LVADs as a long term or destination therapy for the advanced heart failure

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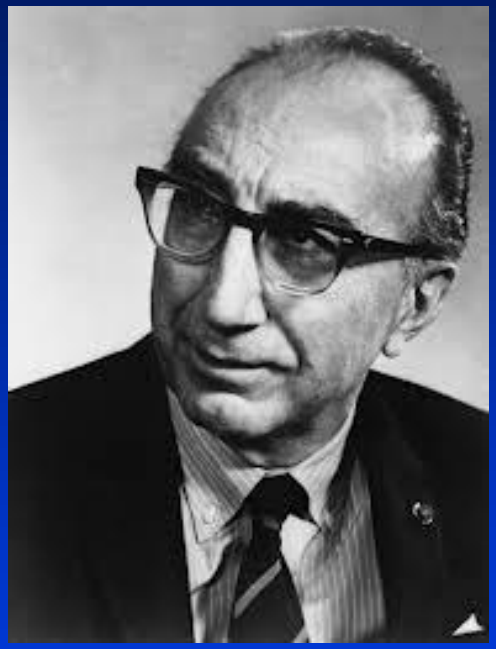
DISCLOSURES

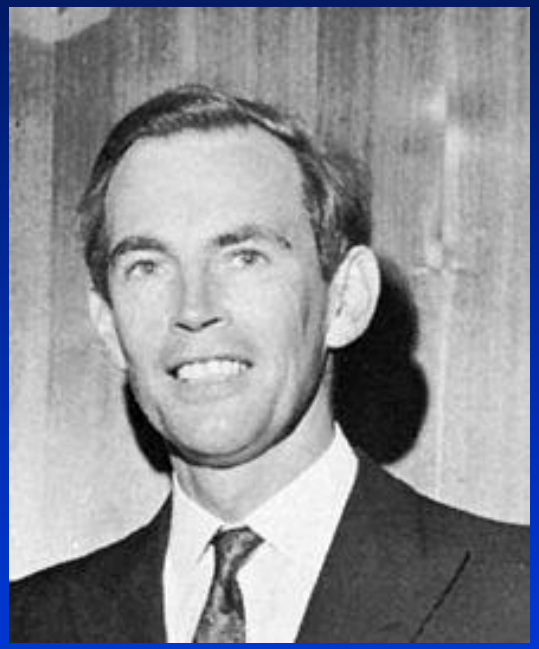
- Conslultancies & lectures within last 2 y:

Boerhinger Ingelheim, Merck, Pfizer, MSD, Sanofi Aventis, Pliva, Krka, Genzyme, Sandoz, Belupo, JGL, Astra Zeneca, Berlin Chemie Menarini, PharmaS, Medtronic, Medis Adria, Marck Medical, Thoratec

Idea of replacing a failing heart



1966. – first VAD - postcardiotomy support for 10 days (De Bakey)



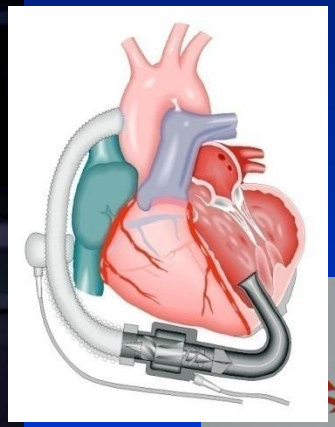
1967. - first human heart transplantation (Bernard)

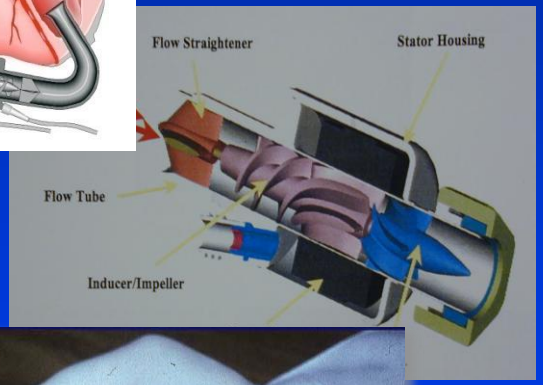
Heart transplantation

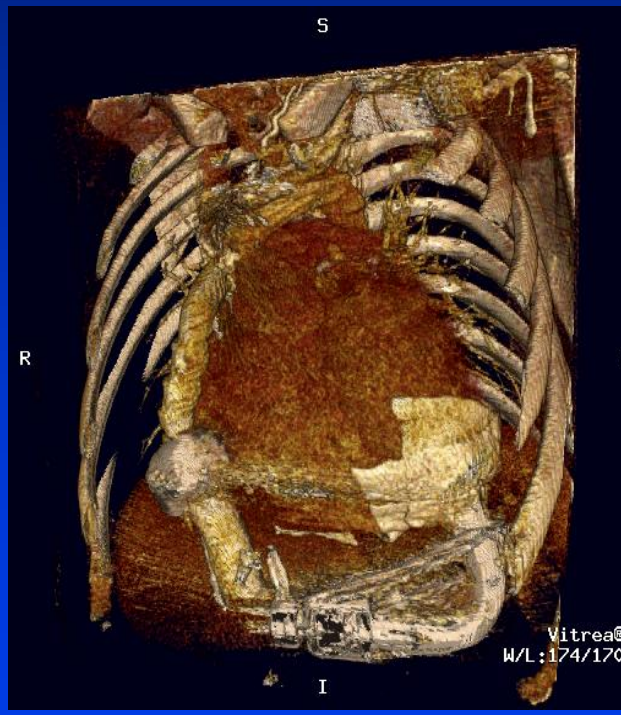
- HTx remains the only curative method for pts with end stage heart failure
- The rate of HTx remained relatively steady during the last 20 y
- Major imbalance between organ supply and demand
- 20% mortality rate among Htx waiting list candidates

Technical break through in VAD technology

First full implantable, miniaturized axial-pump for clinical application







diameter 30,5 mm
length 76,2 mm
weight 93 g

Table 24 Terms describing various uses of mechanical circulatory support (MCS)

Bridge to decision (BTD):	Use of MCS in patients with drug-refractory acute circulatory collapse and at immediate risk of death to sustain life until a full clinical evaluation can be completed and additional therapeutic options can be evaluated.
Bridge to candidacy (BTC):	Use of MCS to improve end-organ function in order to make an ineligible patient eligible for transplantation.
Bridge to transplantation (BTT):	Use of MCS to keep a patient at high risk of death before transplantation alive until a donor organ becomes available.
Bridge to recovery (BTR):	Use of MCS to keep patient alive until intrinsic cardiac function recovers sufficiently to remove MCS.
Destination therapy (DT):	Long-term use of MCS as an alternative to transplantation in patients with end-stage heart failure ineligible for transplantation.

