

**Prognostic utility of the assessment of diastolic function in patients undergoing cardiac resynchronization therapy**

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## ABSTRACT

Conflicting data exist about the relationship between cardiac resynchronization therapy (CRT) and diastolic function.

**Aims of the study** are to assess diastolic patterns in patients undergoing CRT according to the 2016 recommendations of the American Society of Echocardiography/European Association of Cardiovascular Imaging and to evaluate the prognostic value of diastolic dysfunction (DD) in CRT candidates.

### Methods and results

One-hundred ninety-three patients (age:  $67\pm 11$  years, QRS width:  $167\pm 21$  ms) were included in this multicentre prospective study. Mitral filling pattern, mitral tissue Doppler velocity, tricuspid regurgitation velocity, and indexed left atrial volume were used to classify DD from grade I to III. CRT-response, defined as a reduction of left ventricular (LV) end-systolic volume  $>15\%$  at 6-month follow-up (FU), occurred in 132 (68%) patients. The primary endpoint was a composite of heart transplantation, LV assisted device implantation, or all-cause death during FU and occurred in 29 (15%) patients.

CRT was associated with a degradation of DD in non-responders. At multivariable analysis corrected for clinical variables, QRS duration, mitral regurgitation, CRT-response and LV dyssynchrony, grade I DD was associated with a better outcome (HR 0.37, 95% CI: 0.14-0.96).

Non-responders with grade II-III DD had the worse prognosis (HR 4.36, 95% CI: 2.10-9.06).

### Conclusions

The evaluation of DD in CRT candidates allows the prognostic stratification of patients, independently from CRT-response.

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## **Introduction**

Cardiac resynchronization therapy (CRT) has a pivotal role in the management of patients with systolic heart failure (HF) and QRS width > 120 ms(1). Successful CRT has been demonstrated to attenuate HF symptoms, reduce HF-related hospitalization, and to induce left ventricular (LV) remodelling, by a reduction in LV-end systolic volume (LV-ESV) and increase in LV ejection fraction (LVEF)(2).

Recent studies have shown that diastolic dysfunction (DD) is associated with increased mortality in patients with HF and reduced ejection fraction (3),(4). The best modality to assess diastolic function in CRT-candidates is an object of debate and the relationship between diastolic function, CRT-response and survival is not definitely understood(5).

The application of the multiparametric approach proposed by Nagueh et al. in the 2016 Recommendations of the American Society of Echocardiography/European Association of Cardiovascular Imaging(6) is discouraged in patient with left bundle branch block (LBBB) or paced rhythm because of the lack of invasive validation. Despite the intrinsic limitations of recommendations, a recent prospective multicenter study conducted on 450 patients with several different heart disease, demonstrates that the algorithm proposed by Nagueh et al. was able to identify patients with elevated LV filling pressure against the invasive gold standard also in the case of LBBB or paced rhythm (area under the curve=0.84)(7). These results justify testing the value of recent recommendations on diastolic function in CRT candidates.

The aims of the present study are: 1) to describe the impact of CRT on diastolic function assessed using current recommendations; 2) to evaluate the prognostic impact of diastolic dysfunction in CRT candidates.

## **Methods**

### ***Population***

209 patients with systolic HF undergoing CRT implantation according to current guidelines(1) at Oslo University Hospital (Norway), Leuven University Hospital (Belgium),

Rennes University Hospital (France), and Aalst OLV Hospital (Belgium), and Karolinska University Hospital, Sweden between August 2015 and November 2017 were prospectively included in this observational, multicentre study.

Sixteen patients were excluded from the final analysis because of study withdrawal (n=4), lead extraction due to infective endocarditis (n=1), and lack of fundamental echocardiographic data (n=11). At the time of CRT implantation, all patients were receiving optimized medical therapy. Clinical data including age, sex, and treatments were collected for each patient. The functional status was assessed by the estimation of the New York Heart Association (NYHA) functional class. Ischemic heart disease was defined as a history of myocardial infarction and coronary revascularization or angiographic evidence of multiple vessel disease or single-vessel disease with  $\geq 75\%$  stenosis of the left main or proximal left anterior descending artery(8). All patients gave their written informed consent for study participation.

The study was conducted following the “Good Clinical Practice” guidelines of the Declaration of Helsinki and was approved by the Regional Ethical Committees of every participating centre. The study was registered at clinicaltrials.gov (identifier NCT02525185).

### ***Echocardiography***

All patients underwent standard transthoracic echocardiography using a Vivid E9 or E95 ultrasound system (GE Healthcare, Horten, Norway) equipped with an M5S 3.5-MHz transducer at baseline and 6-month follow-up. Two-dimensional, colour Doppler, pulsed-wave and continuous-wave Doppler data were stored on a dedicated workstation for the offline analysis (EchoPAC, GE Healthcare, Horten, Norway). Left atrial, LV volumes, and LVEF were measured by the biplane method, as recommended(9). Indexed LV mass (LVMi) and relative wall thickness (RWT) were assessed as recommended(9).

Mitral regurgitation (MR) was visually assessed from 1 to 3 (1=traces to mild MR; 2= moderate MR; 3=moderate-to-severe MR). Peak velocity of early (E) and late (A) diastolic filling were derived from transmitral Doppler recordings, and the E/A ratio was calculated. Pulsed-wave TDI-

derived early diastolic velocity were obtained at the septal and lateral mitral annulus and the mean value ( $e'$ ) was used to estimate the  $E/e'$  ratio. In the presence of tricuspid regurgitation, continuous Doppler was used to estimate maximal tricuspid velocity ( $TRV_{max}$ ). Inferior vena cava diameter and respiratory changes, and  $TRV_{max}$  were then used to estimating systolic pulmonary artery pressure (PAPs)(10). To assess diastolic function, the algorithm proposed by Nagueh et al. was applied(6). The combination of mitral filling pattern, indexed LA volume ( $LAV_i$ ),  $E/e'$  ratio, and  $TRV_{max}$  was used at both baseline and 6-month FU to classify DD from grade I to grade III. In the case of “grey zone” values for these variables, diastolic function was indicated as “indeterminate”(6) (Figure 1).

### ***Assessment of LV dyssynchrony***

Septal flash (SF) and apical rocking (ApR) were assessed visually by two experienced readers from the KU Leuven. In case of disagreement, a third reading was performed in Leuven by an independent expert to reach a consensus. SF defined as pre-ejection septal shortening or rapid leftward septal motion immediately after onset QRS and was assessed visually in apical 2D images or, when in doubt, with longitudinal strain or M-mode in parasternal views(11). ApR was defined as a transverse rightward motion of the apex immediately after onset QRS, followed by a leftward motion of the apex during ejection(12). LV mechanical dyssynchrony was defined by the presence of SF and/or ApR.

### ***Cardiac resynchronization therapy***

CRT delivery followed a standardized protocol. The right atrial and ventricular leads were positioned conventionally. The LV lead was inserted in a lateral or postero-lateral vein if possible and coronary venography was used to optimize lead placement. The device was programmed in a conventional biventricular pacing and CRT was optimized before discharge if needed.

Positive response to CRT was defined as a decrease in LV end-systolic volume of  $\geq 15\%$ (13). To optimize precision for the assessment of CRT response, all volumes were measured independently

in three different centres (Rennes, Leuven and Oslo). The percent variation in LV-ESV was calculated to evaluate CRT-response and a majority decision was used in cases of disagreement between 2 centers. We also assessed reproducibility for LV-ESVs measured in every centre. The interclass correlation coefficients (ICC) were 0.97 (0.96-0.98,  $p < 0.0001$ ), 0.89 (0.74-0.94,  $p < 0.0001$ ), 0.95 (0.87-0.98,  $p < 0.0001$ ) for the LV-ESVs assessed in Rennes and Oslo, in Rennes and Leuven, and in Oslo et Leuven, respectively. The correlations between the volumes assessed in the centres and the corresponding Bland-Altman plot are displayed in Supplementary Figure 1.

### ***Study endpoints***

The primary endpoint was a composite of heart transplantation, LV assisted device implantation, or all- cause death during follow-up.

### ***Statistical analysis***

Continuous variables are expressed as the mean and standard deviation and were compared using Student's t-test. Categorical data are expressed as frequencies and percentages and were compared by the  $\chi^2$  test. Inter-observer variability for the estimation LV-ESV between the three enrolling centres was assessed by linear regression analysis, and Bland-Altman plots and is displayed in Supplementary Figure 1. Interclass correlation coefficients (ICC) were also reported. The relation between variables was assessed by bivariate analysis with Pearson's correlation coefficients. Cox-regression analysis and Kaplan-Meier curves with log-rank test were used to describe survival data. All statistical analyses were performed using a standard statistical software program (SPSS Version 20.0, IBM, Chicago, IL, USA).

