Chapter 12

Summary and conclusions

The aim of this thesis was to evaluate the association between pacing and heart failure, focusing on the effect of cardiac resynchronization therapy (CRT) on specific subgroups of patients under-represented in randomized clinical trials and on the improvement of selection and risk stratification of patients referred to CRT using novel (imaging) approaches.

In the introduction (Chapter 1), the potential role of pacing as a cause, but most importantly as therapeutic option in heart failure patients is described. It also elaborates on the need of further studies in subpopulations under-represented in randomized clinical trials and on novel approaches to optimise patient selection and risk stratification in CRT.

PART I: PACEMAKER THERAPY AND DEVELOPMENT OF HEART FAILURE

In the first part, **Chapter 2** evaluates the relationship between induction of tricuspid regurgitation (TR) after device implantation (pacemaker or implantable cardioverter defibrillator; ICD) and development of heart failure. In total 239 patients without significant TR prior to ICD or pacemaker implantation were re-evaluated 1-1.5 years after device implantation. Approximately 2/5th of the patients developed clinically significant TR after right ventricular (RV) lead implantation. Patients with significant lead-induced TR showed worse long-term outcome in terms of overall survival (p=0.038) and/or combined with heart failure related events (p=0.017). At multivariate analysis, significant lead-induced TR was independently associated with all-cause mortality (hazard ratio (HR), 1.75, p=0.047) together with age, left ventricular ejection fraction (LVEF) and RV pacing percentage. These findings suggest that patients with RV lead placement are at higher risk for heart failure development and poor long-term prognosis. Therefore, routine echocardiographic follow-up in these patients might help in optimization of patient management.

PART II: CARDIAC RESYNCHRONIZATION THERAPY IN SUBPOPULATIONS UNDER-REPRESENTED IN RANDOMIZED CLINICAL TRIALS

CRT is an effective treatment for heart failure patients who meet the inclusion criteria of the main randomized controlled trials and current guidelines. Latest estimations indicate that around 400 patients/million population/year might be candidate for CRT. However, the number of CRT units implanted in 2011 was 140/million population (data from 16 European countries). Therefore, there is still a significant margin to improve application of current guidelines and improve treatment of heart failure

patients. In **Chapter 3** we reviewed the literature and the evidence for CRT benefit in subpopulations underrepresented in clinical trials. Whether older age, non-left bundle branch block (non-LBBB) QRS morphology or the presence of associated co-morbidities such as renal dysfunction or diabetes contribute to the low use of this guideline-recommended therapy remains unclear. Although dedicated randomized controlled trials in these subpopulations are needed to further determine which patients may benefit from CRT, the current available evidence from registries could be used for clinical decision-making. A careful evaluation of comorbidities and an estimate of life expectancy have been recommended by major societies.

In **Chapter 4** we evaluated the association between diabetes and CRT outcomes. Improvements in clinical, echocardiographic and long-term outcome were evaluated and compared between CRT patients with diabetes and without. At 6-month follow-up, significant LV reverse remodelling was observed both in patients with and without diabetes. However, response to CRT occurred more frequently in patients without diabetes as compared to patients with diabetes (57% vs.45%, $p<0.05$). Despite the less pronounced magnitude of LV reverse remodeling and LV diastolic function improvement among patients with diabetes, patients with diabetes experienced significant benefit from CRT in terms of functional parameters, LV diastolic and LV systolic function, emphasizing that CRT should not be withheld based on presence of diabetes. Determinants of response to CRT among patients with diabetes were LV dyssynchrony, ischemic cardiomyopathy and insulin use. At long-term follow-up (median of 38 months), a superior survival was observed among patients without diabetes. Both primary (all-cause mortality) and secondary (cardiac death or heart failure hospitalization) end points were significantly more frequent among patients with diabetes ($p<0.001$). Particularly, diabetes was independently associated with all-cause mortality together with ischemic cardiomyopathy, renal function, LV end-systolic volume (LVESV), LV dyssynchrony and LV diastolic dysfunction.

