Published in final edited form as:

Heart Rhythm. 2019 June ; 16(6): 928–935. doi:10.1016/j.hrthm.2018.12.023.

Cardiorenal Status using Amino Terminal Pro Brain Natriuretic Peptide and Cystatin C on Cardiac Resynchronization Therapy Outcomes: From the BIOCRT Study

Quynh A. Truong, MD, MPH^{1,2}, Jackie Szymonifka, MA², James L. Januzzi, MD³, Jigar H. Contractor, MD⁴, Roderick C. Deaño, MD MPH⁵, Neal A. Chatterjee, MD³, and Jagmeet P. Singh, MD PhD³

¹Department of Radiology and Medicine, New York-Presbyterian Hospital and Weill Cornell Medicine, New York, NY

²Department of Biostatistics, New York University, New York, NY

³Division of Cardiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

⁴Department of Medicine, New York-Presbyterian Hospital and Weill Cornell Medicine, New York, New York

⁵Department of Medicine, Division of Cardiovascular Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

Abstract

Background: Cardiorenal syndrome (CRS) comprises of a heterogeneous group of acute and chronic cardiac and renal dysfunction.

Objectives: To determine the effect of cardiorenal status using a dual marker strategy with amino-terminal pro brain natriuretic peptide (NT-proBNP) and cystatin C on cardiac resynchronization therapy (CRT) outcomes.

Methods: In 92 patients (age 66 ± 13 ; 80% male; ejection fraction $26 \pm 7\%$), NT-proBNP and cystatin C levels were measured at CRT implantation, and 1 month. NT-proBNP > 1000 pg/mL and cystatin C > 1 mg/L were considered high. Baseline cardiorenal patients were defined as having high NT-proBNP and cystatin C. At 1 month, we categorized CRT patients as (1) irreversible cardiorenal if cystatin C was persistently high, (2) progressive cardiorenal with transition from low to high cystatin C, (3) reversible cardiorenal with transition from high to low cystatin C, and (4) “normal” with stable low cystatin C. Outcomes were 6-month clinical and echocardiographic CRT response and two-year major adverse cardiac event (MACE).

Address for Correspondence: Quynh A. Truong, MD MPH FACC FAHA FSCCT, Associate Professor of Radiology and Medicine, Weill Cornell Medicine, Dept. of Radiology, 525 E. 68th Street, L-024, New York, NY 10021, qat9001@med.cornell.edu, (Tel) 212-746-4095, (Fax) 212-746-2674.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Results: Compared to patients with low NT-proBNP and cystatin C, cardiorenal patients had >9-fold increase risk of CRT non-response (uncompensated: OR 9.0; compensated: OR 36.4, both $p = 0.004$) and >6-fold risk of MACE (uncompensated: HR 8.5, $p=0.005$). Compared to “normal” and reversible patients (referent), irreversible patients had a 9-fold increase for CRT non-response (OR 9.1, $p<0.001$) and had >4-fold risk of MACE (adjusted HR 5.1, $p<0.001$). Irreversible patients were most likely echocardiographic CRT non-responder.

Conclusions: Cardiorenal status by NT-proBNP and cystatin C can identify high-risk CRT patients, and those with both elevated concentrations have worse prognosis.

Keywords

cardiac resynchronization therapy; renal function; natriuretic peptide; heart failure; biomarkers

INTRODUCTION

Cardiorenal syndrome (CRS) comprises a heterogeneous group disorders characterized by acute or chronic cardiac and renal dysfunction, resulting in impaired contractility of the heart and decreased glomerular filtration by the kidneys, which leads to decompensation of volume status.¹ Aggressive treatment of heart failure (HF) may improve CRS driven primarily by dysfunction of the heart and right heart congestion, but intrinsic renal disease is not easily reversed and is associated with increased morbidity and mortality.² However, the interplay between the heart and kidneys makes it a diagnostic challenge to identify patients with intrinsic renal disease and those with reversible renal disease due to HF.

