SUMMARY AND CONCLUSIONS

The general introduction of this thesis (**Chapter 1**) outlined the epidemiology and impact of heart failure in the western world. The frequently observed conduction abnormalities (mainly conduction abnormalities within the left ventricle [LV]) in these patients, and its implications for treatment with cardiac resynchronization therapy (CRT) are briefly discussed. An extensive overview of all the landmark trials in CRT to date is provided, including the selection criteria used in these trials, as well as the end-points and most important findings. Next, optimization of patient selection and outcome within the current selection criteria for CRT are discussed. Finally, a brief outline of future perspectives in the treatment with CRT is provided.

Part I

The first part of the thesis evaluated several determinants of mid-term response and long-term prognosis after CRT. **Part IA** focuses on the response to CRT at 6 months follow-up.

In **Chapter 2**, the predictive accuracy of the previously proposed 65 ms cut-off for LV dyssynchrony using tissue Doppler imaging (TDI) was evaluated in 361 heart failure patients undergoing CRT. Clinical response was defined as an improvement ≥1 New York Heart Association (NYHA) class and echocardiographic response as a reduction in LV end-systolic volume (LVESV) ≥15%. At 6 months follow-up, 259 patients (72%) showed clinical response and 187 patients (52%) showed echocardiographic response. Responders had more LV dyssynchrony than non-responders (91±49 ms vs. 50±44 ms for clinical response and 101±46 ms vs. 55±45 ms for echocardiographic response). In multivariate analysis, LV dyssynchrony remained predictive for response, independent of other characteristics. It was therefore concluded in this validation study that LV dyssynchrony ≥65 ms was an independent predictor of both clinical and echocardiographic response in patients with heart failure undergoing CRT.

In **Chapter 3**, the usefulness of more advanced measures of LV dyssynchrony (2-dimensional [2D] strain) and its predictive value for a positive response after CRT was assessed in 161 patients. The extent of radial strain (RS), circumferential strain (CS), and longitudinal strain (LS) was calculated in each patient. Response to CRT was defined as a decrease in LVESV ≥15% at 6 months follow-up. A total of 88 patients (55%) were classified as responders. Differences in baseline LV dyssynchrony between responders and non-responders were noted only for RS (251±138 ms vs. 94±65 ms, $p<0.001$), whereas no differences were noted for CS and LS. A cut-off value of radial dyssynchrony ≥130 ms was able to predict response to CRT with a sensitivity of 83% and a specificity of 80%.

In **Chapter 4**, it was hypothesized that LV reverse remodeling could be predicted by the left bundle branch block (LBBB) ventricular activation sequence, the biventricular paced activation sequence, and interactions between these 2 conditions. Twelve-lead ECGs during LBBB and CRT were analyzed in 202 consecutive patients for predictors of reverse remodeling at 6 months follow-up. Greater longest baseline LV activation time predicted increased odds

of reverse remodeling (odds ratio [confidence interval] 1.30 [1.11-1.52] per 10-ms increase), whereas higher QRS scores for LV scar predicted reduced reverse remodeling (odds ratio [confidence interval] 0.49 [0.27-0.88] for each 1-point increase from 0 to 4; 0.92 [0.83-1.01] for each 1-point increase >4). After CRT, increasing R amplitudes in leads V1 through V2 (odds ratio [confidence interval] 2.76 [1.01-7.51] for each 1x increase over [baseline Rx4.5]) and left to right frontal axis shift (odds ratio [confidence interval] 2.00 [0.99-4.02]), indicators of ventricular activation wavefront fusion, were positive predictors of reverse remodeling. Predicted probability of reverse remodeling ranged from <20% for patients with adverse predictors to 99% for those with positive predictors. Therefore, analysis of ventricular activation with the use of the 12-lead ECG accurately predicted LV reverse remodeling during CRT.

