University of Alberta

Evaluating Therapies and Outcomes in Acute and Chronic Heart Failure

by

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Dedication

This thesis is dedicated to my father, who is my role model; my mother, for her continuous encouragement; my wife, for her endless love and support; and to my son, who is the joy of my heart.

Abstract

Heart failure is common, and is associated with significant mortality, morbidity, and reduced quality of life. The objective of this thesis is to evaluate some therapeutic interventions and outcomes in patients with acute and chronic heart failure. In the first part, the efficacy of cardiac resynchronization therapy in patients with heart failure was explored, with more focus on patients with mild symptoms. Although cardiac resynchronization was found to reduce mortality and heart failure hospitalization and improve left ventricular ejection fraction in patients with mild symptoms, it did not improve functional outcomes, like quality of life or 6-minute walk test. In the second part of this thesis, the role of peak expiratory flow rate in assessing dyspnea improvement in patients with acute heart failure was evaluated by testing its correlation with NT-proBNP, a known prognostic marker. No significant correlation was found between short term changes in peak expiratory flow and NT-proBNP.

Acknowledgement

I would like to acknowledge my supervisor, Dr. Justin Ezekowitz, for his never-ending support. He has been a great source of motivation and encouragement, and has been proud of my achievements. I would also like to gratefully acknowledge my co-supervisors, Dr. Paul Armstrong and Dr. Finlay McAlister. In addition, I would like to thank Dr. Jeffrey Bakal for his time and efforts. Working with this distinguished team has unlocked my potentials and has changed my life substantially.

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Chapter 1

Introduction

Heart failure (HF) is a syndrome, characterized by abnormal cardiac function that results in symptoms and signs of low cardiac output and/or pulmonary or systemic congestion (1). In acute decompensated heart failure (ADHF), patients present with either new development or worsening of already-existing HF symptoms and signs (2,3), whereas outpatient and ambulatory HF patients are seen as a chronic disease. Regardless of the definition, HF is common, with an estimated prevalence of about 1% in Canada in 2005 (4), and the projected number of incident hospitalizations for HF in Canada is expected to increase (5). Thus, acute and chronic heart failure represent two phenotypes in a spectrum of a single clinical syndrome with significant heterogeneity.

Despite the advancement in pharmacological and device-based therapy, HF is still associated with significant morbidity and mortality (1). In 2004, the estimated average annual in-hospital mortality rate in Canada was 9.5% for patients older than 65 years and 12.5% for patients older than 75 years (6). For those who survive the hospital admission, the risk of re-admission remains high (8.7%, 14.1%, and 23.6% at 30 days, 90 days, and 1 year, respectively) (6).

Chronic heart failure-related morbidity and mortality has decreased significantly with pharmacological and non-pharmacological interventions. In addition, implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) have been shown to improve outcomes in appropriately selected patients who are already on optimal medical therapy (7,8). The rationale for using CRT is based on the fact that ventricular

dyssynchrony is common in HF patients who have evidence of conduction abnormalities, which can reduce the efficacy of ventricular contraction (9). The mechanism of benefit of CRT is thought to be as a result of 1) improved contractile function (without increase in metabolic demands) (10) and 2) reverse remodeling (reduction in left ventricular size and improvement in LVEF) (8,11). Although the evidence for using CRT in certain HF populations is well established, a few questions remain. In the first part of this thesis, a systematic review and meta-analysis of 25 RCTs is presented evaluating a therapy in the chronic, ambulatory patients with HF. The aim of this systematic review was to explore the efficacy and safety of CRT in patients with less symptomatic HF, in patients with narrow QRS duration on ECG, and the use of left ventricular (LV) lead instead of the conventional biventricular CRT.

Similar to chronic heart failure, acute decompensated heart failure (ADHF) has been an area of extensive research. Many trials have been conducted to evaluate novel therapies in ADHF. Overall, some trials reported earlier symptom improvement with certain therapies (12,13), but no mortality benefit has been found with any of the drugs that have been tested in ADHF.

As dyspnea is the most common presenting symptom in these patients, its resolution has been used as one of the end-points in many of these studies. Moreover, for a drug to be approved by regulatory agencies, it has to either make patients feel better, live longer, or both (14). In most of the RCTs in the field of ADHF, dyspnea improvement has mostly been assessed using subjective

tools (Likert scale, visual analog scale). As dyspnea improvement remains a vital outcome in ADHF (for patients, healthcare providers, and regulatory agencies), it is important to assess it objectively. A recent analysis from ASCEND-HF showed that peak expiratory flow rate (PEFR) is a potential tool that can be used for this purpose. (15)

In the second part of this thesis, the correlation between PEFR and NT-proBNP (a well-established marker for the diagnosis, prognosis, and evaluation of new ADHF therapies) was tested in patients with acute HF – the other end of the HF spectrum. The aim of this study was to further assess the utility of PEFR as a measure of improvement in patients with ADHF.

The objectives of the overall thesis are to explore therapy and outcomes in acute and chronic heart failure, and the correlation between commonly used biomarker outcomes to that of a measure of respiratory function.

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Chapter 2

Meta-analysis: Cardiac Resynchronization Therapy for Patients with Less Symptomatic Heart Failure [1]

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[1] A version of this chapter has been published [Al-majed et al. *Ann Intern Med*. 2011 Mar 15;154(6):401-12]

Introduction

Heart failure is a common disorder, affecting approximately 2.5% of adults in North America and Europe (1,2). Heart failure substantially reduces quality of life and has high morbidity (with frequent emergency department visits and HF hospitalizations) and mortality rates, which creates a great economic burden even when patients receive optimal treatment (1,3-7). In a previous systematic review of 4420 patients in 14 trials (7), McAlister and colleagues demonstrated a 22% relative risk reduction in all-cause mortality and a 37% relative risk reduction in HF hospitalization when cardiac resynchronization therapy (CRT) was added to optimal medical therapy. International guidelines recommend CRT for patients with left ventricular ejection fraction (LVEF) of 0.35 or less, New York Heart Association (NYHA) class III or IV symptoms despite medical treatment, wide QRS duration (>120 ms), and sinus rhythm. (2,8-10)

However, important questions remain regarding heart failure and CRT. First, because nearly all participants (91%) in the randomized, controlled trials (RCTs) identified in the prior systematic reviews had NYHA class III or IV symptoms (7), the effect of CRT in patients with less severe symptoms is unclear. Three RCTs (11-13) assessing the efficacy of CRT in patiently with less severe heart failure symptoms have been published since the previous systematic review (7), and recently the European Society of Cardiology extended its recommendation for CRT to include patients with mildly symptomatic heart

failure who have QRS duration of 150 ms or more (14). Second, patients with a narrow QRS duration and severe heart failure symptoms are not considered candidates for CRT, but mechanical and electrical dyssynchrony do not always co-exist, raising questions about whether these patients may benefit from CRT (15,16). Finally, pacing with a left ventricular lead (without placement of a concomitant right ventricular lead) may provide the same benefit as a 3-lead CRT device (17).

In this systematic review, we update the previous systematic review (7) and explore the benefits and harms of CRT in patients with less symptomatic heart failure, patients with a narrow QRS duration on electrocardiography, and the use of a left ventricular lead alone versus standard CRT.

Methods

Data Source and Searches

We updated and followed the protocol used for the previous systematic review (7). This included electronic literature searches supplemented by hand-searching reference lists of included studies and review articles, proceedings booklets from meetings, U.S. Food and Drug Administration reports, and contact with primary study authors and device manufacturers (Table 2-1 showed the databases searched)(7). The search was not limited to studies published in English or to publication status. The search was last updated on 20 December 2010. (Table 2-2 shows the MEDLINE search strategy).

Study selection

We included RCTs that: [1] enrolled patients with heart failure and LVEF of 0.40 or less, regardless of their baseline NYHA functional class; [2] compared CRT with inactive pacing, right ventricular pacing alone, left ventricular pacing alone, implantable cardioverter defibrillator (ICD) alone (for trials of CRT-ICD vs. ICD), or usual care; [3] reported all-cause mortality, heart failure hospitalization, change in LVEF, or change in functional outcomes (NYHA class, quality of life, 6-minute walk test); and [4] included more than 25 participants.

The primary literature search was done by 1 of the authors. Using standardized inclusion or exclusion forms, 2 of the authors then independently reviewed the full texts of all potentially relevant studies. Final decisions about study inclusion or exclusion were reached by consensus.

Data Extraction and Quality Assessment

Data extraction was done by 2 independent reviewers by using standardized data extraction forms. For crossover trials, data from the first period only (before crossover) were used. Quality assessment of all included studies was done by using the 6 domains of the Cochrane tool for assessing risk for bias (18).

Data Synthesis and Analysis

Primary and Secondary Outcomes

The primary outcome for this systematic review is all-cause mortality. Secondary outcomes include heart failure hospitalizations, quality of life, and

functional outcomes (LVEF and 6-minute walk test). Because we expected duration of follow-up to differ among trials, we explored whether the risk ratios (RRs) for the primary outcome varied by duration of follow-up.

Subgroups and Sensitivity Analysis

A priori, we assessed the efficacy of CRT among studies that included patients with NYHA class I or II symptoms compared with NYHA class III or IV symptoms as a separate subgroup analysis; trials were classified as having patients who were predominantly (>50% but <100%) or exclusively (100%) in one NYHA subgroup or the other. Other prespecified subgroups were sex, age, ischemic etiology, QRS duration, year of enrollment, and whether patients received an ICD. Left ventricular lead-only pacing trials versus biventricular lead trials were evaluated separately.

Statistical Analysis

For dichotomous outcomes (mortality and heart failure hospitalization), risk ratios (RRs) and 95% CI were calculated. For continuous outcomes (such as the 6-minute walk test and quality of life scores), weighted mean differences (WMD) and 95% CI were calculated. Intention-to-treat analyses were performed by using the same end point definitions as in the primary studies. We included results from primary study reports and not from their extended follow-up analyses, although these were reviewed for consistency of results. When reported, the components of a primary outcome were analyzed separately.

Because we expected studies to differ in length of follow-up and study participants, we decided *a priori* to use a DerSimonian–Laird random-effects model for all outcomes (19). The I^2 statistic was used to quantify heterogeneity; a value greater than 50% was considered to indicate substantial heterogeneity (18).

Meta regressions were run to explore potential sources of heterogeneity among studies. The studies were weighted by size and variance and regressed against year of publication, age, sex, percentage of patients with key baseline characteristics of interest (ischemia, atrial fibrillation, and left-bundle branch block), percentage in each NYHA class, mean QRS duration, and background ICD use. We examined the effect of duration of follow up on the RR for all-cause mortality by using an additional meta-regression model.

Review Manager, version 4.2 (Cochrane Collaboration, Copenhagen, Denmark), was used to generate the forest plots and unadjusted RRs; meta-regression and other analyses were done by using R, version 2.12 (R Foundation for Statistical Computing, Vienna, Austria) using the metafor command (20).

Role of the Funding Source

The study was not supported by external funding.

Results

Qualitative Results

Study selection and evaluation

The primary literature search yielded 3942 studies (Figure 2-1: flow diagram for study selection). Of these, 11 RCTs (11-13,17,21-27) met the inclusion criteria and were added to the 14 trials (28-41) from the previous systematic review. (7) All of the newly included trials were published, except for Greater-EARTH (27) (Table 2-3: expansion of all trial names). Greater-EARTH was presented at the 2010 Heart Rhythm Society meeting and was included because the principal investigator provided us with the unpublished data for this review. Additional data and clarifications were provided by the principal investigators of another 5 trials.

Table 2-4 shows the funding sources and quality assessment of included studies. Fourteen trials were double-blind (11-13,17,21,23,25,27-29,31,34-36), 8 trials were single-blind (22,26,30,32,33,39-41), 3 trials were open-label (24,37,38). Eighteen trials randomized patients after successful device implantation, (11,17,21-23,25,26,29-36,39-41), 6 trials did so before device implantation (12,13,24,28,37,38), and timing was not clear in 1 trial (27). Sixteen trials used a parallel study design (11-13,17,21,22,24,25,28,29,31,34-38), and 9 trials used a crossover study design (23,26,27,30,32,33,39-41).

Studies included in the systematic review

Table 2-4 summarizes the baseline characteristics of 9082 patients (5080 patients in intervention group and 4002 in the control group) in the 25 trials. CRT was compared with usual care in 3 trials (24,37,38), right ventricular pacing in 5 trials (23,26,33,39,40), left ventricular pacing in 4 trials (17,22,25,27), either right

or left ventricular pacing in 1 trial (32), and backup (inactive) pacing in 4 trials (28,30,31,41). Eight trials compared CRT plus ICD with ICD alone (11-13,21,29,34-36).

