Percutaneous Mitral Valve Repair: Results of the EVEREST II Trial

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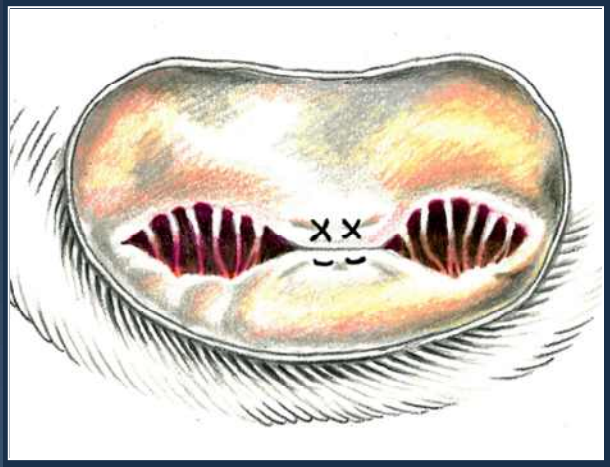
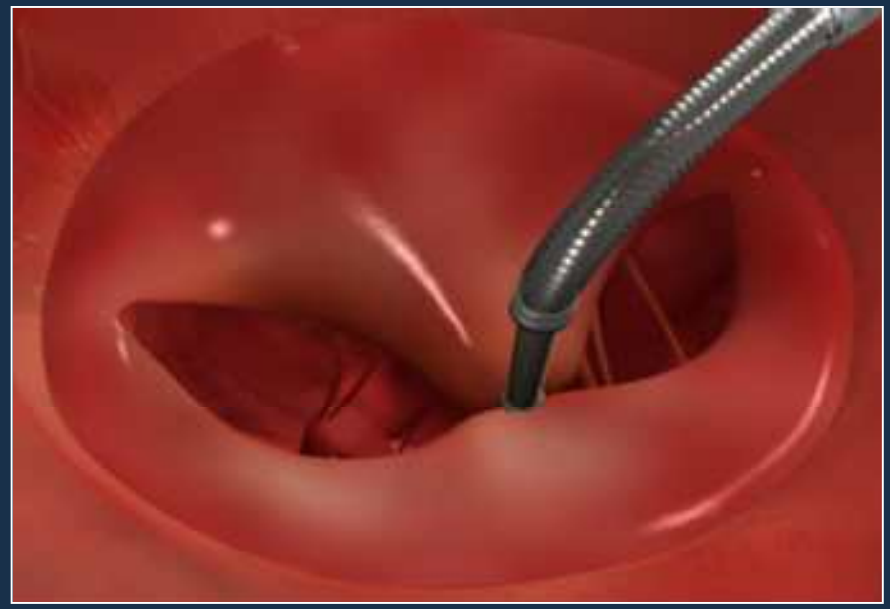
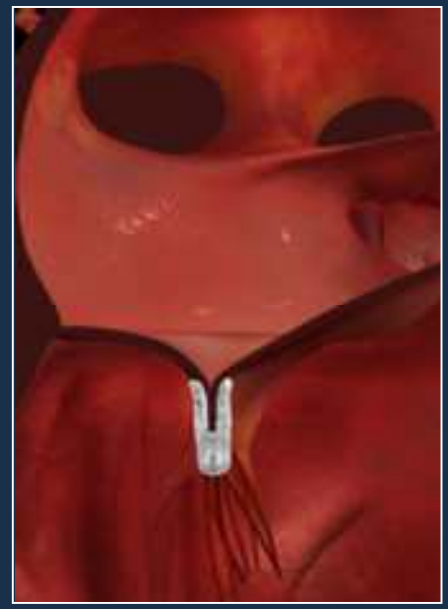
Catheter-based mitral valve repair

