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Left ventricular wall thickness assessed by cardiac computed tomography and CRT outcomes.

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ABSTRACT

Aims. Up to 30% of selected heart failure patients do not benefit clinically from cardiac resynchronization therapy (CRT). Left ventricular (LV) wall thickness (WT) analyzed using computed tomography (CT) has rarely been evaluated in response to CRT and mitral regurgitation (MR) improvement. We examined the association of LVWT and the ability for reverse LV remodeling and MR improvement after CRT.

Methods. 54 patients scheduled for CRT underwent pre-procedural CT. Reduced LVWT was defined as WT<6mm and quantified as a percentage of total LV area. End points were 6-month clinical and echocardiographic response to CRT (NYHA class, LV ejection fraction (LVEF), LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVEDV)), MR improvement and 2-year major adverse cardiac events (MACE).

Results. Patients were divided in 3 groups according to the percentage of LVWT<6mm area: ≤20%; 20-50% and ≥50%. At 6 months, 75%, 71% and 42% of the patients experienced NYHA improvement in the ≤20%, 20-50% and ≥50% group respectively. Additionally, ≤20% group presented higher LVEF, LVEDV and LVESV positive response rate (86%, 59% and 83% respectively). Both 20-50% and ≥50% groups exhibited a lower LVEF, LVEDV and LVESV positive response rate (52% and 42%; 47% and 45%; 53% and 45%, respectively). Additionally, ≥25% of LVWT<6mm inclusive of at least 1 papillary muscle insertion was the only predictor of lack of MR improvement. Lastly, ≥50% group experienced significantly lower 2-years MACE survival free probability.

Conclusion. WT evaluated using CT could help to stratify the response to CRT and predict MR improvement and outcomes.

KEY WORDS: Cardiac resynchronization therapy, response to cardiac resynchronization therapy, mitral regurgitation, computed tomography, left ventricular wall thickness

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CONDENSED ABSTRACT

CRT-recipients with a low percentage of left ventricular wall thickness (LVWT) <6mm (≤20%) significantly improved their echocardiography parameters. Patients with ≥25% of LVWT<6mm inclusive of at least 1 papillary muscle insertion was the only predictor of no mitral regurgitation improvement. Patients with ≥50% of LVWT<6mm experienced poor 2-years outcomes.

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What's New?

-Left ventricular wall thickness (LV WT) measured computed tomography could be associated with the response to CRT.

-CRT candidates with a low percentage of LV WT<6mm (≤20%) significantly improved their clinical status and echocardiography parameters compared to the groups with a larger proportion of reduced LV wall thickness.

-An area ≥25% of LVTW<6mm that including the insertion of at least 1 muscle limits the MR improvement after CRT implantation.

-Patients with ≥50% of LV WT<6mm experienced poor outcomes 2-years post CRT implantation

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ABBREVIATIONS

Cardiac resynchronization therapy = CRT

Computed tomography = CT

Heart failure = HF

Left ventricular = LV

Left ventricular ejection fraction = LVEF

Left ventricular end-diastolic volume = LVEDV

Left ventricular end-systolic volume = LVESV

Mitral regurgitation = MR

Mitral valve = MV

Wall thickness = WT

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INTRODUCTION

Cardiac resynchronization therapy (CRT) improves mortality, morbidity and quality of life in selected heart failure (HF) patients (1; 2). Indeed, CRT implantation has been associated with left ventricular (LV) reverse remodeling and secondary mitral regurgitation (MR) improvement (1; 3). However, up to 30% of device recipients do not benefit clinically from CRT (2). Among the factors influencing the response to CRT, LV morphology and mitral valve (MV) geometry have been previously described. Indeed, LV fibrosis and MV apparatus geometry (analyzed using cardiac magnetic resonance or echocardiography respectively) have been strongly correlated with poor LV function and MR enhancements after CRT implant (3, 4-5). Nonetheless, data regarding the impact of LV myocardial analysis using computed tomography (CT) on LV and MR functions after CRT are scarce.

Dual-source CT is an ideal noninvasive modality that provides pertinent information to guide the CRT implantation procedure (6). Indeed, previous studies have demonstrated that CT can visualize the coronary venous anatomy, detect the presence of myocardial scar and evaluate the LV mechanical dyssynchrony to guide physician for an optimal LV lead pacing site (7-8). However, there is a paucity of data regarding the impact of LV wall thickness (WT) evaluated using CT on response to CRT. In this study, we sought to examine the association between LV WT and LV reverse remodeling and MR improvement after CRT in a prospective cohort.

METHODS

DESIGN OF THE STUDY. The rationale and design of the Dual-Source Computed Tomography to Improve Prediction of Response to Cardiac Resynchronization Therapy (NCT01097733) have been previously published (9). Briefly, 54 refractory HF patients with New York Heart Association (NYHA) functional class II-IV, LV ejection fraction (LVEF)

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≤35% and electrocardiographic QRS duration >120 ms were prospectively enrolled for a CRT implantation procedure between 2010 and 2014. The CT scan protocol was previously described (9). Of note, the distinction between ischemic and non-ischemic etiology was based on the medical record of each patient and especially on the history of angina/myocardial infarction and coronary angiography findings. Patients with normal coronary angiography or with minor coronary lesion (< 50% stenosis) not explaining the cardiomyopathy were classified as a non-ischemic.

After CRT implantation, patients returned for regular clinic visits at 1, 3, 6 months, and annually thereafter. At each follow-up visit, NYHA Class, global assessment, 6-minute walk distance and 12-lead ECG were assessed. At the 6-month follow-up visit, a repeat echo and assessment for CRT response was performed. Study clinical follow-up ended at 2 years. Of note, the impact of LVWT on the response to CRT was assessed among the 54 enrolled patients and the impact of MR improvement was specifically evaluated among the patients with mild to severe MR at baseline (n=38). The study protocol was approved by the institutional review board and all patients provided written informed consent.

LEFT VENTRICULAR WALL THICKNESS ANALYSIS. All CT images were retrospectively analyzed using the ADAS-VT software (Galgo Medical, Barcelona, Spain) by an experienced observer, blinded to the clinical data. The performance and the inter- and intra-observatory reproducibility of the software has been previously described (10-11). To create the model, CT images were exported in DICOM format and integrated in the software. A total of four landmarks were manually placed (center of the aortic annulus, center of the mitral annulus, LV apex and center of the tricuspid annulus). To adjust the model, the contours of the LV endocardium and epicardium were then manually drawn in 3 LV short axis slices. Then, endocardial and epicardial borders were delimited with a semiautomatic

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segmentation algorithm. Lastly, a manual adjustment of the LV endocardial and epicardial boarders was required to fit the surface to the CT images in the short-axis, two chambers and coronal planes. A 3D visualization of the LV was then created and WT was defined using a color threshold. As previously described, normal LV WT was defined as an end-diastolic WT>6mm and WT<6mm suggested reduced LV WT (9-10; 12). For quantitative analysis, the extent of total WT<6mm burden was quantified as a percentage of total LV area. In this work, 10 CT images were used to evaluate the intra- and inter-observer variance. The intraclass correlation coefficient was 0.97 (0.89-0.99) and 0.95 (0.82-0.99) for the intra-observer and inter-observer variability for the total percentage of LV WT<6mm, respectively.