The mean age ranged from 59 years to 73 years, and the trials included predominantly men (Table 2-4). Four trials were restricted to patients with LVEF less than 0.30 (12,13,34,41), 16 trials to those with LVEF less than 0.35 (17,21,22,24,25,27-31,33,35-38,40), and 4 trials to those with LVEF less than 0.40 (11,23,26,39); in 1 trial, LVEF as an inclusion criteria was not clear (32). Twenty-four of the trials included only patients with a QRS duration of 120 ms or greater (mean QRS duration, 148 to 209 ms), whereas the RethinQ Study (21) included patients with a narrower QRS duration but with evidence of mechanical dyssynchrony on echocardiography (172 patients; mean QRS duration, 106 ms).

Three trials (2616 patients) included patients with NYHA I or II exclusively (11,12,36), and 2 trials (158 patients) included predominantly patients with NYHA class I or II symptoms [78% (26) and 69% (27) of patients] but did not report outcomes separately for strata of NYHA classes. One trial (1798 patients) included predominantly patients with NYHA class II symptoms (80%; the remaining 20% had class III symptoms) and reported outcomes separately for strata of NYHA classes, permitting us to split the data into appropriate NYHA subgroups. (13) Of the remaining 19 trials, 11 trials (3445 patients) included patients with NYHA III or IV exclusively (17,21,24,25,30-33,35,37,38) and 8 trials (1065 patients) (22,23,28,29,34,39-41) included predominantly patients with

NYHA III or IV symptoms (62% in 1 trial, 67% in 1 trial, and > 70% in 6 trials) but did not report outcomes separately for strata of NYHA classes.

Quantitative Results

All-cause mortality

Pooled data from all 25 trials show that CRT reduced all-cause mortality by 19% (RR 0.81 [95% CI 0.72 to 0.90]); there was no appreciable statistical heterogeneity among trials (I^2=0%). Excluding trials without events in 1 or both groups did not affect mortality estimates (RR, 0.80 [CI, 0.72 to 0.89]). In the 6 trials that predominantly included patients with NYHA classes I or II symptoms, CRT reduced the risk for all-cause mortality (RR 0.83 [CI 0.72 to 0.96]; I^2 =0%) (Figure 2-2: All-cause mortality with CRT vs. control). Repeating this analysis for the 3 studies that exclusively included patients with NYHA classes I or II symptoms [in addition to the subgroup of patients with NYHA class II symptoms from RAFT (13)] showed similar results (407 deaths in 4054 patients; RR 0.80 [CI 0.67 to 0.96]; I^2 =0%). In the 19 trials enrolling predominantly patients with NYHA III or IV symptoms, CRT reduced the risk for all-cause mortality (RR 0.78 [CI 0.67 to 0.91]; I^2=0%) (Figure 2-2). Repeating this analysis for the 11 studies that included exclusively patients with NYHA classes III or IV symptoms (in addition to the subgroup of patients with NYHA class III from RAFT (13)) showed similar results (666 deaths in 3805 patients; RR 0.80 [CI 0.70 to 0.92]; I^2=0%).

Four studies compared CRT with left ventricular pacing: Two included patients with NYHA class III or IV symptoms (17,25); 1 included patients with NYHA class II, III, or IV patients (22), and 1 included patients with NYHA I,II, and III symptoms (27). Left ventricular pacing alone did not affect on all-cause mortality compared with CRT (RR 0.83, [CI 0.32 to 2.13; I^2 = 27%), although the number of events was small (28 deaths in 677 patients).

Because the trials had different durations of follow-up (ranging from 1 month to approximately 40 months), we examined the effect of follow-up duration on the RR of all-cause mortality. The RR (approximately 0.80) was constant over time (Figure 2-2: Effect of follow-up duration on the efficacy of cardiac resynchronization therapy versus control for all-cause mortality).

Cause-specific mortality

The mortality benefit of CRT was largely driven by a reduction in heart failure-related mortality in the 12 trials that reported this outcome (218 events in 3562 patients; RR 0.64 [CI 0.49 to 0.83]; I^2=0%). However, the CRT and control groups did not differ in the risk for sudden cardiac death (12 trials; 175 events in 3592 patients; RR 1.04 [CI 0.77 to 1.41]; I^2=0%) or in non-cardiac death (7 trials; 41 events in 1910 patients; RR 0.85 [CI 0.46 to 1.57]; I^2=0%).

HF Hospitalization

Overall, CRT was associated with a significant reduction in the risk for hospitalization with heart failure (RR 0.69 [CI 0.58 to 0.82]; I^2= 50%) (Figure 2-4: Heart failure hospitalization with CRT versus control); no appreciable difference

was found between trials enrolling predominantly patients with NYHA class III or IV symptoms (RR 0.65 [CI 0.50 to 0.86; I^2= 57%) and those enrolling predominantly patients with NYHA class I or II symptoms (RR 0.71 [CI 0.57 to 0.87; I^2= 37%), although the absolute rate of HF hospitalization was higher in the former trials (22% vs. 17% in the NYHA I or II trials). CRT was associated with a reduction in heart failure hospitalization in the 2 studies exclusively of patients with NYHA class I or II patients (in addition to the subgroup of patients with NYHA class II from RAFT) (582 events in 3863 patients; RR 0.69 [CI 0.59, 0.80]; I^2=0%) and in the 8 trials that exclusively included patients with NYHA class III or IV symptoms (in addition to the subgroup of patients with NYHA class III from RAFT (13)) (635 in 2361 patients; RR 0.66 [CI 0.51 to 0.87]; I^2=66%). The effects of left ventricular pacing alone on heart failure hospitalization seemed to be similar to those of CRT (3 trials; 36 events in 371 patients; RR 0.96, 95% CI 0.50, 1.87; I^2= 8%).

Given the degree of statistical heterogeneity in the analyses of heart failure hospitalization, which was not explained by NYHA class at baseline, bivariate meta-regression models were used to explore the reasons for statistical heterogeneity. These models demonstrated that the percentage of patients with ischemic heart failure enrolled in the trials explained most of the heterogeneity, because these patients seemed to derive less benefit in heart failure hospitalization than non-ischemic patients. Each 5% increase in the percent of

ischemic patients in an RCT was associated with an 8% relative reduction (CI 3.9% to 12.8%) in the benefits of CRT on heart failure hospitalizations.

Quality of Life

Quality of life was reported in 15 out of the 25 trials. Overall, CRT was associated with a significant improvement in Minnesota Living with Heart Failure Questionnaire (MLHFQ) compared with controls (14 trials; 4283 patients; WMD 6.56 points, [CI 4.08 to 9.04]), but substantial heterogeneity was found (I^2 = 72%) that was largely attributable to symptom status at baseline. Two of the 3 trials (787 participants) including patients with NYHA class I or II symptoms had better MLHFQ scores at baseline [mean MLHFQ score = 40 (35) and 28 (11)] and did not show any appreciable improvement with CRT (WMD 1.82 points [CI -0.77 to 4.41], I^2= 0%). The remaining trials in patients with NYHA class I or II symptoms (12,42) reported no difference between the CRT and control groups in Kansas City Cardiomyopathy Questionnaire (KCCQ) scores (mean change at 12 months, 13.9 vs. 12.1, respectively; p=0.059). In contrast, in the 12 trials (3496 patients) including predominantly patients with NYHA class III or IV symptoms, MLHFQ scores were poorer at baseline and improved statistically and clinically with CRT (WMD 7.39 [CI 4.87 to 9.91]; I^2 = 65%). Results were similar when we repeated this analysis for the 9 trials (2773 participants) of patients with NYHA class III or IV symptoms exclusively (WMD 6.93 [CI 3.90 to 9.96]; I^2 = 71%). Only 1 of the 4 trials (148 patients) that compared CRT with left ventricular pacing alone

evaluated this outcome, (17) and no difference between the groups was reported (WMD 0 points [CI -6.27 to 6.27]).

6-minute walk test (6MWT)

Overall, results of the 6-minute walk test improved in the CRT groups compared with control groups (15 trials, 3475 participants; WMD 17.50 meters [CI 7.05 to 27.94]; I^2 = 57%). Trials including predominantly patients with NYHA class I or II symptoms showed no improvement in 6-minute walk test (3 trials, 890 participants; WMD -4.08 meters [CI -17.79 to 9.63]; I^2 = 0%), whereas trials including predominantly patients with NYHA class III or IV symptoms showed substantial improvement with CRT (12 trials, 2585 participants; WMD 23.34 meters [CI 12.96 to 33.72]; I^2 = 44%). Three trials comparing left ventricular pacing with CRT reported this outcome; no difference between the 2 pacing modalities was observed, although the CI were wide (326 participants; WMD -0.75 meters [CI -21.88 to 20.38]; I^2 = 0%).

Improvement by at least 1 NYHA class

Patients assigned to receive CRT were significantly more likely than controls to have improvement by at least 1 NYHA class (4 trials, 1476 participants; RR 1.60 [CI 1.34 to 1.92; I^2=45%), whereas the 2 studies that compared CRT with left ventricular pacing found no difference between groups (45 patients, RR 0.90 [CI 0.74 to 1.08]; I^2=0%). Of note, none of the trials of patients with NYHA class I or II symptoms reported this outcome.

Left Ventricular Ejection Fraction (LVEF)

CRT improved LVEF compared with the control groups (11 trials, 3202 patients; WMD 0.0364 [CI 0.0189 to 0.0539; I^2=89%); no appreciable difference was detected between trials in patients with predominantly NYHA class I or II symptoms (4 trials; 2165 participants; WMD 0.0463 [CI 0.0188 to 0.0739]; I^2=92%) and trials in patients with predominantly NYHA III or IV symptoms (7 trials; 1037 participants; WMD 0.0297 [CI 0.0097 to 0.0497]). In the 4 studies that compared CRT with left ventricular pacing for this outcome, the study groups did not differ (509 participants; WMD 0.0078 [CI -0.0058 to 0.0215; I^2=0%).

Safety

Table 2-5 shows the implantation success rate and rates of complications. The implantation success rate was 94.4% (CI, 93.8% to 94.8%). Mechanical complications (including coronary sinus dissection or perforation, pericardial effusion or tamponade, pneumothorax, and hemothorax) occurred in 3.2% (CI, 2.8% to 3.6%) of patients, device malfunction in 1.9% (CI, 1.5% to 2.4%), lead problems (including lead dislodgement or repositioning) in 6.2% (CI, 5.6% to 6.8%), and infections in 1.4% (CI, 1.1% to 1.7%). Peri-implantation death occurred in 0.3% of patients (CI, 0.2% to 0.5%).

Assessment for Publication Bias

We tested for publication bias by using a funnel plot for all-cause mortality (Figure 2-5). Although the funnel plot was asymmetrical, the area missing consisted of small positive studies; if anything, this indicates that our

estimates of all-cause mortality may be conservative. A funnel plot for heart failure hospitalization was asymmetrical, indicating potential publication bias; the plot was missing small neutral or negative trials (Figure 2-6).

Discussion

In this systematic review, we confirm that CRT improves LVEF and reduces all-cause mortality and heart failure hospitalization in patients with milder symptoms of heart failure (NYHA class I or II), left ventricular systolic dysfunction, and prolonged QRS duration. The relative magnitude of these benefits (risk reductions of 17% for mortality and 29% for heart failure hospitalization) are similar to that seen in patients with NYHA class III or IV symptoms, left ventricular systolic dysfunction, and prolonged QRS duration. Our findings contrast with those of a recent meta-analysis (43) of 2 trials in patients with NYHA class I or II symptoms (compared with the 6 trials in our analysis) that report no survival benefit with CRT, but a significant reduction in a composite outcome of "any heart failure events."

Of note, 98% of the control patients in our analyses of trials including NYHA class I or II symptoms had an ICD; thus, the benefits of CRT that we found represent incremental benefits additional to the expected benefits from the ICD implanted in both groups in each study. However, CRT did not improve quality of life or functional outcomes, such as results of the 6-minute walk test, in patients with mildly symptomatic heart failure-in contrast to their marked beneficial

effects on these outcomes (similar in magnitude to those of angiotensin-converting enzyme inhibitors) (44) for patients with NYHA class III or IV symptoms at baseline. This is not surprising, given that patients with NYHA class I or II heart failure have less symptom burden and impairment of quality of life at baseline.

