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From Medscape Education Cardiology

Cardiac Resynchronization Therapy: Earlier Identification and Intervention in Heart Failure CME

Kenneth A. Ellenbogen, MD

CME Released: 04/28/2011; Valid for credit through 04/28/2012

The following test-and-teach case is an educational activity modeled on the interactive grand rounds approach. The questions within the activity are designed to test your current knowledge. After each question, you will be able to see whether you answered correctly and will then read evidence-based information that supports the most appropriate answer choice. Please note that these questions are designed to challenge you; you will not be penalized for answering the questions incorrectly. At the end of the case, there will be a short post-test assessment based on material covered in the activity.

Patient History

A 58-year-old black man with heart failure was referred to the cardiology clinic for additional evaluation and treatment. He initially presented to his primary care physician 2 years ago with progressive dyspnea on exertion and orthopnea. Pulmonary edema was noted on physical examination, and he was diagnosed with heart failure. He was prescribed metoprolol, a diuretic, and an angiotensin-converting enzyme (ACE) inhibitor and noted significant improvements over the ensuing 3 months.

He had remained well until recently when he presented to his primary care physician with progressive exertional dyspnea and worsening pulmonary edema. He was hospitalized for a heart failure exacerbation and treated with more aggressive diuresis. On discharge, he was referred to a cardiologist for further evaluation and treatment.

At the time of referral, the patient reported that he had improved significantly since his recent hospitalization. He is now able to walk up to 1 mile on level ground at a slow-to-moderate pace but had to stop several times due to dyspnea. He denied chest pain or significant orthopnea. He had never been hospitalized for heart failure prior to this recent exacerbation. On examination he appeared well and was in no acute distress, and no obvious dyspnea was noted while speaking or walking from the waiting room. Auscultation of his lungs and heart revealed scattered bibasilar crackles and a II/VI holosystolic murmur at the left lower sternal border radiating to the apex. An S3 was present, but no right or left ventricular heave was appreciated. Minimal jugular venous distention was present while supine. Trace pitting edema was noted to the ankles in both lower extremities.

On laboratory testing, his electrolytes were within normal limits; he had preserved renal function; and the B-natriuretic peptide (BNP) level was 150 pg/mL. ECG was ordered and notable for a left bundle branch block (LBBB) and a widened QRS complex of 150 msec (Figure 1). The PR interval was 162 msec; QT/QTc 404/496 msec; P-R-T axes 48, -5, 122; and possible left atrial enlargement was evident.

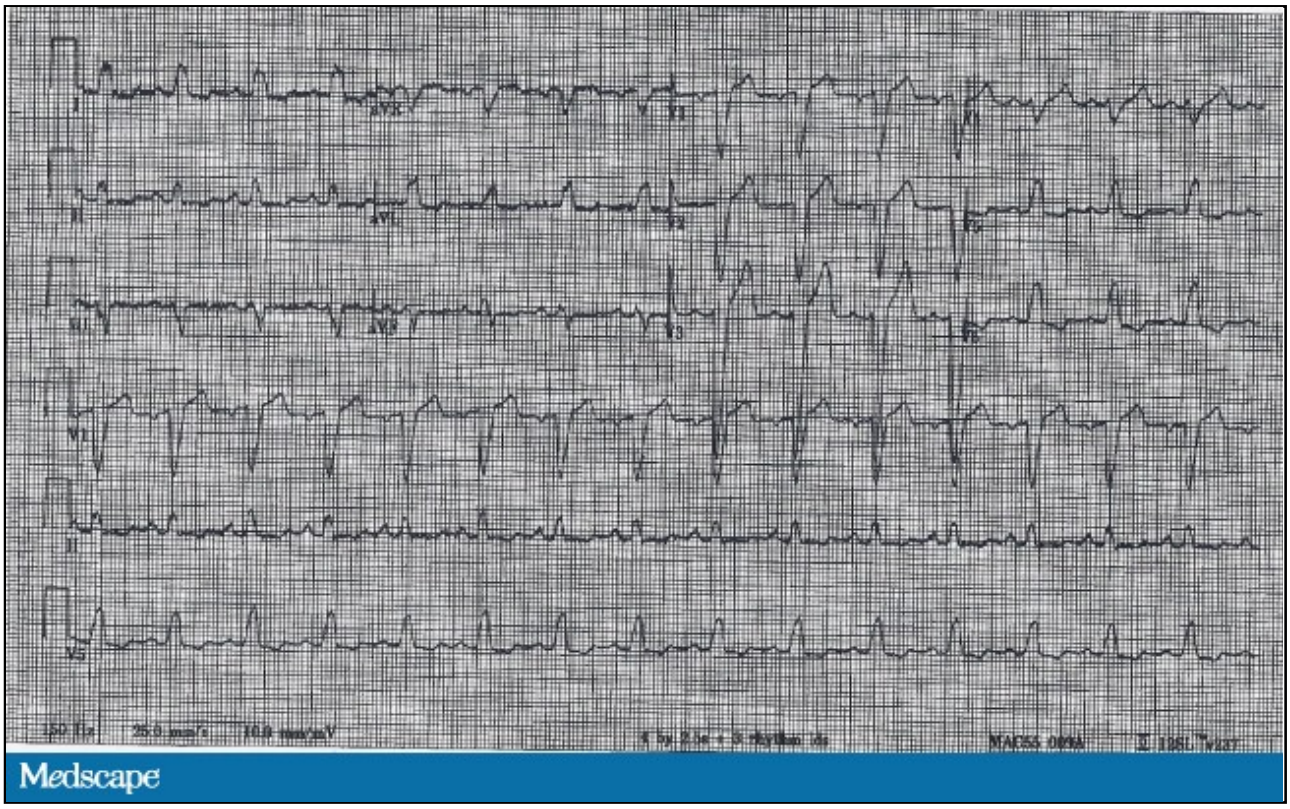

Figure 1. The patient's ECG.

Case

Given the reported symptoms, what is this patient's New York Heart Association (NYHA) functional class?

- Class I
- Class II
- Class III
- Class IV

Save and Proceed

Heart failure is the result of impaired cardiac function from numerous etiologies, the most common of which is coronary ischemia. It is associated with significant impairments in quality of life and decreased survival rates.[1-5] The prevalence is steadily increasing, and heart failure is the fastest-growing cardiovascular diagnosis among Americans.[2,3] In 2006, the American Heart Association (AHA) estimated that 5.8 million people in the United States had heart failure.[2,5] The increasing burden of disease is largely the result of the aging population and advancements in cardiac surgery, interventional procedures, and medical therapies that have prolonged survival in patients with cardiac ischemia.[1,3]

Heart failure is a clinical syndrome hallmarked by a diminished exercise tolerance and capacity due to dyspnea and/or fatigue that is not better explained by other medical disorders or toxicities from medications. Deconditioning and comorbid conditions are common and may contribute to these limitations and confound the clinical syndrome. It is useful to think of congestive heart failure as associated with primarily systolic or diastolic dysfunction. This

distinction is made on the basis of measuring the patient's ejection fraction (EF) with echocardiography.

