Recommendation to Update the Medicare National Coverage Policy for Ventricular Assist Devices (VADs) to include Destination Therapy

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James Long, M.D.,Ph.D., and
Leslie Miller, M.D.

Medicare Coverage Advisory Committee

March 12, 2003

Objectives

- Document the net health benefit of left ventricular assist devices (LVADs) for Destination Therapy in end-stage heart failure (ESHF) patients
- Elucidate ongoing improvements to enhance outcomes with LVAD therapy
- Outline guidelines for responsible dissemination of LVAD therapy

The Evidence Base for Use of Left Ventricular Assist Devices (LVADs) for Destination Therapy

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Treatment Options
End-Stage Heart Failure

- Medical management - limited by poor outcomes
- Cardiac transplantation - limited by donor shortage
- **Mechanical circulatory support devices**
  - Left ventricular assist device (LVAD)

LVAD (HeartMate®)

- Implanted pump restores circulatory support

- Extensive experience and incremental improvement with bridge-to-transplant in more than 3,400 patients since 1986

Critical Clinical Issue

Can LVADs improve net health outcomes when used as a long-term “Destination Therapy” for patients with end-stage heart failure?

REMATCH

Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure

The New England Journal of Medicine

VOLUME 345 NOVEMBER 15, 2001 NUMBER 20

LONG-TERM USE OF A LEFT VENTRICULAR ASSIST DEVICE FOR END-STAGE HEART FAILURE

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Key REMATCH Study Objectives

- **Efficacy:** To evaluate the effect of LVADs on the survival and quality of life (QOL) of patients with end-stage heart failure who are ineligible for cardiac transplantation

- **Safety:** Document and analyze adverse events (AEs) and the incidence of device malfunction and failure

- **Primary hypothesis:** 33% reduction in mortality with equal or improved QOL for LVAD versus optimal medical management (OMM) patients over 2 years

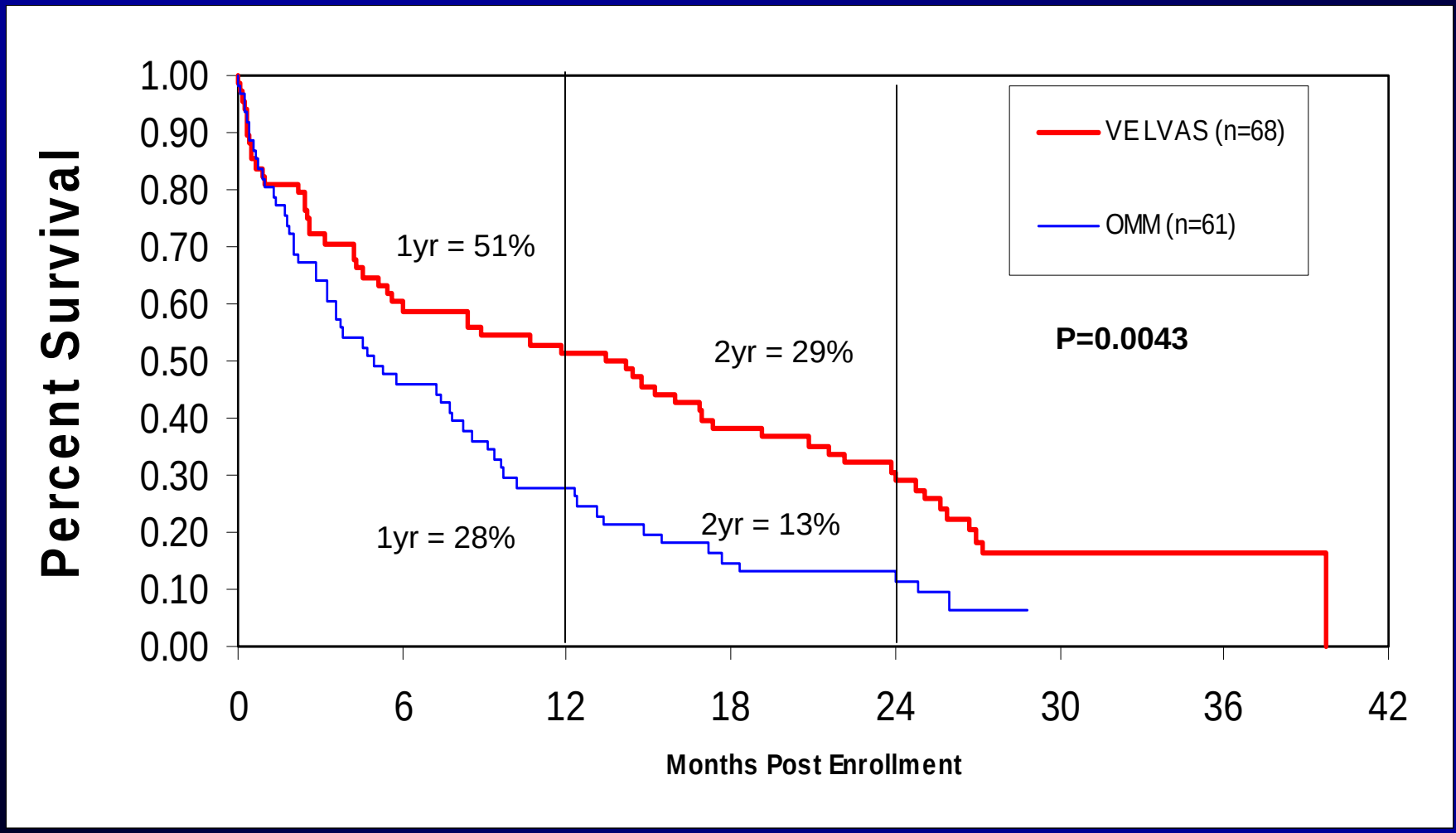
Design of REMATCH Trial

- Columbia University, NIH, and Thoratec
- Multicenter, randomized controlled trial (21 Centers)
- Credentialed investigators: cardiologist and surgeon
- Gatekeeper: reviews each patient eligibility
- Intent to treat analysis - Kaplan-Meier and Logrank
- 129 patients
  - 68 patients randomized to VAD
  - 61 patients randomized to Optimal Medical Management (OMM)

REMATCH Findings

- LVADs reduce mortality 48% in patients with ESHF over 2 years compared to optimal medical management (OMM) controls
- LVAD patients' QOL exceeds OMM controls

Intent to Treat Analysis as of January 15, 2003



Overview of REMATCH Survival Data

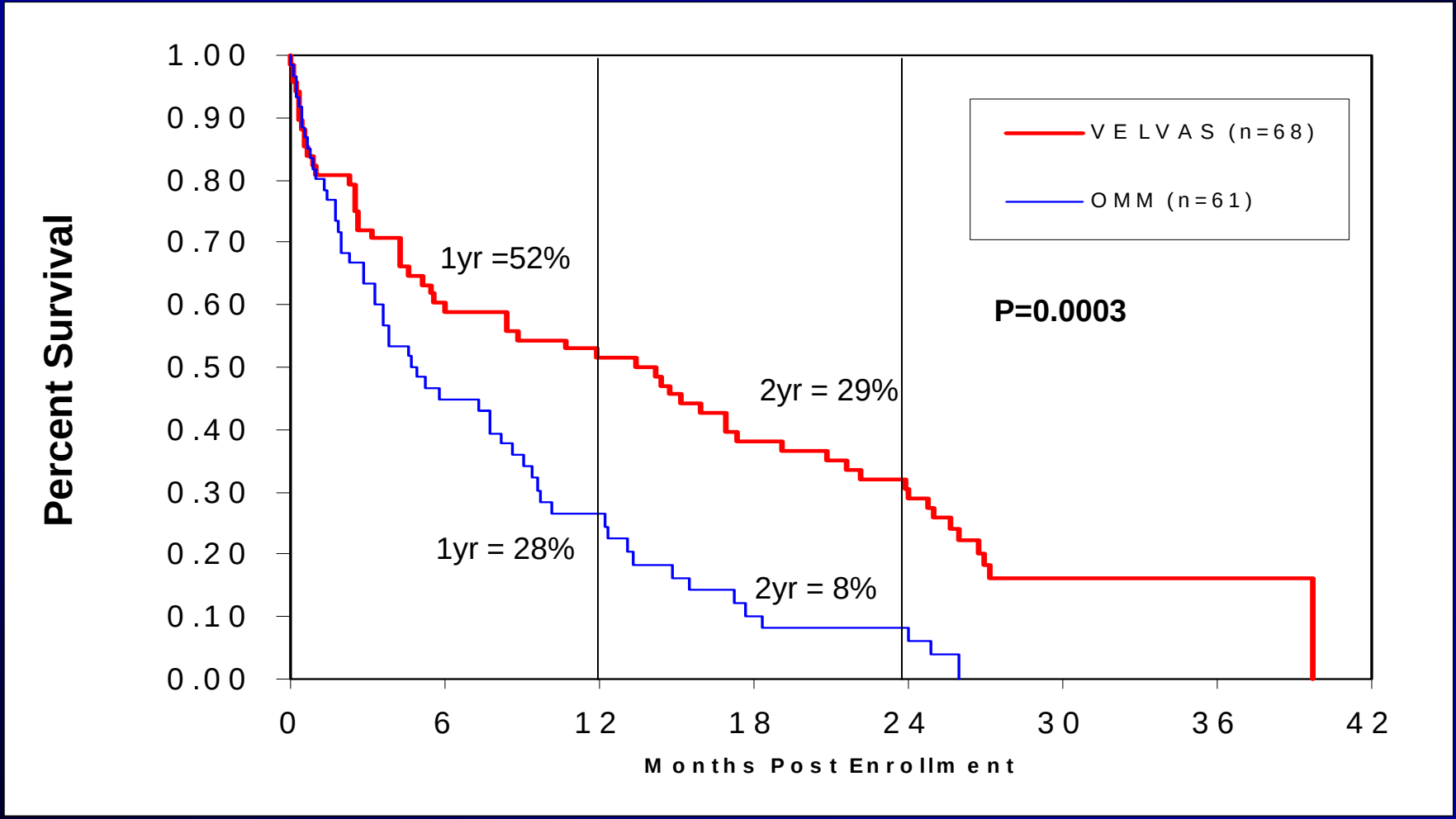
Intent to Treat Analysis

Time of Analysis	Cohort	1 yr Survival	2 yr Survival
NEJM (07/01)	LVAD	52%*	23%
	OMM	25%	8%
	(p-value)	(0.002)	(0.09)
FDA Panel Meeting (2/02 data)	LVAD	51%*	24%
	OMM	28%	8%
	(p-value)	(0.005)	(0.05)
Updated 1/15/03	LVAD	**51%***	**29%***
	OMM	**28%**	**13%**+
	(p-value)	(0.005)	(0.02)

