Impact of an Age-adjusted Comorbidity Index on Survival of Patients with Heart Failure Implanted with Cardiac Resynchronization Therapy Devices

Short title: Use of the age-adjusted comorbidity index in CRT

Adam Ioannou MBBS BSc[1,2], Rui Providencia MD PhD[1], Nikolaos Papageorgiou MD PhD[1], Harry Barber MBBS BSc[2], Debbie Falconer MBBS[2], Sergio Barra MD[3], Girish Babu MD[1], Syed Ahsan MD[1], Edward Rowland MD[1], Ross Hunter PhD[1] (Barts), Martin Lowe PhD[1], Richard Schilling MD[1], Pier Lambiase PhD[2,4], Anthony Chow MD[1]

[1] St. Bartholomew's Hospital, Barts Health NHS Trust, London, UK

[2] University College of London Hospitals NHS Trust, London, UK

[3] Papworth NHS Trust, Cambridge, UK

[4] Institute of Cardiovascular Science, University College of London, London, UK

Corresponding author: Dr Rui Providencia, Cardiologist
Barts Heart Centre, Barts Health NHS Trust,
West Smithfield
London EC1A 7BE, United Kingdom
e-mail: rui_providencia@yahoo.com

Telephone number: +44 020 3765 8647
Fax: +44 020 7791 9670

Original Article
Word count: 3,502

Sources of Funding: Pier D Lambiase is funded by University College of London Hospitals Biomedicine Research Centre, a Partnership between University College of London and University College of London Hospitals NHS Trust, funded by the National Institute for Health Research (NIHR).

Acknowledgements: None.

Disclosures and Conflicts of Interest – Dr. Providência has received training grant from Boston Scientific, and Sorin Group and a Research Grant from Medtronic. Professor Lambiase has research grants and speaker fees from Boston Scientific, St Jude, Research Grants from Medtronic and Biotronik, All other authors have reported that they have no relationships relevant to the contents of this paper to disclose**.**

Abstract

Age is an adverse prognostic factor in patients with heart failure. We aimed to assess the impact of age and non-cardiac comorbidities in the outcome of patients undergoing cardiac resynchronization therapy (CRT), and determine which of these two factors is the most important predictor of survival. The study involved single-centre retrospective assessment of 697 consecutive CRT implants during a 12-year period. Patient comorbidity profile was assessed using the Charlson comorbidity index (CCI), and Charlson Age-Comorbidity Index (CACI). Predictors of survival free from heart transplantation were assessed. CRT-related complications and cause of death analysis were assessed within tertiles of CACI. During a mean follow-up of 1813±1177 days, 347 patients (49.9%) died and 37 (5.3%) underwent heart transplantation. On multivariate Cox regression, female gender (HR=0.78, 95%CI 0.62-0.99,P=0.041), estimated glomerular filtration rate (HR per mL/min=0.99, 95%CI 0.98-0.99,P<0.001), left ventricular ejection fraction (HR per %=0.99, 95%CI 0.98-1.00,P=0.022), New York Heart Association class (HR=1.83, 95%CI1.53-2.20,P<0.001), presence of left bundle branch block (HR=0.70, 95%CI 0.56-0.87,P=0.001), and CACI tertile (HR=1.37, 95%CI 1.18-1.59,P<0.001) were independent predictors of all-cause mortality or heart transplantation. Compared with age, and CCI, CACI was the best discriminator of all-cause mortality. Inappropriate therapies occurred less frequently in higher comorbidity tertiles. In conclusion, patient comorbidity profile adjusted to age impacts on mortality following CRT implantation. Use of the CACI may help refine guideline criteria to identify individuals more likely to benefit from CRT.

Key-words: Charlson index; risk stratification; complications; competing risk.