### **Results**

One-hundred ninety-three patients (age  $67 \pm 11$  years, males 70%) met the eligibility criteria within the study period. Clinical and echocardiographic data from the overall population and according to CRT-response are provided in Table 1 and 2. Ischemic heart disease was diagnosed in



64 (33%) patients. Atrial fibrillation was detected in 11 (5.6%) patients. Typical left bundle branch block (LBBB) according to Strauss(14) was observed in 168 (87%) patients. LV mechanical dyssynchrony was observed in 136 (70%) patients. At 6-month FU, volumetric response to CRT was observed in 132 (68%) patients. Responders were more often women, with a lower prevalence of ischemic cardiomyopathy. LV dyssynchrony was observed in 136 (70%) patients and was prevalent in responders (82% vs 44%,  $p<0.0001$ ). LVMi and RWT were similar in responders and were in favour of an eccentric LV hypertrophy. CRT-induced a significant reduction in MR entity in both responders ( $1.5\pm 0.9$  vs  $1.0\pm 0.05$ ,  $p<0.01$ ) and non-responders ( $1.6\pm 1.0$  vs  $1.2\pm 0.6$ ,  $p<0.01$ ). Responders had less significant LV dilatation at baseline. At follow-up, LVEF, and GLS improved substantially in responders, while in non-responders there were no significant changes. (Table 2).

#### ***Assessment of diastolic dysfunction***

Before CRT implantation, the parameters of diastolic function including E wave velocity,  $E/e'$ ,  $LAV_i$ , and  $TRV_{max}$  were significantly altered in non-responders. CRT delivery was associated with a significant reduction in  $LAV_i$  and  $E/e'$  in responders, whereas only a mild reduction in  $LAV_i$  was observed in non-responders (Table 2).

Before CRT, the prevalence of grade I, grade II, grade III DD in the overall were respectively 55%, 24%, and 13% (Figure 2A). Patients with grade I DD were younger, had less ischemic cardiomyopathy and less impaired renal function. They needed less diuretics and aldosterone-antagonists. Despite the absence of significant difference in LV size and LVEF at baseline, grade I DD was associated with a marked reverse remodelling at FU (Table 3).

The prevalence of grade I DD before CRT delivery was significantly higher in responders (Figure 2B). After CRT, the prevalence of grade III DD increased in non-responders (20% vs 25%,  $p=0.05$ ) (Figure 2C). In responders, CRT was associated with a slightly decreased prevalence of grade I DD, and increased prevalence of “indeterminate” diastolic dysfunction (Figure 2D).

#### ***Predictors of prognosis.***

After a mean follow-up period of 35 months, 27 patients died, 1 patient received LVAD, and 1 patient was transplanted. Three patients reached the primary endpoint before 6-month follow-up and these patients were considered non-responders.

The algorithm by Nagueh et al. was able to predict prognosis in CRT-candidates. As displayed in Table 4, when using Grade I DD as reference, patients assigned to grade II (HR 6.04, 95% CI: 2.32-15.77) and III DD (HR 4.64, 95%CI: 1.49-14.39) had a significant increased risk of events. However, no significant difference was observed between grade II and III DD for the prediction of events (HR 0.77, 95% CI 0.29-2.00). Therefore, Grade II and grade III DD were merged in the multivariable analysis (Table 4, Panel B). Other predictors of prognosis at univariable analysis are displayed in Table 4, Panel A. At multivariable analysis corrected for clinical variables, QRS width, mitral regurgitation, CRT-response and LV dyssynchrony, grade I DD was associated with a better outcome (HR 0.37, 95% CI: 0.14-0.96) (Figure 3). Two multivariable models including alternatively LBBB (Model A) and E/e' ratio, LAVi, and TRV<sub>max</sub> instead of DD grading (Model B) are provided as Supplementary Material. In the multivariable including LBBB, this parameter was not a predictor of prognosis (Figure S2). Similarly, diastolic function parameters lose their predictive value at multivariable analysis (Table 3, Figure S3).

Kaplan-Meier survival curves showed that grade I DD was associated with a significantly better outcome (log-rank  $p < 0.0001$ ) (Figure 4A) and with a significantly reduced risk of events (HR 0.18, 95% CI: 0.07-0.45,  $p < 0.0001$ ).

Grade I DD was associated with a better prognosis among both CRT responders and non-responder. Non-responders with grade II-III DD had the worse outcome (HR 4.36, 95%CI: 2.10-9.06,  $p < 0.0001$ ) (Figure 4B)

Similarly, the assessment of DD allowed the prognostic stratification of patients with and without LV dyssynchrony (log-rank  $p < 0.0001$ ). Patients without SF/ApR and with grade II-III DD had the worse prognosis (HR 4.41, 95%CI: 2.11-9.17,  $p < 0.0001$ ) (Figure 4C).

## Discussion

The present multicentre prospective study applies current recommendations for the assessment of diastolic dysfunction in CRT-candidates and shows that the presence of a relatively preserved diastolic function before CRT implantation is associated with a better prognosis.

### ***Diastolic dysfunction and CRT response***

The effect of CRT on diastolic function are still debated. Some prospective studies showed that a favourable filling pattern(15) and a less dilated left atrium (LA)(16) at baseline are more likely to be associated with a positive LV remodelling after CRT. In contrast, Yu et al. showed that the LV reverse remodelling induced by CRT is not influenced by the diastolic filling pattern at baseline(17).

In our study, the effect of CRT on DD was assessed by the application the 2016 Recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging. By the use of this comprehensive approach, which is based on the simultaneous estimations of several parameters, we observed that CRT was associated with an increased prevalence of grade III DD in non-responders. The degradation of DD in non-responders is probably attributable to the absence of LV reverse remodelling, which has a substantial influence on LV filling pressures.

In our population, CRT did not change the prevalence of grade I to III DD in responders. This observation is in partially in contrast with previous studies on this topic(15),(18),(19) and might be attributable to several different factors. First, the diagnostic algorithm for the classification of DD relies on specific cut-off values, which means that the simple modification of one or more parameters might not be enough to fulfil the criteria necessary for a change in diastolic function class. We observed a significant improvement in E/e' ratio and LAVi in responders, nevertheless, E/E' and LAVi remained above the predefined cut-off in 41% and 27% of patients at 6-month FU. Second, in responders we observed an increased number of "indeterminate" DD at follow-up. This is mainly attributable to discordant DD parameters in patients with undetectable tricuspid

regurgitation after CRT.  $TRV_{max}$  is a parameters that reflects advanced DD due to chronic pressure overload(20).

Almeida et al. have already observed that the addition of  $TRV_{max}$  to the algorithm of Nagueh et al. was associated with an increased sensitivity and a drop of specificity for the detection of DD, particularly in patients with less advanced DD(21). This means that in responders with a significant improvement of LV function and decrease in LV filling pressure, the absence of data on  $TRV_{max}$  at FU, might contribute to with a certain degree of patients' misclassification as "indeterminate DD".

### ***Diastolic dysfunction and prognosis***

In this study we were able to demonstrate that patients with grade I DD undergoing CRT have a significantly better prognosis with respect to patients with more advanced DD at baseline. The prognostic value of the algorithm of Nagueh et al. for the assessment of DD has already been demonstrated in patients with HF and reduced EF (HFrEF)(3).

Our work expands this evidence by showing the prognostic value of the 2016 recommendations in patients with HFrEF undergoing CRT. In our population, grade I DD was an independent predictor of prognosis. Patients with grade I DD at baseline were younger, with lower prevalence of ischemic cardiomyopathy, and kidney failure. Their clinical status was better before CRT-delivery, as evidenced by the lower NYHA class, better kidney function and the lower percentage of patients taking diuretics and aldosterone-antagonists. On the other hand, grade II and III DD at baseline were observed in patients with higher prevalence of ischemic cardiomyopathy, more advanced heart disease, and cardio-renal syndrome. These characteristics have already been associated with increased mortality in patients with a broad spectrum of cardiovascular disease and LV function (22) and might explain why grade II-III DD is associated with a poor survival in both CRT responders and non-responders. The prognostic value of SF/ApR in patients undergoing CRT has already been demonstrated(23). Nevertheless, Stankovic et al. have underscored that some patients with LV mechanical discoordination can have a poor prognosis because factors such as ischemic cardiomyopathy and advanced HF might contribute to their detrimental survival. In our population,

we show that patients with grade I DD have probably less advanced HF, which can contribute its prognostic value in patients undergoing CRT, irrespectively to the presence of LV mechanical dyssynchrony.

### ***Clinical implications***

This study shows that the estimation of diastolic dysfunction by the algorithm proposed by Nagueh et al. is simple and applicable in a prospective cohort of “real life” patients undergoing CRT. Patients with grade I DD at baseline have less advanced HF, which has a fundamental prognostic impact and provide complementary information with respect to LV mechanical dyssynchrony and CRT response which should prompt the assessment of DD in CRT candidates.

### ***Limitations***

The main limitation of this study is the lack of invasive validation for the assessment of LV filling pressure so that the classification of DD dysfunction is based only on the algorithm proposed in current recommendations. Although cardiac catheterization remains the gold standard for the assessment of LV filling pressure, the invasive assessment of LV filling pressure cannot be realized systematically in all patients. The proposed algorithm for the assessment of DD has shown good accuracy in identifying the presence of elevated LV filling pressure in patients with very different cardiac disease, including LBBB and paced rhythm(7). We therefore estimate that our results are reliable and have the merit to be largely applicable in everyday clinical practice. Another weakness of the algorithm is the impossibility to categorize some patients, because of discordances in the predefined diastolic function parameters. This intrinsic limitation of the current algorithm might be overcome in the future by the integration of new parameters, such as the assessment of left atrial deformation. Left atrial reservoir function correlates with LV filling pressure(24), has shown to be associated with prognosis in HF patients(25), and might therefore represent a potential new tool for the evaluation of diastolic dysfunction in CRT candidates(26).

