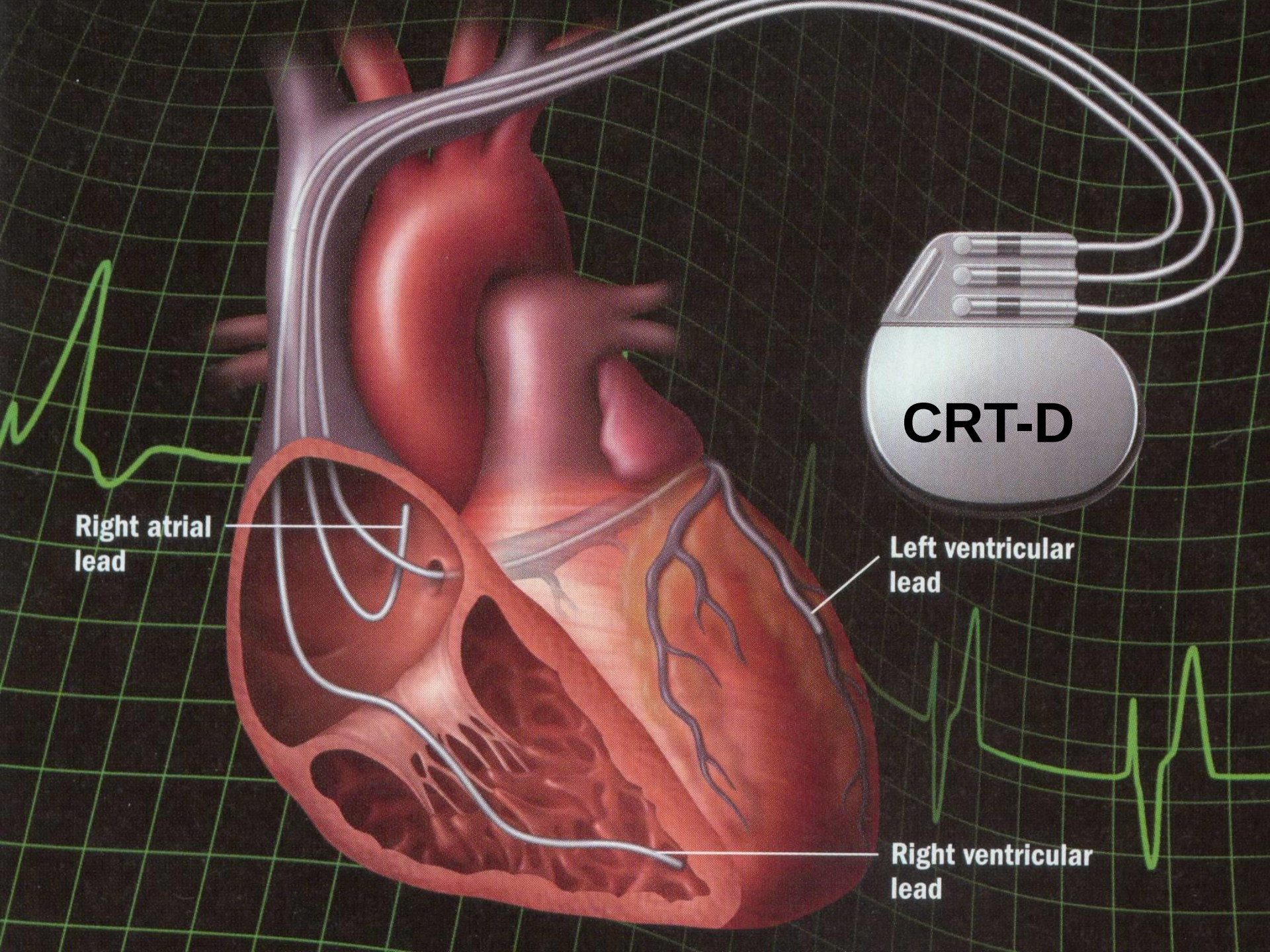
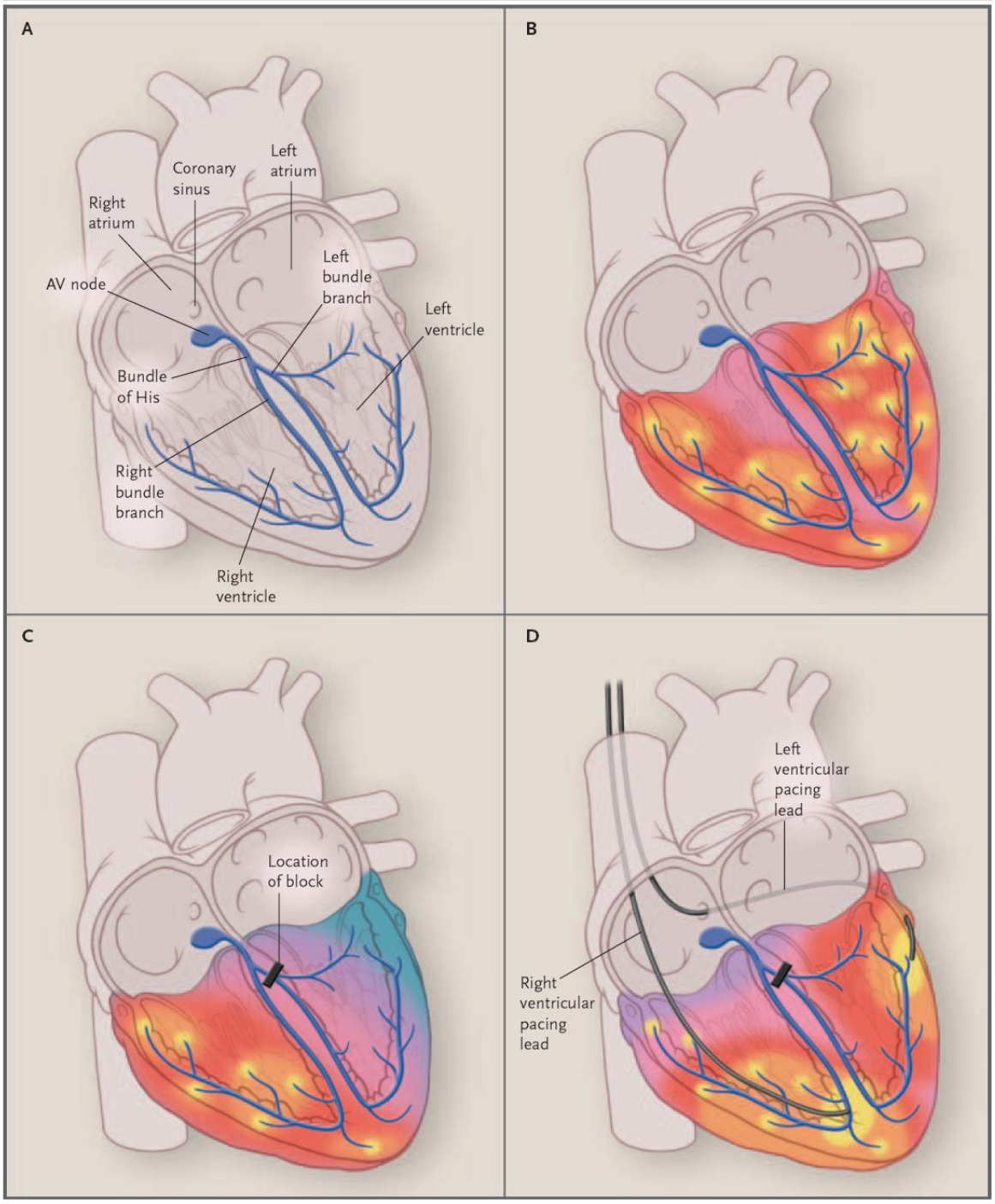
Who is the Ideal Candidate for CRT?
MADIT-CRT Trial

고신의대
차태준

MADIT-CRT

CARDIAC RESYNCHRONIZATION THERAPY


CRT-D
Right atrial lead
Left ventricular lead
Right ventricular lead

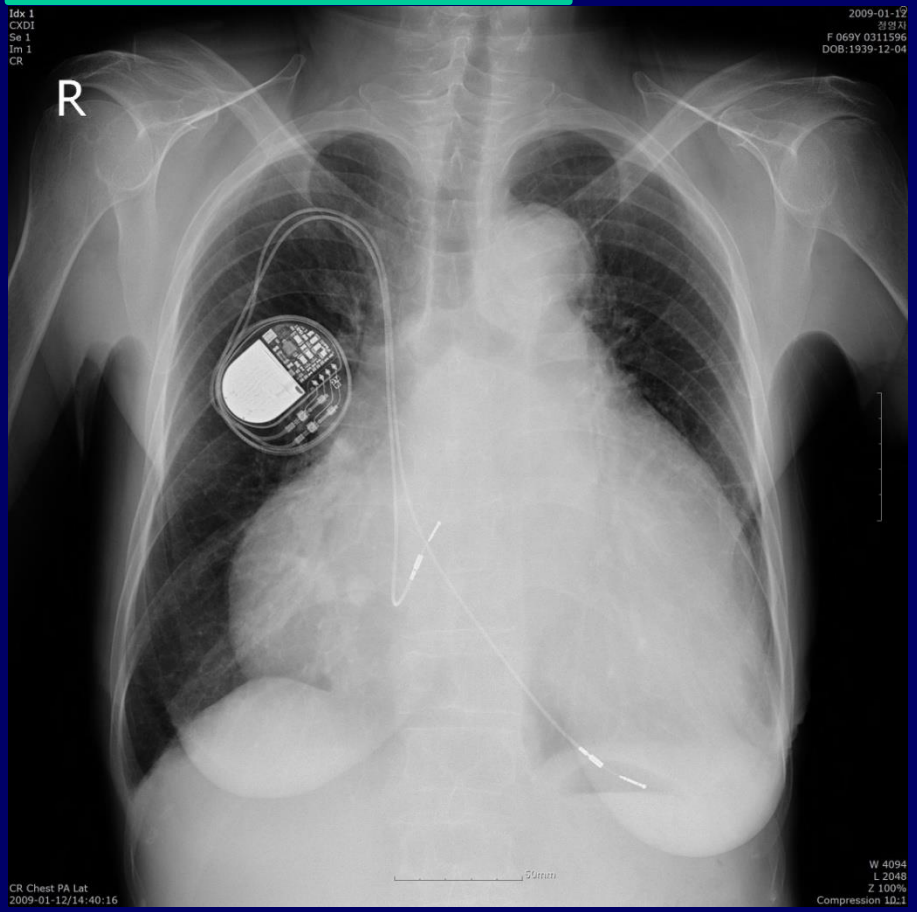

A
Coronary sinus
Left atrium
Right atrium
AV node
Left bundle branch
Left ventricle
Bundle of His
Right bundle branch
Right ventricle
B
C
Location of block
D
Left ventricular pacing lead
Right ventricular pacing lead

Case: Patient information

- Chief complaint: Dyspnea aggravation for several months
- Present illness:
  - 03': High BP & Hypertensive nephropathy diagnosed
    - HD start
  - 05': Sick Sinus Syndrome was diagnosed
    - DDD type pacemaker Implantation
  - 07' May: AF was diagnosed
    - Pacemaker mode change
  - 08' Feb.: DOE aggravation
    - DC cardioversion, Mode change to DDD
  - 09' Jan.: dyspnea aggravation
- Past history
  - DM (-), BP (+), stage IV chronic kidney disease on hemodialysis
- Social history
  - Smoking (-), alcohol (-)