* Statistically significant (p-value)

+ Includes 3 crossover VAD patients, accounting for 5% of OMM patients

“As Treated” Analysis as of January 15, 2003



REMATCH Patient Perspective from Both Sides

Ron Johnstone
Age 70

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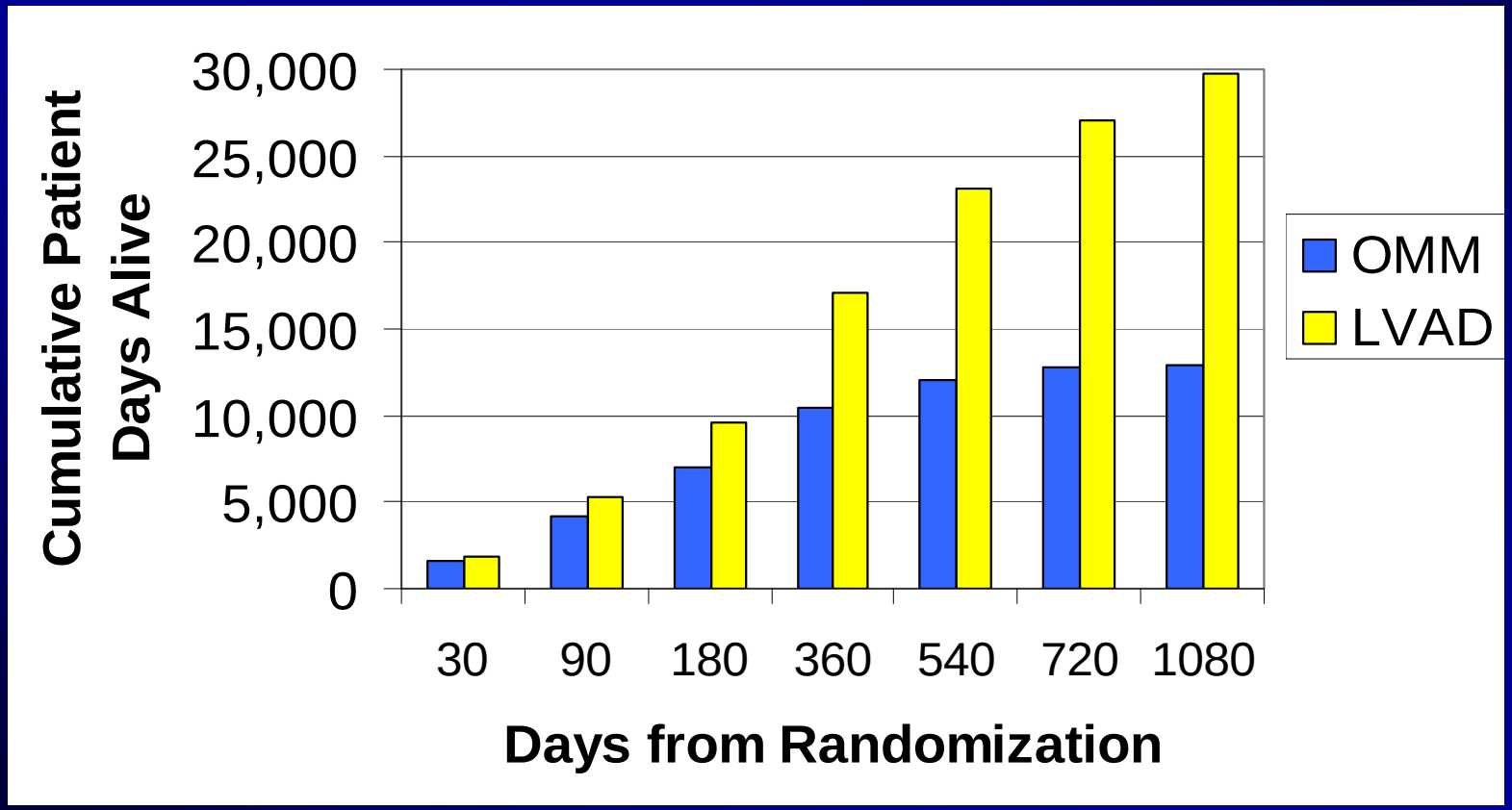
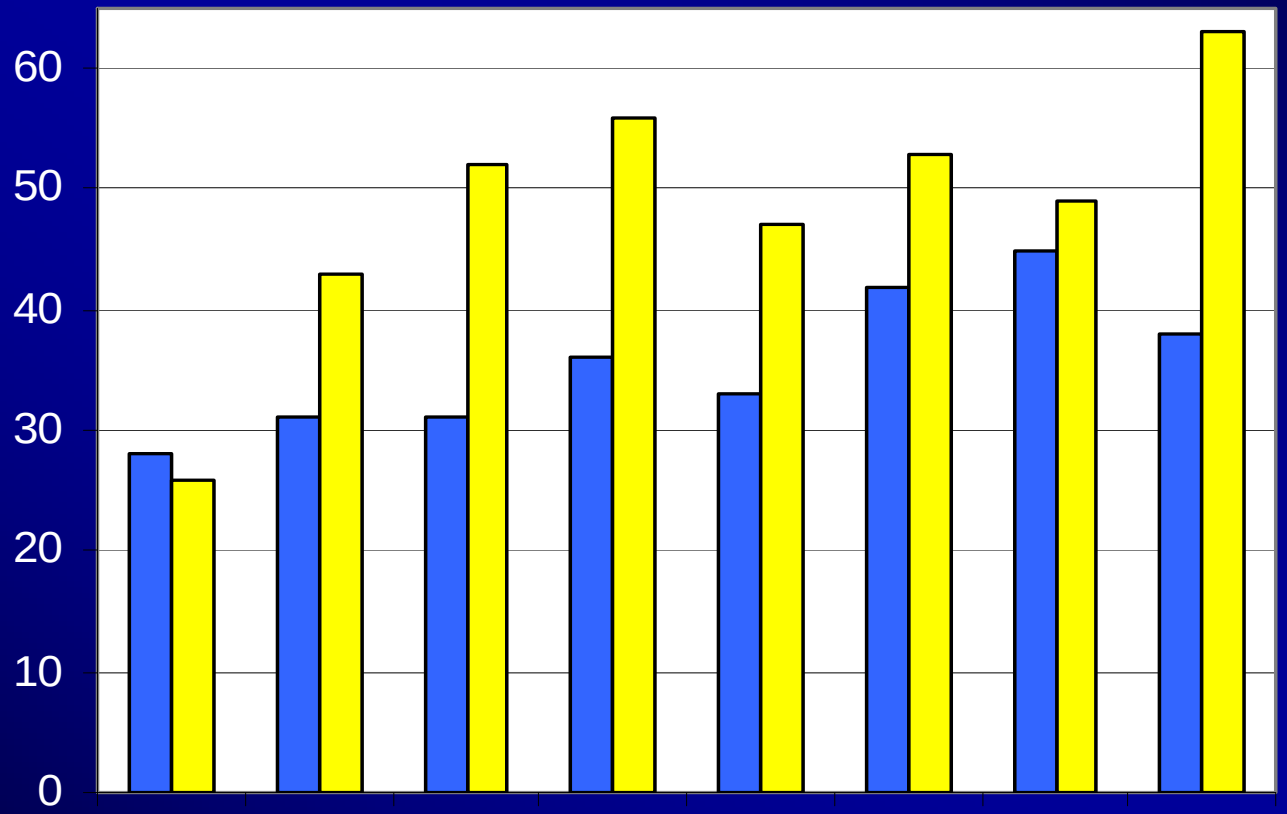
Cumulative Patient Days Alive Graph ("As Treated" Analysis as of Jan 15, 2003)



Pre-specified Quality of Life Measurement Instruments

- **Short-Form General Health Survey (SF-36)**
  - Measures physical function and emotional role
  - Score Range: 0 (worst) - 100 (best)
- **Minnesota Living with Heart Failure (MLWHF) Questionnaire**
  - Measures physical, socioeconomic, psychological impairments
  - Score Range: 0 (best) - 105 (worst)
- **Beck Depression Inventory**
  - Measures level of patient depression
  - Score Range: 0 (no depression) - 64 (severe depression)
- **NYHA Functional Status**
  - Measures functional status
  - Class I (best) - Class IV (worst)

