CIRCULATORY SUPPORT DEVICES PANEL

Monday, March 4, 2002

Thoratec HeartMate VE LVAS

P920014/S016

FDA REVIEW TEAM

- M. Berman
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PROPOSED EXPANDED INDICATION FOR USE

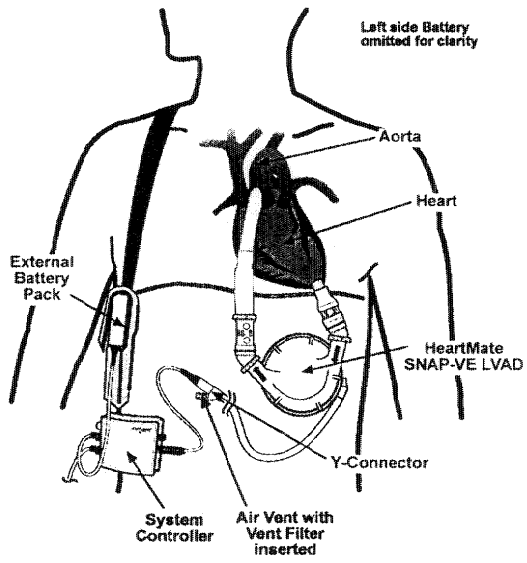
The HeartMate VE LVAS is indicated for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from nonreversible left ventricular failure. The HeartMate VE LVAS is also indicated for use in patients with end-stage left ventricular failure who are ineligible for cardiac transplantation. The HeartMate VE LVAS is intended for use both inside and outside the hospital. (Tab 3.2, page 2)

FDA MUST DETERMINE

- Reasonable assurance of safety and effectiveness (Act, §513(a)(1)(C)).
- Factors considered (21 CFR 860.7(b)
  - Patient population
  - Conditions of use
  - Probable benefit *vs.* probable injury
  - Reliability of the device

DEVICE DESCRIPTION

- Implanted components
  - Blood pump
  - Valved conduits
  - P/O perc tube
- External components
  - Controller
  - Battery packs
  - Accessories



PRECLINICAL EVALUATION
Determined To Be Satisfactory

- Manufacturing
- Sterilization, packaging, shelf life, shipping
- Biocompatibility
- Software
- Electrical safety and EMC
- Hydrodynamic characterization of pump
- Battery performance
- Alarms

PRECLINICAL EVALUATION
Remaining Concerns

- Reliability
  - Internal components
    - Motor
    - Valved conduits
    - Percutaneous tube
- Device End of Life Indicator

RELIABILITY PROTOCOL
Bench Testing

- 15 units on test
  - All VE LVAS, none VE SNAP
- Mock circulatory loop
  - Implanted components in water at 37° C
  - External components in air @ room temp
  - Worst, average, and minimum operating conditions; cycled each week
    - Beat rate, outlet pressure, flow

RELIABILITY RESULTS
Bench Testing

- 10 pumps failed
  - 8 main bearing
  - 1 diaphragm
  - 1 commutator
- 5 remain on test
  - as of 8/3/01

RELIABILITY RESULTS
Bench Testing

- Main bearing failures (N = 8)
  - Mean = 136 x 10^6 cycles (≈ 3.4 years)
  - STDEVP = 24 x 10^6 cycles (≈ 0.6 years)
  - Min = 90.3 x 10^6 cycles (≈ 2.25 years)
  - Max = 158.2 x 10^6 cycles (≈ 3.9 years)
  - Median = 142.6 x 10^6 cycles (≈ 3.6 years)
- Corrective action
  - CAPA #0174; open, not resolved

PREDICTED RELIABILITY
Bench Testing

- 86% reliability at 2 years
  - 60% confidence
- 76% reliability at 2 years
  - 90% confidence
- Mean Time To Failure, pump
  - 4 years @ 60% confidence
  - 3 years @ 90% confidence

OBSERVED END OF PUMP LIFE
Clinical Trial

Days	Cycles	Comment
460	50 (67)	Dust; bearing failure
504	54 (72)	Dust, worn bearings
651	70 (93)	Pump wear
779	84 (106)	Pump wear

OBSERVED DEVICE MALFUNCTIONS
Clinical Trial

- Confirmed inflow valve incompetence
  - 11 patients, 12 events
    - 6 VE, 5 VE SNAP
      - Effectiveness of 90° elbow in outflow tract?
  - Related to pump end of life?
    - Higher pump rate → bearing wear
  - Clinical consequences?
    - Surgery for replacement of inflow conduit

ENGINEERING SUMMARY

- Bench testing did not account for all observed clinical conditions
  - Elevated pump chamber pressure
  - High beat rate (inflow valve incompetence)
- Observed pump end of life events were at low end of reliability prediction
- No objective device end of life indicator
  - Replacement requires major surgery

Clinical Summary

Thoratec HeartMate VE LVAD
Left Ventricular Assist Device

Julie Swain M.D.
FDA/CDRH/ODE/DCRD

Clinical Reviewers

Lesley Ewing M.D.
(cardiology)

Wolf Sapirstein M.D.
Julie Swain M.D.
(cardiac surgery)

Expanded Indication for Use

For use in patients with
end-stage left ventricular failure
who are ineligible for cardiac
transplantation

Primary Effectiveness Endpoint

Survival Benefit

Study Design Assumptions

Mortality at 2 years

Feb '02 data

	Estimate Power 92%	**Worst Case** Power 80%	Obs. KM
OMM	75%	60%	91%
LVAS	50%	40%	76%

Power calculated for 92 study deaths, 128 patients enrolled

Inclusion Criteria

Original Criteria (124/129 pts)

- Ineligible for cardiac transplantation
- NYHA Class IV $\geq$ 90 days (70% on inotropes)
- Intensive medical therapy
- LVEF $\leq$ 25%
- VO_2max $\leq$12 ml/kg/min