Introduction

Over the past decade cardiac resynchronization therapy (CRT) has emerged as one of the most relevant advances in the treatment of heart failure (HF). The majority of the studies have demonstrated improvement in clinical symptoms, exercise capacity, quality of life, and systolic function.[1-3] However, almost 1/3 of patients do not experience any improvement after CRT.[4] Little is known about the parameters that influence the long-term prognosis of these patients. Data suggest that age is a poor prognostic factor in HF patients and in those over 60 years of age it is the strongest predictor of hospitalization or cardiovascular death.[5] However, elderly patients also tend to have more comorbidities,[6] which can contribute to their worse prognosis. Whether the adverse outcome of elderly CRT patients results from age per se, or from a more adverse comorbidity profile remains to be clarified.

The Charlson Comorbidity Index (CCI) is a scoring system that gives varying assigned weights to patient comorbidities and cardiovascular risk factors of known prognostic value, in order to estimate prognosis. In the present study we aimed to assess the role of the CCI in predicting death or transplantation following CRT implantation, and whether age alone or an age adjusted co-morbidity profile, known as the Charlson Age-Comorbidity Index (CACI), is the most important predictor of outcome in these patients.[7,8]

Methods

Between May 2000 and October 2013, 697 consecutive patients were successfully implanted with CRT devices (with or without a defibrillator) in a high-volume center (The Heart Hospital, University College of London NHS Trust, London, UK) and were eligible for this analysis. Patients were not considered for the purpose of this analysis if they were aged <18, if they required intravenous inotropic drug therapy, or had an estimated life expectancy

of <12 months due to a cause other than HF. Choice of a CRT-P or CRT-D was based in the patient's clinical history, risk profile, and past arrhythmic events.

The CCI was originally developed and tested for its ability to predict one-year mortality in a cohort of patients treated for breast cancer at the Yale New Haven Hospital.[7] Nineteen comorbid diseases (some referring to different severity categories of the same disease) were selected with a 1-year mortality risk of 1.2 or more, and the score was adjusted for coexistent disease and illness severity (Supplementary Material – Table S-1). During the validation process it was noted that age was undoubtedly an important predictor of mortality, and was subsequently incorporated in the CACI, in which each decade over 40 adds one to the overall score.[8] When applying the score to our study population we decided to allocate disease severity scores as the following: Mild illness = New York Heart Association (NYHA) class 1 or 2, moderate illness = NYHA class 3, severe illness = NYHA class 4.

As some patients were implanted prior to the MADIT-RIT trial [9], devices were programmed with two ventricular tachycardia zones *ab initium*, based on patient's age and presence of previous ventricular arrhythmia events. The ventricular tachycardia (VT) zone was routinely programmed starting at 170bpm in all devices, unless there was previous documentation of slower VTs occurring. The nominal number of intervals for initial detection was used and detection was set to 2.5s–9.0s (depending on manufacturer) in the VT zone and 1.0s–5.0s in the ventricular fibrillation (VF) zone. Supraventricular tachycardia discriminators were switched on and high-rate timeout turned off. Anti-tachycardia pacing (ATP) and shocks were programmed in the VT and VF zone. Subsequent adjustments to therapies and detection zones were performed during follow-up, or following the occurrence of any arrhythmic events. From 2012 onwards some patients were implanted with quadripolar left ventricular leads. However, the multisite pacing option was not switched on. Different dipoles were used for reduced capture thresholds and to avoid phrenic nerve capture.