SF-36 General Health
Effect of Treatment



Higher score = Better

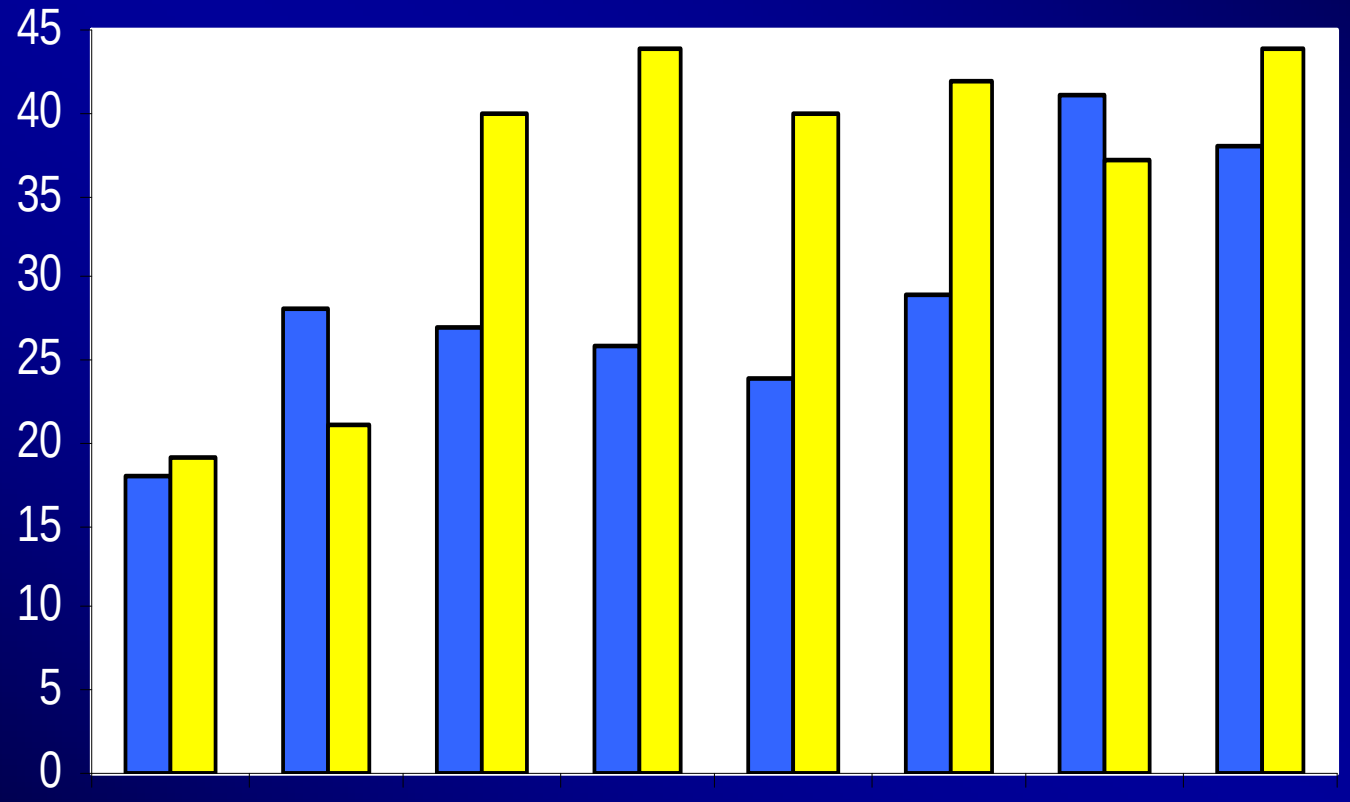
P<0.0001

Month	0	1	3	6	9	12	18	24
OMM	61	37	29	21	18	10	6	3
LVAD	68	42	36	32	29	33	22	8

Patients at interval

Cumulative data over 2 year period (June 2002)

SF-36 Physical Function
Effect of Treatment



Higher score = Better

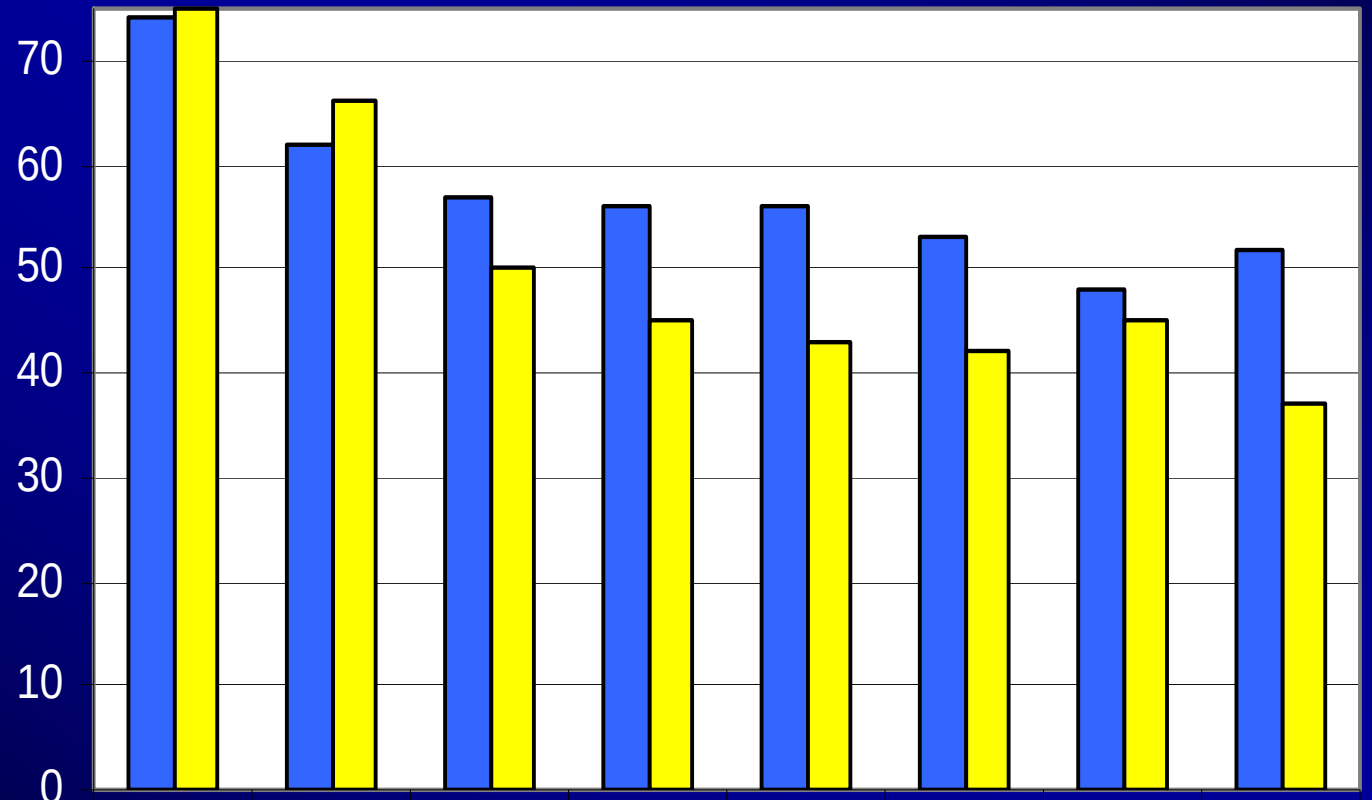
P=0.01

Month	0	1	3	6	9	12	18	24
OMM	61	37	29	21	18	10	6	3
LVAD	68	42	36	32	29	33	22	8

Patients at interval

Cumulative data over 2 year period (June 2002)

MLWHF
Effect of Treatment



Lower score = Better

OMM

LVAD

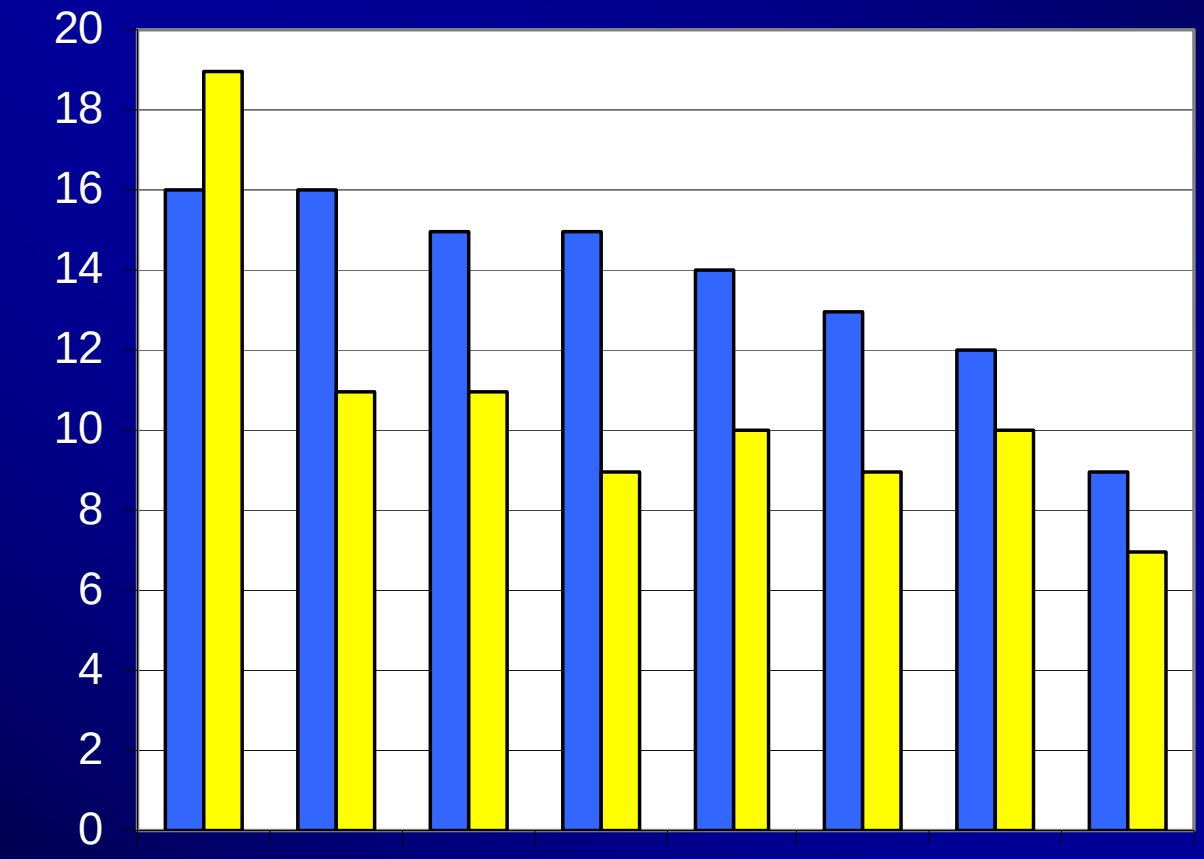
P=0.0007

Month	0	1	3	6	9	12	18	24
OMM	61	36	29	21	18	10	6	3
LVAD	68	41	36	32	29	33	22	8

Patients at interval

Cumulative data over 2 year period (June 2002)