Inclusion Criteria

Later Criteria (5/129 pts)

- Ineligible for cardiac transplantation
- NYHA Class IV ≥ **60** days
- **NYHA Class III or IV > 28 days and IAPB or inotropes**
- Intensive medical therapy
- LVEF ≤ 25%
- VO_2max ≤**14** ml/kg/min

Exclusion Criteria

- Correctable cause of heart failure
- BSA <1.5 m^2
- Pulmonary hypertension
- Creatinine ≥3.5 mg/dl
- Active infection
- History of stroke <90 days, carotid stenosis, impaired cognitive function

Baseline Characteristics (p >.05)

	LVAS n = 68	OMM n = 61
Age	67 (34-84)	70 (40-80)
BSA (m^2)	1.91 (1.53-2.4)	1.9 (1.55-2.36)
Male: female	52:15	50:11
# Caucasian	63	52
Able to do 6 minute walk	27	22
6 minute walk distance (m)	203 (5-421)	175 (31-355)
NYHA IV	65	60
NYHA III	2	1

Study Design

Feb '02 data

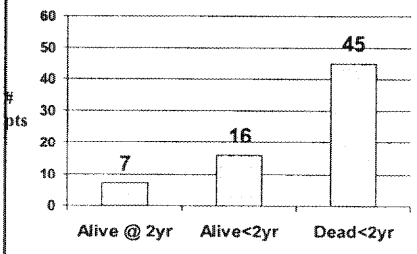
Patients Screened = 968

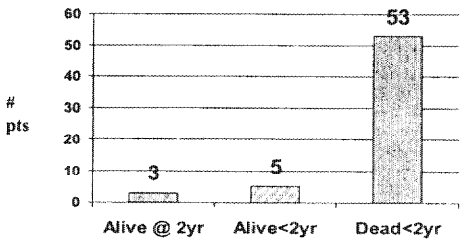
Ratio 7.50

Patients Enrolled = 129

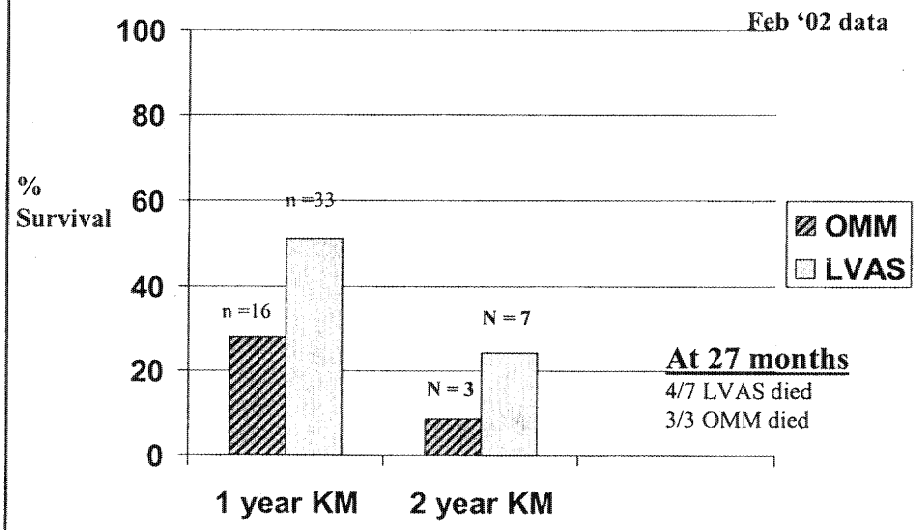
LVAS = 68

OMM = 61





Survival



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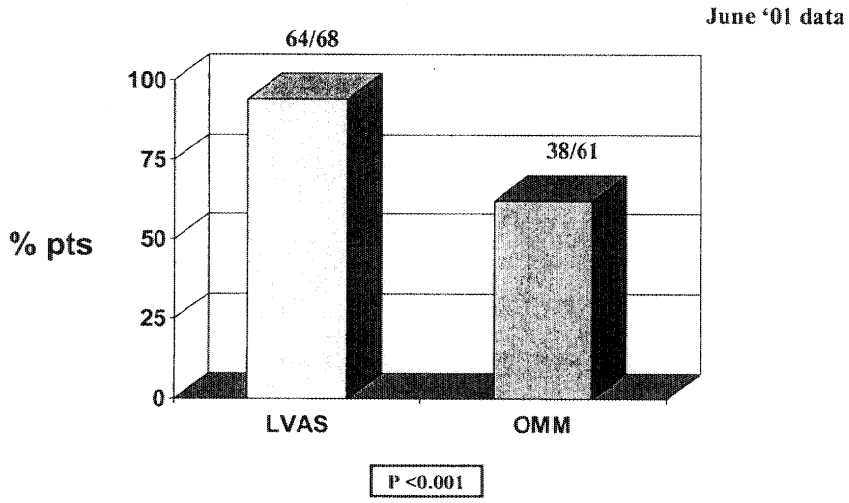
Serious Adverse Events



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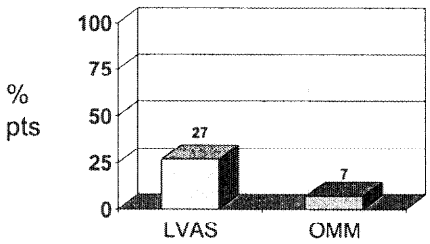
Comparison of Destination and Bridge Therapy SAE's

- Different patient populations
- Different definition for many SAE's
- Different time period
- Different patient care team

Serious Adverse Events
Neurological Dysfunction

June '01 data



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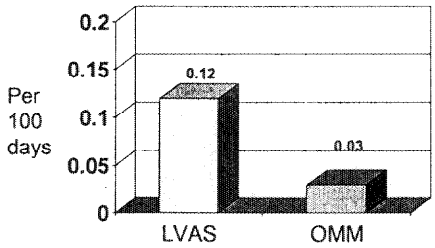