Additionally, the LV was automatically segmented in 17 segments and each segment was considered with reduced WT in case of WT<6mm area location. Depending on this segmentation, the LV was divided in 3 regions: postero-lateral (segments 4-5-10-11-15-16), antero-lateral (1-6-7-12-13) and septal (2-3-8-9-14). Patients were considered to have a thinned region if there was at least 1 segment with reduced WT in each region.

Regarding the MV apparatus analysis, papillary muscles (PM) were manually tagged on DICOM images and then automatically segmented and extracted by the ADAS-VT software. Importantly, the implantation base of the PM was carefully tagged to accurately evaluate the WT below the insertion base. After this segmentation, each PM was added and superimposed on the 3D LV model. PM was considered as inserted in a reduced WT area if the majority of the PM was implanted in a region with a WT<6mm.

END POINTS. End-points included the clinical/echocardiographic response to CRT at 6-months, QRS duration decrease at 6 months, MR improvement at 6 months and the occurrence of major adverse cardiac events (MACE) during 2-years of follow-up.

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The clinical response to CRT endpoints included: 1) change in the NYHA class at 6 months; and 2) change in HF clinical status at 6 months using the patient global assessment. Of note, the global assessment score is a 7-point rating scale, allowing for the evaluation of the patient's own perspective of overall health compared with a previous point in time (13). Patients exhibited HF clinical status response in case of markedly or moderately improvement.

The echocardiographic response to CRT endpoints included: 1) change in left ventricular end-systolic volume (LVESV). LVESV response was defined as reduction in LVESV by ≥15%; 2) change in left ventricular end-diastolic volume (LVEDV). LVEDV response was defined as reduction in LVEDV by ≥10%; and 3) LVEF improvement at 6 months. LVEF response was defined as improvement in LVEF by ≥5% (14).

The intrinsic QRS durations at baseline (pre-CRT) were compared with the biventricular-paced QRS durations at 6 months; the delta QRS was defined as the intrinsic QRS duration (ms) at baseline minus the biventricular-paced QRS at 6 months.

Positive MR improvement at 6 months was defined as improvement by ≥1 class among patient with mild to severe MR at baseline. Of note, the MR was graded semi-quantitatively in an integrative fashion as none (0), trace (1), mild (2), moderate (3) or severe (4). All measurements were performed in accordance with the current guidelines (15).

For the end point of 2-year MACE, we included the composite end point of death, LV assist device implantation, cardiac transplantation, and HF hospitalization.

STATISTICAL ANALYSIS. Qualitative variables are summarized with frequencies (percentage); continuous data as mean ± standard deviation or median (interquartile range) depending on their distribution, which was assessed using the Kolmogorov-Smirnov test. Categorical variables were compared using the $\chi 2$ tests or Fisher's exact test. Continuous

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variables were compared using Student's *t*-test or the Mann-Whitney U-test for two-group comparisons. ANOVA tests or Kruskal-Wallis tests were used to compare continuous variables among three or more groups. Multivariable analysis and odds ratio (OR) was determined using logistic regression. For the purposes of the multivariable analysis, variables with p-values <0.05 in univariate analysis were included. Of note, for the predictor of response to CRT, we used the LVESV parameter to define responder and non-responder patients (responder was defined as reduction in LVESV by ≥15%). Additionally, for the predictor of MR improvement, a receiver-operator curve (ROC) analysis was used to categorize LVWT by selecting clinically-relevant cut-off, which were the closest to the optimal cut-off according to the maximum Youden's index (sensitivity + specificity). Survival rates were summarized using Kaplan–Meier estimates, and log-rank tests were used to compare groups. A p-value <0.05 was considered statistically significant. The analyses were performed with the SPSS statistical package, version 11.0 (SPSS Inc., Chicago, IL).

RESULTS

BASELINE CHARACTERISTICS. Among the 54 patients enrolled in the DIRECT study, the mean area of LV WT<6mm was 62.6±53.7 cm² per patient (30.2±19.5% of the total LV area). To assess the impact of LV WT on the response to CRT, patients were divided into 3 groups according to the percentage of LV WT<6mm related to the total LV area: ≤ 20% (low group=21 patients); 20-50% group (moderate group=21 patients) and ≥ 50% group (high group=12 patients). Of note, to define these 3 groups, we used the tertiles of total percentage of LV WT<6mm. Illustrative examples of patients with ≤ 20%; 20-50% and ≥ 50% of LV WT<6mm are shown in **Figure 1**. Baseline characteristics of the 3 groups were detailed in **Table 1**. Briefly, there was no difference regarding the age, gender, body mass index and atrial fibrillation history. All groups have a mean QRS duration > 150 ms without statistical

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difference in the QRS duration or morphology. Of note, there was a statistically increased gradient of NT-proBNP level between the 3 groups. Regarding the echocardiography parameters, ≤ 20% group had higher LVEF at baseline without difference in LVEDV or LVESV but a non-significant increase in dilated LV from the ≤ 20% to the ≥ 50% group was noted. Additionally, the low LVWT area group had thicker inter-ventricular septum. Regarding the LVWT<6mm area location, there was a significant gradual number of postero-lateral segments with reduced LVWT from the ≤ 20% to the ≥ 50% group.

Of note, supplemental baseline characteristics between patients with ischemic or non-ischemic etiology are presented in the **supplementary material** (**Table 1**). Briefly, ischemic group was significantly older with worse renal function before CRT implantation. Importantly, both groups were similar according to the echocardiographic parameters and CT analysis at baseline.

LEFT VENTRICULAR WALL THICKNESS AND RESPONSE TO CRT. At 6 months, 76%, 71% and 42% of the patients experienced an improvement in NYHA class by ≥1 in the low, moderate and high groups respectively (**Table 2**). Additionally, a majority of patients included in the low and moderate groups (80% and 65% respectively) had a significant improvement of their global assessment, whereas 42% in the ≥50% group experienced no change of worst global assessment (**Figure 2, panel A**). However, despite a high rate of clinical response in the low and moderate LV WT area group, the 6-minute walk distance was only significantly improved in the low group (**Figure 2, panel B**).

Electrocardiographic and echocardiographic response is described in **Figure 3** and **Table 2**. Compared to baseline, biventricular pacing had significantly decreased the QRS duration in the ≤ 20% group (164.0±14.3 vs. 145.7±15.3, p=0.001). In the 20-50% group, although we noted a QRS duration reduction (162.2±26.7 vs. 148.9.1±27.8, at baseline and 6-

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months respectively), this improvement was not statistically significant (p=0.140). Lastly, ≥50% group experienced no electrical remodeling, with no change in QRS duration at 6-months.