Beck Depression Inventory
Effect of Treatment



Lower score = Better

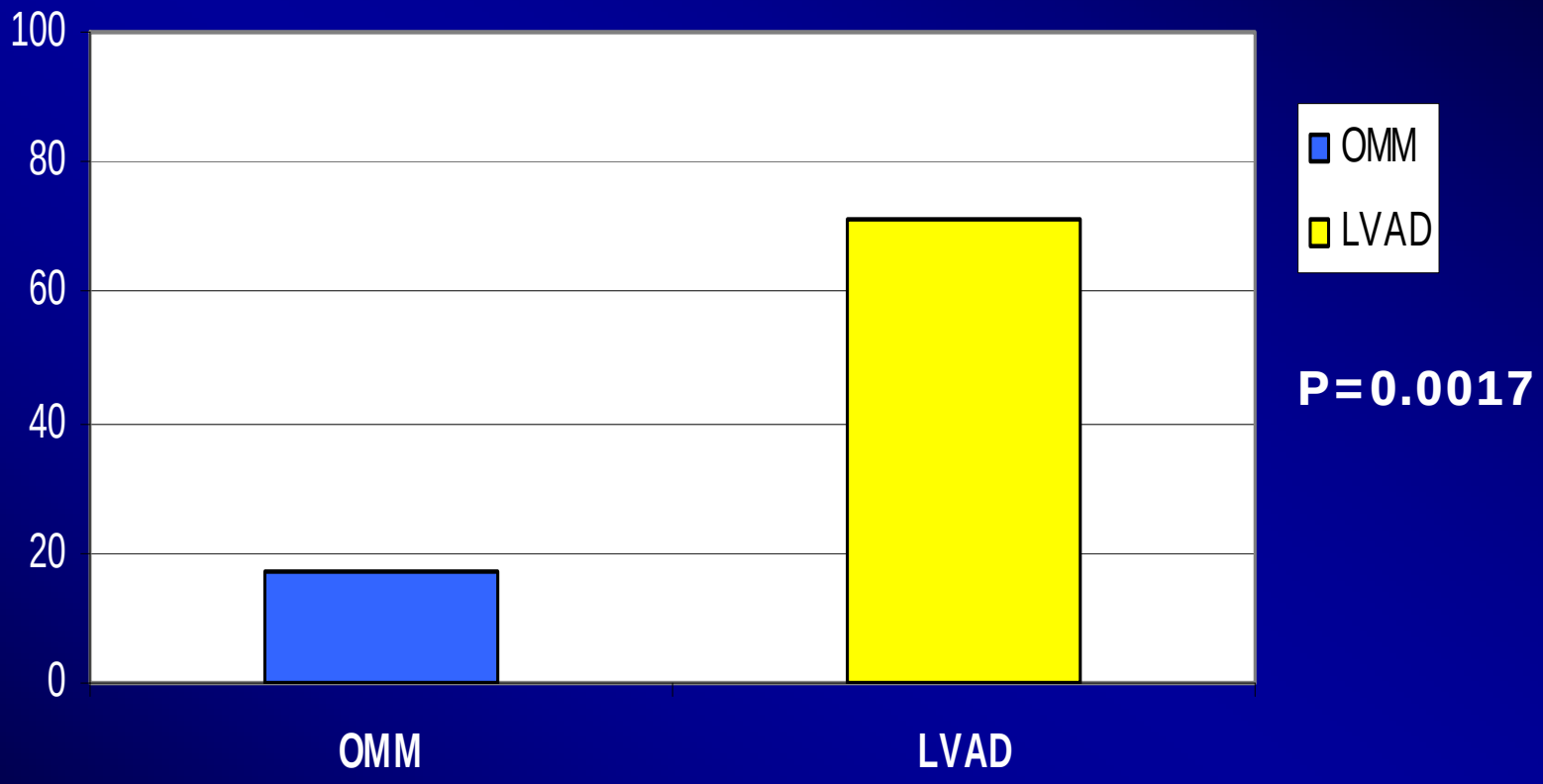
P<0.0001

Month	0	1	3	6	9	12	18	24
OMM	61	35	26	21	17	8	5	3
LVAD	68	39	34	32	29	31	21	7

Patients at interval

Cumulative data over 2 year period (June 2002)

Improved Functional Status At One Year – NYHA Class I / II



P=0.0017

Percent Patients in Class I / II NYHA Analyzed Using Fisher's Exact Test

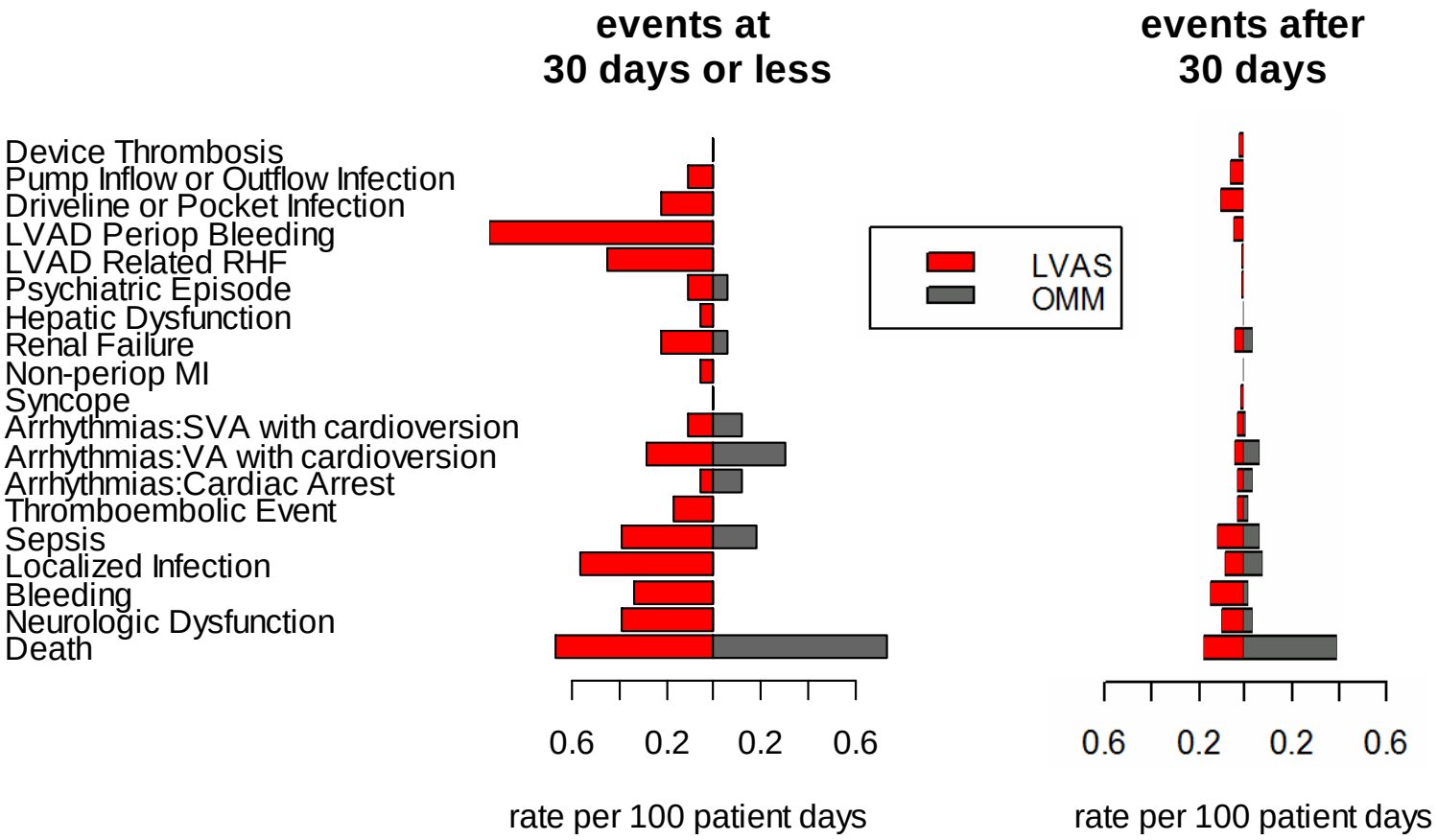
Summary of REMATCH QOL Findings

- QOL was significantly better for LVAD patients compared to OMM patients as measured with every pre-specified instrument

- LVAD scores never worse than OMM except short-term post-operative pain

REMATCH Reported Complication Rates

REMATCH Serious Adverse Events, and Death, rates per 100 patient days



Voting Questions

Is quality of evidence adequate to draw conclusions about net health outcomes in Medicare patients meeting REMATCH criteria?

Does the evidence demonstrate any positive net health outcomes and what is the size of the improvement in net health outcomes of LVADs compared to OMM for these patients?