Chronic kidney disease (CKD) is a common co-morbidity among heart failure patients and has been related to poor prognosis. **Chapter 5** evaluated the impact of CRT implantation in patients with severe renal dysfunction (CKD stage IV). CRT implantation in patients in CKD stage IV was associated with improvement in symptoms, LV systolic performance and in renal function as compared to their counterparts treated with ICD only. At 6-month follow-up, a significant reduction in LVESV was observed in CRT patients as compared to ICD (from 159±78ml to 145±78ml in CRT patients, from 126±54ml to 119±49ml in ICD patients $p=0.048$) and CRT-response was observed in 22 patients (30%). Compared to ICD patients, renal function improved among CRT patients (estimated glomerular filtration rate (eGFR) increased from 25±4 to 30±9ml/min/1.73m^2; interaction time and group $p=0.04$) and was more pronounced among CRT-responders (25±3 to 34±9ml/min/1.73m^2

p<0.001). **Chapter 5** further shows that despite the relatively lower CRT response in this category of very ill patients, when response to CRT occurred, it was associated with better long-term outcome (including survival, heart failure hospitalization and ICD therapy) as compared to CRT non-response or to ICD. The combined end point was observed in 17 ICD and 62 CRT patients. CRT patients showed superior survival as compared to ICD patients (p=0.03). More importantly, CRT-response was independently associated with improved survival free from the combined end point (p=0.04) after adjustment for clinical and echocardiographic parameters.

The incidence and prevalence of heart failure increases significantly with aging and frequently, older patients present with more advanced heart failure stage than young patients. However, it remains unclear the importance of age in the prognosis of CRT candidates. **Chapter 6** evaluated the relationship between aging (>75 years) and CRT benefit and safety. Similar rates of device-related in-hospital (within 24h; p=0.552), early (within 30 days; p= 0.984) and long-term adverse events (entire follow-up HR 0.90, p=0.620) were observed among elderly and non-elderly patients. Furthermore, comparable improvements in clinical symptoms and LV function were observed between the two groups at 6-month follow-up. During long-term follow-up (median 38.6 months), all-cause mortality rate was significantly higher among the elderly patients. However, the differences in cumulative event rates started after 4 years of follow-up (p=0.013) and the cause of death was mainly non-cardiac (29% in the elderly versus 19% in non-elderly, p<0.001). Diabetes (HR 2.322, p=0.019), impaired renal function (HR 0.975,p=0.006) and reduced 6-minute walk distance (HR 0.996, p<0.019) were independently associated with all-cause mortality in elderly patients. This chapter shows us the importance of distinguishing chronology from biology: life expectancy is determined by the time ahead (from the present until death) and not the time past (from the birth until present). These observations underline the importance of providing equal opportunity to elderly patients and not using age the decisive parameter for CRT implantation.

RV function is an independent prognosticator in patients with heart failure and has shown to be important in determining the response to medical therapy in heart failure patients. As shown in **Chapter 7**, improvement in RV function after CRT was an independent predictor of improvement in LV systolic function and was associated with improvement in LV diastolic function. Significant baseline RV dysfunction was observed in 286 (34%) individuals. During long-term follow-up (median 44 months), 288 deaths occurred. RV impairment was associated with a greater incidence of all-cause mortality (p<0.001). Independent predictors of all-cause mortality were functional class, ischemic etiology, diabetes, atrial fibrillation, renal dysfunction, LVESV, LV dyssynchrony and reduced tricuspid annular plane systolic excursion (TAPSE). Importantly, TAPSE added prognostic value to these recognized prognostic

parameters ($p<0.001$). Furthermore, improvement in RV function after CRT was independent of the improvement in LV systolic function but significantly associated with the improvement in LV diastolic function. Importantly, a favorable RV functional response to CRT was associated with superior survival.