Chapter 5 evaluated the extent of agreement between clinical and echocardiographic response to CRT in 440 consecutive heart failure patients treated with CRT, and identified the characteristics of patients with clinical response but without echocardiographic response. At 6 months follow-up, clinical response (≥1 point NYHA functional class improvement or ≥15% increase in 6-minute walk test) was observed in 84% of the patients. Significant reduction (≥15%) in LVESV was noted in 63%. The majority of patients (72%) who improved clinically did show LV reverse remodeling. The patients with clinical response but without echocardiographic response had more often ischemic heart failure as compared to patients with positive clinical and echocardiographic response (69.6% vs. 57.5%, p = 0.021). Moreover, patients with such discordant responses had a more narrow QRS complex (148±31 ms vs. 159±31 ms, p = 0.004), and showed less LV dyssynchrony than patients with concordant positive responses (90±77 ms vs. 171±105 ms, p = 0.001).

In **Chapter 6**, a comprehensive sub-analysis of the Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) trial was performed to investigate the relationship between baseline characteristics and measures of response to CRT. A total of 286 patients were grouped according to relative reduction in LVESV after 6 months of CRT: super-responders (reduction in LVESV ≥30%), responders (reduction in LVESV 15% to 29%), non-responders (reduction in LVESV 0% to 14%) and negative-responders (increase in LVESV). Additionally, 3 sub-groups were formed according to clinical and/or echocardiographic response: +/+ responders (clinical improvement and a reduction in LVESV ≥15%), +/- responders (clinical improvement or a reduction in LVESV ≥15%), and -/- responders (no clinical improvement and no reduction in LVESV ≥15%). Differences in clinical and echocardiographic baseline characteristics between these sub-groups were analyzed. Super-responders were more frequently females, had non-ischemic heart failure, had a wider QRS complex and more extensive mechanical dyssynchrony at baseline. Conversely, negative-responders were more frequently in NYHA class IV and more frequently had a history of ventricular tachycardia (VT). Combined positive responders after CRT (+/+ responders) had more non-ischemic etiology, more extensive mechanical dyssynchrony at baseline and no history of VT. This important sub-analysis of data from PROSPECT demonstrated that gender, etiology of heart failure, QRS

duration, severity of heart failure, a history of VT and presence of baseline mechanical dyssynchrony influence clinical improvement and/or LV reverse remodeling after CRT.

In part **IB**, determinants associated with long-term outcome (prognosis) after CRT were investigated.

Chapter 7 examined the predictive value of systolic dyssynchrony measured by tissue Doppler velocity vs. tissue Doppler strain imaging on long-term outcome after CRT in 239 patients. Baseline echocardiography with TDI was performed and the time to peak systolic velocity during ejection phase (T_s) and the time to peak systolic strain (T_ε) were assessed for dyssynchrony, that is the maximal delay in T_s and the maximal delay in T_ε among the four left ventricular basal segments. Patients with the maximal delay in T_s ≥65 ms showed a lower event rate for cardiovascular mortality (19% vs. 38%, p = 0.005) and other prognostic endpoints. The maximal delay in T_s (hazard ratio [HR] 0.463, p = 0.005) and ischemic etiology (HR 2.716, p = 0.001) were independent predictors of cardiovascular mortality. In contrast, the maximal delay in T_ε ≥80 ms failed to predict any cardiovascular event.

In **Chapter 8**, the relation between the extent of LV reverse remodeling and clinical/echocardiographic improvement after 6 months of CRT with long-term outcome was investigated in a total of 302 CRT candidates. Based on different extents of LV reverse remodeling, 22% of patients were classified as super-responders (decrease in LVESV ≥30%), 35% as responders (decrease in LVESV 15% to 29%), 21% as non-responders (decrease in LVESV 0% to 14%), and 22% negative responders (increase in LVESV). More extensive LV reverse remodeling resulted in more clinical improvement, with a larger increase in LV function and more reduction in mitral regurgitation (MR). In addition, more LV reverse remodeling resulted in less heart failure hospitalizations and lower mortality during long-term follow-up. Respective 1- and 2-year hospitalization-free survival rates were 90% and 70% in the negative responder group compared with 98% and 96% in the super-responder group (p<0.001).