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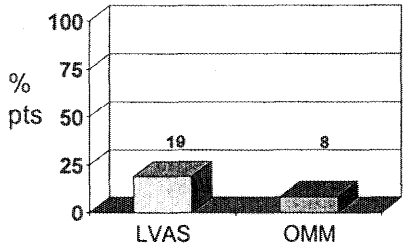
Serious Adverse Events
Local Infections

Jun '01 data



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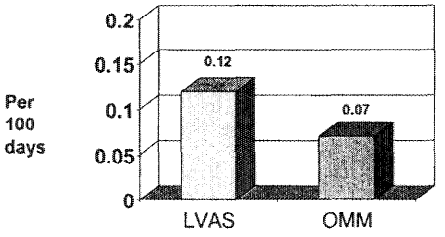

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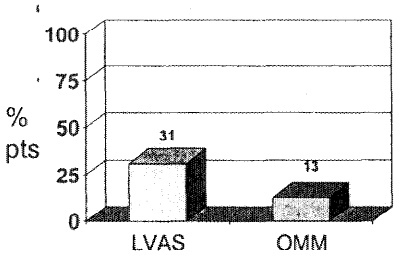
Serious Adverse Events
Sepsis

Jun '01 data



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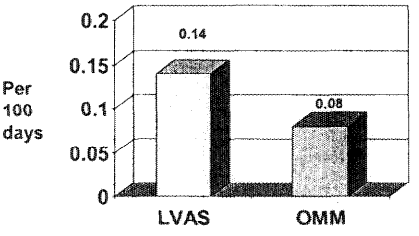

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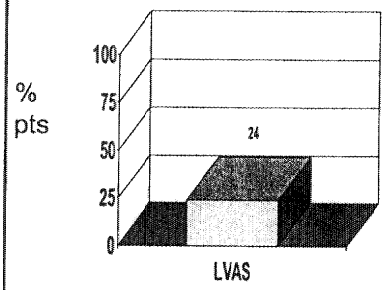
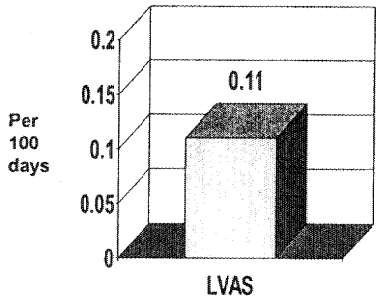
Serious Adverse Events
Percutaneous/Pocket Infections

Jun '01 data





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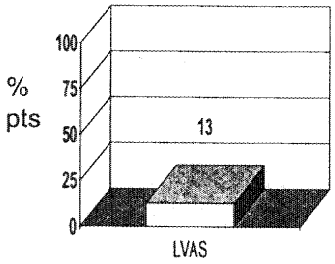
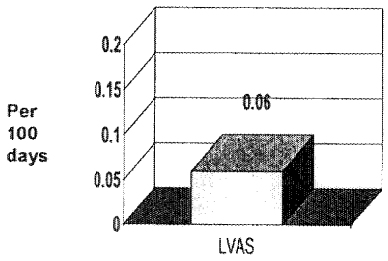
Serious Adverse Events
Pump Housing, Inflow, Outflow Infections

Jun '01 data





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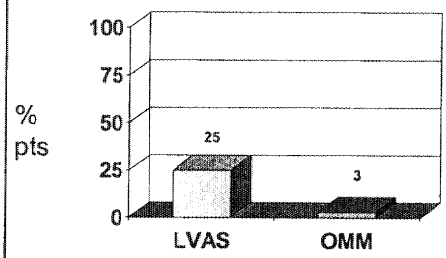
Serious Adverse Events
Bleeding

Jun '01 data



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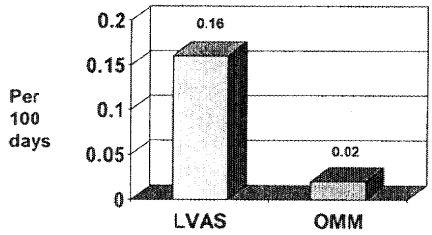
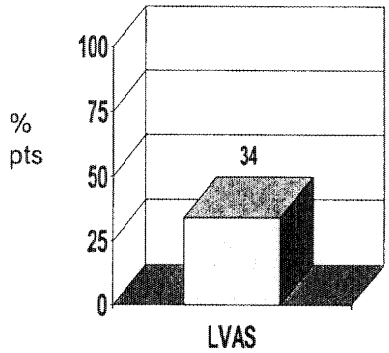
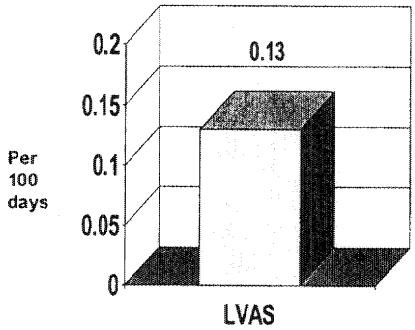