### ***Conclusions***

In CRT candidates, grade I DD is associated with a better prognosis. The evaluation of diastolic function according to the algorithm proposed by recommendations provide valuable prognostic information, which is additive to that provided by LV dyssynchrony or CRT response.

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**Table 1. Characteristics of the overall population and comparison according to CRT-response**

	All (n=193)	Responders (n=132, 68%)	Non-responders (n=61, 32%)	<i>p-value</i>
<b><i>Clinical data</i></b>				
Age, ys	67±11	68±10	66±11	0.25
Males	136 (70)	85 (64)	51 (83)	0.004
Ischemic cardiomyopathy	64 (33)	29 (22)	35 (57)	<0.0001
NYHA	2.31±0.61	2.24±0.5 <sup>o</sup>	2.48±0.65	0.01
GFR, ml/min	63±23	65±23	59±22	0.10
QRS width, ms	167±21	168±19	166±24	0.44
LBBB	168 (87)	113 (89)	50 (82)	0.17
<b><i>Treatment</i></b>				
Beta-blockers, n (%)	183 (95)	128 (97)	55 (90)	0.06
ACEI or Sartans, n (%)	173 (90)	117 (89)	56 (92)	0.34
Aldosterone antagonists, n (%)	75 (39)	49 (37)	26 (43)	0.27
Diuretics, n (%)	165 (85)	90 (68)	75 (45)	0.22
LV dyssynchrony, n (%)	136 (70)	108 (82)	28 (44)	<0.0001
Mitral regurgitation (1-4)	1.6±0.9	1.5±0.8	1.8±1.1	0.06
RWT	0.29±0.13	0.29±0.19	0.29±0.19	0.92
LV mass, g/m <sup>2</sup>	130±39	129±39	134±40	0.43

ACE-I, angiotensin converting enzyme inhibitors; GFR, glomerular filtration rate; LBBB, left bundle branch block; LV, left ventricle; NYHA, New York heart association functional class; RWT, relative wall thickness.

Table 2. Left ventricular systolic and diastolic function

	<i>All patients</i>	<i>CRT-responders</i>			<i>CRT non-responders</i>		
	<b>Baseline</b>	<b>Baseline</b>	<b>6-months</b>	<i>p-value</i>	<b>Baseline</b>	<b>6-months</b>	<i>p-value</i>
<b>LV-EDV, ml</b>	210±86	197±84	141± 64	<0.0001	239±85†	231±89*	0.92
<b>LV-ESV, ml</b>	153±73	143±68	81±50	<0.0001	175±76†	168±78*	0.80
<b>LVEF, %</b>	28±8	29±7	45± 12	<0.0001	28±9	30±10*	0.44
<b>GLS, %</b>	-8.4±3.9	-9.9±3.9	-12.9±3.5	<0.001	-7.1±3.52†	-8.1±2.9*	0.23
<b>LAV<sub>i</sub>, ml/m<sup>2</sup></b>	47±17	47±17	36±18	<0.0001	51±17†	45±16*	0.02
<b>E, cm/sec</b>	76±33	69±27	66±25	0.001	87±34†	79±31*	0.04
<b>E/A</b>	1.3±1.0	1.2±1.0	1.0±0.6	0.27	1.5±0.9	1.5±1.05*	0.79
<b>e' septal, cm/sec</b>	4.2±1.7	4.3±1.7	5.2±1.9	0.01	4.2±1.8	4.7±2.1	0.16
<b>e' lateral, cm/sec</b>	6.5±3.1	6.6±3.1	6.5±3.1	0.85	6.2±3.2	5.8±2.7	0.18
<b>E/e'</b>	16.0±9.3	14.3±7.4	12.5±6.8	0.04	19.7±11.9†	18±12*	0.47
<b>TRV<sub>max</sub>, m/sec<sup>**</sup></b>	2.5±0.6	2.4±0.6	2.4±0.36	0.58	2.7±0.6†	2.6±0.4*	0.22
<b>PAPs, mmHg</b>	32±13	30±12	29±9	0.29	36±16†	35±12*	0.35

†<0.05 vs responders at baseline, \*p<0.05 responders at 6-month follow-up

\*\*At baseline, TRV<sub>max</sub> was detectable in 101 (77%) responders and 51 (83%) non-responders. At follow-up, TRV<sub>max</sub> was detectable in 98 (74%) responders and 46 (75%) non-responders.

EDV, end-diastolic volume; ESV, end-systolic volume; GFR, glomerular filtration rate; GLS, global longitudinal strain; LV, left ventricle; LAV<sub>i</sub>, indexed left atrial volume; LVEF, left ventricular ejection fraction; PAPs, estimated pulmonary systolic pressure; TRV<sub>max</sub>, maximal tricuspid regurgitation velocity.

**Table 3. Clinical and echocardiographic parameters according to diastolic dysfunction. Patients with indeterminate diastolic dysfunction were not included in the analysis.**

	Grade I DD (n=105, 55%)	Grade II-III DD (n=72, 37%)	<i>p-value</i>
<b><i>Clinical data</i></b>			
Age, ys	65±11	69±10	0.007
Males, n (%)	73 (70)	53 (74)	0.34
Ischemic cardiomyopathy, n (%)	26 (25)	32 (44)	0.007
NYHA	2.2±0.6	2.5±0.6	<0.0001
QRS width, ms	165±18	171±24	0.13
GFR, ml/min	68±22	54±22	<0.0001
LBBB, n (%)	94 (90)	60 (83)	0.28
Beta-blockers, n(%)	94 (90)	63 (80)	0.42
ACEI or Sartans, n (%)	101 (96)	68 (94)	0.42
Aldosterone-antagonists n (%)	33 (32)	33 (47)	0.03
Diuretics, n (%)	66 (83)	60 (63)	0.002
<b><i>Echocardiographic data</i></b>			
LV mass, g/m <sup>2</sup>	125±36	135±42	0.07
RWT	0.30±0.16	0.28±0.07	0.23
LV-EDV, ml	201±82	219±90	0.18
LV-ESV, ml	145±69	112±39	0.25
LVEF, %	29±7	27±9	0.22
LV-EDV <sub>FU</sub> , ml	150±66	190±92	<0.0001
LV-ESV <sub>FU</sub> , ml	87±55	132±81	<0.0001
LVEF <sub>FU</sub> , %	45±13	36±13	<0.0001
LV dyssynchrony, n%	81 (77)	43 (60)	0.01

E wave, cm/sec	58±20	98±34	<0.0001
E/A	0.75±0.31	2.2±1.5	<0.0001
LAVi, ml/m <sup>2</sup>	40±13	55±18	<0.0001
E/e'	12±6	22±10	<0.0001
TRV <sub>max</sub> , m/sec	2.2±0.5	2.9±0.5	<0.0001
PAPs, mmHg	26±9	41±14	<0.0001
Responders	86 (82)	36 (50)	<0.0001

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**Table 4. Univariable regression analysis showing clinical and echocardiographic predictors of prognosis (Panel A). The association between diastolic dysfunction grades and outcome at univariable analysis is depicted in Panel B. In this panel, the associations are assessed with different grades of diastolic dysfunction as reference.**

<b>PANEL A</b>	<b>HR (95%CI)</b>
Age	1.03 (0.98-1.07)
NYHA	4.33 (2.08-9.05)
Ischemic etiology	3.55 (0.64-3.52)
LBBB	0.44 (0.19-1.05)
QRS duration	1.2 (1.00-1.04)
LVEF	0.97 (0.92-1.01)
Mitral regurgitation	1.49 (1.01-2.24)
LV dyssynchrony	0.31 (0.15-0.65)
Responders	0.27 (0.13-0.57)
E/e' $>14$	2-64 (1.18-5.88)
LAV <sub>i</sub> $> 34$ ml/m <sup>2</sup>	4.04 (1.51-10.83)
TRV <sub>max</sub> $>2.8$ m/sec	3.08 (1.35-7.00)
<b>PANEL B</b>	
<b>Grade I DD</b>	<b>Ref</b>
Grade II DD (ref grade I)	6.04 (2.32-15.77)
Grade III DD (ref grade I)	4.64 (1.49-14.39)
<b>Grade II DD</b>	<b>Ref</b>
Grade I (ref Grade II)	0.17 (0.06-0.43)
Grade III (ref Grade II)	0.77 (0.29-2.00) 0.59
<b>Grade III DD</b>	<b>Ref</b>
Grade I (ref Grade III)	0.21 (0.07-0.66)
Grade II (ref Grade III)	1.30 (0.50-3.39)