Cardiac resynchronization therapy (CRT) is an adjuvant device therapy used for treatment of refractory HF that improves mortality and relieves symptoms.³ In patients with CRS driven primarily by HF, treatment with CRT improves cardiac function and thus improves renal function.⁴⁻⁶ In patients with co-existing intrinsic renal disease, CRT may not improve renal impairment, leading to worse prognosis in advanced HF and may partially explain the residual CRT non-responders.⁶⁻⁸

Amino terminal pro brain natriuretic peptide (NT-proBNP) is a HF biomarker that is elevated in decompensated states of volume overload.⁹ Cystatin C is a marker of renal function that is sensitive to small variations in the glomerular filtration rate and may be useful in identifying cardiorenal dysfunction.¹⁰⁻¹³ Using a dual-marker strategy of NT-proBNP and cystatin C, NT-proBNP levels can identify compensated and uncompensated HF patients; while cystatin C levels may be able to differentiate patients with co-existing renal dysfunction from those with CRS driven exclusively by HF. Thus, we aim to use a dual-marker strategy with baseline NT-proBNP and cystatin C to identify cardiorenal status and subsequently predict 6-month clinical and echocardiographic CRT response and major adverse cardiovascular events at 2 years. We also examine the prognostic role of serial 1-month levels of cystatin C to evaluate for differences in CRT response.

METHODS

Study Population and Protocol

“Biomarkers to Predict CRT Response in Patients with HF” (BIOCRT; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01949246) # NCT01949246) is a prospective observational study of patients undergoing CRT at a single tertiary care hospital. The study design and inclusion/exclusion criteria were previously reported.¹⁴ Briefly, eligible patients were at least 18 years old, CRT candidates with New York Heart Association (NYHA) Functional Class II-IV, left ventricular (LV) ejection fraction (EF) <35%, QRS interval >120 ms, and a HF exacerbation within the past year. Exclusion criteria include life expectancy <6 months, severe aortic stenosis, recent cardiac surgery or coronary revascularization, HF requiring intravenous infusion therapy, chronic obstructive pulmonary disease, primary pulmonary hypertension, and pregnancy. Blood samples, 12-lead electrocardiography, and 2-dimensional echocardiographic measurements were obtained at the time of device insertion and subsequently at 1-month and 6-months post implantation.

This analysis included 92 patients who had NT-proBNP and cystatin C levels concentrations during CRT implantation and 1-month after treatment. Participants were followed through a time horizon of 2 years. All patients provided written informed consent and the institutional review board approved the study protocol.

Blood Samples

Peripheral venous blood was collected in tubes with and without anticoagulant at the time of device implantation, 1-month, and 6-month follow up visits. Serum was immediately stored in microcentrifuge tubes at -80°C until de-identified samples were analyzed on the first freeze-thaw cycle at an independent laboratory (Dimension Vista; Siemens Healthcare Diagnostics, Newark, DE, USA), which was blinded to the clinical history and the timing of the samples. Supplemental Data 1 details the interassay coefficient of variation for the biomarkers. We calculated estimated glomerular filtration rate (eGFR) with the creatinine value using the Modification of Diet in Renal Disease (MDRD) equation.¹⁵

We defined NT-proBNP concentrations >1000 pg/mL and Cystatin C concentrations > 1mg/L as “high,” as these cut-off values are associated with adverse HF outcomes.^{8, 9, 16} We defined eGFR ≥ 60 mL/min/1.73 m² as normal renal function.¹⁵

Baseline Cardiorenal Status and Reversibility Category Definitions

Baseline cardiorenal status was stratified into 4-categories based on pre-implantation levels of NT-proBNP and cystatin C (Figure 1): (1) uncompensated CRS is defined as high NT-proBNP and high cystatin C; (2) compensated CRS as low NT-proBNP and high cystatin C; (3) uncompensated HF as high NT-proBNP and low cystatin C; and (4) compensated HF as low NT-proBNP and low cystatin C. Similar analysis was performed using eGFR, whereby uncompensated and compensated CRS were defined using abnormal eGFR < 60 mL/min/1.73 m², while uncompensated and compensated HF used normal eGFR.

Cardiorenal reversibility status was stratified into 4-categories based on change in cystatin C at 1-month (Figure 1): (1) irreversible cardiorenal is defined as those with cystatin C that remained elevated at 1-month; (2) progressive cardiorenal as those who transitioned from low cystatin C to high cystatin C; (3) reversible cardiorenal as patients who normalized renal function after CRT; (4) “normal” renal function as patients with persistently low cystatin C at baseline and 1-month. We subsequently considered reversible cardiorenal and “normal” renal function as non-intrinsic renal disease.