Treatment recommendations are largely based on objective measures of the left ventricular ejection fraction (LVEF) and the degree of symptomatic functional limitations. The NYHA Functional Classification System is a widely used, well-validated tool to help risk-stratify patients on the basis of the degree of physical exertion required to illicit performance-limiting symptoms.[6] The American College of Cardiology/American Heart Association (ACC/AHA) guidelines include 4 stages of heart failure on the basis of the development and progression of the disease. This classification is intended to complement the NYHA Functional Classification System, which primarily categorizes the severity of a patient's symptoms (Table 1).

Table 1. NYHA Classification of HF With the ACC/AHA Stages in the Development of HF

NYHA Classification	ACC/AHA HF Stage
None	**A** At high risk for HF but without structural heart disease or symptoms of HF
Class I (mild) Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.	**B** Structural heart disease but without signs or symptoms of HF
Class II (mild) Patients with cardiac disease resulting in slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.	**C** Structural heart disease with prior or current symptoms of HF
Class III (moderate) Patients with cardiac disease resulting in marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitations, dyspnea, or anginal pain.	
Class IV (severe) Patients with cardiac disease resulting in inability to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.	**D** Refractory HF requiring specialized interventions

ACC/AHA = American College of Cardiology/American Heart Association; HF = heart failure; NYHA = New York Heart Association

Data from Hunt SA, et al[5]; Bennett JA, et al.[6]

Case (cont)

Treatment

The patient underwent further evaluation. An echocardiogram revealed mild mitral regurgitation and an EF of only 25%. Cardiac catheterization showed nonobstructive coronary artery disease. Serial blood pressure monitoring revealed adequate control. The patient espoused strict adherence to medical therapy and dietary salt restriction. Given his persistent symptoms despite treatment with an ACE inhibitor, a diuretic, and a beta-blocker, additional therapy was considered.

What agent would be a suitable addition to this patient's regimen?

- An angiotensin receptor blocker
- Isosorbide dinitrate
- Aldosterone antagonist
- Calcium channel blocker

Save and Proceed

The 2009 ACC/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults provide an evidence-based approach to the medical management of heart failure.[5] The majority of patients with heart failure should be routinely managed with a loop diuretic, an ACE Inhibitor, and a beta-blocker. This combination has been shown to improve the long-term prognosis in patients with heart failure.

ACE inhibitors should be recommended for all patients with reduced left ventricular function unless contraindicated. These agents reduce afterload and myocardial oxygen consumption and favorably affect cardiac remodeling. In patients with heart failure ACE inhibitors can reduce symptoms, improve clinical status, and enhance quality of life.[5,7-9] ACE inhibitors have also been shown to reduce the risk for death and the combined risk for death or hospitalization in patients with heart failure.[8.9] For those intolerant of ACE inhibitors, angiotensin receptor blockers should be used. Although using angiotensin receptor blockers in addition to ACE inhibitors theoretically would provide additional afterload reduction and remodeling, this practice should be avoided because this combination has not been shown to offer additional benefits and may be harmful.

Beta-blockers, specifically bisoprolol, carvedilol, or extended-release metoprolol, are recommended for all stable patients with heart failure and a depressed LVEF regardless of the underlying etiology. They should be used with caution or withheld in those in a decompensated state. The principle effect of beta-blockers is their inhibition of the sympathetic nervous system and blunting the effects of catecholamines. Their beneficial effects in patients with heart failure have been well studied and documented. Long-term treatment with beta-blockers has been shown to improve both symptoms and quality of life in patients with heart failure.[5,10-13] Similar to ACE inhibitors, beta-blocker therapy reduces the risk for hospitalization and death in patients with heart failure with or without coronary artery disease.[11]

Peripheral and pulmonary edema are common in patients with heart failure. Pulmonary edema is the result of left ventricular dysfunction and can cause or contribute to orthopnea, sleep fragmentation, and exertional dyspnea. Right ventricular dysfunction and pulmonary hypertension are manifested by peripheral edema. Patients with evidence of fluid retention (pulmonary edema or peripheral edema) should be placed on a sodium-restricted diet and recommended a loop diuretic until clinically euvolemic, and therapy should be continued to prevent the recurrence of fluid retention.[5,14,15] Diuretic therapy is effective in reducing jugular venous pressures, pulmonary congestion, and peripheral edema. Diuretic therapy has also been shown to improve cardiac function, symptoms, and exercise tolerance in patients with heart failure.[14,15] Monitoring of renal function and electrolytes is essential in all patients treated with diuretics.

Patients who remain symptomatic despite treatment with diuretics, ACE inhibitors, and beta-blockers require the addition of other agents. Digoxin can improve symptoms and exercise tolerance in patients with mild-to-moderate heart failure.[16] Isosorbide dinitrate may reduce the occurrence of nocturnal dyspnea and improve exercise tolerance in patients who have persistent limitations despite optimal medical therapy (OMT).[17] The combination of hydralazine and isosorbide dinitrate has been shown to reduce mortality in patients with heart failure, particularly in blacks.[17]

The addition of a low-dose aldosterone antagonist to a loop diuretic is recommended in selected patients with moderate or severe symptoms, especially in those with left ventricular dysfunction after myocardial infarction.

These agents have been shown to reduce hospitalizations and improve survival in patients with severe heart failure.[18,19]

Insertion of an implantable cardioverter-defibrillator (ICD) should be considered in patients with symptomatic heart failure who have a significantly reduced EF, especially in those with documented sustained ventricular arrhythmias, unexplained syncope, or prior cardiac arrest.[5] They are recommended as primary prevention against cardiac arrest and to prolong survival in patients with ischemic cardiomyopathies and an LVEF ≤ 35% who have persistent NYHA class II or greater symptoms despite OMT. These devices are also recommended for patients with good functional capacity and nonischemic cardiomyopathies in association with an LVEF ≤ 30% and persistent NYHA class II symptoms. ICDs are recommended as secondary prevention in patients with heart failure with depressed left ventricular function and a history of cardiac arrest, ventricular fibrillation, or hemodynamically unstable ventricular tachycardia.

Given the excessive mortality and morbidity in patients with heart failure, early detection and preventive measures are essential to improve clinical outcomes. However, despite improvements in medical therapy, survival remains limited.[1] As such, further interventions that can improve quality of life and prolong survival are crucial.

Case (cont)

An aldosterone antagonist was added to the patient's medical regimen. Despite an initial improvement in symptoms, he reported persistent functional limitations during a follow-up appointment. Although the patient reported symptoms consistent with NYHA functional class II limitations, he believed that this was adversely affecting his quality of life. Given his failure to improve despite OMT and his persistent symptoms, he was considered for cardiac resynchronization therapy (CRT) with a biventricular ICD.

Which of the following statements about the use of CRT in this patient with NYHA class II heart failure is correct?

- CRT is not recommended by the ACC/AHA/Heart Rhythm Society (HRS) for patients with NYHA class II symptoms and should not be used
- CRT has been shown to improve both hospitalization and quality of life in patients with NYHA class II heart failure
- Patients with NYHA class II heart failure derive less benefits from CRT than those with NYHA class III or IV symptoms
- CRT improves symptoms and survival in patients with heart failure regardless of their functional classification or duration of their QRS complex

Save and Proceed

The ACC/AHA/HRS recommends CRT as a class Ia indication for individuals with more advanced or more symptomatic heart failure. These recommendations were largely based on the findings of several large clinical trials. The majority of these trials limited enrollment to patients with NYHA functional class III or IV symptoms. However, CRT has been advocated in those with less symptomatic disease as a means to improve health and quality of life and potentially mitigate disease progression.

The REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial purposely enrolled patients with less symptomatic disease.[20] Patients with NYHA class I and II symptoms underwent implantation of biventricular pacing devices. Study participants were randomly assigned to either have the device turned on or off (CRT-ON or CRT-OFF). After 12 months, significant improvements in left ventricular function and dimensions were observed in those receiving CRT (Figure 2). In a subgroup analysis, it appeared that the greatest benefits occurred in those with QRS complexes > 150 msec. After 2 years, hospitalizations in the European cohort

due to heart failure were 62% less frequent in those in the CRT-ON group. The study authors also observed a trend toward reduced mortality in the treatment group. Death occurred in 5.7% of those in the CRT-ON group vs 8.6% in those in the CRT-OFF group (hazard ratio [HR], 0.40; *P* = . 09).[21]

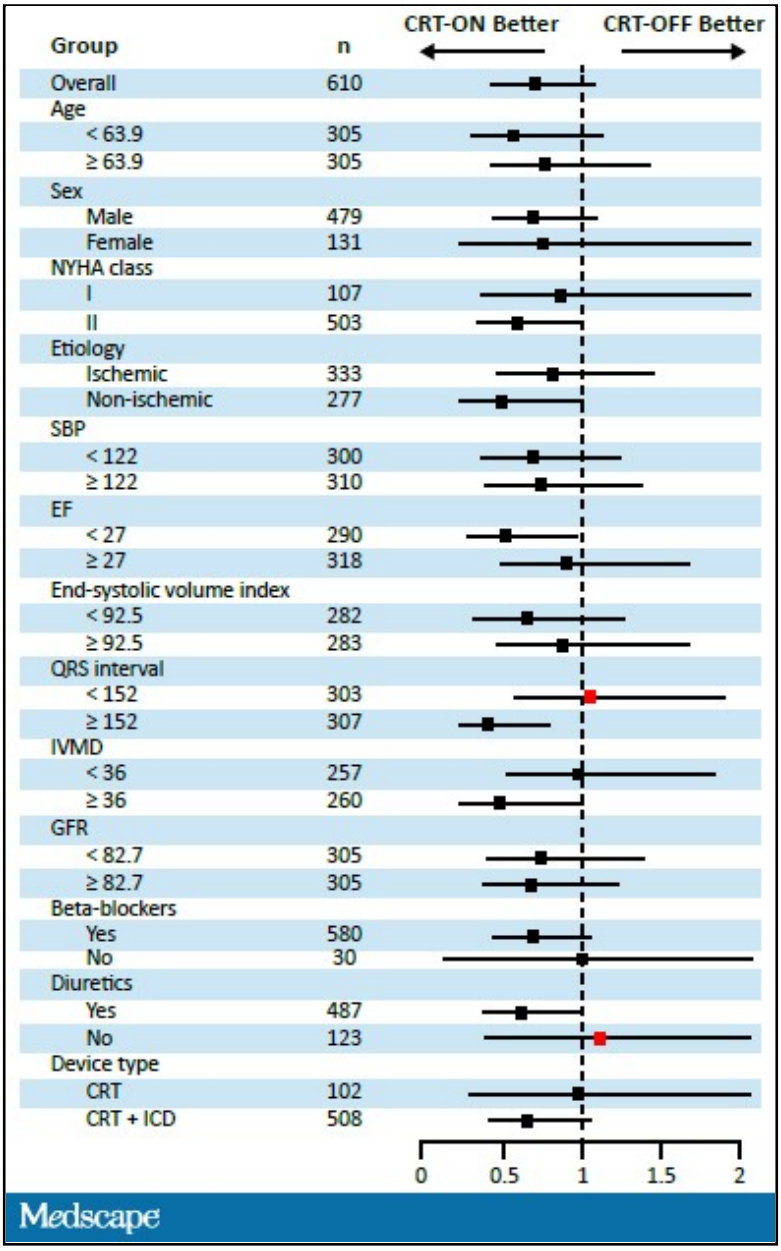

Figure 2. REVERSE: Heart failure clinical composite response.
Data from Linde C, et al.[20]

In the more recent MADIT-CRT (Multicenter Defibrillator Implantation Trial with CRT), 1820 patients with NYHA class I or II symptoms and an indication for an ICD were randomly assigned in a 3:2 ratio to receive an ICD or CRT with a biventricular defibrillator (CRT-D).[22] All enrolled participants had an EF ≤ 30% and a QRS duration ≥ 130 msec. The primary endpoint was death from any cause or nonfatal heart failure events, whichever came first (Table 2). After a mean follow-up of 2.4 years, the investigators found a 41% reduction in nonfatal heart failure events in the CRT-D group. Compared with an ICD alone, CRT was associated with a 3-fold improvement in LVEF and volume. Similar to the REVERSE trial, these benefits were largely confined to those with a QRS duration > 150 msec (Figure 3). No differences in mortality were noted between the 2 interventions. Following the publication of the MADIT-CRT results, the US Food and Drug Administration expanded the indications for CRT-D to include patients with LBBB and NYHA class II or ischemic class I heart failure with an LVEF < 30% and a QRS duration > 130 msec.[23]

Table 2. MADIT-CRT: Primary Endpoints

	ICD n = 731	CRT-D n = 1089	HR (95% CI)	*P* Value
Death or heart failure	25.3%	17.2%	0.66 (0.52-0.84)	.001
Heart failure	22.8%	13.9%	0.59 (0.47-0.74)	<.001
Death	7.3%	6.8%	1.00 (0.69-1.44)	.99

CI = confidence interval; CRT-D = cardiac resynchronization therapy-defibrillator; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; MADIT-CRT = Multicenter Defibrillator Implantation Trial with CRT
Data from Moss AJ, et al.[22]