Safety data and presence of complications including lead dislodgement, lead failure (defined as lead performing inappropriately and requiring replacement), device-related infection (whether pocket or lead infection), phrenic nerve capture refractory to electronic programming (requiring temporarily switching off the left ventricular lead and repositioning or insertion of a new lead), and haematoma requiring drainage or bleeding requiring red blood cell transfusion was recorded. Mortality data (all-cause mortality) and information on patients accepted for heart transplant were collected through hospital reports. In patients who transferred their follow-up to another hospital, long-term follow-up data was retrieved. When patients were lost to hospital follow-up, data was collected through patients' registered general practitioners. Data was collected on echocardiographic (LV ejection fraction improvement) and clinical (NYHA) response within the first six months, and specific causes of death, based on hospital records, primary care data, and coroner reports. Causes of death were grouped within the following pre-specified categories after assessment of all the available information: HF, other cardiovascular (including stroke, acute myocardial infarction, aortic dissection, rupture of abdominal aortic aneurysm, pulmonary embolism, etc.), sudden death (arrhythmic or non-arrhythmic), infectious cause, cancer-related, and other non-cardiovascular, as well as unknown when the quality of the information could not allow the investigators to appropriately identify cause of death. Overall, cause of death assessment was possible among 267 patients (out of 347 deceased, 76.9%).

Data from our local device clinic follow-up records and stored device electrograms (EGMs) during episodes of detected VT, VF, any therapy deliveries, and inappropriate shocks were analysed by a cardiac physiologists specialized in electrophysiogy and a Consultant Electrophysiologist or Senior Electrophysiology Fellow. The occurrence of sustained VT episodes terminated with implantable cardioverter defibrillator (ICD) intervention (shock or anti-tachycardia pacing) was logged. Patients were then classified as having had appropriate

shocks, if a shock was delivered during a VT or VF event. An effective ATP therapy was defined as overdrive ventricular pacing able to restore sinus rhythm following a VT or VF episode. An appropriate ICD intervention was classified as the presence of either an appropriate shock or an effective ATP. The incidence of inappropriate shocks delivered due to misdetection of tachycardia (either supra-ventricular tachycardia, sinus tachycardia, fast atrial fibrillation (AF) or artefact) was also compared between the two treatment groups. From 2011 onwards, home-monitoring systems became available and were widely used for follow-up purposes.

PASW Statistics (SPSS Inc, Chicago, IL) version 18.0 was used for descriptive and inferential statistical analysis. We used c-statistics for assessing the discriminative capacity of age, CCI, and CACI. Comparisons of receiver operating characteristic curve areas and through the integrated discrimination improvement index (IDI) were performed between CACI, CCI and age for predicting mortality or heart transplant. The IDI assesses improvement in risk discrimination by estimating the change in the difference in the mean predicted probabilities of the outcome between those with and without the outcome in question, and was calculated according to the method described by Pencina et al [10] to quantify these reclassifications. Tertiles were used for selecting cut-off points for these 3 variables, as this allowed division of the cohort into three groups with a nearly identical number of patients in each, and sufficient power for comparisons showing a 50% difference among groups for endpoints occurring in at least 25% of patients (β=0.8, and α=0.05). Comparisons across CACI tertiles were performed to assess the prevalence of the different co-morbidities and differences in medication. The ANOVA test, or its non-parametric equivalent when appropriate, was used for comparison of continuous variables; the *Levene's* test was used in order to check the homogeneity of variance. The Chi-square test was used for comparing ratios. When information on timing of events was available, Cox regression was

performed to assess the association of CACI tertiles with outcomes. Kaplan-Meier curves were used to illustrate survival free from heart transplantion in the three CACI tertiles, and the log rank test was used to assess for the presence of differences. Univariate and multivariate Cox regression (using the forward likelihood ratio method, with a probability for step-wise of 0.05) was performed for identifying independent predictors of all-cause mortality or heart transplant. Finally, specific causes of mortality were assessed in the three CACI groups and comparisons performed using chi-square, and binary logistic regression. As during the initial period of study some patients were implanted with a narrow QRS based on the presence of mechanical dyssynchrony, a sub-analysis was conducted of all main assessed endpoints excluding patients with QRS <120ms. Results with $P<0.05$ were regarded as significant.