Majority of patients in randomized controlled clinical trials data evaluating CRT had left bundle branch block (LBBB). Patients with right bundle branch block (RBBB) or nonspecific intraventricular conduction delay (IVCD) were underrepresented in clinical trials. **Chapter 8** evaluated the association between CRT and RBBB. Patients referred for CRT with RBBB exhibited interventricular and LV dyssynchrony, although less than their LBBB counterparts, and the study showed that in patients with RBBB, the presence of pre-implantation LV dyssynchrony may be an important determinant of death or heart failure hospitalization after CRT.

PART III: OPTIMIZATION OF PATIENT SELECTION AND RISK STRATIFICATION IN CARDIAC RESYNCHRONIZATION THERAPY MANAGEMENT

Given the evidence gap between selection criteria of CRT trials and those in clinical practice, we developed a multifactorial risk stratification score that could be used for clinical shared decision-making for application and management of CRT patients. Using pre-implantation data clinical, electro- and echocardiographic data, we derived a CRT specific risk stratification score that enables us to predict mortality at 1 year and 5 years after CRT implantation as discussed in **Chapter 9**. The CRT-SCORE was designed to stratify the survival outcome based on the individual risk and may therefore serve as an essential part of shared-decision making tool in the clinical practice for both application and management of CRT. The model and corresponding risk index predicted risk of 1- and 5-year mortality in a broad sample of CRT candidates using pre-implantation data. The CRT-SCORE was derived from a large cohort of 1053 CRT patients (age 67±10 years, 76% male) and the model was calibrated after 100 multiple-imputed datasets and finally, cross-validated linear prognostic-scores were calculated. Using atrioventricular junction ablation, age, gender, etiology, NYHA class, diabetes, hemoglobin level, renal function, LBBB, QRS duration, atrial fibrillation, LV systolic and diastolic function and mitral regurgitation, CRT-SCORE was calculated and showed a good discriminative ability (AUC 0.773 at 1 year and 0.748 at 5 years). Furthermore, based on distribution of CRT-SCORE, patients from lower and higher risk patient groups were identified. An estimated mean survival of 98% at 1 year and 92% at 5 years were observed in the lowest 5% risk group (CRT-SCORE: -4.42 till -1.60), while the highest 5% risk group (CRT-SCORE: 1.44 till 2.89) showed poor survival: 78% at 1 year and 22% at 5 years. The CRT-SCORE provided

estimates of risk that may assist clinicians in counseling patients and families and guides clinical shared decision-making. Furthermore, by estimation of prognosis, it may facilitate an optimized and tailored outpatient follow-up.

Imaging-derived markers of dyssynchrony have been studied extensively and the additional value of these parameters in clinical practice was considered of limited value. However, as technology improves and advanced imaging modalities become more commonplace, there may be opportunities to discover more reliable and standardized markers of mechanical dyssynchrony that could be of use for the clinical practice. Currently, the use of three-dimensional (3D) echocardiography for assessment of LV volumes is recommended and assessment of LV dyssynchrony gained increasing attention as a growing number of studies demonstrated its added value for identification of CRT benefit. In **Chapter 10,** we evaluated the prognostic value after CRT of the systolic dyssynchrony index (SDI), a 3D echocardiography measure of LV dyssynchrony. SDI has been evaluated as continuous value, in quartiles and with previously proposed cut-off values of SDI >6.4% and SDI > 9.8%. The median SDI was 8.0 % (IQR 5.6-11.3%). During long-term follow-up (median 45 months), the end point (combination of all-cause mortality, heart transplantation and LV assist device implantation) was observed in 94 (23%) patients. SDI was independently associated with the end point together with ischemic etiology, diabetes and renal function (p=0.003) after adjustment for age, ischemic etiology, presence of atrial fibrillation, presence of diabetes, renal function, hemoglobin level, New York Heart Association (NYHA) functional class and postero-lateral LV lead position. The optimal SDI cut-off for detection of the primary end point on receiver operating characteristic curve analysis was SDI >6.8% (area under the curve, 0.634; sensitivity, 59%; specificity, 67%). In **Chapter 10** is demonstrated that SDI is independently associated with long-term prognosis after CRT and might therefore important to optimize risk-stratification in these patients. Therefore, further research with the use of 3D echocardiography in clinical trials is required.