In **Chapter 9**, the effect of renal function on LV reverse remodeling and long-term outcome after CRT, as well as the relation between LV reverse remodeling and changes in renal function at 6 months follow-up were studied. Out of 490 patients undergoing CRT with a mean estimated glomerular filtration rate (eGFR) of 70±28 ml/min/1.73m^2 at baseline, 263 patients (54%) demonstrated response to CRT at 6 months follow-up. Responders had an eGFR of 74±26 ml/min/1.73m^2 vs. 64±28 ml/min/1.73m^2 in non-responders (p<0.001). During long-term follow-up, patients with an eGFR <60 ml/min/1.73m^2 had higher mortality than patients with an eGFR of 60-90 ml/min/1.73m^2 or an eGFR >90 ml/min/1.73m^2 (p<0.001). Finally, responders to CRT had preservation of renal function (Δ eGFR -0.6), while non-responders had a slight worsening in renal function (Δ eGFR -4.7), p<0.05.

Finally, in **Chapter 10**, several baseline characteristics were investigated in relation to long-term prognosis in 716 consecutive heart failure patients treated with CRT. All available data, including clinical and echocardiographic measurements, were analyzed in relation to

2 end-points: all cause mortality and a combined end-point of all cause mortality or major cardiovascular event. During a mean follow-up of 25±19 months, 141 patients (20%) died (primary end-point). Most of these patients (61%) died due to worsening heart failure. A total of 214 patients (30%) reached the secondary end-point. Larger LVESV, less distance covered in the 6-minute walking test, poor renal function, more severe heart failure, male gender, presence of atrial fibrillation, no posterolateral LV lead and no LV dyssynchrony were associated with poor prognosis after CRT.

Part II

The second part of the thesis discussed in detail, issues related to the LV pacing lead.

In **Chapter 11**, a comprehensive analysis of LV dyssynchrony and the site of latest mechanical activation in 248 patients with ischemic and non-ischemic heart failure scheduled for CRT was performed with 2D speckle-tracking. Patients were divided into five QRS configuration sub-groups: narrow QRS, LBBB, right bundle branch block (RBBB), intraventricular conduction delay (IVCD) and right ventricular (RV)-pacing. With speckle-tracking radial strain analysis, the segments with the least and with the most mechanical activation delay were identified and LV dyssynchrony was defined as the time delay between the two. Mean LV dyssynchrony in all patients was 186±122 ms. Site of latest activation was predominantly located in the lateral (27%), posterior (26%) and inferior (20%) segments. Furthermore, extent of LV dyssynchrony was comparable between QRS configuration sub-groups. An unequal distribution of LV segments with the most mechanical delay was observed in the LBBB and RV-pacing sub-groups ($p<0.001$ for both), while in the narrow, RBBB and IVCD sub-groups, a more heterogeneous distribution was noted. No differences in distribution pattern or in extent of LV dyssynchrony were observed between ischemic and non-ischemic heart failure patients. It was therefore concluded that the lateral, posterior and inferior segments take up 73% of total latest activated segments in heart failure patients eligible for CRT, and that the presence of LV dyssynchrony can be observed in all QRS configurations. The site of latest activation may be outside the lateral or posterior segment, making echocardiographic assessment of LV dyssynchrony and site of latest activation a valuable technique to optimize patient outcome after CRT.

In **Chapter 12**, the site of latest mechanical activation was determined by speckle-tracking radial strain analysis and related to the LV lead position on chest X-ray in 244 CRT candidates. Significant LV reverse remodeling (reduction in LVESV from 189±83 ml to 134±71 ml, $p<0.001$) was noted in the group of patients with a concordant LV lead position ($n = 153$, 63%), whereas patients with a discordant lead position showed no significant improvements. In addition, during long-term follow-up (32±16 months), less events (combined for heart failure hospitalizations and death) were reported in patients with a concordant LV lead position. Moreover, a concordant LV lead position appeared to be an independent predictor of hospitalization-free survival after long-term CRT (HR 0.22, $p = 0.004$).

