JOURNAL OF CARDIOVASCULAR DISEASE VOL.2 NO.2 APRIL 2014
ISSN: 2330-4596 (Print) / 2330-460X (Online) http://www.researchpub.org/journal/jcvd/jcvd.html

Analysis of ECG by means of Complexity Index and Association with Clinical Response to Cardiac Resynchronization Therapy

Giulio Molon, *MD**, Jacek Marczyk, *PhD*, Giovanni Virz ì *BS*, Riccardo Bellazzi, *PhD*, Alberto Malovini, *PhD*, Francesco Accardi, *MS*, Sergio Valsecchi, *PhD*, Alessandro Costa, *MD*, and Enrico Barbieri, *MD, PhD*

Abstract

We hypothesized that the analysis of the system complexity, as performed by the OntoCare™ system on the 12-lead ECG collected before and after implantation, could allow the identification of responders to cardiac resynchronization therapy (CRT). The OntoCare™ system measures complexity, analyzing the multi-dimensional structure of the ECG. We investigated the association between therapy impact, as measured by the system, and clinical response. Eighty-seven patients underwent CRT implantation and were followed-up for 3 months. Functional NYHA class improved in 65 patients. The mean Complexity Index was 35 ±11 in spontaneous sinus rhythm and 34 ±10 during CRT, with an Impact of the therapy of 55 ±19%. The Impact was 55 ±18% in patients with improved NYHA class, and 53 ±23% in patients with unchanged or worsened NYHA class (p=0.623). The Impact did not correlate with the change in echocardiographic indices of ventricular remodeling. The impact of CRT as measured by the OntoCare™ system was not associated with clinical or echocardiographic response to CRT. Most probably, the variable response to CRT is a complex phenomenon that is not fully described by ECG data, and additional clinical variables should be monitored to reliably predict it.

***Keywords* — Complexity, CRT, heart failure, ECG.**

Cite this article as: Molon G, Marczyk J, Virz ìG, Bellazzi R, Malovini A, Accardi F, Valsecchi S, Costa A, and Barbieri E. Analysis of ECG by means of complexity index and association with clinical response to cardiac resynchronization therapy. JCvD 2014: in press.

I. Introduction

Albeit a relevant proportion of currently indicated patients benefit from cardiac resynchronization therapy (CRT), 30% to 50% of subjects receiving CRT may be classified as nonresponders[1].

Received on 24 January 2014.
From the "Sacro Cuore-Don Giovanni Calabria" Hospital, Via Don Angelo Sempreboni, 5 – 37024, Negrar,Verona, Italy (**GM, AC, EB**); OntoMed LLC, USA (**JM**); Boston Scientific, Italy (**FA, SV**).
Francesco Accardi and Sergio Valsecchi are employees of Boston Scientific Inc. Jacek Marczyk is the founder and president at OntoMed LLC. The other Authors report no conflicts.
*Corresponding to Dr Giulio Molon: giulio.molon@sacrocuore.it

Therefore, developing new tools to identify responder patients is crucial to improve the overall appropriateness of CRT. Duration of QRS interval ⩾120ms was the inclusion criterion used in major CRT trials. Subgroup analysis, in a recent meta-analysis evaluating the impact of QRS duration on the efficacy of CRT, has shown that CRT significantly reduced all-cause mortality or hospitalization in patients with QRS duration ⩾150ms[2]. The magnitude of effect declined with shorter QRS duration. Furthermore, most patients in the published trials had left bundle branch (LBBB) morphology, which was associated with a more pronounced benefit, compared with non-LBBB patients[3,4]. Nonetheless, although the paced QRS complex often narrows after CRT, previous studies seemed to show that there is no correlation between QRS narrowing and clinical response[5].

These findings encourage further and more detailed investigation of the ECG before and after CRT.

The OntoCare™ system measures complexity, analyzing the structure of information and establishing an innovative means of characterizing generic dynamical systems and biologic signals.

The system makes it possible to quantify the impact of a treatment, measuring the "distance" between pre- and post-treatment status.

We have used the system to perform an analysis of the multi-dimensional structure of the ECG, taking into account the interactions between ECG channels. Particularly, we measured the impact of biventricular stimulation with OntoCare™ system analyzing the ECG performed before and after implantation, and we investigated the association between therapy impact, as measured by the system, and clinical response.