Regarding the echocardiographic response to CRT, patients in low LVWT area group have a significant improvement between baseline and 6 months in LVEF (27.2±5.7 vs. 40.6±9.5%, respectively; p<0.001) and LVESV (146.6±82.9 vs. 93.3±35.0, respectively; p=0.015). Using the responder criteria for LVESV (≥15% relative reduction), LVEDV (≥10% relative reduction), and LVEF (≥5% absolute increase), positive echocardiographic responses to CRT were observed in 86%, 52%, and 81% of patients, respectively. Patients in the moderate area group experienced only LVEF significant improvement with a positive LVEF, LVEDV and LVESV response rate of 52%, 52% and 48% respectively at 6 months. Lastly, patients with ≥ 50% of LVWT>6mm experienced a lower rate of response to CRT at 6 months with 42%, 42% and 25% of LVEF, LVEDV and LVESV improvement using the CRT response definition.

Multivariate analysis for the predictor of response to CRT (based on the LVESV reduction at 6-months) showed that the total percentage of reduced WT area was the only predictors of response to CRT (OR 1.04 (1.003-1.08), p=0.032) (**Supplemental material, Table 2**).

Additionally, the response to CRT was evaluated depending on the underlying cardiomyopathy (**Supplemental material, Table 3**). Importantly, both etiologies in the <20% group had significant LVEF improvement and LVESV reduction. In the 20-50% and >50% groups, there was no significant LVEF improvement and LV volumes reduction in both patient cohorts, i.e. with ischemic and non-ischemic cardiomyopathy. However, there is a trend toward less response in the ischemic group using the LVEF, LVEDV and LVESV criteria.

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Changes in LVEF, LVEDV and LVESV from baseline to 6 months were also evaluated depending on the location of the thinned WT in the postero-lateral, antero-lateral and septal regions. Results are presented in the **supplementary material** (**Table 4**). Briefly, only patients with normal antero-lateral region experienced significant LVEF improvement from baseline to 6 months. Similarly, there was a non-significant trend toward a higher LVEDV and LVESV reduction in patients with normal postero-lateral region.

MITRAL REGURGITATION IMPROVEMENT. Among the 54 patients, 38 (70.4%) had mild to severe MR at baseline and a total of 16 (42.1%) experienced MR improvement by ≥1 class at 6 months. Characteristics of patients with or without MR improvement were described in the **Table 3**. Importantly, no difference was recorded regarding the LV dilation in both groups. However, patients without MR improvement had significantly higher NT-pro BNP level at baseline. Interestingly, patients without MR improvement had larger LVWT<6mm area (41.5±19.4 vs. 22.4±16.1%, p=0.003) associated with a higher number of PM inserted in the reduced LV WT area. ROC analysis for total percentage of LVWT<6mm demonstrated that an optimal cut-off value of 25% differentiated patients with or without MR improvement (C-statistic of 0.77 (95%IC:0.62-0.92)) **supplementary material** (**Figure 1**). In multivariable analysis, an area ≥25% of LVWT<6mm including at least 1 PM insertion was the only predictor of no MR improvement at 6 months (OR 16.82 (95%CI:1.72-164.2), p=0.015). Illustration of PM insertion in reduced LVWT is depicted in **Figure 4, Panel A/B**.

Lastly, as described in the **Figure 4, Panel C**, patients with MR improvement had significant lower rate of basal segments with reduced WT (0.9 vs. 1.7, p=0.045), especially in the lateral location. Additionally, results showed a trend toward fewer reduced WT segments

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in mid and apical locations among the 16 patients with MR improvement. Of note, patients with MR improvement exhibited a lower rate of postero-lateral WT<6mm segments.

LEFT VENTRICULAR WALL THICKNESS AND MACE OUTCOMES. Among the 54 CRT recipients, MACE occurred in 9 (16.7%) patients after 2-years of follow-up. Among those, all experienced at least one HF hospitalization, one was subsequently implanted with a LV assist device and cardiovascular death occurred in 5 patients. None of these CRT recipients underwent heart transplantation. Of note, 4 patients who died were in the ≥ 50% group and death occurred 10.0±6.8 months after CRT implantation. First MACE occurred after a mean time of 10.9±5.9 months after CRT implantation and low and moderate area groups had higher MACE-free survival probability than the high area group (**Figure 5**).

DISCUSSION

MAIN RESULTS. Our study is amongst the first to evaluate the role of CT in quantifying the extent of LV wall thickness in prognosticating response to CRT. The main results of this study are: 1) LV WT could help to stratify the response to CRT and predicts MR improvement. 2) CRT candidates with a low percentage of LV WT<6mm (≤20%) significantly improved their clinical status and echocardiography parameters compared to the groups with a larger proportion of reduced LV wall thickness. 3) Patients without MR improvement had larger LVWT<6mm area associated with a higher number of PM inserted in the reduced LV WT area. 4) Lastly, patients with ≥ 50% of LV WT<6mm were at higher risk of MACE.

LEFT VENTRICULAR MORPHOLOGY AND RESPONSE TO CRT. Among the factors influencing the response to CRT, LV myocardial morphology has been

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investigated in HF patients. Indeed, among 97 non ischemic patients, those with midwall fibrosis detected by CMR via late gadolinium enhancement were less likely to exhibit LV reverse remodeling (16). Similarly, Taylor *et al*. evaluated the impact of CMR among 89 CRT candidates and showed that LV lead deployment over non-scarred segments was associated with better response and clinical outcomes after CRT (5). However, data regarding LV CT analysis and CRT benefit are unclear (9). Variability in the measurement of WT (i.e. end-diastole or end-systole) can impact it predictive value. WT measured during maximal systolic thickening could possibly under-estimate the real burden of reduced WT area compared to end-diastol measurement. Indeed, a recent editorial has suggested that the quantification of reduced WT is more accurate during the end-diastole (12). In our study, we observed a graded enhanced response to CRT with increasing WT. Similarly, WT as a marker for adverse events in CRT recipients has been evaluated among the patients enrolled in the MADIT-CRT study (17). In this work, relative WT at baseline was the best echocardiographic predictor for ventricular tachyarrhythmia events compared with commonly used echocardiographic measurements and rightfully suggested that WT can mirror the extent of LV fibrosis and scarring on one hand and the extent of the remodeling process on the other hand (17). In the current study, advanced deleterious remodeling process could explain poor response to CRT in patients with a larger baseline area of WT<6mm. Indeed, moderate (20-50%) and high (≥50%) groups had both numerical higher LVEDV and LVESV at baseline compared to the low area patients. However, the moderate group experienced more favorable response to CRT than the high group and higher fibrosis and more scar response in these patients may explain that they less likely experienced LV reverse remodeling. Notably, we found that patients within the ≥50% group had no QRS reduction after CRT compared to baseline ECG, thereby explaining the LV function improvement, as previously described (18).