The improvements in LVEF that we documented for trial participants regardless of NYHA class are consistent with prior studies (7,36,45,46). Although data from REVERSE and MADIT-CRT suggested that the benefits of CRT on left ventricular remodeling were greatest in patients with longer QRS durations and non-ischemic heart failure, (47,48) and a sub-study from MIRACLE also suggested greater LV remodeling with CRT in patients with non-ischemic disease (46), without access to individual-patient data, we could not explore whether this finding persisted in other trial data sets. Certainly, the benefits of CRT on the composite clinical outcome was greatest in MADIT-CRT and RAFT patients with QRS duration > 150 ms. It is worth noting that CRT is the only positive "inotropic therapy" that has been shown to improve both cardiac systolic function and patient survival.

An important question about CRT, as with any intervention that has been tested in only a selected range of patients and depends on specialized technical expertise to implant, is how generalizable the benefits demonstrated in RCTs will be when the device is used in clinical practice by less experienced clinicians working in smaller-volume centers (49-51). This is particularly relevant for CRT,

because approximately 38% of the patients (18 of the RCTs) in our efficacy analysis were randomly assigned only after successful device implantation. As a result, these RCTs may overestimate the potential benefit from CRT and underestimate the risk, because patients who could not tolerate the procedure or in whom implantation was unsuccessful were not included in the trial data. We anticipate that data from the National Cardiovascular Data Registry and ongoing cohort studies will be vital in establishing the clinical effectiveness and safety of CRT and tracking changes over time as device implanters, the tools for implantation, and the sophistication of the devices change—complication rates for left ventricular lead placement may be higher in the community. Such data will also be important to inform future cost-effectiveness analyses of CRT; current estimates (52,53) based on analyses using trial data and restricting use of CRT in their models to patients with NYHA class III or IV symptoms will not be applicable as indications for CRT expand.

Although we followed current recommendations for performing a systematic review and obtained unpublished data from several of the primary studies included in our meta-analysis, our study has limitations. Substantial statistical heterogeneity was present in some analyses and could not be explained by the variables considered in the meta-regressions; however, subgroup analyses and meta-regressions are post hoc analyses and generally underpowered. In addition, the conclusions about the implications for clinical practice are limited for some subgroups of patients who were excluded from or

underrepresented in the trials: those with bradyarrhythmias, atrial fibrillation, chronic kidney disease, or right bundle branch block. Finally, most of the trial participants were younger and relatively healthier than patients with heart failure encountered in clinical practice.

What are the implications of our findings? Our data support the expansion of indications for CRT to less symptomatic patients with heart failure who have LVEF less than 0.35 and QRS duration greater than 120 ms and are in sinus rhythm (Table 2-6: Summary of Current Evidence for CRT in Patients With Heart Failure). However, 85% of less symptomatic patients in these trials had NYHA II symptoms, and high-quality evidence to support this therapy in patients with asymptomatic left ventricular dysfunction or NYHA class I symptoms is inconclusive.

Our data also illuminate other issues about CRT for which randomized trial evidence is sparse and thereby highlight research priorities. For example, whether CRT is as efficacious in patients with atrial fibrillation (54) as in those with sinus rhythm is unclear (55). This is an important research question for future randomized trials because less than 1% of participants in CRT trials had atrial fibrillation, but almost 30% of all CRT devices are implanted in patients with atrial fibrillation (56,57). Moreover, although preliminary observations (58) suggest that CRT reduces symptom burden in patients with LVEF greater than 0.35, prolonged QRS, and NYHA class III or IV symptoms that are refractory to optimal medical therapy, an RCT is needed before practice recommendations

can be made (59). Nonetheless, 10% to 15% of patients who received CRT devices in the United States and Europe have LVEF greater than 0.35 (56,57,60). Finally, the most pressing research priority for CRT should be to establish a uniform definition of "CRT response." A recent review pointed out the poor correlations among the 17 most frequently used definitions for CRT response and the fact that although 99% of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) participants would have been defined as CRT responders by at least 1 of these commonly used criteria, 94% would also have been defined as CRT non-responders by at least 1 of the criteria (61).

Of note, our meta-regression analysis showed that inclusion of a higher proportion of patients with ischemic heart failure in the RCTs was associated with less benefit from CRT in reducing heart failure hospitalization, but no differential effect on mortality was observed. Studies in patients with NYHA class I or II symptoms (62), and class III or IV symptoms (46) have shown that an ischemic cause of heart failure is associated with less benefit from CRT. Thus, understanding which patients with ischemic heart disease should receive a CRT device, and the roles of scar tissue, wall thinning, limited myocyte viability, and sub-endocardial ischemia in making this decision, also warrant future research.

It had been estimated that CRT was indicated in fewer than 10% of symptomatic patients with heart failure who have left ventricular systolic dysfunction (63,64). However, as our systematic review reveals, the evidence base has evolved substantially since these earlier estimates, and CRT may now

be indicated for most of the 40% of patients with systolic heart failure who have a QRS duration greater than 120 ms (65). However, more than one third of current CRT recipients do not have functional or echocardiographic improvement after activation of their CRT (7), indicating that relying on RCT eligibility criteria to define which patients should undergo device implantation is imperfect. As such, we believe establishing criteria for case selection so that CRT devices are preferentially implanted in the patients who are most likely to benefit is of vital importance for researchers, clinicians, and policymakers.

Tables

Table 2-1: Databases Searched

MEDLINE: in-process and other non-indexed citations
Ovid MEDLINE Daily and Ovid MEDLINE, 1950 to present
EMBASE
PubMed
Cochrane Central Register of Controlled Trials
Health Technology Assessment Database
International Pharmaceutical Abstracts
Web of Science (Science Citation Index Expanded)
National Library of Medicine Gateway
Conference Papers Index (CSA)
OCLC PapersFirst
OCLC Proceedings First
ProQuest Dissertations and Theses
U.S. Food and Drug Administration Web site
Clinical trials Web sites
Australia New Zealand Clinical Trials Registry
CenterWatch
Clinical Center, National Institutes of Health
ClinicalStudyResults.org
ClinicalTrials.gov (National Institutes of Health)
Current Controlled Trials (BioMed Central)
Cardiosource (American College of Cardiology)
www.theheart.org

Table 2-2: MEDLINE Search Strategy (November 2006–December 2010)

1. exp Heart Failure/
2. exp Ventricular Dysfunction, Left/
3. CHF.mp.
4. chronic heart failure.mp.
5. exp Heart Diseases/
6. congestive heart failure.mp.
7. exp Ventricular Dysfunction/
8. exp Cardiac Pacing, Artificial/ or exp Pacemaker, Artificial/ or cardiac resynchronization.mp.
9. exp Pacemaker, Artificial/ or biventricular pacing.mp.
10. biventricular pacer.mp.
11. biventricular stimulation.mp.
12. multisite pacemaker.mp.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7
14. 8 or 9 or 10 or 11 or 12
15. 13 and 14
16. randomized controlled trial.pt.
17. clinical trial.pt.
18. randomi?ed.ti,ab.
19. placebo.ti,ab.
20. dt.fs.
21. randomly.ti,ab.
22. trial.ti,ab.
23. groups.ti,ab.
24. or/16-23
25. animals/
26. humans/
27. 25 not (25 and 26)
28. 24 not 27
29. 15 and 28
30. limit 29 to yr="2006 –Current

Table 2-3: Glossary- Trial Abbreviations

B-LEFT HF: Biventricular versus Left Univentricular Pacing with ICD Back-up in Heart Failure Patients

BELIEVE: Bi vs Left Ventricular Pacing: An International Pilot Evaluation on Heart Failure Patients with Ventricular Arrhythmias

CARE-HF: Cardiac Resynchronization–Heart Failure

COMBAT: Conventional Versus Biventricular Pacing in Heart Failure and Bradyarrhythmia

COMPANION: Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure

DECREASE-HF: Device Evaluation of CONTAK RENEWAL 2 and EASYTRAK 2: Assessment of Safety and Effectiveness in Heart Failure

Greater-EARTH: Evaluation of Resynchronization Therapy For Heart Failure In Patients With A QRS Duration Greater Than 120 ms

HOBIPACE: Homburg Biventricular Pacing Evaluation

MADIT-CRT: Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy

MIRACLE: Multicenter InSync Randomized Clinical Evaluation

MIRACLE ICD: Multicenter InSync Randomized Clinical Evaluation ICD

MUSTIC SR: Multisite Stimulation in Cardiomyopathies–Sinus Rhythm

MUSTIC AF: Multisite Stimulation in Cardiomyopathies–Atrial Fibrillation

PATH-CHF: Pacing Therapies for Congestive Heart Failure

RAFT: Resynchronization/Defibrillation for Ambulatory Heart Failure

RethinQ: Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS

REVERSE: REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction

RHYTHM ICD: Resynchronization for Hemodynamic Treatment for Heart Failure Management

VecTOR: Ventricular Resynchronization Therapy Randomized Trial

Table 2-4: Characteristics of Included Randomized, Controlled Trials and Baseline Characteristics of Patients

Study, Year(Reference)*	Duration Funding Risk of Bias	Group	N	Mean Age (SD), *y*	Men *%*	Ischemic *%*	NYHA Class, *%*				Mean LVEF (SD)	Mean QRS Duration (SD), *ms*	AF *%*
							1	2	3	4			
MUSTIC SR, 2001 (30)	3 mo Industry High	CRT first	29	64 (11)	66	NR			100		0.23 (0.07)	172 (22)	Ex.
		Inactive first	29	64 (8)	83	NR			100			175 (19)	
MUSTIC AF, 2002 (33)	3 mo Industry High	CRT first	25	65 (9)	84	NR			100		0.23 (0.07)	209 (21)†	100
		RV first	18	66 (9)	78	NR			100		0.30 (0.12)	208 (12)†	100
MIRACLE, 2002 (31)	6 mo Industry Unclear	CRT	228	64 (11)	68	50			90	10	0.22 (0.06)	167 (21)	Ex.
		Inactive	225	65 (11)	68	58			91	9	0.22 (0.06)	165 (20)	
PATH-CHF, 2002 (32)	1 mo Industry High	CRT first	24	59 (7)	46	42			88	12	0.21 (0.06)	174 (30)	Ex.
		Uni-V first	17	60 (5)	59	6			82	18	0.20 (0.07)	178 (34)	
PATH-CHF II, 2003 (41)	3 mo Industry High	CRT first	43	61 (9)	70	44		37		63	0.23 (0.07)	154 (18)	Ex.
		Inactive first	43	58 (8)	63	33		28		72	0.23 (0.08)	157 (23)	
Higgins et al, 2003 (34)	3 mo Industry Low	CRT + ICD	245	66 (11)	85	71		32	60	8	0.21 (0.07)	160 (27)	Ex.
		ICD	245	66 (11)	83	67		33	57	10	0.22 (0.07)	156 (26)	
MIRACLE ICD, 2003 (35)	6 mo Industry Low	CRT + ICD	187	67 (11)	76	64			88	12	0.24 (0.07)	165 (22)	Ex.
		ICD	182	68 (9)	78	76			89	11	0.24 (0.06)	162 (22)	
COMPANION 2004 (37)	15 mo Industry High	CRT	617	67‡	67	54			87	13	0.20‡	160‡	Ex.
		Usual care	308	68‡	69	59			82	18	0.22‡	158‡	
MIRACLE-ICD II, 2004 (36)	6 mo Industry Unclear	CRT + ICD	85	63 (13)	88	55		100			0.24 (0.07)	166 (25)	Ex.
		ICD	101	63 (12)	92	58		100			0.25 (0.07)	165 (23)	
CARE-HF, 2005 (38)	29.4 mo Industry Low	CRT	409	67 (60–73)§	74	40			94	6	0.25 (0.22–0.29)§	160 (152–180)§	Ex.
		Usual care	404	66 (59–72)§	73	36			93	7	0.25 (0.21–0.29)§	160 (152–180)§	