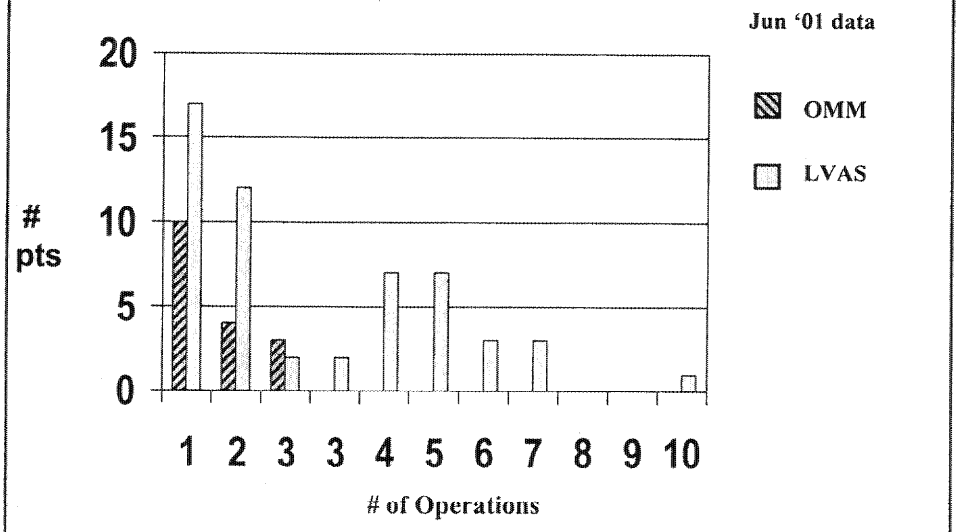
Serious Adverse Events
Perioperative Bleeding

Jun '01 data





Serious Adverse Events
Operations (all types, after original implant)



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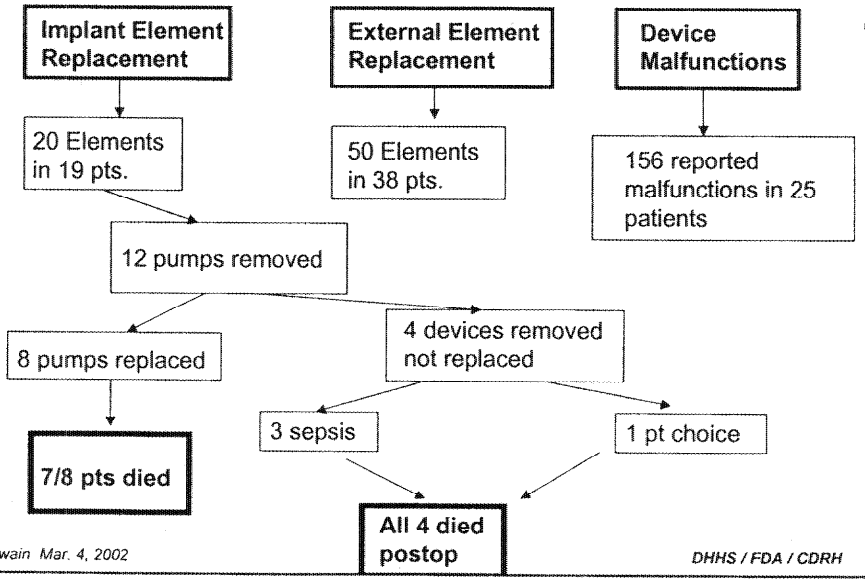
Jun '01 data

Device Malfunction Analysis



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Withdrawal from Treatment

Jun '01 data

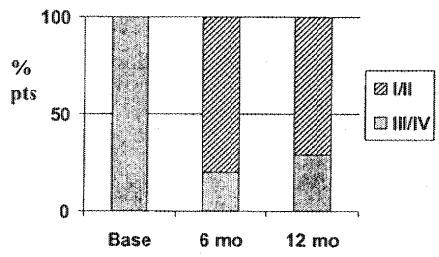
- 4 OMM patients chose to have treatment withdrawn within 1 month of randomization, 8 others chose to have treatment withdrawn later (total 12/61)

- 7 LVAS patients (or their family) chose to have device turned off or did not agree to replacement, and 6 more chose to have treatment withdrawn (total 13/68)

Secondary Endpoints

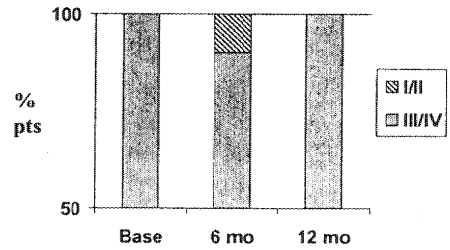
- NYHA class
- Quality of Life Questionnaires
- Functional Status
  - 6-minute walk
  - VO2 max
- Hospitalizations, length of stay
- Adverse Events
- Device Malfunction

NYHA Class Results



LVAS patients significantly improved at 6 and 12 months

LVAS



OMM

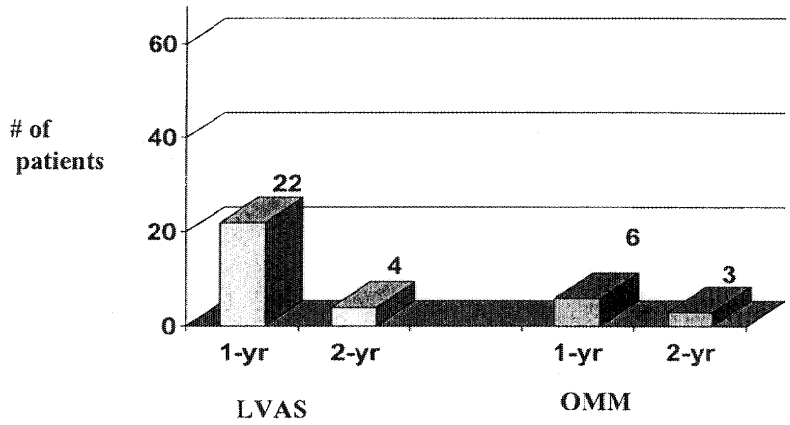
Jun '01 data

Quality of Life Results

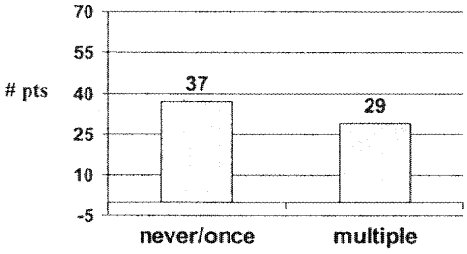
- **What is the effect on physicians and patients of not being selected for the device**
- **Placebo effect in unblinded study may be important**
- **Sample bias for missing data (e.g. may select out patients with neurological damage)**
- **Expect consistency between NYHA, QOL, 6-min walk, MVO_2**