MCS = mechanical circulatory support.

ESC HF Guidelines, 2012

1st generation

- Large pulsatile, positive displacement pumps with a lot of moving parts, limited to the pts with BSA > 1.5m2
- Novacor LVAS
- Thoratec IVAD
- Thoratec HM XVE
- Extracorporeal: Thoratec PVAD, Berlin Heart Excor, Toyobo LVAS

1994. - FDA approved the pulsatile ventricular assist device (VAD) HeartMate XVE later called HeartMate I as the first VAD for bridge to transplantation (Thoratec Corporation, Pleasanton, CA)

REMATCH

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

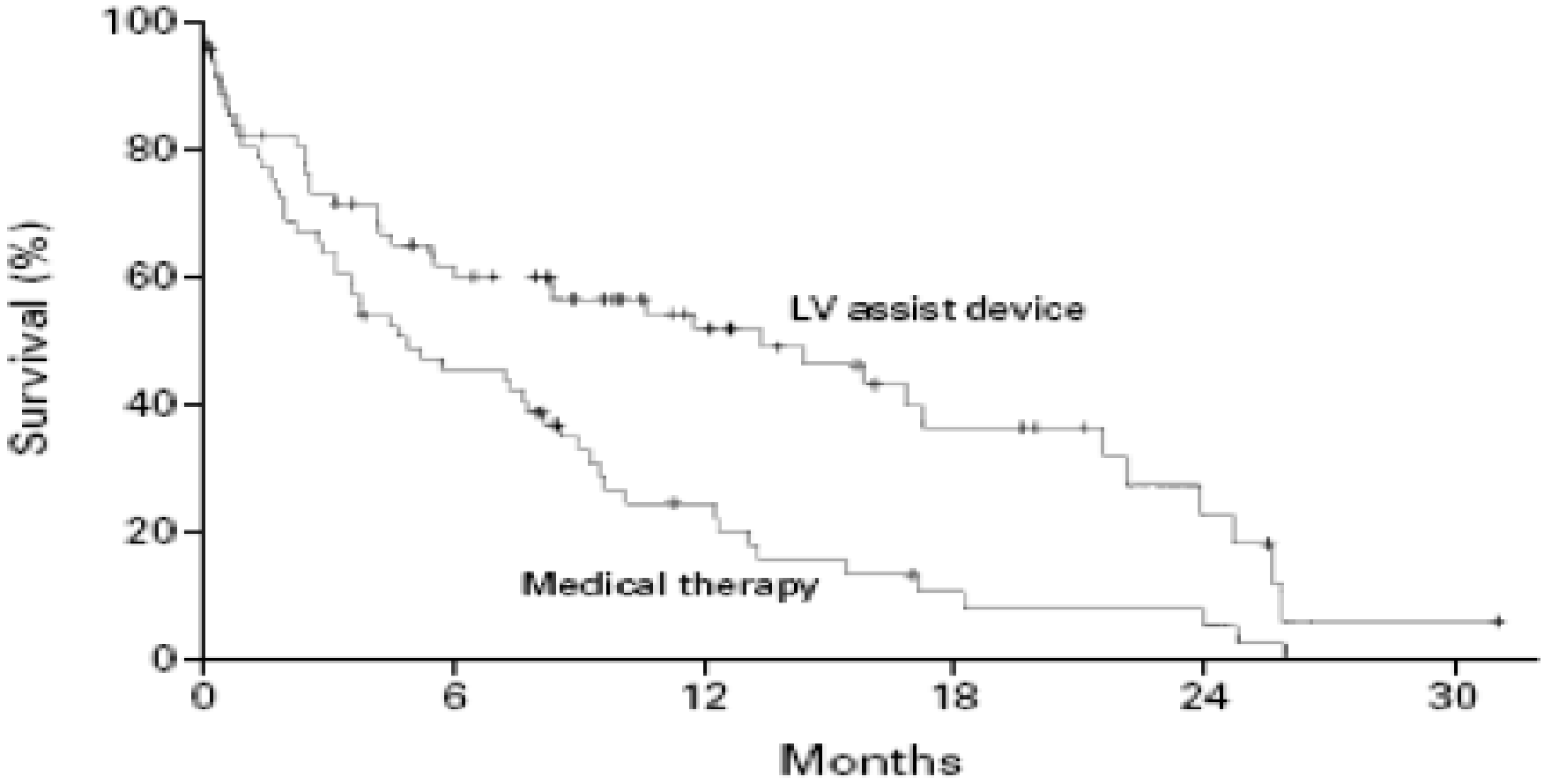
The New England Journal of Medicine

VOLUME 345 NOVEMBER 15, 2001 NUMBER 20

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

ERIC A. ROSE, M.D., ANNETINE C. GELIJNS, PH.D., ALAN J. MOSKOWITZ, M.D., DANIEL F. HEITJAN, PH.D., LYNNE W. STEVENSON, M.D., WALTER DEMBITSKY, M.D., JAMES W. LONG, M.D., PH.D., DEBORAH D. ASCHEIM, M.D., ANITA R. TIERNEY, M.P.H., RONALD G. LEVITAN, M.SC., JOHN T. WATSON, PH.D., AND PAUL MEIER, PH.D., FOR THE RANDOMIZED EVALUATION OF MECHANICAL ASSISTANCE FOR THE TREATMENT OF CONGESTIVE HEART FAILURE (REMATCH) STUDY GROUP*