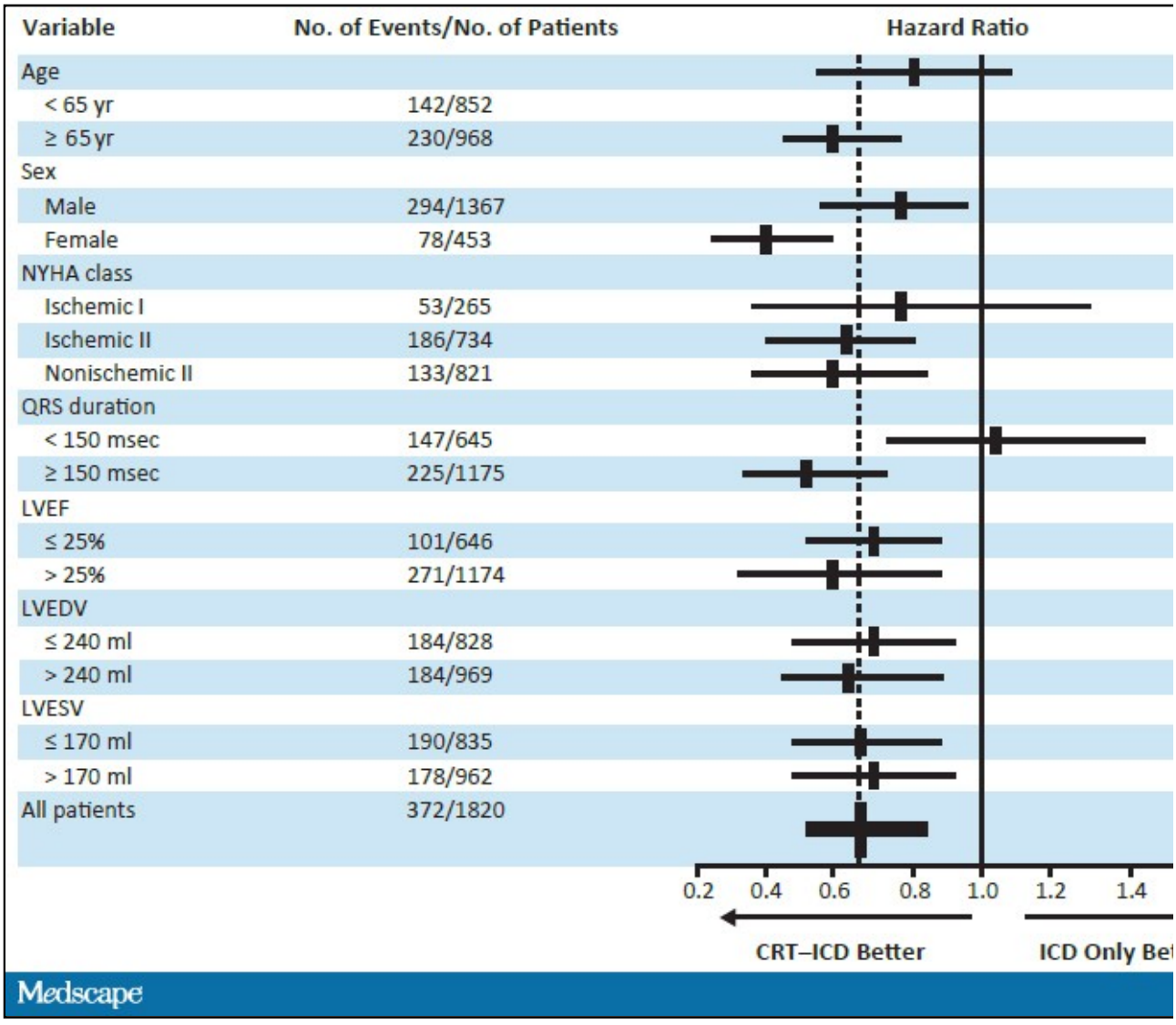

Figure 3. MADIT-CRT (Multicenter Defibrillator Implantation Trial with CRT): Risk for death or heart failure.
Data from Moss AJ, et al.[22]

RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial) investigated the effect of CRT in patients with mild-to-moderate heart failure.[24] In this trial, 1798 patients with NYHA class II or III heart failure, an

LVEF ≤ 30%, and a QRS duration ≥ 120 msec were randomly assigned to receive either an ICD alone or an ICD plus CRT. The primary outcome was death from any cause or hospitalization for heart failure. After a mean follow-up of 40 months, the primary outcome occurred in 33.2% of the ICD-CRT group and 40.3% of the ICD-only group (HR, 0.75; 95% confidence interval [CI], 0.64-0.87; *P* < .001). Mortality was significantly less common in the ICD-CRT group and occurred in 20.5% compared with 26.1% among those in the ICD-only group (HR, 0.75; 95% CI, 0.62-0.91; *P* = .003). Similarly, 19.5% of the ICD-CRT group were hospitalized for heart failure vs 26.1% in the ICD-only group (*P* < .001) (Table 3; Figure 4). The study authors concluded that the addition of CRT to an ICD reduced hospitalization for heart failure and improved survival among patients with NYHA class II or III heart failure.

Table 3. RAFT: Primary and Secondary Outcomes

	ICD n = 904	**CRT-D n = 894**	**HR (95% CI)**	***P* Value**
Primary Outcome				
Death from or hospitalization for heart failure	40.3%	33.2%	0.75 (0.64-0.87)	< .001
Secondary Outcomes				
Death from any cause	26.1%	20.8%	0.75 (0.62-0.91)	.003
Death from cardiovascular cause	17.9%	14.5%	0.76 (0.60-0.96)	.02
Hospitalization for heart failure	26.1%	19.5%	0.68 (0.56-0.83)	< .001

CI = confidence interval; CRT-D = cardiac resynchronization therapy-defibrillator; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; RAFT = Resynchronization-Defibrillation for Ambulatory Heart Failure Trial

Data from Tang AS, et al.[24]