Results

Our cohort was composed of nearly a third of women, and mean age was 64.7±14.0. Almost 75% of patients were implanted with CRT-Ds, and 30% had their devices upgraded. Table 1 provides detailed information on the baseline comorbidities and medication of this population. The cut-off points for defining tertiles for CACI and age were 4 and 6, and 61.2 and 72.9 years, respectively. Best cut-off values of CACI score for all-cause mortality and/or heart transplant, and for death within the first year, were 5 and 6, respectively, almost overlapping with the tertiles.

Patients in higher CACI tertiles were older, and more often of male gender. The prevalence of AF was similar in the three subsets of patients. Higher comorbidity patients more frequently had ischaemic cardiomyopathy, and CRT-Ps. Oral anticoagulation, beta-blockers, calcium channel blockers, and spironolactone, were used more often in the lowest CACI tertile, and antiplatelets, angiotensin converting enzyme inhibitors or angiotensin

receptor blockers, statins, loop diuretics and oral nitrates were more frequent in higher CACI tertiles (Table 1).

During a mean of 1813±1177 days (median 5.0 years), 347 patients (49.9%) died and 37 (5.3%) underwent heart transplantation (Table 2). Infection, lead dislodgement, and lead failure occurred each in 6 to 7% of patients. Only 14 patients (2.0%) were lost to follow-up within the first 5 years post-implant. All cause mortality, and survival free from heart transplantation significantly increased 93% and 65%, respectively, per CACI tertile (Figure 1). On the other hand, heart transplantation occurred more frequently in patients in the first tertile. The incidence of appropriate ICD interventions was comparable within the 3 tertiles, but inappropriate therapies occurred 42% less frequently per each tertile increase (Table 2 and Figure 2). Phrenic nerve issues requiring CS lead repositioning, new lead insertion, or switching off, occurred in 2.7% of patients (n=19), and there was a trend for this happening more frequently in the first tertile. Sub-analysis of main outcomes in patients with QRS ≥120ms showed similar results (Supplementary Material - Table S-7).

Among age, CCI and CACI, the latter displayed the better discrimination for all-cause mortality (c-statistic=0.66, 95%CI 0.62-0.70, c-statistic=0.66, 95%CI 0.62-0.70, and c-statistic=0.70, 95%CI 0.66-0.74, P<0.001, respectively; P for comparisons: Age vs. CCI P=0.938, Age vs. CACI P=0.018, and CCI vs. CACI P=0.002), and all-cause mortality or heart transplant (c-statistic=0.61, 95%CI 0.57-0.65, c-statistic=0.62, 95%CI 0.58-0.66, and c-statistic=0.65, 95%CI 0.61-0.69, respectively; P for comparisons: Age vs. CCI P=0.677, Age vs. CACI P=0.026, and CCI vs. CACI P=0.058). Through measures of risk reclassification (IDI and relative IDI), the CACI was shown to improve risk stratification compared with CCI and age, leading to a more accurate reclassification of patients in 4.8% and 10.4% of cases for all-cause mortality or heart transplant, and 7.5% and 13.3% for all-cause mortality, respectively (Supplementary Material – Table S-2).

Even though age was a predictor of the primary endpoint on univariate analysis, on multivariate Cox regression, only female gender, estimated glomerular filtration rate (eGFR), LVEF, NYHA class, presence of left bundle branch block, and CACI tertile were independent predictors of all-cause mortality or heart transplantation (Table 3). Being implanted with a CRT-D was not an independent predictor of survival. However, sensitivity analysis for CRT-D survival benefit according to CACI tertile showed overlapping survival curves for CRT-D and CRT-P throughout the whole follow-up for patients in the highest CACI tertile (log rank P=0.849), suggesting no survival benefit of CRT-D in this population stratum. Interestingly, analysis of CRT-D benefit in elderly patients, showed a significant survival benefit in the older patient-tertile (log rank P=0.010) (Supplementary Material – Figure S-1). Older patients implanted with CRT-Ps had comparable eGFR (49±18 vs. 49±19; P=0.911), NYHA class (2.8±0.6 vs. 2.7±0.7; P=0.361) to CRT-D patients in the same tertile, and higher LVEF (30±9 vs. 27±8; P=0.011).