RHYTHM ICD, 2005 (29)	12 mo Industry Unclear	CRT + ICD	119	NR	NR	NR	1	5	87	7	0.26 (0.08)	169 (16)	Ex.
		ICD	59	NR	NR	NR	2	6	87	6	0.23 (0.06)	167 (15)	
VecTOR, 2005 (28)	6 mo Industry Unclear	CRT	59	67 (10)	63	NR		29	65	6	<0.35	>140	Ex.
		Inactive pacing	47										
BELIEVE, 2006 (22)	12 mo Unclear Low	CRT + ICD	33	67 (8)	88	58		42	58		0.26 (0.06)	176 (25)	Ex.
		LV + ICD	36	67 (7)	94	69		33	67		0.25 (0.06)	169 (31)	
HOBIPACE, 2006 (39)	3 mo Govnt. Unclear	CRT	15	70 (8)	77	57	Mean (SD), 3.0 (0.6)				0.26 (0.08)	174 (42)	37
		RV	15										
DECREASE-HF, 2007 (25)	6 mo Industry Unclear	Simultaneous and equential BiV + ICD	205	66 (11)	68	66			98	2	0.23 (0.07)	167 (16)	Ex.
		LV + ICD	101	67 (10)	65	62			97	3	0.23 (0.07)	165 (15)	
RD-CHF, 2007 (40)	3 mo Unclear High	CRT first	25	73 (9)	100	56	Mean (SD), 3.2 (0.4)				0.24 (0.10)	212 (28)	56
		RV first	19	74 (6)	79	47					0.27 (0.09)	199 (21)	63
RethinQ, 2007 (21)	6 mo Industry Unclear	CRT + ICD	87	60 (12)	71	54			100		0.25 (0.05)	107 (12)	Ex.
		ICD	85	58 (14)	58	51			99		0.26 (0.06)	106 (13)	
Piepoli et al, 2008 (24)	12 mo Unclear Unclear	CRT	44	71 (7)	70	61			90	10	0.24 (0.01)	164 (18)	Ex.
		Usual care	45	73 (9)	73	56			89	11	0.23 (0.07)	160 (20)	
REVERSE, 2008 (11)	12 mo Industry Unclear	CRT on||	419	63 (11)	78	56	18	82			0.27 (0.07)	153 (21)	Ex.
		CRT off||	191	62 (12)	80	51	17	83			0.26 (0.07)	154 (24)	
MADIT-CRT, 2009 (12)	2.4 y Industry Unclear	CRT + ICD	1089	65 (11)	74	54	14	86			0.24 (0.05)	>150 ms: 64.2%	Ex.
		ICD	731	64 (11)	76	55	16	85			0.24 (0.05)	>150 ms: 65.1%	
B-LEFT HF, 2010 (17)	6 mo Industry Low	CRT + ICD	90	66 (10)	76	53			93	7	0.26 (0.06)	160 (19)	Ex.
		LV + ICD	86	66 (9)	73	51			94	6	0.25 (0.06)	162 (20)	

COMBAT, 2010 (23)	3 mo Industry Unclear	RV-BiV-RV	27	57 (15)	68	23		16	52	32	0.29 (0.07)	154 (13)	Ex.
		BiV-RV-BiV	27	59 (13)	63	10		17	52	31	0.30 (0.09)	148 (16.4)	
RAFT, 2010 (13)	40 mo Govnt.+ industry Low	CRT+ICD	894	66 (9)	85	69		79	21		0.22 (0.05)	157 (24)¶	13
		LV+ICD	86	66 (9)	81	65		81	19		0.22 (0.05)	158 (24)¶	13
Greater-EARTH, 2010 (27)	6 mo Govnt. Unclear	BiV first (+ICD)	61	62 (8)	72	48	8	59	33		024 (0.07)	157 (25)	NR
		LV first (+ICD)	60	60 (10)	78	55	8	63	28		0.24 (0.06)	153 (22)	
Van Geldorp et al, 2010 (26)	6 mo Industry Unclear	CRT first	19	64 (11)	79	26	26	47	26		0.36 (0.09)	196 (29)	63
		RV first	18	67 (10)	76	47	24	59	18		0.36 (0.11)	193 (23)	41

AF = atrial fibrillation; BiV = biventricular; CRT = cardiac resynchronization therapy; Ex= excluded; Govnt.= Government; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LV = left ventricular; LVEF = left ventricular ejection fraction; NR = not reported; NYHA = New York Heart Association classification; RBBB = right bundle branch block; RV = right ventricular; Uni-V first = 4 RV and 36 LV.

*For expansions of study names, see the Glossary.

† Paced QRS duration.

‡ Median.

§ Median (range)

|| 83% with ICD in all patients.

¶ Intrinsic QRS duration (n = 826).

Table 2-5: Peri-implantation and Postimplantation Complication Rates in the Included Trials*

Study, Year (Reference)†	Implantation Success Rate, *n/N (%)* [95% CI]	Peri-implantation Death, *n/N (%)* [95% CI]	Mechanical Complications, *n/N (%)*‡ [95% CI]	Device Malfunction, *n/N (%)*§ [95% CI]	Lead Problems, *n/N (%)*‖ [95% CI]	Infection, *n/N (%)* [95% CI]
MUSTIC SR, 2001 (30)	58/64 (90.63) [80.70–96.48]	1/58 (1.72) [0.04–9.24]	2/58 (3.45) [0.42–11.91]	2/67 (2.99) [0.36–10.37]	8/67 (11.94) [5.30–22.18]	NR
MUSTIC AF, 2002 (33)	54/59 (91.53) [81.32–97.19]	0/59 (0.00) [0.00,6.06]	2/54 (3.70) [0.45–12.75]	NR	5/54 (9.26) [3.08–20.30]	NR
MIRACLE, 2002 (31)	528/571 (92.47) [89.99–94.50]	NR	35/571 (6.13) [4.31–8.42]	2/453 (0.44) [0.05–1.59]	30/524 (5.73) [3.90–8.07]	7/524 (1.34) [0.54–2.73]
PATH-CHF, 2002 (32)	41/41 (100) [91.40–100]	0/41 (0.00) [0.00–8.60]	NR	NR	NR	NR
PATH-CHF II, 2003 (41)	86/89 (96.63) [90.46–99.30]	NR	6/98 (6.12) [2.28–12.85]	NR	1/86 (1.16) [0.03–6.31]	1/92 (1.09) [0.03–5.91]
Higgins et al, 2003 (34)	501/501 (100) [99.27–100]	2/490 (0.41) [0.05–1.47]	22/448 (4.91) [3.10–7.34]	NR	31/448 (6.92) [4.75–9.68]	5/443 (1.13) [0.37–2.61]
MIRACLE ICD, 2003 (35)	379/429 (88.34) [84.92–91.22]	NR	25/364 (6.87) [4.49–9.97]	NR	46/364 (12.64) [9.40–16.49]	2/364 (0.55) [0.07–1.97]
COMPANION, 2004 (37)	1158/1294 (89.49) [87.69–91.11]	5/1294 (0.39) [0.13–0.90]	22/1212 (1.82) [1.14–2.74]	NR	NR	NR
MIRACLE-ICD II, 2004 (36)	191/210 (90.95) [86.23–94.46]	1/191 (0.52) [0.01–2.88]	7/210 (3.33) [1.35–6.75]	4/191 (2.09) [0.57–5.28]	28/210 (13.33) [9.05–18.69]	NR
CARE-HF, 2005 (38)	390/409 (95.35) [92.84–97.18]	2/409 (0.49) [0.06–1.76]	24/409 (5.87) [3.80–8.61]	NR	24/409 (5.87) [3.80–8.61]	3/409 (0.73) [0.15–2.13]
RHYTHM ICD, 2005 (29)	183/205 (89.27) [84.20–93.15]	5/205 (2.44) [0.80–5.60]	33/205 (16.10) [11.35–21.86]	20/205 (9.76) [6.06–14.67]	22/205 (10.73) [6.85–15.80]	1/205 (0.49) [0.01–2.69]
VecTOR, 2005 (28)	120/144 (83.33) [76.22–89.02]	NR	NR	11/120 (9.17) [4.67–15.81]	8/120 (6.67) [2.92–12.71]	NR
BELIEVE, 2006 (22)	NR	NR	NR	NR	NR	NR
HOBIPACE, 2006 (39)	NR	NR	NR	1/30 (3.33) [0.08–17.22]	2/30 (6.67) [0.82–22.07]	NR
DECREASE-HF, 2007 (25)	342/358 (95.53) [92.84–97.42]	3/342 (0.88) [0.18–2.54]	NR	NR	NR	NR
RD-CHF, 2007 (40)	46/56 (82.14) [69.60–91.09]	NR	NR	1/44 (2.27) [0.06–12.02]	4/56 (7.14) [1.98–17.29]	3/44 (6.82) [1.43–18.66]

RethinQ, 2007 (21)	246/250 (98.40) [95.95–99.56]	2/250 (0.80) [0.10–2.86]	5/172 (2.91) [0.95–6.65]	2/172 (1.16) [0.14–4.14]	13/172 (7.56) [4.09–12.58]	6/172 (3.49) [1.29–7.44]
Piepoli et al, 2008 (24)	44/44 (100) [91.96–100]	NR	NR	1/44 (2.27) [0.06–12.02]	1/44 (2.27) [0.06–12.02]	NR
REVERSE, 2008 (11)	621/642 (96.73) [95.04–97.96]	NR	13/642 (2.02) [1.08–3.44]	1/642 (0.16) [0.00–0.86]	66/642 (10.28) [8.04–12.89]	NR
MADIT-CRT, 2009 (12)	1790/1820 (98.35) [97.66–98.89]	1/1820 (0.05) [0.00–0.31]	30/1820 (1.65) [1.11–2.34]	19/1820 (1.04) [0.63–1.63]	44/1820 (2.42) [1.76–3.32]	17/1820 (0.93) [0.55–1.49]
B-LEFT HF, 2010 (17)	180/186 (96.77) [93.11–98.81]	1/180 (0.56) [0.01–3.06]	NR	11/180 (6.11) [3.09–10.67]	35/180 (19.44) [13.93–25.99]	NR
COMBAT, 2010 (23)	64/68 (94.12) [85.62–98.37]	NR	NR	NR	2/60 (3.33) [0.41–11.53]	1/60 (1.67) [0.04–8.94]
RAFT, 2010 (13)	841/894 (94.07) [92.32–95.53]¶	1/1798 (0.06) [0.00–0.31]	30/1798 (1.67) [1.13–2.37]	NR	81/1798 (4.51) [3.59–5.57]	37/1798 (2.06) [1.45–2.83]
Greater-EARTH, 2010 (27)	NA	NA	NA	NA	NA	NA
van Geldorp et al, 2010 (26)	38/40 (95) [83.08–99.39]	NR	1/38 (2.63) [0.07–13.81]	NR	2/38 (5.26) [0.64–17.75]	NR
Total	7901/8374 (94.35) [93.84–94.84]	24/7708 (0.31) [0.20–0.46]	257/8099 (3.17) [2.80–3.58]	75/3968 (1.89) [1.49–2.36]	453/7372 (6.18) [5.64–6.76]	83/5931 (1.40) [1.12–1.73]

NA = not available; NR = not reported.

*Percentages indicate simple pooled risk.

†For expansions of study names, see the Glossary.

‡ Includes coronary sinus dissection or perforation, pericardial effusion or tamponade, pneumothorax, and hemothorax.

§Includes pacing threshold problems, sensitivity issues, and inappropriate shocks.

||Includes lead dislodgement or repositioning.

¶Successful left ventricular lead implantation.