REMATCH

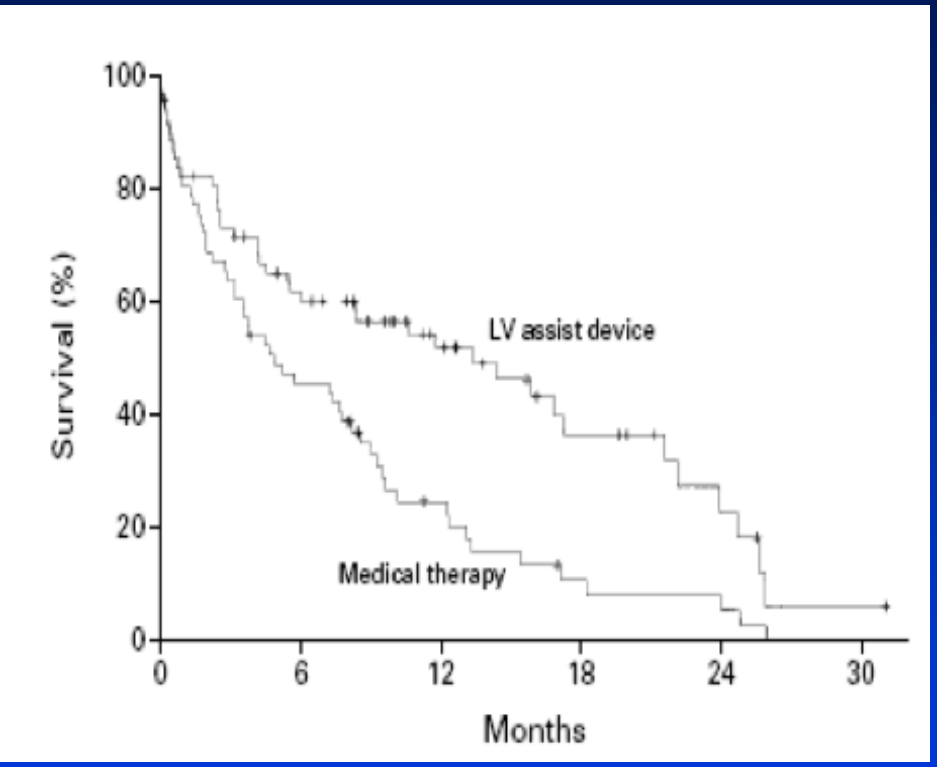


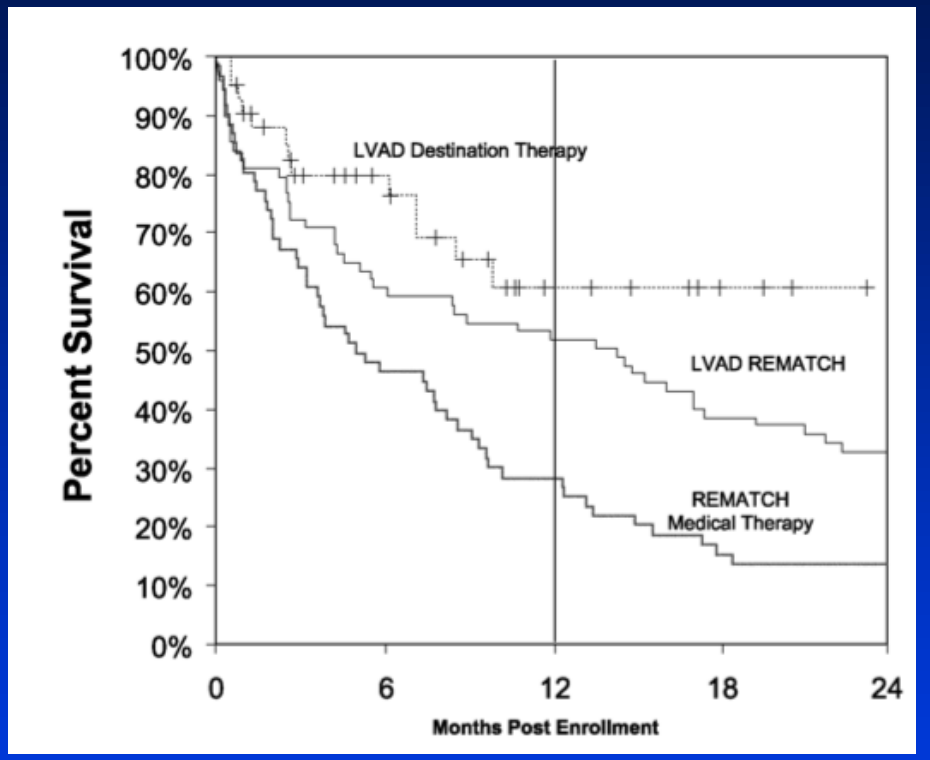
Roase et al, NEJM, Vol 345, No 20. Nov 2001

Overal reduction of mortality with 48% with LVAD.
Survival at 1 y 52% vs 25%; at 2 y 23% vs 8%
2 y survival increases to 32% at FU
Mean survival 408 vs 150 days

REMATCH

post REMATCH DT trial





Rose et al, NEJM, Vol 345, No 20. Nov 2001

Long JW et al. Destination Therapy with the HeartMate XVE LVAS: improved outcomes since the REMATCH study. CHF. 2005; 11:133-138

NOVACOR

- INTrEPID (Rogers et al. JACC 2007; 50:741-47)
- Similar population as in the REMATCH
- Advanced HF on inotropes
- Except younger age: 60 vs 66 y
- 55 pts enrolled
- Result: superior survival in
- 6 mo (46% vs 22%) and 12 mo (27% vs 11%)

