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Review Article

Cardiac Resynchronization Therapy in Heart Failure Management

Hilman Zulkifli Amin, Siska Suridanda Danny

Heart failure (HF) is a worldwide health problem with high prevalence rate. The prevalence is over 23 million worldwide. It is a chronic disease characterized by the inability of the heart to pump an adequate amount of blood to achieve the demand of the different organ systems and/or doing so at increased filling pressures. Despite many recent advances in medication, the rate of people with HF is rising. This health challenges need to be answered properly. One of the new important treatment for HF is cardiac resynchronization therapy (CRT). Many patients with HF also have an abnormality of the heart's electrical system resulting in asynchronous contraction pattern of heart muscle.
The ultimate goal of CRT is to restore synchrony of the heart rhythm in HF patients. CRT implantation in heart failure patients with proper indications like wide QRS complexes, low left ventricular ejection fraction (LVEF), and left bundle branch block (LBBB) has been proved to reduce morbidity, mortality, and also improve symptoms and quality of life (QoL).

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Keywords: heart failure, cardiac resynchronization therapy

[1]Faculty of Medicine, Universitas Indonesia
[2]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia

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Tinjauan Pustaka

Terapi Resinkronisasi Jantung pada Penanganan Gagal Jantung

Hilman Zulkifli Amin, Siska Suridanda Danny

Gagal jantung (GJ) merupakan masalah kesehatan utama dunia dengan tingkat prevalensi yang tinggi. Di seluruh dunia, prevalensi GJ mencapai 23 juta orang. GJ merupakan penyakit kronik dengan karakteristik berupa ketidakmampuan jantung dalam memompa darah untuk memenuhi kebutuhan sistem organ dan atau diikuti dengan terjadinya peningkatan tekanan isi sekuncup. Meskipun telah banyak kemajuan dalam pengobatan GJ, jumlah penderita GJ terus meningkat. Tantangan dalam dunia kesehatan ini perlu segera dipenuhi. Salah satu terapi baru dan penting dalam penanganan GJ ialah terapi resinkronisasi jantung (TRJ). Terdapat banyak pasien GJ juga mengalami abnormalitas sistem konduksi jantung yang menyebabkan terjadinya ketidaksinkronan pola kontraksi otot jantung.
Tujuan utama dari TRJ ialah mengembalikan sinkronisasi ritme jantung pada pasien GJ. Pemasangan TRJ pada pasien GJ dengan indikasi yang tepat dan sesuai seperti kompleks QRS yang lebar, ejeksi fraksi ventrikel kiri yang rendah, dan blok berkas cabang kiri telah terbukti dapat menurunkan angka morbiditas, mortalitas, dan juga meningkatkan kualitas hidup serta memperbaiki gejala.

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Kata kunci: gagal jantung, terapi resinkronisasi jantung

Heart failure (HF) is a chronic disease characterized by the inability of the heart to pump an adequate amount of blood to achieve the demand of the different organ systems and/or doing so at increased filling pressures.[1] HF caused by the weakening of the heart muscle. It is most commonly caused by irreversible damage from coronary artery disease, but may also be result of viral infections, genetic factors, or toxins.[2]

Alamat Korespondensi
dr. Hilman Zulkifli Amin, Faculty of Medicine, Universitas Indonesia, Jl. Salemba Raya No. 6, Jakarta, Indonesia. E-mail: *hilman_amin@yahoo.co.id*

HF is a worldwide health problem with high prevalence rate. The prevalence is over 23 million worldwide.[3] This disease carries substantial risk of morbidity and mortality. Over 2.4 million patients are hospitalized and nearly 300,000 deaths annually are directly attributable to HF. There is a dramatic increase in the prevalence of HF. The growing prevalence of HF might reflect increasing incidence, an aging population, improvements in the treatment of acute cardiovascular disease and HF, or combination of these factors. Since then, medications are the mainstay therapy for patients with HF.

Medications help rid the body extra fluid, strengthen the heart's contraction, and ease the heart's workload by relaxing the blood vessels and reducing

the resistance to pumping blood.[3] Despite many recent advances in medication, the rate of people with HF is rising. This health challenges need to be answered properly. One of the new important treatment for HF is cardiac resynchronization therapy (CRT). Many patients with HF also have an abnormality of the heart's electrical system resulting in asynchronous contraction pattern of heart muscle.

