Should Cardiac Resynchronization Therapy Be Used in Patients With Class I-II Heart Failure and a Wide QRS?

Cardiac Resynchronization Therapy for Mild Heart Failure

The Time Has Come

Carl R. Reynolds, MD; Michael R. Gold, MD, PhD

Current guidelines recommend cardiac resynchronization therapy (CRT), previously known as biventricular pacing, in patients with left ventricular (LV) systolic dysfunction (ejection fraction [EF] ≤35%), QRS prolongation (>120 ms), and New York Heart Association (NYHA) class III or IV heart failure (HF). These recommendations come after multiple prospective, randomized trials demonstrated the benefits of CRT in advanced HF that included >6000 subjects. These initial trials targeted secondary prevention in the highest-risk cohorts, which was similar to the development of many other cardiovascular therapies. Such examples include implantable cardioverter-defibrillator (ICD) therapy initially used only for cardiac arrest survivors or lipid-lowering therapy restricted to use after myocardial infarction. Today a majority of patients receive these therapies as primary prevention. Thus, it is logical and not surprising that a therapy as successful as CRT would be evaluated in subjects with mild HF. Two such studies were published recently: the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study and the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT).2–5 Taken together, these trials randomized 2430 subjects with NYHA class I or II HF to CRT or to no CRT. The results show beneficial effects of CRT very similar to those observed for severe HF cohorts. Specifically, this therapy improves functional status, reduces HF hospitalizations, and promotes reverse remodeling. The results from REVERSE and MADIT-CRT provide strong, new support to expand the use of CRT to all patients with HF and a wide QRS.

Trials of CRT in Severe HF

Strong evidence exists to support the ability of CRT to cause LV reverse remodeling; specifically, decreased LV end-systolic volume (ESV) and end-diastolic diameter, increased LV EF, and decreased mitral valve regurgitation are observed.6 Most importantly, data also demonstrate reduction in HF hospitalizations and all-cause morbidity and mortality with long-term follow-up.7–9

Response by Tang and Francis on p 202

In the Multicenter In Sync Randomized Clinical Evaluation (MIRACLE) trial, severe HF patients were randomized to CRT plus optimal pharmacological therapy (OPT) versus OPT alone.9 Patients were required to have an EF ≤35% and QRS ≥130 ms for inclusion. NYHA class, quality of life score, 6-minute walk distance, and reverse remodeling were all significantly improved with CRT. Whereas the composite end point of death or worsening HF requiring hospitalization was more favorable with CRT versus OPT (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.37 to 0.96),
all-cause mortality did not differ significantly between groups (HR, 0.73; 95% CI, 0.34 to 1.54).

In the Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure (CARE-HF) trial, NYHA class III or IV patients were randomized to CRT plus OPT versus a control group of OPT alone. Secondary end points of LV reverse remodeling significantly improved in the intervention group. Likewise, the primary composite end point of death or unplanned hospitalization for a cardiovascular event was significantly better with CRT (HR, 0.63; 95% CI, 0.51 to 0.77), confirming the findings from MIRACLE. The most important new result from CARE-HF, however, was that the composite end point difference was not driven solely by reduced hospitalizations. Mortality significantly improved with CRT (HR, 0.64; 95% CI, 0.48 to 0.85), but this was observed only with an extended follow-up (mean, 29.4 months).

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial was the largest seminal investigation of CRT in severe HF. A total of 1520 patients with NYHA class III or IV, EF ≤35%, and QRS ≥120 ms were randomized to OPT alone versus OPT plus either CRT with pacing alone (CRT-P) or a device with both CRT and implantable cardioverter-defibrillator capabilities (CRT-D). There was a significant 20% reduction in the primary end point (death or hospitalization from any cause) with either CRT-P or CRT-D. Compared with OPT, all-cause mortality was more favorably reduced with CRT-D (HR, 0.64; 95% CI, 0.48 to 0.86) than with CRT-P (HR, 0.76; 95% CI, 0.58 to 1.01). The demonstrated incremental benefit of an ICD in addition to biventricular pacing was a unique feature of the COMPANION study design.