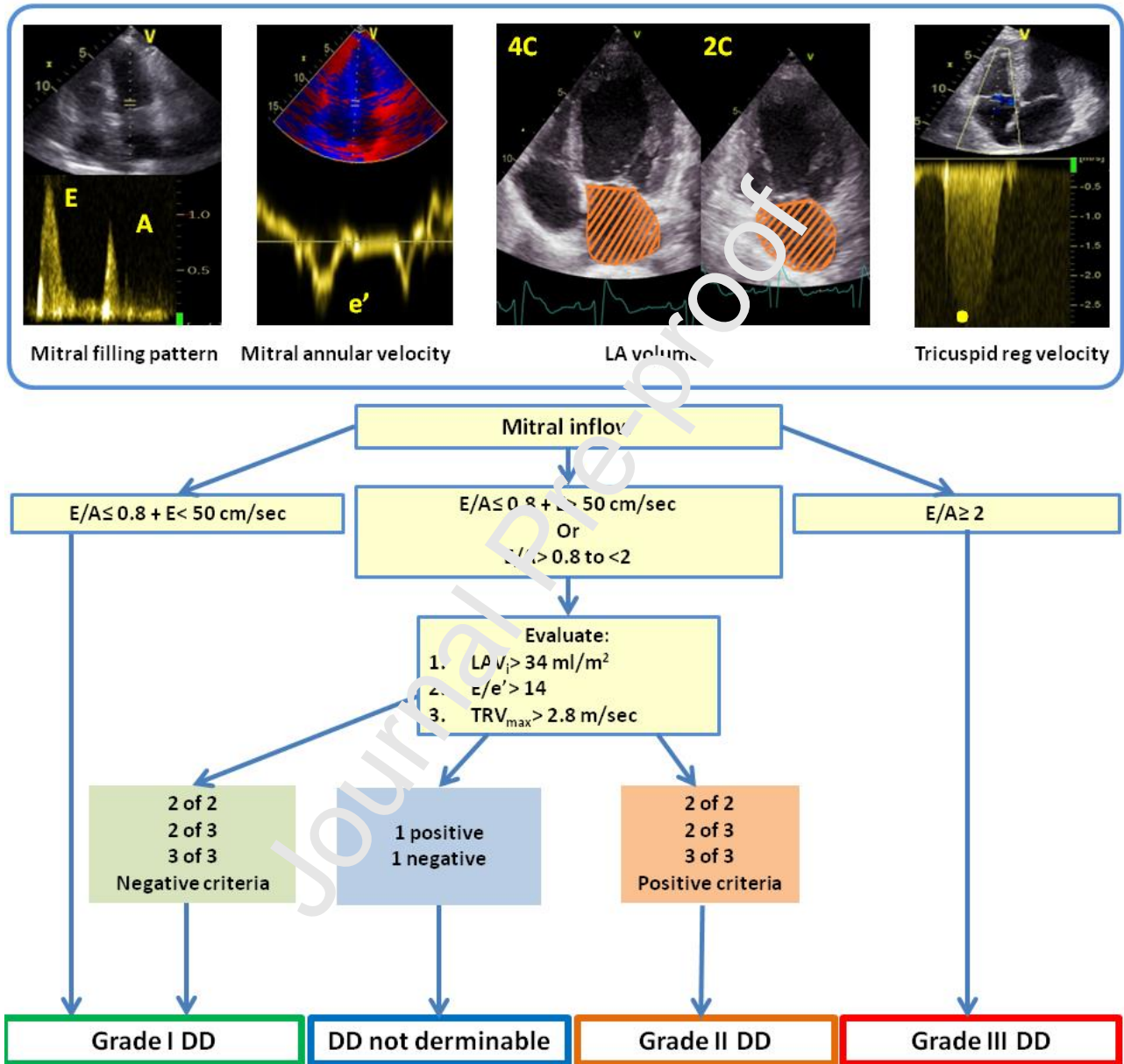


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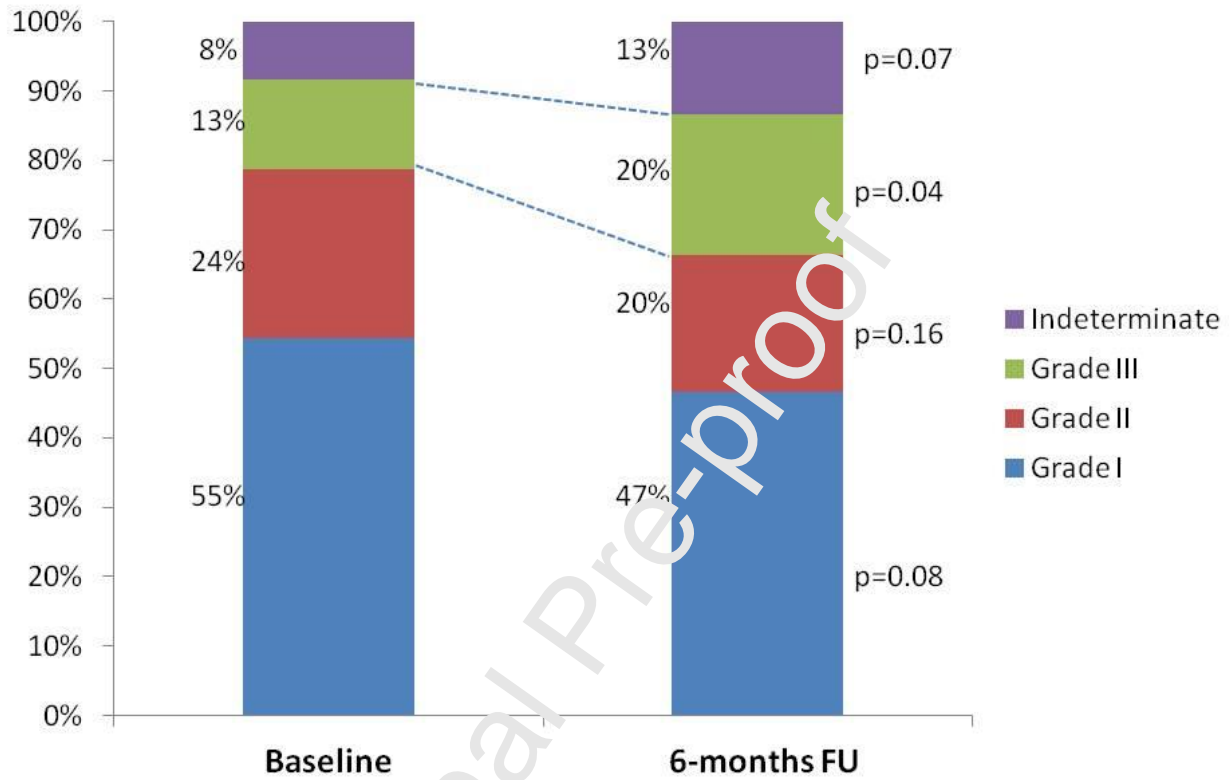
**Figure 1. Algorithm for the assessment of diastolic dysfunction**

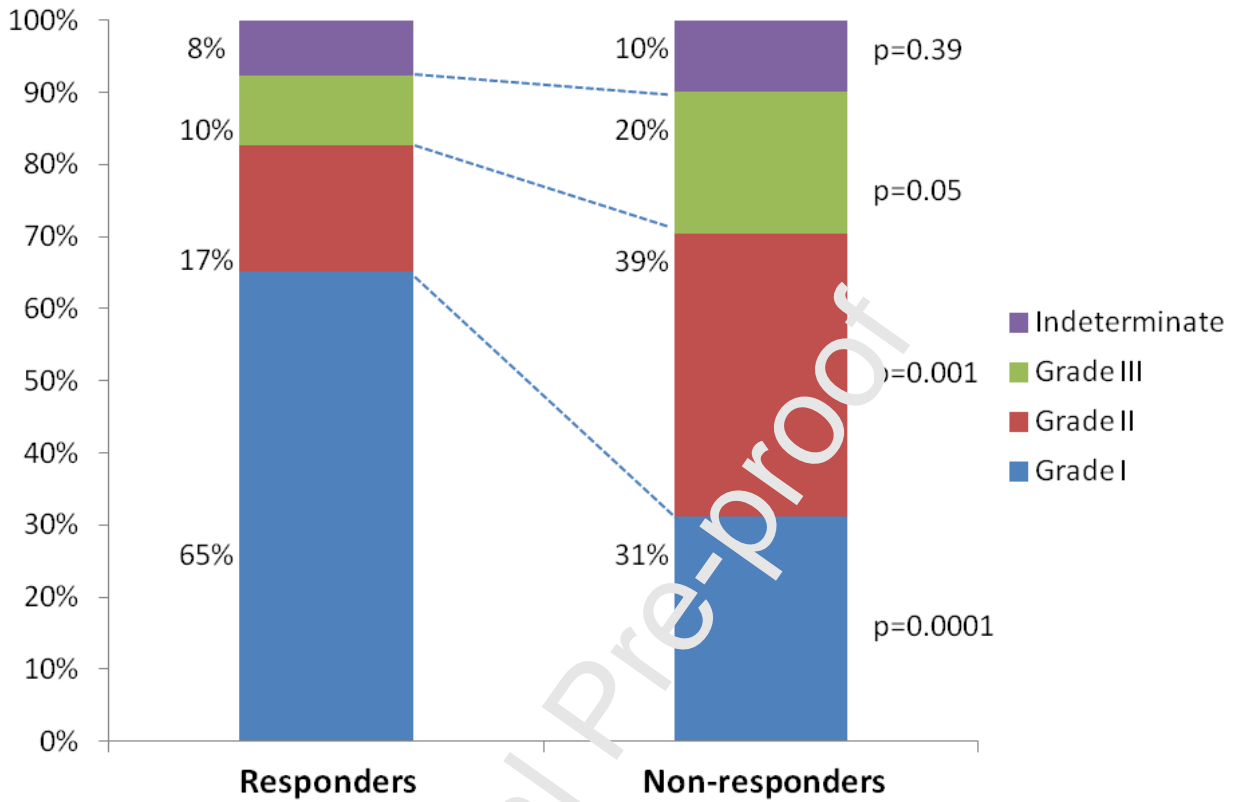
2C, 2-chamber view; 4C, 4-chamber view; DD, diastolic dysfunction, LA, left atrium, LAVi, indexed left atrial volume;  $TRV_{max}$ , maximal tricuspid regurgitation velocity