Heart Electrical System Conduction In HF

The normal heart rhythm is originated by an electrical signal from a region of the right atrium (RA) known as the sinoatrial or SA node. After that, the electrical signal run through both atria and make them pump blood into the ventricles.[3] The atrioventricular node or AV node, then is reached by an electrical signal. The signal then spreads through specialized routes called the left and right bundle branch branches. Finally, the bundle branches stimulate both ventricles to contract synchronously. This electrical system conduction is important for optimal blood pumping to all over body.

The most common abnormality conduction in HF patient is left bundle branch block (LBBB).[3] Because of this block, the right ventricle made an earlier contraction than the left ventricle, instead of simultaneously. The result is an asynchronous contraction of the ventricles. Eventually, cardiac pump will lose its efficiency. Almost 40% of HF patients have an asynchronous ventricular contraction caused by electrical delay, most often LBBB. The appearance of this electrical delay on an electrocardiogram (ECG) is widening of the QRS complex.

Cardiac Resynchronization Therapy (CRT)

The ultimate goal of CRT is to restore synchrony of the heart rhythm in HF patients. It is a unique type of cardiac pacemaker.[5] Pacemakers usually being used to prevent symptoms associated with symptomatic slow heart rates. The patient's heart rate is continuously monitored by the pacemaker. The heart rate is stimulated by the pacemaker by delivering a tiny electrical charge when necessary.[3] Common pacemakers have 2 leads, one in the right atrium and one in the right ventricle, in order to keep the normal pump function relationship between bottom and top of the heart. These leads are connected to a pulse generator placed under the skin in the upper chest.

CRT is a specialized type of pacemakers, that have a third lead which is positioned in a vein on the outer surface of the left ventricle, in addition to the 2 leads used by common pacemakers.[3,5] This allows a synchronous pumping action of left and right ventricle.

There are two types of CRT, a CRT pacemaker and a combination CRT pacemaker with defibrillation therapy (CRT-D).[5] Both help to coordinate the heart pumping action and improve blood flow. In CRT-D, it also has the ability to detect and treat malignant heart rhythms, which some individuals with a damaged heart muscle may be at risk for developing. The decision of which device to use depends on the physician.

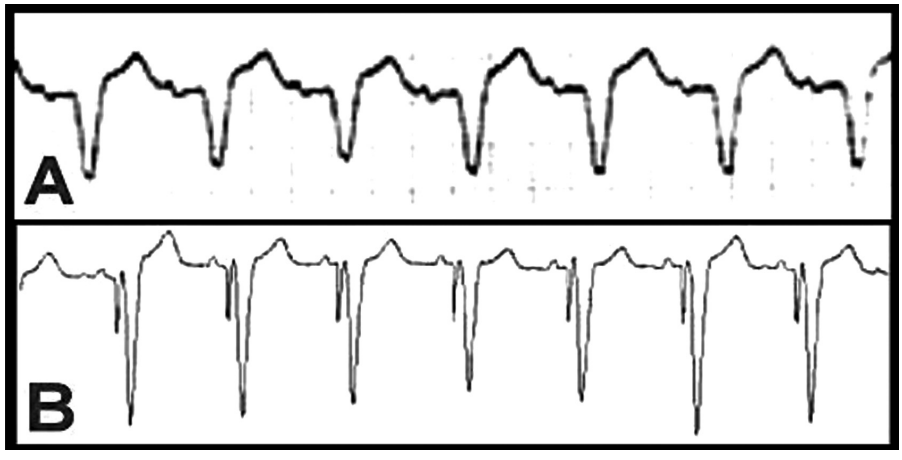

Figure 1. LBBB and Improvement of Conduction System by CRT[4]

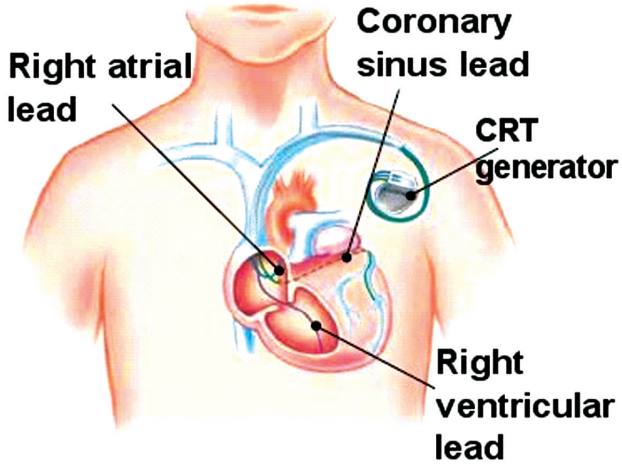

Figure 2. CRT Lead Placement[4]