**Early Trials of New Indications for CRT**

With such overwhelmingly positive results from CRT studies, including MIRACLE, CARE-HF, and COMPANION, subsequent clinical trials were designed to evaluate expanded indications for CRT. Two major targets for expansion were advanced HF patients with narrow QRS complexes (<120 ms) and patients with mild HF (NYHA class I and II).

The earliest studies to report outcomes of patients with mild HF were Cardiac Resynchronization Therapy for the Treatment of Heart Failure in Patients With Intraventricular Conduction Delay and Malignant Ventricular Tachyarrhythmias (CONTAK CD) and Effects of Cardiac Resynchronization on Disease Progression in Patients With Left Ventricular Systolic Dysfunction, an Indication for an Implantable Cardioverter-Defibrillator, and Mildly Symptomatic Chronic Heart Failure (MIRACLE ICD II). In CONTAK CD, CRT led to a greater degree of LV reverse remodeling across all classes of HF, even with NYHA class II. In MIRACLE ICD II, CRT plus OPT significantly promoted LV reverse remodeling compared with the control of OPT without CRT. Results of both trials proved encouraging and generated hypotheses for larger, more definitive studies.

Meanwhile, some investigators evaluated a different strategy for CRT expansion, employing it as a therapy for HF patients with narrow QRS. The Cardiac-Resynchronization Therapy in Heart Failure With Narrow QRS Complexes (RETHINQ) study enrolled NYHA class III patients with an EF ≤35%, a QRS <130 ms, and mechanical dysynchrony determined by echocardiography. All patients received the same device and were randomized to CRT-ON or CRT-OFF programming. The primary end point, change in peak VO₂, was not improved with CRT. The result of a prespecified analysis of patients with a QRS of 120 to 130 ms, however, showed a significant improvement in peak VO₂ with CRT. This suggests that electric dyssynchrony, as evidenced by QRS prolongation, may be necessary to realize the beneficial effects of CRT. Evaluation of CRT in Narrow QRS Patients With Mechanical Dyssynchrony From a Multicenter (ESTEEM-CRT) study further evaluated the role of CRT in patients with narrow QRS. Preliminary reports of this detailed hemodynamic and functional study showed no effect of CRT on acute or chronic measures.

The role of echocardiography, LV lead placement, and programmed pacing intervals on the response to CRT continues to evolve. However, despite the potential utility of these parameters to improve the response rate, the more consistent conclusion, dating back to the earliest investigations of CRT, remains that a prolonged QRS best predicts a positive response to CRT. Accordingly, the next generation of trials to expand the indications for CRT has tended toward minimally symptomatic and asymptomatic HF patients with a low EF and a wide QRS.

**REVERSE and MADIT-CRT**

**Trial Designs**

These studies used 2 clinical composite end points commonly used in CRT trials. The first is hospitalization for HF or all-cause mortality. Combining mortality with HF hospitalization has the effect of increasing event rate and avoiding any discrepancy with classifying terminal HF events; this is considered acceptable and is widely used in HF trials.

The clinical composite response is another commonly used end point. Patients are classified as improved, unchanged, or worsened, and the distribution is compared between randomized arms of the study. Secondary end points for these studies are chosen to reflect the physiological and anatomic changes associated with LV pacing: such examples include improvement of LV EF, LV ESV index, or LV ESV, exercise capacity, and clinical HF class. Most study designs also include a standard quality of life measurement tool. This end point is commonly used in HF pharmacological studies and was chosen by the REVERSE investigators because it added sensitivity in detecting a treatment effect.

The REVERSE study followed 610 patients for a maximum of 2 years. Inclusion criteria included an EF of ≤40%, a QRS duration ≥120 ms, and NYHA class I or II HF. All patients were implanted with a CRT device with or without...
ICD and were then randomized to CRT-ON or CRT-OFF. Patients in North America were randomized for 1 year, whereas those in Europe remained in their blinded, randomized assignment for 2 years. The reason for this unusual difference based on geography was due in part to regulatory concerns and for the need for longer-term health economic data. The primary end point was the percentage of patients with worsened clinical composite response. Patients were considered worsened if they died, had a HF hospitalization, crossed over to the other study arm because of HF, or moved to a more severe NYHA class. The prespecified and powered secondary end point was LV ESV index.