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LEFT VENTRICULAR WALL THICKNESS AND MITRAL REGURGITATION IMPROVEMENT AFTER CRT. In our current study we observed that PM insertion site is probably crucial. Indeed, patients without MR improvement had larger LVWT<6mm area associated with a higher number of PM inserted in the reduced LV WT area. This result possibly highlighted the critical link between the LV morphology at the site of MV apparatus insertion and suggests that normal WT could promote a MV apparatus remodeling after CRT. Our result is supported by previous work that demonstrated that the lack of scar at the PM insertion sites using echocardiography was associated with MR improvement (19). Lastly, we observed that patients without MR improvement had larger area of reduced WT in the basal segments. Similarly, previous study showed that CRT enhanced the mitral annular deformation by resynchronizing LV basal segments (20). Consequently, normal WT adjacent to the MV annulus could potentially improve mitral annulus deformation in CRT recipients, leading to a decrease of the annular diameter.

COMPUTED TOMOGRAPHY AS A TOOL TO PREDICT OUTCOMES IN CRT CANDIDATES. In our study we show that patient with ≥50% area of LVWT<6mm had poor 2-years outcomes compared to ≤20% and 20-50% groups. Of note, this result is consistent with a previous study that demonstrated that CRT patients with low relative WT at baseline had significantly higher risk for ventricular arrhythmias and death (17). Additionally, advanced deleterious remodeling process could explain the worse outcomes in patients with a larger area of WT<6mm. Indeed, we showed that this subgroup of patients had lower LVEF and higher NT-pro BNP level at baseline.

CLINICAL IMPLICATIONS. These results bring important information and could be helpful in daily clinical practice. First, in contrast to other cardiac imaging technique, CT

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provides some benefit. Indeed, compared to CMR, CT can be much more easily and quickly performed in patients previously implanted with a device (pacemaker or implantable cardioverter defibrillator) and who require an up-grade to CRT. Additionally, echocardiography measurement requires a relatively high image quality, depends more heavily on operator experience and cannot provide an extensive description of the WT compared to CT. Second, LV WT using CT analysis could stratify the response to CRT in HF patients, depending on the total area with WT<6mm (≤20%; 20-50% and ≥50%) and may assist the physician to optimize the HF management. Indeed, patient with low or moderate percentages of LV WT<6mm (≤20% and 20-50%) experience few MACE events during 2-years of follow-up compared to patients with a larger area of LV WT<6mm, who exhibited 33.3% of cardiac death. Physicians should consequently carefully manage this last group associated with probably low chance of long-term CRT benefit expected but only temporary HF status stabilization.

LIMITATIONS. The limited sample size makes our study hypotheses generating, and will require validation in larger studies. The relationship between wall thickness and fibrosis is difficult to define and will require evaluation through studies using multi-modality imaging (i.e. CMR and CT). Lastly, due to the small number of MACE events, we were not able to provide a multivariate analysis to evaluate the impact WT on the outcomes.

CONCLUSION

LV WT evaluated using cardiac CT could help to stratify the response to CRT and MR improvement in HF patients. This needs to be further validated in a larger cohort of patients receiving CRT.

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FIGURES

Figure 1: Example of left ventricular wall thickness segmentation using the ADAS software in patients with ≤20%, 20-50% and ≥50% of LV WT<6mm, respectively. Panel A: Antero-posterior view; Panel B: Postero-anterior view; Panel C: Lateral view; Panel D: Inferior view.

Figure 2: Clinical response to CRT from baseline to 6 months. Panel A: Global assessment at 6 months; Panel C: 6-minute walk distance evolution between baseline and 6 months.

Figure 3: Electrocardiographic and echocardiographic response to CRT from baseline to 6 months. Panel A: QRS duration change from baseline to 6 months. Panel B: Individual changes in LVEF from baseline to 6 months. Panel C: Change in LVEDV and LVESV from baseline to 6 months.

LVEF=Left ventricular ejection fraction; LVESV=Left ventricular end-systolic volume; LVEDV=Left ventricular end-diastolic volume.

Figure 4: Panel A and B Illustrative examples of WT segmentation and PM insertion. Star=Anterior PM insertion; Arrow=Posterior PM insertion. Panel A: patient with 45% of LVWT<6mm and PM insertion in normal WT area who experienced MR improvement at 6 months. Panel B: patients with 46% of LVWT<6mm and posterior PM inserted in reduced WT area without MR improvement. **Panel C: LV segmentation and location of each reduced WT segments in patient with or without MR improvement.**

MR=Mitral regurgitation; WT=Wall thickness

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Figure 5: MACE free survival probability.

MACE=Major adverse cardiac event.

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Table 1: Baseline characteristics

ACEI=Angiotensin-converting enzyme inhibitor; ARB=Angiotensin II receptor blocker; ICD=Implantable cardioverter defibrillator; LBBB=Left bundle branch block; LV=Left ventricular; LVEF=Left ventricular ejection fraction; LVEDV=Left ventricular end-diastolic volume; LVESV=Left ventricular end-systolic volume; NT-proBNP=N-terminal pro-brain natriuretic peptide; RBBB=Right bundle branch block; WT=Wall thickness.

	≤ 20% **(n=21)**	**20 – 50%** **(n=21)**	**≥ 50%** **(n=12)**	**p Value**
Computed tomography analysis				
-LV area with WT<6mm, cm²	9.8 (4.4-16.4)	34.9 (24.9-43.3)	55.4 (53.2-59.9)	**<0.001**
-Postero lateral LV segments with WT<6mm	1.0 (0.0-2.0)	2.0 (1.0-3.0)	4.0 (2.5-4.5)	**<0.001**
-Antero leteral LV segments with WT<6mm	0.0 (0.0-1.0)	2.0 (1.0-2.0)	3.0 (1.5-3.0)	**<0.001**
Age, yrs	63.1±10.4	63.2±13.5	60.7±10.1	0.810
Ischemic cardiomyopathy	8 (38.1)	8 (38.1)	4 (33.3)	0.956
Male gender	14 (66.7)	17 (80.9)	9 (75.0)	0.570
Body mass index, km/m²	30.9±6.8	27.5±5.2	30.0±3.9	0.148
Hypertension	12 (57.1)	9 (42.9)	6 (50.0)	0.651
Diabetes mellitus	9 (42.9)	3 (14.3)	1 (8.3)	**0.034**
Atrial fibrillation	4 (19.0)	1 (4.8)	3 (25.0)	0.227
Previous device				
-Pacemaker	3 (14.3)	1 (4.8)	0 (0)	0.269
-ICD	6 (28.6)	7 (33.3)	10 (83.3)	**<0.001**

