underlying conduction abnormality leading to progressive LV dilatation and systolic dysfunction may have more favorable responses to CRT than those who have progressive cardiac remodeling (eg, from a myocardial ischemic event) with corresponding emerging conduction delays secondarily due to LV dilatation, regardless of degree of symptoms. In other words, for a patient who is minimally symptomatic but with longstanding left bundle-branch block and progressive cardiac dysfunction, the impetus to consider early CRT may be stronger because the therapeutic indication may deter the underlying cause. However, it is often difficult to make such distinctions in the clinical setting, but at least the presence of a marked ventricular conduction delay (eg, QRS duration >150 ms as indicated in both subgroup analyses for MADIT-CRT and REVERSE) has been shown to be an important prerequisite for favorable CRT responses.

The investigators are to be congratulated for performing an important and meticulous analysis for the REVERSE trial. Is the study robust enough to change guidelines and therefore patient care? In the absence of mortality differences for both MADIT-CRT and REVERSE, a lingering question remains: Can early implantation of CRT, rather than deferring the procedure until more advanced symptoms ensue, effectively alter the natural history of disease progression to justify the cost and the risk? Convincing physicians as well as asymptomatic and mildly symptomatic patients to universally adopt CRT±D implantation may require a greater degree of confidence than provided by findings of this study alone. Clearly, the subgroup of patients who have shown consistent benefits was those with truly wide QRS duration and a nonischemic form of systolic heart failure. After all, a therapy that restores coordination of ventricular contraction among the cardiac chambers may best serve those who present with an underlying conduction delay even in the absence of advanced symptoms. The stakes here are high, and some have even argued that one should carefully weigh all of the collective data before changing practice guidelines or suggesting an alteration in clinical practice. The study by St John Sutton et al7 makes a strong case that nonischemic patients with mild heart failure, a reduced LV ejection fraction, and a wide QRS duration (>150 ms) should at least be considered for CRT. Particularly in those with higher propensity to reverse LV remodeling, these findings provide strong support for CRT especially if future studies with longer follow-up indicate a concomitant incremental clinical or mortality benefit. Beyond this possible new indication for selected patients, the argument for CRT in truly asymptomatic (NYHA class I) patients is less strong. We may not need to wait for long, as the Canadian Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT) is well under way and may provide additional important validation. One has the sense that the underlying biology can be changed by CRT. An improvement in the abnormal size and shape of the LV back toward control, if observed early in the course of the disorder, has perhaps the best chance of preventing progression and thus interrupting the natural course of systolic heart failure.

Disclosures
Dr Francis has served as a member of the Advisory Board for Novartis, Forest Pharmaceuticals, and Sanoﬁ-Aventis and has received honoraria for speaking from Boston Scientiﬁc Inc. Dr Tang has served as a consultant for Medtronic Inc and Merck & Co and has received research grant support from Abbott Laboratories.

References
Early Cardiac Resynchronization Therapy and Reverse Remodeling in Patients With Mild Heart Failure: Is It Time?
Gary S. Francis and W.H. Wilson Tang

Circulation. 2009;120:1845-1846; originally published online October 26, 2009; doi: 10.1161/CIRCULATIONAHA.109.902205
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 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/120/19/1845

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/