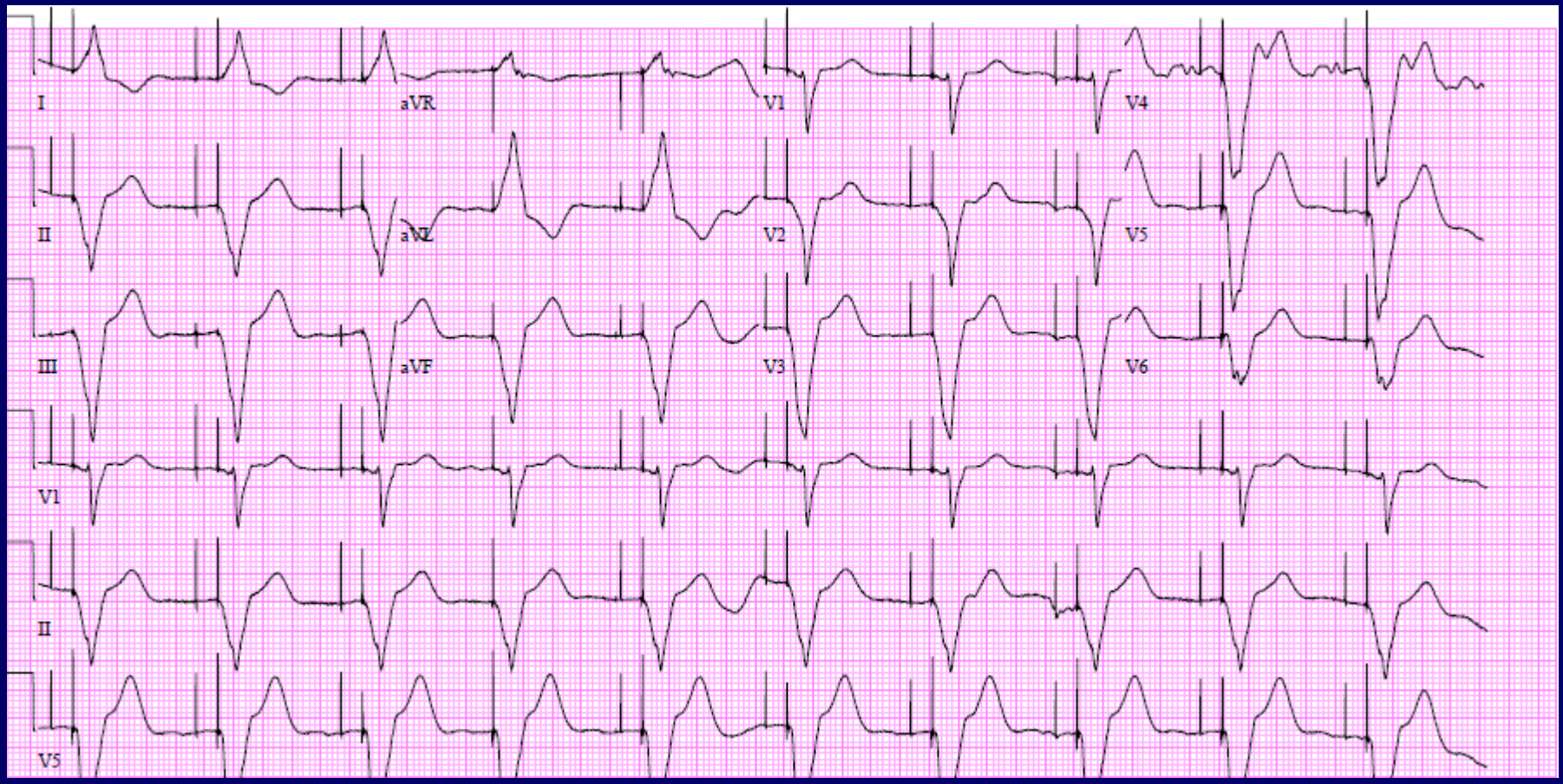
Initial CPA

09.01.12	CT ratio: 82%

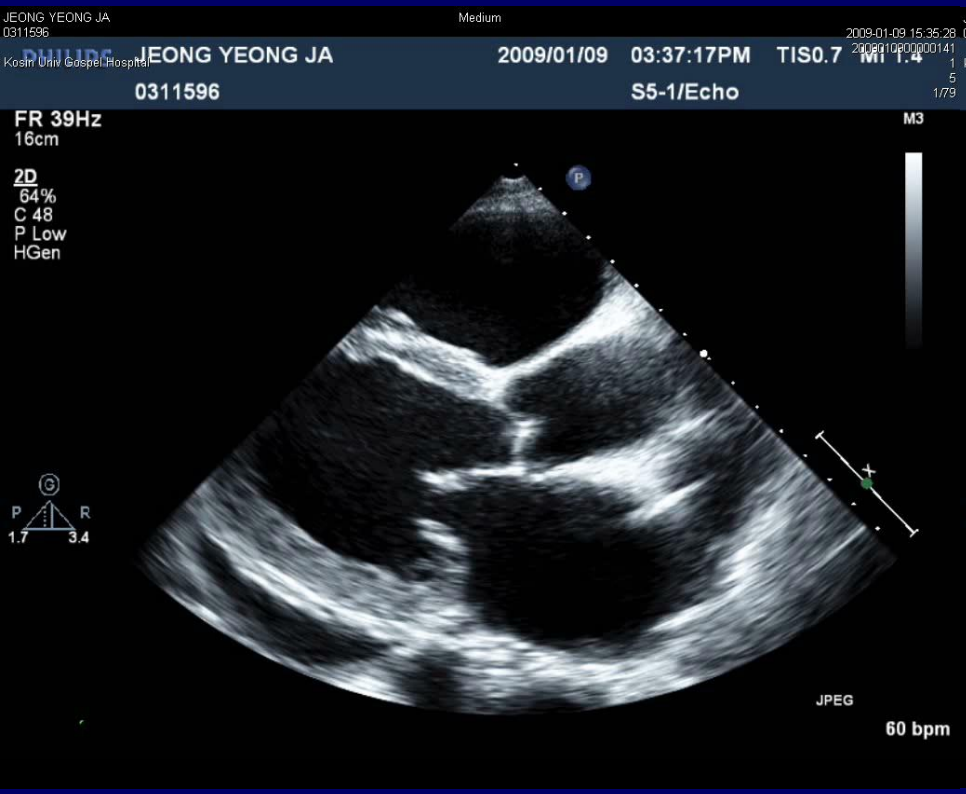


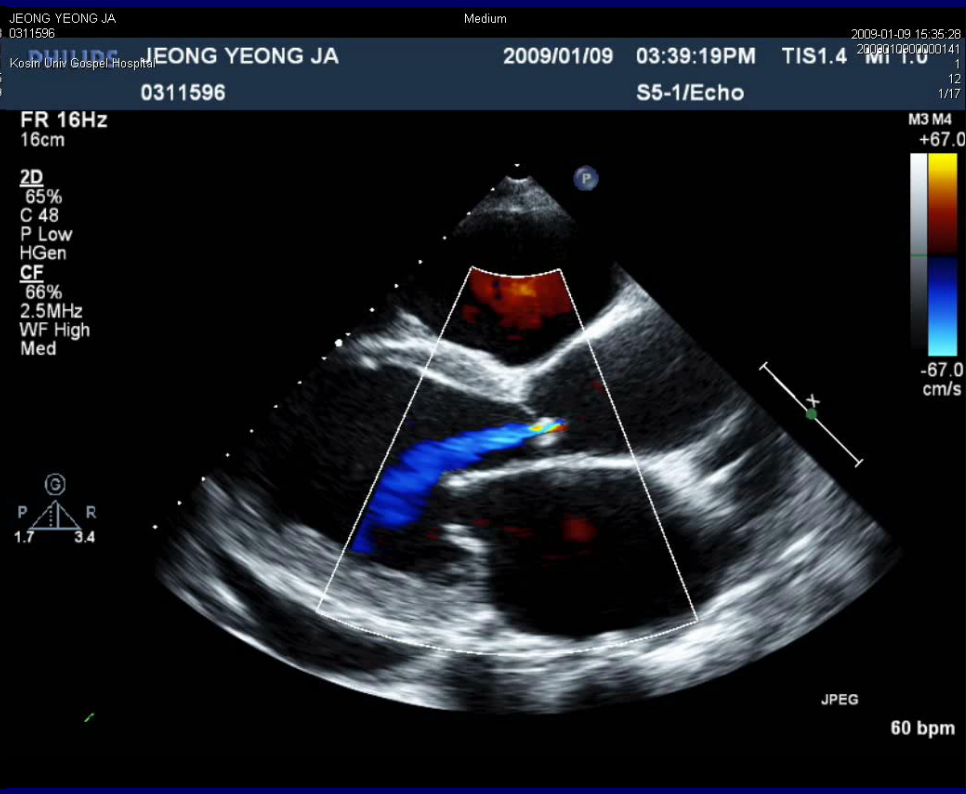
Initial ECG

09.01.12	QRS duration: 238ms

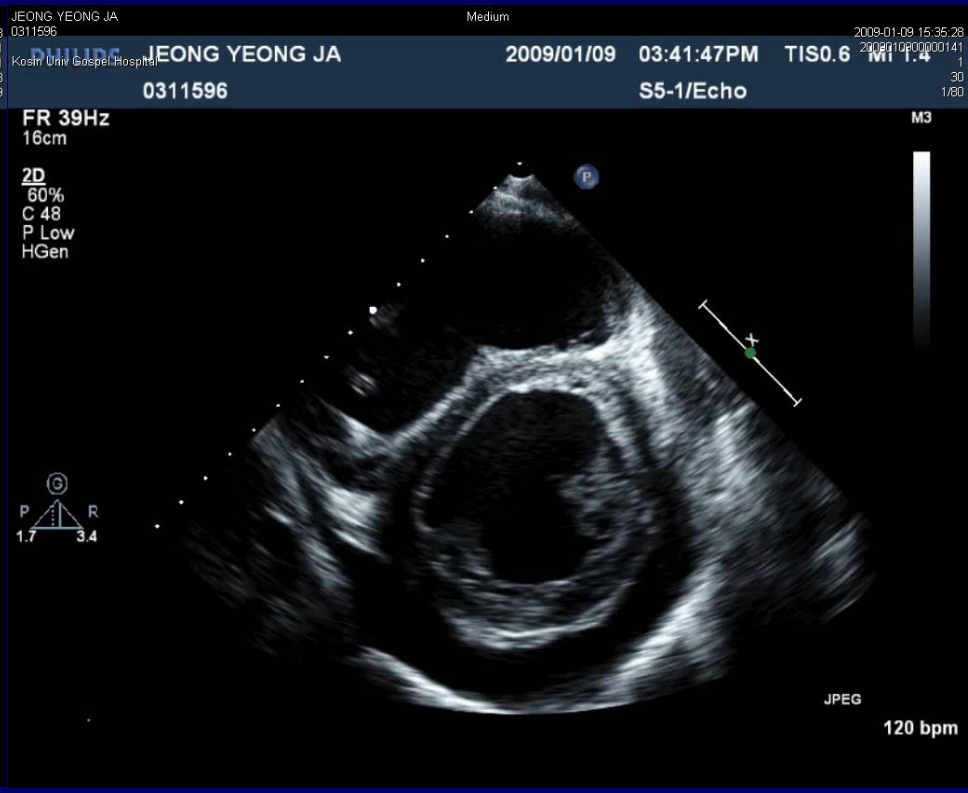


Initial Echo

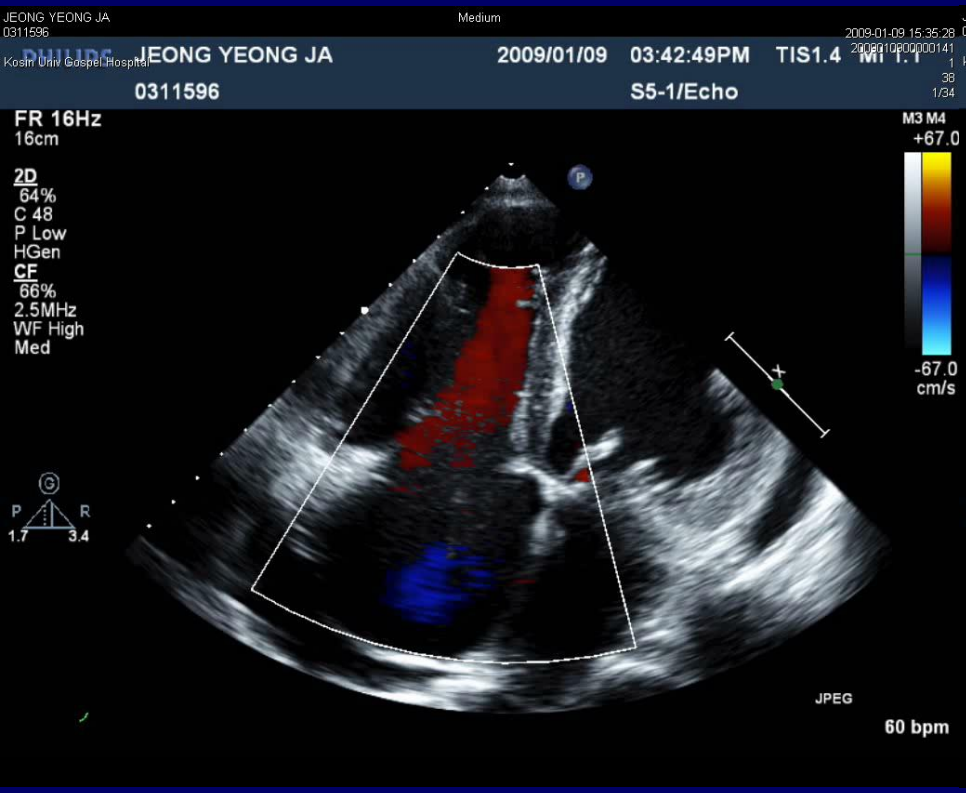


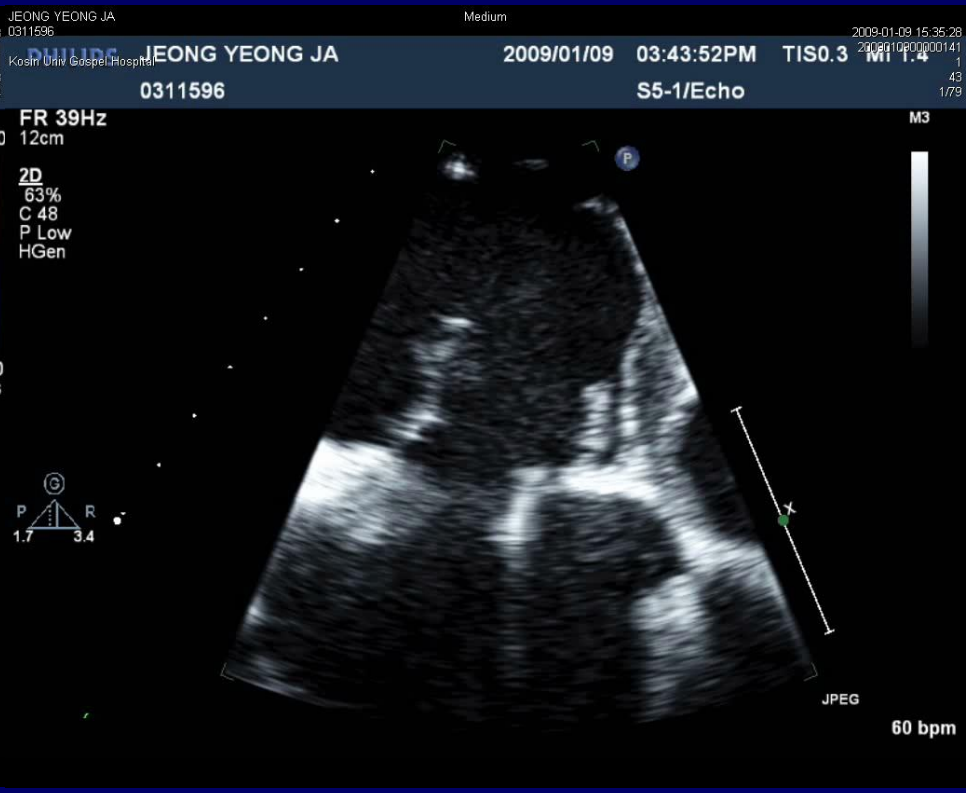


Initial Echo

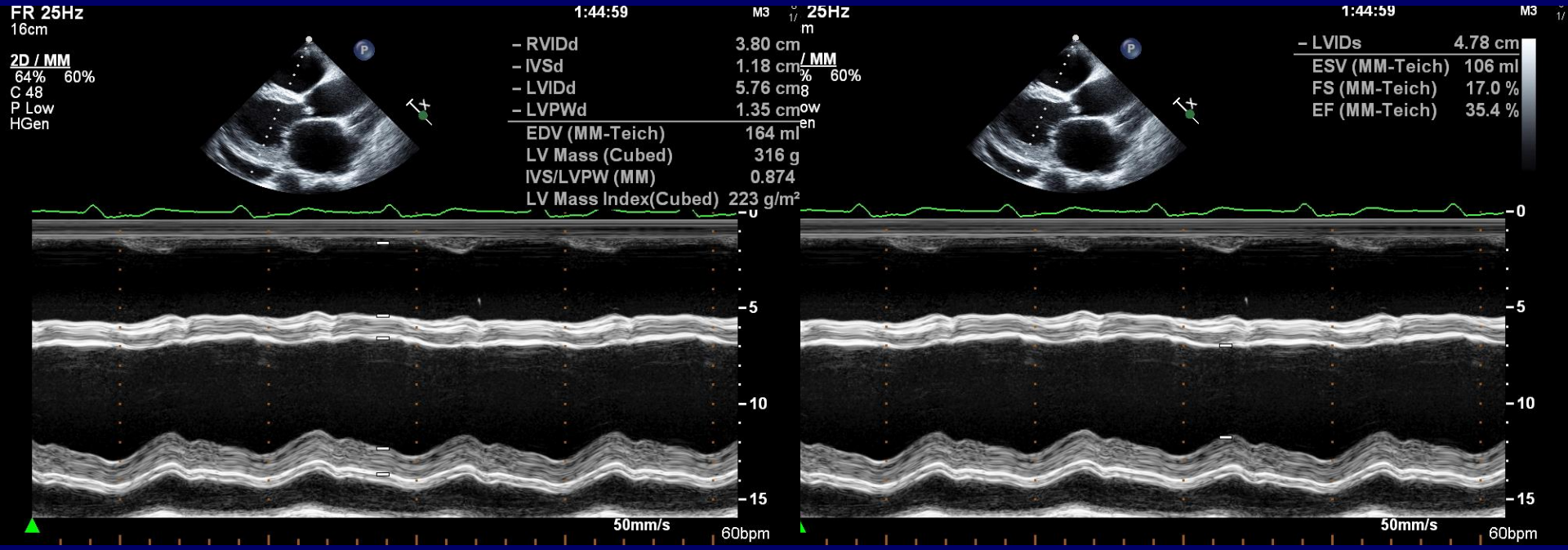


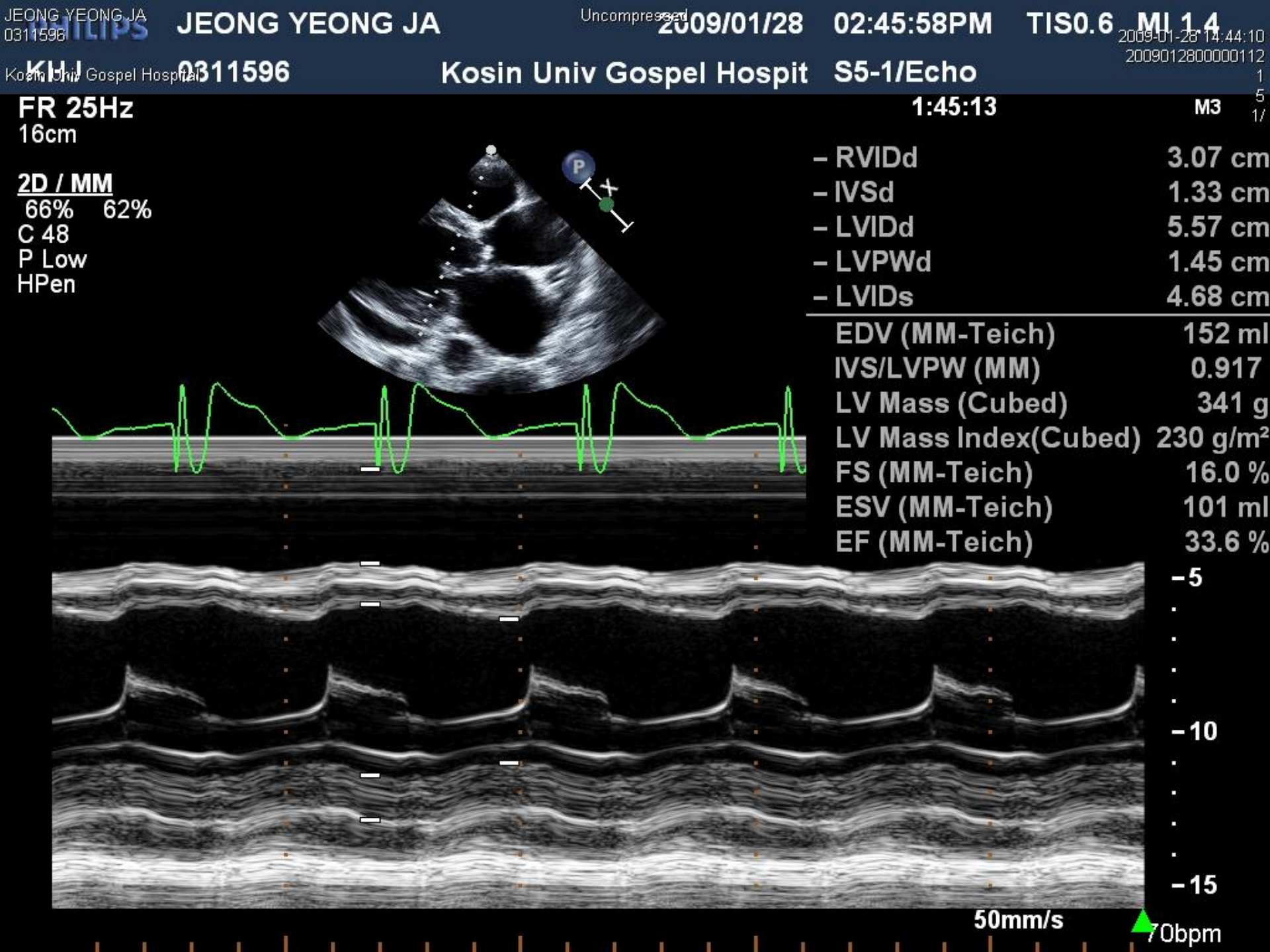
Initial Echo



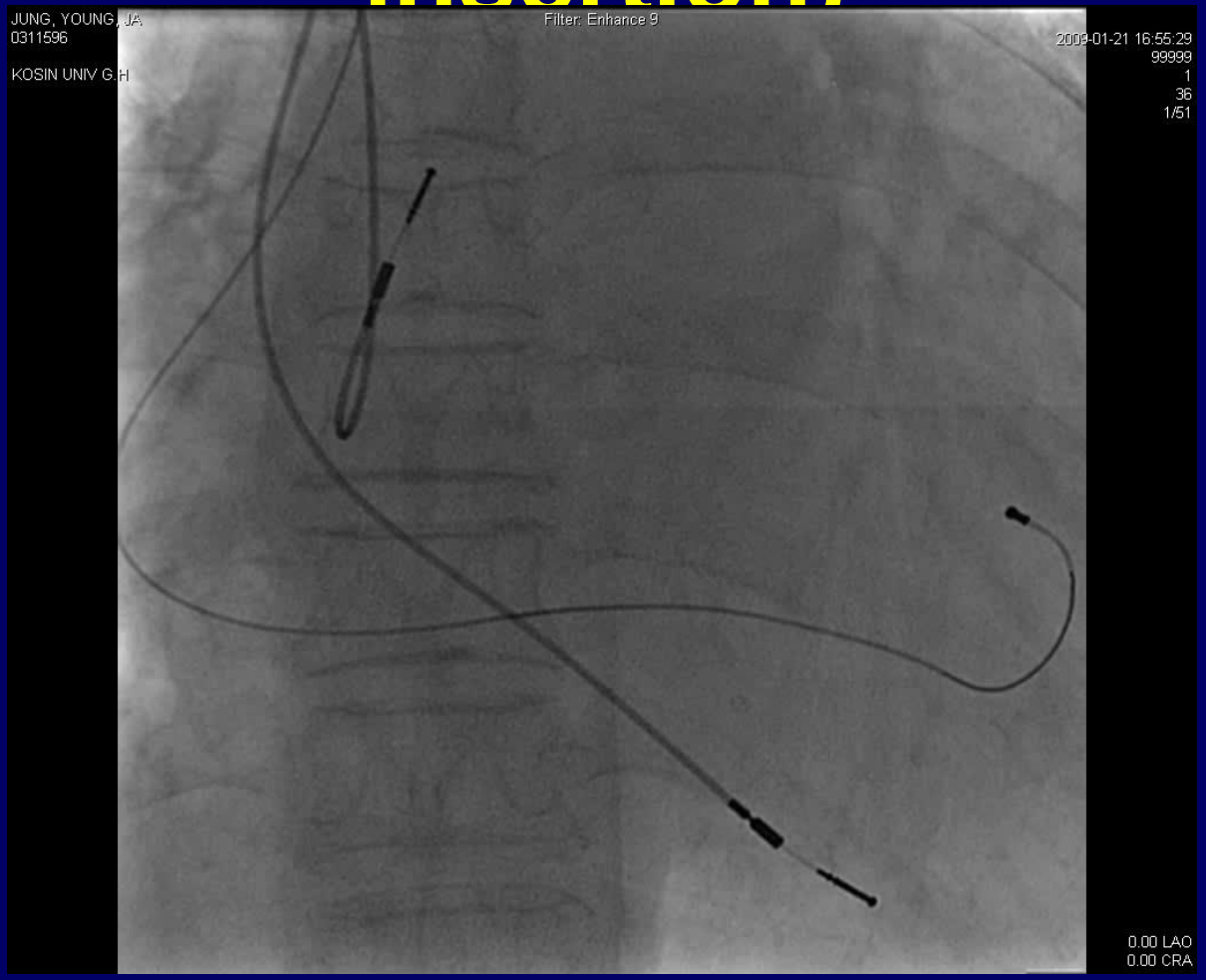


Initial Echo




JEONG YEONG JA
0311596
JEONG YEONG JA
Uncompressed
2009/01/28 02:45:58PM
TIS0.6 MI 1.4
2009-01-28 14:44:10
20090128000000112
KHJ
0311596
Kosin Univ Gospel Hospit
S5-1/Echo
Kosin Univ Gospel Hospital
FR 25Hz
16cm
1:45:13
M3
2D / MM
66% 62%
C 48
P Low
HPen
– RVIDd 3.07 cm
– IVSd 1.33 cm
– LVIDd 5.57 cm
– LVPWd 1.45 cm
– LVIDs 4.68 cm
EDV (MM-Teich) 152 ml
IVS/LVPW (MM) 0.917
LV Mass (Cubed) 341 g
LV Mass Index(Cubed) 230 g/m²
FS (MM-Teich) 16.0 %
ESV (MM-Teich) 101 ml
EF (MM-Teich) 33.6 %
–5
–10
–15
50mm/s
70bpm