MitraClip System







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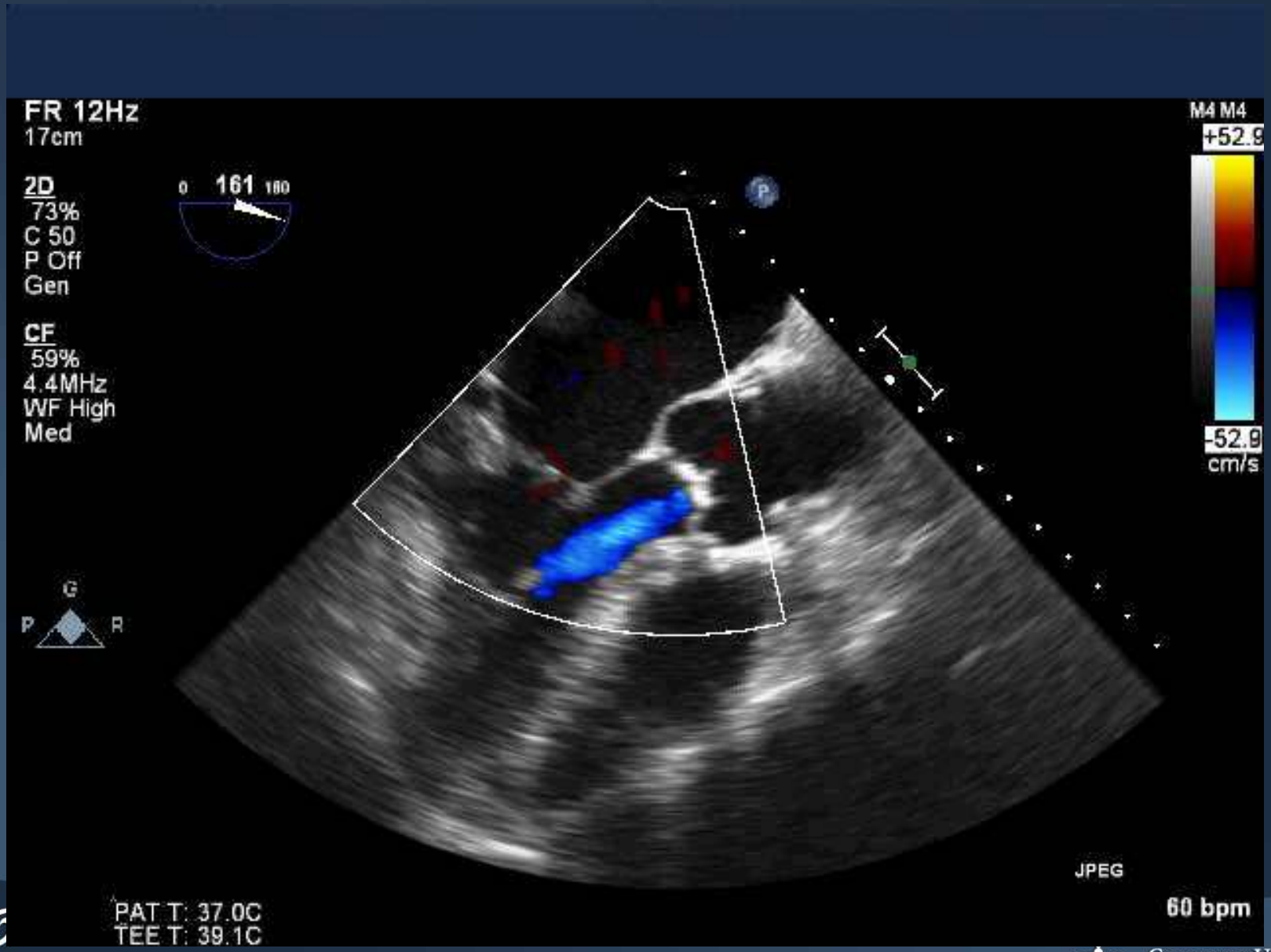
Baseline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CF
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WF High
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M4 M4
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cm/s
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JPEG
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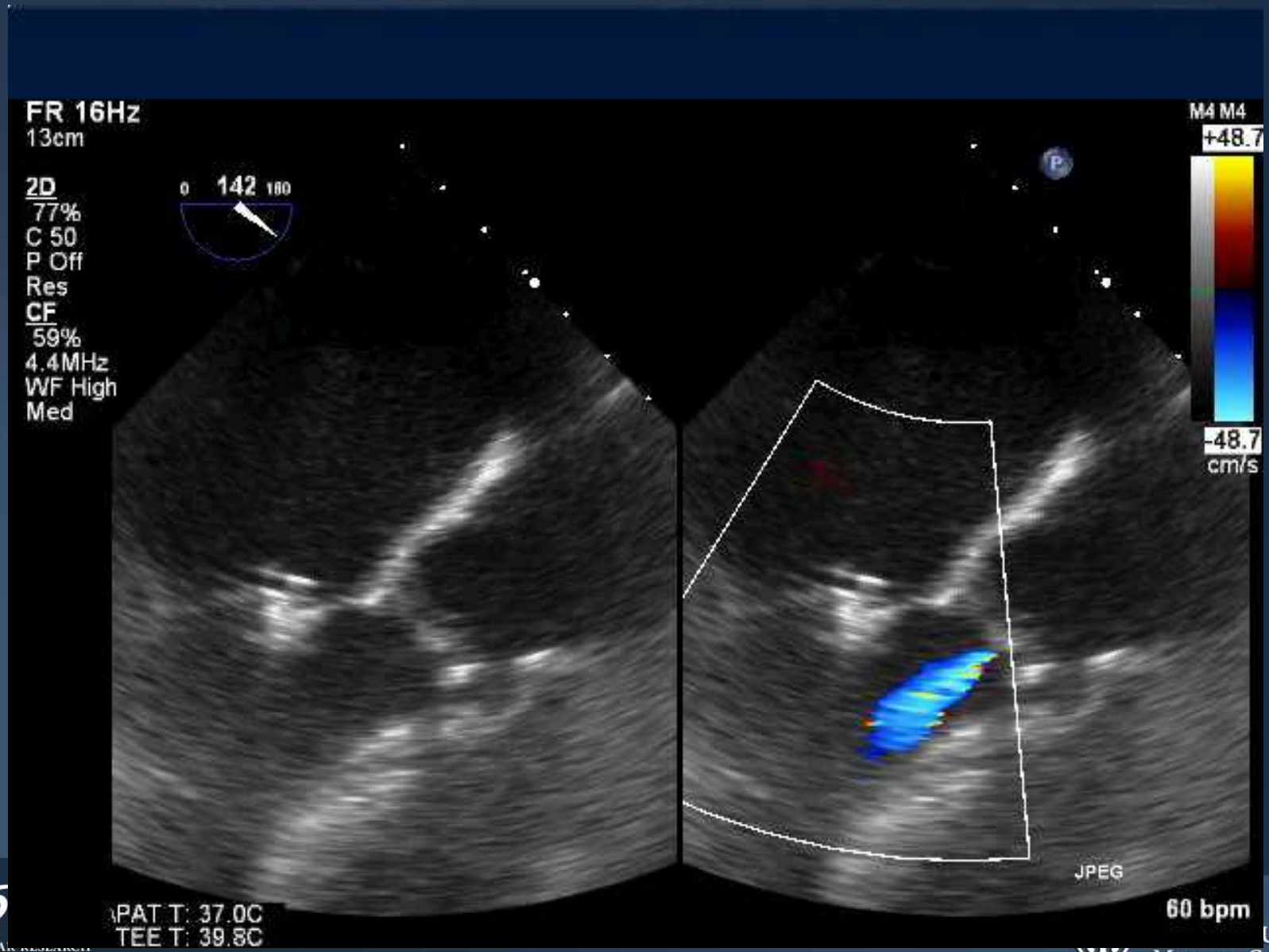
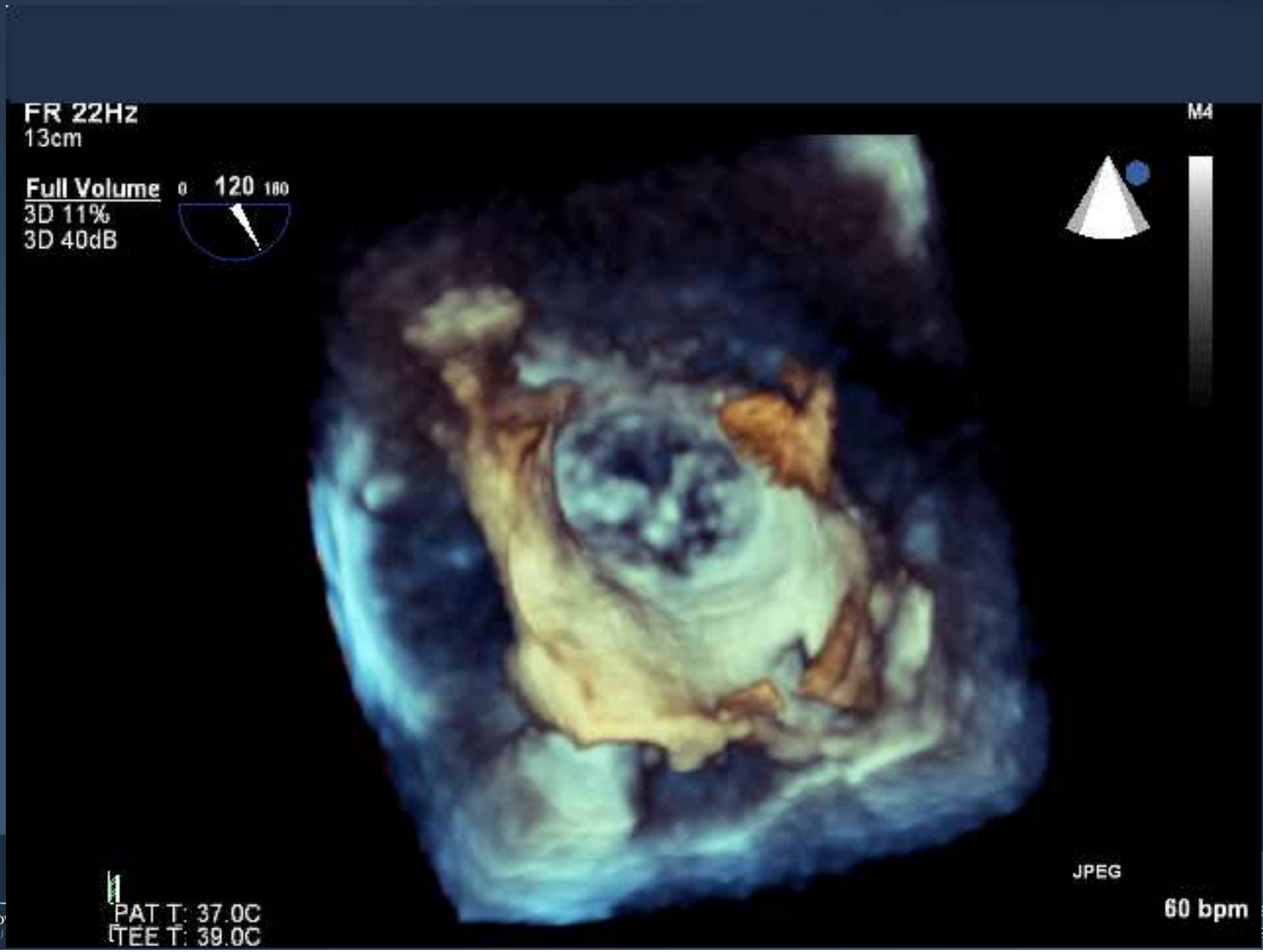
TEE T: 39.1C

Post Procedure



Atrial view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3D 11%
3D 40dB
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180
M4
JPEG
60 bpm
PAT T: 37.0C
TEE T: 39.0C

evalve clip MV repair: clinical experience

Study	Population	n
EVEREST I (Feasibility)*	Non-randomized	55
EVEREST II*	Pre-randomization	60
EVEREST II	High Risk Registry	78
EVEREST II (Pivotal)	Randomized patients (2:1 MitraClip to Surgery)	279 184 MitraClip 95 Surgery
REALISM (Continued Access)	High Risk & Non High Risk	266
European Experience		472
	Total	1,115 MitraClip

*Percutaneous Mitral Valve Repair Using the Edge-to-Edge Repair: Six months Results of the EVEREST Phase I Clinical trial, JACC 2005;46:2134-2140.
Percutaneous Mitral Repair with the MitraClip System: Safety and Midterm Durability in the Initial EVEREST Cohort, JACC 2009; 54:686-694.

EVEREST II: randomized clinical trial

Study design

279 Patients enrolled at 37 sites

Significant MR (3+-4+)
Specific Anatomical Criteria

↓

Randomized 2:1

Device Group
MitraClip System
N=184

Control Group
Surgical Repair or Replacement
N=95

Echocardiography Core Lab and Clinical Follow-Up:
Baseline, 30 days, 6 months, 1 year, 18 months, and annually through 5 years

EVEREST II: randomized clinical trial

Key inclusion/exclusion criteria

Inclusion

- Candidate for MV Surgery
- Moderate to severe (3+) or severe (4+) MR
  - Symptomatic
    - >25% EF & LVESD ≤55mm
  - Asymptomatic with one or more of the following
    - LVEF 25-60%
    - LVESD ≥40mm
    - New onset atrial fibrillation
    - Pulmonary hypertension

ACC/AHA Guidelines
JACC 52:e1-e142, 2008

Exclusion

- AMI within 12 weeks
- Need for other cardiac surgery
- Renal insufficiency
  - Creatinine >2.5mg/dl
- Endocarditis
- Rheumatic heart disease
- MV anatomical exclusions
  - Mitral valve area <4.0cm^2
  - Leaflet flail width (≥15mm) and gap (≥10mm)
  - Leaflet tethering/coaptation depth (>11mm) and length (<2mm)

EVEREST II: randomized clinical trial

Baseline demographics and co-morbidities

	Device (%) n=184	Control (%) n=95	*P*
Age (mean)	67.3 years	65.7 years	0.32
Male	62.5	66.3	0.60
Congestive heart failure	90.8	77.9	<0.01
Coronary artery disease	47.0	46.3	>0.99
Myocardial infarction	21.9	21.3	>0.99
Angina	31.9	22.2	0.12
Atrial fibrillation	33.7	39.3	0.42
Cerebrovascular disease	7.6	5.3	0.62
Peripheral vascular disease	6.5	11.6	0.17
Cardiomyopathy	17.9	14.7	0.61
Hypercholesterolemia	61.0	62.8	0.80
Hypertension	72.3	78.9	0.25
Moderate to severe renal disease	3.3	2.1	0.72
Diabetes	7.6	10.5	0.50
Previous cardiovascular surgery	22.3	18.9	0.54
MR Severity: 3+ to 4+	95.7	92.6	0.48
MR Etiology: Degenerative / Functional	73 / 27	73 / 27	0.81