II. Methods

Patient selection, baseline and follow-up assessment

Consecutive patients with symptomatic heart failure regardless of optimal medical treatment and with current indications for CRT underwent successful implantation of a biventricular defibrillator (ICD) and were prospectively enrolled in this study. All patients gave written informed

consent approved by the Institutional Review Board.

Before device implantation, following baseline data were collected: medical history, clinical examination, 12-lead electrocardiogram, New York Heart Association (NYHA) class, and echocardiographic parameters. Specifically, following measures were taken: left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD).

At 3 months visit, patients underwent in-office follow-up examination, including 12-lead electrocardiogram and assessment of changes in functional NYHA class and echocardiographic parameters.

OntoCare™ analysis

OntoCare™ is a software tool which enables users to measure the impact or effectiveness of therapy based on pre- and post-treatment data. Raw 12-lead ECG data is used to quantify therapy effectiveness (Fig. 1). The first step in the analysis is to establish for each ECG the so-called System Map. The map is composed of nodes (ECG leads) – arranged along the diagonal – links, and connectors. When a pair of nodes is correlated – there is a relationship between the corresponding ECG leads – two segments, originating in these nodes, cross in the correspondence of a connector (Fig. 2).

Once a System Map has been obtained, one may compute the ECG Complexity as a function of the System Map's topology (i.e. the Adjacency Matrix) and the Entropy Matrix, containing the entropies computed for each significant relationship between the ECG channels. Such relationships are based on a proprietary algorithm, which transforms x-y scatterplots into images and computes a generalized correlation coefficient based on the image's entropy content. While conventional Shannon's entropy represents the information content for a single channel, the above complexity measure represents the total amount of structured information in a multi-channel data set.

The Impact of Therapy is measured as the topological distance of the two System Maps. In other words, OntoCare™ compares the topologies of the two System Maps and relates their difference to the first System Map, which represents the patient in a pre-therapy situation.

Statistical analysis

Continuous data were expressed as means±standard deviation and categorical data were expressed as percentages. Differences between mean data were compared by a t-test for Gaussian variables and by Mann-Whitney nonparametric test for non-Gaussian variables. Differences in proportions were compared by a Chi-square analysis or Fisher's exact test, as appropriate. Logistic regression analysis was used to identify predictors of response to CRT. A P-value <0.05 was considered significant for all tests. Statistical correlations between variables were tested by means of linear regression analysis. All statistical analyses were performed by using STATISTICA software, version 7.1 (StatSoft, Inc., Tulsa, OK, USA).

III. Results

Patient population and clinical outcome

Eighty-seven consecutive patients undergoing implantation of a biventricular ICD were followed-up for 3 months. The baseline characteristics are summarized in Table I.

At 3 months visit, functional NYHA class improved by 2 classes in 12 patients, by 1 class in 53 patients, was unchanged in 20 patients and worsened in 2. The mean values of echocardiographic parameters at follow-up are reported in Table II for all patients, for patients with improved functional NYHA class and for patients with unchanged or worsened NYHA class.

In the overall population, LVEF significantly improved at 3-month follow-up, along with a decrease in LV volumes and LVESD. Left ventricular end-diastolic diameter showed only a trend toward reduction (p = 0.051). These improvements were apparent only in patients with improved functional NYHA class, while in patients with unchanged or worsened NYHA class we observed only a slight increase in LVEF.

Table 1. Demographics and baseline clinical parameters of the study population.

Parameter	(n=87)
Male gender, n (%)	62 (71)
Age, years	77±12
QRS duration, ms	164±25
NYHA class	
- **Class II, n (%)**	22 (25)
- **Class III, n (%)**	63 (73)
- **Class IV, n (%)**	2 (2)
LV ejection fraction, %	28±7
LVEDV, ml	196±66
LVESV, ml	141±55
LVEDD, mm	69±8
LVESD, mm	54±10

Abbreviations: NYHA = New York Heart Association; LV = Left ventricular; LVEDV = Left ventricular end-diastolic volume; LVESV = Left ventricular end-systolic volume; LVEDD = Left ventricular end-diastolic diameter; LVESD = Left ventricular end-systolic diameter.

OntoCare™ analysis of ECG

The analysis of baseline 12-lead ECG collected in spontaneous sinus rhythm revealed a mean Complexity Index of 35±11 in the overall population. The ECG collected during CRT pacing showed a mean Complexity Index of 34±10.

Table 2. Echocardiographic parameters recorded at 3-month follow-up visit for all patients, for patients with improved functional NYHA class and for patients with unchanged or worsened NYHA class.