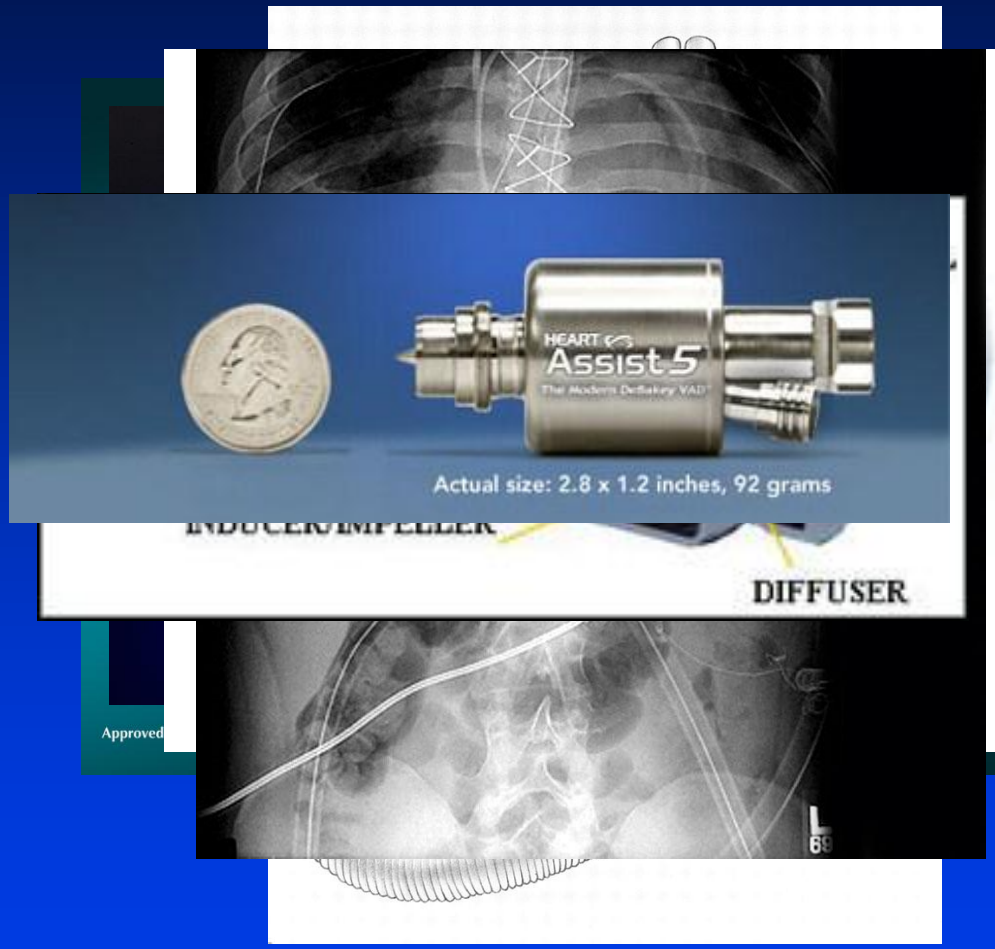
→ RELIANT (Novacor vs HM XVE) - stopped

2nd generation

- Axial pumps which utilize continuous flow
- Continuous pusless flow is well tolerated and improves neurocognitive disturbancies just as pulsatile LVADs
- Single moving rotor minimizes devices tear resulting to mechanical stability for years
- Due to smaller size less prone to infections and enable implantation in pts with smaller BSA

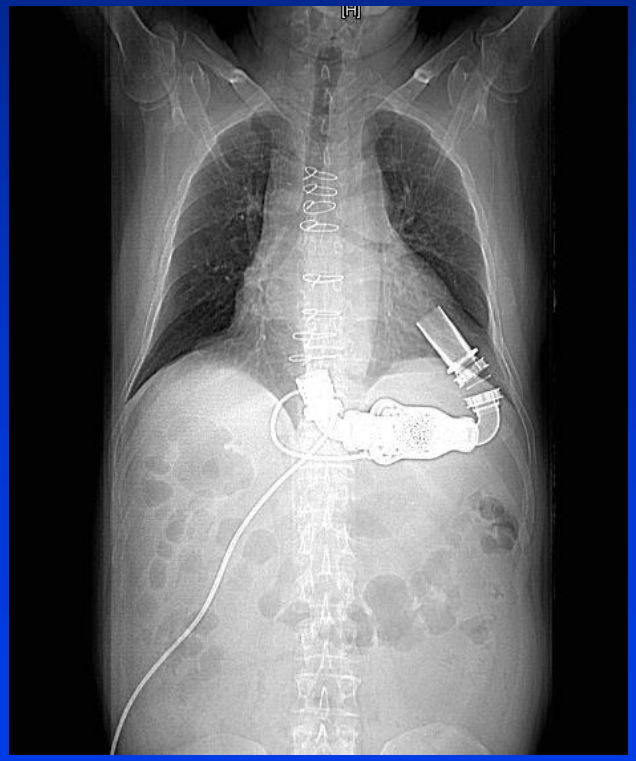
2nd generation: smaller in size, continuous flow

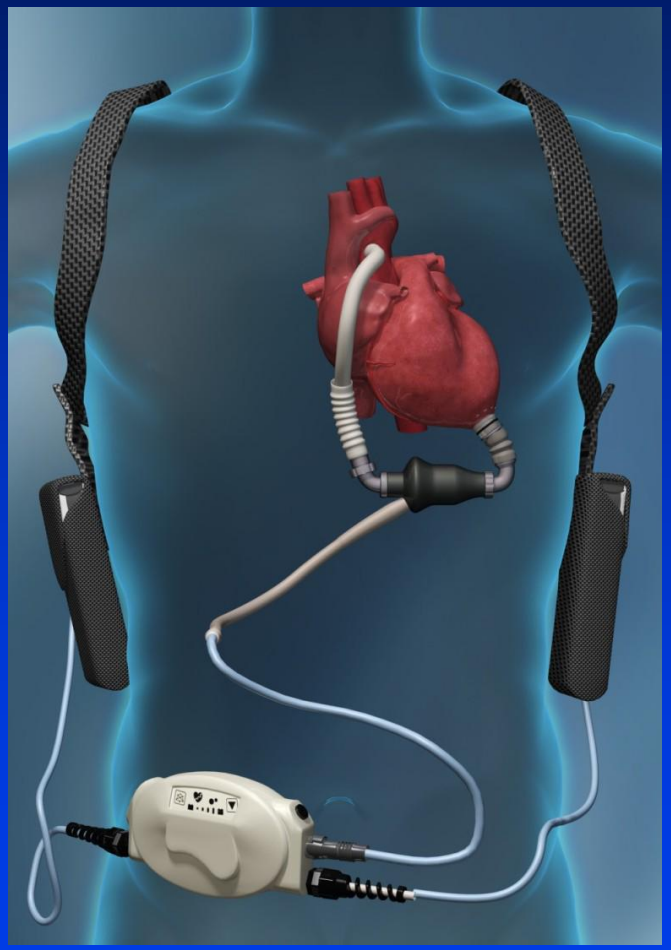
- Jarvik 2000
- HeartMate II
- MicroMed DeBakey