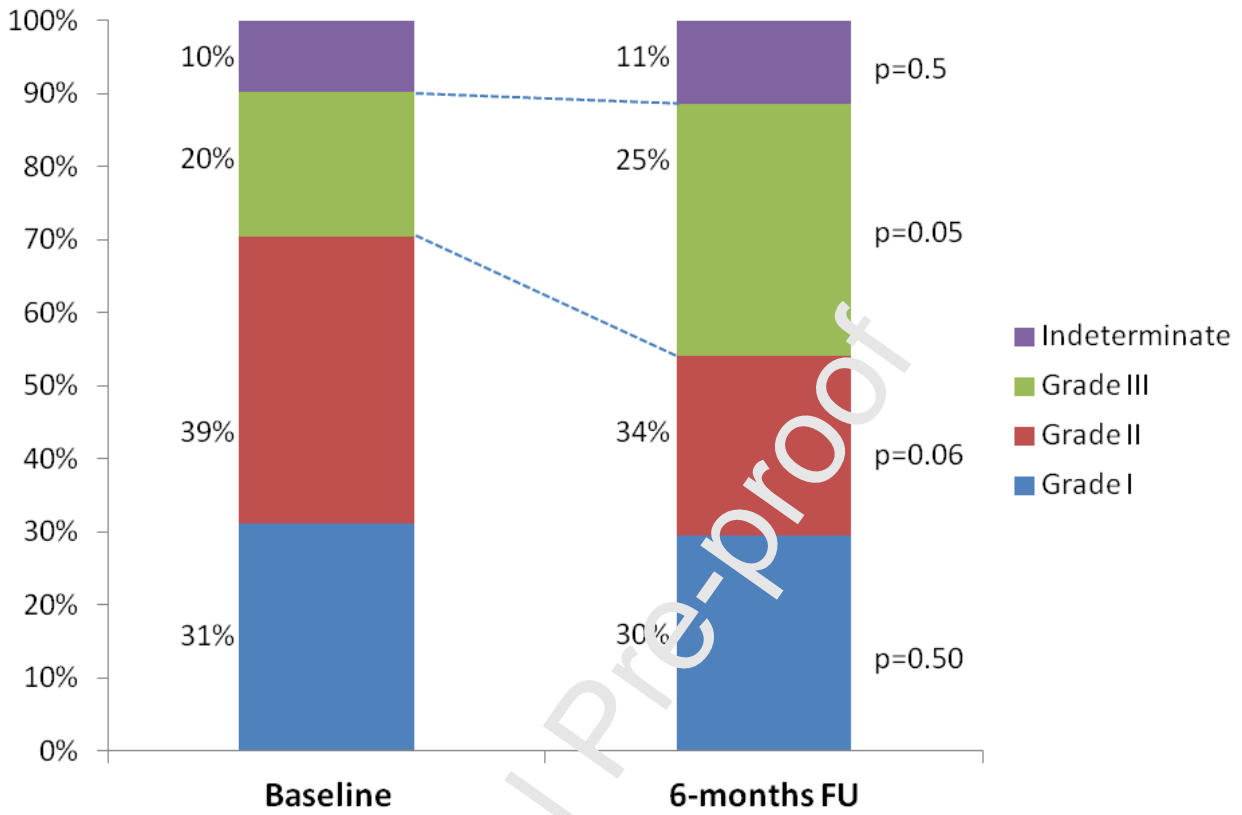


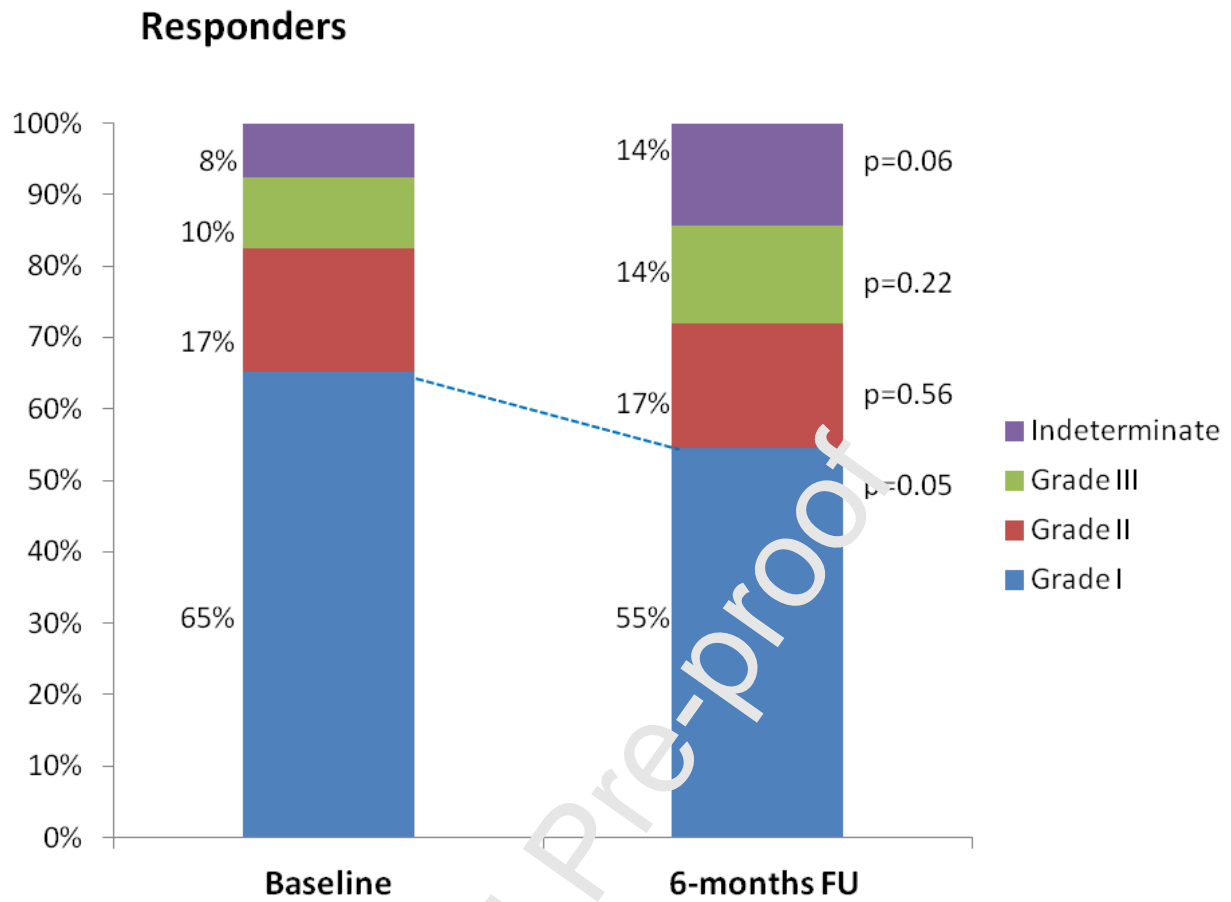
**Figure 2 A. Prevalence of diastolic dysfunction at baseline (A) and 6-month follow-up (B) in the overall population**

**All**



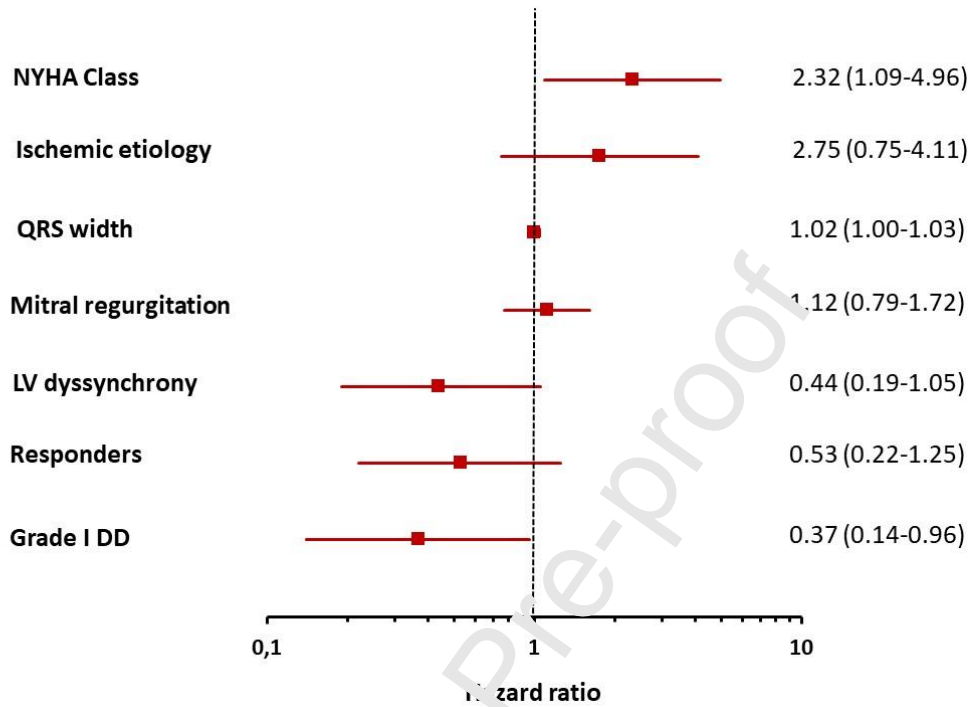
**Figure 2B Prevalence of diastolic dysfunction at baseline in responders and non-responders****Baseline**