Change to CRT, (LV lead insertion)

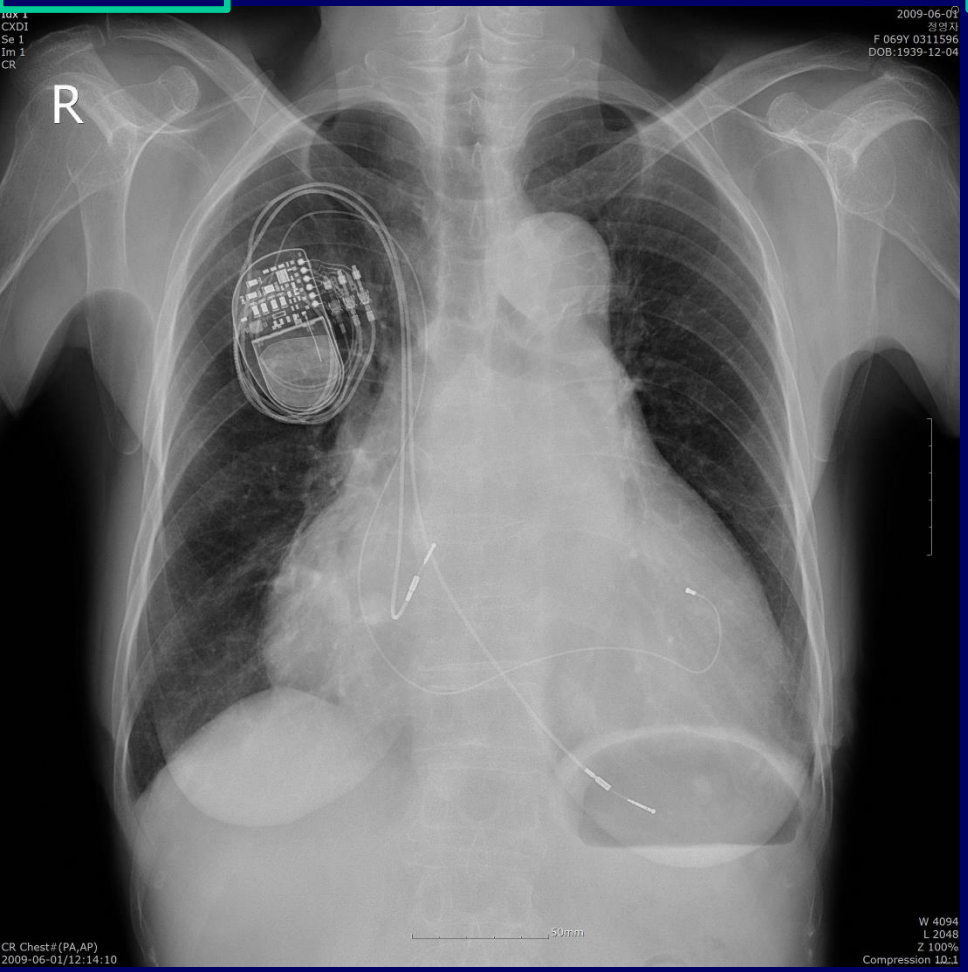


F/U after 10 month

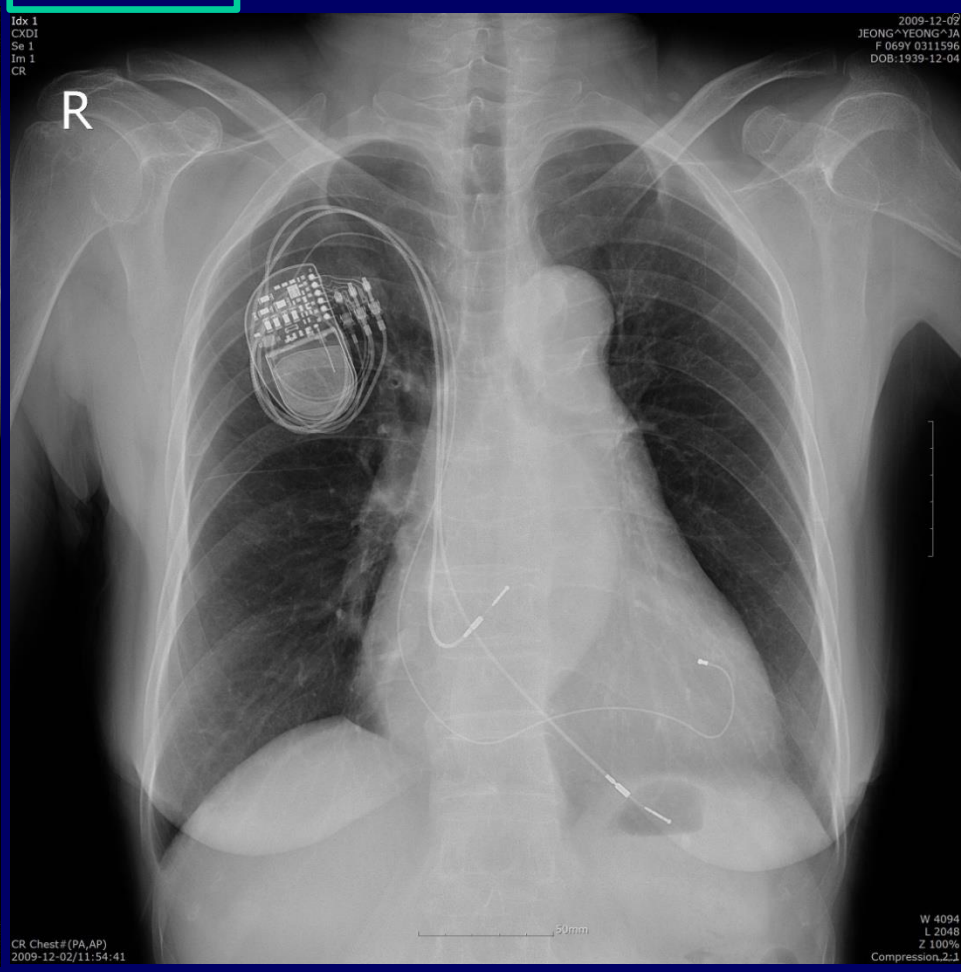
09.11.17	QRS duration: 184ms

F/U after 10 month

09.06.01

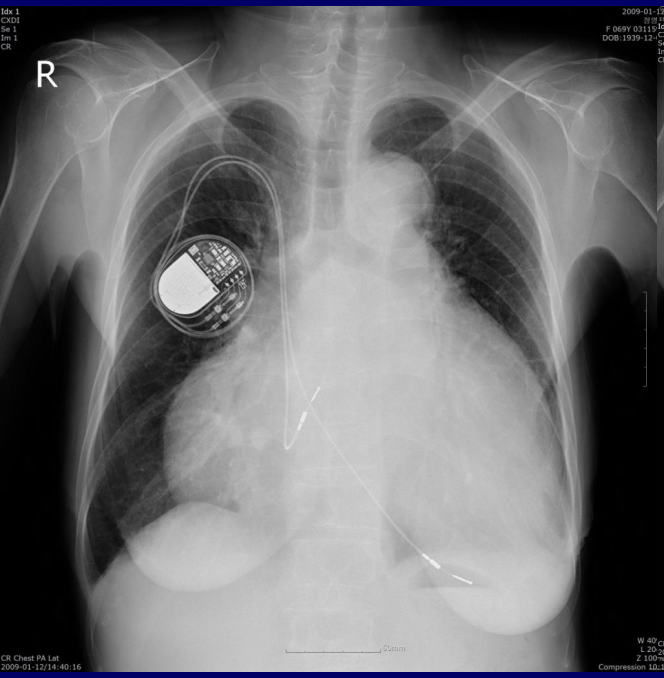


09.12.02



F/U after 10 month

09.01.12



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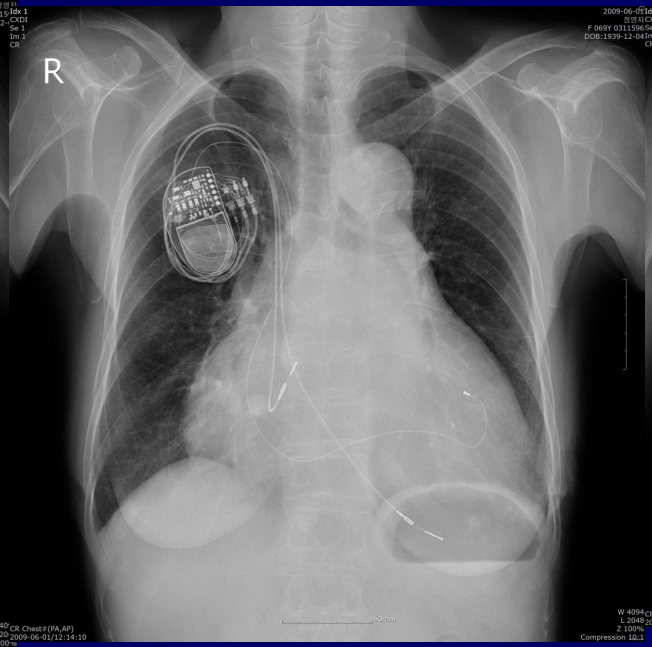

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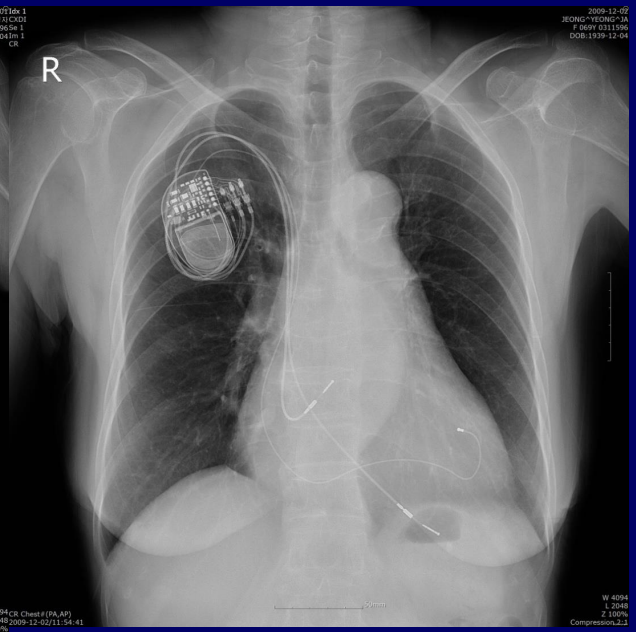
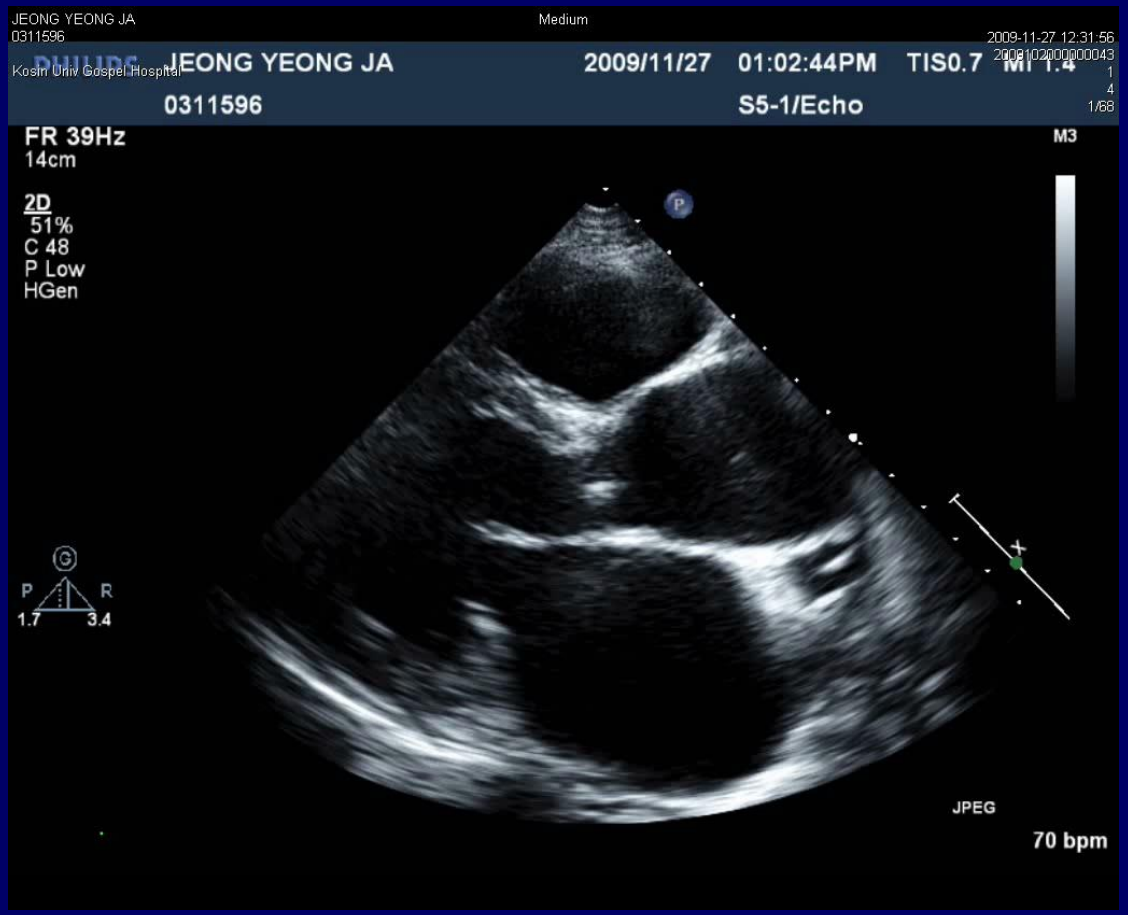
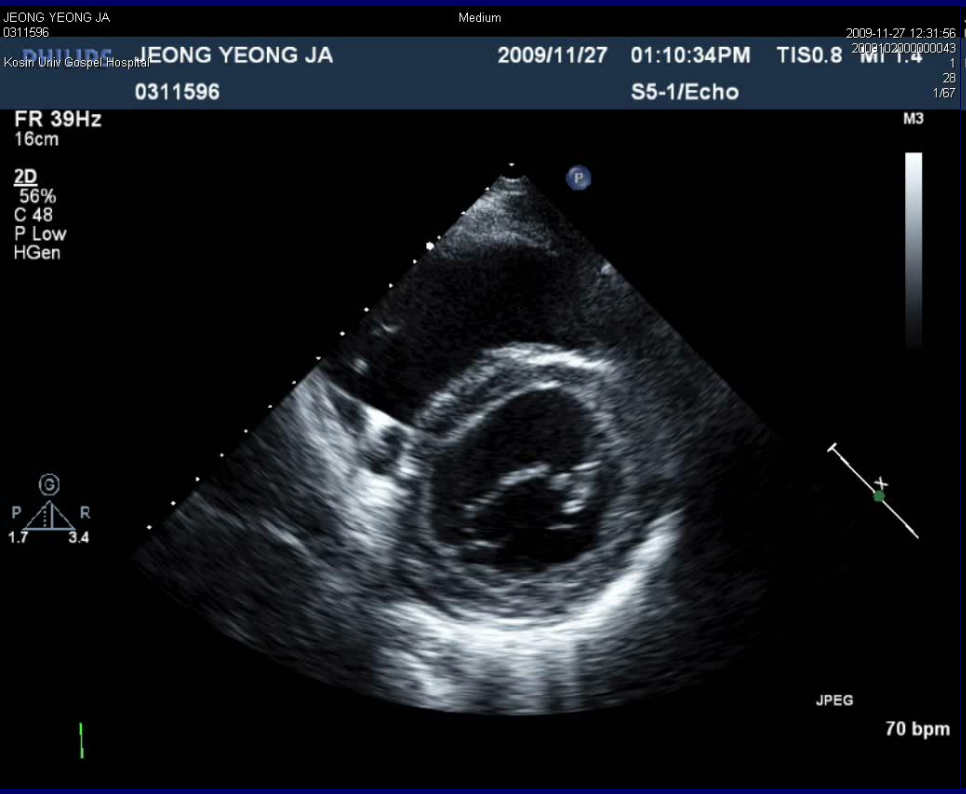
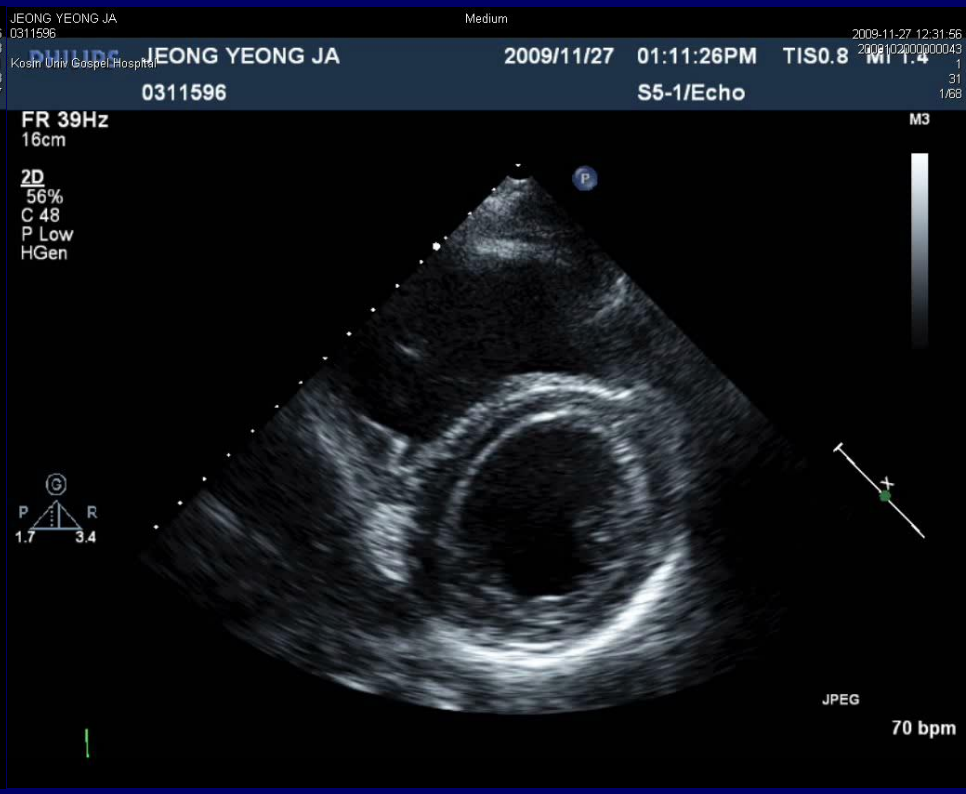