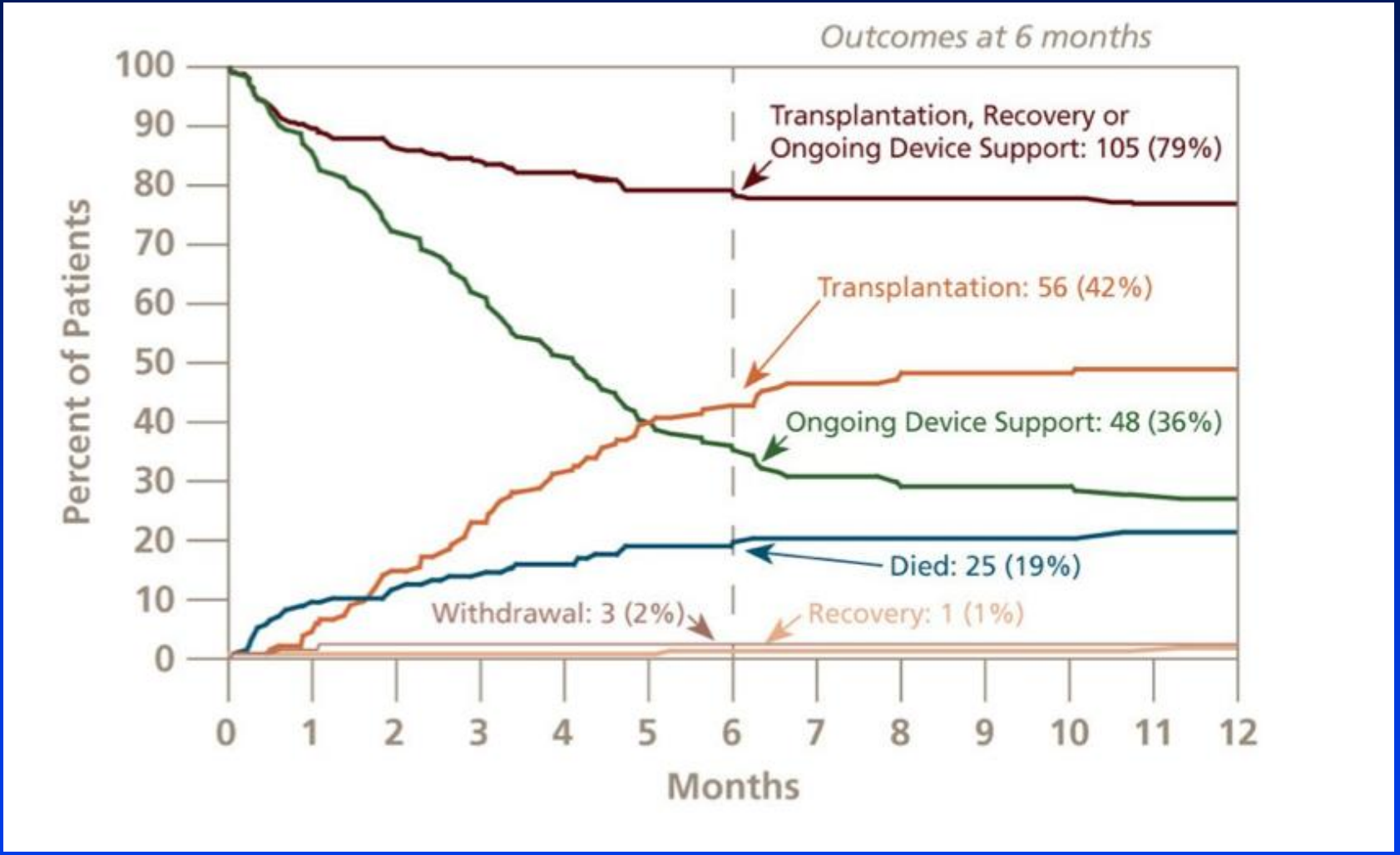
Heart Mate II

- Small, advanced axial flow blood pump
- Constructed of a medical-grade titanium alloy



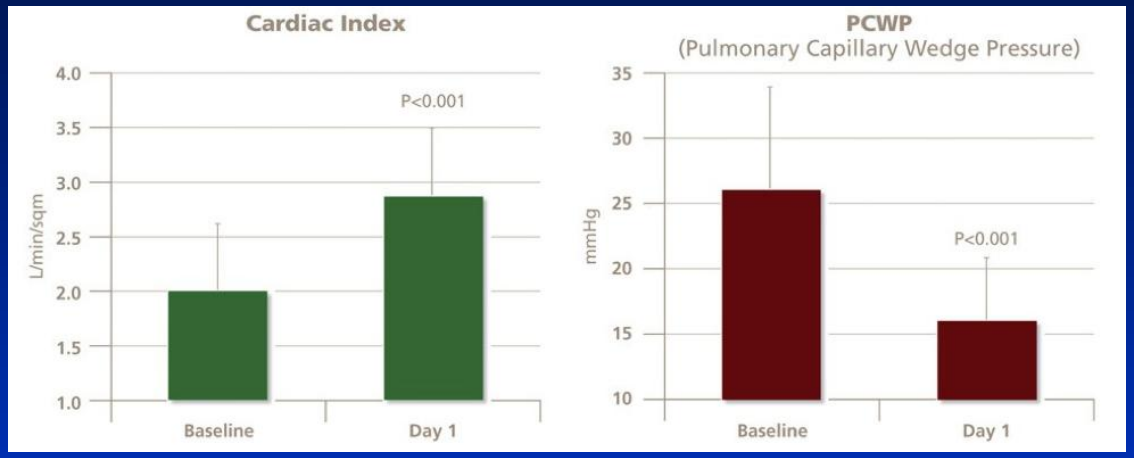


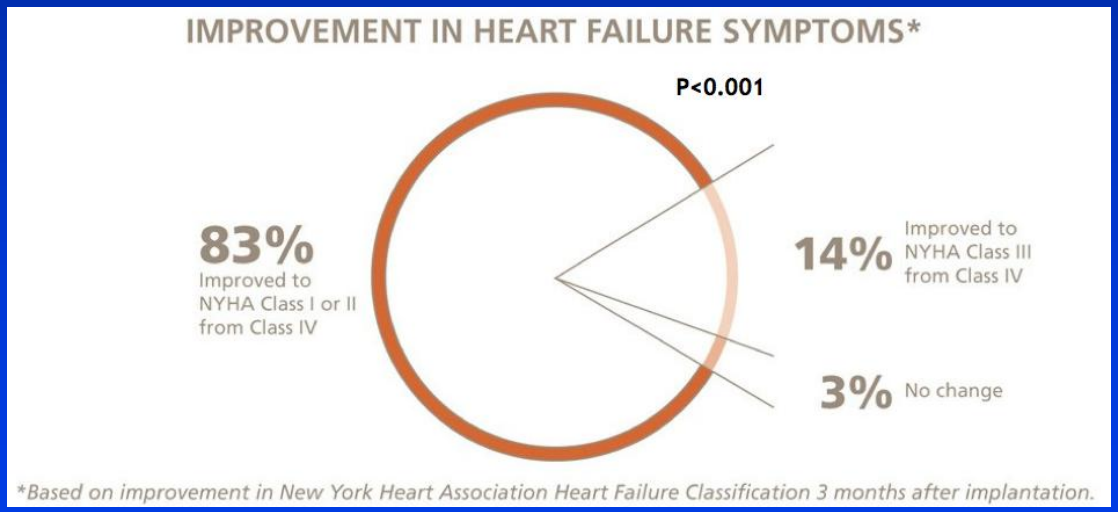
HeartMate II BTT Clinical Trial –
non-randomized trial in which all subjects received the HeartMate II LVAS and were compared to an objective performance criterion