Quality of Life
(Number of Patients Tested)

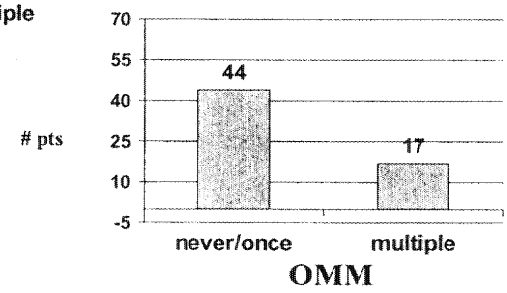
Jun '01 data



6 minute Hall Walk
(number of tests performed)



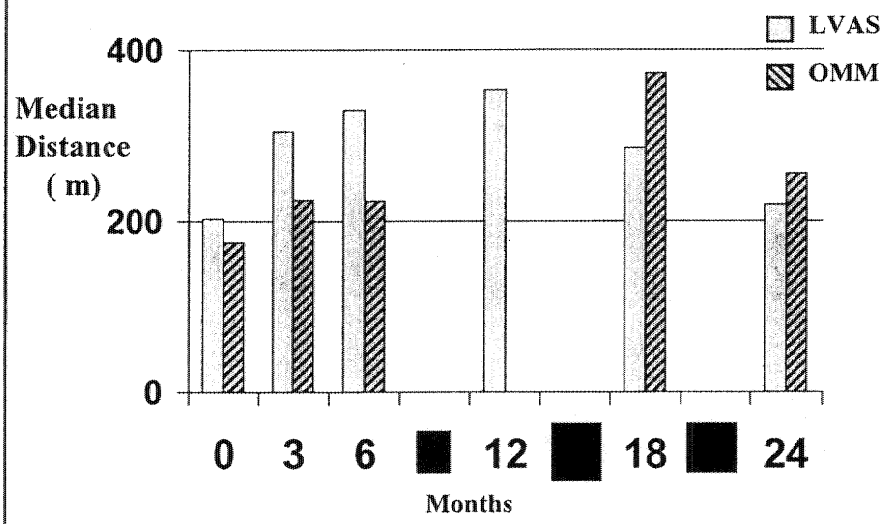
Inadequate data for comparison



Jun '01 data

6 minute Hall Walk

Jun '01 data



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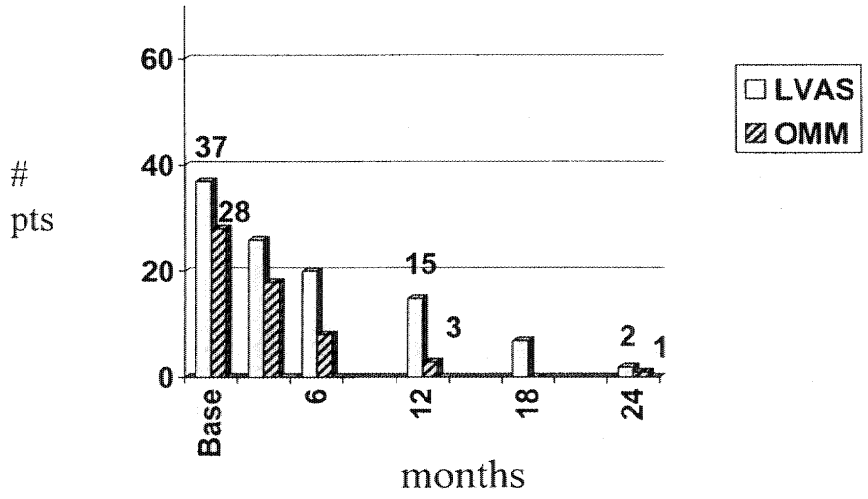
Peak VO_2 (ml/kg/min)



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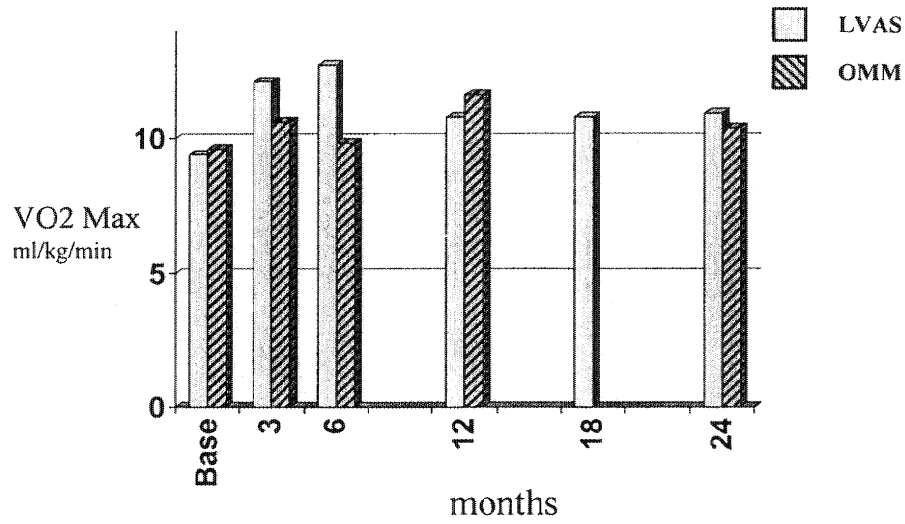
Peak VO_2 (ml/kg/min)