**Figure 2C Prevalence of diastolic dysfunction at baseline and 6-month FU in non-responders****Non-responders**

**Figure 2D Prevalence of diastolic dysfunction at baseline and 6-month FU in responders**

**Figure 3. Forest plot depicting the main predictors of prognosis at multivariable regression analysis.**

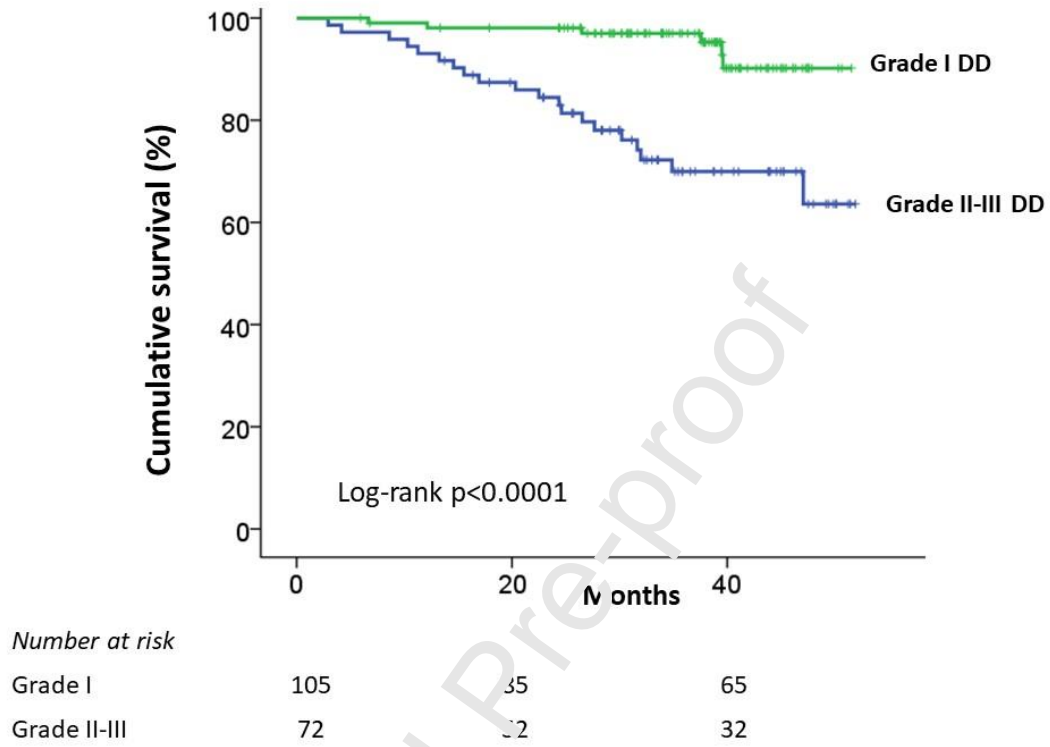
DD, diastolic dysfunction; NYHA, New York Heart Association functional class





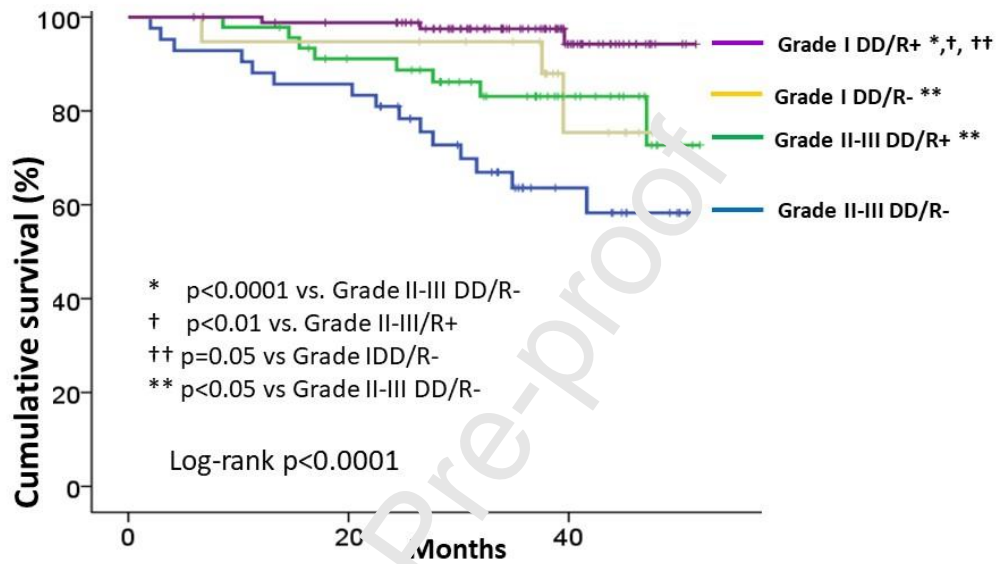
**Figure 4A. Kaplan-Meier curve depicting survival according to diastolic dysfunction**

DD, diastolic dysfunction



**Figure 4B Kaplan-Meier curve depicting survival according to diastolic dysfunction and CRT-response**

DD, diastolic dysfunction; R+, CRT positive response; R-, CRT negative response

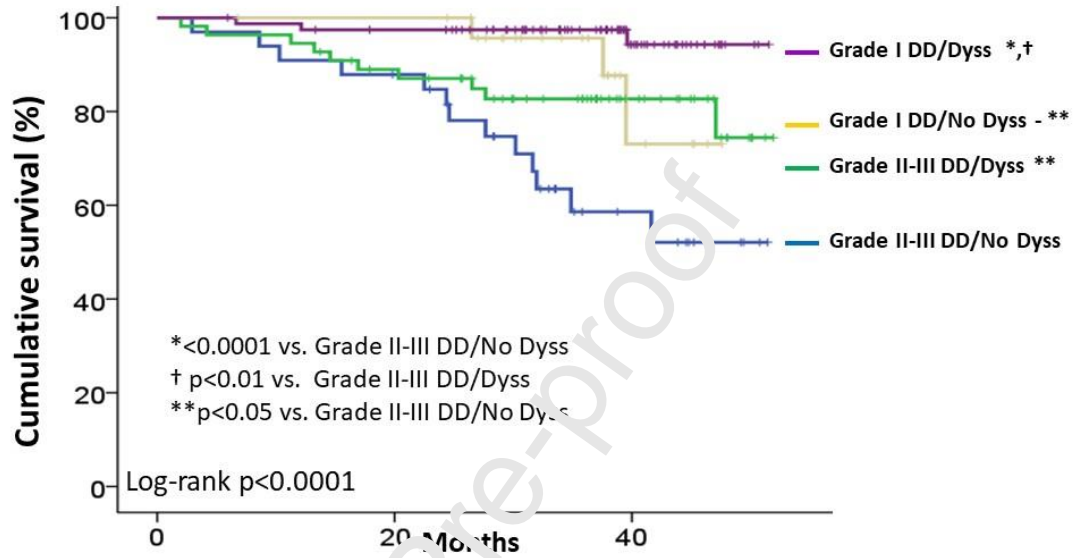


Number at risk

Grade I DD/R+	86	33	26
Grade I DD/R-	46	38	16
Grade II-III DD/R+	19	18	6
Grade II-III DD/R-	42	35	12

**Figure 4C Kaplan-Meier curve depicting survival according to diastolic dysfunction and left ventricular dyssynchrony**

DD, diastolic dysfunction; No Dyss, absence of left ventricular dyssynchrony; Dyss, presence of left ventricular dyssynchrony



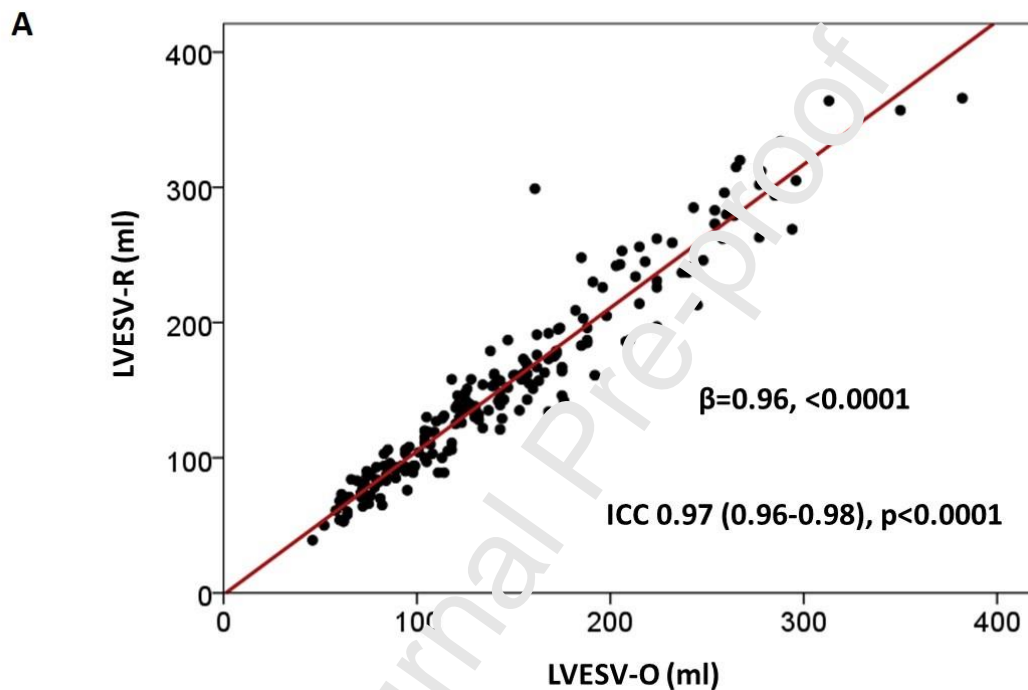
Number at risk

	0	20	40
Grade I DD/Dyss	79	74	28
Grade I DD/No Dyss	26	20	5
Grade II-III DD/Dyss	55	45	19
Grade II-III DD/No Dyss	33	28	9