F/U after 10 month

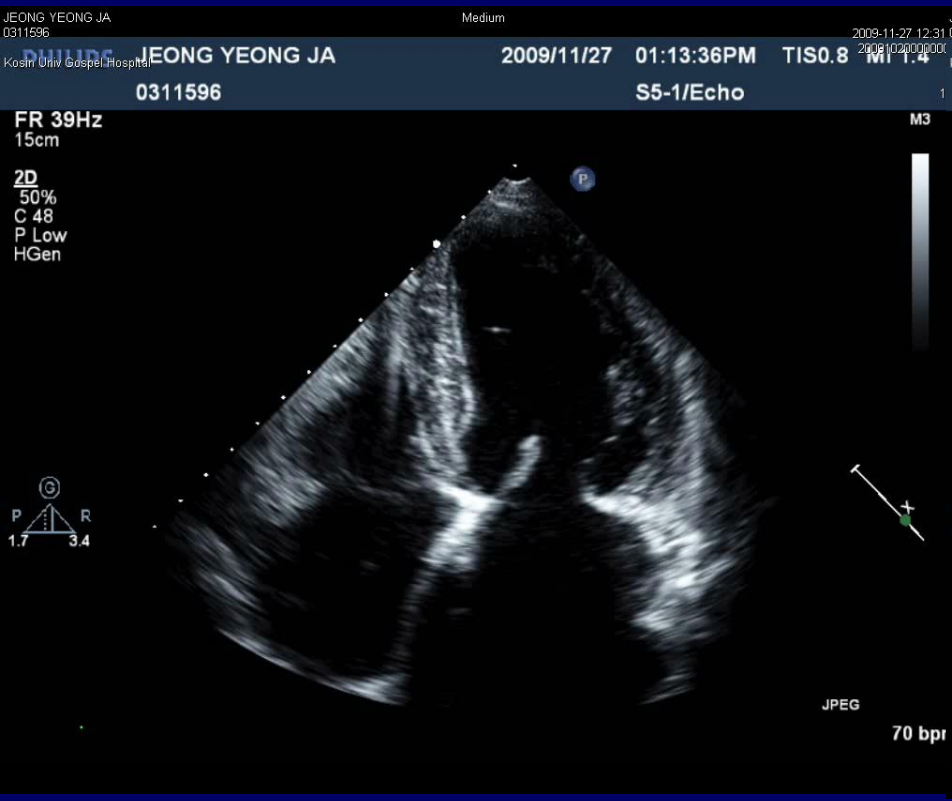


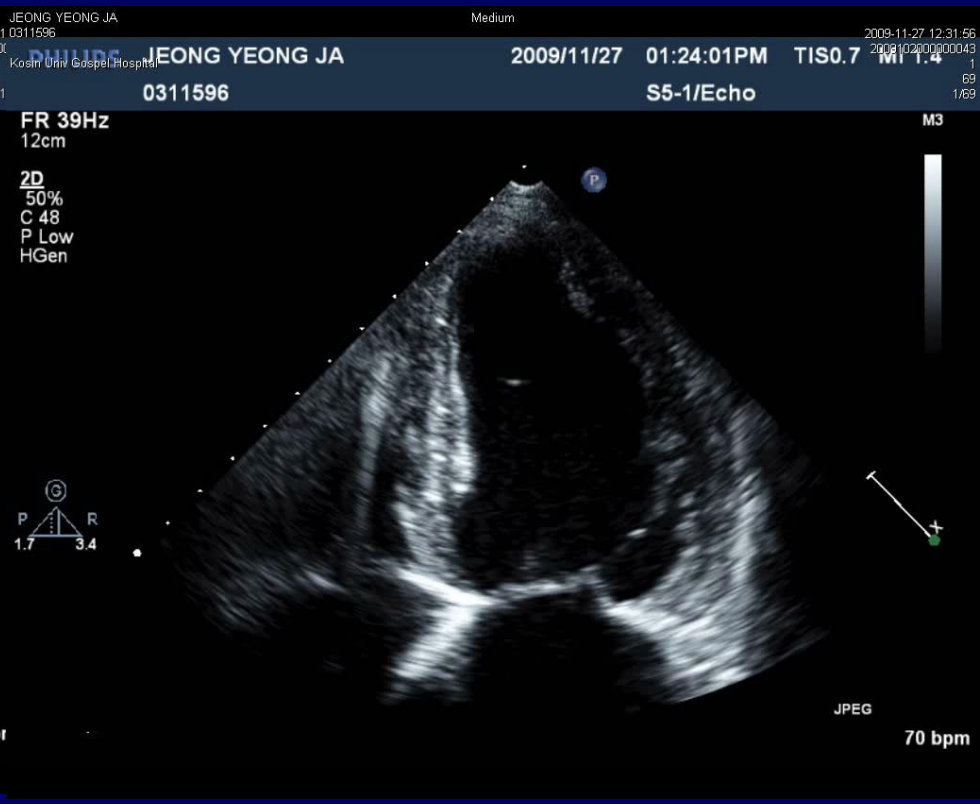
F/U after 10 month



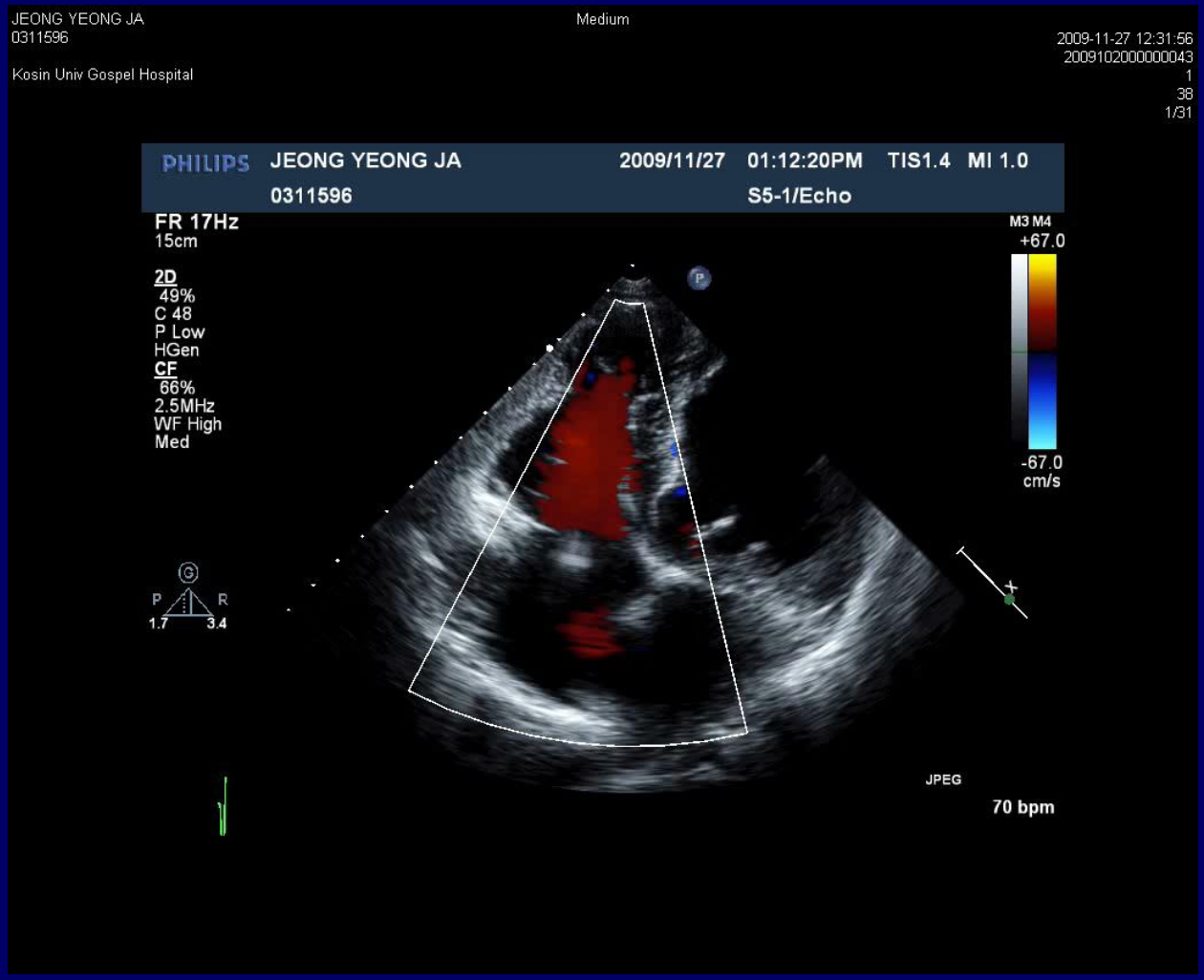


F/U after 10 month



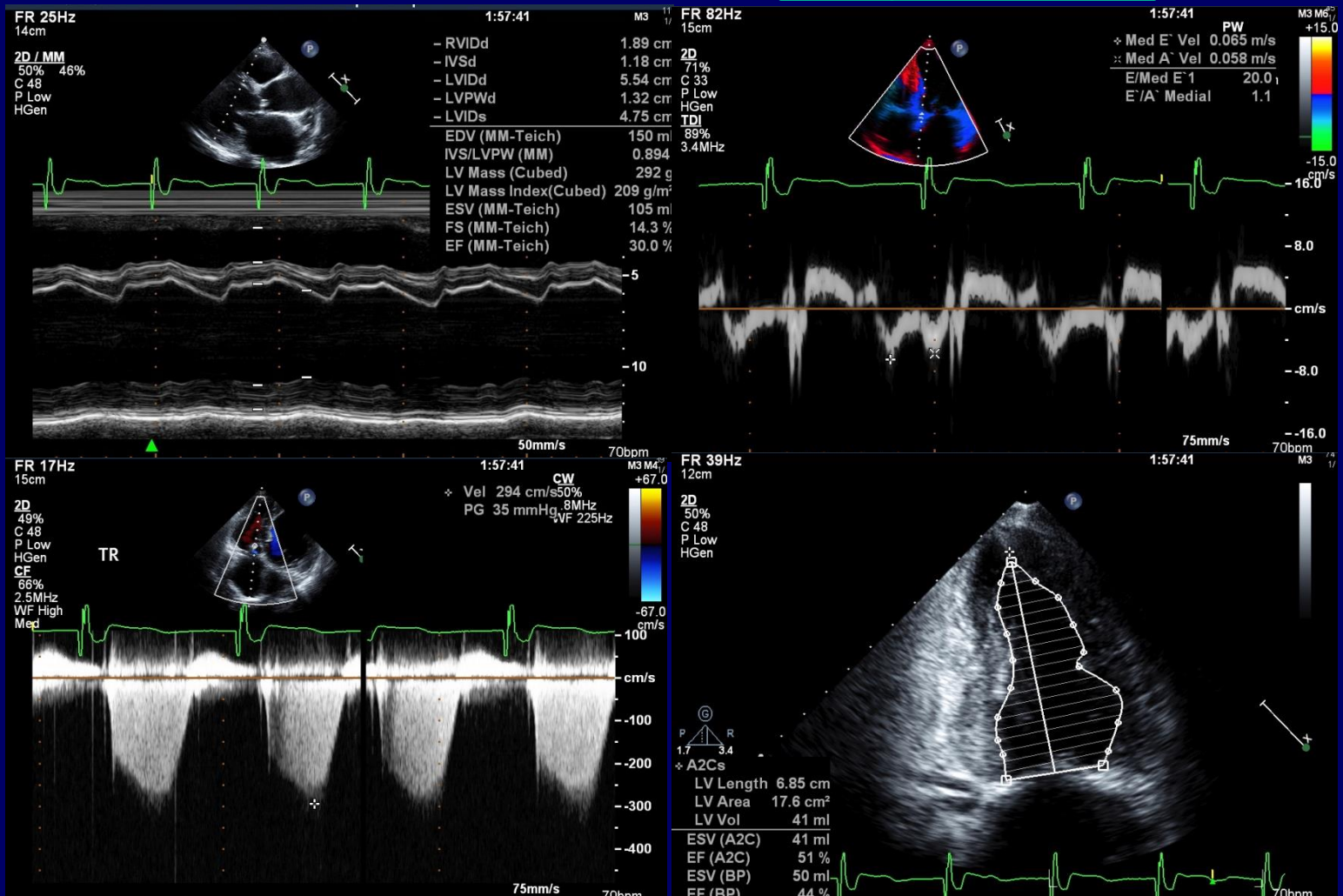


F/U after 10 month

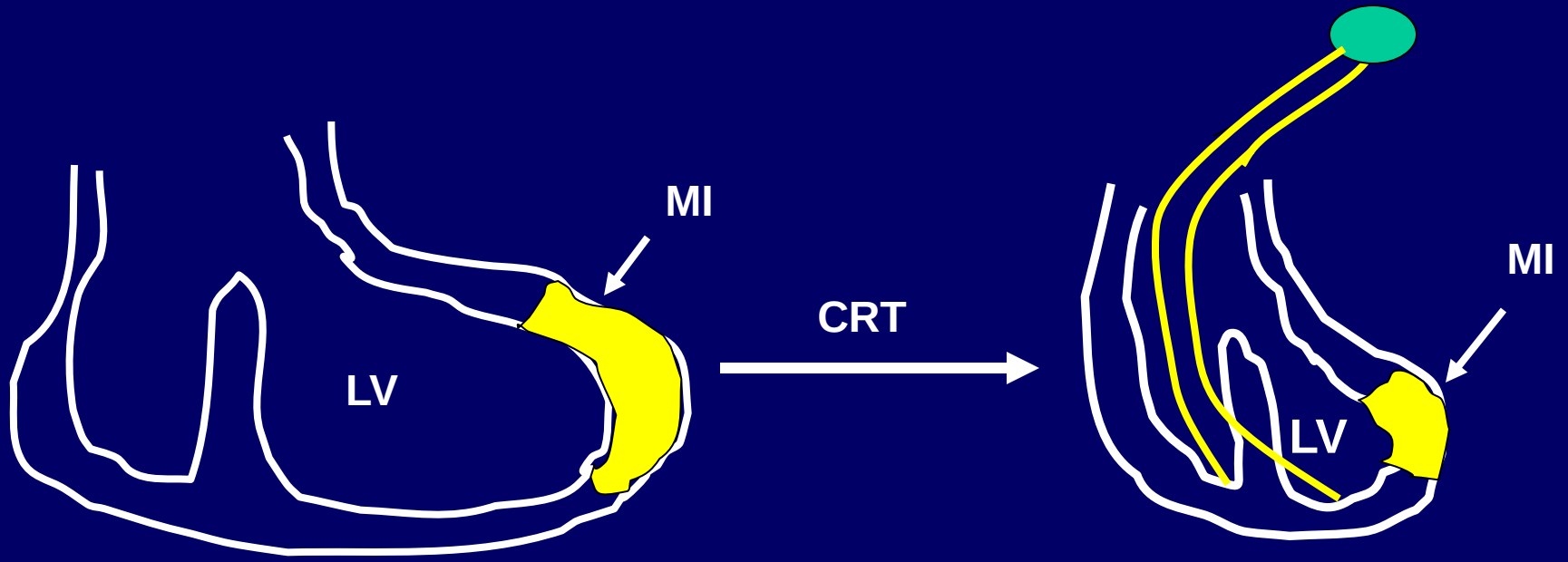


F/U after 10 month

E/E’	39.3 → 20.0



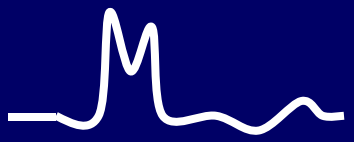
REVERSE REMODELING WITH CRT (BIV) in NYHA Class III-IV



EF=0.20

NYHA III-IV

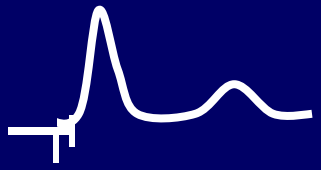
ECG



QRS = 0.15s

EF=0.36

NYHA II-III



QRS = 0.14s

CRT 급여 기준

- 가) **(1)** 심구혈률 **≤ 35%**
  (2) QRS 간격 **≥ 120ms**
  (3) Sinus Rhythm
  (4) NYHA class III 또는 거동이 가능한 **class IV** 환자
  - **3**개월 이상의 적절한 약물치료
    ※ 적절한 약물치료: **(ACE inhibitor/Angiotensin Receptor Blocker +Diuretics ± Beta-blocker)**
- 나**. CRT-D(CRT-Defibrillator) : CRT-P** 와 **ICD** 기준에 모두 적합한 경우

Cardiac Resynchronization Therapy (CRT)

CRT reverses the remodeling of the heart in cardiac patients with severe heart failure (NYHA class III-IV) and wide QRS resulting in reduced heart failure and death