Table 2-6: Summary of Current Evidence for CRT in Patients With Heart Failure

Comparison	Patient Characteristics			Trials (Participants), *n (n)*	Quality of Evidence	Magnitude of Effect of CRT	Conclusion
	NYHA Class	ECG Criteria	LVEF				
CRT vs. usual care or right ventricular, left ventricular, or inactive pacing; CRT + ICD vs. ICD alone	I	QRS duration >120 msec; sinus rhythm	<0.40	4 (391 with NYHA I); all reported outcomes combined with NYHA class II	Low (post hoc meta-regression analysis)	Indeterminate	Inconclusive
	II	QRS duration >120 msec; sinus rhythm	<0.35	6 (4572)	High (several large RCTs); no heterogeneity	Reduce mortality: RR, 0.83 (95% CI, 0.72–0.96)	Definite benefit
				4 (4349)	High (3 large RCTs); moderate heterogeneity	Reduce HF hospitalizations: RR, 0.69 (CI, 0.57–0.87)	Definite benefit
				2 (787)	High (several RCTs); no heterogeneity	No effect on quality of life: WMD, 1.82 points (CI, -0.77–4.41)	Inconclusive
				4 (2165)	High (large RCT); substantial heterogeneity	Improves LVEF: WMD, 4.63% (CI, 1.88%–7.39%)	Definite benefit
	III or IV	QRS duration >120 msec; sinus rhythm	<0.35	19 (4510)	High (several large RCTs)	Reduce mortality: RR, 0.79 (CI, 0.68–0.91)	Definite benefit
				11 (2663)	High (several large RCTs); substantial heterogeneity	Reduce HF hospitalization: RR, 0.65 (CI, 0.50–0.86)	Definite benefit
				12 (3496)	High (several large RCTs); substantial heterogeneity	Improves MLHFQ by 7 points (CI, 4.87–9.91)	Definite benefit
				7 (1037)	High (large several RCTs); substantial heterogeneity	Improves LVEF: WMD, 2.97% (CI, 0.97%–4.97%)	Definite benefit

	III or IV	QRS duration <130 msec; sinus rhythm	<0.35	1 RCT (172)	Low (small trial with wide CIs)	No effect on mortality (RR, 2.44 [CI, 0.49–12.25]) or hospitalization	Inconclusive; ongoing trials, EchoCRT (*n* > 1000) (NCT00683696) and Lesser-EARTH (*n* = 120) (NCT00900549)
	III or IV	QRS duration >120 msec; atrial fibrillation	<0.35	1 RCT limited to patients with AF	Low (small trial with wide CIs)	No difference between CRT and control	Inconclusive; ongoing studies, APAF (NCT00111527)
				4 trials included different proportion of patients with AF	Low (post-hoc meta-regression analysis)		
	Any	Any QRS duration; brady-arrhythmia	Any	No RCTs identified	No available evidence	Not applicable	Inconclusive; ongoing trials, BLOCK-HF (NCT00267098)
CRT vs. LV pacing (both with ICD)	Any	Any	<0.35	4 RCTs; mostly small to medium-sized, with low event rates	Low (small trials with wide CIs)	No difference in mortality, HF hospitalization, or functional outcomes	Inconclusive; ongoing study, Lesser-EARTH (NCT00900549)

AF = atrial fibrillation; APAF = Assessment of Cardiac Resynchronization Therapy in Patients With Permanent Atrial Fibrillation; BLOCK-HF = Biventricular Versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block; CRT = cardiac resynchronization therapy; ECG = electrocardiography; EchoCRT = Echocardiography Guided Resynchronization Therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator; Lesser-EARTH = Evaluation of Resynchronization Therapy for Heart Failure; LV = left ventricle; LVEF = left ventricular ejection fraction; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NYHA = New York Heart Association; RCT = randomized, controlled trial; RR = relative risk; WMD = weighted mean difference

Figures

Figure 2-1: Flow diagram for study selection

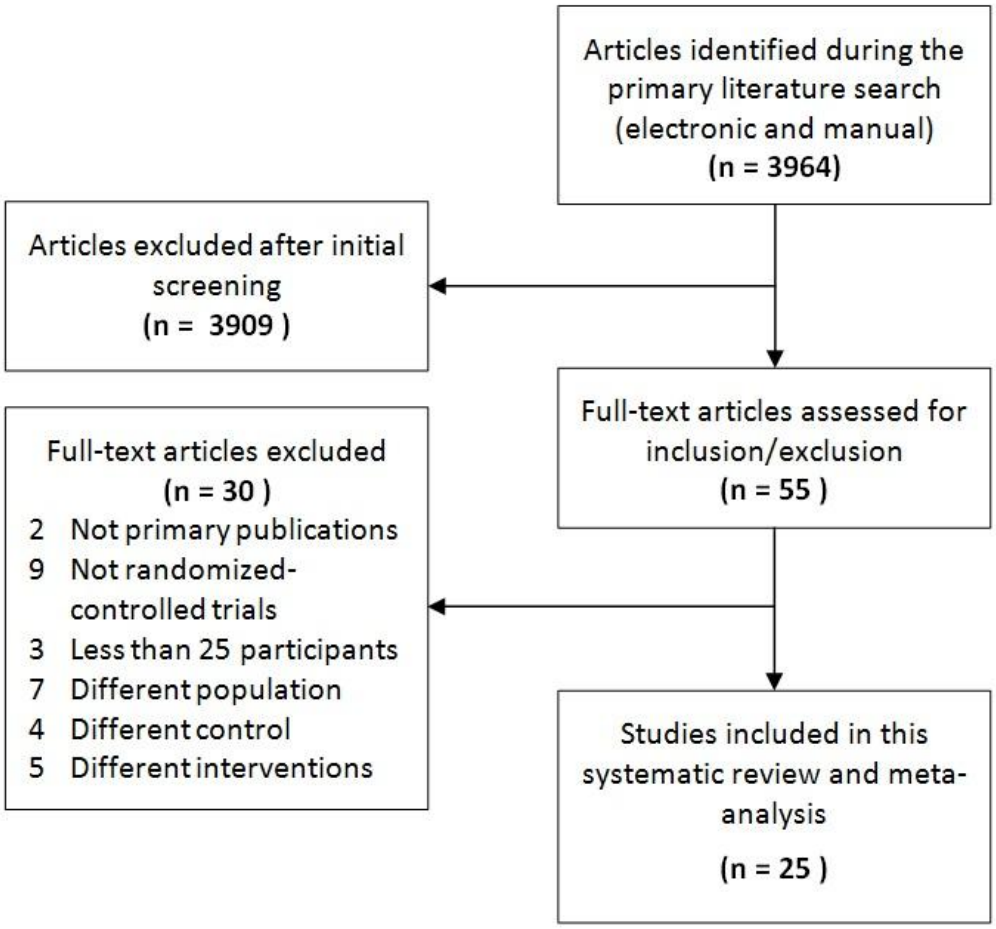
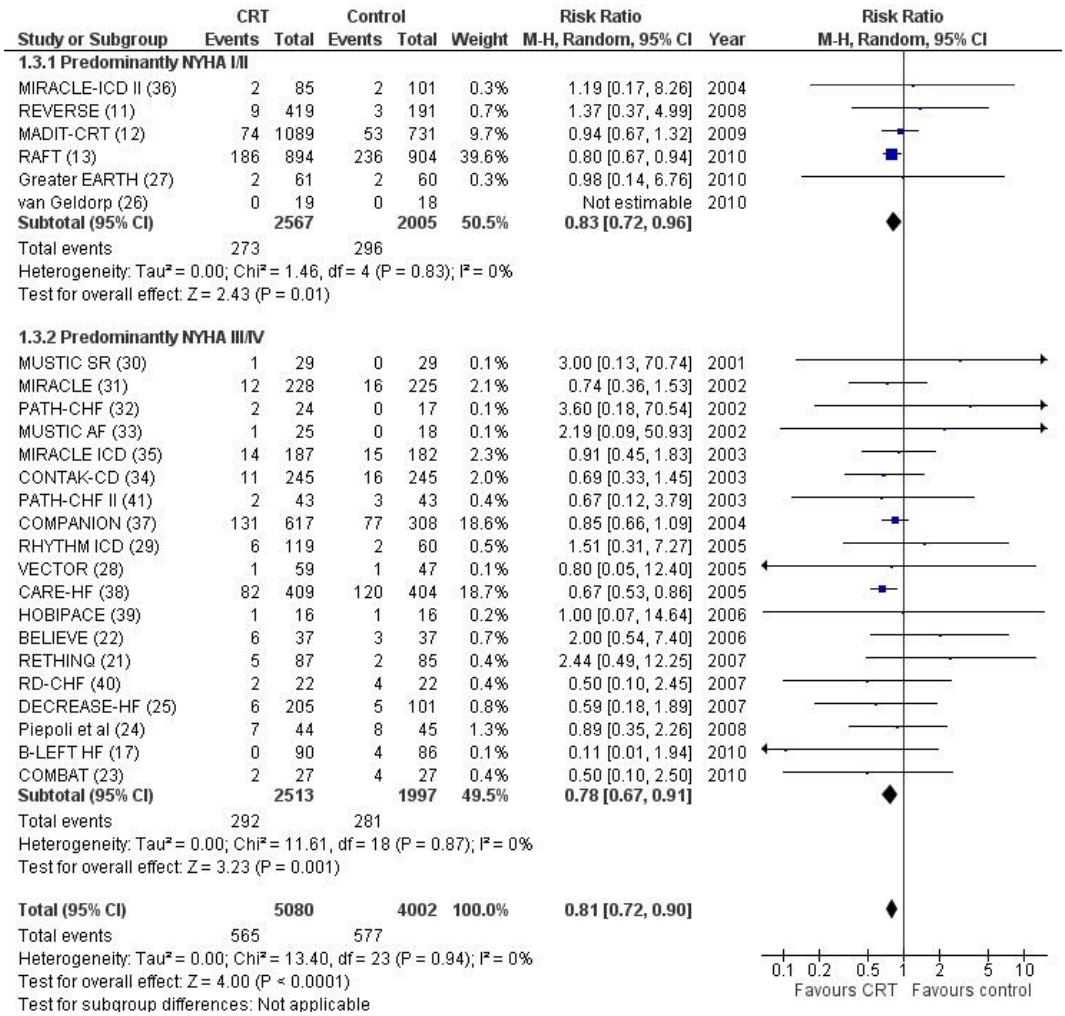


Figure 2-2: All-cause mortality with CRT vs. control



<u>Figure 2-3</u>: Heart failure hospitalization with CRT versus control

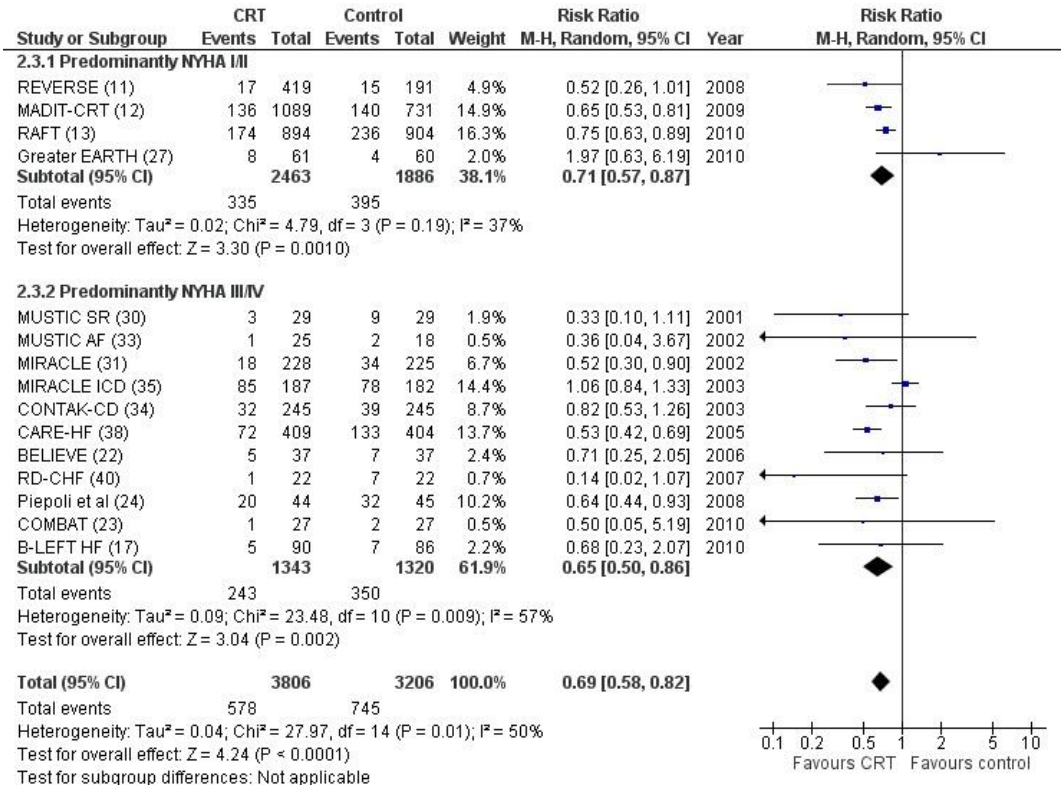


Figure 2-4: Effect of follow-up duration on the efficacy of cardiac resynchronization therapy versus control for all-cause mortality.