Finally, cause of death analysis revealed that even though HF death was significantly more frequent in higher comorbidity tertiles (P<0.001), the relative percentage of deaths it accounted for was numerically lower in higher CACI patients (Table 4 and Figure 3). Other cardiovascular death, non-cardiovascular death, and cancer-death were also more frequent in higher CACI tertile patients. The percentage of unknown cause of death was comparable across the 3 groups: 21.8% (n=12), 27.6% (n=34), and 20.1% (n=34), from the first to the third tertile, respectively (P=0.446).

Discussion

Our findings suggest use of the CACI score is a reliable measure of outcomes in HF patients who are being considered for CRT, with those patients grouped in the highest tertile having the greatest incidence of all-cause mortality during the follow-up period. In our

sample, we confirmed that variables like gender,[9] eGFR,[11] LVEF,[12] NYHA class,[13] presence of left bundle branch block,[14] and CACI tertiles were all significant predictors of prognosis. Furthermore, CACI was a much better discriminator of survival than CCI and age. Unlike these variables, data suggesting a role for CACI as a predictor of survival following CRT is sparse. Theuns et al,[15] used the Charlson model to determine the impact of comorbidity on survival in CRT-D patients, and found a CCI score was associated with increased mortality, and a CACI score≥5 is an independent predictor of mortality. The same group has recently compared CACI with 2 other risk scores, the *Seattle Heart Failure Model* (SHFM), and the *Multicenter Automatic Defibrillator Implantation Trial II* (MADIT II) score, and found that the SHFM was the best prognosticator.[16] However, unlike our study, this study includes only 413 patients implanted with CRT-Ds, and 410 patients with single and dual chamber ICDs, and focused only on 5-year survival, leaving other aspects like complications and ICD interventions out of the analysis.

It is well documented that non-cardiac comorbidity has a negative impact on HF patients, and as the number of comorbidities increases so does the number of hospitalisations.[17] Pulmonary conditions (such as chronic obstructive pulmonary disease and bronchiectasis) carried the highest risk of hospitalisation and subsequent mortality, followed closely by chronic kidney disease.[17,18] Both diabetes and renal dysfunction have already been demonstrated to be strong predictors of death post CRT implantation, and both comorbid conditions, along with pulmonary disease, are incorporated in the Charlson model.[19] Additionally a raised Charlson score, has been previously associated with both an increase in hospital readmission rates and mortality in HF patients.[20] Furthermore the benefits of CRT decrease with an increased age at the time of implantation.[21] Hence, our study demonstrated that CACI is an even stronger predictor of mortality, which is likely to be due to the fact it takes into consideration the patient's age, which CCI doesn't. Age is of great

prognostic significance in HF patients and therefore the CACI has superior merit to the CCI; but CACI is also of greater prognostic value than age alone.

Post-procedural complication rates were similar across all three CACI tertiles, however tertile 1 did have increased rates of inappropriate shocks; despite this, patients in this group had a better overall prognosis. An explanation for inappropriate shocks being more frequent in healthier patients may be because these patients have less comorbidities, are more active and have more inappropriate shocks resulting from sinus tachycardia. Furthermore, they may have more paroxysmal forms of AF, occurring as tachycardic episodes, while patients in higher tertiles already have persistent AF and more likely have a rate-controlled response. Patients in the lower tertiles are generally healthier, younger, have less comorbidities, a lower NYHA class, and therefore are likely to be more active. Most HF patients present with multiple comorbidities and are therefore at a high risk of death from non-cardiological causes. Identification of such patients is rarely performed in clinical practice, but if considered is likely to improve patient selection for CRT.[22,23] Even though there are no current recommendations regarding life expectancy when considering CRT implantation, patients will only be considered for ICD implantation if their life expectancy is greater than one year.[1] We believe that this expected longevity cut-off could be more effectively replaced by a standardised scoring system that took a holistic view of each patient's health status, number of comorbidities, and quality of life. A recent meta-analysis of four large randomised controlled trials of primary prevention ICDs, came to the conclusion that the benefit of ICD over optimal medical therapy could be mitigated by the number of comorbidities, with those with less than two comorbidities experiencing greater survival benefit,[24] suggesting that scoring systems that consider comorbidities, such as CACI, may predict post-procedural outcomes in HF patients. Although this study looked at ICD implantation, the same concept of competing comorbidities could be applied to CRT, and aid