Chapter 13 analyzed the relative merits of LV dyssynchrony, LV lead position, and myocardial scar to predict long-term outcome after CRT. In 397 ischemic heart failure patients, 2D speckle-tracking imaging was performed, with comprehensive assessment of LV radial dyssynchrony, identification of the segment with latest mechanical activation, and detection of myocardial scar in the segment where the LV lead was positioned. Segments with <16.5% radial strain in the region of the LV pacing lead were considered to have extensive myocardial scar. The LV lead position was derived from chest X-ray. In 271 patients (68%), the LV lead was placed at the latest activated segment (concordant LV lead position), and the mean value of peak radial strain at the targeted segment was 18.9±12.6%. Larger LV radial dyssynchrony at baseline was an independent predictor of superior long-term survival (HR 0.995, p = 0.001), whereas a discordant LV lead position (HR 2.086, p = 0.001) and myocardial scar in the segment targeted by the LV lead (HR 2.913, p<0.001) were independent predictors of worse outcome. Addition of these 3 parameters yielded incremental prognostic value over the combination of clinical parameters.

In **Chapter 14**, the relationship between the site of latest mechanical activation as assessed with gated myocardial perfusion SPECT (GMPS), LV lead position and response to CRT was evaluated in 90 patients with advanced heart failure. In 52 patients (58%), the LV lead was positioned at the site of latest mechanical activation (concordant), and in 38 patients (42%) the LV lead was positioned outside the site of latest mechanical activation (discordant). CRT response (reduction in LVESV ≥15% at 6 months follow-up) was more often documented in patients with a concordant LV lead position than in patients with a discordant LV lead position (79% vs. 26%, p<0.01). More importantly, patients with a concordant LV lead position showed significant improvement in LV ejection fraction (LVEF), LVESV and LV end-diastolic volume (LVEDV) (p<0.05 for all), whereas patients with a discordant LV lead position showed no significant improvement in these variables.

Chapter 15 aimed to investigate whether sequential biventricular pacing provides substantial benefits over conventional simultaneous stimulation in ischemic vs. non-ischemic patients. In 69 patients, the V-V pacing interval was optimized by measuring LV systolic performance and LV dyssynchrony at every 20 ms interval. Optimized sequential pacing provided a significant improvement in LV systolic function compared to simultaneous pacing and was associated with a significant reduction in LV dyssynchrony (from 33±31 ms to 19±24 ms, p<0.001). The increase in LVEF was greater in non-ischemic as compared to ischemic patients. However, V-V optimization yielded a larger improvement in LV systolic performance in ischemic patients (p = 0.03). Finally, a significant correlation was observed between LV scar tissue and optimal V-V interval (r = 0.58, p<0.001), with a larger extent of scar related to a larger level of LV pre-activation, probably reflecting slow intra-LV conduction.

In **Chapter 16**, the requirement for coronary sinus (CS) lead intervention after CRT and the effectiveness of endovascular replacement were assessed in 577 patients. During a median follow-up time of 645 days, 7% of the patients required a CS lead intervention. Cause of

the intervention was an elevated threshold (n = 13), loss of capture (n = 20), or intractable phrenic nerve stimulation (n = 6). Fifteen patients required a CS lead intervention before first scheduled follow-up (2 months after implantation). Thirteen patients needed a CS lead intervention more than 6 months after implantation. The first endovascular replacement was successful in 86% (32 of 37), whereas a second endovascular approach failed in 66% (2 of 3). It was concluded that the long-term requirement for CS lead interventions is 7% and that endovascular repositioning or replacement is successful in the majority of cases.

Part III

In the third part of the thesis several special considerations in the treatment of heart failure patients with CRT were discussed in detail.