Indications and Benefits of CRT in Heart Failure Management

Many conclusive evidences of CRT benefits in HF from several randomized clinical trials (RCTs).[6] The inclusion criteria used in the most RCTs was, New York Heart Association (NYHA) functional class III-IV in sinus rhythm (SR), low left ventricular ejection fraction (LVEF) < 35%, and duration of QRS interval ≥ 120 ms. The Cardiac Resynchronization in Heart Failure (CARE-HF) trials with 813 patients evaluated all-cause mortality, hospitalization, NYHA functional class, and quality of life (QoL).[6,7] This study was double-blinded and randomized trial. The result was CRT proved to reduce all-cause mortality, hospitalization, improved NYHA functional class, and QoL. Other study showing similar result was Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial. This study even has larger subjects which was 1520 patients.[6,8] The result was also the same that CRT could reduced all-cause mortality or hospitalization. Other studies like Multisite Stimulation in Cardiomyopathy (MUSTIC), Pacing Therapies in Congestive Heart Failure (PATH-CHF), and Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trials also showed superiority of CRT in HF paients.[6,9-11] These studies proved that CRT could improved QoL, NYHA functional class, 6-minutes walk distance (6MWD), LVEF, and peak VO_2.

However, in accordance to the low number of subjects enrolled in RCTs, the evidence in HF patients with NYHA functional class IV was limited (from 7 to 15%).[6] Ambulatory HF patients functional class IV showed a significant reduction in the combined primary endpoint of time to all-cause mortality and hospitalization as shown in a sub-study of COMPANION trial.[6,8] The summary of the RCTs of CRT benefit in HF patients with NYHA functional class III-IV, sinus rhythm, poor left ventricular ejection fraction (LVEF), and prolonged QRS interval (≥120 ms) will be shown on the table below.

Other topic related to the CRT benefit in HF patients was the impact of QRS duration on the efficacy of CRT. Subgroup analysis, in a recent meta-analysis from COMPANION and CARE-HF trials, evaluating the impact of QRS duration on the efficacy of CRT, has shown that, in NYHA functional class III-IV HF patients, CRT significantly reduced all-cause mortality or hospitalization in patients with QRS duration ≥ 150 ms.[6-8] The effect and benefit of CRT declined with shorter QRS duration. These studies also supported by Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial.[6,12] It showed that patients with a QRS duration ≥ 150 ms, has a most benefit effect from CRT and suggested that it might not effective in patients with QRS < 150 ms. In addition, most patients in the RCTs had LBBB morphology, which was associated, with a more pronounced benefit, compared with non-LBBB patients. It was shown in the MADIT-CRT, Resynchronization-Defibrillation for Ambulatory Heart Failure (RAFT), and Resynchronization Reverses Remodelling in Systolic Left Ventricular Dysfunction (REVERSE) trials, and a meta-analysis of COMPANION, CARE-HF, MADIT-CRT, and RAFT.[6,12-14] Patients with complete LBBB, showed a greater benefit on the composite of morbidity and mortality from CRT, compared with patients with non-specific IVCD or RBBB.[6] However, patients with LBBB had longer QRS duration, and therefore analyses by morphology may be confounded by QRS duration. On the other hand, the MADIT-CRT trial showed that non-LBBB patients did not derive clinical benefit from CRT (statistically not significant 24% increased risk).[6,12] Other trials also showed consistent results that indicated clinical benefit of CRT in LBBB patients.[5] Based on this evidence, current class I recommendations were restricted to patients with complete LBBB. The relationship between QRS duration and morphology requires further research.