LVAD Net Health Outcomes

- Clinically meaningful, statistically significant survival benefit over 2 years observation and at 1 and 2 years
- Improved QOL in LVAD patients in multiple pre-specified functional and subjective domains
- Adverse events reasonable given the patients' terminal condition and benefit demonstrated
- Net health outcome: substantially more effective

Objectives

- Document the net health benefit of LVADs for Destination Therapy in ESHF patients
- **Elucidate ongoing improvements to enhance outcomes with LVAD therapy**
- Outline guidelines for responsible dissemination of LVAD therapy

REMATCH And Beyond: Device Improvement and Refinement of Best Practices

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REMATCH LVAD Patients

REMATCH Experiences Form a Basis for Improved Outcomes

- **Destination Therapy is now an extended indication for a very good, incrementally improving LVAD**

- Evolution in clinical understanding and management

HeartMate LVAD Incremental Improvements

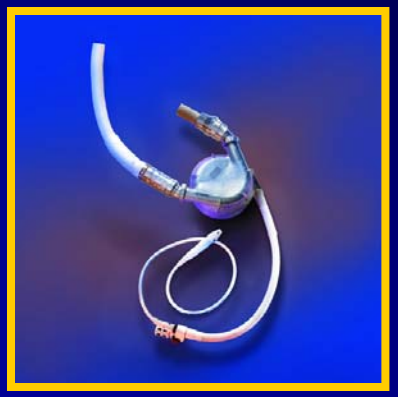
VE
Single lead left lower quadrant exit site

SNAP - VE
- Outflow Bend Graft Relief
- Locking Screw Rings
- Improved System Controller Battery Module

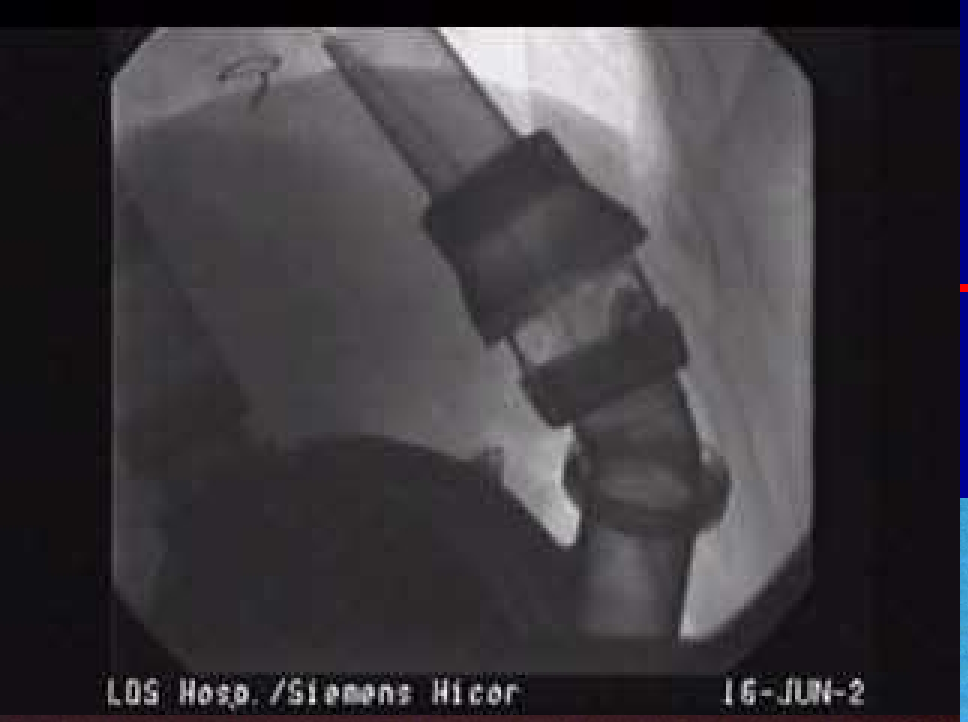
VE
Double lead

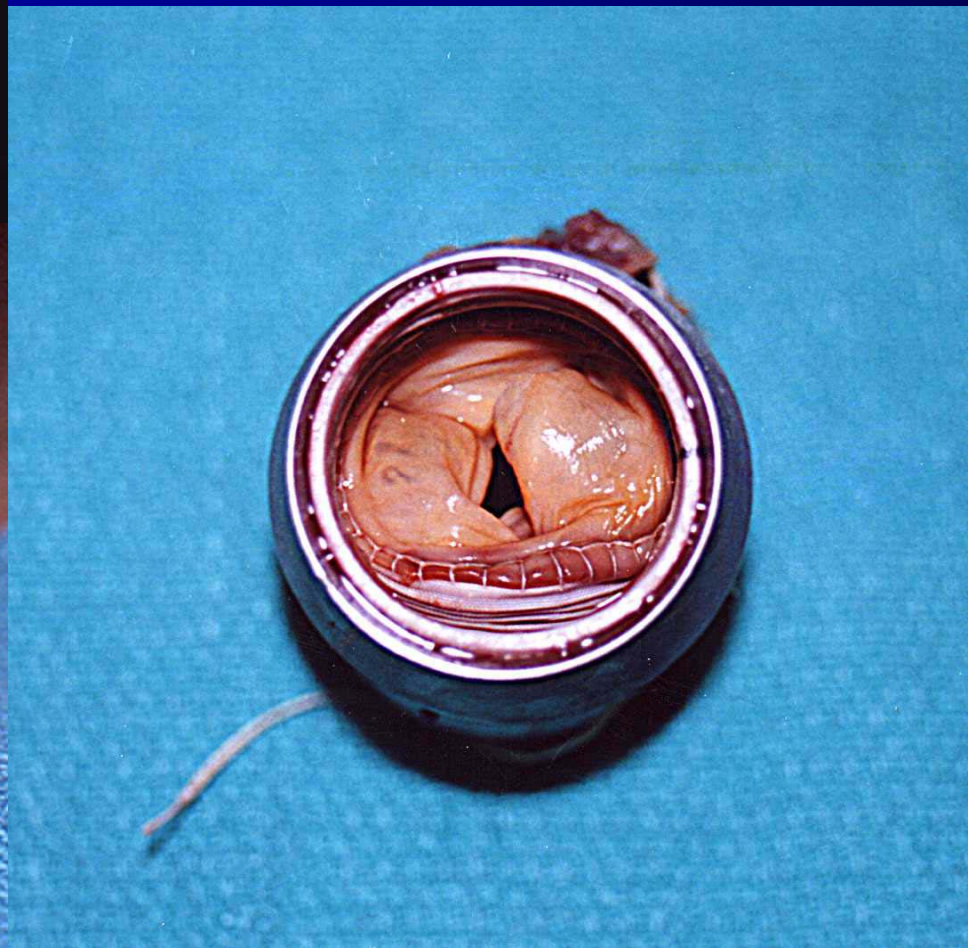
VE
Single lead right upper quadrant exit site

XVE
- Extended, smaller diameter lead
- More flexible lead
- Low stress diaphragm
- Direct System Controller connection
- Opti-Fill™ System Software

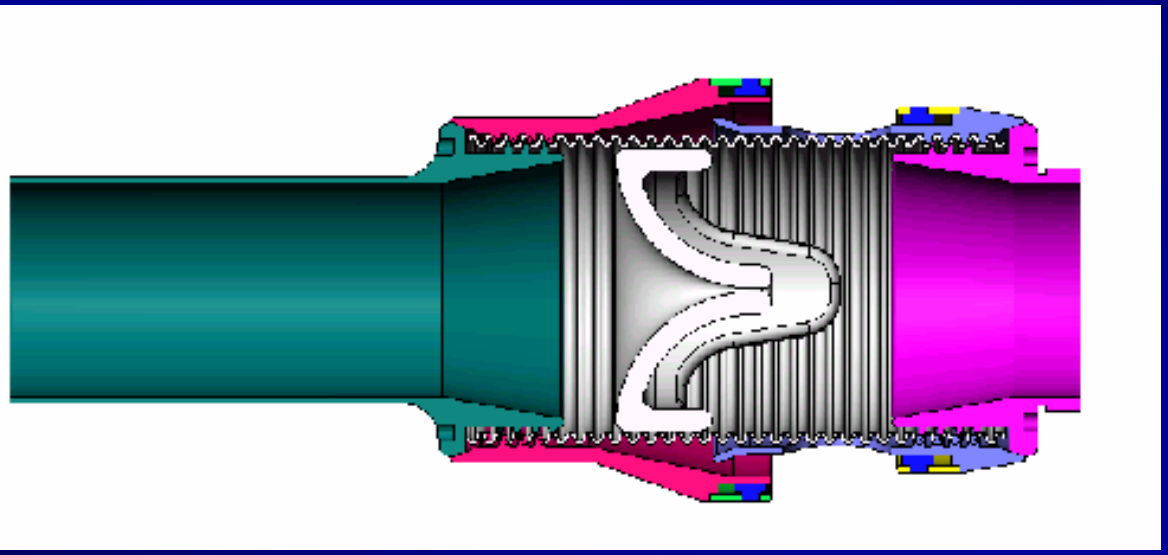


HeartMate LVAD
Inflow Valve Regurgitation



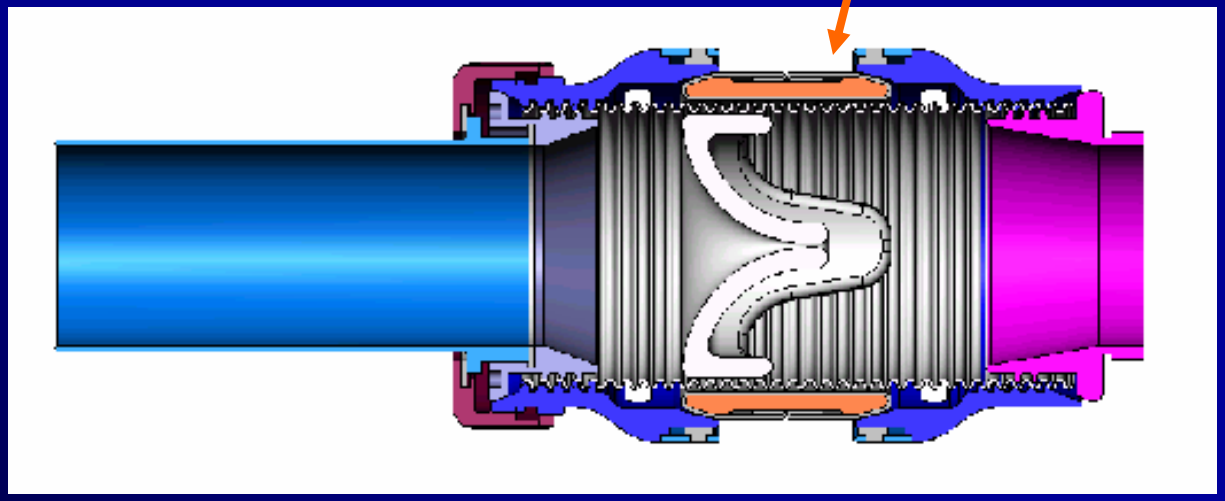


HeartMate LVAD
Inflow Valve Modifications



CURRENT inflow valve assembly

Reinforcing PTFE sleeve



NEW reinforced inflow valve assembly

REMATCH Experiences Form a Basis for Improved Outcomes

- Destination Therapy is now an extended indication for a very good, incrementally improving LVAD