PATH-CHF: JACC 2001

MUSTIC: NEJM 2001

MIRACLE: NEJM 2002

CONTAK-CD: JACC 2003

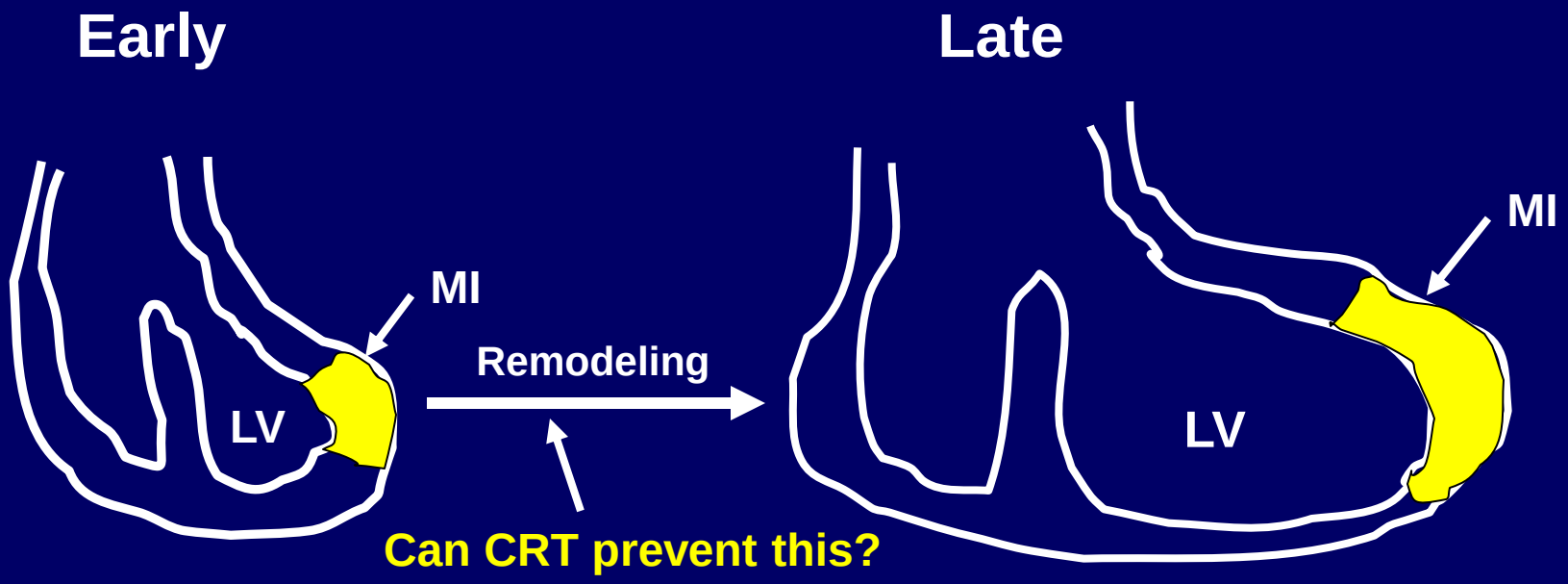
COMPANION: NEJM 2004

CARE-HF: NEJM 2005

MADIT-CRT (2005-2009)

Primary Hypothesis: in minimally symptomatic cardiac pts. (NYHA I/II) with ischemic or nonischemic cardiomyopathy, decreased EF, and wide QRS, CRT-D will reduce mortality or HF event (whichever comes first) when compared to ICD-only therapy.

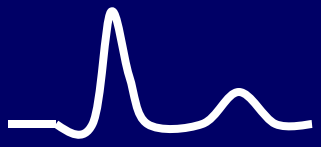
DYSFUNCTIONAL REMODELING



EF=0.30

NYHA I-II

ECG



QRS = 0.12s

EF=0.20

NYHA III-IV

QRS = 0.16s

MADIT-CRT (2005-2009)

Eligibility:

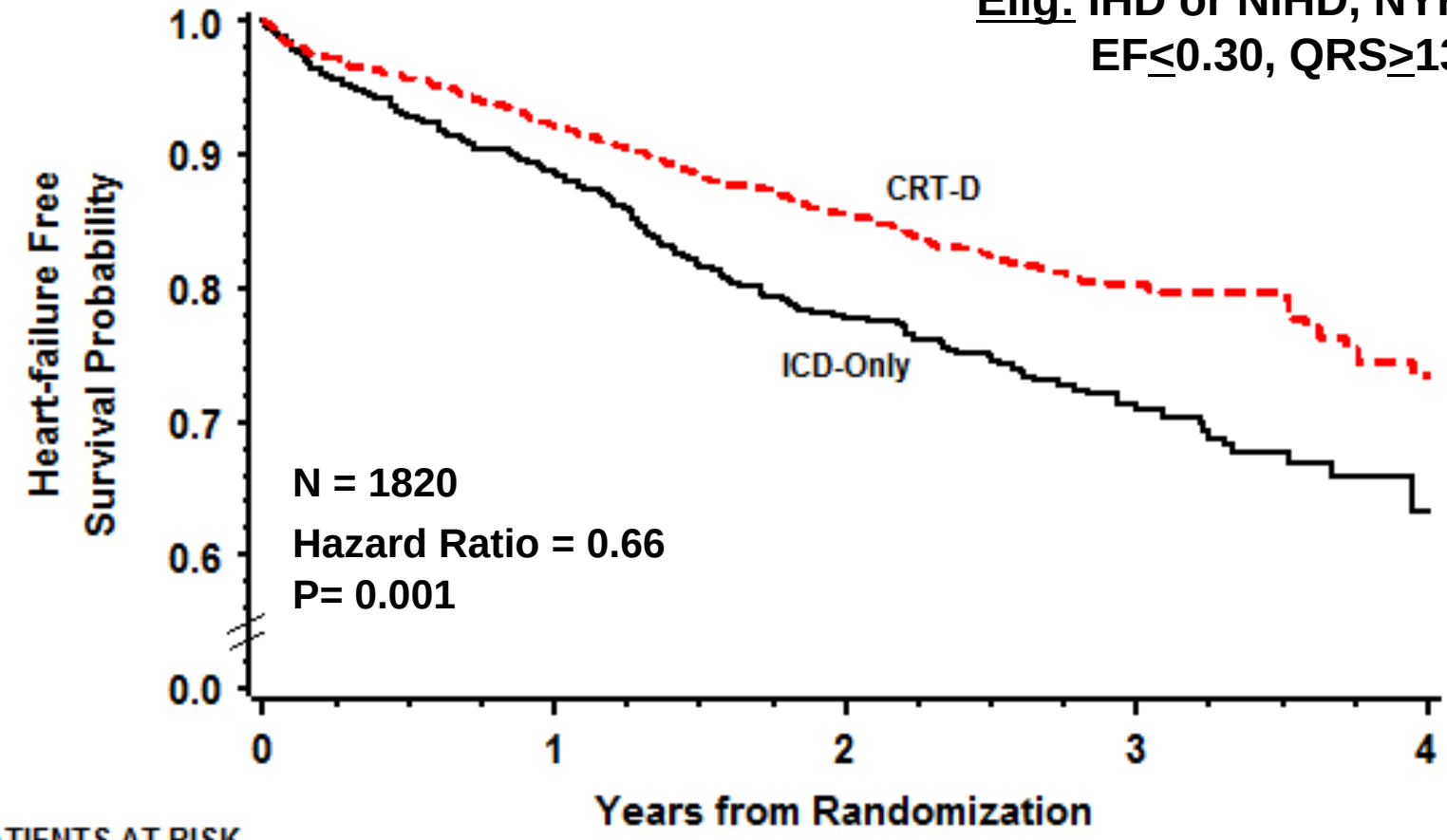
- **EF≤0.30**
- **QRS≥0.13s**
- **Ischemic heart disease NYHA I or II**
- **Non-ischemic heart disease NYHA II**

Exclusion:

- **NYHA III/IV**
- **CABG, PTCA, or MI past 3 mo.**
- **Chronic AF**
- **Implanted ICD, CRT, or CRT device**

MADIT-III: MADIT-CRT

Elig: IHD or NIHD, NYHAI/II, EF≤0.30, QRS≥130ms

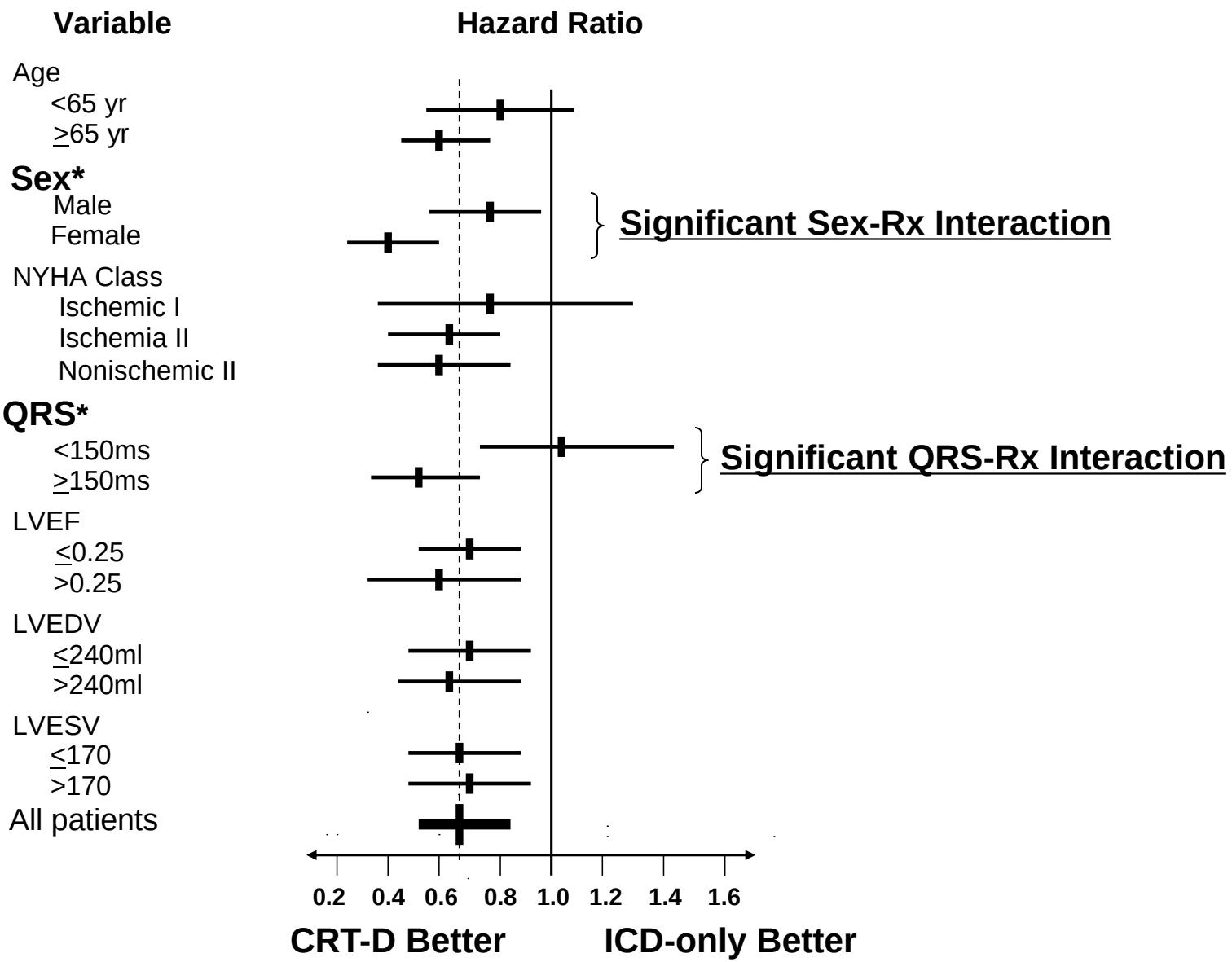


PATIENTS AT RISK

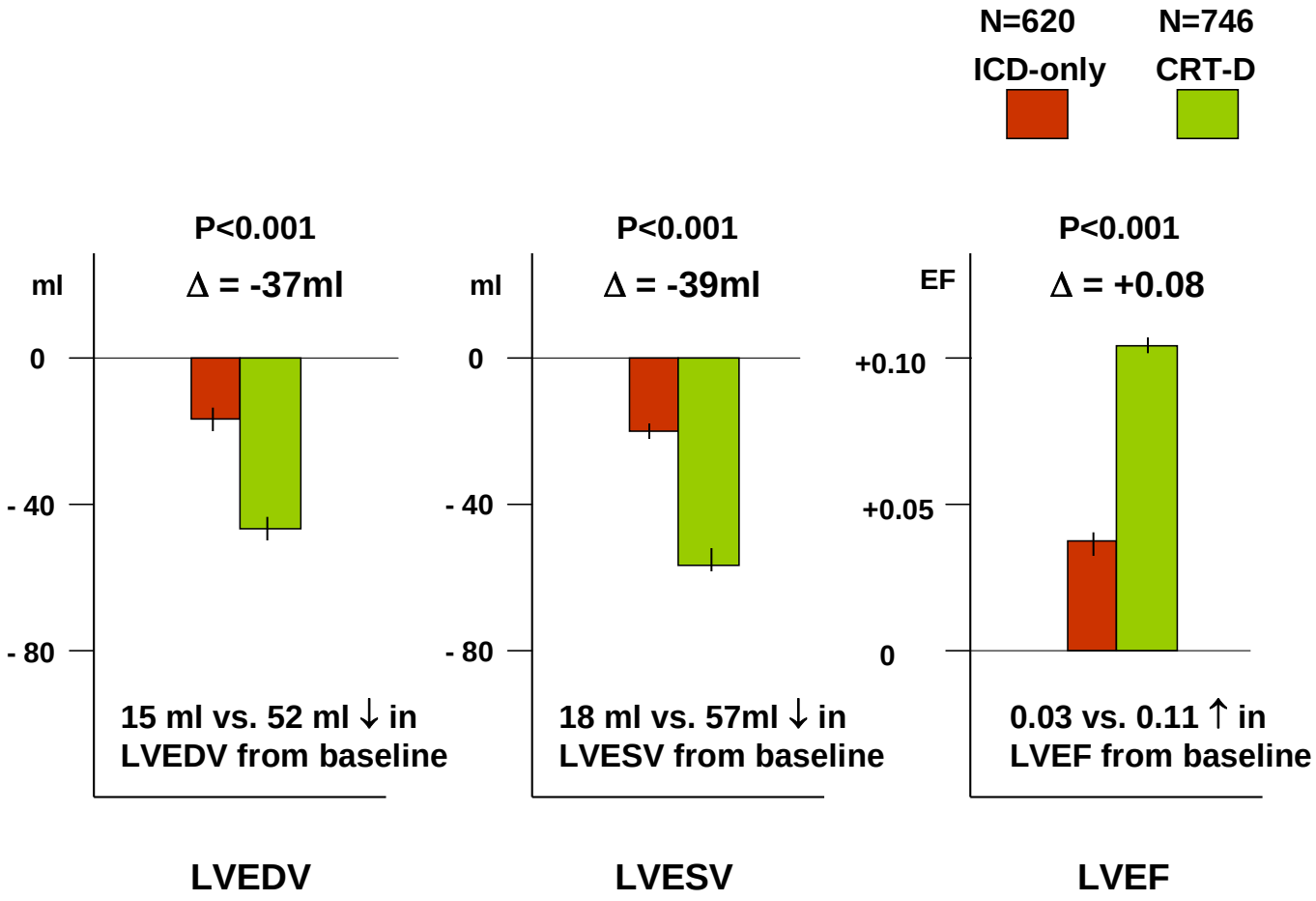
ICD-Only	731	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT-D	1089	985 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

Moss AJ, et al. NEJM 2009

CRT-D:ICD Hazard Ratios for Prespecified Subgroups

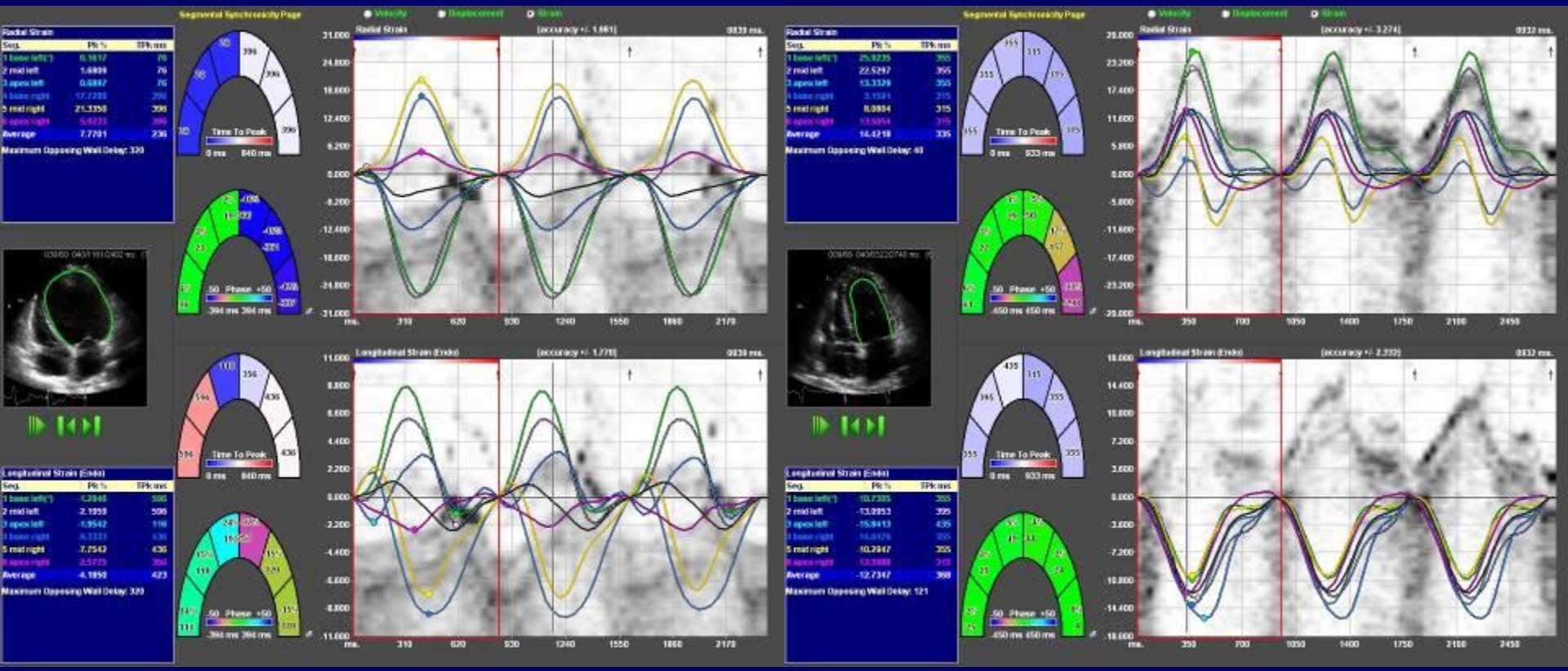


Mean Changes in Echo LV Volumes and EF from Baseline to 1-year by Treatment Group



CRT-D therapy is associated with significant reduction in heart size and improvement in heart function.