EVEREST II: randomized clinical trial
demographic comparison

	EVEREST II RCT	2008 STS Database		Isolated 1st Elective Operation for MR*
	n=279	Repair	Replace	High Volume Hospitals (>140/Yr)
Age yrs (mean)	68	60	61	59
≥65 yrs	58%	37%	45%	n/a
≥75 yrs	32%	n/a	n/a	0%
NYHA Class III or IV	50%	26%	45%	n/a
CHF	86%	41%	58%	n/a
Hypertension	75%	60%	67%	43%
Diabetes Mellitus	9%	13%	23%	6.5%
COPD / Chronic Lung Disease	15%	17%	29%	n/a
EF (mean)	60%	53%	55%	56%

EVEREST II: randomized clinical trial
Primary endpoints

Safety
- Major Adverse Event Rate at 30 days
- Per protocol cohort
- Superiority hypothesis

Effectiveness
- Clinical Success Rate
  - Freedom from the combined outcome of
    - Death
    - MV surgery or re-operation for MV dysfunction
    - MR >2+ at 12 months
- Per protocol cohort
- Non-inferiority hypothesis

Pre-Specified MAEs
Death
Major Stroke
Re-operation of Mitral Valve
Urgent / Emergent CV Surgery
Myocardial Infarction
Renal Failure
Deep Wound Infection
Ventilation >48 hrs
New Onset Permanent Atrial Fib
Septicemia
GI Complication Requiring Surgery
All Transfusions ≥2 units

EVEREST II: randomized clinical trial
Additional analysis

Intention to Treat

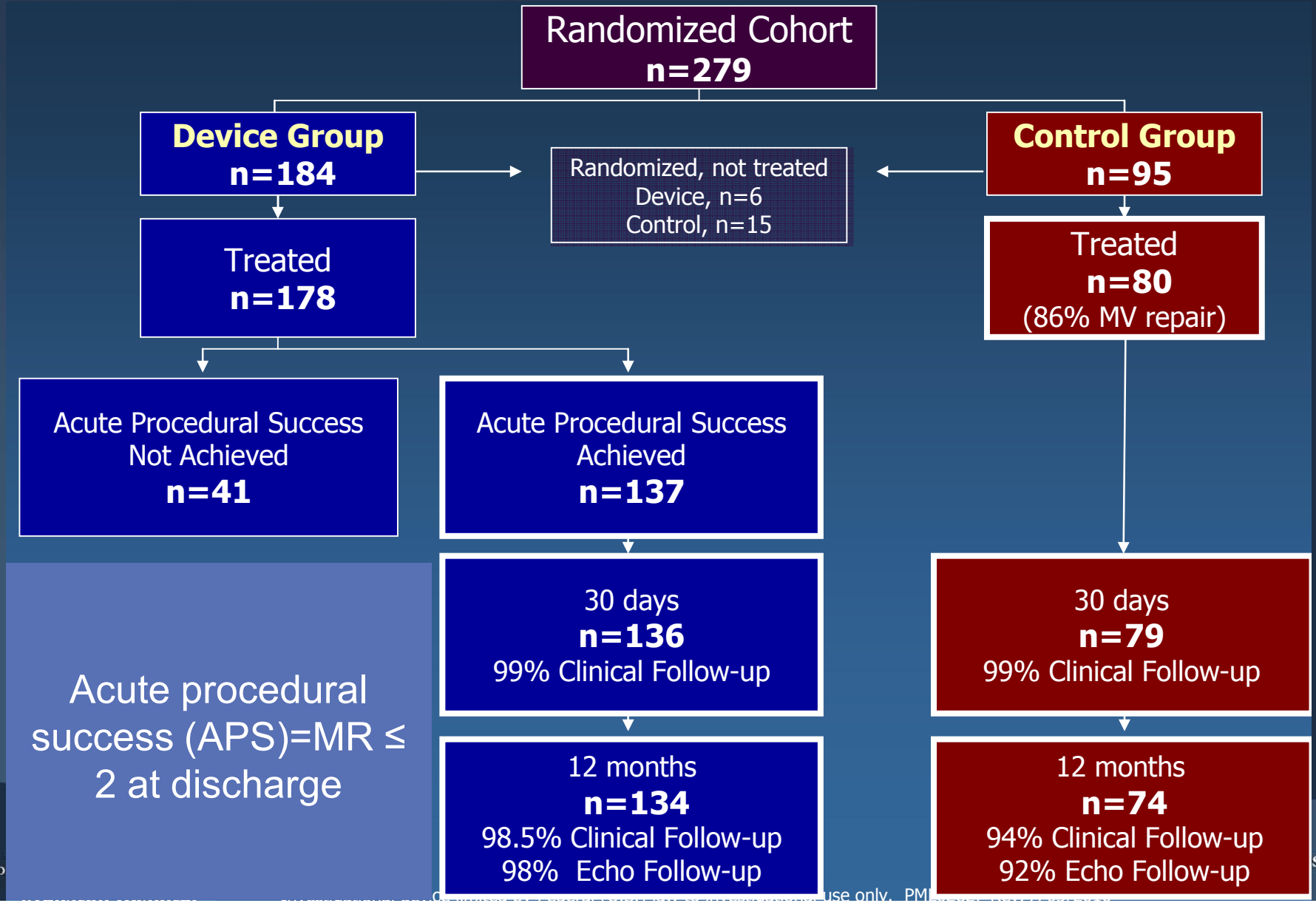
- Safety
  - Major Adverse Event Rate at 30 days
- Effectiveness
  - Freedom from the combined outcome of death, MV surgery >90 days or re-operation for valve dysfunction >90 days post Index procedure, and MR >2+ at 12 months

Clinical Benefit (per protocol cohort)

- MR Severity
- Left Ventricular Function
- NYHA Functional Class
- Quality of Life (SF-36 Survey)