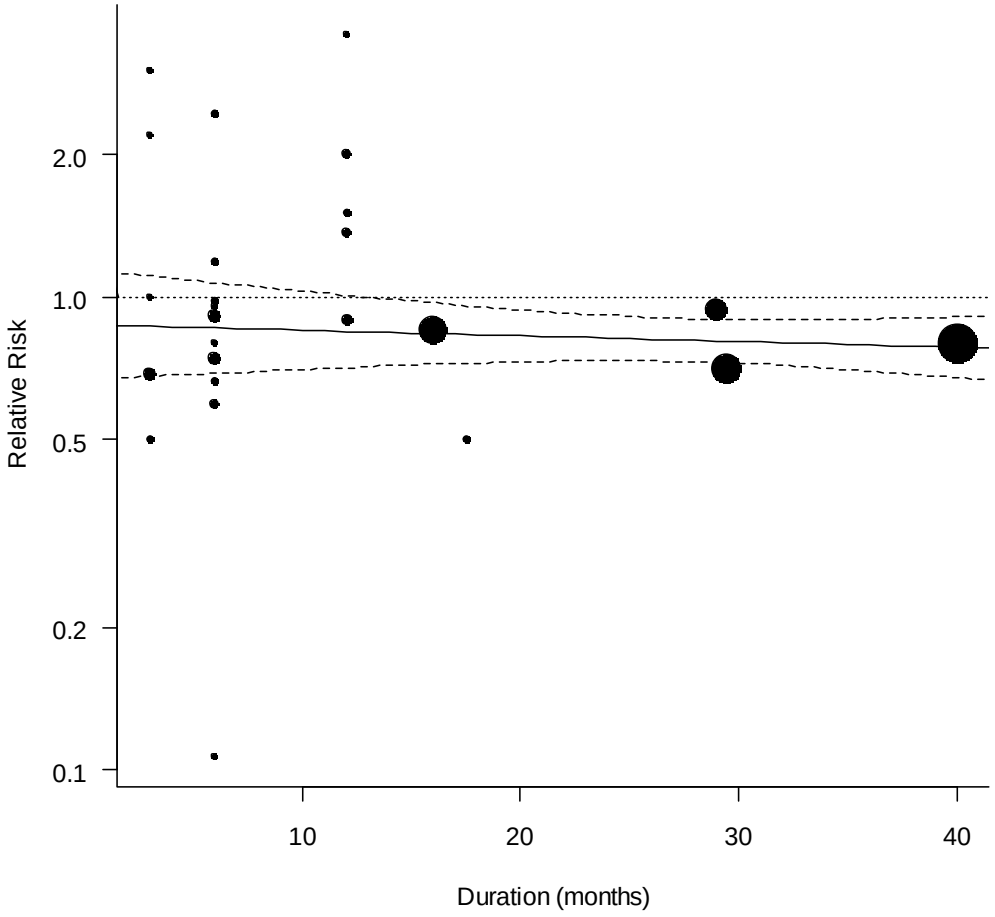


Figure 2-5: Funnel plot of all-cause mortality

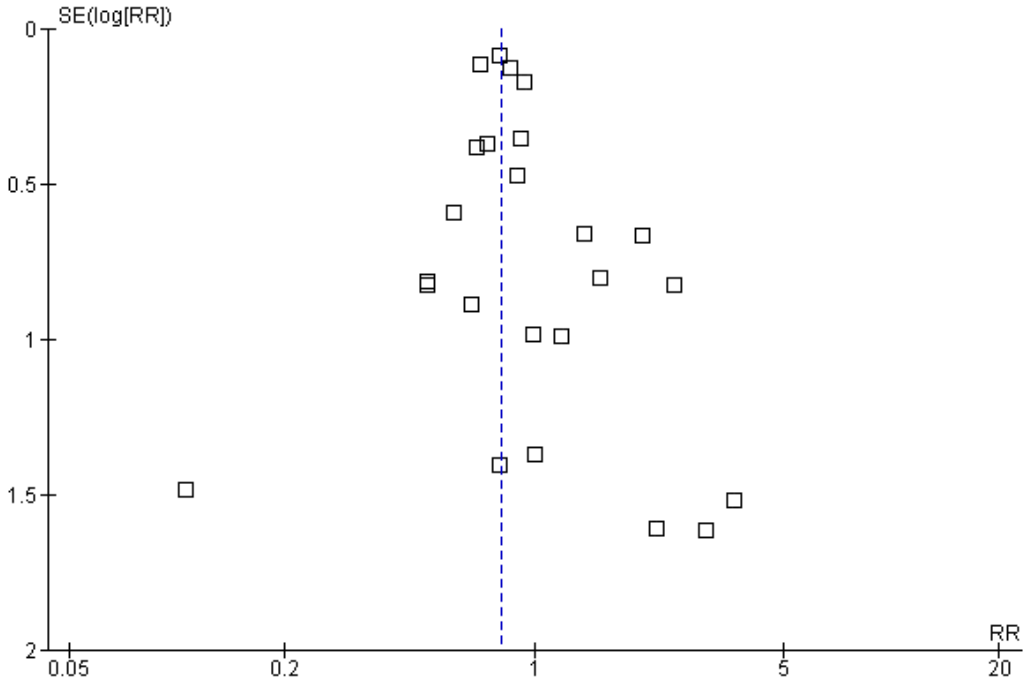
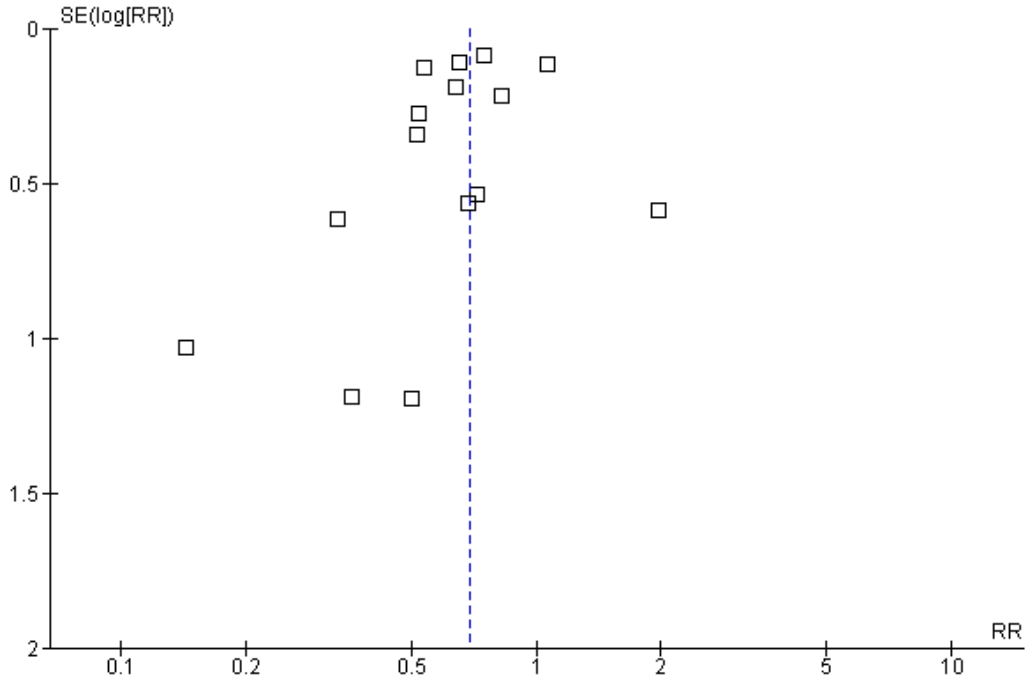


Figure 2-6: Funnel plot of HF hospitalization



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Chapter 3

Correlation Between Peak Expiratory Flow Rate and NT-proBNP in Patients with Acute Heart Failure. An Analysis from ASCEND-HF trial [1]

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[1] A version of this chapter is being prepared for submission for publication.

Introduction

Acute decompensated heart failure (ADHF) is a syndrome characterized by either new development or worsening of heart failure signs and symptoms, including dyspnea (1,2). Because many patients present with worsening dyspnea (3,4), its resolution has been used as primary endpoint in many randomized clinical trials (5-8). However, dyspnea resolution has been largely assessed using subjective, ordered scale measures of dyspnea improvement (e.g., visual analog scales, Likert scale).

The pathophysiology of dyspnea in ADHF is complex and remains unclear (9). Various mechanisms have been mentioned in the literature (9,10). Airway obstruction and airflow limitation seem to contribute to dyspnea in ADHF, and few studies have described the presence of obstructive ventilatory dysfunction in patients hospitalized with heart failure (11-17). The mechanism of airway obstruction in heart failure is not well understood. In the initial stages, peripheral airway narrowing that is in part related to engorged pulmonary blood vessels in the bronchovascular sheath is a possible contributing factor (11). With progression, larger airway narrowing can occur (12).

One of the bedside tests that can be used for assessment of airway obstruction and airflow limitation is peak expiratory flow rate (PEFR), which has been found to have good correlation with the forced expiratory volume in one second (FEV_1) (18,19). A recent prospectively designed sub-study of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure

(ASCEND-HF) trial looked at the utility of serial peak expiratory flow rate (PEFR) measurements in ADHF patients as an objective tool for assessing overall improvement. This study showed that PEFR significantly improves within 24 hours of initiating treatment for ADHF, and that changes in PEFR from baseline to 24 hours predicted significant improvement in a dyspnea index (13).

Natriuretic peptides are a well-established marker for the diagnosis, prognosis, and evaluation of new ADHF therapies. Various studies have assessed the correlation between natriuretic peptides and several clinical and hemodynamic variables but improvement in dyspnea is only weakly linked to a reduction in natriuretic peptides. There have been no studies correlating natriuretic peptides with objective measures of respiratory function in ADHF. Accordingly, the objective of this study was to test the correlation between changes in NT-proBNP and PEFR during the first 24-72 hours of admission with ADHF.

Methods

The ASCEND-HF trial evaluated the use of nesiritide in patients with ADHF. The study design and the results have been published. (5,20) Briefly, patients were included in the study if they had ADHF that has occurred within 24 hours before receiving the first intravenous HF-related medication. In addition, they also needed to meet the following: 1) dyspnea at rest or with minimal exertion, 2) respiratory rate ≥ 20 breaths/minutes and/or pulmonary congestion or edema

with rales ≥ one-third from the lung base, and 3) one or more of the following objective measures of HF: pulmonary edema on chest X-ray, BNP level ≥ 400 pg/ml or NT-proBNP ≥ 1000 pg/ml, pulmonary capillary wedge pressure > 20 mmHg, or LVEF < 40% in the previous 12 months. The exclusion criteria are described in the main paper. Of relevance to this study, patients were excluded if they had severe pulmonary disease (defined as severe chronic or acute lung disease that might interfere with the ability to interpret the dyspnea assessments [eg, severe chronic obstructive pulmonary disease, active asthma, or acute pneumonia])

Respiratory sub-study

Among the 7007 patients in the ASCEND-HF, 421 patients participated in a prospectively designed sub-study that aimed at objectively assessing dyspnea in ADHF using PEFR. The design and results of this sub-study has been published previously. (13) Briefly, these 421 patients underwent PEFR testing at baseline (before drug infusion) and subsequently at 1, 6, and 24 hours. Dyspnea was assessed using a 7-point Likert scale at 6 and 24 hours.

Biomarker sub-study

Among the total number of patients participating in the main trial, 808 patients were enrolled in the ASCEND-HF biomarker sub-study. Blood samples for biomarkers were obtained in serum and EDTA plasma at baseline, 48–72 h, and 30 days, and were immediately centrifuged and stored at –80^{o}C for subsequent analysis. As patients enrolled in the ASCEND-HF study received nesiritide, we

used NT-proBNP in this sub-study, which was measured at the core laboratory using a clinically available assay (VITROS NTproBNP, Ortho Clinical Diagnostics). (21)

Outcomes

The primary outcome was the correlation between the change in PEFR (baseline and 24 hours), and the change in NT-proBNP (baseline and 48-72 hours). The secondary outcome evaluated if changes in PEFR and NT-proBNP added to the prediction of clinical outcomes, namely: HF-rehospitalization or death within 30 days.

Statistical Analysis

Continuous variables are presented as medians and interquartile ranges (IQR) and categorical variables as frequencies and percentages. Wilcoxon rank sum tests were to test for differences between continuous variables, and *chi-squared* test was used to test differences between categorical variables. Variables were transformed to normality where necessary. Pearson's correlation coefficient was used to test the correlation between baseline PEFR and baseline NT-proBNP and also between 24-hour PEFR and 48-72 hour NT-proBNP. In addition, the same method was used to test the correlation between the absolute and relative change in PEFR from baseline to 24 hours and absolute and relative change in NT-proBNP from baseline to 48-72 hours. Sensitivity analyses were performed by removing outliers identified in the graphical analysis of the boxplot and repeating the correlation analysis. Cox proportional hazard regression analysis

was used to test whether changes in log (PEFR) and changes in log (NT-proBNP) add to the prediction of HF-rehospitalization or death within 30 days, both in univariate as well as in multivariate analysis in ASCEND-HF model for 30-day HF-rehospitalization or death (which included hypotension at baseline, serum sodium, age, log (BUN), history of cerebrovascular disease, log (creatinine), history of depression, resting dyspnea at baseline, elevated jugular venous pressure (JVP), and history of chronic respiratory disease) (21).