End points

Clinical CRT response was defined by improvement in the Heart Failure Clinical Composite Score (HF CCS) at 6 months. The HF CCS is a composite score of subjective metrics, including NYHA functional class and global assessment score, in addition to objective measures, such as HF hospitalization and mortality.¹⁷ CRT responders improved their HF CSS, while non-responders had unchanged or worsened HF CSS. A committee of two cardiologists who were blinded to the biomarker results adjudicated CRT response with disagreement resolved by consensus with a third cardiologist. Major adverse cardiovascular event (MACE) was the composite endpoint of death, cardiac transplant, left ventricular assist device, and HF hospitalization at 2 years. Echocardiographic CRT response were defined using two metrics at 6 months: EF responder as an absolute increase of 5% in LV EF, and ESV responder as a decrease in ESV of 15%.¹⁸

Statistical Analysis

Descriptive statistics were reported as either mean $\pm$ standard deviation, for normally distributed variables, or as a median with interquartile range, for non-normal, continuous variables. Nominal variables were reported as frequencies and percentages. For continuous variables, we used t-test or the Wilcoxon rank-sum test for dichotomous comparisons and analysis of variance (ANOVA) or Kruskal-Wallis test for multi-group comparisons. For nominal variables, Fisher’s exact test was used. Spearman correlation was used to illustrate the strength of correlation between NT-proBNP and cystatin C levels. Logistic regression was used to determine the association between cardiorenal and reversibility status to CRT response. Cumulative event rates were estimated using Kaplan-Meier methodology and comparisons were made using the stratified log-rank test. Cox proportional hazards models were used to assess the association of risk factors with MACE. A 2-tailed p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SAS (Version 9.4, SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Characteristics

Table 1 depicts the baseline characteristics of 92 patients and as stratified by baseline cardiorenal status (Supplemental Table 1). Participants were predominantly male, NYHA Functional Class III, with multiple co-morbidities of patients undergoing CRT and had severely reduced LV function (median EF 26%).

Cardiorenal Status and Baseline NT-proBNP and Cystatin C Levels

At the time of implantation, median NT-proBNP was 1673 pg/mL and median cystatin C was 0.95 mg/L (Supplemental Table 2). There was moderate positive correlation between baseline NT-proBNP and cystatin C ($r=0.45$, $p < 0.001$).

Figure 2 depicts the median NT-proBNP and cystatin C values by cardiorenal status at implantation, 1-month, and 6-months. Uncompensated cardiorenal status had the highest NT-proBNP levels throughout the study. At 6-months, uncompensated HF, compensated HF, and compensated cardiorenal reduced their NT-proBNP levels, while uncompensated cardiorenal did not reduce NT-proBNP levels. Compared with the compensated cardiorenal group, the uncompensated cardiorenal group had significantly higher cystatin C levels at baseline. Further, when compared with the compensated HF group, the uncompensated HF group had significantly higher cystatin C levels.

Similarly, when comparing eGFR across groups, patients with uncompensated cardiorenal had the lowest eGFR while compensated HF had the highest eGFR ($p<0.001$, Supplemental Table 1).

Cardiorenal Status and Clinical Outcomes

At 6-months, 38 patients (41%) were CRT non-responders, of which 11 (12%) died. At 2 years, 25 patients (27%) suffered MACE. At device implantation, 37% of patients had uncompensated cardiorenal, 7% had compensated cardiorenal, 26% had uncompensated HF, and 30% had compensated HF. Overall, NT-proBNP and cystatin C levels were higher in CRT non-responders and those with MACE (Supplemental Table 2).

Table 2 and Supplemental Figure 1 depict the unadjusted and adjusted odds for CRT-non-response stratified by pre-implantation cardiorenal status using cystatin C and eGFR. Using cystatin C, compensated cardiorenal and uncompensated cardiorenal status had significantly higher risk of CRT non-response compared with compensated HF status. Compensated cardiorenal had over 30-fold increase in the odds of CRT non-response, while those with uncompensated cardiorenal had a 9-fold increase in the odds of non-response, even after adjustment for variables such as LBBB and ischemic cardiomyopathy. The odds for CRT non-response were adjusted for differences in baseline demographics between the cardiorenal groups and remained statistically significant. However, the risk of CRT non-response was not significantly increased in uncompensated HF. Notably, there were no statistically significant association between cardiorenal status and CRT non-response when eGFR was used to define the cardiorenal status (Table 2).

Figure 3 depicts the Kaplan-Meier estimates of the cumulative probability of 2-year MACE as stratified by baseline cardiorenal status. Uncompensated cardiorenal status at implantation was associated with greater than 8-fold increase in MACE relative to those with compensated HF. The risk of MACE did not differ significantly amongst the compensated cardiorenal, uncompensated HF, and compensated HF groups.