Miller LW, Pagani FD, Russell SD, et al. N Engl J Med 2007;357:885-96

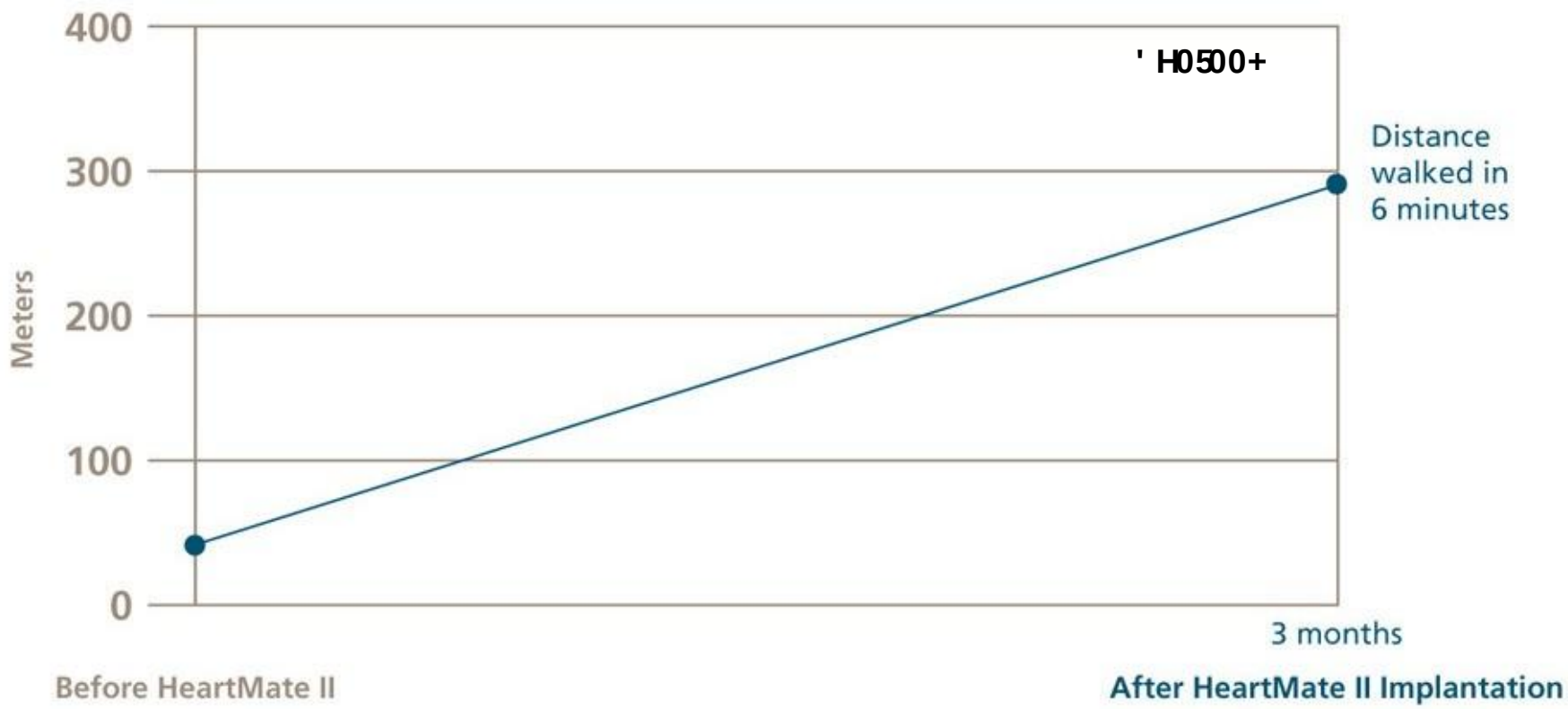
HeartMate II BTT – Hemodynamic and Functional Status Response





Miller LW, Pagani FD, Russell SD, et al. N Engl J Med 2007;357:885-96

6 min. walk



Miller LW, Pagani FD, Russell SD, et al. N Engl J Med 2007;357:885-96

HM II DT Pivotal Trial

- Randomization 200 pts with NYHA IIIb or IV
- EF ≤ 25%
- VO2 max. ≤ 14 ml/kg/min
- or: inotropes at least 14 days
- or: IABP for 7 days
- HM II (134) vs. HM XVE (66)
- Primary end point: 24 m survival without disabling stroke and rthe need for an operation/repairing/replacing the VAD

Slaughter et al. NEJM 2009; 361:2241-2251

HM II Destination Trial

In a randomized clinical study of 200 participants at 38 centers,

46 percent of 134 participants with the HeartMate II were still living after two years with no disabling stroke or need for a reoperation for device replacement or repair compared with 11 percent of 66 participants in the control group.

In addition, data collected in a separate registry of smaller stature women and men indicated that the device worked well in this specific population.

Slaughter MS, Rogers JG, Milano CA, et al. for the HeartMate II Investigators. Advanced heart failure treated with continuous-flow left ventricular assist devices. N Engl J Med. 2009;361:2241–51.

HeartMate II vs HeartMate I

End Point	Continuous-Flow LVAD (N=134)	Pulsatile-Flow LVAD (N=66)	Hazard Ratio (95% CI)	P Value
	no. (% [95% CI])			
Survival free from disabling stroke and reoperation to repair or replace LVAD at 2 yr (primary composite end point)	62 (46 [38–55])	7 (11 [3–18])		<0.001
First event that prevented patient from reaching the primary end point				
Disabling stroke†	15 (11 [6–17])	8 (12 [4–20])	0.78 (0.33–1.82)	0.56
Reoperation to repair or replace pump‡	13 (10 [5–15])	24 (36 [25–48])	0.18 (0.09–0.37)	<0.001
Death within 2 yr after implantation	44 (33 [25–41])	27 (41 [29–53])	0.59 (0.35–0.99)	0.048
Any	72 (54 [45–62])	59 (89 [82–97])	0.38 (0.27–0.54)	<0.001

Slaughter et al. N Engl J Med. 2009 Dec 3;361(23):2241-51.