Results

Among the 421 patients in the respiratory sub-study and the 808 patients in the biomarkers sub-study, we identified 158 patients in whom data for PEFR and NT-proBNP were available (figure 3-1). Table 3-1 shows the baseline characteristics of these patients. Compared to the population of patients in the respiratory sub-study, patients in the current sub-study were older, more likely to be male, Caucasian, have a prior myocardial infarction, worse renal function and less likely to have a history of heart failure admission in the preceding year. In this sub-study, 48.7% received nesiritide compared to 49.4% in the overall respiratory sub-study.

In this sub-study, PEFR increased from 230 L/min at baseline to 277 L/min at 24 hours (increased by 13.8%, IQR 6.3% to 33.3%, p value <0.001). This increase in PEFR within 24 hours was similar to what was found in the main ASCEND-HF respiratory sub-study (13). From baseline to 48-72 hours, NT-proBNP

decreased from 6306 pg/mL to 3882 pg/mL (decreased by 35.3%, IQR 15.9% to 62.3%, p value <0.001) (table 3-2). However, there was no significant correlation between absolute changes in PEFR within 24 hours and NT-proBNP within 48-72 hours (n= 130, r =0.02, p= 0.86). Comparable results were found when we tested the correlation of the relative changes between the two variables (n = 130 r = -0.09, p= 0.30). Although there was a marginally statistically significant correlation between baseline PEFR and baseline NT-proBNP, it was small in magnitude (n= 152, R= -0.16, p= 0.05). Similar results were found when we tested the correlation between 24-hour PEFR and 48-72 hour NT-proBNP (n= 145, R= -0.17, p= 0.04) (Table 3-3).

Table 3-4 shows HF-rehospitalization or death within 30 days in various Cox proportional hazard models. The log transformation of the absolute change in PEFR within 24 hours (Δ log PEFR) was not a significant predictor of HF-rehospitalization or death within 30 days in univariate analysis (HR 1.11, p=0.7). The results were similar (HR 1.37, p=0.64) when Δ log PEFR was added the overall ASCEND-HF model for HF-rehospitalization or death within 30 days. Similarly, the log transformation of the absolute change in NT-proBNP within 48-72 hours (Δ log NT-proBNP) was not a significant predictor of HF-rehospitalization or death within 30 days in univariate analysis (HR 1.33, p=0.21). Adding Δ NT-proBNP to the overall ASCEND-HF model for HF-rehospitalization or death within 30 days did not alter the results (HR 1.21, p=0.46). When both Δ log

PEFR and Δ log NT-proBNP were added to the overall ASCEND-HF model, results were largely similar (PEFR: HR 1.38, p=0.62; NT-proBNP: HR 1.11, p=0.31).

Discussion

In this sub-study of the ASCEND-HF trial, we found weak correlation between baseline PEFR and baseline NT-proBNP as well as between PEFR at 24-hours and NT-proBNP at 48-72 hours. However, no significant correlation between short-term changes in PEFR and in NT-proBNP was found. Additionally, in this small cohort, changes in PEFR or NT-proBNP were not predictive of HF-rehospitalization or death within 30 days.

PEFR is commonly used in the assessment of patients with bronchial asthma, and it has been frequently used as an end point in bronchial asthma trials (22). The recent ASCEND-HF respiratory sub-study is thus far the largest study that evaluated the role of PEFR as an objective end-point for assessing overall improvement in patients with ADHF. Few other studies have evaluated the use of PEFR in the emergency room for the differentiation of cardiac vs. respiratory causes of dyspnea. (12,14,23) Although patients who were ultimately diagnosed to have a respiratory cause for dyspnea had lower PEFR than those with cardiac cause of dyspnea, the PEFR for the “cardiac” patients was also low (56% to 58% of predicted) (14,23).

BNP is a neurohormone that is released mainly from the cardiac ventricles. Pro-BNP is the precursor of BNP, and is cleaved by proteases into a

physiologically inactive N-terminal segment (NT-proBNP), and the physiologically active C-terminal segment (BNP). Both BNP and NT-proBNP are released into the blood stream in response to increased filling pressure and stretching of the myocytes. With its physiological actions [diuresis, natriuresis, vasodilatation, inhibition of renin-angiotensin-aldosterone system (RAAS)], the net effect of BNP is a reduction in both preload and after load. Of note, levels of circulating BNP and NT-proBNP also depend on other factors, like age, gender, renal function, and body mass index (24). Because it is a recombinant BNP, nesiritide infusion affects blood levels of endogenous BNP, and currently available assays cannot differentiate between endogenous vs. exogenous BNP. In the other hand, nesiritide does not affect blood levels of endogenous NT-proBNP (25). Key studies of BNP and NT-proBNP have primarily targeted 3 main aspects: 1) the role of these natriuretic peptides in establishing the diagnosis of HF in the Emergency Department, 2) assessing the efficacy and safety of BNP (or NT-proBNP) guided heart failure therapy, and 3) their role in prognosis. Studies evaluating the use of measuring BNP (26) or NT-proBNP (27) in establishing the diagnosis of acute heart failure concluded that measuring BNP or NT-proBNP is mostly useful when the clinical presentation is unclear. As a result, international HF guidelines recommend measuring natriuretic peptides in the evaluation of patients in whom the “clinical diagnosis of heart failure is uncertain” (28-31). Studies that looked at BNP- (or NT-proBNP)-guided HF therapy showed that the natriuretic peptides levels decrease after initiation of heart failure treatment.

However, the results of these studies showed inconsistent results for hard clinical end-points (32-39). A recent meta-analysis included some of these studies, and showed that BNP-guided HF therapy reduced all-cause mortality, but did not reduce hospitalization or survival free of hospitalization (40). Finally, the role of measuring BNP and NT-proBNP at baseline, at discharge, and/or the change between admission and discharge has been extensively evaluated in many studies. From this perspective, it is evident that natriuretic peptides have significant long and short term prognostic value both in acute and chronic heart failure (41-49).

To the best of our knowledge, there are no studies correlating natriuretic peptides with objective measures of respiratory function in ADHF. However, various studies tried to assess the relationship between the natriuretic peptides and different other variables. For example, modestly-sized studies evaluated the correlation between BNP (or NT-proBNP) and invasive hemodynamic monitoring. Overall, there seems to be a variable degree of positive correlation between natriuretic peptides and pulmonary capillary wedge pressure (PCWP) (50-53). Other studies evaluated the association between natriuretic peptides and HF symptoms in out-patient settings and reported a positive correlation (i.e. higher levels of natriuretic peptides were found in patients with more advanced NYHA class) (54-56). In a similar context, at least two studies evaluating the relationship between BNP and 6-minute walk test showed mixed results (57,58). Other studies looked at the correlation between BNP and quality of life in

patients with heart failure, and concluded that there was no such correlation (57,59). In different context, the relationship of PEFR with other variables in patients with ADHF has not been extensively studied. The recent ASCEND-HF respiratory sub-study showed a small but statistically significant correlation between the change in PEFR and the change in dyspnea index measured by Likert scale (between baseline and 24 hours) (13). In another study, PEFR was found to be proportional to the New York Heart Association (NYHA) functional class (the higher the NYHA class, the lower the PEFR), but testing for correlation between PEFR and NYHA class was not done (60).

We did not find significant correlation between short-term changes in PEFR and NT-proBNP. It is possible that PEFR and NT-proBNP simply measure different aspects of improvement after initiating therapy for ADHF, hence the lack of correlation. However, there are a few other potential explanations for this lack of association. Both absolute PEFR values and NT-proBNP levels share some factors that could alter their absolute values, like age, gender, and body habitus (24,61). These factors have different associations with PEFR and NT-proBNP (for example: older patients tend to have higher BNP levels but lower absolute PEFR values compared to younger patients). It is theoretically possible that those factors could have, in part, contributed to the difficulty of showing significant correlation between PEFR and NT-proBNP. In addition, we noticed that the PEFR in around 1/3 of the patient in this current sub-study either did not change or got worse over the first 24 hours. Similarly, the NT-proBNP level in around 1/5 of

the patients either did not change, or got worse within the first 48-72 hours. Although this could be in part because of factors like worsening renal function (which affects NT-proBNP levels) or fatigue and poor effort (which can affect PEFR measurement), it could also be because some patients "responded" to ADHF therapy earlier/more than others. Considering the relatively small sample size, we have elected not to do sub-group analyses of any kind, as it would be difficult to make solid conclusions from such methods. In addition, sub-group analysis was not planned *a priori*. Another potential explanation for the lack of association is the fact that the second PEFR measurement and the second NT-proBNP measurement were not done simultaneously (24 hours vs. 48-72 hours, respectively). However, we feel that this is less likely to be the sole explanation. It is also possible that more time is needed between the baseline and the second measurement of both PEFR and NT-proBNP for their changes to show any correlation. We have seen that PEFR continued to improve within the first 24 hours. It is possible that the PEFR continues to improve over the first few days after admission with ADHF. It might be reasonable for future studies to test the correlation of the change in PEFR and natriuretic peptides between baseline and hospital discharge.

Although assessing the prognostic value of NT-proBNP was not the primary aim of this study, it should be mentioned that we did not find the absolute change in NT-proBNP from baseline to 48-72 hours to be significant predictor of HF-rehospitalization or death within 30 days. However, most of the

studies that linked natriuretic peptides to prognosis looked at either admission and/or discharge BNP or NT-proBNP. The studies that looked at the prognostic utility of either the absolute or relative change in natriuretic peptides from admission with ADHF to hospital discharge showed mixed results (41,46,49). In addition, in our study, the absolute change of NT-proBNP was between baseline and 48-72 hours (compared to pre-discharge in other studies). The relatively small sample size in this sub-study could have also contributed to this finding.

Conclusions

Dyspnea is a common subjective outcome measured in clinical trials of ADHF. However, two objective tools for the assessment of improvement in ADHF (PEFR and NT-proBNP) do not appear to be strongly correlated. Baseline PEFR and baseline NT-proBNP appear to be correlated as do PEFR at 24 hours and NT-proBNP at 48-72 hours. However, there was no significant correlation between short-term changes in PEFR and in NT-proBNP. As our study showed that PEFR continued to improve within 24 hours, future studies should evaluate the utility of measuring PEFR at hospital discharge, and assess if the change in PEFR from baseline to hospital discharge correlate with the change in natriuretic peptides from baseline to hospital discharge.