Table 1. Summary of Randomized Clinical Trials[6] (With permission of Oxford University Press (UK) (c) European Society of Cardiology, www.escardio.org) Evaluating CRT in HF patients and Sinus Rhythm

Trial	No. Patients	Design	NYHA Functional Class	LVEF	QRS	Primary End-points	Secondary End-points	Main Findings
MUSTIC-SR	58	Single-blinded, crossover, randomized CRT vs OMT, 6 months	III	<35%	≥150 ms	6MWD	NYHA class, QoL, peak VO2LV volumes, MR hospitalizations, mortality	CRT-P improved 6MWD, NYHA class, QoL, peak VO2, reduced LV volumes and MR and reduced hospitalizations
PATH-CHF	41	Single-blinded, crossover, randomized RV vs LV vs BiV, 12 months	III-IV	NA	≥150 ms	Peak VO2, 6MWD	NYHA class, QoL hospitalizations	CRT-P improved NYHA class, QoL and 6MWD and reduced hospitalizations
MIRACLE	453	Double-blinded, randomized CRT vs. OMT, 6 months	III-IV	≤35%	≥130 ms	NYHA class, 6MWD , QoL	Peak VO2 LVEDD, LVEF, MR clinical composite response	CRT-P improved NYHA class, QoL and 6MWD and reduced LVEDD, MR and increased LVEF
MIRACLE-ICD	369	Double-blinded, randomized CRT-D vs. ICD, 6 months	III-IV	≤35%	≥130 ms	NYHA class, 6MWD , QoL	Peak VO2 LVEDD, LVEF, MR clinical composite response	CRT-D improved NYHA class, QoL, peak VO2
CONTAK-CD	490	Double-blinded randomized CRT-D vs. ICD, 6 months	II-IV	≤35%	≥120 ms	NYHA class, 6MWD , QoL	LV volume, LVEF composite of mortality, VT/VF, hospitalizations	CRT-D improved 6MWD, NYHA class, QoL, reduced LV volume and increased LVEF
MIRACLE-ICD II	186	Double-blinded, randomized CRT-D vs. ICD, 6 months	II	≤35%	≥130 ms	Peak VO2	VE/VCO2, NYHA, QoL, 6MWD, LV volumes and EF, composite clinical endpoint	CRT-D improved NYHA, VE/CO2 and reduced LV volumes and improved LVEF
COMPANION	1520	Double-blinded randomized OMT vs. CRT-P / or vs. CRT-D, 15 months	III-IV	≤35%	≥120 ms	All-cause mortality or hospitalization	All-cause mortality, cardiac mortality	CRT-P and CRT-D reduced all-cause mortality or hospitalization

CARE-HF	813	Double-blinded randomized OMT vs. CRT-P 29.4 months	III-IV	≤35%	≥120 ms	All-cause mortality or hospitalization	All-cause mortality, NYHA class, QoL	CRT-P reduced all-cause mortality and hospitalization and improved NYHA class and QoL
REVERSE	610	Double-blinded, randomized CRT-ON vs. CRT-OFF, 12 months	I-II	≤40%	≥120 ms	% worsened by clinical composite endpoint	LVESV index, heart failure hospitalizations and all-cause mortality	CRT-P/CRT-D did not change the primary endpoint and did not reduce all-cause mortality but reduced LVESV index and heart failure hospitalizations
MADIT-CRT	1820	Single-blinded, randomized CRT-D vs. ICD, 12 months	I-II	≤30%	≥130 ms	All-cause mortality or heart failure hospitalizations	All-cause mortality and LVESV	CRT-D reduced the endpoint heart failure hospitalizations or all-cause mortality and LVESV. CRT-D did not reduced all-cause mortality
RAFT	1798	Double-blinded, randomized CRT-D vs. ICD 40 months	I-II	≤30%	≥120 ms	All-cause mortality or heart failure hospitalizations	All-cause mortality and cardiovascular death	CRT-D reduced the endpoint all-cause mortality or heart failure hospitalizations. In NYHA III, CRT-D only reduced significantly all-cause mortality

CARE-HF (Cardiac Resynchronization-Heart Failure); CONTAK-CD (CONTAK-Cardiac Defibrillator); COMPANION (Comparison of Medical Therapy, Pacing and
Defibrillation in Heart Failure); CRT-D (Cardiac Resynchronization therapy with Defibrillator); CRT-P (Cardiac Resynchronization Therapy Pacemaker); LV (Left Ventricular; LVEDD (Left Ventricular End-Diastolic Dimension); LVEF (Left Ventricular Ejection Fraction); LVESV (Left Ventricular End-Systolic Volume); MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy); MIRACLE (Multicenter InSync Randomized Clinical Evaluation); MIRACLE-ICD (Multicenter InSync Implantable Cardioverter Defibrillator trial); MR (Mitral Regurgitation); MUSTIC (Multisite Stimulation in Cardiomyopathies); No (Number of Patients) ; NYHA (New York Heart Association); PATH-CHF (Pacing Therapies in Congestive Heart Failure Trial); QoL(Quality of Life Score); RAFT (Resynchronization Defibrillation for Ambulatory Heart Failure Trial); VE/VCO2 (Minute Ventilation/ Minute Volume Carbondioxide Production); VF (Ventricular Fibrillation); VO2 (Volume of Oxygen); VT (Ventricular Tachycardia; 6MWD (6-min Walk Distance)