the decision of whether a patient should receive a CRT-P instead of a CRT-D. Compared to age, use of the CACI in our cohort led to a 10% more accurate discrimination of the probability of dying or undergoing heart transplantation, suggesting that CACI may be a more accurate prognosticator, and therefore a more useful support tool regarding treatment decisions. This was confirmed in the sensitivity analysis for survival benefit of CRT-D in the highest CACI tertile, illustrated by Kaplan-Meier curves, which suggested that patients with a worse comorbidity profile appear not to benefit from a defibrillator on top of CRT, whereas age alone should not be the main driver in such a decision, as some elderly patients may still benefit from a defibrillator. Ideally, a thorough assessment of the patient, with a careful comorbidity assessment, should be performed. Then, the potential benefit of CRT (or the lack of it) should be discussed, and a final decision based on procedural risk, estimated survival benefit, and patient preference should be achieved.

Our study does have some limitations, namely the fact that some patients with a narrow QRS underwent CRT implantation prior to the release of the most recent changes in guidelines and therefore would now no longer be eligible for therapy (a sub-analysis after excluding these patients is available as Supplementary Material – Table S-7 - and shows similar results). Also, even though the percentage of unknown cause of death was comparable across the 3 groups, we believe that more complete information would have allowed clearer and definitive interpretation of data.

In summary, our study demonstrates that patient comorbidity profile adjusted to age impacts on mortality following CRT implantation. It also emphasizes the importance of non-cardiac disease in HF patients and its impact on prognosis. Use of the CACI may allow the identification of individuals more likely to benefit from CRT and who should clearly be implanted with a device, and possibly also identify those who will derive a better survival benefit and quality of life from specialized treatment of other non-cardiac comorbidities.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2016;18:891-975.

2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) StudyInvestigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* 2005;352:1539-1549.

3. Butter C, Auricchio A, Stellbrink C, Fleck E, Ding J, Yu Y, Huvelle E, Spinelli J; Pacing Therapy for Chronic Heart Failure II Study Group. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. *Circulation.* 2001;104:3026-3029.

4. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ,Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J; MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. *N Engl J Med.* 2002;346:1845-1853.

5. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, Ostergren J, Michelson EL, Pieper KS, Granger CB. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J.* 2006;27:65-75.

6. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med.* 2002;162:2269-2276.

7. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40:373-383.

8. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol.* 1994;47:1245-1251.

9 Providência R, Marijon E, Lambiase PD, Bouzeman A, Defaye P, Klug D, Amet D, Perier MC, Gras D, Algalarrondo V, Deharo JC, Leclercq C, Fauchier L, Babuty D, Bordachar P, Sadoul N, Piot O, Boveda S. Primary Prevention Implantable Cardioverter Defibrillator (ICD) Therapy in Women-Data From a Multicenter French Registry. *J Am Heart Assoc.* 2016;5(2). pii: e002756.

10. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med.* 2008;27:157-172.

11. Khatib M, Tolosana JM, Trucco E, Borràs R, Castel A, Berruezo A, Doltra A, Sitges M, Arbelo E, Matas M, Brugada J, Mont L. EAARN score, a predictive score for mortality in patients receiving cardiac resynchronization therapy based on pre-implantation risk factors. *Eur J Heart Fail.* 2014;16:802-809.