Post approval study for HeartMate II® in destination therapy (DT)

- prospective evaluation of the first 247 patients with HM II implanted as DT
- enrollment from Jan – Sep 2010
- follow up - two years
- comparison group 133 patients enrolled in the primary data cohort in the DT pivotal trial

Jorde et al. Two-Year Outcomes in the Destination Therapy Post-FDA-Approval Study with a Continuous Flow Left Ventricular Assist Device: A Prospective Study Using the INTERMACS Registry 2013 Apr;32(Suppl):S10

Adverse events and outcomes

	Lenght of stay (d)	Bleeding req surg.	Isch. Stroke (events/pt-yr)	Hem. Stroke (events/pt-yr)	Device infection (events/pt-yr)	1 yr survival	2 yr survival
TR (n=133)	27	30%	0.06	0.07	0.48	68±4%	58±4%
PA (n=247)	21	11%	0.04	0.05	0.22	76±3%	62±3%

Jorde et al. Two-Year Outcomes in the Destination Therapy Post-FDA-Approval Study with a Continuous Flow Left Ventricular Assist Device: A Prospective Study Using the INTERMACS Registry 2013 Apr;32(Suppl):S10

3rd generation – miniaturized continuous flow centrifugal or axial pumps

- Levacor VAD (WorldHeart)
- HeartWare (HVAD)
- VentrAssist
- DuraHeart
- Berlin Heart Incor

3rd generation VADs

- WorldHeart Levacor VAD → terminated

- Terumo Dura Heart
  - CE mark
  - in 2011. German pt. surpasses 5 years of support on DuraHeart LVAS

HeartWare Ventricular Assist system (HW VAS)

- 2009. CE mark for BTT
- May 2012. addendum to CE mark for DT
- November 2012. FDA approved for BTT
- June 2013. FDA approved to enroll pts. in DT trial

- so far cca. 2500 HVADs were implanted worldwide

Clinically relevant evidence-based data

ADVANCE

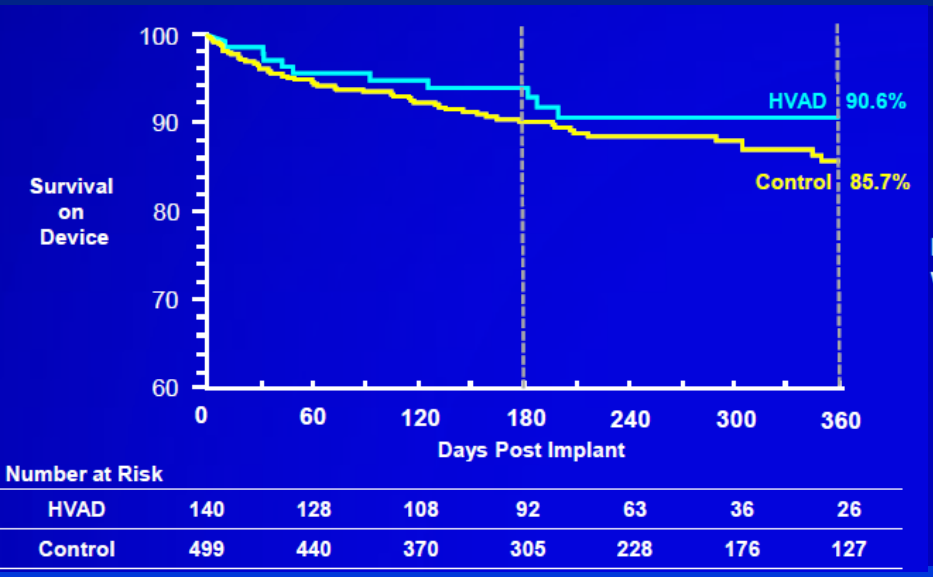
Objective: to evaluate safety and efficacy of HVAD in pts. listed for HTx with refractory advanced HF

- multi-center, prospective, non-randomized, two arm study
- HVAD (N=332- pivotal trial + continuous access protocol) vs. control (INTERMACS, N=499)
- primary endpoint: non-inferiority to control
- secondary endpoints: descriptive statistics (survival, QoL, functional class, SAE)

J Heart Lung Transplant. 2013 Jul;32(7):675-83. doi: 10.1016/j.healun.2013.04.004.

ADVANCE
secondary endpoints

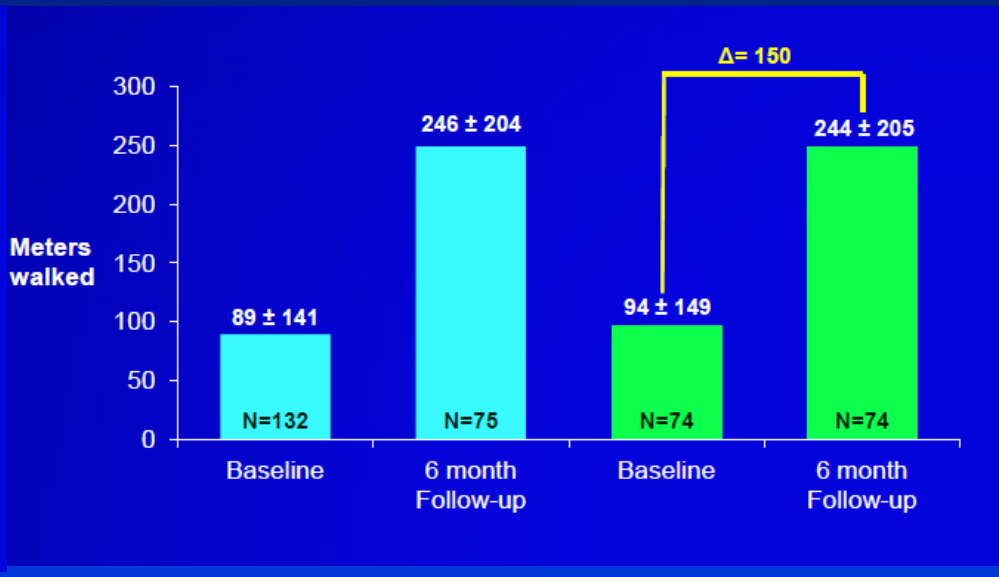
survival at 360 days



Number at Risk

HVAD	140	128	108	92	63	36	26
Control	499	440	370	305	228	176	127

functional status by 6MWT



J Heart Lung Transplant. 2013 Jul;32(7):675-83. doi: 10.1016/j.healun.2013.04.004.

Clinically relevant evidence-based data
ADVANCE

- HeartWare VAD met the criterion of noninferiority to the control ($p<0.001$) but not superiority:
  - The treatment-group success was 92.0%
  - Control-group success was 90.1%
- There appears to be less bleeding and infection with the new device
- The incidence of stroke was higher than might have been expected with the smaller size of the device