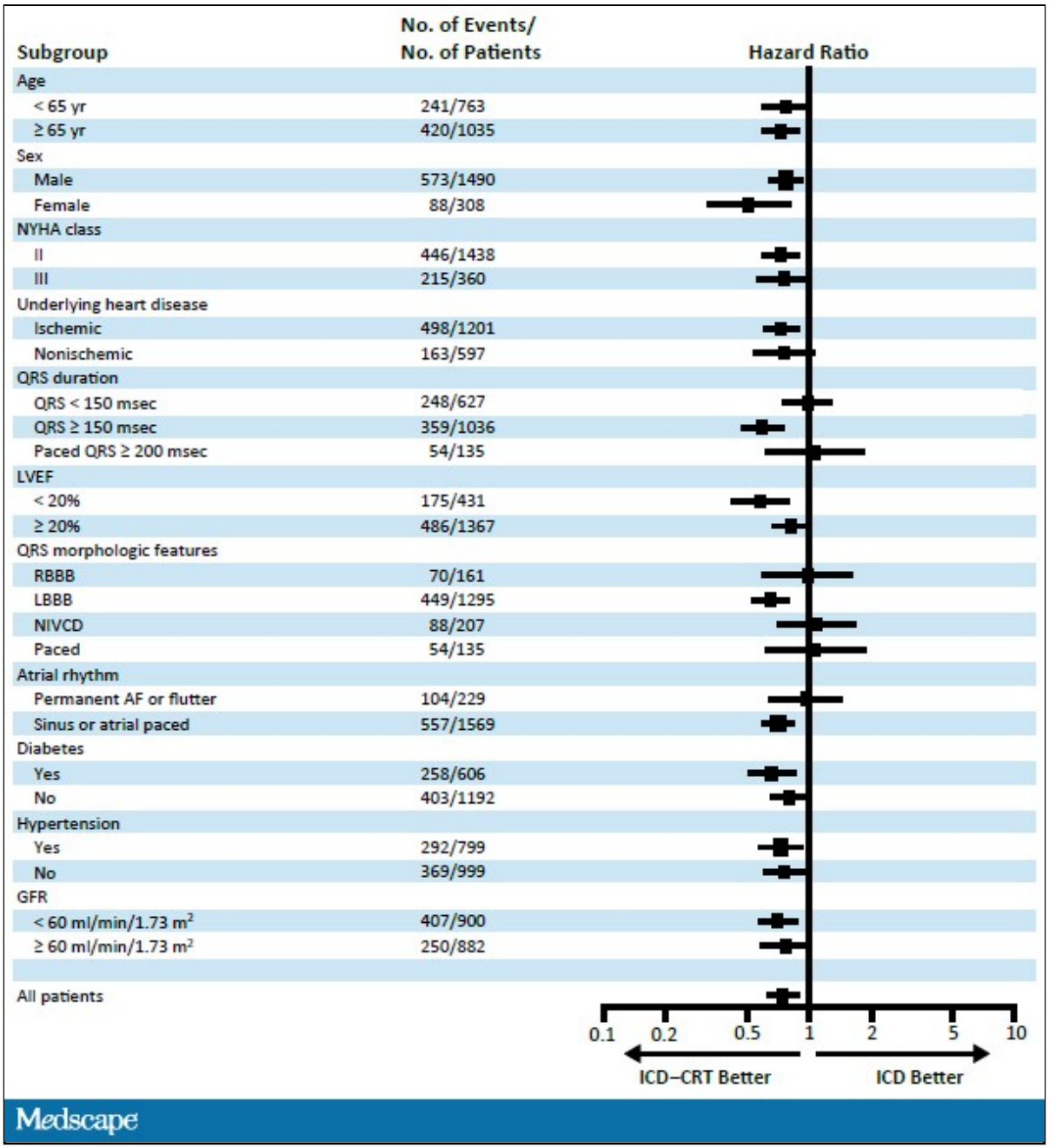

Figure 4. RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial): Subgroup analyses of death or hospitalization for heart failure.
Data from Tang AS, et al.[24]

Whether CRT can be used in a prophylactic role to mitigate disease progression and offer long-term improvements in clinical outcomes has yet to be determined. However, given the results of these trials, CRT appears to have a beneficial role in those with less symptomatic heart failure. Both symptoms and cardiac function were improved, and there is some evidence that CRT may portend improvements in survival. Although, as expected, it appears that these benefits are restricted to those with a widened QRS complex.

When discussing the potential benefits of CRT with this patient, which clinical benefit would be least likely?

- He is less likely to develop cardiac rhythm disturbances such as atrial flutter and atrial

fibrillation

- He can expect improvement in exercise tolerance
- He will feel better due to improved LVEF and cardiac hemodynamics
- He is less likely to be hospitalized for heart failure exacerbations and to live longer

Save and Proceed

CRT has become an increasingly used therapeutic option for patients with symptomatic heart failure despite OMT. CRT is performed by implantation of a biventricular ICD with leads attached to the right atrial and right ventricular endocardium and the left ventricular epicardium via the coronary sinus vein branches. CRT allows stimulation of both ventricles to facilitate simultaneous ventricular contraction and improving ventricular dyssynchrony.

When added to OMT, CRT has been shown to reduce both morbidity and mortality associated with heart failure.[20-33] CRT provides incremental benefits that significantly improve quality of life, functional class, and exercise capacity. CRT also improves cardiac function and hemodynamic and objective measures of functional capacity, including an increased peak oxygen uptake during exercise and improved 6-minute walk distances. In a recent meta-analysis, the use of CRT in patients with heart failure was associated with a 32% reduction in hospitalizations and a reduction of about one quarter in all-cause mortality.[31]

The results of 2 early clinical trials showing a positive benefit in symptomatic improvement and survival strongly influenced the current ACC/AHA/HRS guidelines for CRT.

The COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure) trial enrolled 1520 patients with NYHA functional class III and IV heart failure who had a QRS width ≥ 120 msec and an LVEF ≤ 35%.[28] All study participants were in sinus rhythm and had a PR interval > 150 msec. Patients were randomly assigned to 1 of 3 groups: OMT alone; OMT and CRT with a biventricular pacemaker (CRT-P); and OMT and CRT-D.

In this trial, both forms of CRT resulted in superior outcomes with CRT-D performing slightly better than CRT-P (Table 4; Figure 5). Specifically, mortality declined by 24% in those receiving CRT-P and 36% in those with CRT-D (*P* = .06). Similarly, hospitalizations decreased by 34% in the CRT-P group and 40% in those receiving CRT-D. Compared with OMT, the investigators observed marked reductions in all-cause cardiac and heart failure hospitalization rates with CRT with or without a defibrillator in patients with advanced heart failure.

Table 4. Results From the COMPANION Trial

	OMT	CRT-P	*P* [a]	HR (95% CI)	CRT-D	*P**	HR (95% CI)
Primary endpoint[b]	68%	56%	.014	0.81 0.69-0.96	56%	.010	0.80 0.68-0.95
Secondary endpoint[c]	19%	15%	.06	0.76 0.58-1.01	12%	.004	0.64 0.48-0.86
12-month death from or hospitalization for cardiovascular cause	60%	45%	.002	0.75 0.63-0.90	44%	< .001	0.72 0.60-0.86
12-month death from or hospitalization for heart failure	45%	31%	.002	0.66 0.53-0.87	29%	< .001	0.60 0.49-0.75

CI = confidence interval; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure; CRT-D = cardiac resynchronization therapy with a biventricular defibrillator; CRT-P =

CRT with a biventricular pacemaker; HR = hazard ratio
[a] *P* values vs OMT
[b]12-month death from or hospitalization from any cause
[c]12-month death from any cause
Data from Bristow MR, et al.[28]