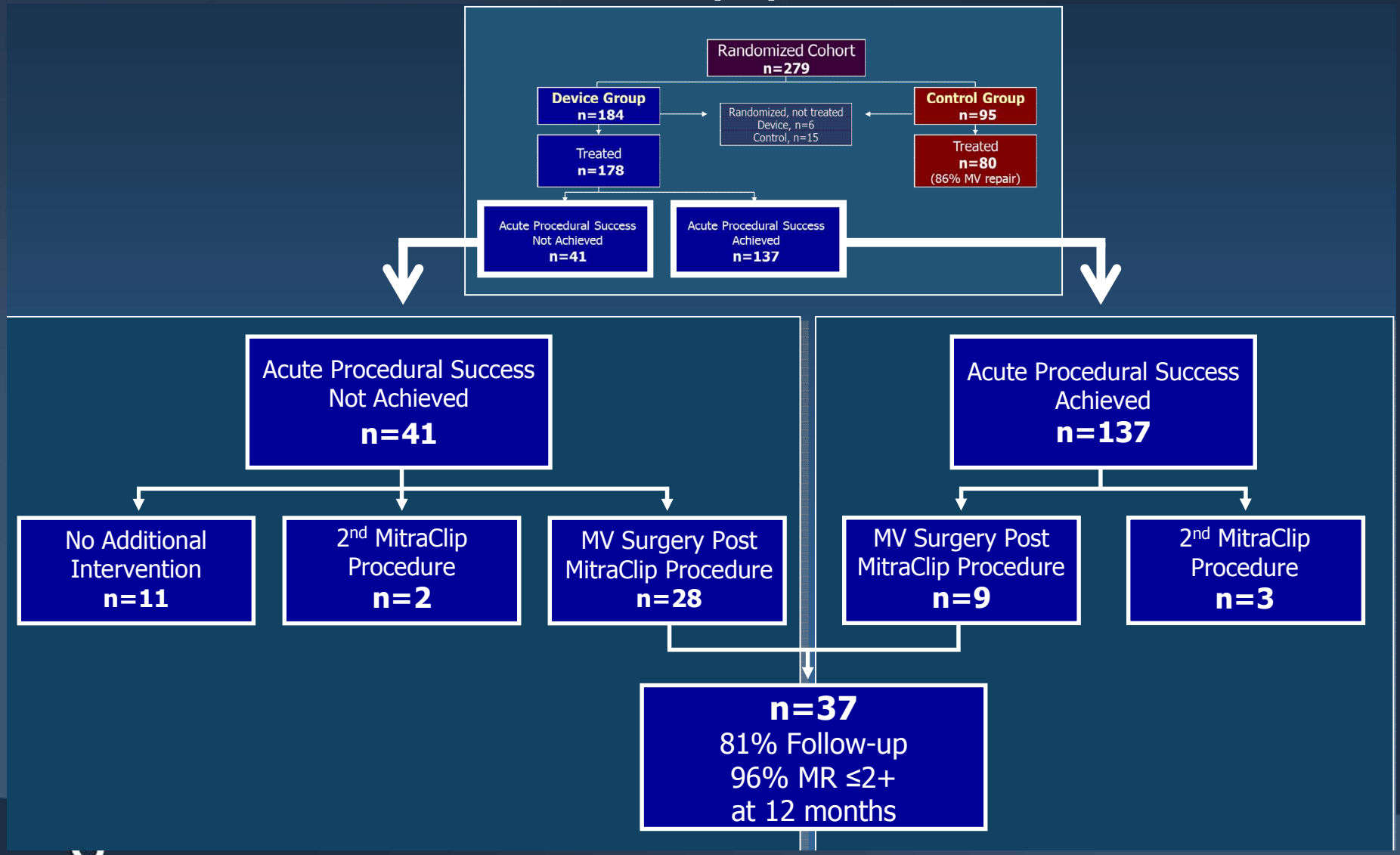
EVEREST II: Patient flow

Per protocol cohort: Analysis of device performance



EVEREST II: Patient flow

Post MitraClip procedure



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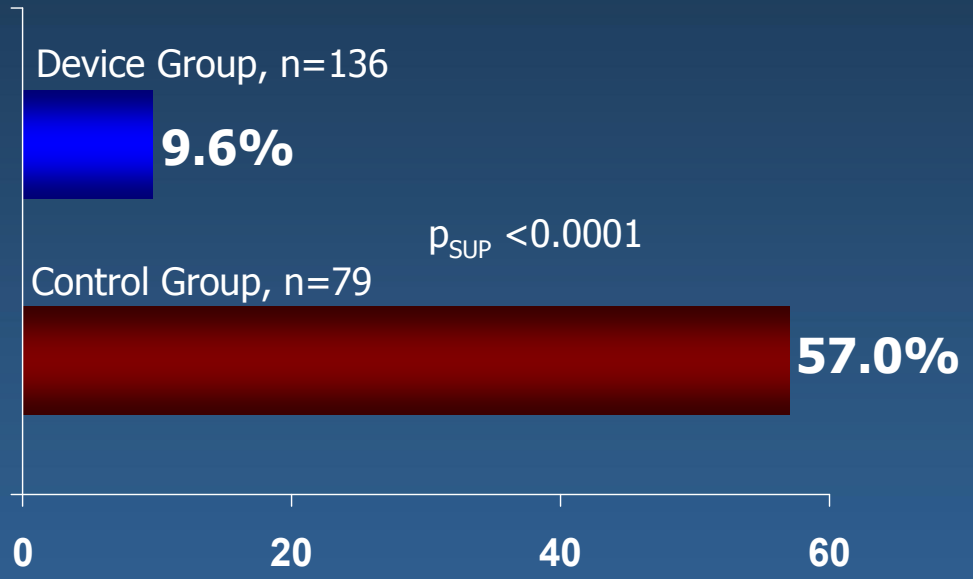
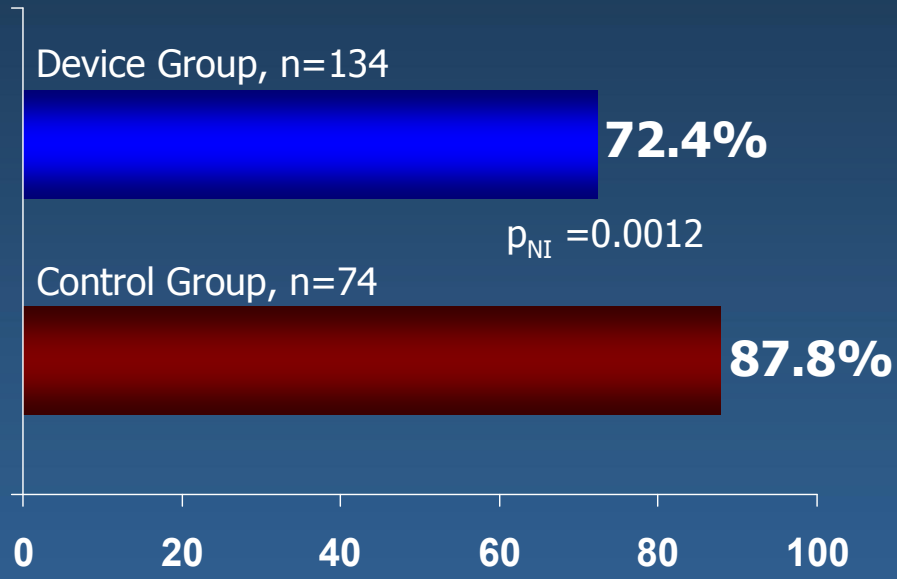
EVEREST II: Primary endpoints
Per protocol cohort

Safety
Major Adverse Events
30 days



Met superiority hypothesis
- Pre-specified margin = 6%
- Observed difference = **47.4%**
- 97.5% LCB = 34.4%

Effectiveness
Clinical Success Rate*
12 months



Met non-inferiority hypothesis
- Pre-specified margin = 31%
- Observed difference = **15.4%**
- 95% UCB = 25.4%

LCB=lower confidence bound
UCB=upper confidence bound

*Freedom from the combined outcome of death, MV surgery or re-operation for MV dysfunction, MR≥2+ at 12 months

EVEREST II: Primary safety endpoint

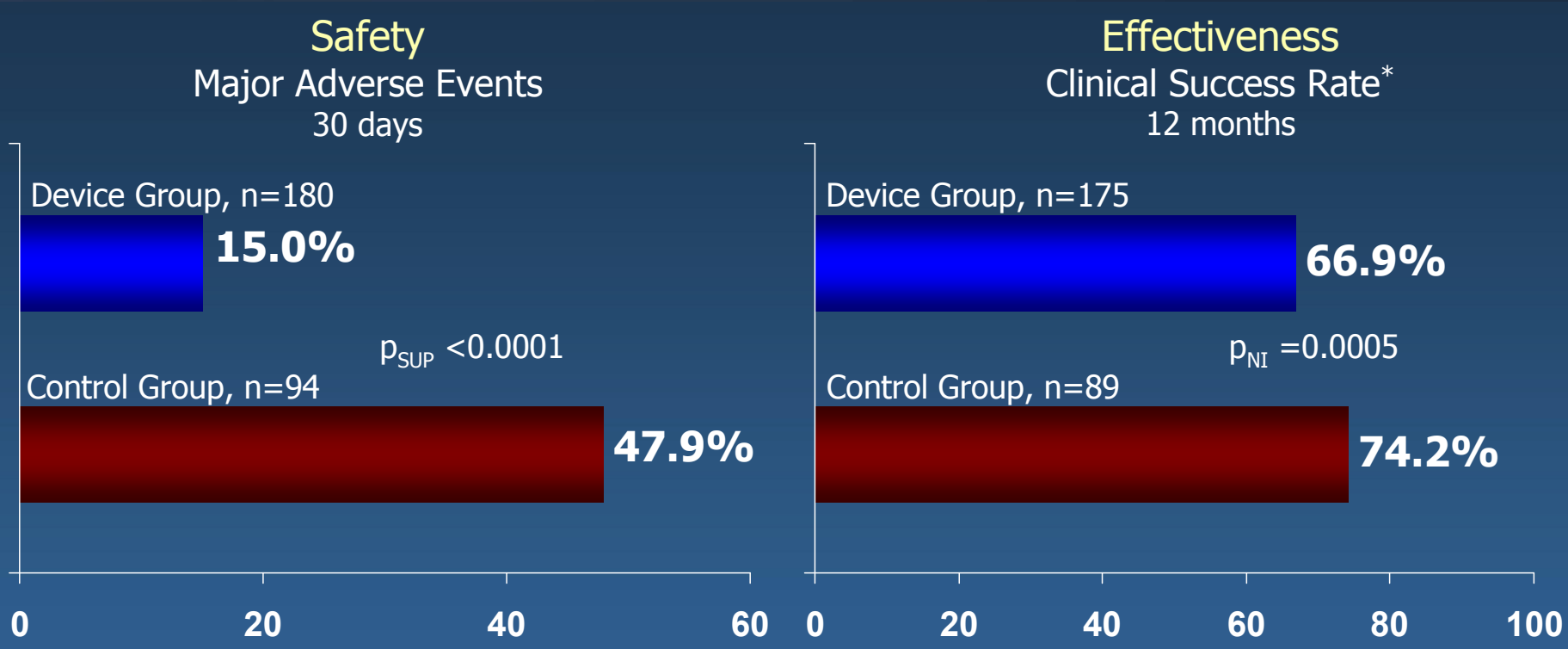
Per protocol cohort

30 Day MAE, non-hierarchical	# Patients experiencing event Device Group (n=136)	 Control Group (n=79)
Death	0	2 (2.5%)
Major Stroke	0	2 (2.5%)
Re-operation of Mitral Valve	0	1 (1.3%)
Urgent / Emergent CV Surgery	0	4 (5.1%)
Myocardial Infarction	0	0
Renal Failure	0	0
Deep Wound Infection	0	0
Ventilation >48 hrs	0	4 (5.1%)
New Onset Permanent Atrial Fib	0	0
Septicemia	0	0
GI Complication Requiring Surgery	1 (0.7%)	0
All Transfusions ≥2 units*	12 (8.8%)	42 (53.2%)
TOTAL % of Patients with MAE	**9.6%**	**57.0%**
	p<0.0001*	
	(95% CI 34.4%, 60.4%)	