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NYHA, functional class				0.556
-II	3 (14.3)	5 (23.8)	1 (8.3)	
-III	17 (80.9)	16 (76.2)	11 (91.7)	
-IV	1 (4.8)	0 (0)	0 (0)	
6-minute walk distance, m	268.3±130.7	341.1±116.9	276.1±131.7	0.177
Baseline medication				
-Beta blockers	20 (95.2)	19 (90.5)	11 (91.7)	0.833
-ACEI/ARB	13 (61.9)	18 (85.7)	11 (91.7)	0.076
-Spironolactone	8 (38.1)	5 (23.8)	7 (58.3)	0.141
-Diuretics	13 (61.9)	13 (61.9)	10 (83.3)	0.381
Electrocardiogram				
-Intrinsic QRS duration, ms	164.0±14.3	162.2±26.7	152.7±20.6	0.346
-QRS morphology				0.559
-LBBB	16 (76.2)	16 (76.2)	8 (66.6)	
-RBBB	1 (4.8)	2 (9.5)	2 (16.7)	
-Undetermined BBB	1 (4.8)	2 (9.5)	2 (16.7)	
-Paced QRS	3 (14.3)	1 (4.8)	0 (0)	
Laboratory parameters				
-Creatinine, mg/dL	1.0±0.9	1.1±0.9	1.1±1.0	0.416
-NT-proBNP, pg/mL	361.0 (188.2-1113.0)	908.0 (630.7-1738.0)	1730.0 (1179.5-3438.5)	**<0.001**
Echocardiography				
-LVEF, %	27.2±5.7	26.4±6.8	21.2±6.7	**0.031**
-LVEDV, ml	208.3±93.0	235.7±96.2	265.4±81.8	0.149
-LVESV, ml	146.6±82.9	172.5±79.3	202.6±69.4	0.145
-Left atrial diameter, mm	41.1±6.6	44.5±5.7	45.2±4.2	0.082

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-Interventricular septum, mm	10.6±1.3	9.4±1.5	9.4±1.9	**0.036**
-Posterior wall thickness, mm	10.4±2.3	10.3±2.0	10.0±1.7	0.836
-Mitral regurgitation, class				0.490
-I	8 (38.1)	7 (33.3)	1 (8.3)	
-II	9 (42.9)	7 (33.3)	4 (33.3)	
-III	3 (14.3)	4 (19.0)	6 (50.0)	
-IV	1 (4.8)	3 (14.3)	1 (8.3)	
LV lead location				
-Non-apical location	19 (90.5)	21 (100)	10 (83.3)	0.190
-Postero-lateral location	14 (66.7)	16 (76.2)	12 (100)	0.084
Biventricular pacing at 6 months, %	99.0 (98.0-99.0)	99.0 (96.5-99.0)	98.0 (96.2-99.0)	0.392

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Table 2: Echocardiographic and clinical response to CRT

LVEF=Left ventricular ejection fraction; LVEDV=Left ventricular end-diastolic volume; LVESV=Left ventricular end-systolic volume.

Group	Parameters	Baseline	6 months	Change	p value	Response definition	Response rate at 6 months (%)
≤ 20% (n=21)	LVEF, %	27.2±5.7	40.6±9.5	+ 13.5±8.0	**<0.001**	≥5% absolute increase	**86% (n=18)**
	LVEDV, ml	208.3±93.0	157.3±54.2	- 14.6±25.6	0.100	≥10% relative reduction	**52% (n=11)**
	LVESV, ml	146.6±82.9	93.3±35.0	- 28.6±25.2	**0.015**	≥15% relative reduction	**81% (n=17)**
	NYHA I/II/III/IV, %	0/14/81/5	30/50/20/0	+ 1.0±0.7	**<0.001**	≥1 class improvement	**76% (n=16)**
20 – 50% (n=21)	LVEF, %	26.4±6.8	31.3±7.8	+ 4.9±5.6	**0.036**	≥5% absolute increase	**52% (n=11)**
	LVEDV, ml	235.7±96.2	202.7±70.8	- 5.6±35.4	0.236	≥10% relative reduction	**52% (n=11)**
	LVESV, ml	172.5±79.3	140.5±61.4	- 10.8±34.3	0.173	≥15% relative reduction	**48% (n=10)**
	NYHA I/II/III/IV, %	0/24/76/0	23/48/29/0	+ 0.7±0.7	**0.004**	≥1 class improvement	**71% (n=15)**
≥ 50% (n=12)	LVEF, %	21.2±6.7	24.2±5.4	+ 3.1±4.1	0.230	≥5% absolute increase	**42% (n=5)**
	LVEDV, ml	265.4±81.8	246.9±69.8	- 5.6±21.6	0.557	≥10% relative reduction	**42% (n=5)**
	LVESV, ml	202.6±69.4	190.9±58.6	- 5.5±23.1	0.669	≥15% relative reduction	**25% (n=3)**
	NYHA I/II/III/IV, %	0/8/92/0	17/42/33/8	+0.6±0.9	**0.038**	≥1 class improvement	**42% (n=5)**

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Table 3 Baseline characteristics between patients with or without MR improvement

ACEI=Angiotensin-converting enzyme inhibitor; ARB=Angiotensin II receptor blocker; ICD=Implantable cardioverter defibrillator; LBBB=Left bundle branch block; LV=Left ventricular; LVEF=Left ventricular ejection fraction; LVEDV=Left ventricular end-diastolic volume; LVESV=Left ventricular end-systolic volume; NT-proBNP=N-terminal pro-brain natriuretic peptide; RBBB=Right bundle branch block; WT=Wall thickness.

	MR improvement by ≥1 class (n=16)	**No MR improvement (n=22)**	**p Value**
Age, yrs	59.5±10.1	65.7±10.2	0.073
Male gender	12 (75.0)	16 (72.2)	0.829
Ischemic cardiomyopathy	5 (31.2)	8 (36.4)	0.553
Body mass index, km/m²	28.3 (23.5-34.4)	27.4 (26.0-30.6)	0.657
Hypertension	4 (25.0)	12 (54.5)	0.137
Diabetes mellitus	1 (8.3)	4 (33.3)	0.374
Atrial fibrillation	2 (12.5)	4 (18.2)	0.981
NYHA, functional class			0.425
-II	4 (25.0)	3 (13.6)	
-III	12 (75.0)	19 (86.4)	
-IV	0 (0)	0 (0)	
Baseline medication			
-Beta blockers	15 (93.7)	19 (86.4)	0.624

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-ACEI/ARB	10 (62.5)	17 (77.3)	0.471
-Spironolactone	6 (37.5)	10 (45.4)	0.875
-Diuretics	10 (62.5)	18 (81.8)	0.267
Electrocardiogram			
-QRS duration, ms	171.5±25.6	162.7±20.7	0.251
-LBBB morphology	11 (68.7)	14 (63.6)	0.985
Laboratory parameters			
-Creatinine, mg/dL	1.0±0.2	1.1±0.2	0.460
-NT-proBNP, pg/mL	813.0 (365.5-1243.5)	1651 (1100.0-3248.0)	**0.007**
Echocardiography			
-LVEF, %	26.2±7.0	23.5±7.4	0.268
-LVEDV, ml	246.8±90.2	241.6±106.0	0.873
-LVESV, ml	167.0 (124.0-251.0)	157.0 (107.2-206.0)	0.477
-Left atrial diameter, mm	45.9±4.9	43.2±6.2	0.144
-Inter ventricular septum, mm	9.7±1.7	9.8±2.2	0.867
-Post wall thickness, mm	9.5±2.5	10.1±1.5	0.428
-Mitral regurgitation, class			0.547
-II	10 (62.5)	10 (45.5)	
-III	4 (25.0)	9 (40.9)	
-IV	2 (12.5)	3 (13.6)	
LV computed tomography analysis			
-Total of LV WT<6mm, %	22.4±16.1	41.5±19.4	**0.003**
-Papillary muscle inserted in LV WT<6mm			
-0	13 (81.3)	6 (27.3)	**0.004**
-1	3 (18.7)	14 (63.6)	