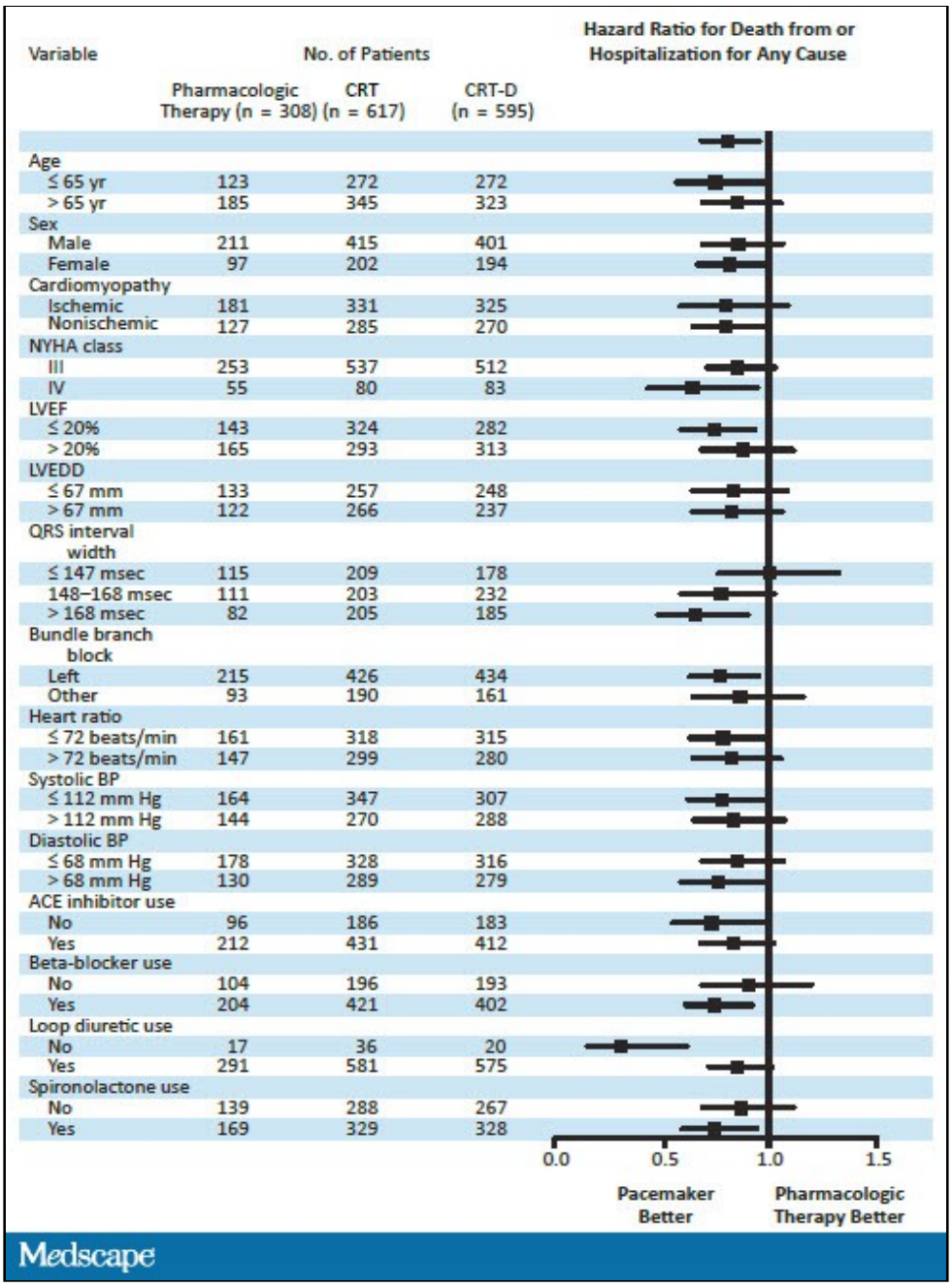

Figure 5. Hazard ratios for primary endpoint in COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure).
Data from Cleland JG, et al.[35]

In the CARE-HF (CArdiac REsynchronization in Heart Failure) trial, 813 patients with NYHA class III/IV heart failure, an EF ≤ 35%, and an enlarged left ventricular end-diastolic diameter were randomly assigned to OMT alone or OMT plus CRT-P.[26] Study participants were followed for 2.5 years. Similar to the COMPANION trial, all patients were in a sinus rhythm. A QRS duration of at least 120 msec was required for enrollment and for those with QRS duration > 120 msec but < 150 msec, 2 of an additional 3 criteria for ventricular dyssynchrony by

echocardiography were required.

The study authors found that CRT improved quality of life and reduced the risk for death (Table 5; Figure 6). In this trial, CRT resulted in a 37% reduction in the combined endpoint of mortality and hospitalization compared with OMT alone. In addition, CRT produced a 10% absolute risk reduction for death. This increased to 13.4% during extended follow-up.[34] Measures of quality of life and NYHA functional class were also significantly improved. The investigators concluded that implantation of a cardiac resynchronization device should be routinely considered in patients with symptomatic, advanced heart failure. Furthermore, the investigators concluded that only 9 individuals needed to be treated to prevent 1 death and 3 hospitalizations. This trial was the first study demonstrating a significant reduction in mortality with CRT pacemakers compared with OMT alone (Figure 6).

Table 5. Results From the CARE-HF Trial

	OMT	CRT	*P**	HR (95% CI)
Primary endpoint[a]	55%	39%	< .001	0.63 (0.51-0.77)
Secondary endpoint[b]	30%	20%	< .002	0.64 (0.48-0.85)
Unplanned hospitalization for a cardiovascular event	46%	31%	< .001	0.61 (0.49-0.77)
Death from any cause or unplanned hospitalization for worsening heart failure	47%	29%	< .001	0.54 (0.43-0.68)
Unplanned hospitalization for worsening heart failure	33%	18%	< .001	0.48 (0.36-0.64)

CARE-HF = CArdiac REsynchronization in Heart Failure; CI = confidence interval; CRT = cardiac resynchronization therapy; HR = hazard ratio; OMT = optimal medical therapy

[a]Composite of death from any cause or unplanned hospitalization for a major cardiovascular event

[b]Death from any cause

Data from Cleland JG, et al.[35]

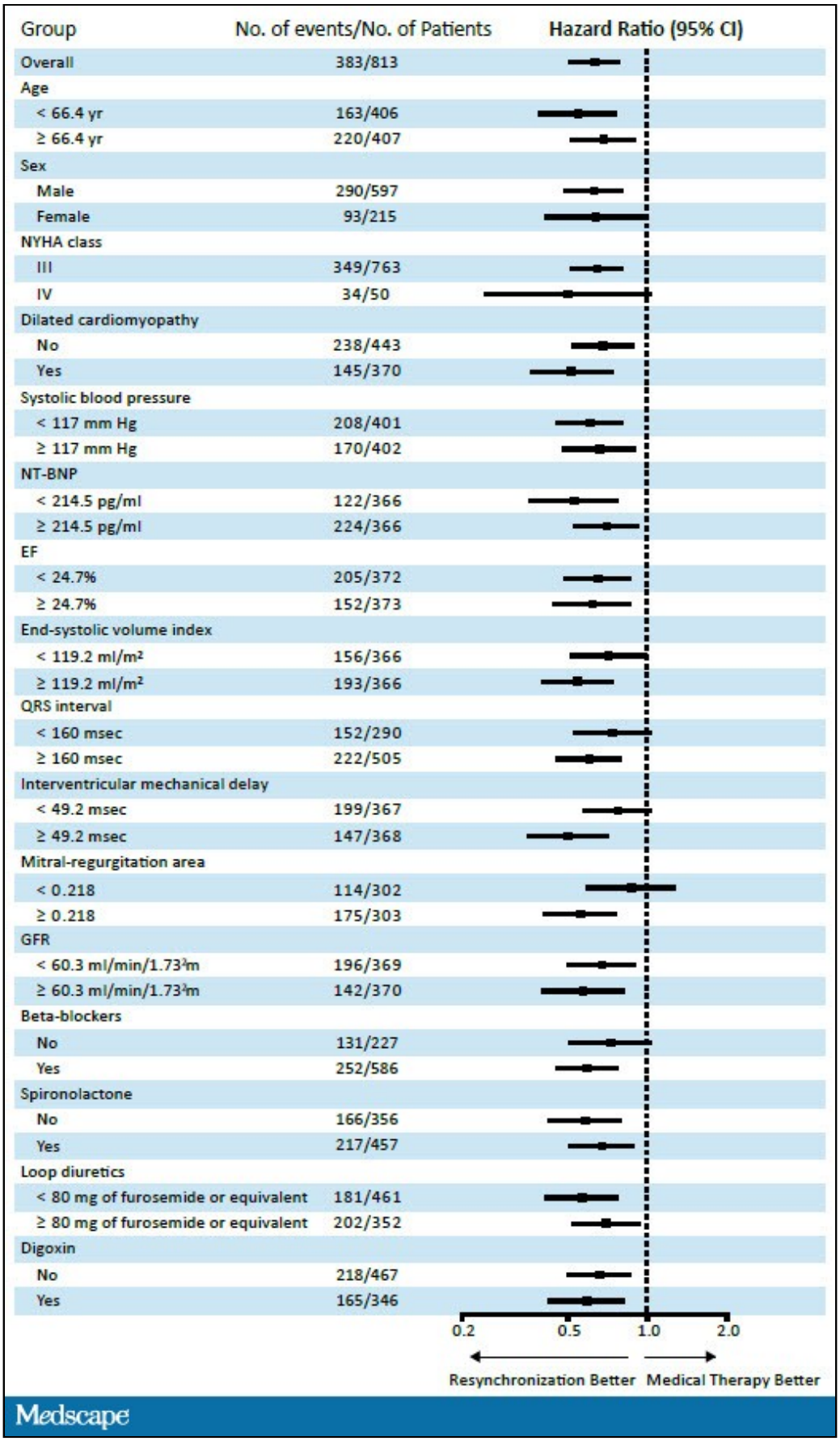

Figure 6. CARE-HF (CArdiac REsynchronization in Heart Failure): primary endpoint.