- **Evolution in clinical understanding and management**

Patient Management Improvements

- Patient management improved during the course of the study

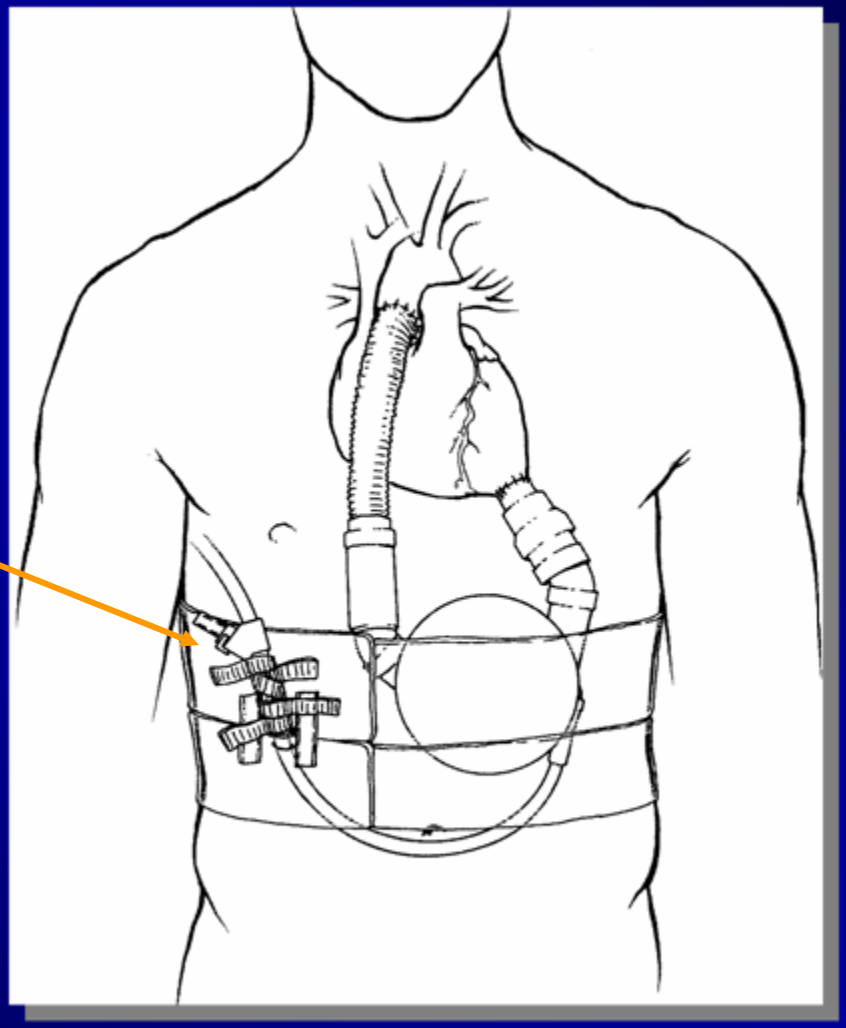
- Patient outcomes (center to center variations) led to sharing “best practices” e.g. infection control

Management Effect
Aggressive Infection Control

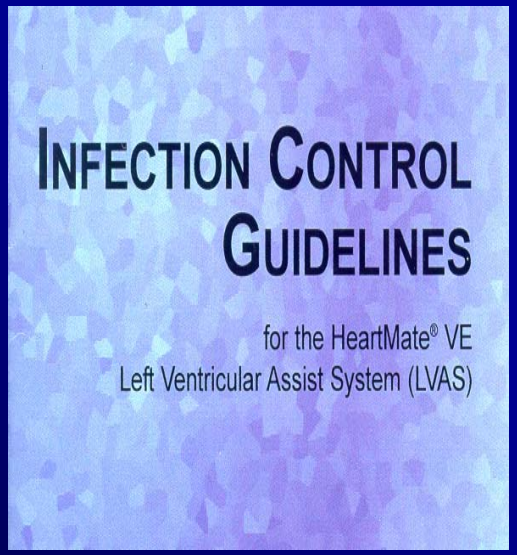
	Two Centers	All Other REMATCH Centers
Number LVAD pts	16	52
% of Total # of LVAD pts	24%	76%
Cumulative days of use	5,768	17,856
Median duration of use (days)	424	297
Infection Rate per patient-year		
Serious sepsis	0	0.72

Reducing Infection: Driveline Binder

Stabilizes driveline at exit site

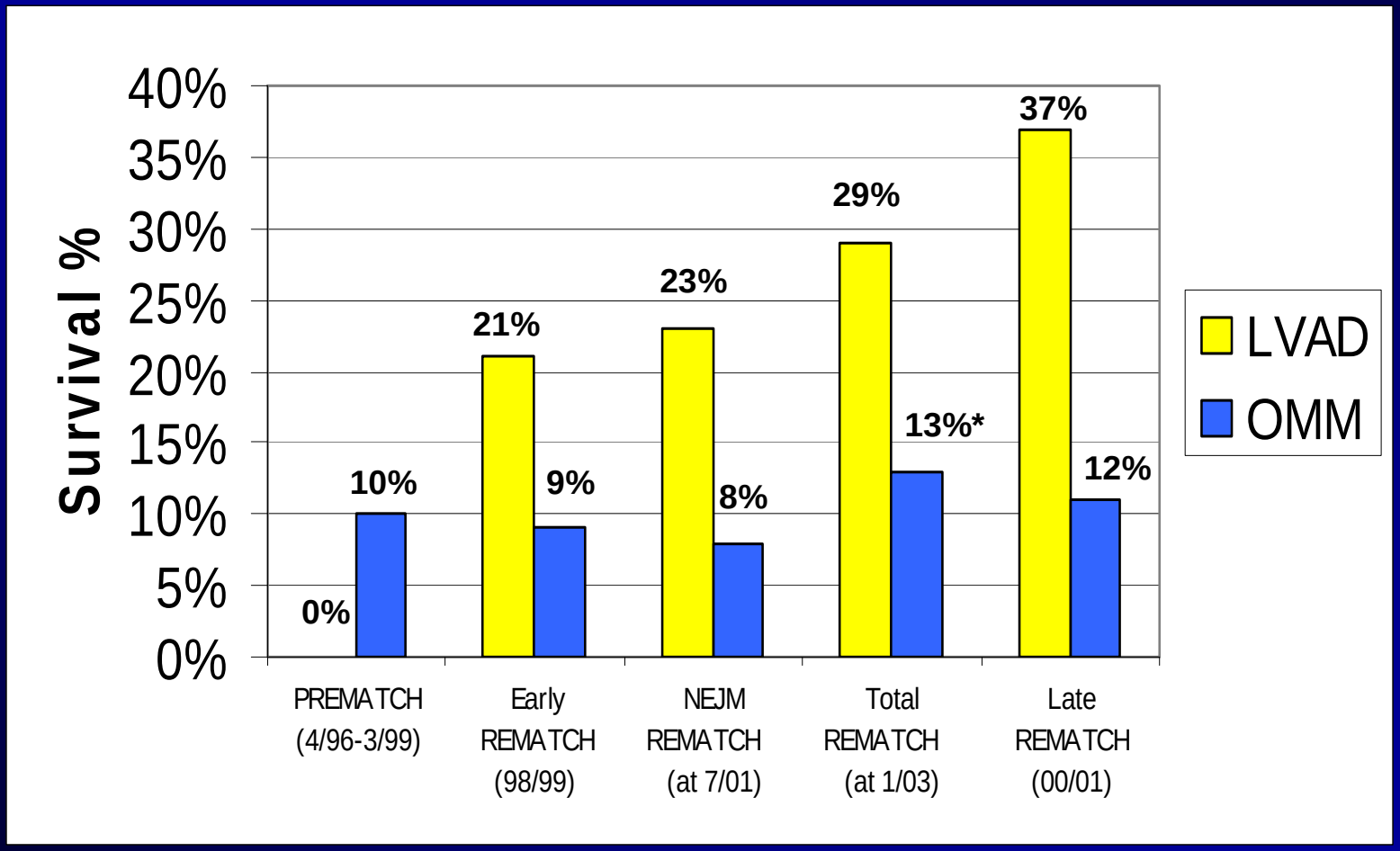


Management Effect
Infection Control Guidelines



	BEFORE	AFTER
Number Implanted	25	43
% with Serious Infection	68% →	41%
Avg. duration of support	360 days	363 days

Improved Outcomes in 2-year LVAD Survival



* Includes 3 crossover VAD patients, accounting for 5% of OMM patients

Panel Question

Are management and extent of complications adequately described?

Yes - with ongoing learning and sharing

Panel Question

Does the demonstrated extension of life and improvement in the quality of life justify the risks of LVAD implantation?

Yes

Panel Question

Have improvements in LVAD therapy in end-stage heart failure patients since REMATCH affected the applicability of the results?

REMATCH is still applicable and likely underestimates achievable LVAD benefit.