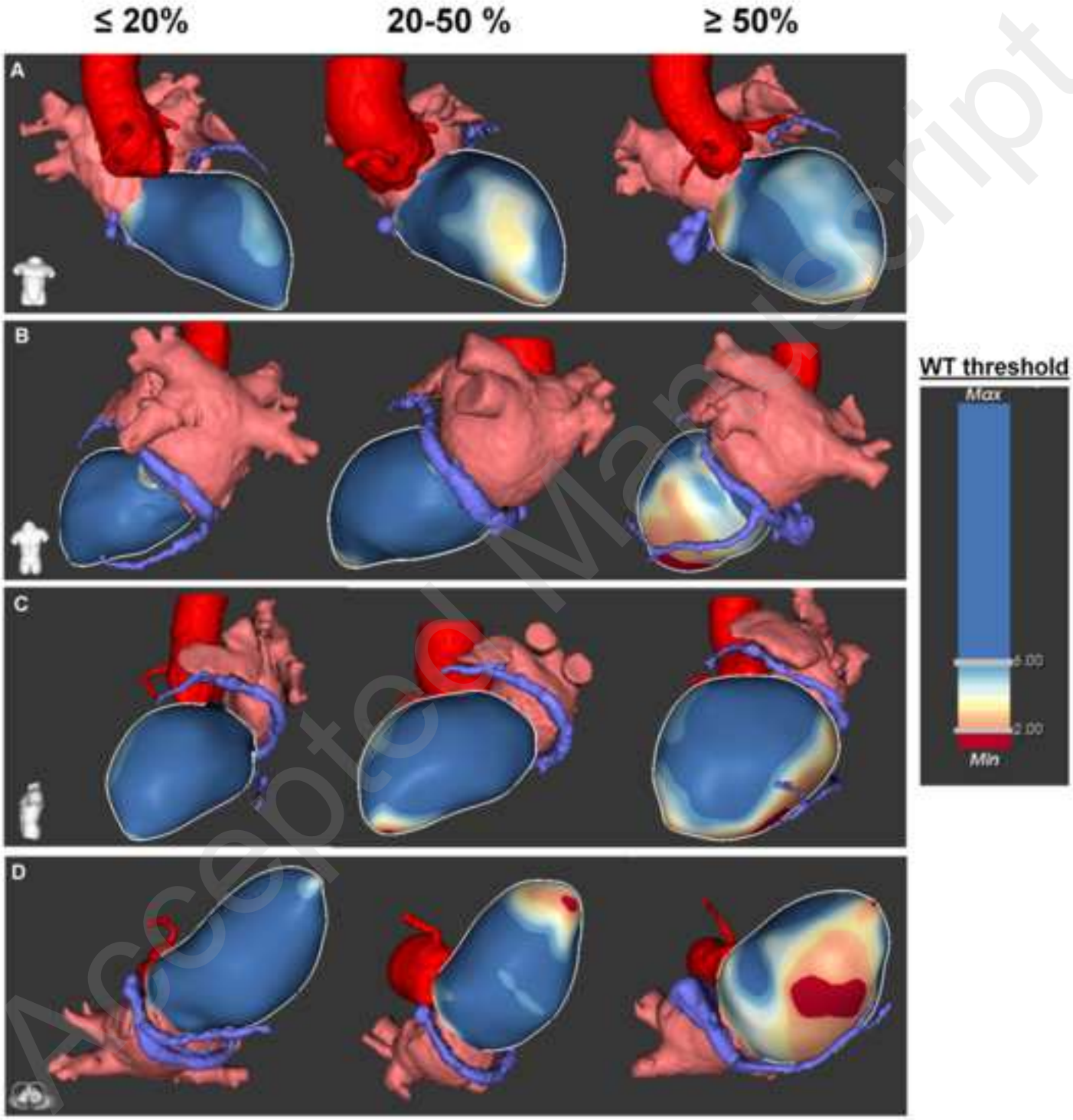
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-2	0 (0)	2 (9.1)	
-Posterior MV pillar	3 (100)	13 (59.1)	**0.031**
-Anterior MV pillar	0 (0)	5 (22.7)	0.061
LV lead location			
-Non-apical location	15 (93.7)	19 (86.4)	0.624
-Postero-lateral location	14 (87.5)	21 (95.4)	0.562
Biventricular pacing at 6 months, %	99.0 (98.0-99.0)	98.0 (96.7-99.0)	0.388
Bi-ventricular pacing QRS duration at 6 months, ms	155.3±22.8	152.1±21.1	0.664