12. Gasparini M, Klersy C, Leclercq C, Lunati M, Landolina M, Auricchio A, Santini M, Boriani G, Proclemer A, Leyva F. Validation of a simple risk stratification tool for patients implanted with Cardiac Resynchronization Therapy: the VALID-CRT risk score. *Eur J Heart Fail.* 2015;17:717-724.

13. Schuchert A, Muto C, Maounis T, Frank R, Ella RO, Polauck A, Padeletti L; Mascot Study Group. One-year outcome after CRT implantation in NYHA class IV in comparison to

NYHA class III patients. *Clin Res Cardiol.* 2013;102:505-511.

14. Lund LH, Benson L, Ståhlberg M, Braunschweig F, Edner M, Dahlström U, Linde C. Age, prognostic impact of QRS prolongation and left bundle branch block, and utilization of cardiac resynchronization therapy: findings from 14,713 patients in the Swedish Heart Failure Registry. *Eur J Heart Fail.* 2014;16:1073-1081.

15. Theuns DA, Schaer BA, Soliman OI, Altmann D, Sticherling C, Geleijnse ML, Osswald S, Jordaens L. The prognosis of implantable defibrillator patients treated with cardiac resynchronization therapy: comorbidity burden as predictor of mortality. *Europace.* 2011;13:62-69.

16. Akoudad S, Dabiri Abkenari L, Schaer BA, Sticherling C, Levy WC, Jordaens L, Theuns DA. Comparison of Multivariate Risk Estimation Models to Predict Prognosis in Patients With Implantable Cardioverter Defibrillators With or Without Cardiac Resynchronization Therapy. Am J Cardiol. 2017;119:1414-1420.

17. Braunstein JB, Anderson GF, Gerstenblith G, Weller W, Niefeld M, Herbert R, Wu AW. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol.* 2003;42:1226-1233.

18. Hawkins NM, Virani S, Ceconi C. Heart failure and chronic obstructive pulmonary disease: the challenges facing physicians and health services. *Eur Heart J.* 2013;34:2795-2803.

19. Bai R, Di Biase L, Elayi C, Ching CK, Barrett C, Philipps K, Lim P, Patel D, Callahan T, Martin DO, Arruda M, Schweikert RA, Saliba WI, Wilkoff B, Natale A. Mortality of heart failure patients after cardiac resynchronization therapy: identification of predictors. *J Cardiovasc Electrophysiol.* 2008;19:1259-1265.

20. Muzzarelli S, Leibundgut G, Maeder MT, Rickli H, Handschin R, Gutmann M, Jeker U, Buser P, Pfisterer M, Brunner-La Rocca HP; TIME-CHF Investigators.. Predictors of early

readmission or death in elderly patients with heart failure. *Am Heart J.* 2010;160:308-314.

21. Barnett D, Phillips S, Longson C. Cardiac resynchronisation therapy for the treatment of heart failure: NICE technology appraisal guidance. *Heart.* 2007;93:1134-1135.

22. Albert CM. Prediction of sudden cardiac death in patients with coronary heart disease: the challenge ahead. *Circ Cardiovasc Imaging.* 2008;1:175-177.

23. Duray GZ, Schmitt J, Richter S, Israel CW, Hohnloser SH. Arrhythmic death in implantable cardioverter defibrillator patients: a long-term study over a 10 year implantation period. *Europace.* 2009;11:1462-11468.

24. Steinberg BA, Al-Khatib SM, Edwards R, Han J, Bardy GH, Bigger JT, Buxton AE, Moss AJ, Lee KL, Steinman R, Dorian P, Hallstrom A, Cappato R, Kadish AH, Kudenchuk PJ, Mark DB, Inoue LY, Sanders GD. Outcomes of implantable cardioverter-defibrillator use in patients with comorbidities: results from a combined analysis of 4 randomized clinical trials. *JACC Heart Fail.* 2014;2:623-629.