Cardiorenal Reversibility using 1-month Cystatin change

Figure 4 depicts the median NT-proBNP and cystatin C levels at baseline, 1-month, and 6-months in patients defined as “irreversible,” “progressive,” or “normal or reversible.” After 1-month of treatment, 36% of patients had irreversible cardiorenal, 16% had progressive cardiorenal, 8% had reversible cardiorenal, and 48% had normal renal function. Supplemental Table 3 stratifies baseline characteristics by 1-month cardiorenal reversibility status. Those with irreversible cardiorenal were more likely to be male and have diabetes, while those with non-intrinsic renal tended to be younger.

Amongst the reversibility groups, the highest NT-proBNP levels at 6 months were in the irreversible cardiorenal group (median 3074 pg/mL), followed by progressive cardiorenal (1693 pg/mL), reversible cardiorenal (1376 pg/mL) and normal renal (383 pg/mL), $p < 0.001$. Figure 4A depicts the baseline, 1-month, and 6-month NT-proBNP levels with normal and reversible cardiorenal status combined.

Renal dysfunction at 1-month post CRT was associated with a 6-fold increase in CRT non-response. Table 3 shows the unadjusted and adjusted risk of CRT non-response by 1-month cardiorenal reversibility status. Those with persistently elevated cystatin C levels at 1-month, the irreversible cardiorenal group, had the greatest risk for CRT non-response with nearly a 14-fold increase in the odds of non-response.

Figure 3 depicts the Kaplan-Meier estimates of the cumulative probability of 2-year MACE by 1-month cardiorenal reversibility groups. Compared to those with non-intrinsic renal, irreversible cardiorenal patients had a 5-fold risk of MACE, which remained significant when adjusted for co-variables, while progressive cardiorenal had similar MACE risk. Notably, patients who reversed their renal dysfunction had no MACE in the 2 year follow up; and thus, normal and reversible groups were combined.

Cardiorenal and Reversibility Status on Echocardiographic CRT Response

Table 4 summarizes the echocardiographic CRT response at 6 months as stratified by cardiorenal and reversibility status. Uncompensated cardiorenal and irreversible patients had the least change in EF and ESV at 6-month Echo. Moreover, uncompensated cardiorenal patients trended to be EF non-responder and ESV non-responder (both $p = 0.06-0.08$), while irreversible patients were most likely to be EF non-responder and ESV non-responder (both $p = 0.05$).

DISCUSSION

In this study, CRS was common in patients undergoing CRT with more than a third of patients having uncompensated cardiorenal status at baseline and irreversible cardiorenal status at 1-month post treatment. Our findings suggest a pre-implantation dual-marker strategy with NT-proBNP and cystatin C might be used to categorize the 4-categories of HF and CRS (compensated and uncompensated) as well as identify high-risk CRT patients. We found uncompensated cardiorenal status at device implantation was associated with over 9-fold increase risk of 6-month CRT clinical non-response, an 8-fold increase risk of 2-year MACE, and trended to have the least change in EF and ESV. Biomarker responses at 1-

month provided early prognosis for risk of adverse cardiovascular outcomes: irreversible cardiorenal status fared worst with 14-fold increase risk of clinical non-response to CRT, 5-fold increase in MACE, and the highest likelihood for EF and ESV non-response. The findings suggest that cardiorenal disease may be responsible in part for decreased efficacy of CRT and NT-proBNP and cystatin C may be used for patient selection and early monitoring of treatment effect.

Dysfunction of the heart or kidneys results in bidirectional injury of other organs through hemodynamic alterations and dysregulation of the neurohormonal milieu.¹⁹ CRS encompasses a broad spectrum of disorders in which the acute or chronic dysfunction of one organ leads to acute or chronic injury of the other organ.¹ Cardiorenal status remains a challenge to identify, but increasingly biomarkers are examined in a multi-marker approach to improve accuracy in diagnosis and prognostication.²⁰ Cardiorenal biomarkers were selected for their collective ability to identify disease in both the heart and kidneys. NT-proBNP detects cardiac decompensation as it is increased in response to volume overload, while cystatin C offers a reasonable estimate of renal function and offers incremental value in over traditional markers of renal function in predicting morbidity and mortality.^{11–13, 21–24} Moreover, in this analysis, when using cystatin C to define cardiorenal status, there were differences amongst cardiorenal status for CRT non-response but not when using eGFR to define cardiorenal status. This is in keeping with our prior observation that cystatin C had incremental value beyond conventional markers of serum creatinine and estimated glomerular filtration rate for predicting CRT non-response.⁸