MADIT-CRT, on the other hand, enrolled 1820 patients for an average duration of 2.4 years. Subjects were required to have an EF of ≤30%, QRS duration of ≥130 ms, and NYHA class I or II heart failure. Patients were randomized to be implanted with either a CRT device with ICD (CRT-D) or an ICD only so that there was no blinding of randomized treatment arm. The primary end point was all-cause mortality or occurrence of first HF event, defined as either a hospital admission for HF or outpatient treatment of HF requiring intravenous therapy. A secondary end point, LV ESV, was also prespecified.

Populations Studied
REVERSE enrolled patients in North America and Europe at 73 centers. The average EF was 26.7±7%. Mean QRS was 153±22 ms, and 82% of patients were classified as NYHA class II.

MADIT-CRT also enrolled patients in North America and Europe (110 centers). Mean EF was 24±5%. Nearly two thirds of subjects’ QRS duration was >150 ms, and, similar to REVERSE, >80% of patients studied were classified as NYHA class II.

Results
In REVERSE, the primary clinical end point (the percentage of patients with worsened clinical composite score) did not meet statistical significance at 12 months. However, at 24 months, which was the predetermined duration of randomized study for the European cohort, the proportion of patients with worsened clinical response was statistically different. Of note, at 12 and 24 months there were significant differences in the more commonly used full distribution of clinical composite response as opposed to simply the percentage who worsened (Figure 1).

In the European cohort, 19% of patients in the CRT-ON group had a worsened clinical composite response versus 34% in the CRT-OFF group (P=0.01). LV ESV index was reduced by 27.5±31.8 mL/m² in the CRT-ON arm versus 2.7±25.8 mL/m² in the group without CRT (Table).

In MADIT-CRT, the primary end point reached statistical significance, as did the secondary end point of LV reverse remodeling. In the CRT-D group, 17.2% of subjects experienced death or a HF event, whereas 25.3% reached the primary end point in the ICD-only group (P<0.001). The Kaplan-Meier estimates of probability of survival free from
HF show the curves separating by ~6 months and continuing to diverge for the remainder of the study period (Figure 2). The secondary end point of LVESV decreased by 57 mL in the CRT-D arm versus 18 mL in the ICD-only arm (P<0.001), reiterating the prominent reverse remodeling effect of CRT observed in REVERSE (Table).

Importantly, MADIT-CRT was stopped early on the recommendation of the independent Data and Safety Monitoring Board. This occurred after a prespecified superiority boundary was crossed by the CRT-D group.

**Subgroup Analyses**

Several patient characteristics were associated with a more dramatic response to CRT in both MADIT-CRT and REVERSE. Subjects with wider QRS (>150 ms and >152 ms, respectively) showed a statistically significant benefit compared with the subjects with shorter QRS.18,19 In REVERSE, the clinical benefit was also significantly greater among nonischemic cardiomyopathy patients and the group with EF <27%. The MADIT-CRT investigators observed a greater response to CRT among women, but similar results were found among ischemic and nonischemic patients.

**Summary of Benefits**

The major statistically significant findings from these studies are a 41% reduction in risk of first HF event in MADIT-CRT and a 53% risk reduction in time to first HF hospitalization in REVERSE. Moreover, both trials show significant LV reverse remodeling with CRT (Table). Although an independent mortality benefit was not observed in either trial, the investigators set an ambitious goal for such a short follow-up period. The totality of evidence provides reason to view the results with optimism rather than dismissal. For example, hospitalizations for HF have been shown to correlate directly with HF mortality.22 In addition, LV reverse remodeling was shown in 1 study to be more accurate than clinical improvement in predicting mortality benefit with CRT.23 The significant results from REVERSE and MADIT-CRT therefore provide encouraging signs of a likely eventual mortality benefit from CRT.

**The Case for CRT**

CRT improves quality of life, promotes reverse LV remodeling, and markedly reduces HF hospitalizations in patients with LV dysfunction and QRS prolongation, regardless of severity of symptoms. HF weighs heavily on healthcare in the United States. This diagnosis has been implicated in >20% of hospitalizations of people aged >65 years. The incidence of the disease is estimated now at >550,000 cases per year, and the cost to treat all of these patients exceeds $33 billion in the United States alone.24,25 Asymptomatic LV dysfunction is believed to be as common as symptomatic HF.26,27 Clearly, the opportunity exists in this very large population of patients to offer a new, effective therapy to slow or prevent an insidious slide toward worsened quality of life and eventual death.