MADIT-CRT: Changes in Dyssynchrony (Regional Strain) from Baseline to 12 Months with CRT-D

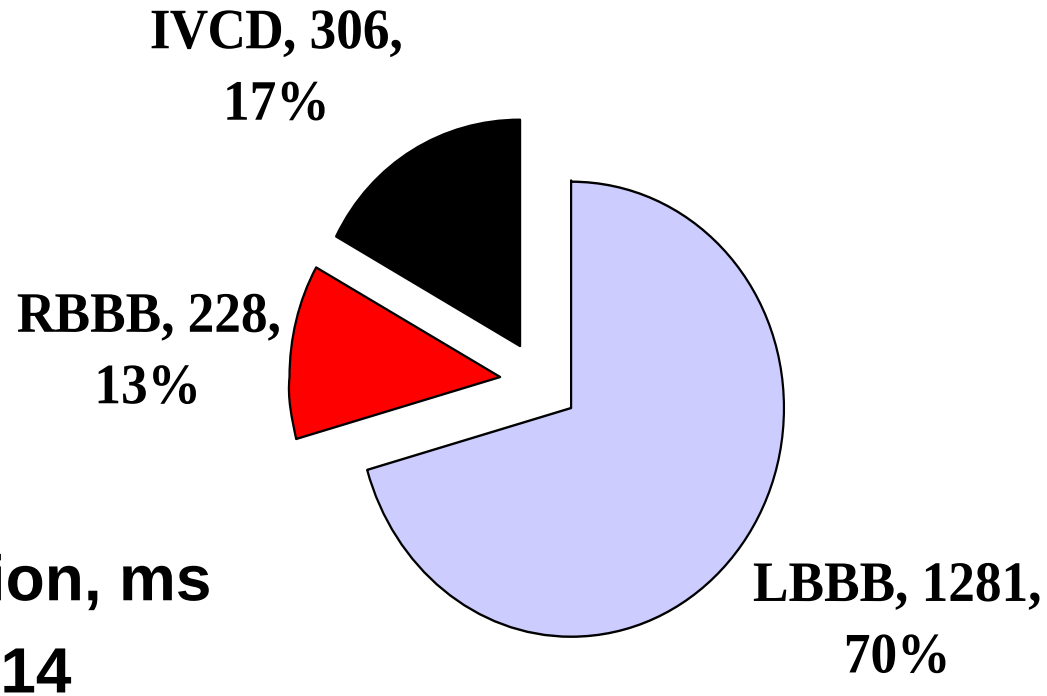


Baseline

12-Months

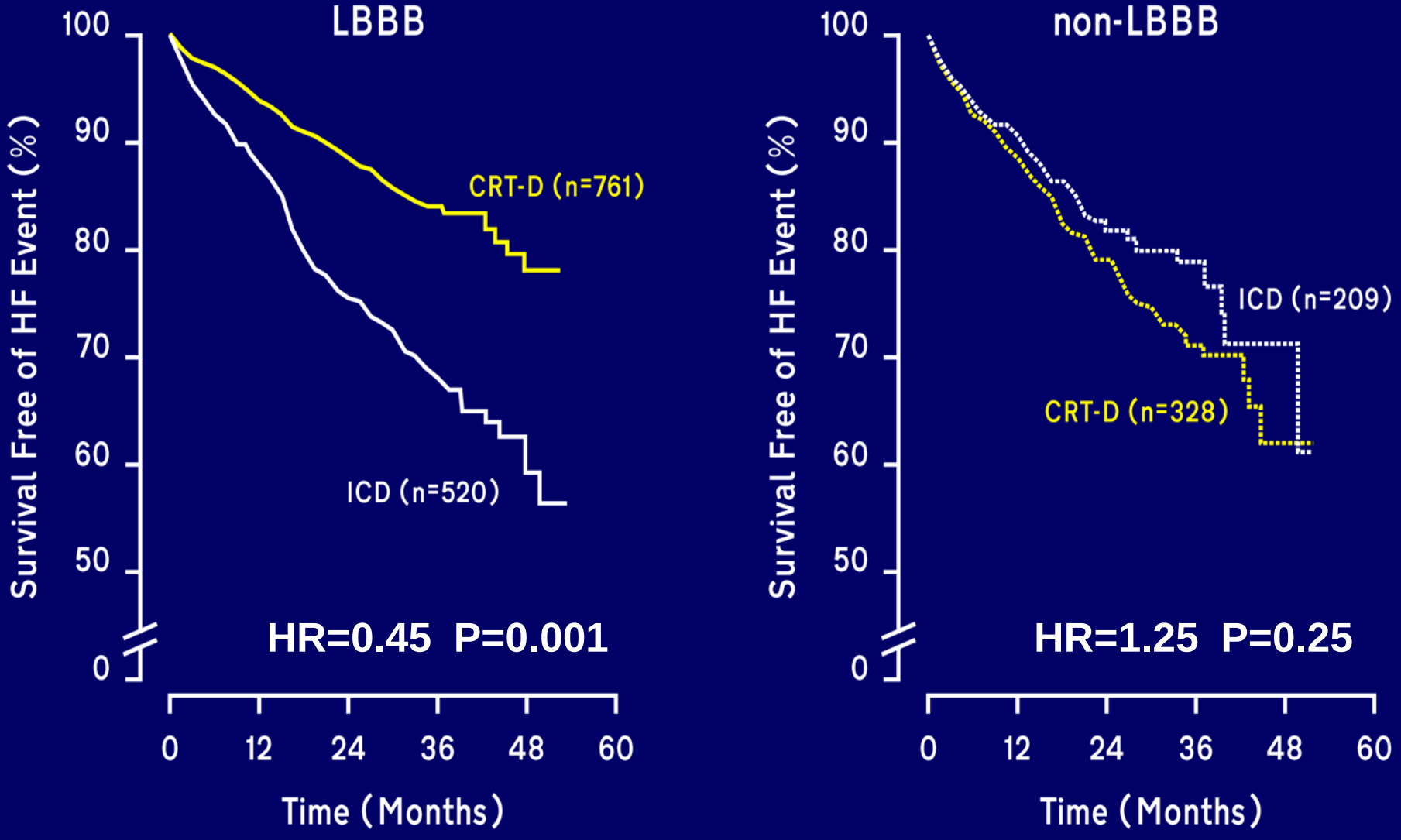
MADIT-CRT Echo Core Lab (Dr. Scott Solomon)

QRS Morphology in MADIT-CRT

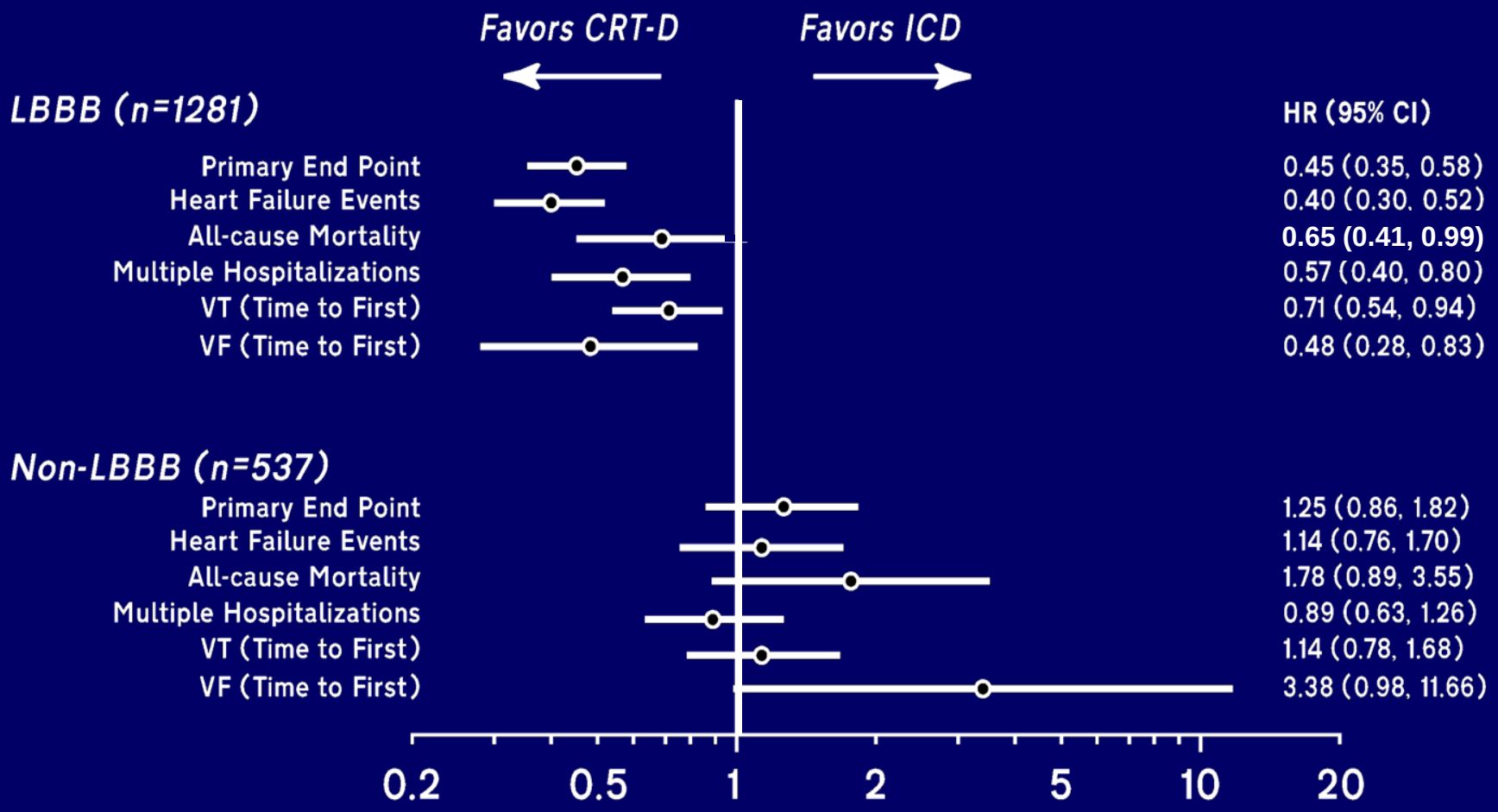


	QRS Duration, ms
IVCD	142±14
RBBB	153±15
LBBB	163±19

MADIT-CRT: Outcome by LBBB & Non-LBBB



MADIT-CRT: Outcomes in LBBB & Non-LBBB



MADIT-CRT: CONCLUSIONS

- CRT reduces the risk of heart failure/death in NYHA class I/II pts. with low EF and wide QRS
- Women obtain a significantly greater benefit from CRT-D than men
- Improvement in cardiac substrate with CRT-D associated with reduction in VT/VF
- Patients with LBBB obtain the best benefit from CRT-D with marked reduction in heart failure and death during 30 months of follow-up

Current Guidelines for CRT-D Therapy

- **Established**
  - **EF≤35%**
  - **NYHA III or ambulatory NYHA IV**
  - **QRS≥120ms**
  - **sinus rhythm**
- **New FDA Approval (MADIT-CRT Criteria)**
  - **EF≤30%, NYHA I/II, QRS≥130ms, and LBBB**

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The Influence of Left Ventricular Ejection Fraction on the Effectiveness of Cardiac Resynchronization Therapy

MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy)

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Rochester, New York; Budapest, Hungary; Bochum, Germany; and Boston, Massachusetts

Objectives The goal of this study was to evaluate the influence of left ventricular (LV) lead position on the risk of ventricular tachyarrhythmia in patients undergoing cardiac resynchronization therapy (CRT).

Background Left ventricular ejection fraction (LVEF) is a surrogate marker of heart failure (HF) status and associated risk. Data on the effectiveness of cardiac resynchronization therapy with defibrillator (CRT-D) in patients with mild HF and better LVEF are limited.

Methods In the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) study, the echocardiography core laboratory assessed baseline LVEF independent of the enrolling centers and identified a range of LVEFs, including those >30% (i.e., beyond the eligibility criteria). Echocardiographic response with CRT, defined as percent change in left ventricular end-diastolic volume (LVEDV), was analyzed in 3 prespecified LVEF groups: >30%, 26% to 30%, and ≤25%. The primary endpoint was HF or death. Secondary endpoint included all-cause mortality.

Results LVEF was evaluated in 1,809 study patients. There were 696 (38%) patients with LVEF >30% (in the range of 30.1% to 45.3%); 914 patients (50.5%) with LVEF 26% to 30%; and 199 patients with LVEF ≤25% (11%). The mean reduction in LVEDV with CRT-D therapy at the 1-year follow-up was directly related to increasing LVEF (LVEF >30%: 22.3%; LVEF 26% to 30%: 20.1%; and LVEF ≤25%: 18.7% reduction, respectively [p = 0.001]). CRT-D treatment similarly reduced the risk of HF/death in patients with LVEF >30% (hazard ratio [HR]: = 0.56 [95% confidence interval (CI): 0.39 to 0.82], p = 0.003), LVEF 26% to 30% (HR: 0.67: [95% CI: 0.50 to 0.90], p = 0.007), and LVEF ≤25% (HR: 0.57 [95% CI: 0.35 to 0.95], p = 0.03; all p values for LVEF-by-treatment interactions >0.1).

Conclusions In MADIT-CRT, the clinical benefit of CRT was evident regardless of baseline LVEF, including those with LVEF >30%, whereas the echocardiographic response was increased with increasing LVEF, indicating that CRT might benefit patients with better LVEF. (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy [MADIT-CRT]; NCT00180271) (J Am Coll Cardiol 2013;61:936–44) © 2013 by the American College of Cardiology Foundation

Distribution of Baseline LVEF Identified by the Centers and Measured by the Echocardiography Core Laboratory in All Patients

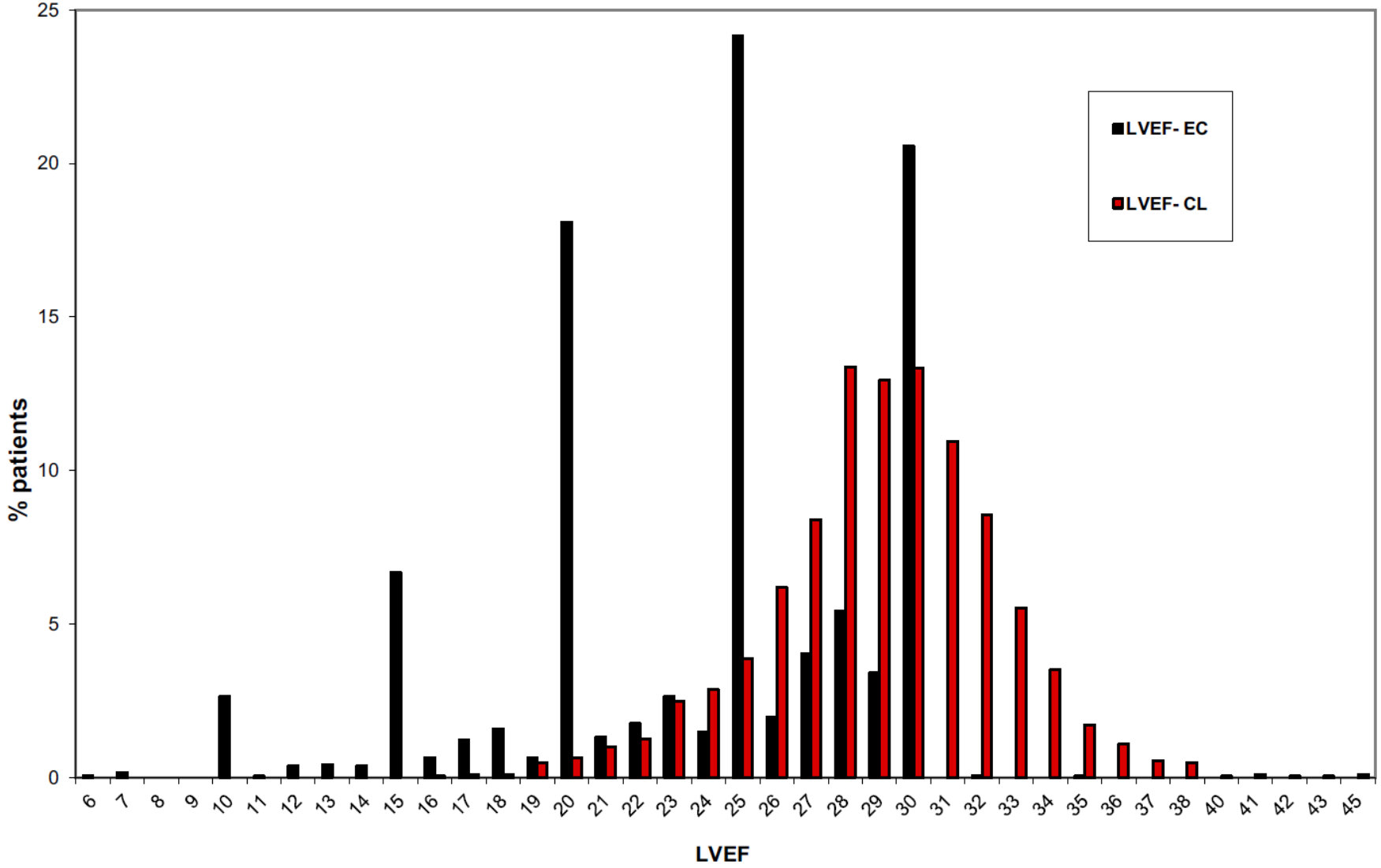
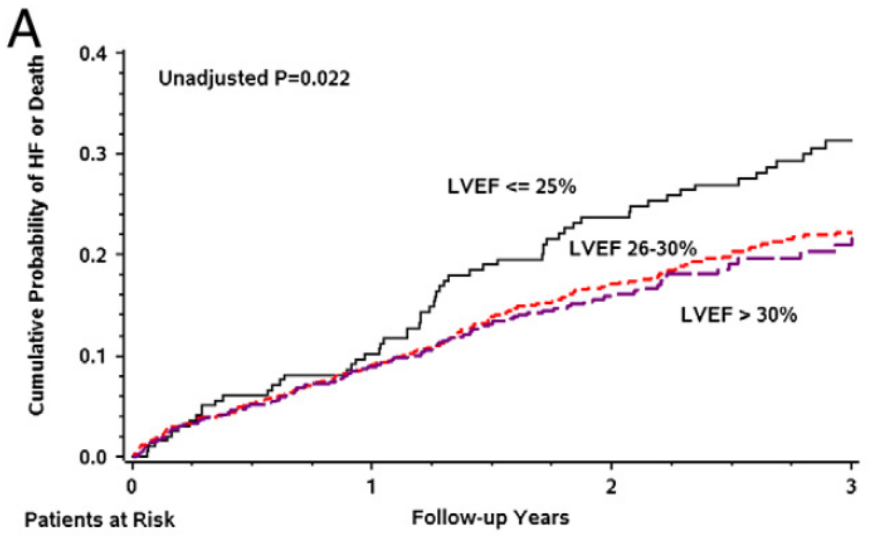