Prior studies have examined HF outcomes in the patients with cardiorenal diseases and found improvement in heart failure morbidity with CRT.^{1, 4, 22, 25} However, we found that cardiorenal dysfunction significantly increases risk of CRT non-response at 6-months and uncompensated cardiorenal increases risk of 2-year MACE. NT-proBNP alone is not sufficient to elucidate prognosis, as pre-treatment elevations of NT-proBNP do not identify patients at increased risk of adverse outcomes.²⁶ Compensated and uncompensated HF status had similar risk of CRT non-response and MACE. On the other hand, a dual biomarker strategy provides important prognostic information for patients, families, and clinicians, by identifying a subgroup of HF patients who have higher cardiovascular risk despite receiving CRT.

Cardiorenal disease portends poor outcomes in HF because it identifies a state of dysfunction extending beyond the heart. Shared risk factors predispose individuals to develop both cardiac and renal dysfunction, leading to uncompensated cardiorenal status. Furthermore, interorgan communication allows dysfunction in one organ to cause distant dysfunction in the other through activation of the neurohormonal and renin-angiotensin-aldosterone systems, increased sodium and water retention, and systemic inflammation.^{1, 19} Systemic changes lead to cardiac remodeling and worsening glomerular filtration that cyclically worsens disease in both organs and may explain the decreased efficacy of resynchronization therapy.

At 1-month, we found that more than a third of patients with cardiorenal disease at baseline failed to improve renal function with CRT. Failure to reverse cardiorenal dysfunction might

reflect intrinsic renal disease associated with more severe HF, but it may also simply reflect more severe degrees of cardiovascular dysfunction, leading to worse renal function. Regardless, lack of improvement in CRS increased the risk of CRT non-response and MACE. Examining cardiorenal disease in patients undergoing CRT provides an opportunity to understand the variable response patients have to CRT. As expected, CRT may improve cardiac function, but often does not improve renal dysfunction. Because of continued renal disease, patients will continue have higher risk of morbidity and mortality. Early identification of high risk CRT patients, allows the clinician an opportunity to intervene, especially in centers where multidisciplinary care teams are employed.²⁷

Study Limitations

The study population was cohort of patients undergoing CRT at a single tertiary care center who were predominantly male, had mild-moderate renal insufficiency, and had significant left ventricular systolic dysfunction with primarily NYHA functional class III disease, which may limit generalizability. Small population size restricted the power to examine subgroups and limited the variable model. However, we adjusted for covariates of clinical significance and were able to determine significant findings. Larger studies are needed to precisely define the magnitude of effect cardiorenal status portends on clinical outcomes. Future studies identifying the underlying pathophysiological “crosstalk” can offer greater insight into the drivers of cardiorenal dysfunction and identify future targets for treatment to improve CRT and cardiorenal outcomes.

CONCLUSIONS

CRT patients with CRS, especially irreversible, have worse prognosis compared to those with acute renal injury or “normal” renal function. Cardiorenal status by a dual-marker strategy of NT-proBNP and cystatin C as well as irreversibility status with serial 1-month Cystatin C can identify CRT patients with highest risk for MACE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources: The study was supported by NIH/NHLBI K23HL098370. The reagents/assays were provided and performed by Siemens Healthcare Diagnostics.

Disclosures: Drs. Contractor, Deaño, Chatterjee, as well as Ms. Szymonifka, report no disclosures. Dr. Januzzi is supported in part by the Hutter Family Professorship, receives grant support from Siemens, Singulex, Prevencio, and Roche, and has served as a consultant to Roche Diagnostics, Critical Diagnostics, Abbott, GE, Amgen, and Novartis. Dr. Singh receives grant support from St. Jude Medical, Medtronic Inc., Boston Scientific Corp., Sorin Group, Biotronik, BG Medicine and Siemens. Dr. Truong received grant support from Ziosoft, Inc.