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FIGURE 1

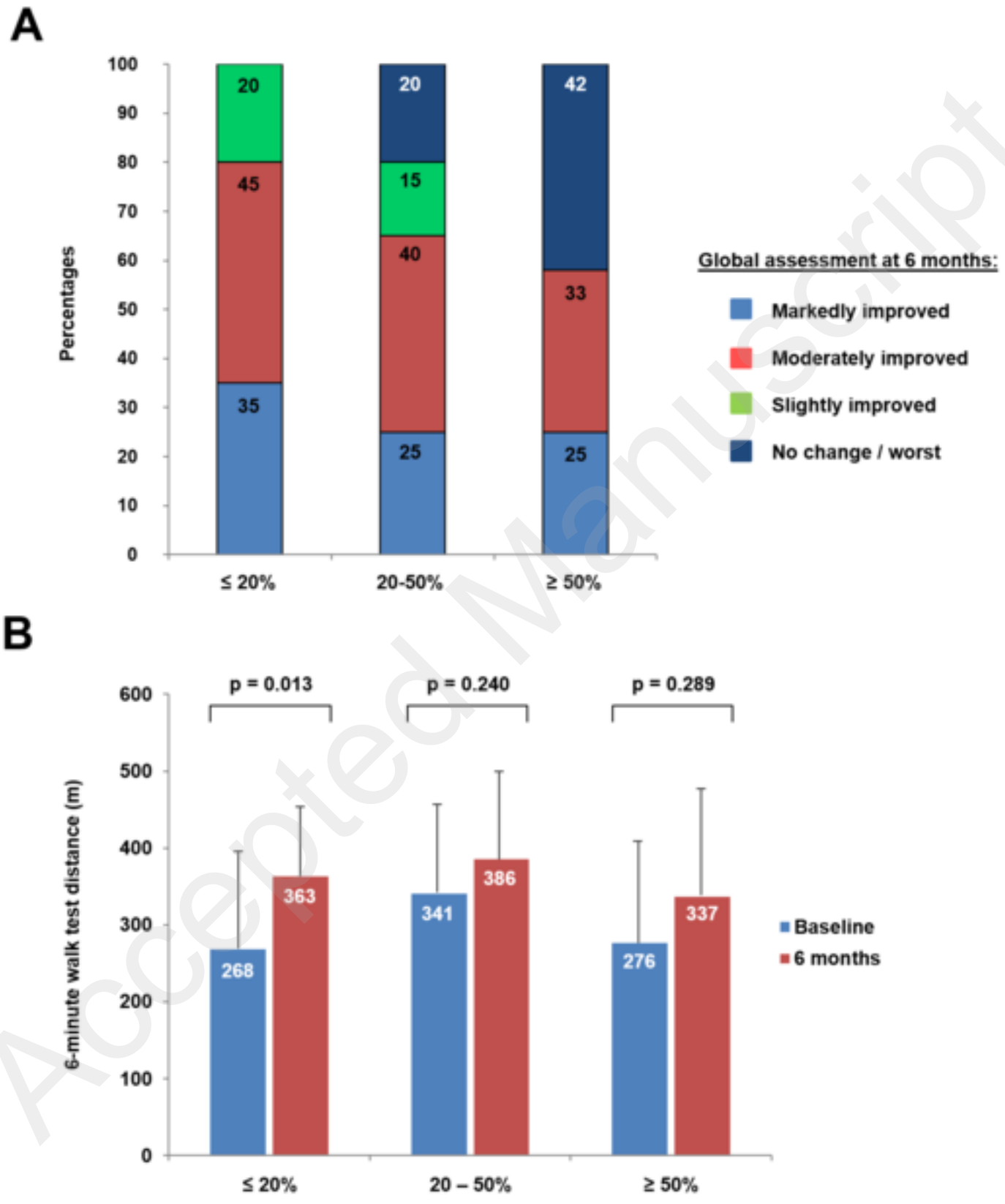
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FIGURE 2

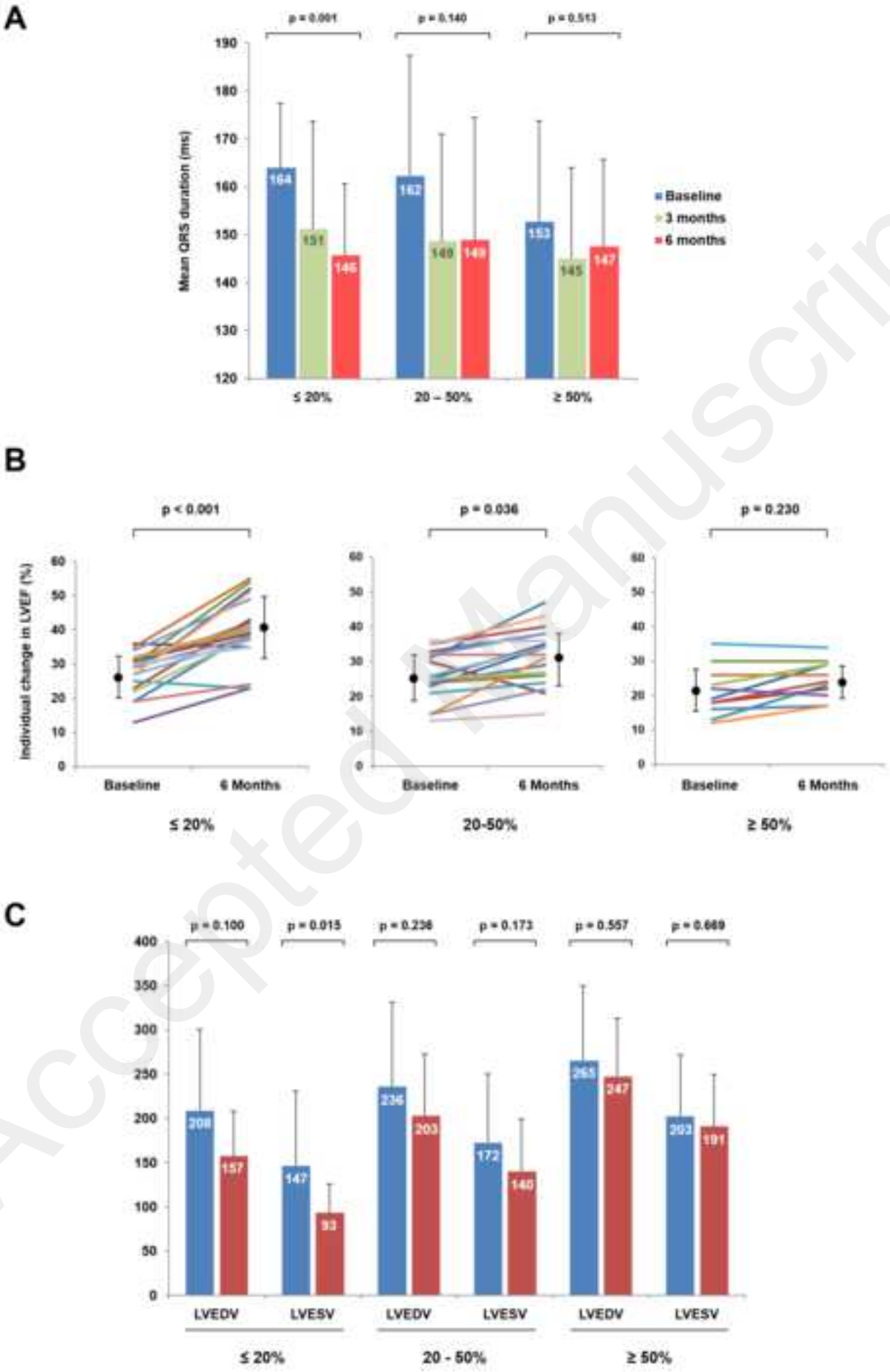
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FIGURE 3