Despite the compelling data, there are several potential objections to implementing CRT in mild HF. These include the lack of mortality benefit observed in REVERSE and MADIT-CRT, the perceived excessive cost of the treatment, and the added complexity of LV lead implantation.

**The Issue of Mortality**

Whereas a mortality benefit with CRT was demonstrated in CARE-HF, this has not yet been shown in mild HF. There are several possible reasons for this discrepancy. Mortality was low in these trials, and follow-up was relatively short. In REVERSE, the maximum follow-up period was 24 months; this was in the European cohort, in which the death rate was 5.7% with CRT-ON and 8.6% with CRT-OFF (HR, 0.40; P=0.09). In MADIT-CRT, follow-up occurred through an average of 2.4 years. The death rate was 6.8% in the CRT-D group and 7.3% in the ICD-only group (HR, 1.00; P=0.99). CARE-HF, in contrast, followed patients for a mean of 29.4 months. In the cardiac resynchronization group, 82 deaths occurred compared with 120 in the medical therapy group (20% versus 30%; P<0.002). However, of probably even greater importance is the control group in these studies. In CARE-HF, the control population was

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**Table. Comparison of Echocardiographic Indicators of Reverse Remodeling**

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>MIRACLEIII</th>
<th>CARE-HFII</th>
<th>REVERSEV</th>
<th>MADIT-CRTIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time interval of follow-up, mo</td>
<td>6</td>
<td>18</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Improvement in EF, %</td>
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<td>28</td>
<td>25</td>
<td>46</td>
</tr>
<tr>
<td>Change in LV ESV, %</td>
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<td>25</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>Change in LV EDV, %</td>
<td>12</td>
<td>Not available</td>
<td>23</td>
<td>21</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; EF, ejection fraction; LV, left ventricular; ESV, end-systolic volume; EDV, end-diastolic volume.

*Data from the European cohort of REVERSE.

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**Figure 2.** Kaplan-Meier estimate of the primary end point of MADIT-CRT. Survival curves separate early in follow-up and continue to diverge, with CRT-ICD conveying a significant benefit compared with ICD only.
treated with optimal medical therapy and no device, whereas all control patients in MADIT-CRT and >80% in REVERSE had ICD therapy, which, by itself, reduces mortality. Thus, it is not surprising that a survival benefit was more easily demonstrated in CARE-HF. If, however, a mortality benefit is required before CRT is approved for mild HF, then a longer follow-up period, many more patients, and likely a control population without devices are needed. Such a study would be very costly and likely unethical.

It should be noted that an incremental mortality benefit of CRT in the presence of ICD therapy has never been demonstrated, even in severe HF. CARE-HF compared OPT with CRT-P with no ICD or CRT-D. In COMPANION, the only major CRT trial to include separate CRT-P and CRT-D arms, CRT-P reduced all-cause mortality by 24%, although this result narrowly missed statistical significance (P=0.059), CRT-D reduced mortality by 36% (P=0.003). This study did not formally compare the 2 device arms with each other, and the differences between arms were small, and therefore this question remains unanswered.28 Although an ICD and biventricular pacemaker reduce mortality in HF via different mechanisms, we do not know the degree of effect overlap. Unless a trial is designed to randomize eligible HF patients to either an ICD or CRT-P, this will also remain an uncertainty. Requiring a mortality benefit, therefore, is arbitrary at best. At worst, it can be viewed as a misguided attempt to keep healthcare costs down without the support of scientific evidence.