*p<0.0001 if include Major Bleeding only

EVEREST II: Safety and effectiveness

Intention to treat cohort



Met superiority hypothesis

- Pre-specified margin =2%
- Observed difference = **32.9%**
- 97.5% LCB = 20.7%

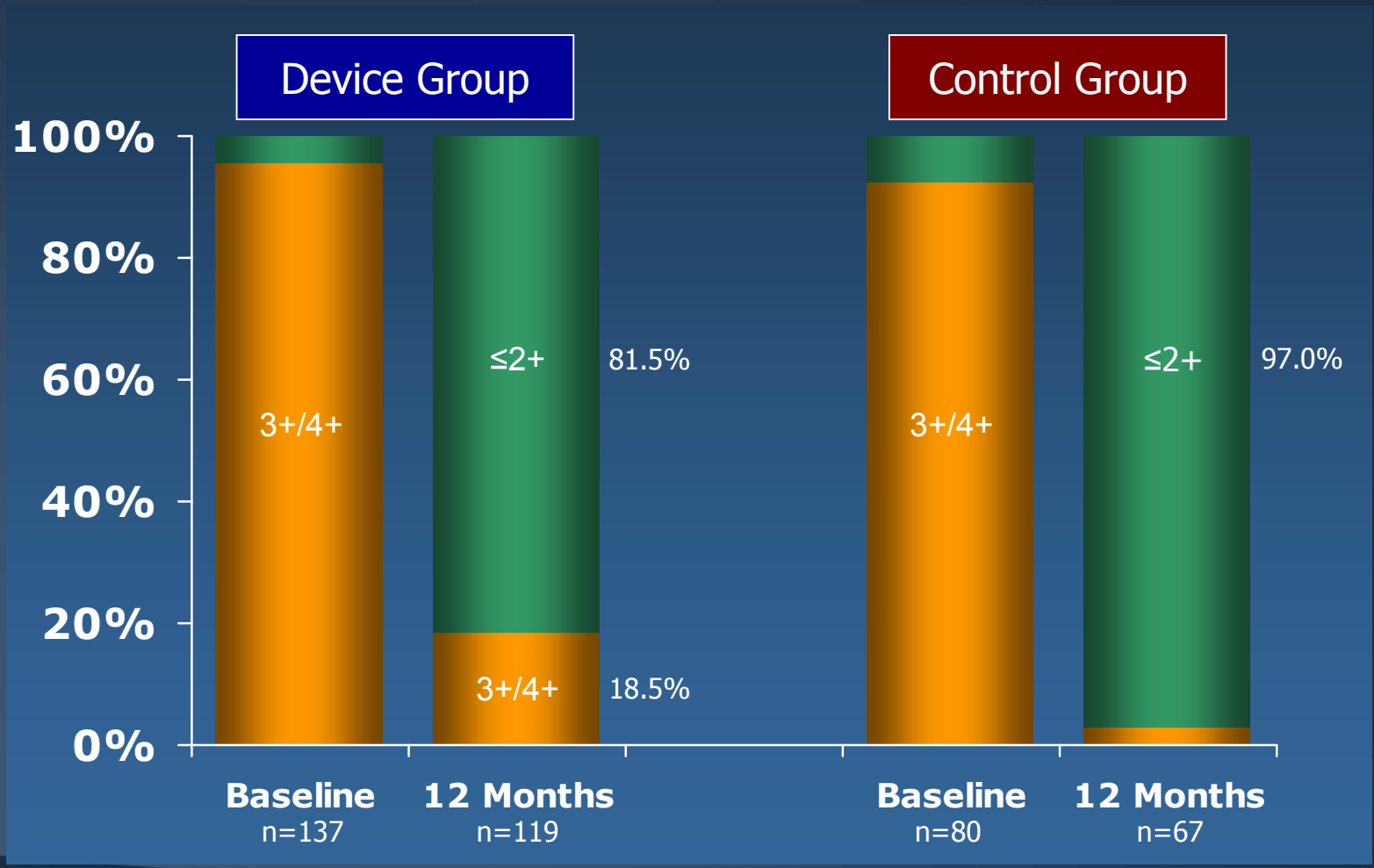
Met non-inferiority hypothesis

- Pre-specified margin = 25%
- Observed difference = **7.3%**
- 95% UCB = 17.8%

LCB=lower confidence bound
UCB=upper confidence bound

*Freedom from the combined outcome of death, MV surgery or re-operation for MV dysfunction, MR≥2+ at 12 months

EVEREST II: MR reduction
per protocol cohort



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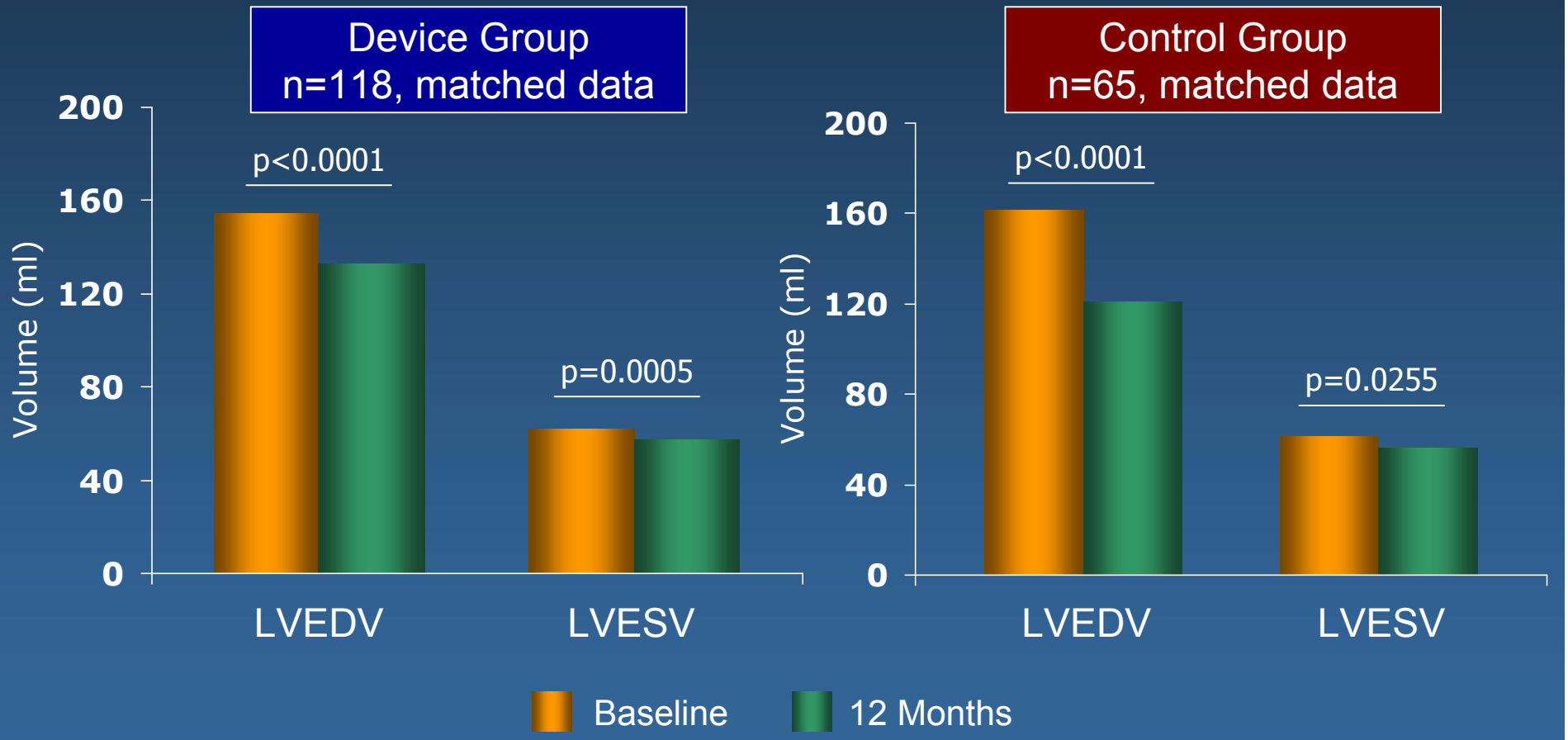
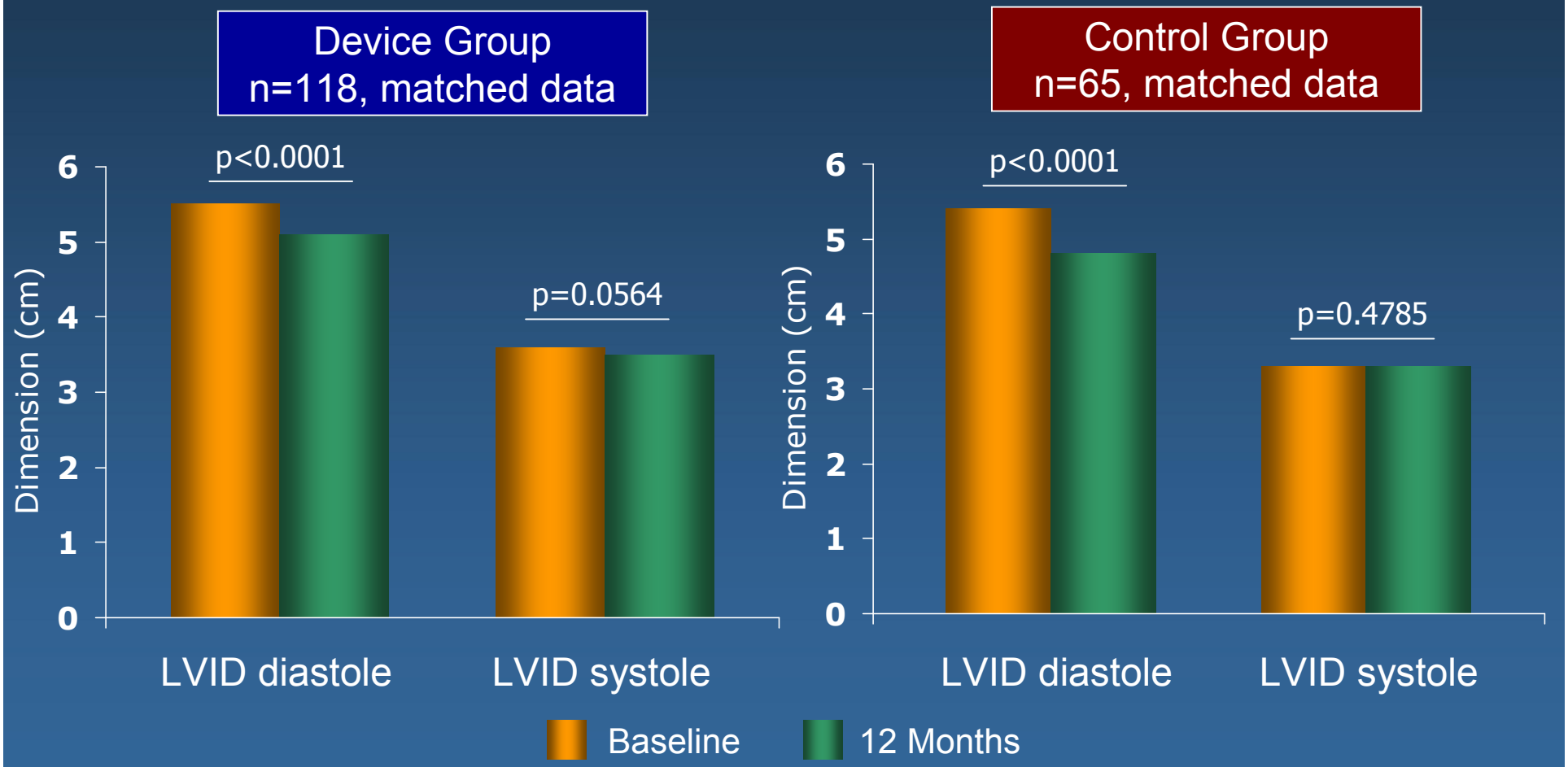
EVEREST II: LV volume