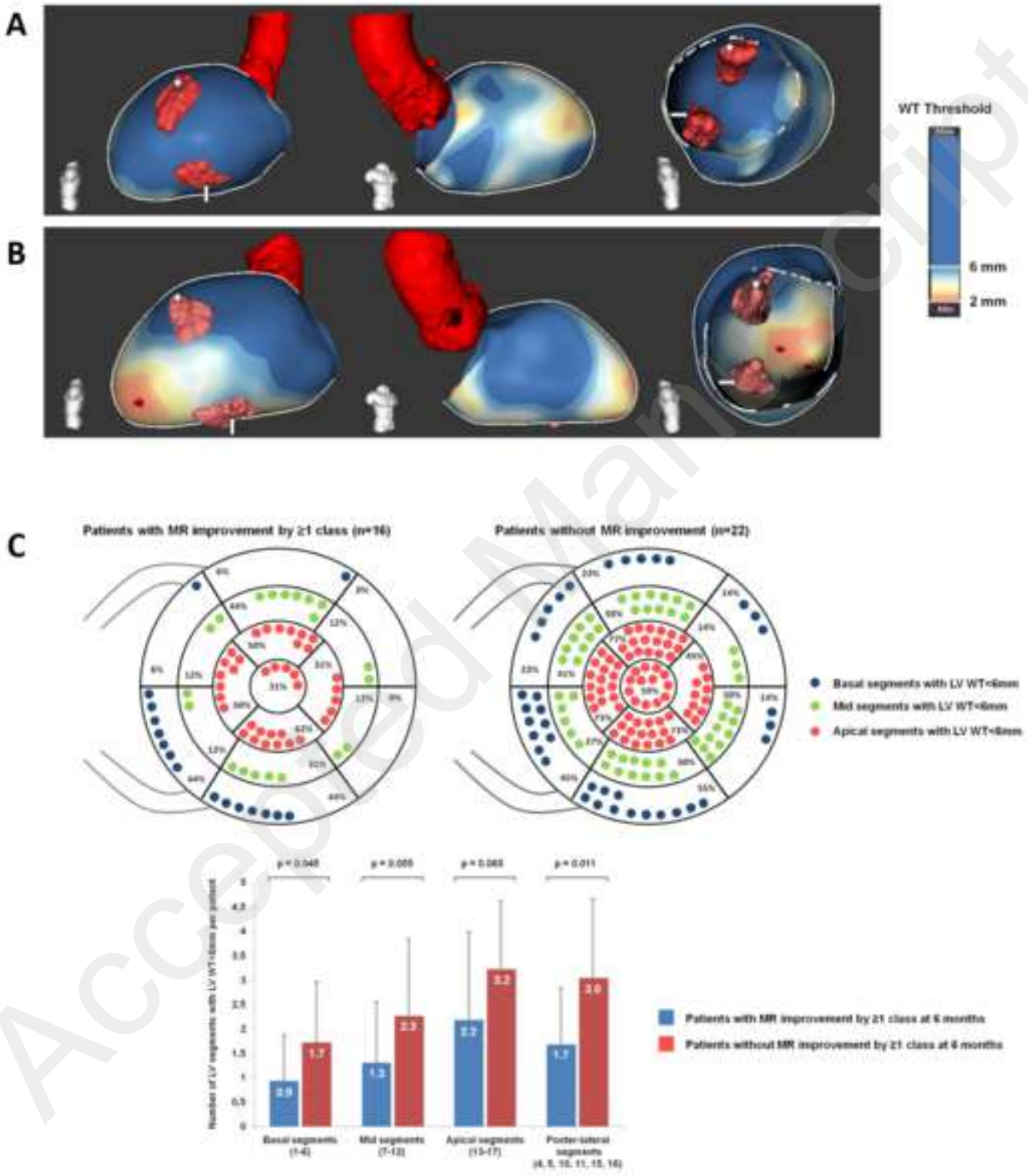
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FIGURE 4

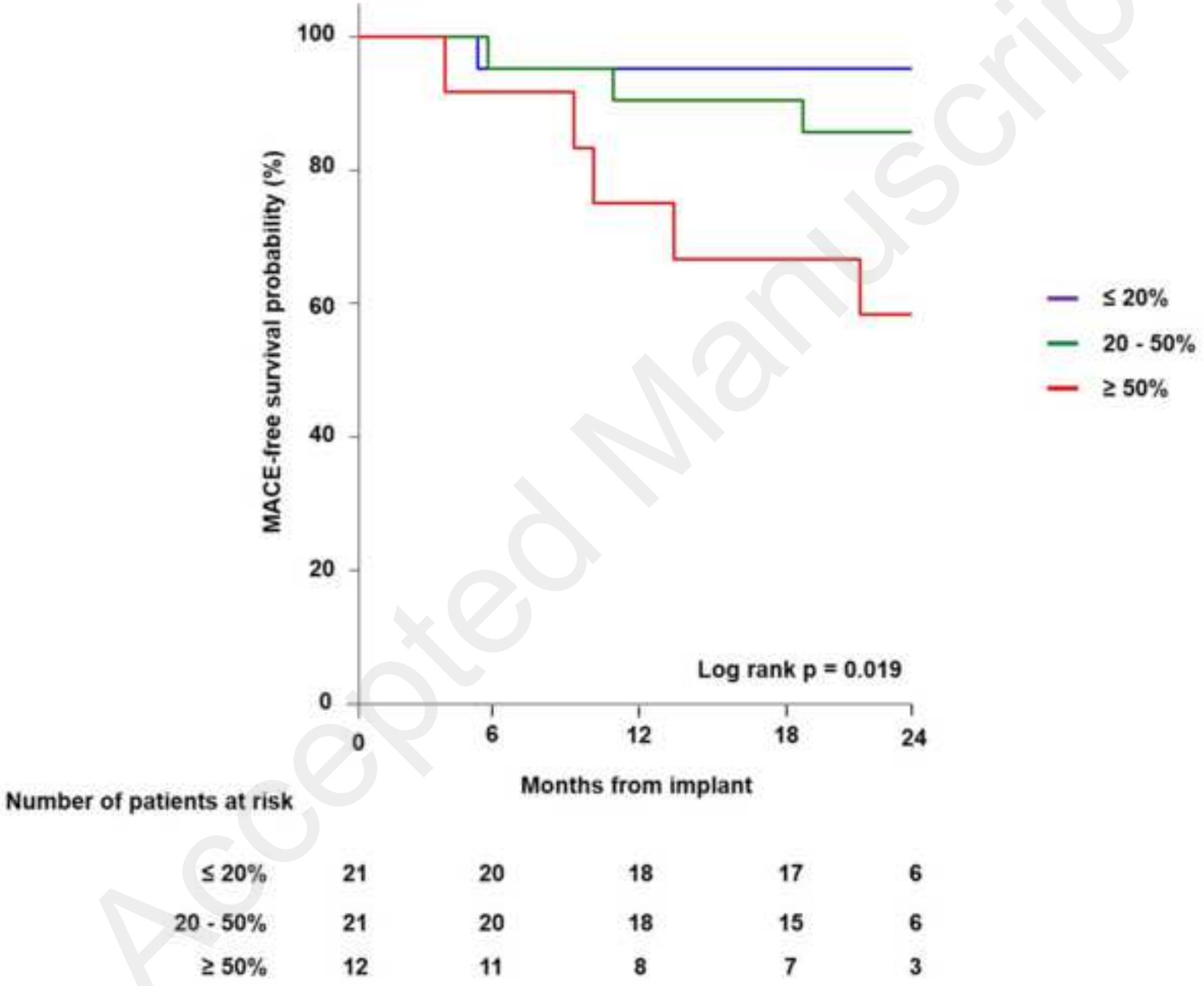
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FIGURE 5

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