Most studies evaluating the impact of scar on improvements after CRT focused on presence of myocardial scar tissue and showed that the amount of scar tissue appears to determinant of response to CRT. Global contrast-enhanced myocardial T_1 mapping is an emerging non-invasively quantification technique of diffuse interstitial myocardial fibrosis. In **Chapter 11,** we quantified diffuse interstitial myocardial fibrosis using myocardial contrast-enhanced T_1 mapping and evaluated its impact on LV reverse remodeling after CRT. In 40 patients with non-ischemic cardiomyopathy myocardial T_1 mapping was performed using an inversion-recovery Look-Locker sequence after gadolinium injection and myocardial contrast-enhanced T_1 time values were assessed from segments without delayed-contrast enhancement and normalized for heart rate. The mean myocardial contrast-enhanced T_1 time was 351±46ms.

At 6-month follow-up, LV reverse remodeling was assessed and a reduction from 156±73 to 119±70 ml was in LV end-systolic volume.

Myocardial contrast-enhanced T_1 time showed a significant correlation with LV reverse remodeling (r=0.5, p=0.001) together with hemoglobin level, renal function, LV dyssynchrony and presence of delayed-contrast enhancement (DCE). Multivariate regression analysis identified myocardial contrast-enhanced T_1 time (β -0.160, p=0.022), LV dyssynchrony (β -0.267, p=0.002), and renal function (β -0.334, p=0.021) as independent associates of LV reverse remodelling and might therefore be used to optimize patient selection.

CONCLUSIONS

Development and progression of heart failure is a known complication due to RV pacing. Additionally, this thesis has shown that significant lead-induced TR due to the mechanical presence of an RV lead though the tricuspid valve was associated with worse long-term prognosis.

CRT is one of the main therapeutic breakthroughs in heart failure of the last decade, reducing morbidity and mortality in these patients. Published data has demonstrated 60-70% efficacy of this therapy in improving LV function, inducing LV reverse remodeling and improving long-term outcome of heart failure patients. However, the associated costs and risks demand an accurate selection of heart failure patients to maximize the results. The evidence provided by large randomized controlled trials supports the recommendations for CRT in heart failure patients who remain symptomatic despite optimal medical treatment (NYHA functional class II-IV), have poor LVEF (≤35%) and wide QRS complex (≥120 ms).

However, patients included in landmark trials do not completely mirror patients undergoing CRT in the clinical practice, who are usually older and have more frequently associated comorbidities such as renal dysfunction, diabetes or atrial fibrillation. Therefore, current recommendations on CRT for these subgroups of patients remain unclear. This thesis shows a beneficial, although limited, effect of CRT also in elderly, in patients with diabetes and CKD stage 4, and therefore suggests that this therapy should not be withheld based on certain co-morbidities or on age alone. Furthermore, it shows that in patients referred to CRT with RBBB, the presence of pre-implantation LV dyssynchrony is an important determinant of prognosis and may help in patient selection. In addition, our studies demonstrated that when a favourable improvement in RV function is observed after CRT, patients show also a better prognosis.

To improve risk stratification in the clinical practice, this thesis proposed a CRT-SCORE using heart failure and CRT-specific parameters, which showed to provide valuable risk estimation that may assist clinicians in counseling patients and families and guides clinical shared decision-making. Furthermore, by estimation of prognosis, it may facilitate an optimized and tailored outpatient follow-up.

Finally, novel approaches to optimize patient selection are presented in this thesis. SDI, a 3D echocardiography LV dyssynchrony measurement showed to be independently associated with long-term prognosis after CRT. In addition, presence of diffuse myocardial fibrosis was evaluated with T_1 mapping, a novel CMR techniques and its association with CRT efficacy in term of LV reverse remodeling has been demonstrated in patients with non-ischemic cardiomyopathy.