Parameter	All patients (87)	p-value	NYHA Class improved (65)	p-value	NYHA Class unchanged or worsened (22)	p-value
LVEF, %	36 ±9	<0.001	37 ±9	<0.001	34 ±9	0.038
LVEDV, ml	168 ±64	0.033	159 ±55	0.011	201 ±84	0.871
LVESV, ml	109 ±53	0.003	102 ±45	0.001	135 ±72	0.605
LVEDD, mm	66 ±9	0.051	65 ±9	0.059	67 ±8	0.589
LVESD, mm	49 ±11	0.019	49 ±11	0.035	51 ±10	0.336

Abbreviations: LVEF = Left ventricular ejection fraction; LVEDV = Left ventricular end-diastolic volume; LVESV = Left ventricular end-systolic volume; LVEDD = Left ventricular end-diastolic diameter; LVESD = Left ventricular end-systolic diameter; p-values versus baseline.

The paired comparison of Complexity Index revealed an Impact of the therapy of 55 ±19% at 3 months. Specifically, the Impact was 55 ±18% in patients with improved functional NYHA class, and 53 ±23% in patients with unchanged or worsened NYHA class (p = 0.623). Similarly, the Complexity Index in spontaneous sinus rhythm and during CRT pacing did not differ between patients with improved NYHA class and with unchanged or worsened NYHA class (Fig. 3).

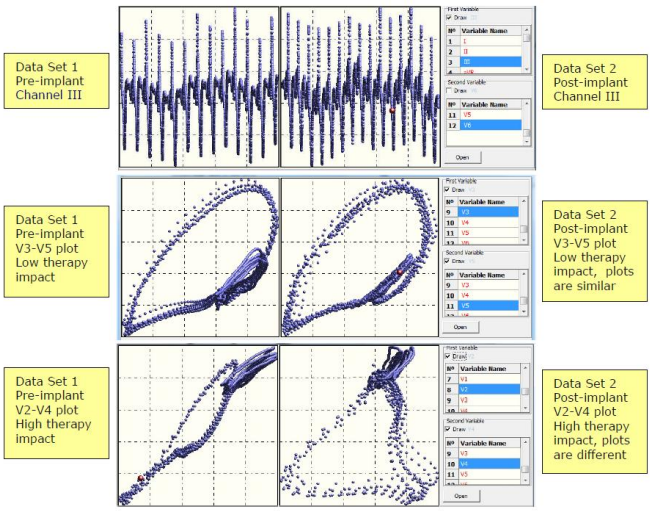

Figure 1. Example of pre- and post-treatment ECG (channel III in top plot) and V3-V5 (low impact) and V2-V4 (high impact) scatter plots.

Logistic regression analysis revealed that worsened NYHA class was associated with baseline NYHA class value, LVEDV and LVESV, while no significant association was detected with complexity indices (Table III).

Moreover, the Impact of the therapy did not correlate with the change in LVEDD (r = 0.001), LVESD (r = -0.094), LVEDV (r = 0.087), LVESV (r = 0.049) and LVEF (r = -0.119; all p > 0.05).

IV. Discussion

The present study showed that the impact of biventricular stimulation as measured by the OntoCare™ system was not associated with the clinical and echocardiographic response to CRT at mid-term follow-up.

The system analyzed the multi-dimensional structure of the ECG collected before and after implantation, assessing the interactions between ECG channels. However, the present analysis showed no association between baseline values of Complexity Index and improvement in functional status after CRT. Similarly, the Complexity Index during CRT and the so-called Impact of the Therapy did not differ between patients with improved NYHA class and with unchanged or worsened NYHA class. Moreover, no correlation was detected between the Impact of the therapy and echocardiographic indices of ventricular reverse remodeling.

CRT is an effective treatment for patients with systolic heart failure and electrocardiographic evidence of ventricular dyssynchrony, as shown by several trials[6-9]. Current international guidelines support CRT in eligible heart failure patients with the highest level of evidence[10].

Pre-specified subgroup analyses of data collected in large CRT trials demonstrated that patients with a QRS duration ⩾ 150ms benefited most from CRT[8,9,11]. Meta-analyses[2] using aggregate data from randomized trials showed that CRT was effective in reducing adverse clinical events in patients with baseline QRS duration⩾150ms and suggested that CRT might not reduce events in patients with a QRS<150ms. Similarly, sub-group analyses based on QRS morphology[3,8,9,12] suggested that patients with complete LBBB showed a greater benefit on the composite of morbidity/mortality from CRT, compared with patients with non-specific intraventricular conduction delay or right bundle branch block. Based on this evidence, current class I recommendations were restricted to patients with complete LBBB.