In **Chapter 17**, the impact of QRS duration and etiology of heart failure on the pattern of LV long- and short-axis dyssynchrony using TDI and 2D speckle-tracking imaging was investigated. A total of 448 heart failure patients from two cardiac centers were examined for the occurrence of longitudinal dyssynchrony by TDI, and for radial dyssynchrony by 2D speckle-tracking imaging. In addition, region(s) of the latest mechanical contraction were determined. Longitudinal dyssynchrony was identified in 263 (59%) patients and radial dyssynchrony in 185 (41%). A total of 125 (28%) patients had both longitudinal and radial dyssynchrony, 138 (31%) had only longitudinal, 60 (13%) had only radial, and 124 (28%) had neither form of dyssynchrony. TDI showed that the single most delayed segment was the septal, lateral, anterior, inferior, anteroseptal and posterior wall in 12%, 27%, 12%, 19%, 7% and 13% of patients, respectively, while multisegmental delay occurred in 10% of patients. These figures were 10%, 8%, 5%, 10%, 12%, 14% and 41%, respectively, using 2D speckle-tracking. When compared between patients with wide and narrow QRS complexes, both longitudinal (63% vs. 53%) and radial (49% vs. 36%) dyssynchrony parameters were more frequently positive in the wide QRS group (both $p<0.05$). When compared between non-ischemic and ischemic patients, the prevalence of longitudinal dyssynchrony was comparable (61% vs. 57%, $p = 0.467$), while radial dyssynchrony was marginally more common in the non-ischemic group (47% vs. 37%, $p = 0.049$). However, the distributions of the most delayed segment between the sub-groups were similar when assessed by the same echocardiographic method. In patients with advanced systolic heart failure, the patterns of longitudinal and radial dyssynchrony are therefore heterogeneous, and mechanical dyssynchrony tends to be more prevalent in the wide QRS group and the non-ischemic group.

Chapter 18 evaluated the diagnostic accuracy for several ECG criteria in determining significant RV dilatation in heart failure patients who have LBBB on the surface ECG. Standard 12-lead ECGs were obtained in 173 heart failure patients with known LBBB. From the ECG, 3 criteria for RV dilatation were defined; presence of terminal positivity in lead aVR (late R wave in lead aVR), low voltage (<0.6 mV) in all extremity leads and an R/S ratio <1 in lead V5. Significant RV dilatation was defined as either an RV base-to-apex length ≥86 mm, or an RV

diastolic area ≥33 cm^2. Eighty-six patients (50%) had a late R wave in lead aVR, 36 patients (21%) had low voltage in the extremity leads and 67 patients (39%) had an R/S ratio <1 in lead V5. An RV base-to-apex length ≥86 mm was present in 67 patients (39%), while 62 patients (36%) had an RV diastolic area ≥33 cm^2. Any combination of 2-3 positive criteria could predict an RV base-to-apex length ≥86 mm with a positive predictive value (PPV) of 89% and a negative predictive value (NPV) of 88%. Similarly, an RV diastolic area ≥33 cm^2 was predicted with a PPV of 80% and a NPV of 88%.

In **Chapter 19**, the effects of CRT in NYHA functional class IV heart failure patients was investigated. A total of 61 patients with symptoms according to NYHA functional class IV were evaluated before CRT implantation and at 6 months follow-up for clinical changes according to the Clinical Composite Score (CCS) and changes in LV volumes and function. Additionally, survival was evaluated during long-term follow-up. At 6 months follow up, 9 (15%) patients had died and 2 (3%) patients were admitted for worsening heart failure. The remaining 39 (64%) patients improved according to the CCS. Reductions in both LVESV (from 167±88 ml to 147±93 ml, p = 0.009) and LVEDV (from 211±100 ml to 199±113 ml, p = 0.135) were observed, as well as a significant improvement in LVEF (from 22±8% to 28±9%, p<0.001). During a mean follow-up of 30±26 months, 36 patients (59%) died, 27 (75%) of which due to worsening heart failure. Respective 1- and 2-year mortality rates were 25% and 38%. It was concluded that although CRT reduces LV volumes and improves cardiac function in patients with NYHA functional class IV heart failure, mortality remains high.