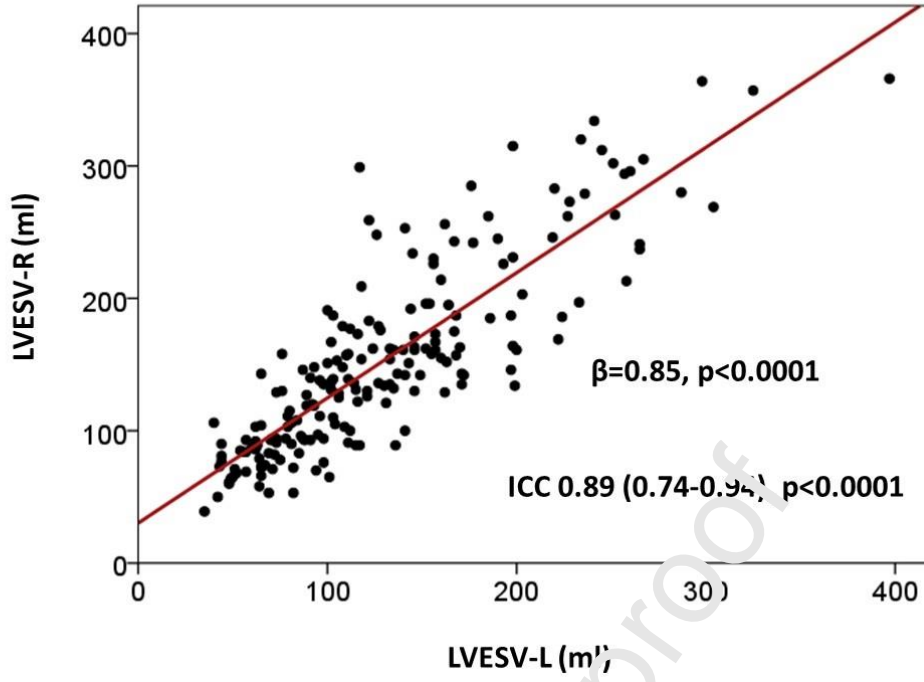
**Supplementary Figure 1 A-F.**

Inter observer variability for left end-systolic volume between the 3 enrolling centres is displayed as linear regression with inter-class correlation coefficients and Bland-Altman plots.

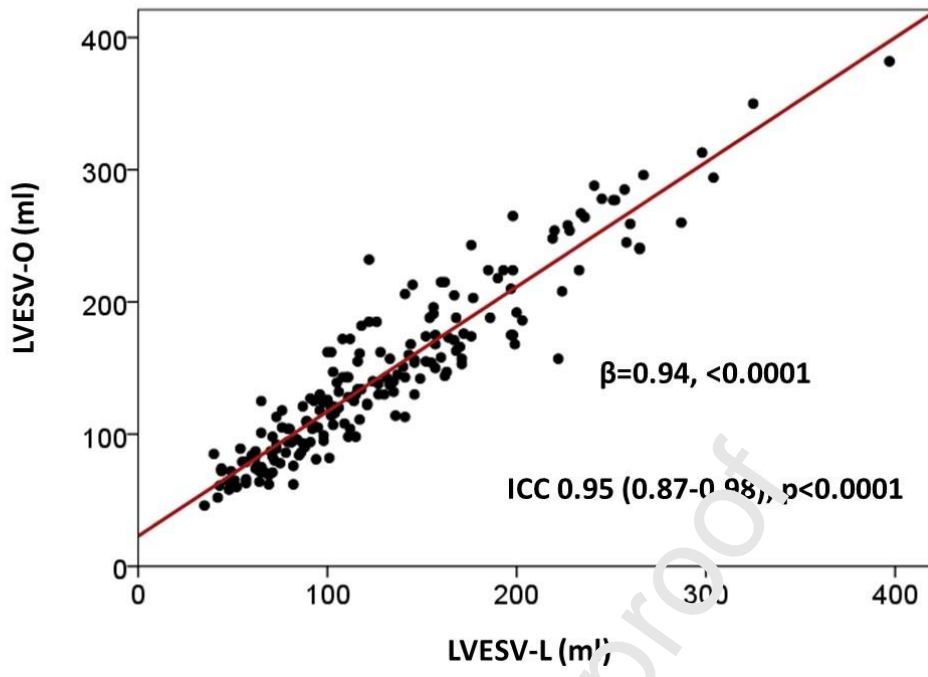
ICC, interclass correlation coefficient; CI, confidence interval; LVESV, left ventricular end-systolic volume, O= Oslo, R=Rennes, L=Leuven.



B

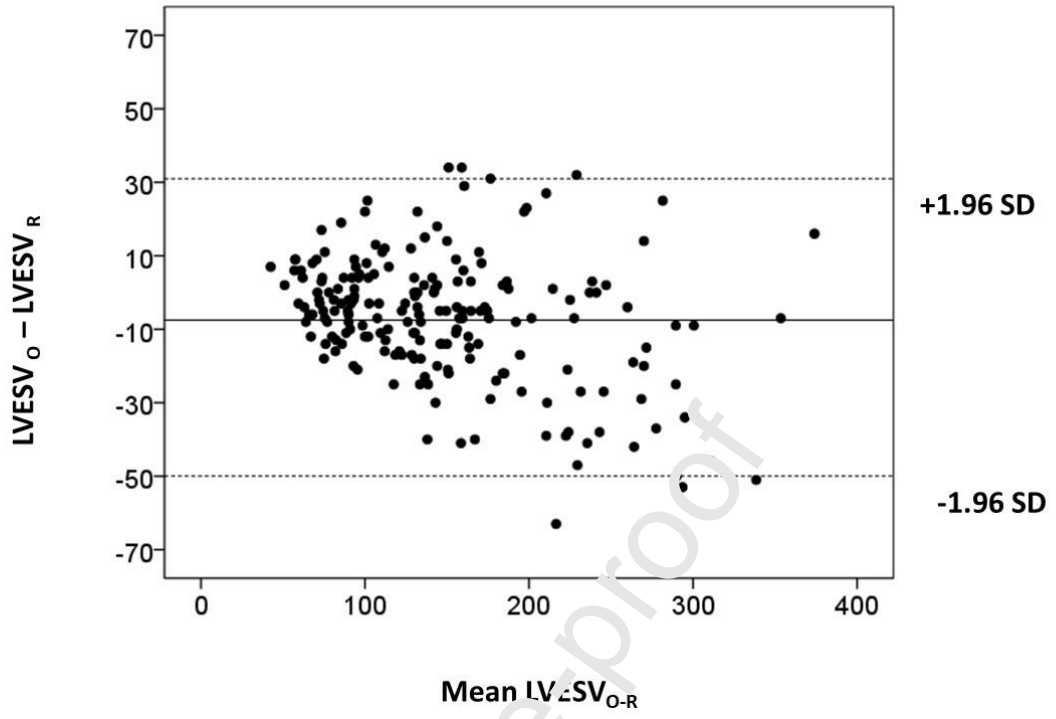


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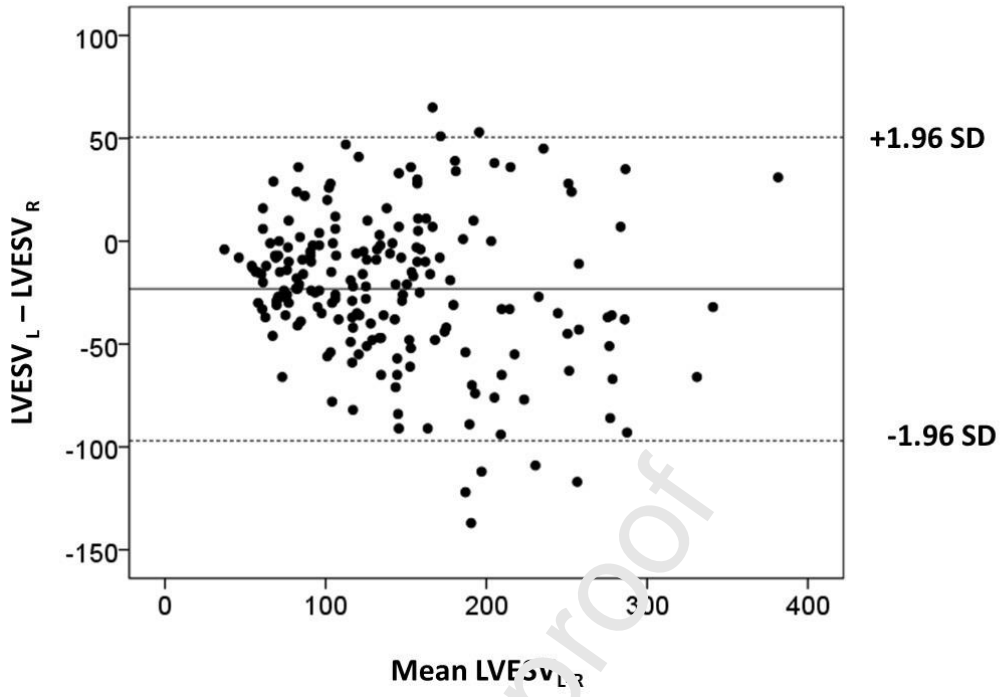
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D