References

1. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008;52:1527–1539. [PubMed: 19007588]

2. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004;164:659–663. [PubMed: 15037495]
3. Chen Y, Duan C, Liu F, Shen S, Chen P, Bin J. Impact of etiology on the outcomes in heart failure patients treated with cardiac resynchronization therapy: a meta-analysis. *PLoS One* 2014;9:e94614. [PubMed: 24732141]
4. Garg N, Thomas G, Jackson G, Rickard J, Nally JV Jr., Tang WH, Navaneethan SD. Cardiac resynchronization therapy in CKD: a systematic review. *Clin J Am Soc Nephrol* 2013;8:1293–1303. [PubMed: 23660183]
5. Friedman DJ, Singh JP, Curtis JP, Tang WH, Bao H, Spatz ES, Hernandez AF, Patel UD, Al-Khatib SM. Comparative Effectiveness of CRT-D Versus Defibrillator Alone in HF Patients With Moderate-to-Severe Chronic Kidney Disease. *J Am Coll Cardiol* 2015;66:2618–2629. [PubMed: 26670062]
6. Singal G, Upadhyay GA, Borgquist R, et al. Renal Response in Patients with Chronic Kidney Disease Predicts Outcome Following Cardiac Resynchronization Therapy. *Pacing Clin Electrophysiol* 2015;38:1192–1200. [PubMed: 26179289]
7. Lin G, Gersh BJ, Greene EL, Redfield MM, Hayes DL, Brady PA. Renal function and mortality following cardiac resynchronization therapy. *Eur Heart J* 2011;32:184–190. [PubMed: 21068051]
8. Chatterjee NA, Singh JP, Szymonifka J, Deano RC, Thai WE, Wai B, Min JK, Januzzi JL, Truong QA. Incremental value of cystatin C over conventional renal metrics for predicting clinical response and outcomes in cardiac resynchronization therapy: The BIOCRT study. *Int J Cardiol* 2016;205:43–49. [PubMed: 26710332]
9. Januzzi JL Jr., Rehman SU, Mohammed AA, et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. *J Am Coll Cardiol* 2011;58:1881–1889. [PubMed: 22018299]
10. Gao C, Zhong L, Gao Y, Li X, Zhang M, Wei S. Cystatin C levels are associated with the prognosis of systolic heart failure patients. *Arch Cardiovasc Dis* 2011;104:565–571. [PubMed: 22117908]
11. Dupont M, Wu Y, Hazen SL, Tang WH. Cystatin C identifies patients with stable chronic heart failure at increased risk for adverse cardiovascular events. *Circ Heart Fail* 2012;5:602–609. [PubMed: 22899766]
12. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, Siscovick DS, Stehman-Breen C. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 2005;352:2049–2060. [PubMed: 15901858]
13. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *Am J Kidney Dis* 2002;40:221–226. [PubMed: 12148093]
14. Truong QA, Januzzi JL, Szymonifka J, et al. Coronary Sinus Biomarker Sampling Compared to Peripheral Venous Blood for Predicting Outcomes In Patients with Severe Heart Failure Undergoing Cardiac Resynchronization Therapy: The BIOCRT Study. *Heart Rhythm* 2014.
15. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006;145:247–254. [PubMed: 16908915]
16. Kim H-N, Januzzi JL. Natriuretic Peptide Testing in Heart Failure. *Circulation* 2011;123:2015–2019. [PubMed: 21555724]
17. Packer M Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail* 2001;7:176–182. [PubMed: 11420770]
18. Park MY, Altman RK, Orencole M, Kumar P, Parks KA, Heist KE, Singh JP, Picard MH. Characteristics of responders to cardiac resynchronization therapy: the impact of echocardiographic left ventricular volume. *Clin Cardiol* 2012;35:777–780. [PubMed: 22886700]
19. Husain-Syed F, McCullough PA, Birk HW, Renker M, Brocca A, Seeger W, Ronco C. Cardio-Pulmonary-Renal Interactions: A Multidisciplinary Approach. *J Am Coll Cardiol* 2015;65:2433–2448. [PubMed: 26046738]