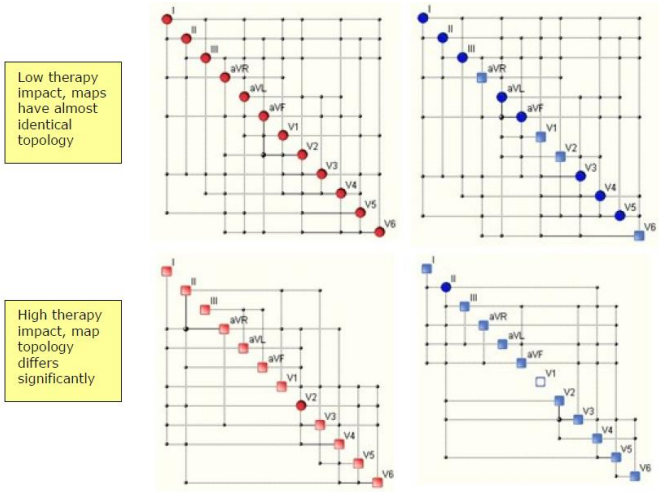

Figure 2. ECG System maps. The map is composed of nodes (variables) – arranged along the diagonal – links, and connectors. When a pair of nodes is correlated – there is a relationship between the corresponding variables – two segments, originating in these nodes, cross in the correspondence of a connector. Once both data sets (pre and post treatment) have been read and processed, OntoCare™ performs a topological map comparison in order to establish the degree of data similarity. If the maps are similar, this points to a low impact of therapy. If, on the other hand, data similarity is low, this points to a large impact of therapy. Two cases are illustrated: low therapy impact (upper panel) and high impact (lower panel).

Table 3. Univariate analysis of factors predicting worsened NYHA class.

	OR	95% CI	p
Male gender	0.76	0.26 – 2.44	0.629
Age (>75 years)	0.99	0.95 – 1.03	0.494
NYHA Class III or IV	0.17	0.05 – 0.50	0.002
QRS duration	1.00	0.98 – 1.02	0.990
LV ejection fraction	0.98	0.90 – 1.05	0.537
LVEDV	1.01	1.00 – 1.02	0.017
LVESV	1.01	1.00 – 1.02	0.018
LVEDD	1.04	0.99 – 1.11	0.249
LVESD	1.02	0.98 – 1.07	0.461
Complexity Index in spontaneous sinus rhythm	1.03	0.98 – 1.08	0.265
Complexity Index during CRT	0.98	0.94 – 1.02	0.334
Impact of the therapy	0.09	0.01 – 1.47	0.102

Previous studies demonstrated that QRS narrowing after CRT does not correlate with hemodynamic and clinical improvement[13,5]. In some cases the QRS complex after CRT may actually lengthen or remain unchanged despite substantial improvement in mechanical LV dyssynchrony. Increased QRS duration with CRT does not necessarily reflect the presence of ventricular areas with slow conduction resulting in more heterogeneous myocardial activation.

With LV-only pacing, there is an obvious discrepancy between QRS duration (compared with baseline) and hemodynamic and clinical improvement[14]. Thus, in patients with heart failure, the paced QRS duration cannot be assumed to reflect a more heterogeneous propagation pattern of LV activation and prolonged duration of mechanical activation.

Our study was aimed at performing a detailed investigation of the ECG before and after CRT. We hypothesized that the analysis of the system complexity and in particular the analysis of the impact of the treatment, as performed by the OntoCare™ system on the 12-lead ECG collected before and after CRT, could allow the identification of responders to CRT.

Complexity is a natural and holistic property of every system. The OntoCare™ system measures complexity, analyzing the structure of information.

System complexity can be measured if data are available, and data that may be processed are multi-channel data recorded in an intensive care unit, ECG, EEG, certain classes of images. The system makes it possible to quantify the instantaneous stability of a patient, defined as the rate of change of complexity over time, or the impact of treatment (surgery, drugs, implantation, etc.), measuring the "distance" between pre and post-treatment status. However, we showed that the analysis of system complexity did not allow the identification of patients with positive clinical and echocardiographic response to CRT. In particular, there was no correlation between the change in patient's status at mid-term follow-up, based on clinical and echocardiographic measurements, and the impact of the treatment, as measured by the system in terms of similarity between pre- and post-CRT ECG data sets. This result seems in agreement with aforementioned studies showing a lack of association between clinical improvement after CRT and changes in QRS duration[13,5].