In **Chapter 20**, the effect of CRT on cerebral blood flow was evaluated. In this particular study, LV systolic function and cerebral blood flow were assessed in 35 heart failure patients, before and 6 months after CRT. Additionally, 15 heart failure patients, not being candidates for CRT were included as a control group. Peak-systolic velocity (PSV), end-diastolic velocity (EDV), mean velocity and pulsatility index (PI = [PSV-EDV] / mean velocity) were obtained with the use of transcranial Doppler from the right middle cerebral artery. At 6 months follow-up, PSV significantly increased from 83±20 cm/s to 100±20 cm/s (p = 0.001), EDV increased from 29±7 cm/s to 37±8 cm/s (p<0.001) and mean velocity increased from 47±10 cm/s to 58±11 cm/s (p<0.001), only in responders to CRT (reduction in LVESV ≥15%). Conversely, no significant changes in cerebral blood flow were observed in non-responders and controls. Therefore, CRT induced an increase in cerebral blood flow and this increase was related to the improvement in LV systolic function.

In **Chapter 21**, in was hypothesized that the acute response in baroreflex sensitivity (BRS) after the institution of CRT has predictive value for mid-term response. One day after implantation of a CRT device in 33 patients, non-invasive BRS and heart rate variability (HRV) was measured in 2 conditions: CRT device switched on and switched off (on/off order randomized). CRT responders were defined as patients in whom LVESV at 6 months follow-up had decreased by ≥15%. In responders, CRT increased BRS by 30% (p = 0.03); this differed significantly (p = 0.02) from the average BRS change (-2%) in non-responders. CRT also increased

HRV by 30% in responders (p = 0.02), but there was no significant difference found compared with the increase in HRV (8%) in non-responders. Receiver-operating characteristic (ROC) curve analysis revealed that the percent BRS increase had predictive value for the discrimination of responders and non-responders (area under the curve, 0.69; maximal accuracy, 0.70). These findings suggest that the autonomic nervous system is actively involved in CRT-related reverse remodeling.

Chapter 22 investigated whether LV reverse remodeling is influenced by interruption of CRT, and, whether long-term continuous pacing is necessary in patients with reverse LV remodeling. A total of 135 recipients of CRT were selected after showing LV reverse remodeling. During interruption of CRT, an acute deterioration in LV function, MR, and LV desynchronization were noted in responder patients (with significant LV reverse remodeling). For comparison, 100 non-responder patients (without LV reverse remodeling) showed no significant echocardiographic changes during interruption of CRT. Despite the presence of LV reverse remodeling, interruption of CRT resulted in worsening of LV function and desynchronization and therefore, continuous long-term pacing is warranted to maintain the beneficial effects of CRT.

PART IV

In the fourth and final part of the thesis, the possible future applications and emerging indications of CRT were described.

In **Chapter 23**, an overview was given on the use of CRT outside the current guidelines, and the potential indications for patient groups that are currently not considered to have a class I indication for CRT. Furthermore, an summary was provided on strategies to optimize outcome of patients by means of multimodality cardiac imaging.

Chapter 24 aimed to elucidate the possible beneficial effect of CRT in heart failure patients with a narrow QRS complex. A total of 123 consecutive heart failure patients with a narrow QRS complex (<120 ms) undergoing CRT were included at 2 centers. Several widely accepted measures of mechanical dyssynchrony were evaluated: LV filling ratio (LVFT/RR), LV pre ejection time (LPEI), inter ventricular mechanical dyssynchrony (IVMD), opposing wall delay (OWD) and anteroseptal posterior wall delay with speckle-tracking (ASPWD). Measures of dyssynchrony were frequently observed in patients with a narrow QRS complex. Nonetheless, for LVFT/RR, LPEI and IVMD, presence of predefined significant dyssynchrony was less than 20%. Significant intraventricular dyssynchrony was more widely observed. With ROC curve analyses, both OWD and ASPWD demonstrated to be useful in predicting response to CRT in narrow QRS patients with a cut-off value of 75 ms and 107 ms, respectively.