In HF patients with NYHA functional class I-II, sinus rhythm, LVEF ≤ 30-40% and QRS duration ≥ 120-130 ms, four RCTs which were MADIT-CRT, RAFT, REVERSE, and Multicenter InSync Implantable Cardioverter Defibrillator (MIRACLE-ICD) trials have demonstrated that CRT improves LV function, all-cause mortality and HF hospitalizations.[6,12-15] However, improvement in functional status or quality of life among patients randomized to CRT were not too significant. Most patients enrolled had NYHA functional class II; only 15% in Resynchronization Reverses Remodelling in Systolic Left Ventricular Dysfunction (REVERSE) and 18% in Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) were in NYHA functional class I. CRT did not reduce all-cause mortality of HF events among NYHA functional class I patients. Therefore, the recommendation is restricted to patients in NYHA functional class II.

Finally, there is no evidence of benefit in patients with HF and QRS < 120 ms. In the Cardiac Resynchronization Therapy In Patients with Heart Failure and Narrow QRS (RethinQ) trial, CRT did not improve peak oxygen consumption (primary endpoint) or QoL in the subgroup of patients with QRS < 120 ms and evidence of echocardiography dysscynhrony.[6,16]

Table 2. Indications for CRT in HF Patients and Sinus Rhythm[6] (With permission of Oxford University Press (UK) (c) European Society of Cardiology, www.escardio.org)

Recommendations	Class[a]	Level[b]
1) **LBBB with QRS duration >150 ms.** CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment.[d]	**I**	**A**
2) **LBBB with QRS duration 120–150 ms.** CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment.[d]	**I**	**B**

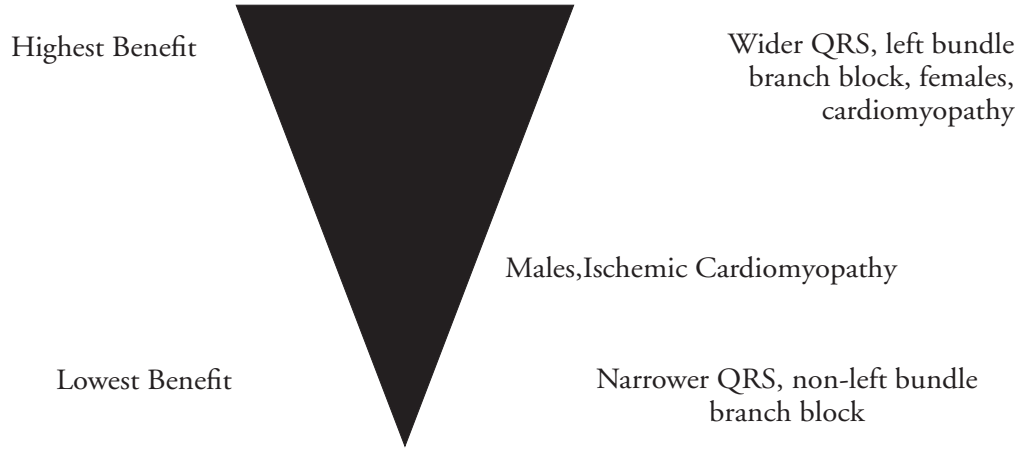

Figure 3. Benefit Scale of CRT Based on Clinical Factors6 (With permission of Oxford University Press (UK) (c) European Society of Cardiology, www.escardio.org)

3) **Non-LBBB with QRS duration >150 ms.** CRT should be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment.[d]	**IIa**	**B**
4) **Non-LBBB with QRS duration 120–150 ms.** CRT may be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment.[d]	**IIb**	**B**
5) CRT in patients with chronic HF with QRS duration <120 ms is not recommended	**III**	**B**

CRT (Cardiac Resynchronization Therapy); HF (Heart Failure); LBBB (Left Bundle Branch Block); LV (Left Ventricular); LVEF (Left Ventricular Ejection Fraction); NYHA (New York Heart Association)

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendation(s).