Some limitations should be considered when interpreting the results of this analysis. In particular, the small sample size may account for the lack of significance obtained in some of the reported comparisons. Moreover, a longer follow-up would have enhanced the validity of the present findings. Indeed, most studies investigating CRT effects reported the effects after 1 or even 3 years of therapy[15,16]. Nonetheless, measuring early response of CRT, in terms of functional status improvement and echocardiographic signs of reverse remodeling, has been frequently adopted in previous studies[17].

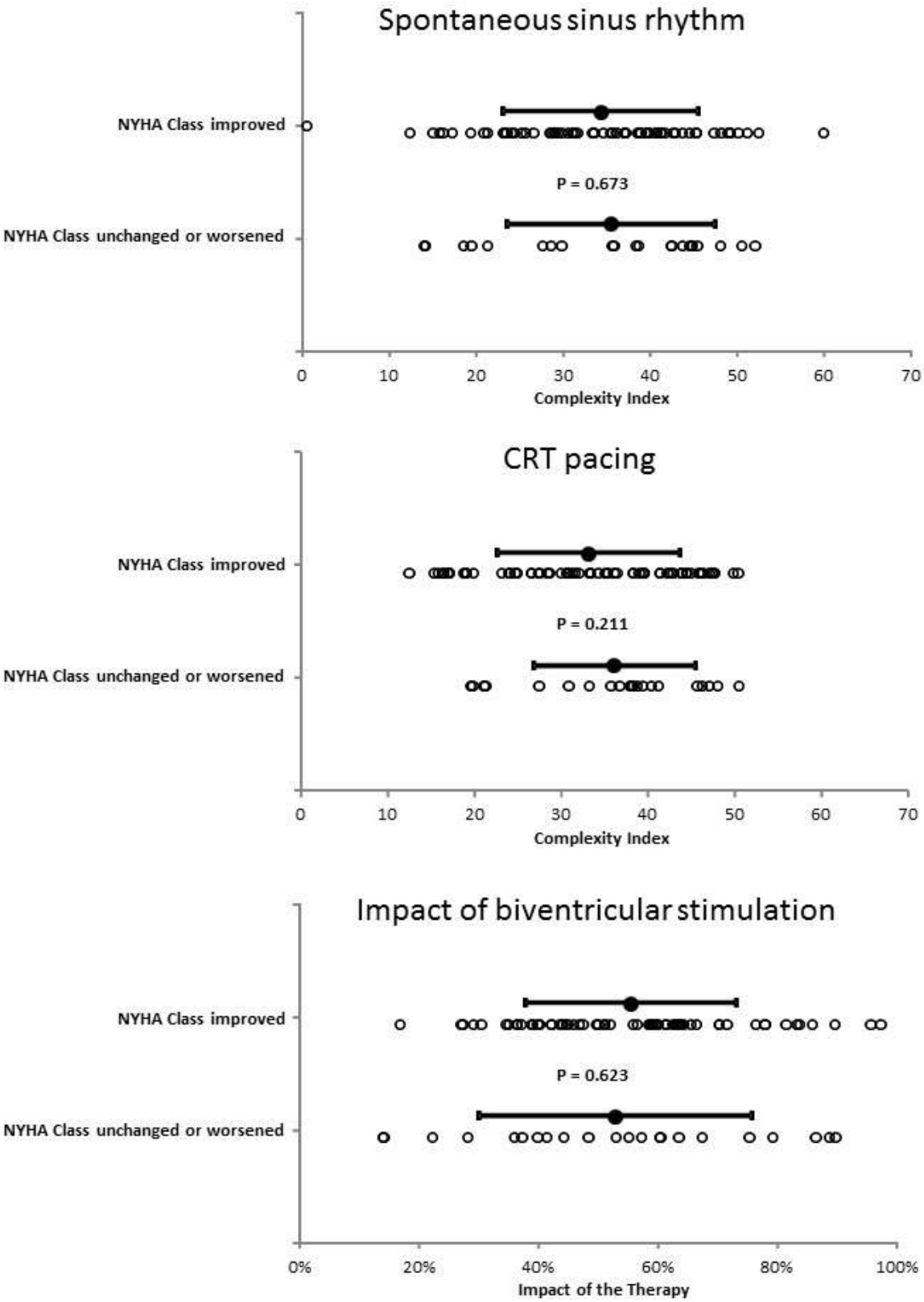

Figure 3. Complexity Index in spontaneous sinus rhythm and during CRT pacing, and Impact of the therapy values in patients with improved NYHA class and with unchanged or worsened NYHA class. The open circles represent individual values and full circles with bars represent the mean values with standard deviations.