The Vital Question of Cost
The current healthcare environment puts an emphasis on the cost of treatment, and cost analysis is increasingly utilized when new therapies are evaluated. A cost-effectiveness analysis of CRT in COMPANION estimated the 7-year expense of CRT without ICD at $59 900. Adding ICD capability increased the price to $82 200.29 A cost analysis from the Sudden Cardiac Death in Heart Failure Trial data gives a cumulative 5-year estimate of a single-chamber ICD at $61 938,30 but these amounts are only part of the consideration. Because a major benefit of CRT is quality of life, a more comprehensive measure would be the quality-adjusted life-year (QALY) gained. The same COMPANION analysis places a cost-effectiveness ratio of CRT-P at $19 600 per QALY added. CRT-D, on the other hand, looked much less attractive in this analysis, costing $160 000 per QALY gained.29 As a general rule, a cost <$50 000 per incremental QALY is considered acceptable in the United States, whereas estimates >$100 000 may be viewed as too expensive to justify.31

This analysis was performed from COMPANION data, which, of course, enrolled NYHA class III and IV patients. How the estimates would shift when similar analyses from the REVERSE or MADIT-CRT data are performed is a matter of speculation. Although the initial cost of CRT is substantial, if it effectively halts an insidious disease process, it would have a long period of relatively inexpensive therapeutic utility that would offset the initial price. Predicting the cost of a therapy with a more distant time horizon is especially influential when the resource outlay is highly skewed toward the extreme of the time period studied, as is the case with CRT. The most important variables influencing the cost-effectiveness of ICDs in an analysis of MADIT-II data were cost of implantation and the time duration of the mortality benefit.32,33 In MADIT-II, the number needed to treat to save 1 life was 17 at 20 months, but it fell dramatically by 96 months to a number needed to treat of 6.34 This analysis of MADIT-II used outcomes data of up to 15 years’ duration, with which they created a survival model to predict cost. At the extremes of the spectrum, they estimated a cost-effectiveness ratio for an ICD in the MADIT-II population to be $367 000 at 3 years versus $67 800 per life-year gained at 15 years. The cost of initial device and lead implantation had the greatest effect on reducing cost in this analysis. This overall cost pattern could be expected to be similar in studies of CRT in mild HF. Given the low mortality in mild HF compared with advanced HF, the cost-effectiveness ratio of CRT should continue to improve with extrapolation to longer follow-up because a greater number of patients can be expected to survive longer. Such an extrapolation can be done with the use of a disease simulation model, saving the time and expense of the particularly long randomized controlled trial that would be required.

A preliminary report of the first such analysis was made by Linde and colleagues.35 They used data from the European REVERSE cohort and made use of regression analysis to predict survival over time. The authors found that the CRT-ON group gained 0.94 life-years or 0.80 QALYs compared with the CRT-OFF group at 24 months. Their cost-effectiveness analysis puts the value of this at €14 278 per QALY added. With contemporaneous exchange rates, this equates to $18 543 per additional QALY, nearly identical to the $19 600 quoted by the analysis of COMPANION by Feldman et al.29 This amount is highly favorable by current standards and provides strong support for the use of CRT in NYHA class I and II HF.

Experts have asked, “Can the money for CRT in mild HF be better spent elsewhere?”36 Asking this question argues for an alternative to CRT. What is this alternative? Does it lie in prevention efforts: treating risk factors like hypertension, diabetes mellitus, and elevated cholesterol? This approach has already been implemented with the use of medicines such as statins, angiotensin-converting enzyme inhibitors, and β-blockers in patients with as early as stage A HF (patients without symptoms or structural cardiac changes but with risk factors for developing HF). The perception that CRT is too expensive stems partly from the high initial cost of the devices paired with the fact that a mortality benefit has not yet been fully realized in clinical trials. CRT used for mild HF is in a unique position because it does not result in immediate prolongation of life like ventricular assist devices or heart transplantation, yet it requires a much larger immediate investment than noninvasive therapies like medications. OPT used very early in HF may eventually cost as much as or more than CRT in mild HF, but the cost is amortized over
a long period. CRT, on the other hand, requires a high initial investment, but the cost becomes more favorable as the investment matures.

The most obvious alternative to CRT in mild HF is simply not employing the therapy until the disease advances to severe, symptomatic disease. A cost comparison between CRT in mild versus severe HF has not been performed, but major variables that would need to be considered include both the advantages with earlier implantation (eg, averted HF hospitalizations and added QALYs) and the disadvantages (eg, added procedures over a lifetime and morbidity from procedural complications).