Case (cont)

After receiving counseling in regard to the risks and benefits of CRT, the patient elected to undergo implantation of a biventricular defibrillator. His ECG revealed sinus rhythm with a left bundle branch pattern, a prolonged PR interval of 160 msec, and a QRS duration of 150 msec. Repeat echocardiography showed persistent left ventricular dysfunction with an EF of 30% and dyssynchrony between the left and right ventricles.

The patient was admitted for the procedure, and the biventricular ICD was placed without obvious complications. He was discharged home with close follow-up.

The patient has a QRS duration of 150 msec. Which of the following statements is correct about the role of CRT in patients who have a widened QRS complex?

- A widened QRS complex is a poor marker for underlying ventricular dyssynchrony
- The majority of patients in heart failure will display a widened QRS complex
- CRT is equally effective in patients with either normal or widened QRS complexes
- Determination of underlying ventricular dyssynchrony by echocardiography is not necessary to identify patients likely to benefit from CRT

Save and Proceed

Case (cont)

Electrical conduction disturbances are common in heart failure and are associated with an increased risk for mortality.[36,37] As normal cardiac conduction becomes impaired, cardiac electrical activation becomes prolonged leading to a loss of synchrony between the septum and lateral wall of the left ventricle.[37] This mechanical dyssynchrony further impairs contractility and subsequently leads to further reductions in left ventricular function and EF. Biventricular pacing resynchronizes the left and right ventricle and the activation of the different walls of the left ventricle to improve ventricular function, increase the EF, and reduce mitral regurgitation.

Echocardiography has become an invaluable tool to help identify dyssynchrony.[33,38] Conduction delays and the loss of coordinated myocardial contraction can occur in 3 different forms: atrioventricular dyssynchrony, interventricular dyssynchrony, and intraventricular dyssynchrony. In atrioventricular dyssynchrony, left ventricular diastolic filling is abnormal. Atrial systole is prematurely terminated, which abbreviates both active and passive filling of the ventricles. Interventricular dyssynchrony describes delays in systolic contractions between the left and right ventricles. This mechanical delay may be estimated by the difference between the aortic and pulmonary pre-ejection periods (timing of the flow of blood from the start of ventricular systole until it passes across the aortic or pulmonary valves). Greater interventricular delay between the segments of the left ventricle portend worse outcomes and may predict improved therapeutic response to CRT in some but not all studies.[26] The delay in peak systolic contraction between 2 or more ventricular myocardial segments refers to intraventricular dyssynchrony.

Although echocardiography can be an invaluable tool in the evaluation of patients with cardiomyopathies, diagnosis of heart failure, and assessment of the response to therapy, it is not required to absolutely identify those who would benefit from CRT therapy. ECG cannot reliably identify underlying mechanical cardiac dyssynchrony. A prolonged PR > 240 msec interval suggests atrioventricular dyssynchrony, and a widened QRS complex is highly correlated with dyssynchronous ventricular contractions. Further, the QRS complex is not a marker specifically for cardiac dyssynchrony in those with more advanced heart failure; however, the wider the QRS the more likely that mechanical dyssynchrony is likely to be present. One third of patients with advanced heart failure (NYHA class III or IV symptoms and a reduced EF < 35%) have a QRS complex of > 120 msec.[39] In a multivariate analysis

identifying the clinical variables most predictive of mortality, a widened QRS complex was independently associated with worse outcomes.[40] Other predictive variables included a reduced LVEF, worsening NYHA functional class, hyponatremia, renal insufficiency, and symptoms refractory to medical therapy.[40]

However, the majority of patients with heart failure do not have prolonged QRS complexes. In addition, nearly half of those with heart failure and a normal QRS are found to have dyssynchrony on further investigation.[41] Although the QRS width can help identify patients for CRT, it does not always reflect those with underlying ventricular dyssynchrony and may miss some individuals who could potentially benefit from this therapy. As such, there may be a beneficial role for CRT in those with a normal QRS duration. It has been hypothesized that patients with a narrow QRS complex may benefit from CRT if they also have concomitant dyssynchrony. This hypothesis is being tested in ongoing clinical trials.

The RethinQ (Resynchronization Therapy in Normal QRS) trial attempted to determine whether CRT would be beneficial in patients with a normal QRS duration who demonstrable dyssynchrony on echocardiography.[30] All patients received a CRT-D device and CRT was inactivated in the control group. After 6 months, no differences in peak oxygen consumption or left ventricular function were noted (Table 6). Given this, it appears that a widened QRS complex is essential for optimal patient selection. However, the true clinical utility of CRT in patients with ventricular dyssynchrony despite a normal QRS is under continued investigation.

Table 6. RethinQ: Effect of Cardiac Resynchronization

Variable	Median Change (95% CI)		*P* Value
	Control	CRT Group	
Peak O_2 consumption	0.5 (-0.3-1.1)	0.4 (-0.6-1.2)	.63
Left ventricular function			
• Change in ejection fraction	2.0 (0.3-4.2)	1.2 (-0.4-4.4)	.83
• Change in end diastolic volume	-11 (-30 to -2)	-16 (-29 to -8)	.71
• Change in end systolic volume	-18 (-28 to -8)	-19 (-34 to -12)	.81
• Change in end diastolic diameter	-1 (-2 to -1)	0 (-2-0)	.49
• Change in end systolic diameter	0 (-2-2)	-1 (-3-0)	.34

CI = confidence interval; CRT = cardiac resynchronization therapy; RethinQ = Resynchronization Therapy in Normal QRS
Data from Beshai JF, et al.[30]

If the patient becomes more symptomatic and is reclassified as NYHA class III, which of the following statements about the use of CRT would be correct?

- Patients experiencing symptomatic improvement can decrease or potentially discontinue

medical therapy with ACE inhibiters and beta-blockers

- In patients with advanced heart failure, CRT reduces symptoms by at least 1 NYHA class but has not been shown to improve survival
- The safety and efficacy of CRT in more advanced disease has not been validated because the majority of patients enrolled in clinical trials had NYHA class II symptoms
- Patients with NYHA class IV symptoms experience similar improvements in symptoms, exercise capacity, and hospitalization rates as those with class III symptoms

Save and Proceed

Several clinical trials have firmly established the efficacy and clinical benefits of CRT in patients with advanced heart failure. When added to OMT, CRT has been shown to reduce symptoms, improve functional capacity, increase exercise tolerance, decrease hospitalizations, and prolong survival.[20-32] In a systematic review of 2601 pooled patients from published clinical trials, CRT was associated with a 49% decrease in the rate of hospitalization for heart failure and a 23% relative reduction in mortality.[27]

The MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial was the first large, double-blind, randomized controlled study assessing the benefits of CRT in patients with NYHA class III or IV heart failure.[29] In this trial, CRT resulted in improvement in functional capacity and symptoms as well as a reduction in hospitalization. Compared with controls, patients in the CRT group experienced significant improvements in quality-of-life scores (P = .02), a greater median decrease in NYHA functional class (P = .007), and an increase in treadmill exercise duration (P < .001).