LVADs are Effective Therapy

- REMATCH trial sets the stage for:
  - Device improvement
  - Improving patient management
  - Enhancing patient outcomes

- REMATCH provides a basis for responsible dissemination
  - Transferring knowledge
  - Assuring expertise and proper resources
  - Tracking outcomes for further refinement of Best Practices

Responsible Dissemination of LVADs as Destination Therapy

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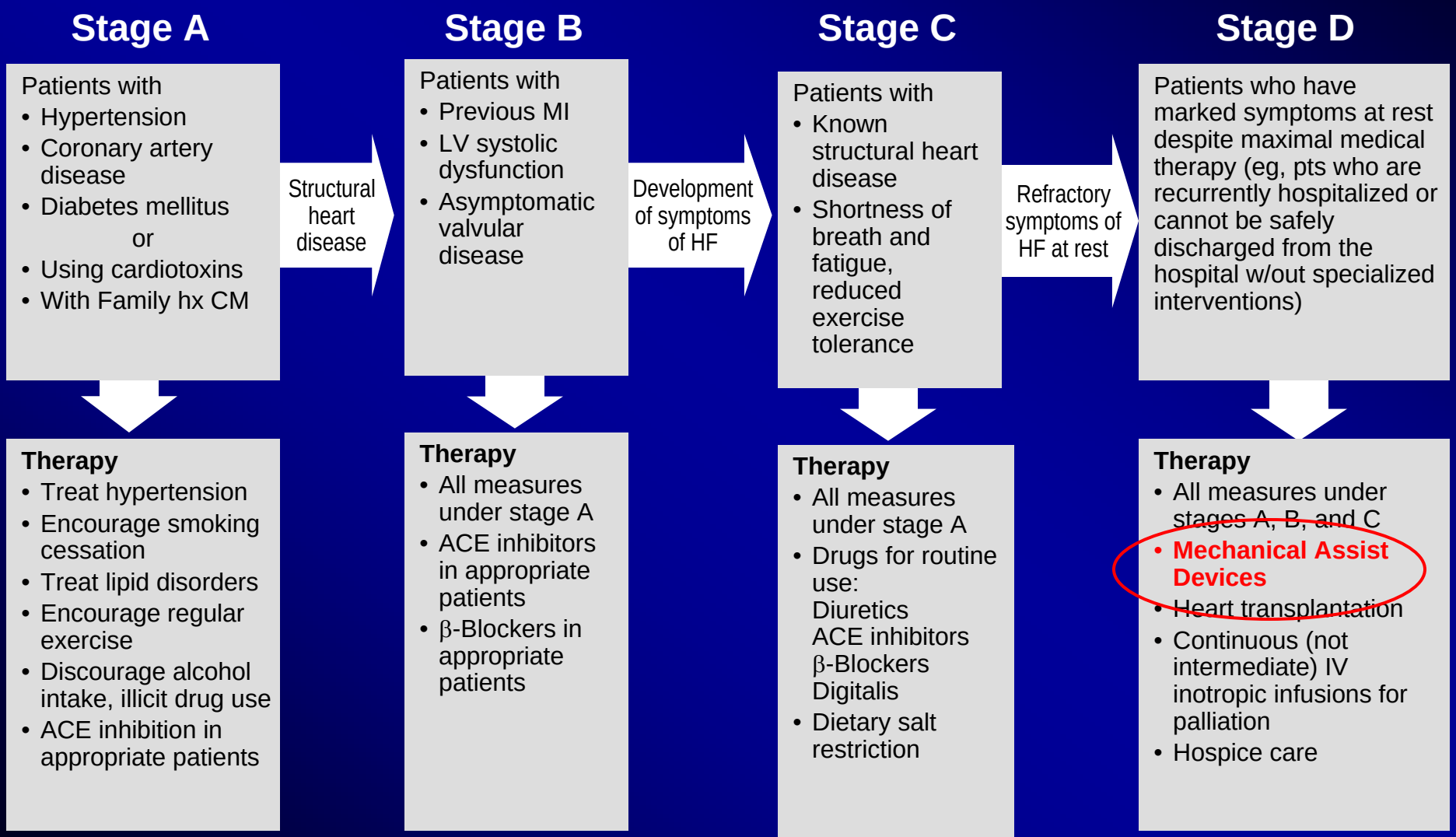
ACC / AHA Guidelines



Source: ACC/AHA Guidelines for Evaluation and the Management of Chronic Heart Failure in the Adult, December 2001

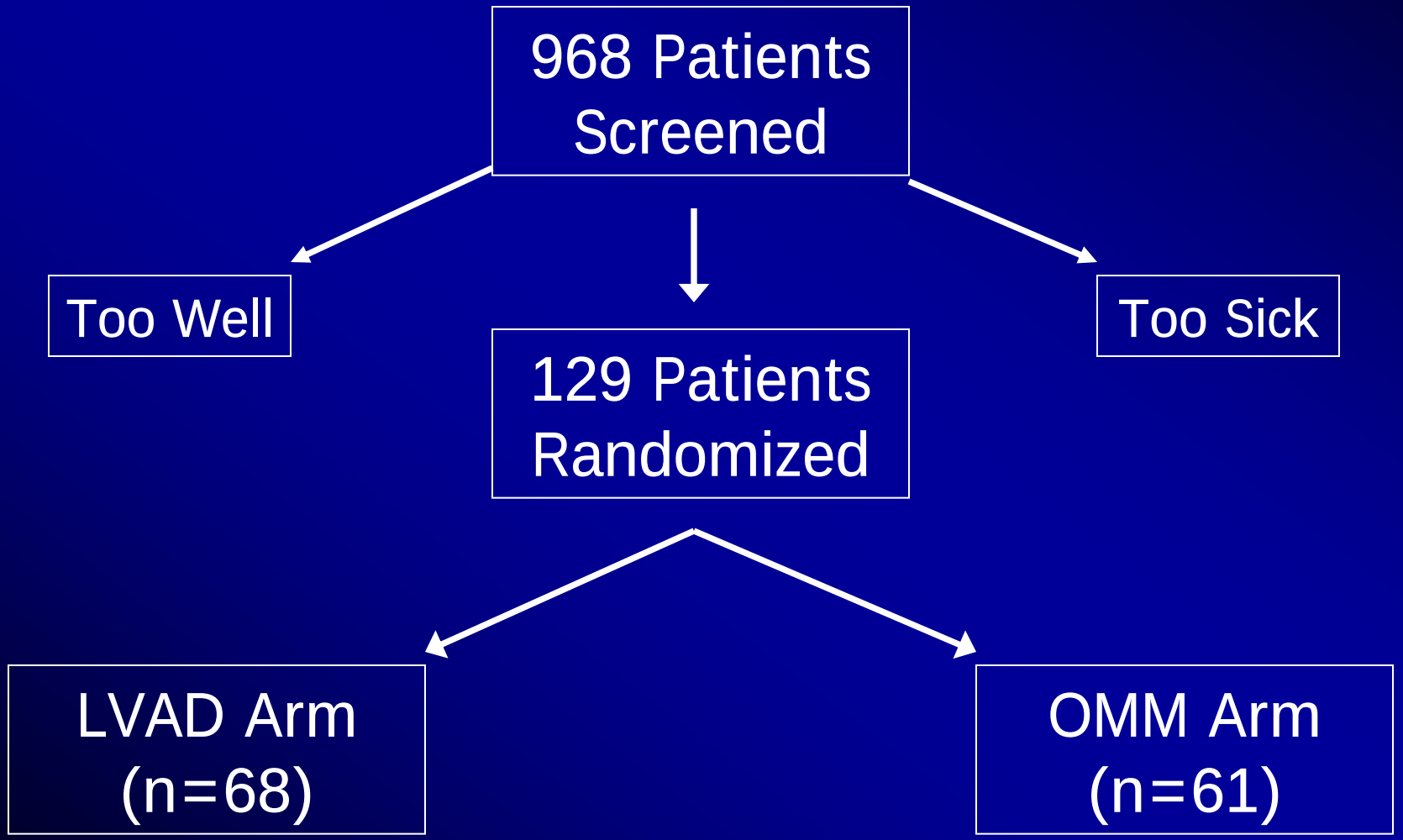
REMATCH Eligibility Criteria

- NYHA Class IV symptoms despite optimal medical therapy, including digoxin, ACE inhibitors and beta blockers, for at least 60 of 90 days
- LVEF $\leq$ 25%
- Peak VO2 $\leq$ 14 ml/kg/min or IV inotrope dependent
- Ineligible for cardiac transplantation

REMATCH Exclusion Criteria

- Patients with a body surface area < 1.5 m^2;
- Patients with active systemic infections;
- Patients with significant irreversible comorbidities that would limit individually or collectively survival (e.g., severe advanced lung, liver or kidney disease)
- Patients with a co-existing terminal condition (e.g., advanced metastatic cancer)

Patient Enrollment



Panel Question

Should the evaluation to determine candidacy be performed only by a heart transplant center?

No, but non-transplanting Destination Therapy centers should have appropriate arrangements with approved transplant center to insure proper patient selection

REMATCH Baseline Patient Profiles

	OMM (N=61)	LVAD (N=68)	P
Age (years)	68±8.2	66±9.1	0.16
LVEF (%)	17±4.5	17±5.2	0.92
Cardiac Index (l/min/sq.m)	2±0.61	1.9±0.99	0.36
Serum Creatinine (mg/dl)	1.8±0.66	1.7±0.65	0.35
IV Inotropes (%)	72	65	0.45