[d]Patients should generally not be implanted during admission for acute decompensated HF. In such patients, guideline-indicated medical treatment should be optimized and the patient reviewed as an out-patient after stabilization. It is recognized that this may not always be possible.

Other randomized and double-blind study named Evaluation of Resynchronization Therapy for Heart Failure in Patients with a QRS Duration Lower Than 120 ms (LESSER-EARTH) was prematurely stopped due to safety concerns.[6,17]

CRT In Heart Failure Management With Atrial Fibrillation (AF)

There are two ways of considering CRT for AF patients, first, AF patients with moderate to severe HF with a hemodynamic indication for CRT. Second, patients with a fast ventricular rate with HF or LV dysfunction justifying a strong rate control strategy with an AV junction ablation.[6]

In the first way of considering CRT for AF patients were described in Multisite Stimulation in Cardiomyopathies (MUSTIC) AF trial.[6,18] There was a slight but significant improvement in functional status in patients with NYHA functional class III, low LVEF, AF rhythm, and QRS ≥ 120 ms at 6-month and 1-year follow-up. In the Ablate and Pace in AF (APAF) trial, in the patients with low LVEF, NYHA functional class ≥ III, AF rhythm, and QRS ≥ 120 ms, CRT significantly reduced the primary endpoint, including death, hospitalizations or worsening of HF, as well as beneficial effect on LV reverse remodeling.[6,19]

Second way, combination of AV junction ablation and CRT in uncontrolled heart rate of AF patients provided highly efficient rate control, regularization of the ventricular response, and also improved symptoms.[6] Hence, CRT may prevent the potential LV asynchrony. The multi-center, randomized, and prospective APAF trial with 186 patients studied about CRT implantation followed by AV junction ablation.[6,19] During a median follow-up of 20 months, CRT significantly decreased the primary composite endpoint (of death due to HF, hospitalization or worsening due to HF) by 63% in the overall population. The effects and efficacy of CRT were significantly consistent in patients who had EF ≤ 35%, NYHA functional class ≥ III, and QRS width ≥ 120 ms, thus meeting the requirement of the guidelines.

Conclusion

The prevalence of HF is still high. This disease carries substantial risk of morbidity and mortality. Over 2.4 million patients are hospitalized and nearly 300,000 deaths annually are directly attributable to HF. HF is characterized by the inability of the heart to pump an adequate amount of blood to achieve the demand of the different organ systems and/or doing so at increased filling pressures. The most common abnormality

Table 3. Indications for CRT in HF Patients and Atrial Fibrillation[6] (With permission of Oxford University Press (UK) (c) European Society of Cardiology, www.escardio.org)

Recommendations	Class[a]	Level[b]
1) **Patients with HF, wide QRS and reduced LVEF:** 1A) CRT should be considered in chronic HF patients, intrinsic QRS ≥120 ms and LVEF ≤35% who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment[d], provided that a BiV pacing as close to 100% as possible can be achieved.	**IIa**	**B**
1B) AV junction ablation should be added in case of incomplete BiV pacing.	**IIa**	**B**
2) **Patients with uncontrolled heart rate who are candidates for AV junction ablation.** CRT should be considered in patients with reduced LVEF who are candidates for AV junction ablation for rate control.	**IIa**	**B**

AV (Atrioventricular); CRT (Cardiac Resynchronization Therapy); HF (Heart Failure); ICD (Implantable Cardioverter Defibrillator); LVEF (Left Ventricular Ejection Fraction); NYHA (New York Heart Association)
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendation(s).
[d]Patients should generally not be implanted during admission for acute decompensated HF. In such patients, guideline-indicated medical treatment should be optimized and the patient reviewed as an out-patient after stabilization. It is recognized that this may not always be possible.

conduction in HF patient is left bundle branch block (LBBB). Because of this block, the right ventricle made an earlier contraction than the left ventricle, instead of simultaneously. The result is an asynchronous contraction of the ventricles. Eventually, cardiac pump will lose its efficiency.. Almost 40% of HF patients have an asynchronous ventricular contraction caused by electrical delay, most often LBBB. CRT, a specialized and unique pacemaker, plays an important new role as a novel treatment in HF patients, despite many recent advances in medication. HF patients with proper and right indications like wide QRS complexes, low left ventricular ejection fraction (LVEF), LBBB, SR with conduction delay, and permanent AF have shown improvement of symptoms and QoL. Thus, CRT have been proven to reduce morbidity and mortality in HF patients.

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