Per protocol cohort (pre-specified hypothesis)

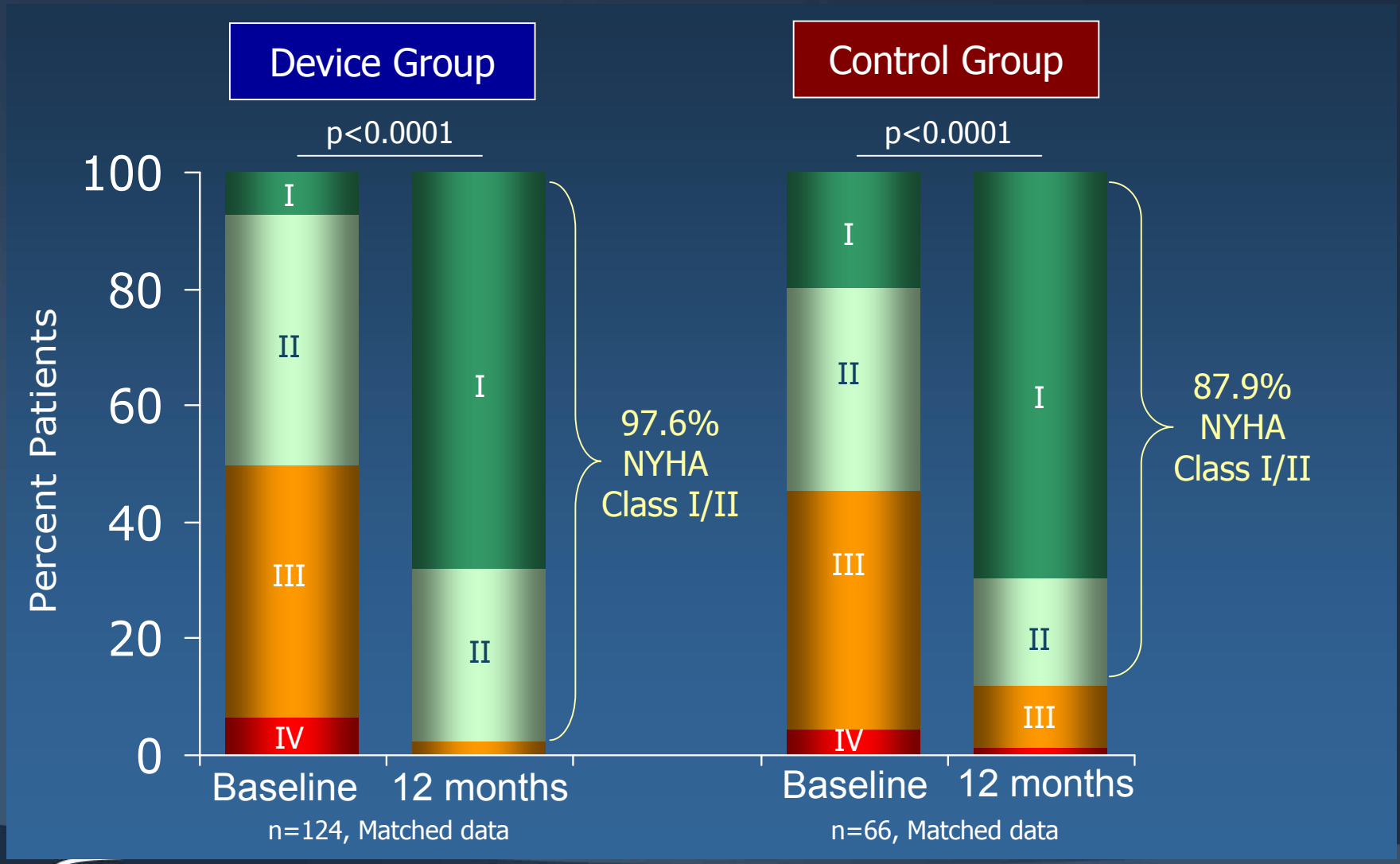


EVEREST II: LV dimension

Per protocol analysis (pre-specified hypothesis)