As stated previously, the cost per QALY gained becomes more favorable with longer survival, but the lifetime cost per patient increases. Both cost per QALY gained and lifetime cost could be more favorable, and any cost analysis needs to acknowledge that current costs and device longevity averages are not immutable. As an example, if device lifespan improves with a larger battery, the cost of the therapy decreases. The incentives for developing and implanting more durable and less expensive devices are often not in place, however.37

Lead dislodgement, infection, and other complications add to the cost. The REVERSE investigators reported a 10% LV lead-related complication rate, whereas the MADIT-CRT authors reported a need to reposition the LV lead in 4.0% of subjects. With improved techniques and equipment, this rate could be expected to fall. Implanting patients earlier in the disease process would subject larger numbers of relatively more functional patients to procedural morbidity. However, lower device implantation complication rates have been observed in milder structural heart disease compared with more negatively remodelled hearts, and this might offset, to some degree, added procedural risk in the population of mild HF patients.38

NYHA class has long served as a clinical indicator of disease severity in HF, and CRT trials have used this measure to initially study patients presumed to have the most to gain, followed only recently by MADIT-CRT and REVERSE. The results of these 2 trials suggest that using NYHA class might have major limitations when it comes to the complex task of apportioning healthcare resources because the outcomes are not dramatically different from the results in CARE-HF and MIRACLE (Table). Skeptics, however, suspect that the patients in the 2 trials of mild HF patients may have been more symptomatic than the authors claimed and that they were, in fact, similar to the patients from the trials of severe HF. These critics suspect that subjects tended less toward NYHA class II and more toward NYHA class III, a transition associated with dramatically worse prognosis. REVERSE and MADIT-CRT have been further criticized for not requiring an objective assessment of NYHA class such as V̇O₂max. Evidence against this claim of a “stacked deck,” however, can be found in the baseline measures of functional status and overall mortality in both trials, as mentioned previously. Rates in both trials are comparable or even lower than published epidemiological data.22,39 NYHA class is notoriously difficult to standardize and furthermore has been shown to be a poor predictor of future cost in patients with LV dysfunction and recent myocardial infarction.25 However, 6-minute walk times and quality of life indicators are consistent with mild HF. The Kansas City Cardiomyopathy Questionnaire has been shown by Chan et al25 to more accurately identify HF patients likely to be high utilizers of health resources in the future. Utilizing more sophisticated yet accessible tools such as the Kansas City Cardiomyopathy Questionnaire instead of NYHA class might prove to hold great utility, potentially streamlining the delivery of a limited resource to patients with the most to gain, patients who, by extension, are the ones who would make CRT as economically advantageous as possible.

**Conclusion**

The recent studies of CRT in mild HF show comparable reverse remodeling, improvement in clinical response, and reductions in hospitalizations to those observed with more severe HF. On the basis of these observations, CRT should be utilized more widely and is appropriate for NYHA class I and II patients. Mortality benefits have not yet been realized, but this is due to too short follow-up periods in a lower-risk population. Criteria for biventricular pacing should be based on EF and ECG parameters alone; no other subgroups have consistently seen a marked benefit from CRT. Degree of symptoms has not proven to be a reliable predictor of response to CRT. Additional predictors of risk and resource utilization might help to target appropriation of CRT. Because CRT has clearly been shown to reduce hospitalizations in mild HF, this might lead to significant societal cost savings. Cost analyses have not yet been published but will soon support the argument that CRT can recoup much of its cost in early HF (if given time) and provide a great long-term return on investment.

**Disclosures**

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**References**


Response to Reynolds and Gold

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The ability of clinicians “to apply the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of the individual patient” does not equate to an approach of blindly following the inclusion and exclusion criteria from successful randomized controlled trials. One must weigh the risks and benefits that one may encounter in everyday clinical practices. It is not a matter of debating whether cardiac resynchronization therapy can restore synchrony and provide potential benefits. It does. The larger unknown is whether such broad inclusion criteria provided by the published trials have expanded beyond a finite patient population and may therefore yield lower benefits. The number-needed-to-treat calculation is likely vastly different among different subgroups. In other words, those with more consistent findings of clinical and biological improvements with cardiac resynchronization therapy (like QRS ≥150 ms, New York Heart Association functional class II) are more likely to provide greater confidence for clinicians to justify this otherwise invasive and costly intervention—a viewpoint now shared by our European colleagues according to their latest guideline recommendations. Any expansion of this doctrine will benefit from more experience, more clinical and mechanistic observations, and further investigations.
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