Table 1 Clinical Characteristics of All Patients in Terms of Baseline LVEF Ranges

Clinical Characteristic	LVEF ≤25% (n = 199)	LVEF 26% to 30% (n = 914)	LVEF >30% (n = 696)	p Value
Age (yrs)	61.4 ± 11.0	64.3 ± 10.8	65.3 ± 10.4	<0.001
Females	36 (18)	220 (24)	195 (28)	0.012
CRT-D treatment	115 (58)	554 (61)	416 (60)	0.755
Ischemic NYHA class I	25 (13)	121 (13)	118 (17)	0.077
Ischemic NYHA class II	74 (37)	388 (42)	267 (38)	0.162
Nonischemic NYHA class II	100 (50)	405 (44)	311 (45)	0.300
Worst NYHA class >2 (>3 months before enrollment)	24 (13)	102 (12)	56 (8)	0.063
QRS complex (ms)	166.6 ± 22.5	159.1 ± 20.0	154.4 ± 17.6	<0.001
LBBB	168 (84)	656 (72)	450 (65)	<0.001
RBBB	9 (5)	111 (12)	106 (15)	<0.001
IVCD	22 (11)	146 (16)	139 (20)	0.006
Heart rate	69.8 ± 12.0	67.8 ± 10.6	67.0 ± 10.7	0.007
Systolic blood pressure	119.2 ± 17.5	121.9 ± 16.7	124.4 ± 18.1	<0.001
ACE inhibitors/ARB	163 (82)	685 (75)	546 (78)	0.168
Beta-blocker	180 (90)	854 (93)	653 (94)	0.236
Diuretics	142 (71)	653 (69)	446 (64)	0.035
Digitalis	68 (34)	241 (26)	156 (22)	0.003
LVEDV indexed by BSA	150.7 ± 40.7	125.5 ± 26.7	112.9 ± 19.1	<0.001
LVESV indexed by BSA	116.6 ± 32.4	90.5 ± 19.8	76.6 ± 13.7	<0.001
LAV indexed by BSA	57.0 ± 10.7	48.4 ± 8.8	41.2 ± 7.9	<0.001



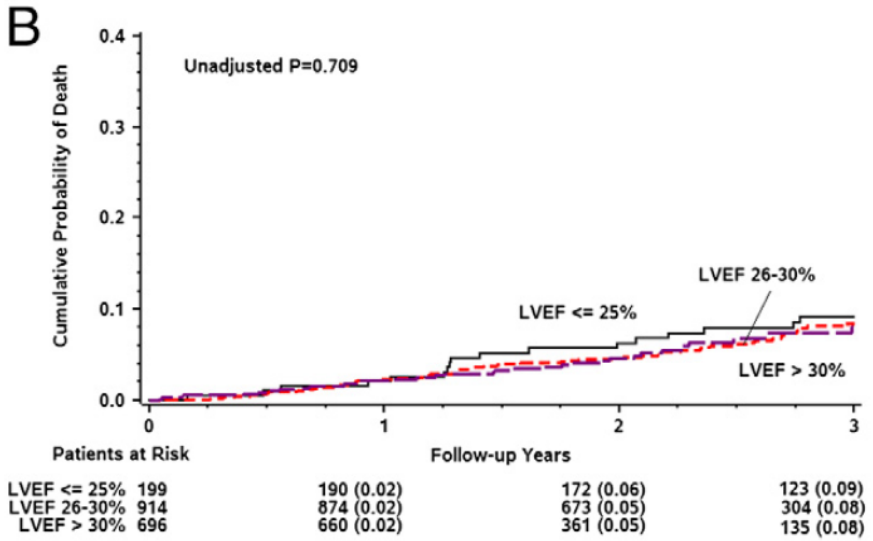


Figure 2 **Kaplan-Meier Estimates of the Cumulative Probability of Various Factors in all Patients With LVEF ≤25%, LVEF 26% to 30%, and LVEF >30%**

Table 2 Baseline LVEF Groups and the Risk of HF/Death

Parameter	HF/Death		
	Hazard Ratio	95% CI	p Value
LVEF ≤25 %: LVEF 26% to 30%	1.55	1.16–2.08	0.003
LVEF ≤25 %: LVEF >30%	1.66	1.21–2.28	0.002
LVEF 26% to 30 %: LVEF >30%	1.07	0.84–1.36	0.588
LVEF (continuous)	0.95	0.92–0.98	0.001

Model was adjusted for treatment, ischemic etiology of cardiomyopathy, NYHA class >2 greater than 3 months before enrollment, baseline heart rate, and age at enrollment.

HF = heart failure; CI = confidence interval; other abbreviations as in Table 1.

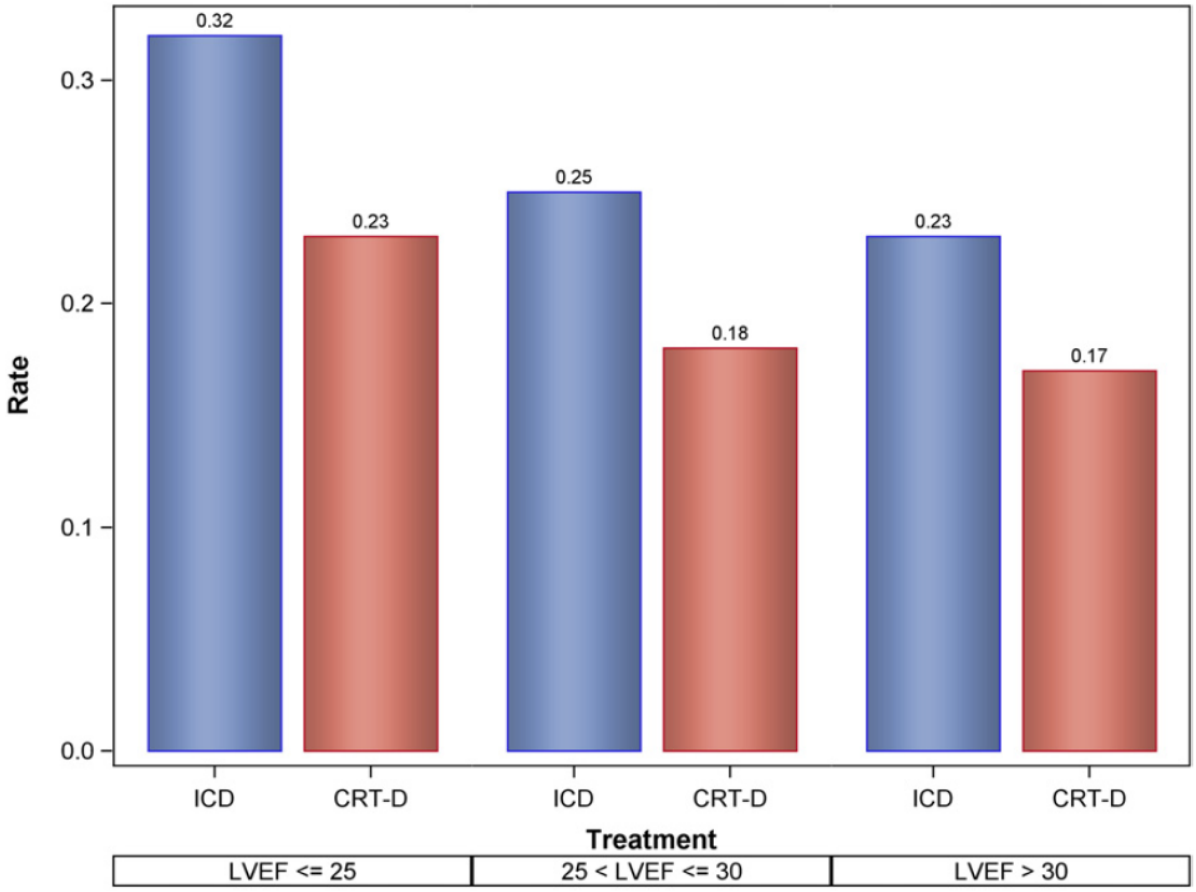


Figure 3 Kaplan-Meier 2.5-Year Event Rates of the Cumulative Probability of HF/Death Episodes by Treatment Arm in Patients With LVEF ≤25%, LVEF 26% to 30%, and LVEF >30%

Table 3 Treatment Effect of CRT-D Stratified According to Baseline LVEF Groups for the Primary Endpoint of HF/Death

	Endpoint: HF/Death		
Parameter	Hazard Ratio	95% CI	p Value
LVEF ≤25%	0.57	0.35–0.95	0.031
LVEF 26% to 30%	0.67	0.50–0.90	0.007
LVEF >30%	0.56	0.39–0.82	0.003

Model was adjusted for female sex, ischemic etiology, and QRS duration. Interaction p values with treatment are >0.1 in all patient groups and LVEF subgroups.

Abbreviations as in Tables 1 and 2.

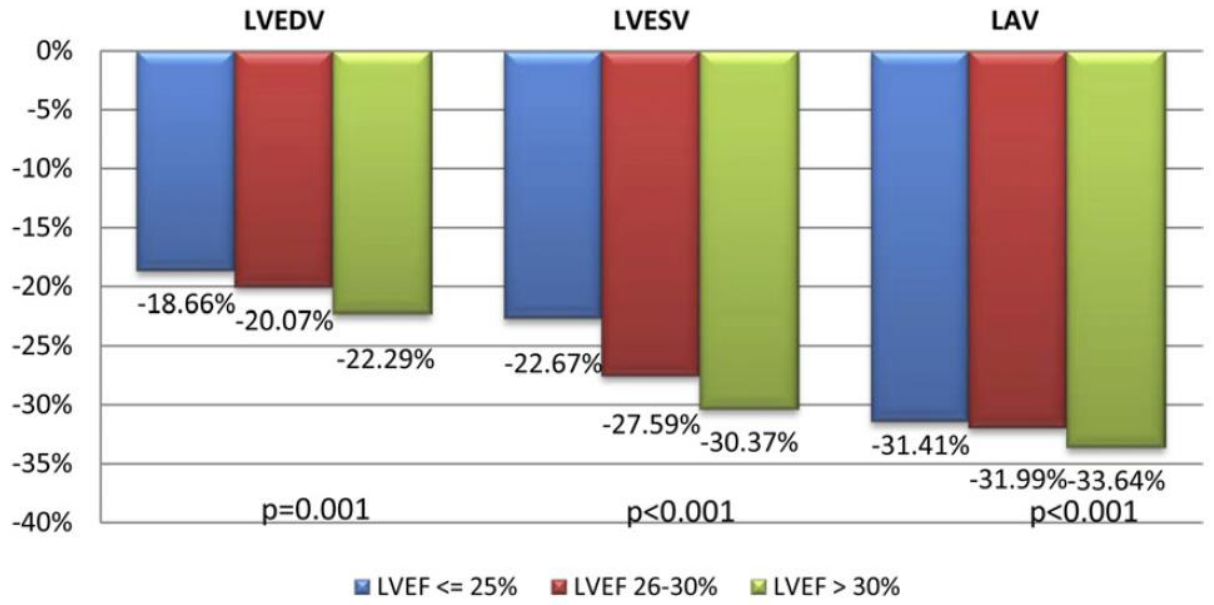


Figure 4 **Effects of CRT-D on Echocardiographic Parameters After 1 Year in Patients With LVEF ≤25%, LVEF 26% to 30%, and LVEF >30%**

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CME

Reduction in Life-Threatening Ventricular Tachyarrhythmias in Statin-Treated Patients With Nonischemic Cardiomyopathy Enrolled in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy)

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Table 1 Baseline Clinical Characteristics of Study Patients by Statin Usage at Enrollment

Variable	Statin Users (n = 499)	Statin Nonusers (n = 322)	p Value
Age, yrs	63 ± 10	59 ± 12	<0.001
Female	37 (184)	42 (135)	0.15
Randomization to CRTD treatment arm	62 (309)	58 (187)	0.32
QRS duration, ms	164 ± 20	162 ± 20	0.21
NYHA functional class III or IV >3 months before enrollment	12 (60)	10 (32)	0.43
Past history of ventricular arrhythmias	4 (20)	6 (19)	0.26
Past history of atrial arrhythmias	10 (49)	6 (19)	0.12
Diabetes mellitus	37 (184)	16 (51)	<0.001
Hypertension	63 (314)	50 (161)	0.001
Blood pressure, mm Hg			
Systolic	122 ± 16	121 ± 17	0.90
Diastolic	71 ± 10	72 ± 10	0.18
Cigarette smoking	8 (40)	13 (42)	0.03
Blood urea nitrogen >26 mg/dl (9.3 mmol/l)	22 (110)	17 (54)	0.10
Creatinine, mg/dl	1.1 ± 0.3	1.07 ± 0.3	0.05
Right bundle branch block	3 (15)	4 (13)	0.45
Left bundle branch block	91 (454)	89 (287)	0.26
Body mass index >30 kg/m^2	39 (194)	35 (113)	0.28
Drug therapy used			
Class 1 antiarrhythmic agents	0.4 (2)	0.3 (1)	0.46
Amiodarone	4 (19)	5 (17)	0.36
Aldosterone antagonists	39 (194)	39 (126)	0.90
Beta-blocking agents	95 (474)	94 (303)	0.42
Digoxin	28 (139)	35 (112)	0.03
Angiotensin-converting enzyme inhibitor	77 (384)	79 (254)	0.46
Angiotensin-receptor-blocker	23 (114)	21 (67)	0.47
Diuretics	69 (344)	67 (215)	0.44
Echocardiographic parameters			
Left ventricular ejection fraction, %	29 ± 3	29 ± 4	0.50
Left ventricular end-systolic volume index (ml/m^2)	89 ± 25	92 ± 26	0.09
Left ventricular end-diastolic volume index (ml/m^2)	125 ± 31	129 ± 32	0.50
Left atrial volume index (ml/m^2)	45 ± 9	47 ± 10	0.02

Values are mean ± SD or % (n).

CRTD = cardiac resynchronization therapy with a defibrillator; NYHA = New York Heart Association functional class.

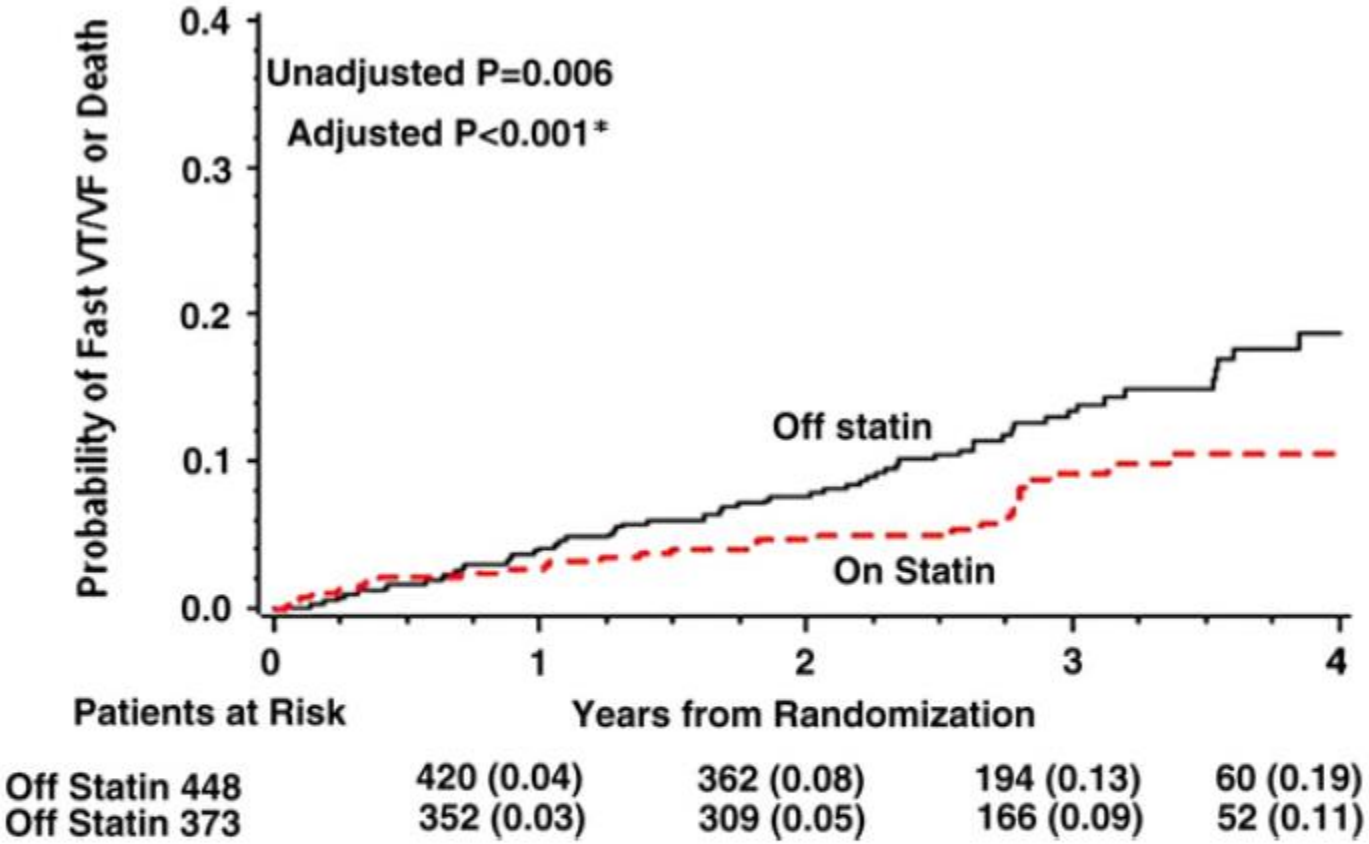


Figure 1 **Cumulative Probability for the Occurrence of Fast VT/VF or Death by Statin Treatment**

Follow-up is censored upon change in statin usage after enrollment. *See Table 2 for multivariate model details. VF = ventricular fibrillation; VT = ventricular tachycardia.