V. CONCLUSIONS

The impact of CRT as measured by the OntoCare™ system was not associated with clinical or echocardiographic response to CRT. Most probably, the variable response to CRT is a complex phenomenon that is not fully described by ECG data, and additional clinical variables should be monitored to reliably predict it.

REFERENCES

[1] Birnie DH, Tang AS. The problem of non-response to cardiac resynchronization therapy. *Curr Opin Cardiol*. **2006**;21(1):20-6.

[2] Sipahi I, Carrigan TP, Rowland DY, Stambler BS, Fang JC. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. *Arch Intern Med*. **2011**;171(16):1454-62.

[3] Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom D, Daubert JP, Eldar M, Gold MR, Goldberger JJ, Goldenberg I, Lichstein E, Pitschner H, Rashtian M, Solomon S, Viskin S, Wang P, Moss AJ; MADIT-CRT Investigators. Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation*. **2011**;123(10):1061-72.

[4] Gervais R, Leclercq C, Shankar A, Jacobs S, Eiskjaer H, Johannessen A, Freemantle N, Cleland JG, Tavazzi L, Daubert C; CARE-HF investigators. Surface electrocardiogram to predict outcome in candidates for cardiac resynchronization therapy: a sub-analysis of the CARE-HF trial. *Eur J Heart Fail*. **2009**;11(7):699-705.

[5] Cleland J, Freemantle N, Ghio S, Fruhwald F, Shankar A, Marijanowski M, Verboven Y, Tavazzi L. Predicting the long-term effects of cardiac resynchronization therapy on mortality from baseline variables and the early response a report from the CARE-HF (Cardiac Resynchronization in Heart Failure) Trial. *J Am Coll Cardiol*. **2008**;52(6):438-45.

[6] Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. **2005**;352(15):1539-49.

[7] Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. **2004**;350(21):2140-50.

[8] Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. **2009**;361(14):1329-38.

[9] Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med*. **2010**;363(25):2385-95.

[10] Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE; ESC Committee for Practice Guidelines (CPG), Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; Document Reviewers, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bänsch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J*. **2013**;34(29):2281-329.

[11] Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C; REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) Study Group. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol*. **2008**;52(23):1834-43.

[12] Gold MR, Thébault C, Linde C, Abraham WT, Gerritse B, Ghio S, St John Sutton M, Daubert JC. Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study. *Circulation*. **2012**;126(7):822-9.

[13] Nelson GS, Curry CW, Wyman BT, Kramer A, Declerck J, Talbot M, Douglas MR, Berger RD, McVeigh ER, Kass DA. Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. *Circulation*. **2000**;101(23):2703-9.

[14] Leclercq C, Faris O, Tunin R, Johnson J, Kato R, Evans F, Spinelli J, Halperin H, McVeigh E, Kass DA. Systolic improvement and mechanical resynchronization does not require electrical synchrony in the dilated failing heart with left bundle-branch block. *Circulation*. **2002**;106(14):1760-3.

[15] Sardu C, Marfella R, Santulli G. Impact of Diabetes Mellitus on the Clinical Response to Cardiac Resynchronization Therapy in Elderly People. *J Cardiovasc Transl Res*. **2014** Feb 6. [Epub ahead of print].

[16] D'Ascia SL, D'Ascia C, Marino V, Lombardi A, Santulli R, Chiariello M, Santulli G. Cardiac resynchronisation therapy response predicts occurrence of atrial fibrillation in non-ischaemic dilated cardiomyopathy. *Int J Clin Pract*. **2011**;65(11):1149-55.

[17] Cleland J, Freemantle N, Ghio S, Fruhwald F, Shankar A, Marijanowski M, Verboven Y, Tavazzi L. Predicting the long-term effects of cardiac resynchronization therapy on mortality from baseline variables and the early response a report from the CARE-HF (Cardiac Resynchronization in Heart Failure) Trial. *J Am Coll Cardiol*. **2008**;52(6):438-45.