Tables

Table 3-1: Baseline characteristics

Variable	This sub-study	All patients in the respiratory sub-study (not included in this sub-study)	P value
Age: mean (SD)	74(63-82)	70(59-79)	<0.001
female: n (%)	24.1	34.2	0.001
Race: (%)			
White	86.1	68.2	<0.001
Black	8.9	24.9	
Asian	1.9	3.3	
Other	3.2	3.6	
Medical history: (%)			
Heart failure admission 1 year prior to admission	32.2	42.3	0.001
Prior myocardial infarction	46.2	39.0	0.018
Ischemic etiology for HF	52.5	42.0	0.003
Hypertension	80.4	79.1	0.616
Atrial fibrillation or flutter	50.0	46.1	0.211
Diabetes mellitus	47.5	44.7	0.368
Chronic respiratory disease	21.7	21.4	0.930
Measurements			
Weight (kg)	83(72.2-100)	84.2(72.6-102.0)	0.623
Blood pressure (mmHg)			
Systolic	120(111-136)	123(110-137)	0.359
Diastolic	69(60-84)	71(62-84)	0.025
Heart rate (beats/min)	77(68-90)	78(68-91)	0.557
Respiratory rate (breaths/min)	24(22-26)	24(20-24)	0.010
Baseline BNP (pg/mL)	1196(713-1971)	1106(584-1914)	0.139
Baseline NT-proBNP (pg/mL)			
Local, n=113	4482(2694-10498), n=83	4482(2707-9048)	0.628
Core, n=158	6330(3648-14665)	6330(3648-14665)	--
Creatinine (umol/L)	128(98-170)	114.9(88.4-150)	<0.001
BUN/Urea (mg/dL)	10.4(7.1-14.3)	8.2(5.8-12.3)	<0.001
Hemoglobin (g/dL)	12.3(11.2-13.5)	12.5(11.1-13.6)	0.209
LVEF (%)	25(20-38)	25(20-40)	0.989
LVEF ≤40%	73.7	73.8	0.976
LVEF >40%	26.3	26.2	
Medical or device therapy, %			
ACE inhibitor or ARB	69.6	65.3	0.151
Beta-blocker	76.6	69.8	0.019

Aldosterone blocker	15.8	18.3	0.310
Nitrates (oral or topical)	27.9	24.7	0.246
Loop diuretic	96.8	96.9	0.944
Implantable cardioverter-defibrillator	5.7	10.9	0.008
Biventricular pacemaker	3.2	2.1	0.305
Study drug administration			
Time from hospitalization to randomization (hours)	15.9(5.7-22.9)	16.2(6.7-22.3)	0.475
Use of study drug bolus	70.3	67.5	0.343

Table 3-2: Change in PEFR and NT-proBNP

Variable	Baseline		24 hours		48-72 hours		Percent change		P value
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	
PEFR	153	230 (160,340)	148	277 (200,375)			147	13.8 (-6.3,33.3)	<0.001
NT-proBNP	157	6306 (3648,13500)			143	3882 (1663-8926)	143	35.3 (15.9,62.3)	<0.001

Table 3-3: The correlation between PEFR and NT-proBNP (Pearson's correlation coefficient)

Correlation coefficient P value n	PEFR At baseline	PEFR at 24 hours	NT-proBNP At baseline	NT-proBNP At 48-72 hours	PEFR Difference between baseline and 24h	NT-proBNP Difference between baseline and 48-72 hrs
PEFR At baseline	1.00 414	0.81 <0.001 402	-0.16 0.05 152	0.17 0.04 150	-0.13 0.008 402	-0.004 0.96 136
PEFR at 24 hours	0.81 <0.001 402	1.00 404	-0.15 0.07 147	-0.17 0.04 145	0.48 <0.001 402	0.002 0.98 131
NT-proBNP At baseline	-0.16 0.05 152	-0.15 0.07 147	1.00 157	0.87 <0.001 140	-0.005 0.95 146	-0.42 <0.001 140
NT-proBNP At 48-72 hours	0.17 0.04 150	-0.17 0.04 145	0.87 <0.001 140	1.00 154	-0.03 0.76 144	0.09 0.29 140
PEFR Difference between baseline and 24h	-0.13 0.008 402	0.48 <0.001 402	-0.005 0.95 146	-0.03 0.76 144	1.00 402	0.02 0.86 130
NT-proBNP Difference between baseline and 48-72 hrs	-0.004 0.96 136	0.002 0.98 131	-0.42 <0.001 140	0.09 0.29 140	0.02 0.86 130	1.00 140

Table 3-4: HF-rehospitalization or death within 30 days

Model		HR	95% CI	p value	n
Δ log PEFR		1.11	0.65 to 1.92	0.7	153
Δ log PEFR when added to ASCEND-HF model		1.37	0.74 to 1.34	0.64	151
Δ log NT-ProBNP		1.33	0.84 to 2.1	0.21	157
Δ log NT-ProBNP when added to ASCEND-HF model		1.21	0.73 to 1.99	0.46	155
Δ log PEFR + Δ log NT-ProBNP when added to ASCEND-HF model	Δ log PEFR	1.38	0.74 to 2.5	0.62	150
	Δ log NT-ProBNP	1.11	0.62 to 2.00	0.31	

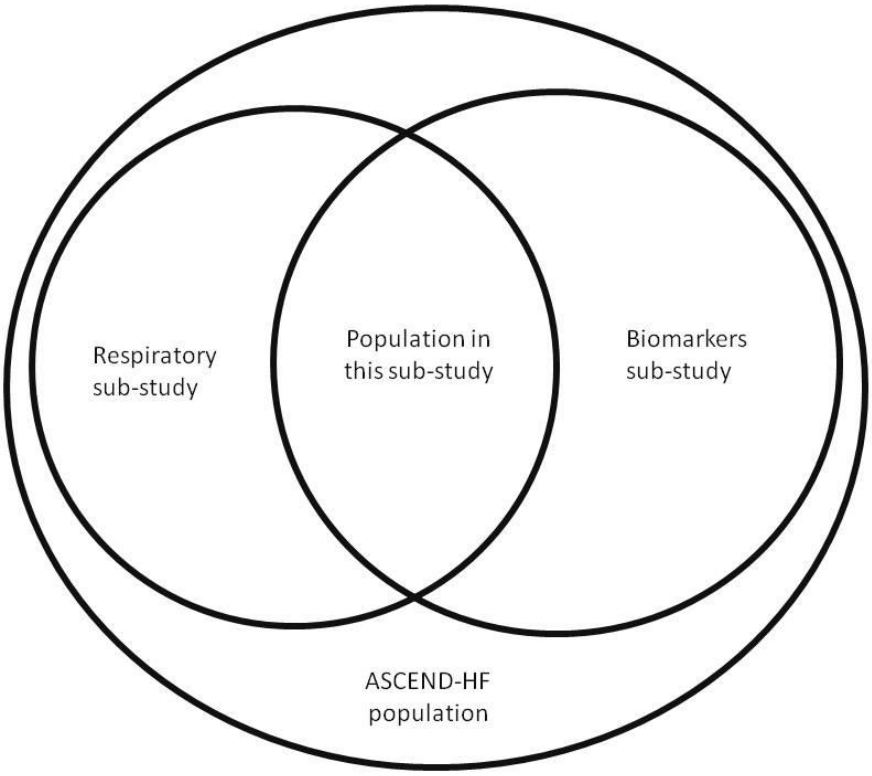
Δ log PEFR: log transformation of the absolute difference in PEFR between baseline and 24 hours

Δ log ntBNP: log transformation of the absolute difference in NT-proBNP between baseline and 48-72 hours

ASCEND-HF model for HF-rehospitalization or death **at 30 days included the following covariates**: hypotension at baseline, serum sodium, age, log (BUN), history of cerebrovascular disease, log (creatinine), history of depression, resting dyspnea at baseline, elevated jugular venous pressure (JVP), and history of chronic respiratory disease.

Figures

Figure 3-1. Population of patients included in this sub-study of ASCEND-HF



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Chapter 4

Discussion and Conclusions

In this thesis, we evaluated the spectrum of the clinical syndrome of HF to explore the efficacy and safety of CRT, as well as the correlation between a commonly evaluated biomarker (NT-proBNP) and a measure of respiratory function. Importantly, the CRT meta-analysis demonstrated a clear signal of efficacy for a reduction in mortality in patients with less symptomatic HF, but no improvement in other important clinical outcomes such as quality of life or 6-minute walk test. In the acute, symptomatic patients in the ASCEND-HF trial, we found a lack of correlation between the most commonly used biomarker used in trials as a surrogate marker, NT-proBNP, and PEFR, an objective marker of respiratory function. Whether or not surrogate outcomes of respiratory function should be utilized as complementary and in conjunction to other markers in chronic HF remains to be explored, as PEFR shows a clinically meaningful change in AHF patients.

The first part of this thesis, a systematic review of 25 RCTs demonstrated that CRT is efficacious in patients with left ventricular dysfunction, prolonged QRS duration, and mild heart failure symptoms to a degree that is similar to patients with moderate to severe heart failure symptoms. Few meta-analyses have been conducted since this systematic review was published in 2011, and they have largely revealed consistent results (1-4).

The decision to implant a CRT device, however, should be made with caution, as there are still some challenges, one of which is predicting which patients will “respond” to CRT. Because of the lack of a generally acceptable

definition, studies used different clinical and/or echocardiographic criteria to define CRT response. The rate of non-response after CRT implantation has been reported to be up to 40% (5,6). Various clinical and technical variables are thought to contribute to poor (or good) response to CRT; including gender, etiology of LV dysfunction, QRS width and/or morphology, myocardial viability at pacing site, and LV or RV lead position (6,7). In addition, the benefit of CRT in patients with atrial fibrillation, which is common if HF population (8), is less clear. At the time of publication of our meta-analysis, the Ablate and Pace in Atrial fibrillation (APAF) trial was still on-going. In the APAF trial, 186 patients with permanent AF, reduced LV function, and wide QRS duration were randomized (after AV junction ablation and CRT implantation) to RV pacing vs. CRT. The results of this trial have been recently published, and it showed that CRT reduces HF-related death, HF hospitalization, worsening HF, but not all-cause death (9). Among the other trials that have recently been published (i.e. after the publication of our meta-analysis) is the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) Trial (10). In this trial, 691 patients who had an indication for pacing for atrioventricular block, NYHA class I, II, III symptoms, and LVEF of 50% or less were randomized to RV pacing or CRT (with ICD if indicated). CRT was superior to RV pacing for the composite primary outcome of time to all-cause death, an urgent care visit for heart failure that required intravenous therapy, or a 15% or more increase in the left ventricular end-systolic volume index. CRT was superior to RV pacing for the

composite secondary outcome that included HF hospitalization. However, there was no difference in all-cause mortality (10). Finally, the lesser-EARTH was another RCT that included patients with reduced LVEF <35%, narrow QRS (less than 120 ms), and symptoms of HF in 6-minute walk test. Ventricular dyssynchrony was not among the inclusion criteria. CRT-ICD devices were implanted at baseline, and patients were subsequently randomized to CRT-on vs. CRT-off. This trial showed that CRT did not improve clinical outcomes of LV remodeling and was associated with potential harm (11). The EchoCRT trial is another trial that is looking at the efficacy of CRT in HF patients with narrow QRS, but with evidence of ventricular dyssynchrony in echocardiography, and is still on-going (NCT00683696).

In the second part of this thesis, we evaluated the utility of an objective tool for assessment of dyspnea relief in patients with ADHF. The relationship of NT-proBNP with PEFR, an objective measure of respiratory function, was assessed in a sub-study of the ASCEND-HF trial. There was no correlation between short term changes in PEFR and NT-proBNP.

An objective tool for assessment of dyspnea improvement in patients with ADHF is still lacking (12). Our overall aim from this study was to further evaluate if PEFR can serve this purpose. As natriuretic peptides have an established role in the diagnosis and prognosis of patients with HF (13-16), we hypothesized that change in NT-proBNP and change in PEFR will be correlated.

However, our results showed that these variables were not significantly correlated. Targeting natriuretic peptides, as well as other surrogates in ADHF, have not always led to positive results when it comes to hard clinical end-points (17). In addition, using BNP as a surrogate marker for functional improvement is not always recommended (18,19). Although a significant correlation between PEFR and NT-proBNP was not seen, there is likely value of both these markers in evaluating patients with ADHF. It is possible that these two variables assess different aspects of acute heart failure syndromes. Future studies in this field should consider focusing on different aspects of the utility of PEFR as a method of assessing dyspnea improvement (for example, using % predicted instead of absolute PEFR, which eliminates the effect of other confounding factors, like age or body habitus).

Conclusions

Patients with acute and chronic HF have significant morbidity and mortality. New therapies are needed, and evaluating those already in clinical practice for effectiveness is clearly needed. Moving advanced cardiac devices to less symptomatic patients needs careful consideration as patient-reported outcomes such as quality of life are not improved yet there is a reduction in mortality. Similarly, new therapies for AHF need to be evaluated fully with biomarkers, symptom improvement, respiratory function and clinical outcomes.

Summary

In this thesis, we tried to explore the therapy and outcomes in heart failure (acute and chronic). In a meta-analysis of 25 RCTs, CRT was found to improve mortality, HF hospitalization, and LV remodeling in appropriately selected patients, regardless of severity of symptoms at baseline, without improving functional outcomes in patients with mild symptoms. Future studies should try to come up with a universally accepted definition of "CRT non-responders", and attempts should be made to identify demographic, clinical, and/or technical variables that may contribute to this. In another study, we evaluated the correlation between PEFR (which has recently been found to be of value in assessing dyspnea improvement in ADHF) and NT-proBNP (a well established biomarker for diagnosis and prognosis in HF). Although we did not find significant correlation, we think that both markers are of value, as prognostic value of natriuretic peptide is well established, and there is a potential value for PEFR to be an objective end-point for assessment of improvement in ADHF. Probably these two variables are evaluating different aspects of acute heart failure syndromes, hence the lack of correlation.

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