To date, over 4000 patients have been enrolled in clinical trials assessing the safety and efficacy of CRT in patients with heart failure. As expected, the majority of patients were men (75%) with a mean age of 64 years. The applicability of these trials is somewhat limited because they primarily included only those individuals with severely symptomatic heart failure; three fourths had NYHA functional class III symptoms; and 10% had NYHA class IV symptoms. Ischemia was the etiology for heart failure in the majority of patients, and nearly all had significantly impaired left ventricular function, a widened QRS complex, and were in sinus rhythm. Although these variables may limit the scope of patients studied, they reflect the common patient with advanced heart failure and the primary indications for CRT.

Pooled data from 9 randomized controlled trials found that CRT significantly improved symptoms and exercise capacity and reduced the rates of hospitalization and mortality.[27] Also, these improvements were similar for NYHA class III and IV symptoms. Compared with controls, CRT improved 6-minute walk distances by 23 m (95% CI, 9-38 m). Symptoms were also improved with 57% of CRT-treated patients improving at least 1 NYHA class compared with only 34% of controls (relative risk [RR], 1.6; 95% CI, 1.1-2.5). Hospitalizations due to heart failure were significantly reduced with CRT (RR, 0.65; 95% CI, 0.48-0.88; number needed to treat [NNT] = 12). All-cause mortality was also reduced in those receiving CRT compared with controls, with a number needed to treat to prevent 1 death of 27.

What would the role for CRT be if the patient were 10 years older (68 years of age) with NYHA class I heart failure and RBBB?

- CRT is contraindicated in patients with RBBB
- CRT is just as effective in individuals with RBBB as those with LBBB
- RBBB morphology prevents accurate assessments of the therapeutic response to CRT
- CRT may not be beneficial in patients with RBBB; limited published retrospective data suggest that these patients may not experience a benefit from CRT therapy

Save and Proceed

Unlike clinical trials, real-world clinical practice involves patients who do not share all clinical characteristics or are free of the confounding variables required for enrollment in clinical trials. Recommendations for CRT are largely based on the duration and not the morphology of the QRS complex, and only a limited number of patients enrolled in the initial clinical trials had an RBBB. Unfortunately, RBBB are frequently observed in patients with heart failure, and our understanding of the clinical utility and potential therapeutic benefit of CRT in patients with RBBB is limited.

Using pooled data from nearly 15,000 patients in the Medicare Implantable Cardioverter-Defibrillator Registry, Bilchick and colleagues assessed the rates of death and hospitalizations from heart failure in patients with CRT and CRT-ICDs.[42] For all registered patients, 1- and 3-year mortality rates were 12% and 32%, respectively. However, certain patient characteristics were associated with worse outcomes. Specifically, patients with RBBB, class IV symptoms, advanced age, and ischemia as the etiology for their cardiomyopathy had a significantly higher adjusted HR for death. Compared with RBBB, patients with LBBB experienced better outcomes with CRT.

Chandra and colleagues specifically assessed the outcomes of CRT in patients with pure RBBB or RBBB with a concomitant left hemiblock.[43] Among patients who underwent CRT, 44 were identified with RBBB, 18 of which had pure RBBB and 26 had RBBB and coexisting left hemiblock. Response to CRT, defined as an increase in the EF > 5% or an improvement in NYHA class, was considerably worse in those with a pure RBBB. Improvements in the EF occurred in 22.2% of patients with a pure RBBB compared with 69.2% of those with a left hemiblock (P = .005). None of the patients with RBBB experienced improvements in their NYHA class, whereas 26.9% of those with a left hemiblock noted improvements of at least 1 NYHA class (P = .03).

The role of CRT in patients with RBBB remains unclear. As with most interventions, the selection of treatments and interventions must be individualized. However, it appears that patients with RBBB do not experience similar therapeutic benefits from this therapy. From the existing published data, it seems that the morphology of the QRS is as important as its duration to identify those most likely to benefit from CRT.

Case (cont)

Following successful implantation of a biventricular ICD, the patient experienced a marked reduction in his symptoms. During follow-up he reported improvements in his exercise capacity and is now able to walk 2-3 miles at a brisk pace without having to stop to rest (NYHA class I). On a repeat echocardiogram obtained 6 months after initiating CRT, his EF had increased to 40% and his left ventricular volumes were decreased by 20%.

According to the ACC/AHA/HRS guidelines, which of the following patients would have a class I indication for CRT?

- NYHA class III symptoms with an EF of 45% and a QRS complex of 110 msec
- NYHA class I symptoms with an EF of 30% and a QRS complex of 130 msec
- NYHA class IV symptoms with an EF of 45% and a QRS complex of 140 msec
- NYHA class III symptoms with an EF of 30% and a QRS complex of 150 msec

Save and Proceed

Like all medical interventions, the likelihood of successful CRT is largely dependent on proper patient selection, and not all patients with heart failure should be considered for placement of a biventricular ICD. CRT should be considered for patients in sinus rhythm with current or recent NYHA functional class III or IV heart failure

symptoms and severely impaired left ventricular systolic function.[25,33,44,45]

Several clinical practice guidelines for the proper use of CRT are available, all of which share similar class I indications. Common indications for CRT implantation are listed in Table 7, according to recent guidelines from the ACC/AHA/HRS, the European Society of Cardiology (ESC), and the German Society of Cardiology (DGK).[25,44,45]

Table 7. ACC/AHA/HRS and DGK Guidelines for CRT Implantation

	NYHA Class	Ejection Fraction	QRS Duration	ACC/AHA/HRS Recommendation	DGK
Sinus rhythm	III or IV	≤ 35%	≥ 120 msec	Ia	Class I with QRS ≥ 150 msec and/or a LBBB
Frequent right ventricular stimulation	III or IV	≤ 35%		IIa	IIb
Atrial fibrillation	III or IV	≤ 35%	≥ 120 msec	IIb	IIa
Sinus rhythm	II	≤ 35%		IIb[a]	
Sinus rhythm	II	≤ 35%	≥ 150 msec		IIb

ACC = American College of Cardiology; AHA = American Heart Association; CRT = cardiac resynchronization therapy; DGK = German Society of Cardiology; HRS = Heart Rhythm Society; LBBB = left bundle branch block; NYHA = New York Heart Association

[a]With frequent right ventricular stimulation

Conclusion

Heart failure is a common condition in clinical practice, which is steadily increasing in prevalence. A diminished quality of life is common, and symptoms of fatigue and dyspnea limit functional performance in most individuals. Medical therapy with diuretics, ACE inhibitors, aldosterone antagonists, and beta-blockers should be initiated in all patients unless contraindicated. For those with persistent symptoms despite optimal medical management, particularly in those with an EF < 35% and a widened QRS complex on ECG, CRT can have an additive effect to improve symptoms and survival. CRT on top of good medical therapy improves quality of life, exercise performance, leads to anatomic remodeling with a decrease in ventricular size, and prolongs survival. It is an important addition to medical therapy in patients with heart failure and a prolonged QRS on OMT.

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