In **Chapter 25**, 41 patients who were enrolled in a "narrow" QRS sub-study from the earlier mentioned PROSPECT trial were analyzed. These patients had a QRS complex <130 ms, but documented evidence of mechanical dyssynchrony by any of 7 pre-defined echocardiographic measures. After 6 months of CRT, 26 (63.4%) patients showed improvement

according to the CCS, 4 (9.8%) remained unchanged and 11 (26.8%) worsened. In patients with paired data, the 6-minute walking distance increased from 334±118 m to 382±128 m, (p = 0.003) and quality-of-life score improved from 44.2±19.7 to 26.8±20.2 (p<0.0001). Furthermore, there was a significant decrease in LV end-systolic diameter (from 59±9 mm to 55±12 mm, p = 0.002) and in LV end-diastolic diameter (from 67±9 mm to 63±11 mm, p = 0.007). These results from a large multicenter trial suggest that CRT may have a beneficial effect in heart failure patients with a narrow QRS complex and mechanical dyssynchrony as assessed by echocardiography.

Chapter 26 evaluated CRT as a therapeutic option in heart failure patients with functional MR and high operative risk, and investigated the effect of MR improvement 6 months after CRT on long-term prognosis. A total of 98 consecutive patients with moderate-severe functional MR and high operative risk underwent CRT according to current guidelines. Thirteen (13%) patients died before 6 months follow-up. In the remaining 85 patients, significant reduction in MR was observed in all evaluated parameters. In particular, 42 (49%) patients improved ≥1 grade of MR and were considered MR improvers. Survival was superior in MR improvers as compared to MR non-improvers, log rank p<0.001. More importantly, MR improvement was an independent prognostic factor for survival (HR 0.35, p = 0.043).

CONCLUSIONS

In the last decade, CRT has evolved as a very successful treatment strategy in selected patients with drug refractory heart failure. Evidence of large clinical trials undeniably established the beneficial effects of CRT in addition to optimal medical treatment on both morbidity and mortality. These effects include improved LV systolic function, improved clinical status, improved exercise tolerance and improved quality of life. The outcomes of these large trials resulted in the fact that since many years, CRT is considered a class I indication in patients with end-stage heart failure (NYHA class III-IV) with an LVEF ≤35% and a QRS complex duration ≥120 ms.

Nonetheless, about 30% of patients do not demonstrate response and it has become clear that many factors determine outcome in patients undergoing CRT. Several patient characteristics have a strong influence on both response at 6 months follow-up and prognosis during long-term follow-up. Most important among these characteristics are gender, the presence of atrial fibrillation, renal failure and the presence of significant LV dyssynchrony. In addition to these patient characteristics, the position of the LV pacing lead in relation to the site of latest activation and potential scar tissue may have a great influence on outcome, especially in patients with ischemic etiology of heart failure. Integration of patient characteristics, LV lead position with information on LV dyssynchrony and scar tissue may help to improve patient selection and response to CRT.

As large trials continued, more evidence for the benefit of CRT in other patient populations came available. As a result, CRT is also considered a class I indication in patients with mild symptoms of heart failure (NYHA class II) with an LVEF ≤35% and a QRS complex duration ≥150 ms since 2010. It is not unlikely that the favorable effects of CRT will be extended to other patient groups in the coming years. These groups include asymptomatic (NYHA class I) patients, patients with a narrow QRS complex (<120 ms) or patients with heart failure but preserved LVEF (≥45%). Many clinical trials are still underway and the future for CRT cannot be predicted at this moment. Apart from the earlier mentioned, previously known beneficial effects, CRT also seems to improve other conditions frequently observed in patients with systolic heart failure. The improved LV systolic function induced by CRT increases cerebral blood flow (which is regularly decreased in heart failure patients). In addition to improved cerebral blood flow, CRT induced improvement in LV function also results in stabilization of renal function, which is also frequently decreased in heart failure patients. Finally, patients with severe functional MR and high operative risk also derive benefit from CRT. In these patients, CRT leads to a decrease in MR, which in turn results in improved prognosis. Perhaps CRT may one day be used as an effective treatment strategy in these patient groups.