20. van Kimmenade RR, Januzzi JL Jr., Baggish AL, Lainchbury JG, Bayes-Genis A, Richards AM, Pinto YM. Amino-terminal pro-brain natriuretic Peptide, renal function, and outcomes in acute heart failure: redefining the cardiorenal interaction? *J Am Coll Cardiol* 2006;48:1621–1627. [PubMed: 17045898]
21. Laterza OF, Price CP, Scott MG. Cystatin C: an improved estimator of glomerular filtration rate? *Clin Chem* 2002;48:699–707. [PubMed: 11978596]
22. Sumida H, Yasue H, Yoshimura M, Okumura K, Ogawa H, Kugiyama K, Matsuyama K, Kikuta K, Morita E, Nakao K. Comparison of secretion pattern between A-type and B-type natriuretic peptides in patients with old myocardial infarction. *J Am Coll Cardiol* 1995;25:1105–1110. [PubMed: 7897123]
23. McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE, Tunstall-Pedoe H, McMurray JJ, Dargie HJ. Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 1998;351:9–13. [PubMed: 9433422]
24. O’Riordan SE, Webb MC, Stowe HJ, Simpson DE, Kandarpa M, Coakley AJ, Newman DJ, Saunders JA, Lamb EJ. Cystatin C improves the detection of mild renal dysfunction in older patients. *Ann Clin Biochem* 2003;40:648–655. [PubMed: 14629803]
25. Tsutamoto T, Wada A, Sakai H, et al. Relationship between renal function and plasma brain natriuretic peptide in patients with heart failure. *J Am Coll Cardiol* 2006;47:582–586. [PubMed: 16458140]
26. Brouwers C, Versteeg H, Meine M, Heijnen CJ, Kavelaars AM, Pedersen SS, Mommersteeg PM. Association between brain natriuretic peptide, markers of inflammation and the objective and subjective response to cardiac resynchronization therapy. *Brain Behav Immun* 2014;40:211–218. [PubMed: 24704567]
27. Altman RK, Parks KA, Schlett CL, et al. Multidisciplinary care of patients receiving cardiac resynchronization therapy is associated with improved clinical outcomes. *Eur Heart J* 2012;33:2181–2188. [PubMed: 22613342]

Baseline Cardiorenal Status	NT-proBNP / Cystatin C	Reversibility Status	Cystatin C Baseline / 1 month
Compensated HF	Low / Low	"Normal" Renal Function	Low / Low
Uncompensated HF	High / Low	Reversible Cardiorenal	High / Low
Compensated CRS	Low / High	Progressive Cardiorenal	Low / High
Uncompensated CRS	High / High	Irreversible Cardiorenal	High / High

NT-proBNP level:
 High > 1000 pg/mL
 Low ≤ 1000 pg/mL

Cystatin C level:
 High > 1 mg/L
 Low ≤ 1mg/L

Figure 1.
 Baseline Cardiorenal Status and 1-month Reversibility Status Definitions

Figure 2.
Cardiorenal biomarker levels (a) NT-proBNP and (b) cystatin C stratified by cardiorenal status

Figure 3.
Kaplan-Meier estimates of 2-year MACE-free survival by (a) baseline cardiorenal status and (b) 1-month reversibility

Figure 4.
(a) NT-proBNP and (b) cystatin C by 1-month reversibility status

Table 1.

Baseline demographics.

Continuous values are reported as mean±standard deviation or median [interquartile range].

All Patients n=92	
Patient characteristics	
Age, years	66 [57, 77]
Male, n (%)	74 (80)
BMI, kg/m ²	27.0 [24.1, 32.1]
Diabetes, n (%)	25 (27)
Hypertension, n (%)	58 (63)
Ischemic cardiomyopathy, n (%)	44 (48)
Device, n (%)	39 (42)
PPM, n (%)	18 (20)
ICD, n (%)	26 (28)
NYHA,	
I, n (%)	0 (0)
II, n (%)	6 (7)
III, n (%)	83 (90)
IV, n (%)	3 (3)
Medications	
ACEI/ARB, n (%)	75 (82)
BB, n (%)	80 (87)
Spironolactone, n (%)	31 (34)
Diuretics, n (%)	70 (76)
ECG parameters	
QRS duration, ms	163±26
LBBB, n (%)	48 (52)
Paced rhythm, n (%)	19 (21)
Echocardiography parameters	
LVEF, %	26±7
LV dimensions, mm	
End-diastole (EDD)	62 [57, 66]
End-systole (ESD)	54 [48, 58]
LV volumes, cm ³	
End-diastole (EDV)	214 [181, 286]
End-systole (ESV)	154 [131, 209]
Renal Markers	
Creatinine (mg/dL)	1.3 [1.0, 1.5]
eGFR (mL/min/1.73 m ²)	58 [45, 77]

Unadjusted and adjusted risk of clinical CRT non-response stratified by baseline cardiorenal status as defined by NT-BNP and the renal metrics of cystatin C and eGFR.

Table 2.