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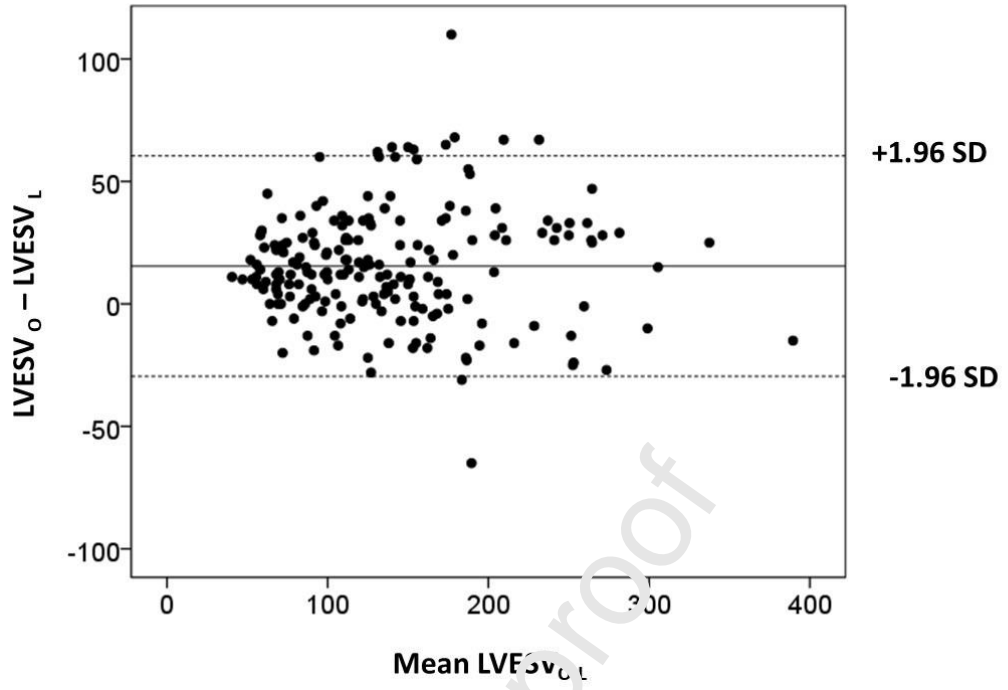
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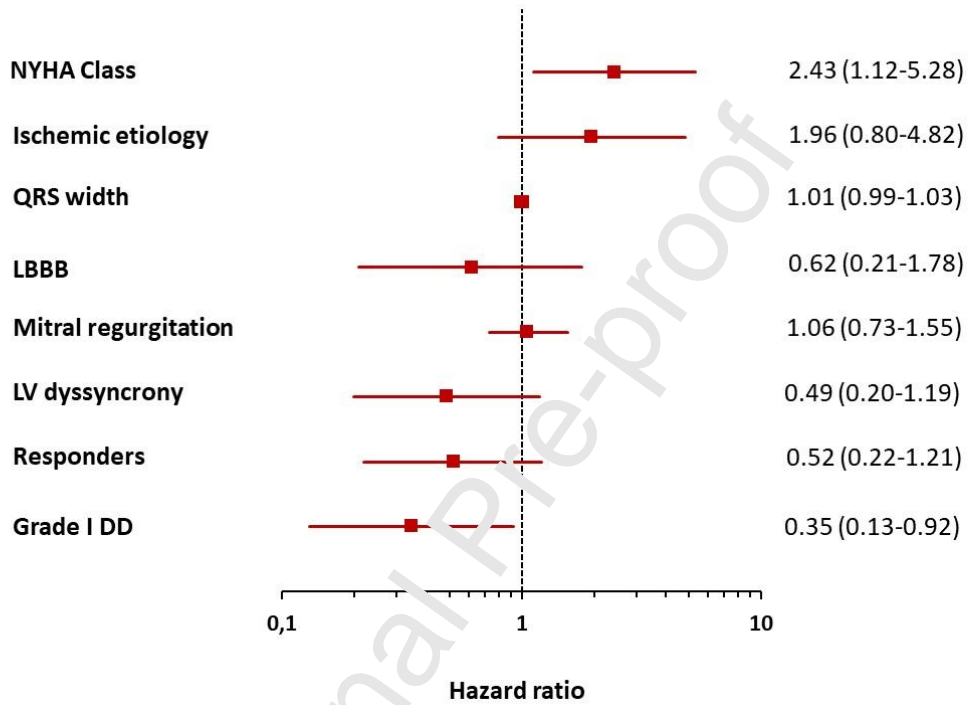
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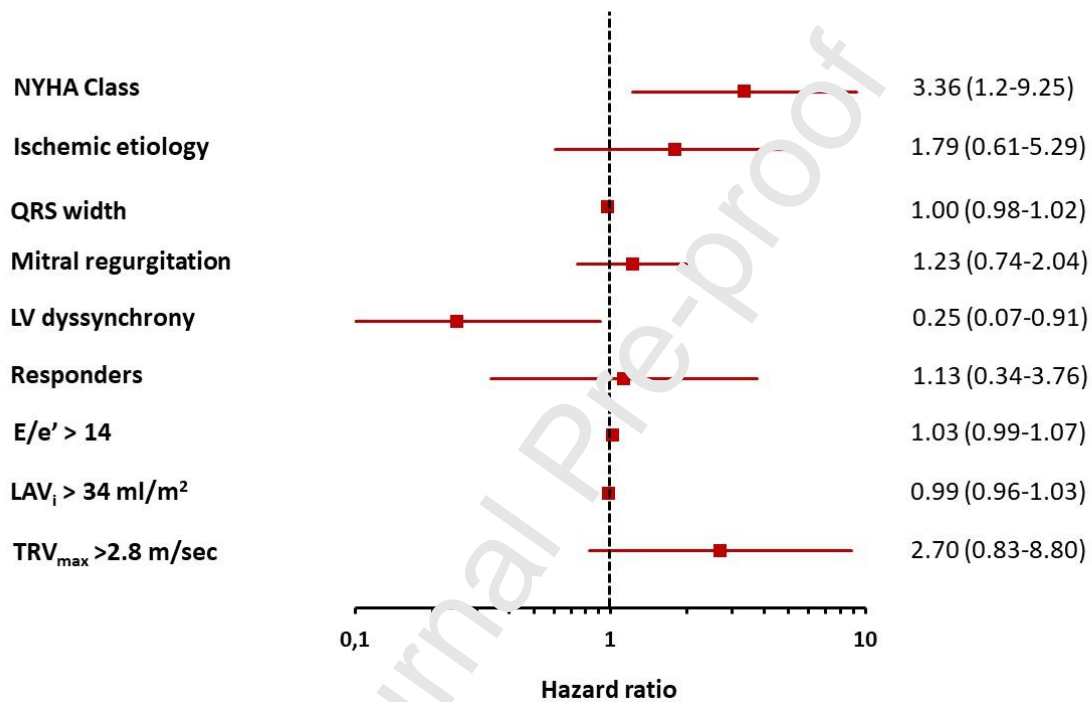
**Supplementary Figure 2 Forest plot depicting the main predictors of prognosis at multivariable regression analysis in an alternative model including left bundle branch block**

DD, diastolic dysfunction; LBBB, left bundle branch block; NYHA, New York Heart Association functional class.



**Supplementary Figure 3. Forest plot depicting the main predictors of prognosis at multivariable regression analysis in an alternative model including  $E/e'$ , indexed left atrial volume and maximal tricuspid regurgitation velocity for the assessment instead of the diastolic dysfunction grading proposed by Nagueh et al.**

LAV<sub>i</sub>, indexed left atrial volume; NYHA, New York Heart Association functional class; TRV<sub>max</sub>, maximal tricuspid regurgitation velocity



#### Highlights

- Conflicting data exist about the relationship between cardiac resynchronization therapy (CRT) and diastolic function.
- One-hundred ninety-three patients (age:  $67 \pm 11$  years, QRS width:  $167 \pm 21$  ms) were included in this multicentre prospective study about the value of imaging for CRT. CRT was associated with a degradation of diastolic dysfunction in non-responders. Grade I diastolic dysfunction was associated with a better outcome (HR 0.36, 95% CI: 0.14-0.85).
- Non-responders with grade II or grade III diastiloc dysfunction had the worse prognosis (HR 4.36, 95% CI: 2.10-9.06).

- So, the evaluation of diastolic dysfunction in CRT candidates is crucial for best stratification of patients according to their own risk of cardio-vascular event, independently from CRT-response.

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