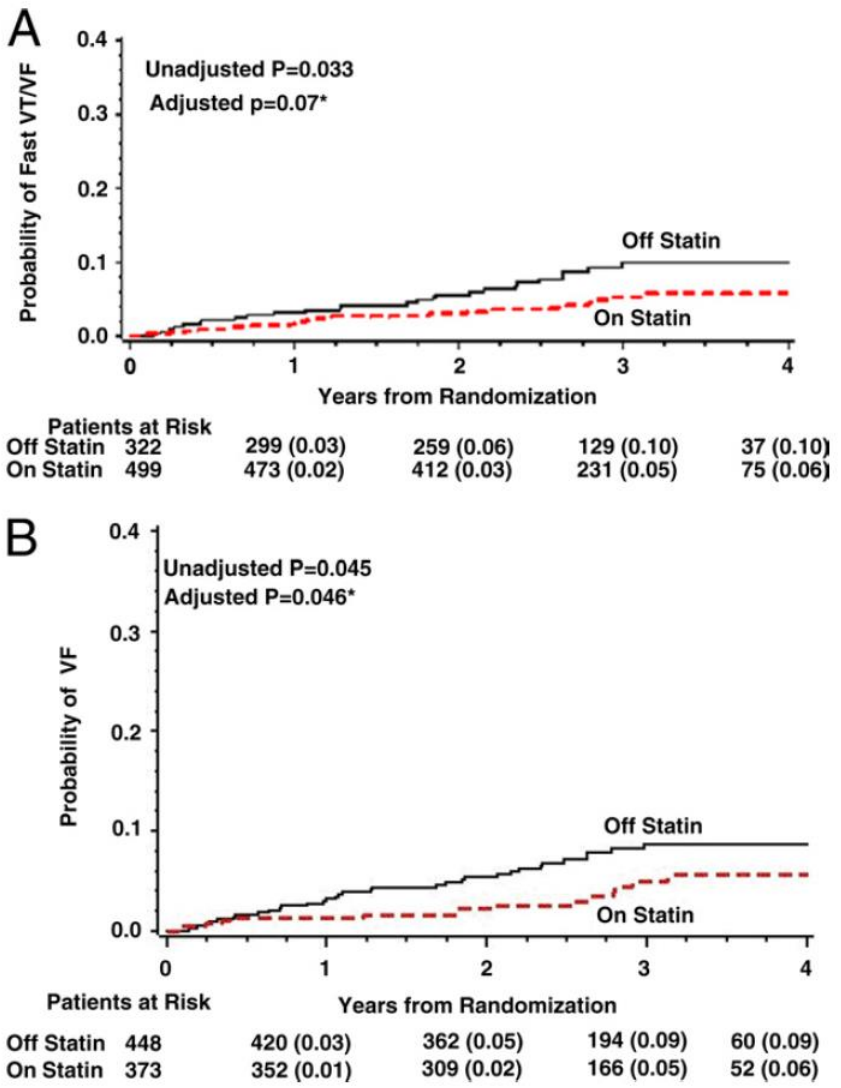
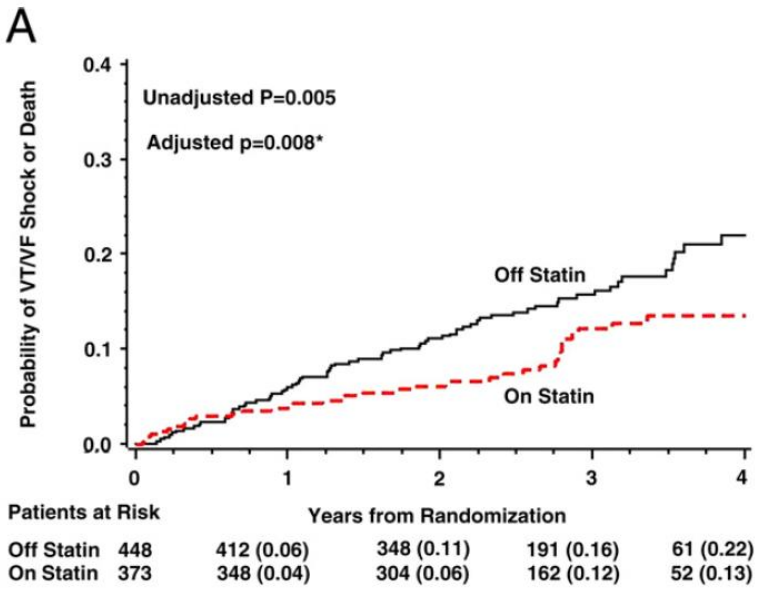


Figure 2 **Cumulative Probability for the Occurrence of Fast VT/VF by Statin Treatment**

Cumulative probability for the occurrence of fast VT/VF by statin treatment **(A)** and the probability for the occurrence of VF by statin treatment **(B).** Follow-up is censored upon change in statin usage after enrollment. *See Table 2 for multivariate model details. Abbreviations as in Figure 1.



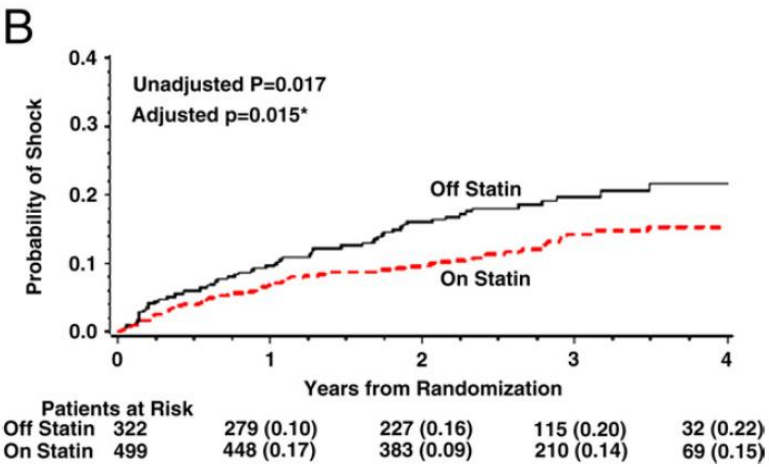


Figure 3 **Cumulative Probability for the Occurrence of VT, VF, Appropriate Shocks, or Death by Statin Treatment**

Cumulative probability for the occurrence of VT, VF, appropriate shocks, or death by statin treatment **(A)** and the probability for the occurrence of appropriate shock only by statin treatment **(B)**. Follow-up is censored upon change in statin usage after enrollment. *See Table 3 for multivariate model details. Abbreviations as in Figure 1.

Table 2 Multivariate Analysis: Risk Factors for Life-Threatening Ventricular Tachyarrhythmias in Study Patients

	Endpoint								
	Fast VT/VF or Death*			Fast VT/VF*			VF		
Covariate	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Time-dependent statin therapy	0.23	0.13–0.40	<0.001	0.57	0.31–1.05	0.071	0.53	0.29–0.99	0.046
Ejection fraction†	0.70	0.58–0.85	<0.001	0.71	0.54–0.92	0.010	0.71	0.55–0.93	0.012
History of prior atrial arrhythmias	2.40	1.38–4.19	0.002	1.29	0.51–3.27	0.589	1.33	0.53–3.38	0.545

Further adjusted for age, diabetes mellitus, hypertension, left ventricular end systolic volume indexed to body surface area and resynchronization treatment. *Fast ventricular tachycardia (VT) was defined as a VT with a cycle length <320 ms. †Per 5% increase in baseline left ventricular ejection fraction.

CI = confidence interval; HR = hazard ratio; VF = ventricular fibrillation.

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Predictors of Super-Response to Cardiac Resynchronization Therapy and Associated Improvement in Clinical Outcome

The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) Study

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San Francisco, California; Boston, Massachusetts; and Rochester, New York

Objectives The authors investigated predictors of left ventricular ejection fraction (LVEF) super-response to cardiac resynchronization therapy with defibrillator (CRT-D) and whether super-response translated into improved event-free survival in patients with mildly symptomatic heart failure (HF).

Background Few data exist on predictors of super-response to CRT-D and associated morbidity and mortality in mildly symptomatic HF populations.

Methods Patients were assigned to CRT-D with paired echocardiograms at baseline and at 12 months (n = 752). Super-response was defined by the top quartile of LVEF change. Best-subset regression analysis identified predictors of LVEF super-response. Kaplan-Meier survival analysis and Cox proportional hazards regression were performed to investigate associations of response category with development of nonfatal HF event or all-cause death.

Results All 191 super-responders experienced an LVEF increase of ≥14.5% (mean LVEF increase 17.5 ± 2.7%). Six predictors were associated with LVEF super-response to CRT-D therapy: female sex (odds ratio [OR]: 1.96; $p = 0.001$), no prior myocardial infarction (OR: 1.80; $p = 0.005$), QRS duration ≥150 ms (OR: 1.79; $p = 0.007$), left bundle branch block (OR: 2.05; $p = 0.006$), body mass index <30 kg/m^2 (OR: 1.51; $p = 0.035$), and smaller baseline left atrial volume index (OR: 1.47; $p < 0.001$). Cumulative probability of HF or all-cause death at 2 years was 4% in super-responders, 11% in responders, and 26% in hypo-responders (log-rank $p < 0.001$ overall). In multivariate analysis, hyporesponse was associated with increased risk of HF or all-cause death, compared with super-response (hazard ratio: 5.25; 95% confidence interval: 2.01 to 13.74; $p = 0.001$).

Conclusions Six baseline factors predicted LVEF super-response in CRT-D–treated patients with mild HF. Super-response was associated with reduced risk of subsequent cardiac events. (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy [MADIT-CRT]; NCT00180271) (J Am Coll Cardiol 2012;59: 2366–73) © 2012 by the American College of Cardiology Foundation

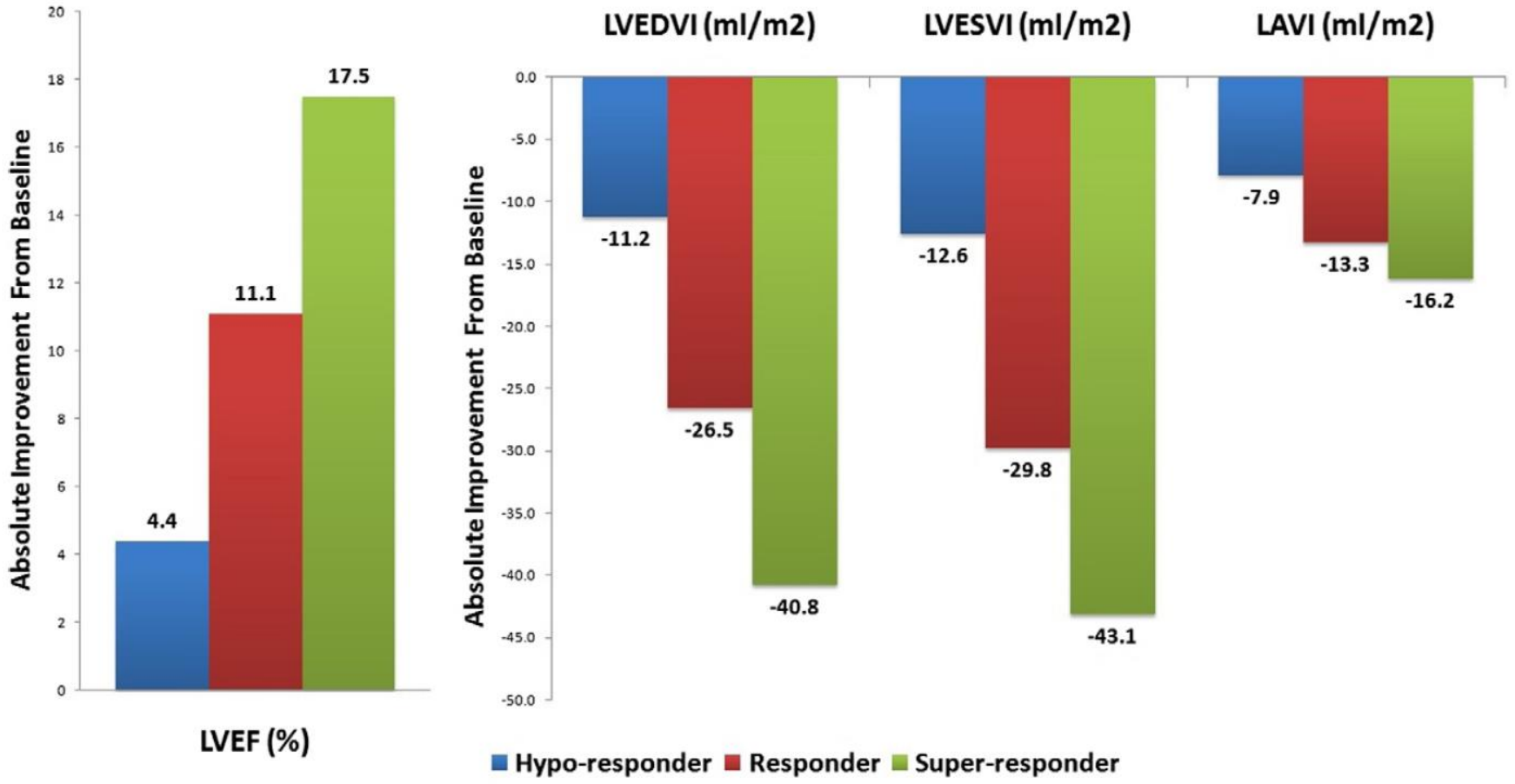

Figure 1 **Changes in Echocardiographic Parameters in Super-Responder, Responder, and Hypo-Responder Categories**

Changes in mean echocardiographic variables between baseline and 12-month follow-up among responder groups. LAVI = left atrial volume index; LVEDVI = left ventricular end diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end systolic volume index.

Table 3 Multivariate Analysis of Predictors of LVEF Super-Response

Variable	Odds Ratio	95% Confidence Interval	p Value
Female	1.96	1.32–2.90	0.001
QRS duration ≥150 ms	1.79	1.17–2.73	0.007
LBBB	2.05	1.24–3.40	0.006
Body mass index <30 kg/m^2	1.51	1.03–2.20	0.035
No prior myocardial infarction	1.80	1.20–2.71	0.005
Left atrial volume index, SD*	1.47	1.21–1.79	<0.001

*Per 1-U SD below mean.
Abbreviations as in Table 1.

EDITORIAL COMMENT

Device Therapy in Heart Failure

Has CRT Changed "the Sickest Benefit the Most" to "the Healthiest Benefit the Most?"*

Maurizio Gasparini, MD, Paola Galimberti, MD

Rozzano-Milan, Italy

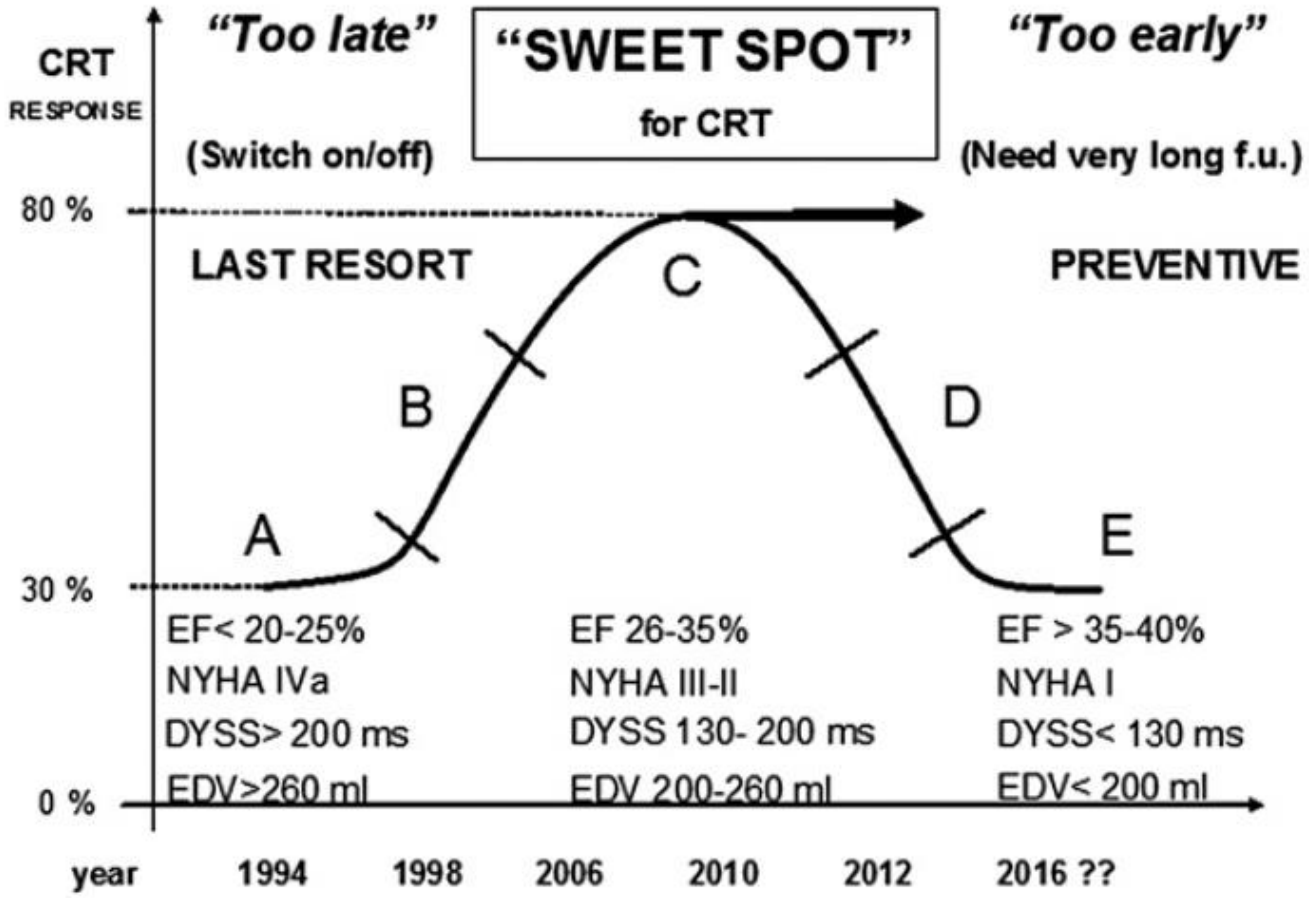

Figure 1 **Comparison of Theoretical CRT Response According to Baseline LVEF, NYHA Class, DYSS, and EDV**

CRT = cardiac resynchronization therapy; DYSS = dyssynchrony; EDV = end-diastolic volume; f.u. = follow-up; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

THANK YOU