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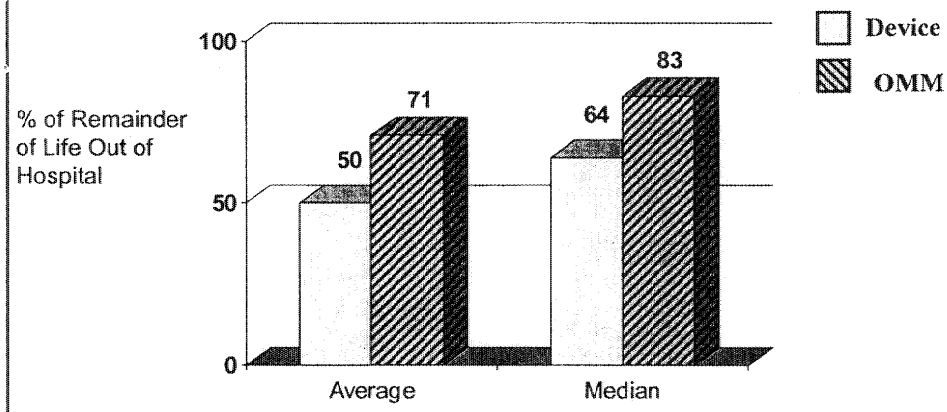
Hospitalization



Jun '01 data

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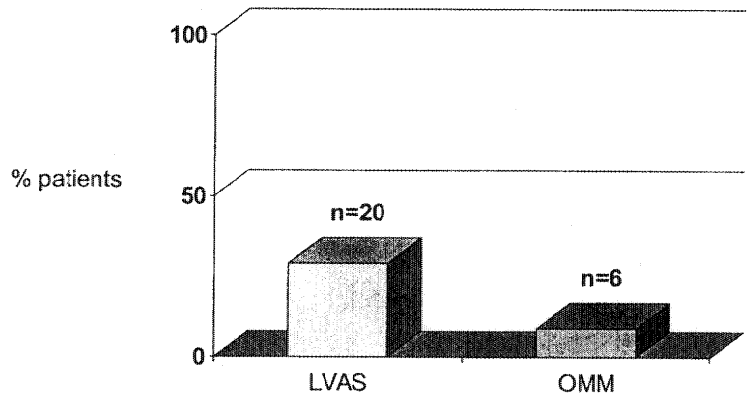
Death During Initial Hospitalization

Jun '01 data



Clinical Summary

- In a very advanced heart failure population LVAS use produced a survival benefit
- The mortality and morbidity associated with use of the LVAS was considerable
- Interpretation of functional testing data is limited by the small amount of data available

Statistical Comments

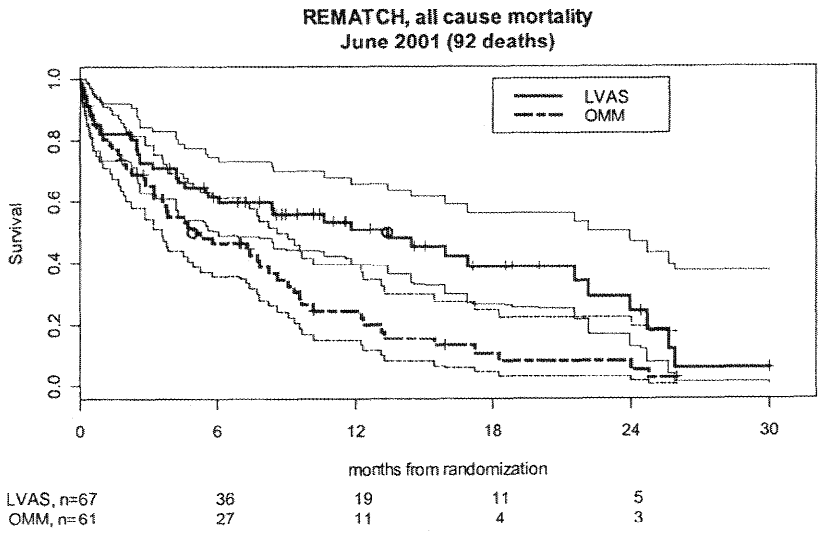
Thoratec HeartMate VE LVAS
Left Ventricular Assist Device

Gerry Gray, Ph.D.
FDA/CDRH/OSB/DBS

Study Synopsis

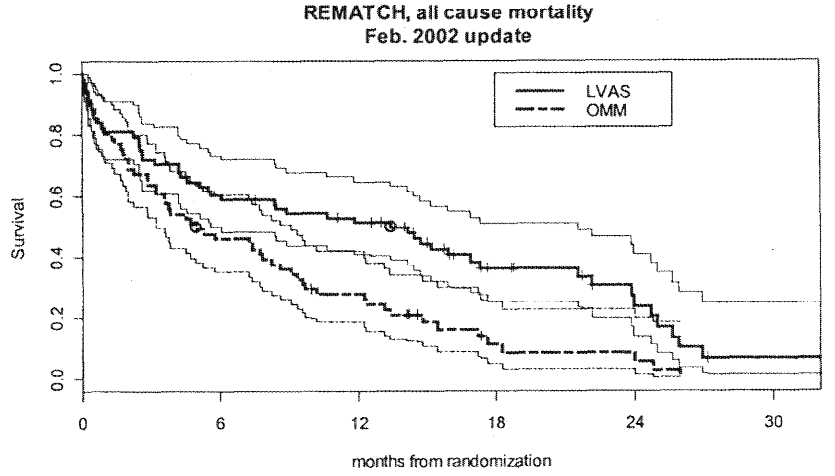
- Patients randomized 1:1 OMM:LVAS
- Primary endpoint: two-year mortality
- Three interim analyses at 23 death intervals, trial designed to stop at 92 deaths
  - O'Brien-Fleming; final critical p=0.044)
- Complete follow-up for survival analyses
- As of 6/28/01, 128 patients enrolled (61 OMM, 67 LVAS), 40 deaths in LVAS arm, 52 deaths in OMM arm
  - as of 2/01/02, 129 enrolled; 50 LVAS, 56 OMM deaths