EVEREST II: NYHA functional class
per protocol cohort



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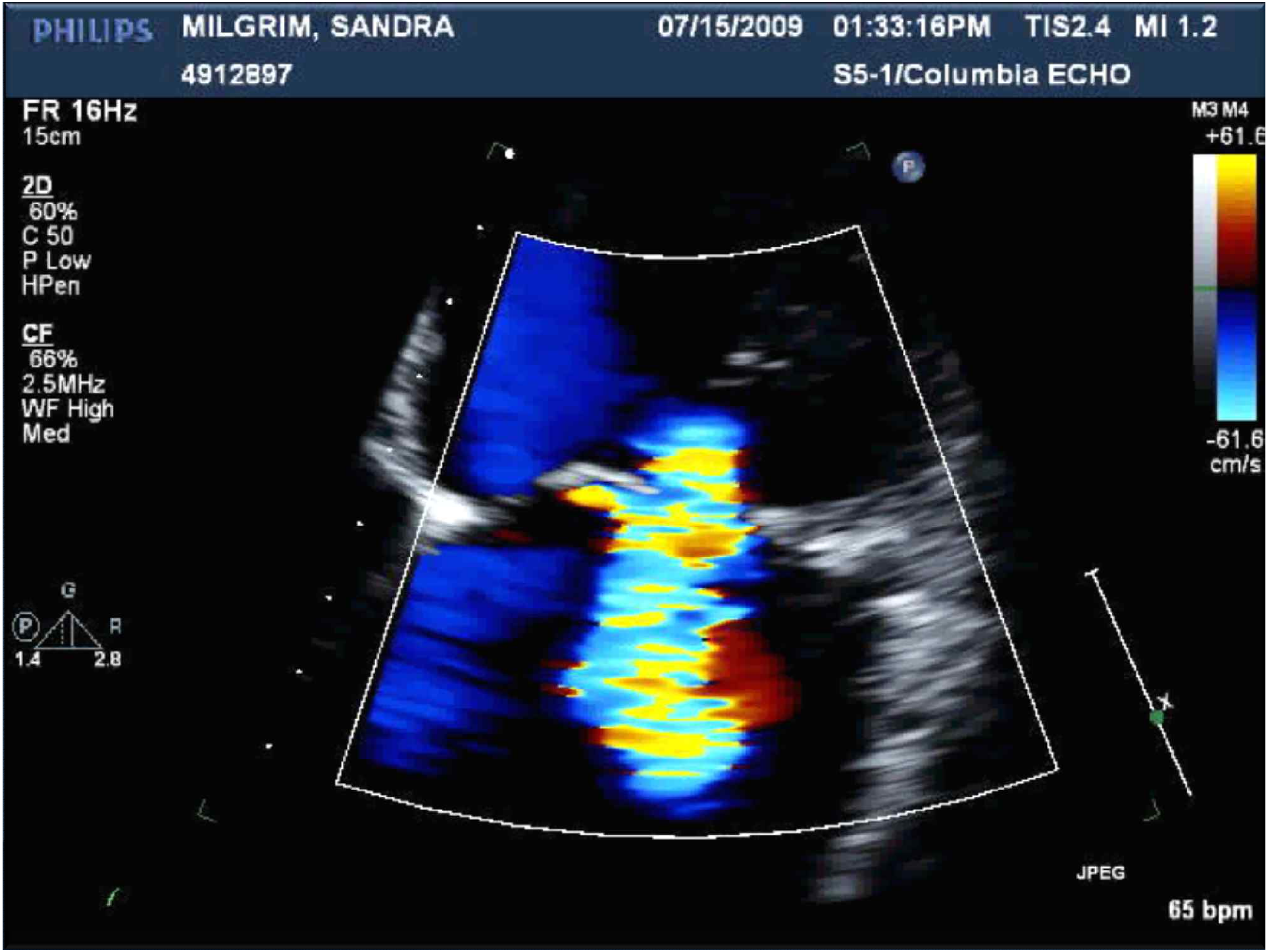
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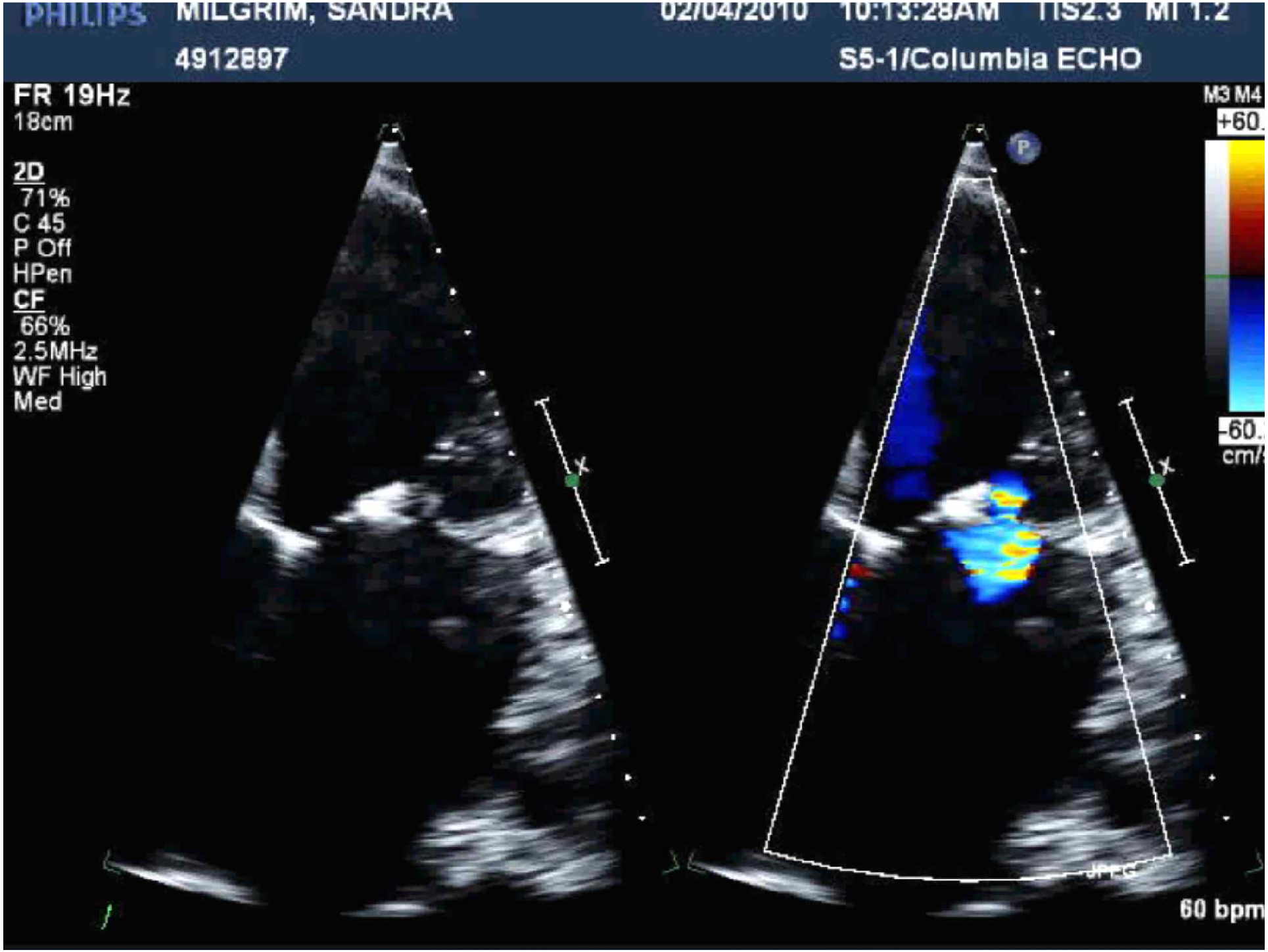
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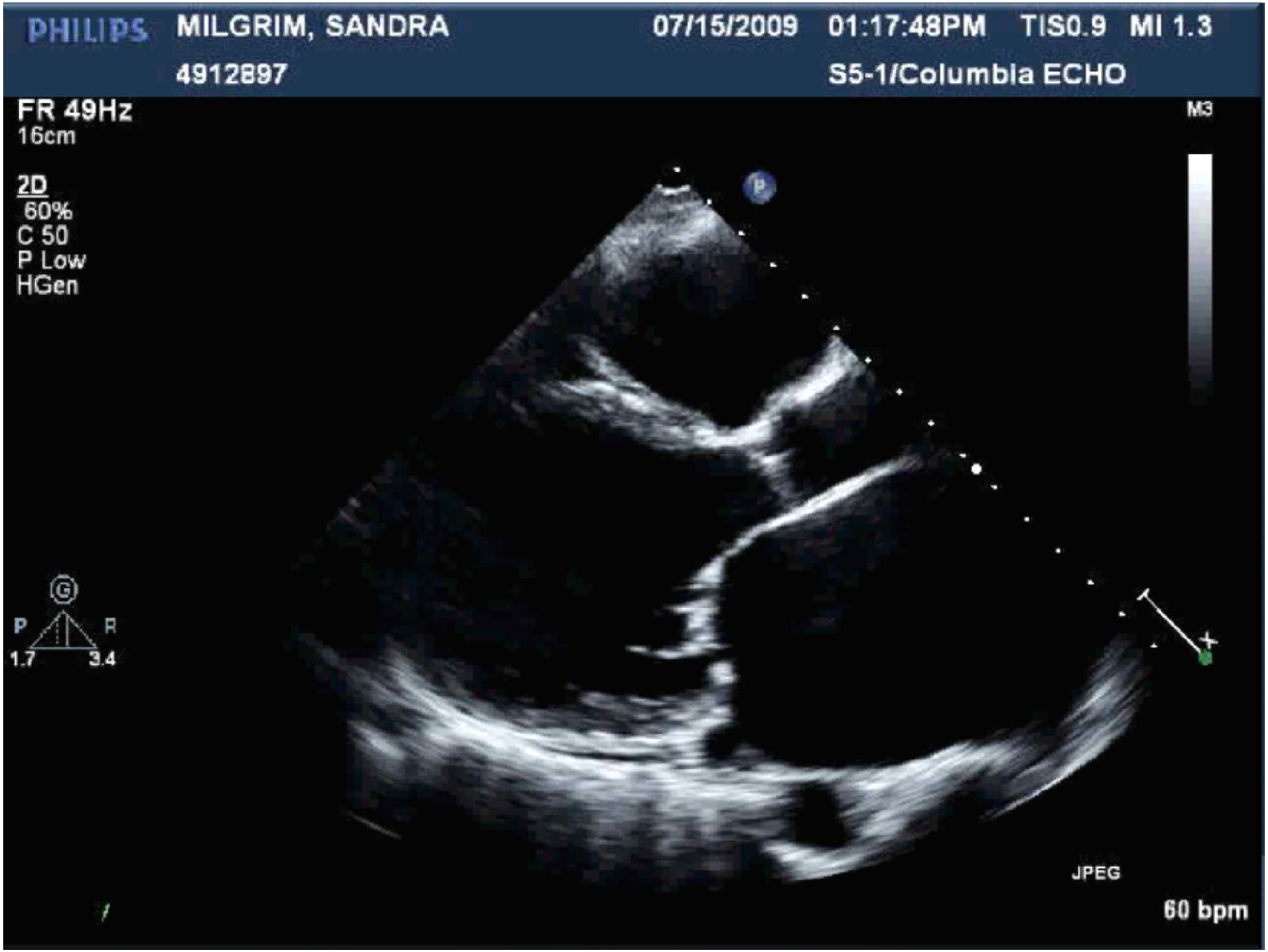
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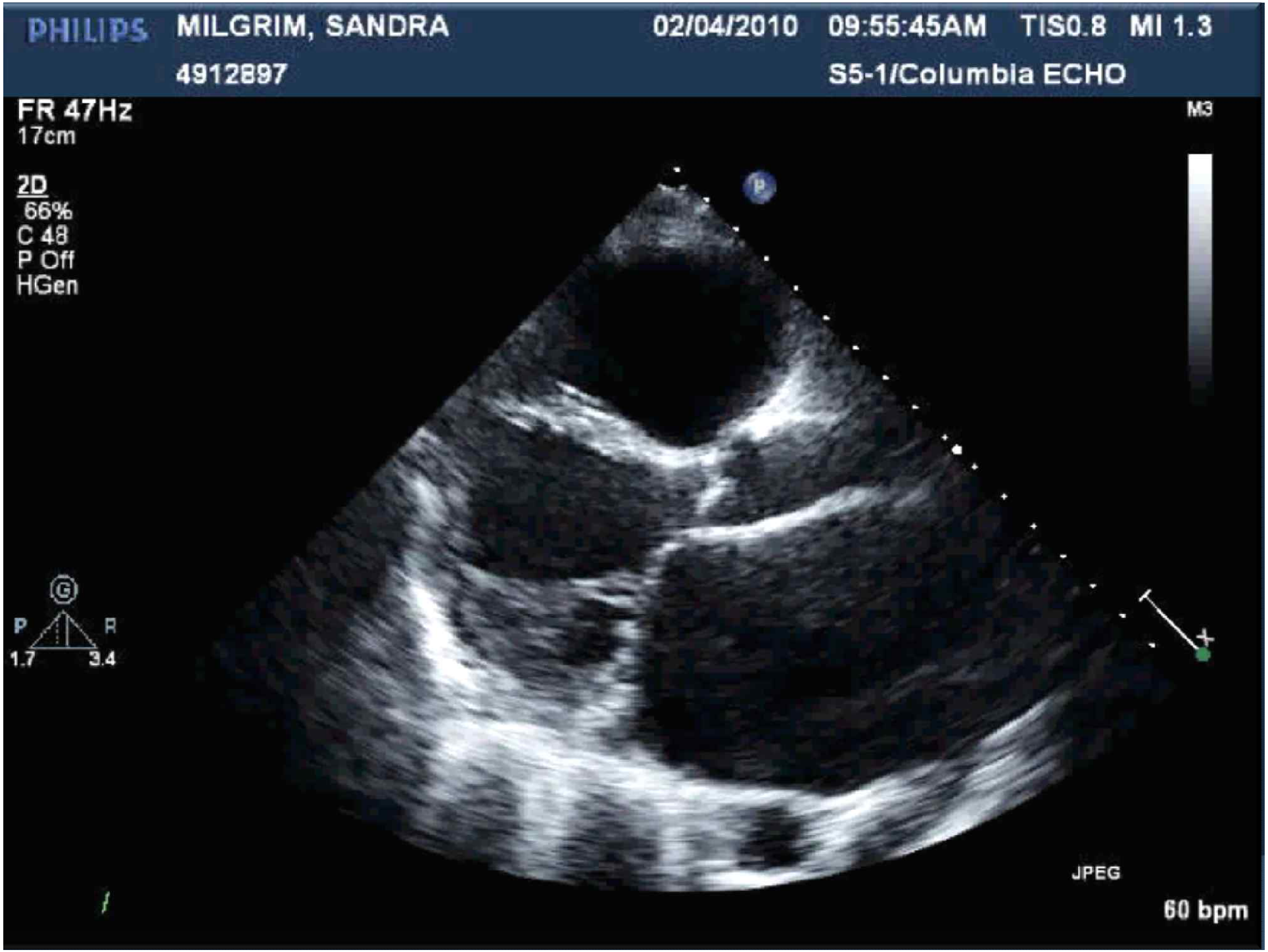
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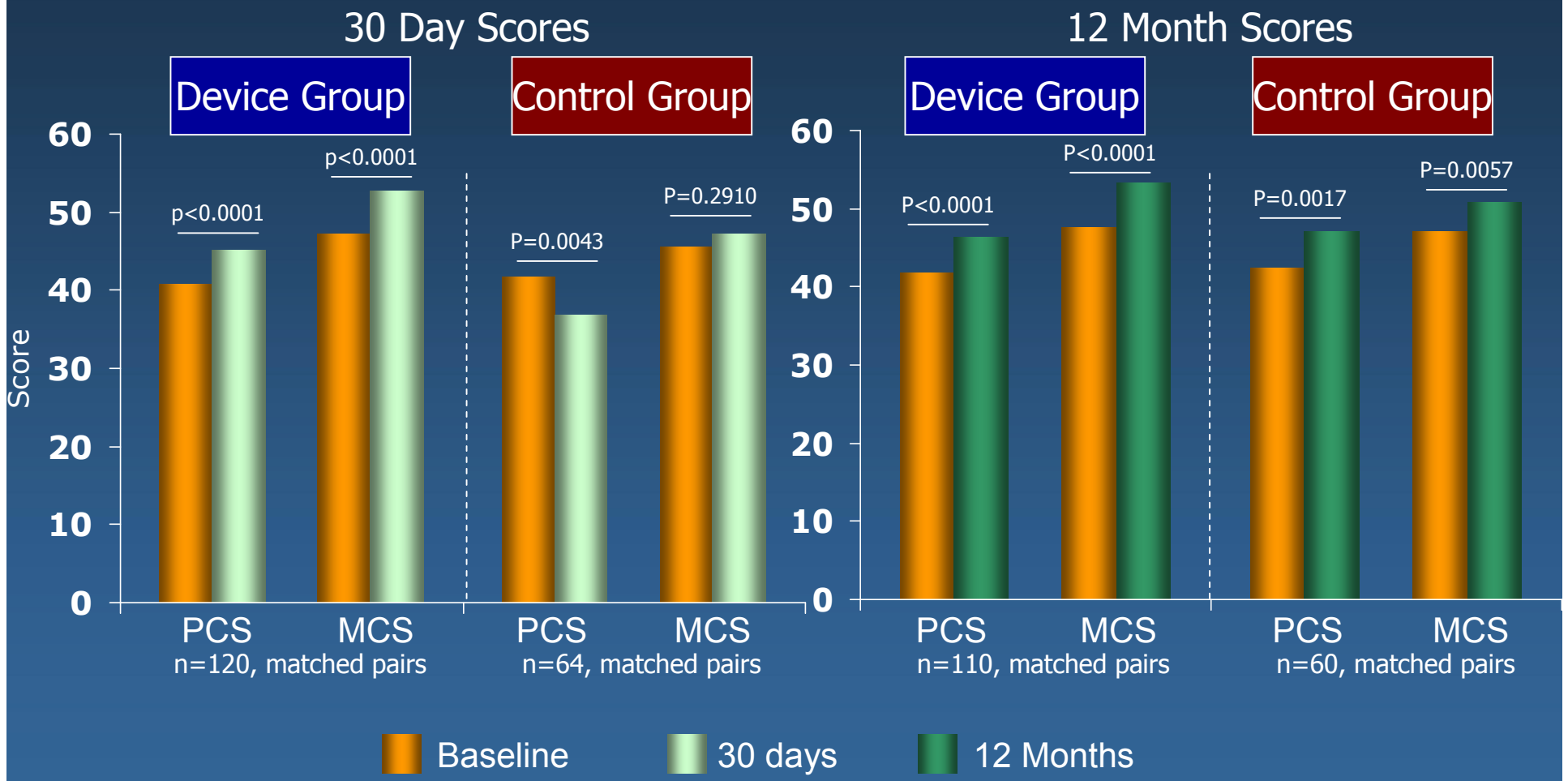
60 bpm

EVEREST II: Quality of life, SF-36 survey

Per protocol cohort



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EVEREST II: summary

- Safety & effectiveness endpoints met
  - Safety: MAE rate at 30 days
    - MitraClip device patients: 9.6%
    - MV surgery patients: 57%
  - Effectiveness: Clinical Success Rate at 12 months
    - MitraClip device patients: 72%
    - MV Surgery patients: 88%
- Clinical benefit demonstrated for MitraClip System and MV surgery patients through 12 months
    - Improved LV function
    - Improved NYHA Functional Class
    - Improved Quality of Life
- Surgery remains an option after the MitraClip procedure