No statistical differences in VAD and OMM groups

REMATCH vs Other Class IV HF Trials Defines a New Class V (Stage E) Severity

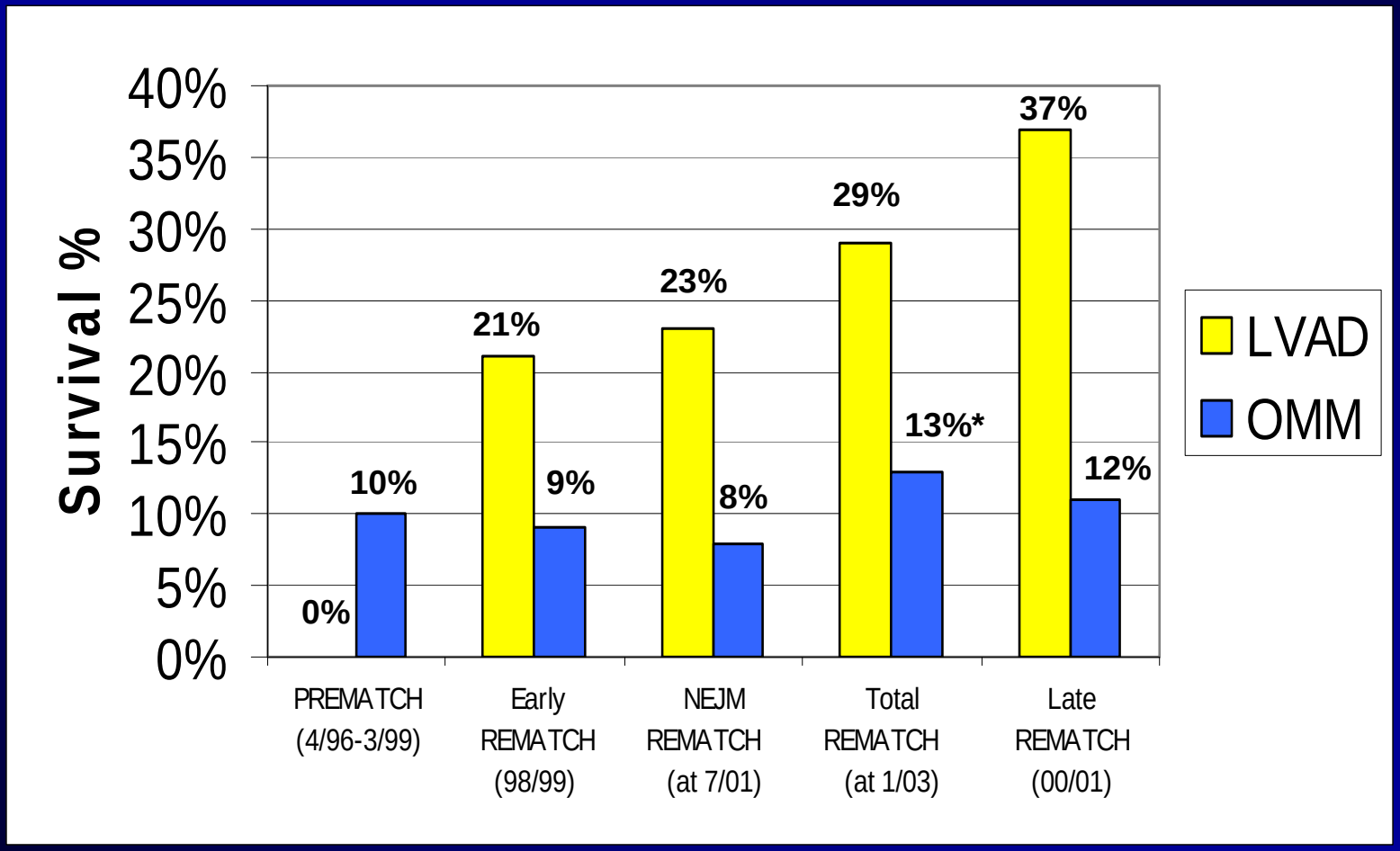
	REMATCH	FIRST	PROMISE	COPERNICUS	RALES	CONSENSUS
LVEF (%)	17	19	21	20	25	—
NYHA	IV	IV	III-IV	IIIB-IV	III-IV	IV
SBP	103	105	115	123	122	119
Na	135	137	139	137	—	138
Creatinine	1.8	—	1.5	1.5	1.2	1.4
1 year mortality	75%	49%	40%	18.5%	24%	45%

Source: Lynne Warner Stevenson, MD (3/4/02)

REMATCH Patient Population

- REMATCH defined a new subset of the patients with severe heart failure and would be applicable to approximately 15% of all Class IV HF patients
- Severity of illness far exceeded all previous heart failure clinical trials with a control patient mortality 4x observed in recent beta-blocker trials
- *Outcomes worse than AIDS, breast, colon, and lung cancer*

Improved Outcomes in 2-year LVAD Survival



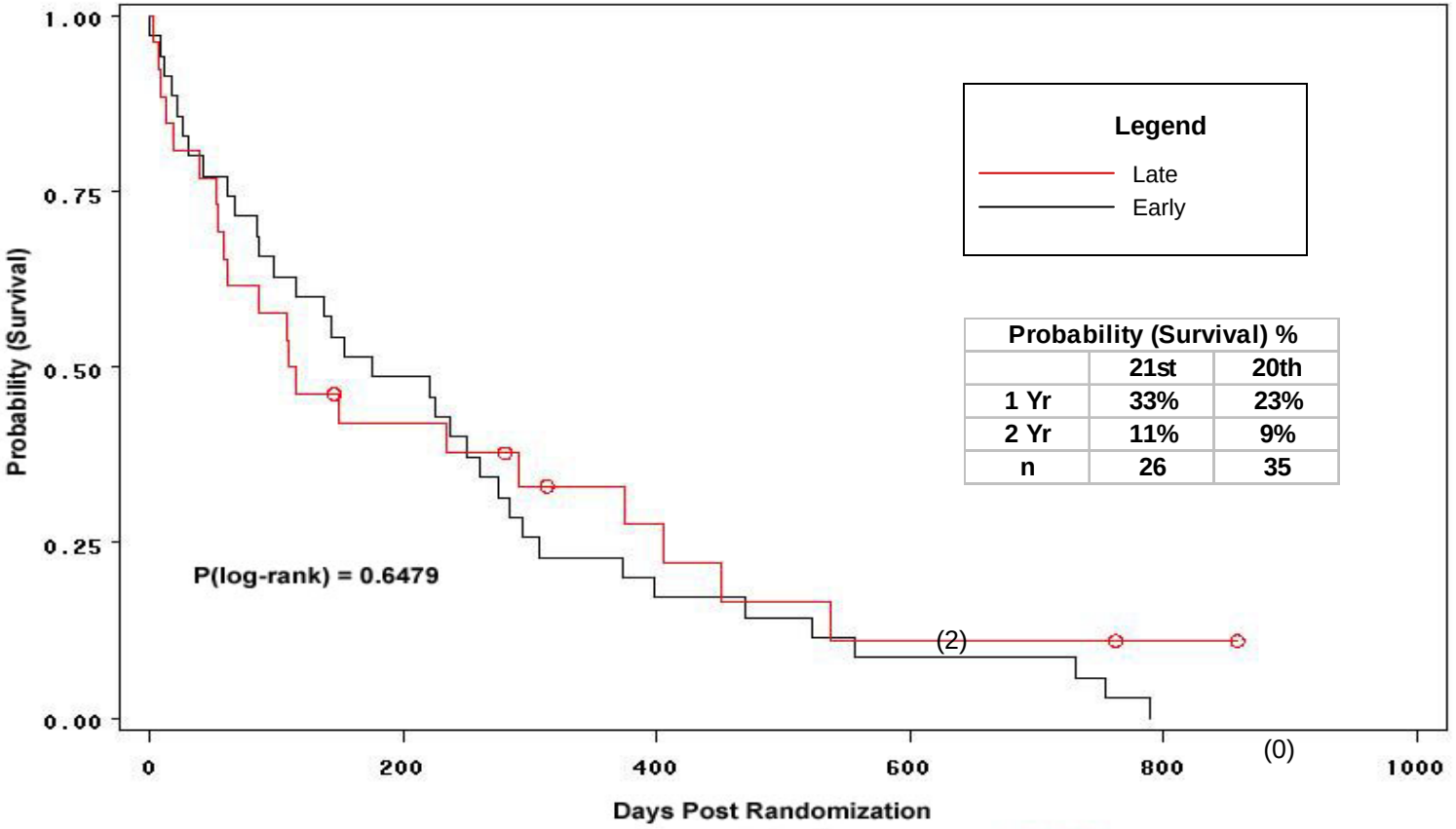
* Includes 3 crossover VAD patients, accounting for 5% of OMM patients

REMATCH Therapies At Baseline: N=129

• Diuretics	124 (96%)
• Digoxin	111 (86%)
• ACEI	74 (57%)
• AII antagonists	18 (14%)
• Nitrates	54 (42%)
• Hydralazine	18 (14%)
• B-Blockers	28 (22)%
• Amiodarone	56 (43%)
• IV inotropic agents	91 (71%)

29% not able to tolerate

REMATCH: OMM Survival by Era Early (’98-’99) vs Late (’00-’01)



Probability (Survival) %		
	21st	20th
1 Yr	33%	23%
2 Yr	11%	9%
n	26	35

No Survival Benefit
Recent Drug Trials

Class/Type	Agent	Trial
Phosphodiesterase Inhib	Milrinone	PROMISE/OPTIME
Central NE Deplete	Moxonidine	MOXCON
Calcium. Blkr	Felodipine/Amlodipine	VHFIII/PRAISE
TNF-antibody	Enbrel	RENAISSANCE
Angiotensin Recept Block	Valsartan	ValHFT
Endothelin Receptor	Bosentan, Tazosentan	RITZ, HEAT, REACH
Neutral Endopeptidase	Omipatrilat	OVERTURE
Oral inotrope	Digoxin	DIG Trial

Panel Question

Have improvements in medical management in end-stage heart failure patients since REMATCH affected the applicability of the results?

REMATCH is still applicable.

Panel Question

Initially, should there be specific facility and personnel requirements?

Yes

Professional Criteria for Destination Therapy

Cardiologist

- Experienced and trained in management and treatment of end-stage heart failure patients
- Understanding of advanced heart failure therapies and experience with VADs

Cardiac Surgeon

- Experience in evaluating therapeutic options for patients with heart failure
- Previous experience and recently trained in VAD implantation

Facility Criteria for Destination Therapy

- Experienced team trained and equipped to manage patients with end-stage heart failure and VADs
- Experience with open heart surgery and dedicated cardiac care unit
- Arrangement and coordination with Medicare approved heart transplant center for patient evaluation

Facility Criteria for Destination Therapy

Diagnostic and support services for full evaluation and follow up including:

- Cardiology
- Anesthesiology
- Immunology
- Infectious Disease
- Pulmonary
- Nephrology
- Social services
- Patient education
- Psychological support including end-of-life
- Nutrition
- Radiology
- Nursing

Panel Question

Should data reporting be required?

Yes. A Registry should be maintained to document VAD outcomes with Destination Therapy.

Summary and Conclusions

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Strong Evidence Supports VAD Use in Patients Meeting REMATCH Criteria

- Clinical data from REMATCH clearly establish that VADs provide a substantial survival and quality of life benefit for patients with Class IV end-stage heart failure

- Decade of data from the use of VADs as a "bridge-to-transplant" further documents strength of evidence

Magnitude of Net Health Benefit

- Substantially more effective
- Potential to achieve breakthrough impact
- Destination Therapy should now be responsibly disseminated

Bottom Line

- Patients live longer and feel better
- Evidence clearly supports Medicare coverage


YOUNG MEN WANTED
FOR U.S. NAVY.