All Cause Mortality



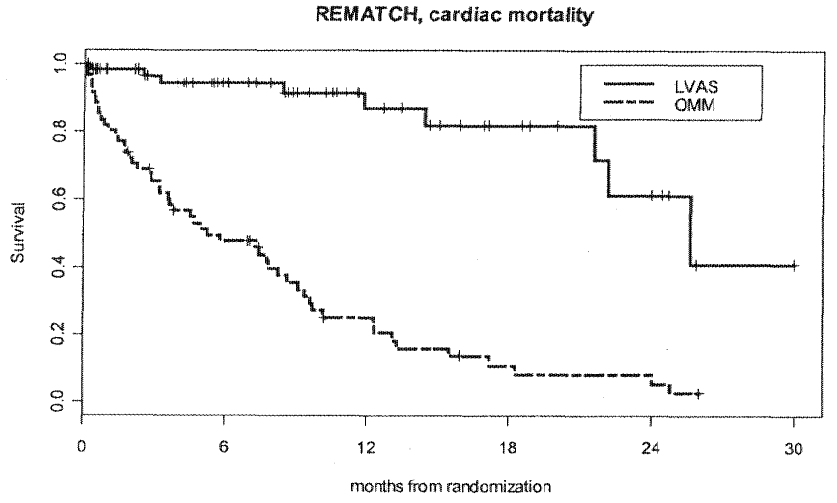
LVAS, n=67	36	19	11	5
OMM, n=61	27	11	4	3

All Cause Mortality - Update



LVAS, n=68	41	33	15	7
OMM, n=61	28	16	4	3

Cardiac Mortality



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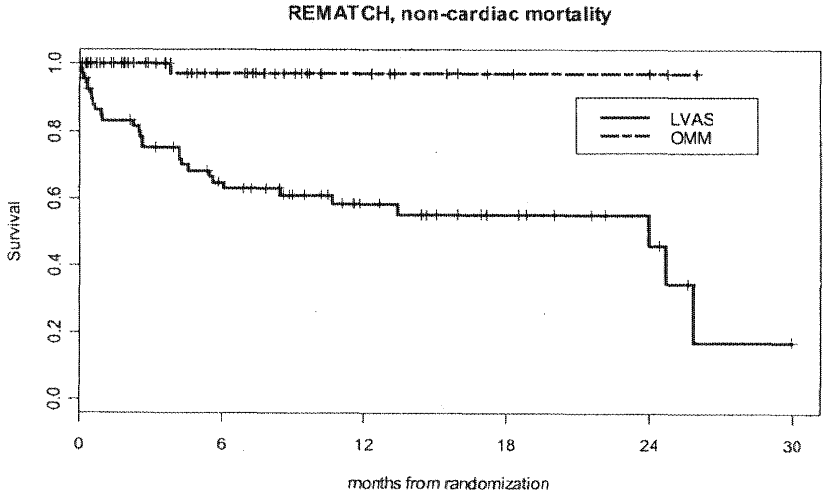
Non-Cardiac Mortality



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Mortality Results Summary

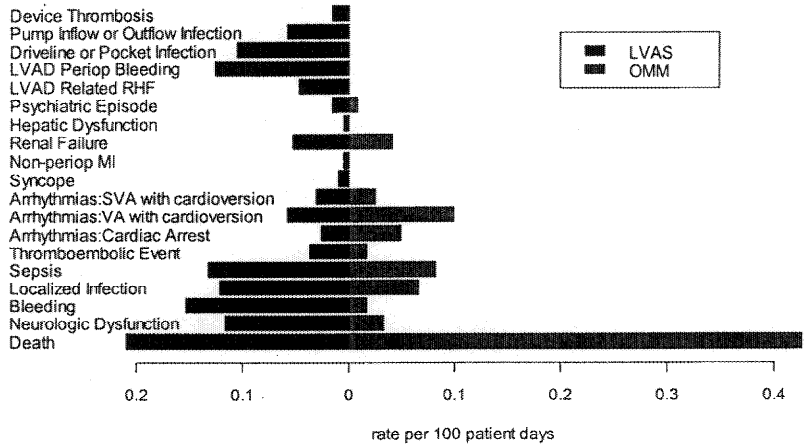
- Significant increase in median survival time (OMM 150 days, LVAS 405 days)
- Significant difference between K-M survival curves (logrank test p = 0.003)
- Significant difference in mortality at one year point (19 LVAS, 11 OMM patients at risk, mortality 50.8% vs. 24.4%)
- Marginal significance in mortality at two year point (updated data; 7 LVAS, 3 OMM patients at risk, mortality 23.7% vs. 8.3%)
- Cardiac, non-cardiac mortality not independent
- Relative "drop off" in LVAS survival at ~22 months? (only 11 patients @ 22 mo.)

Adverse Events

- Numbers of adverse events (AE) and serious adverse events (SAE) per person both significantly greater for the LVAS arm
- Rates per 100 patient days also significantly greater