Cardiorenal Status defined by NT-BNP cutpoint of 1000 pg/mL and Cystatin C cutpoint of 1 mg/L									
	Unadjusted OR (95% CI)	p-value	Age-adjusted OR (95% CI)	p-value	LBBB-adjusted OR (95% CI)	p-value	ICM-adjusted OR (95% CI)	p-value	p-value
Uncompensated CRS	11.0 (3.1 – 39.2)	<0.001	9.0 (2.4 – 33.3)	<0.001	9.2 (2.5 – 33.6)	<0.001	9.0 (2.5 – 33.1)	<0.001	<0.001
Compensated CRS	30.0 (2.7 – 328.5)	0.005	36.4 (3.2 – 416.0)	0.004	30.8 (2.8 – 343.2)	0.005	44.7 (3.8 – 530.9)	0.005	0.003
Uncompensated HF	2.5 (0.6 – 9.8)	0.20	2.4 (0.6 – 9.8)	0.21	2.2 (0.5 – 8.8)	0.27	3.1 (0.7 – 13.1)	0.27	0.12
Compensated HF	1.0 (reference)	--	1.0 (reference)	--	1.0 (reference)	--	1.0 (reference)	--	--
Cardiorenal Status defined by NT-BNP cutpoint of 1000 pg/mL and eGFR cutpoint of 60 mL/min/1.73 m ²									
	Unadjusted OR (95% CI)	p-value	Age-adjusted OR (95% CI)	p-value	LBBB-adjusted OR (95% CI)	p-value	ICM-adjusted OR (95% CI)	p-value	p-value
Uncompensated CRS	3.8 (1.2 – 12.2)	0.02	2.7 (0.8 – 9.4)	0.11	3.0 (0.9 – 10.1)	0.07	3.1 (0.9 – 10.3)	0.07	0.06
Compensated CRS	2.5 (0.5 – 12.6)	0.26	2.3 (0.4 – 11.4)	0.33	2.6 (0.5 – 13.0)	0.25	2.2 (0.4 – 11.6)	0.25	0.34
Uncompensated HF	3.8 (1.0 – 14.7)	0.05	4.0 (1.0 – 15.9)	0.05	3.5 (0.9 – 13.8)	0.07	3.8 (1.0 – 15.4)	0.07	0.06
Compensated HF	1.0 (reference)	--	1.0 (reference)	--	1.0 (reference)	--	1.0 (reference)	--	--

Table 3.

Unadjusted and adjusted risk of clinical CRT non-response stratified by 1-month reversibility status as defined by cystatin C.

	Unadjusted OR (95% CI)	p-value	Age-adjusted OR (95% CI)	p-value	LBBB-adjusted OR (95% CI)	p-value	ICM-adjusted OR (95% CI)	p-value
Irreversible	10.4 (3.6 – 29.9)	<0.001	9.1 (3.1 – 26.7)	<0.001	9.5 (3.2 – 27.7)	<0.001	9.6 (3.3 – 28.3)	<0.001
Progressive	1.9 (0.53 – 7.1)	0.32	1.5 (0.4 – 5.8)	0.58	1.9 (0.5 – 7.0)	0.35	2.0 (0.5 – 7.6)	0.30
Normal and Reversible	1.0 (reference)	--	1.0 (reference)	--	1.0 (reference)	--	1.0 (reference)	--

Table 4.

Echocardiographic CRT response at 6-month as stratified by baseline cardiorenal and 1-month reversibility status using NT-proBNP and cystatin C. Left ventricular (LV) ejection fraction (EF) response defined as absolute increase of 5% in EF. LV end systolic volume (ESV) response defined as decrease in ESV of 15%.

Continuous values are reported as median [interquartile range].

	EF, %	EF non-responder	ESV, cm3	ESV non-responder
All Patients	8 [2, 14]	29/80 (36%)	-41 [-66, -10]	27/72 (38%)
Cardiorenal Status				
Uncompensated CRS	4 [-1, 10]	15/27 (56%)	-20 [-52, 10]	14/24 (58%)
Compensated CRS	11 [2, 16]	1/4 (25%)	-53 [-68, 4]	1/4 (25%)
Uncompensated HF	9 [3, 14]	8/24 (33%)	-64 [-101, -26]	5/20 (25%)
Compensated HF	11 [6, 18]	5/25 (20%)	-44 [-62, -17]	7/24 (33%)
	p=0.02	p=0.06	p=0.03	p=0.08
Reversibility Status				
Irreversible	2 [-2, 8]	14/25 (56%)	-21 [-61, 7]	13/23 (57%)
Progressive	7 [4, 14]	4/14 (29%)	-52 [-91, -9]	5/12 (42%)
Normal and Reversible	11 [4, 15]	11/41 (27%)	-47 [-68, -18]	9/37 (24%)
	p=0.009	p=0.05	p=0.14	p=0.04