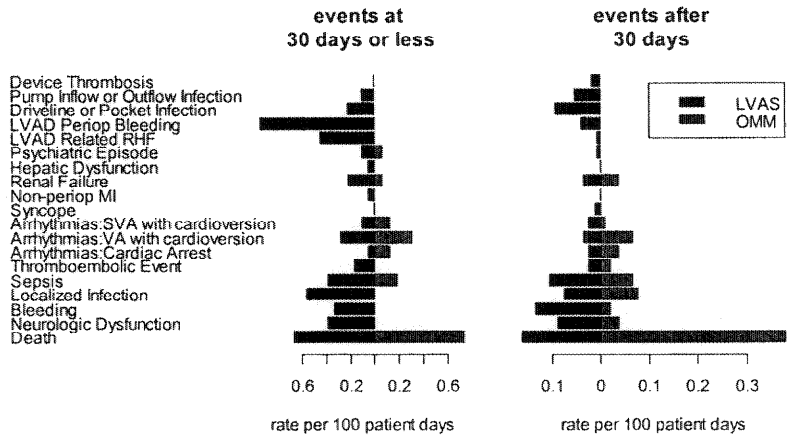
Death and Serious Adverse Events

REMATCH, SAE and death, rates per 100 patient days



Death and Serious Adverse Events

REMATCH, SAE and death, rates per 100 patient days



Hospitalization Time

	LVAS		OMM	
	median	total	median	total
Days in hospital	61	4450 (24%)	16	1756 (15%)
Days out of hospital	141	13,961 (76%)	105	10,085 (85%)
TOTAL		18,411		11,841

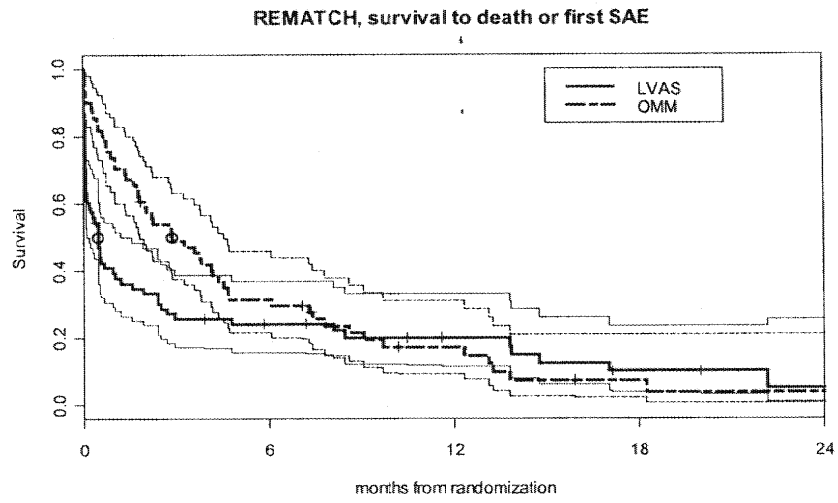
How to combine?

- Panel will be asked to weigh survival benefit vs. adverse event rate
- Two possible ways to formally combine the death and adverse event results
  - Hierarchical ranking
  - Survival to death or some other "bad event"
  - (these are not the only two possibilities)

Combined death & SAE

- Hierarchical ranking
  - rank patients by most important outcomes first, then break ties by secondary outcomes
  - e.g. rank by death time, or if alive by # of days in hospital
  - If death time is most important then regardless of other ranking factors, improvement always significant in favor of device.

Survival to death or first SAE



First SAE or Death

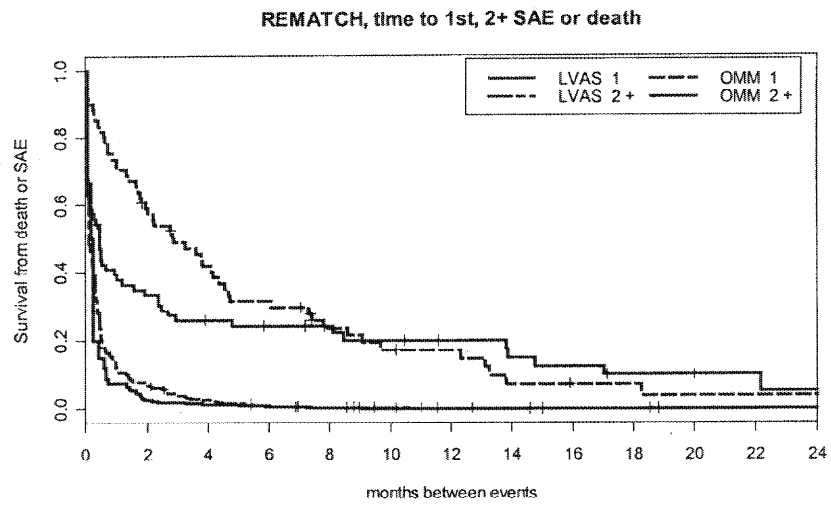
	LVAS	OMM
Death	2	28
Other SAE	56	25
None	10	8

Updated data, n=129 patients

Subsequent SAE or death

- Clinical impression from case reports that the first "bad event" often initiates a cascade of events leading ultimately to death
  - is this impression borne out in formal analysis?
  - Is there a difference between the two groups in the timing of the 2nd, 3rd, 4th events?

Conditional survival to death or SAE



Similar results for unpooled 2+; distribution of death vs.. SAE similar to first event

Functional Status Summary

P-values, tests for difference in improvement between LVAS, OMM

		3 Mo.	6 Mo.	12 Mo.
NYHA class		<0.001	<0.001	<0.001
Hall Walk		ns	ns	ns
Peak VO_2		ns	ns	ns
QOL	SF36 – physical	0.052	ns	ns
	SF36 – mental	ns	ns	ns
	Beck	0.055	0.002	0.055
	Minnessota LWHF	ns	0.018	ns
	EuroQOL general	0.003	<0.001	ns
	EuroQOL self assessment	0.002	<0.001	ns

Statistical Summary

- Significant decrease in mortality for LVAS arm (median survival time, logrank test, or pointwise)
- SAE rates much higher in LVAS arm
- LVAS treatment resulted in decreased cardiac mortality rates and increased non-cardiac mortality rates
- Survival past two years poor in both groups
- Some indication of relative LVAS "drop off" in survival at about 22 months (but few patients)
- Difference between groups almost entirely in time to first event, not time between subsequent events.
  - Odds of death vs. SAE always higher for OMM
- Functional status favors LVAS, but not consistently