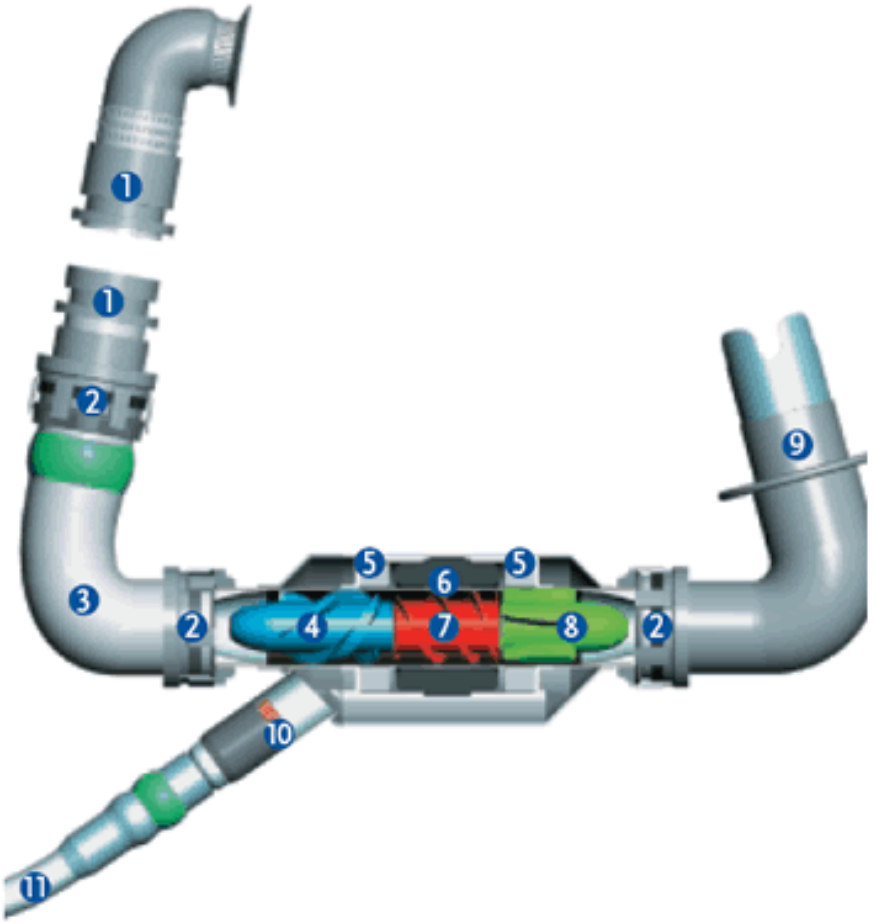
J Heart Lung Transplant. 2013 Jul;32(7):675-83. doi: 10.1016/j.healun.2013.04.004.

Clinically relevant evidence-based data
ENDURANCE

- "first-in-kind" trial (head-to-head VAD trial)
- a prospective, randomized, un-blinded, multi-center, non-inferiority clinical trial to evaluate the use of the HeartWare® Ventricular Assist System as a destination therapy in advanced HF pts.
- N=450 (June 2010- May 2012)
- Primary endpoint: stroke-free survival at two years (follow up ends in May 2014.!)
- Secondary endpoints: incidence of bleeding, major infection, device failure, as well as health and functional status improvement.
- the largest trial to date for the long-term use of a left ventricular assist device
- EXPECTING RESULTS…..

manufacturers' data: www.heartware.com

INCOR Berlin Heart
design

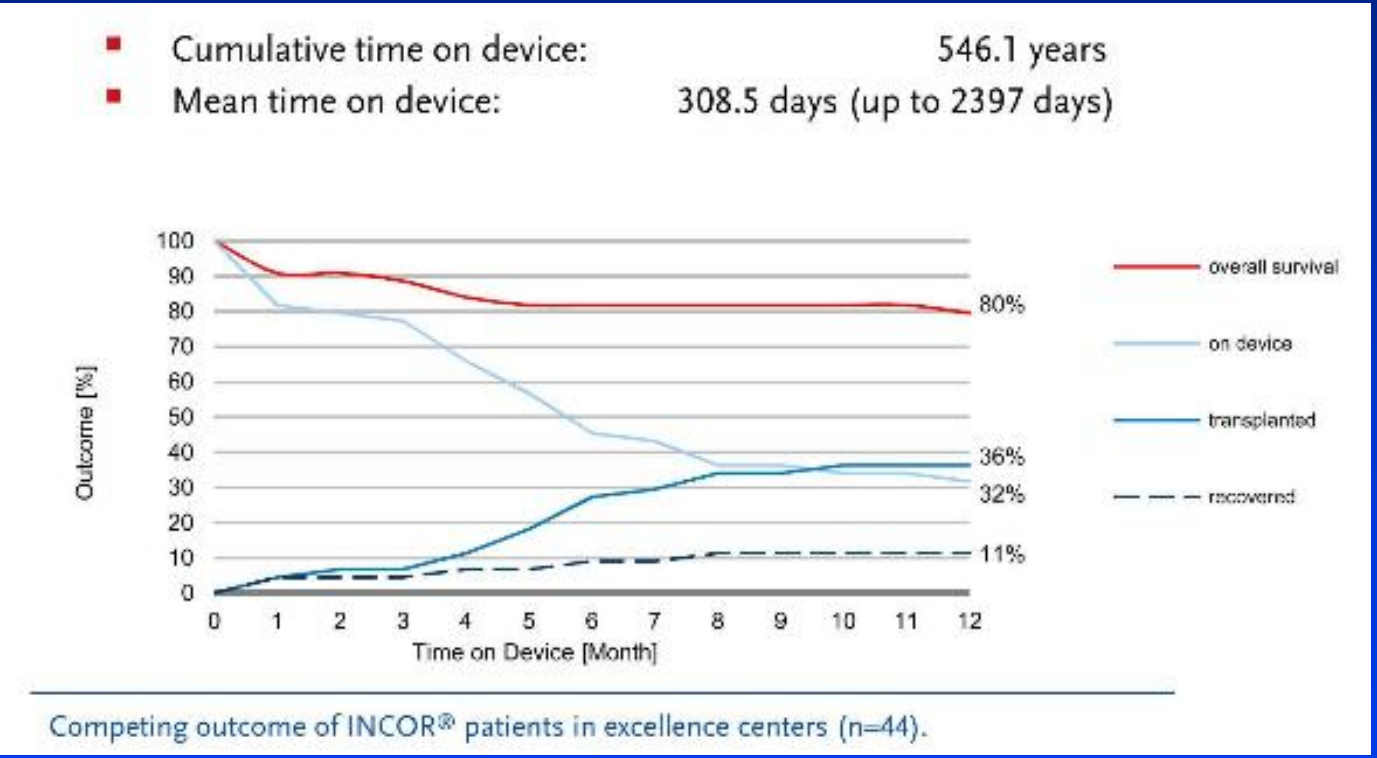


1 Outflow Cannula (interrupted view)
2 Snap-in Connector
3 Outflow Angle Section
4 Outflow Guide Vane
5 Bearing Coil
6 Motor Coil
7 Impeller
8 Inflow Guide Vane
9 Inflow Cannula
10 Glass-to-Metal Seal
11 Cable

INCOR Berlin Heart

Clinical update information- May 2013

- data from BerlinHeart database (from 44 implant centers)*



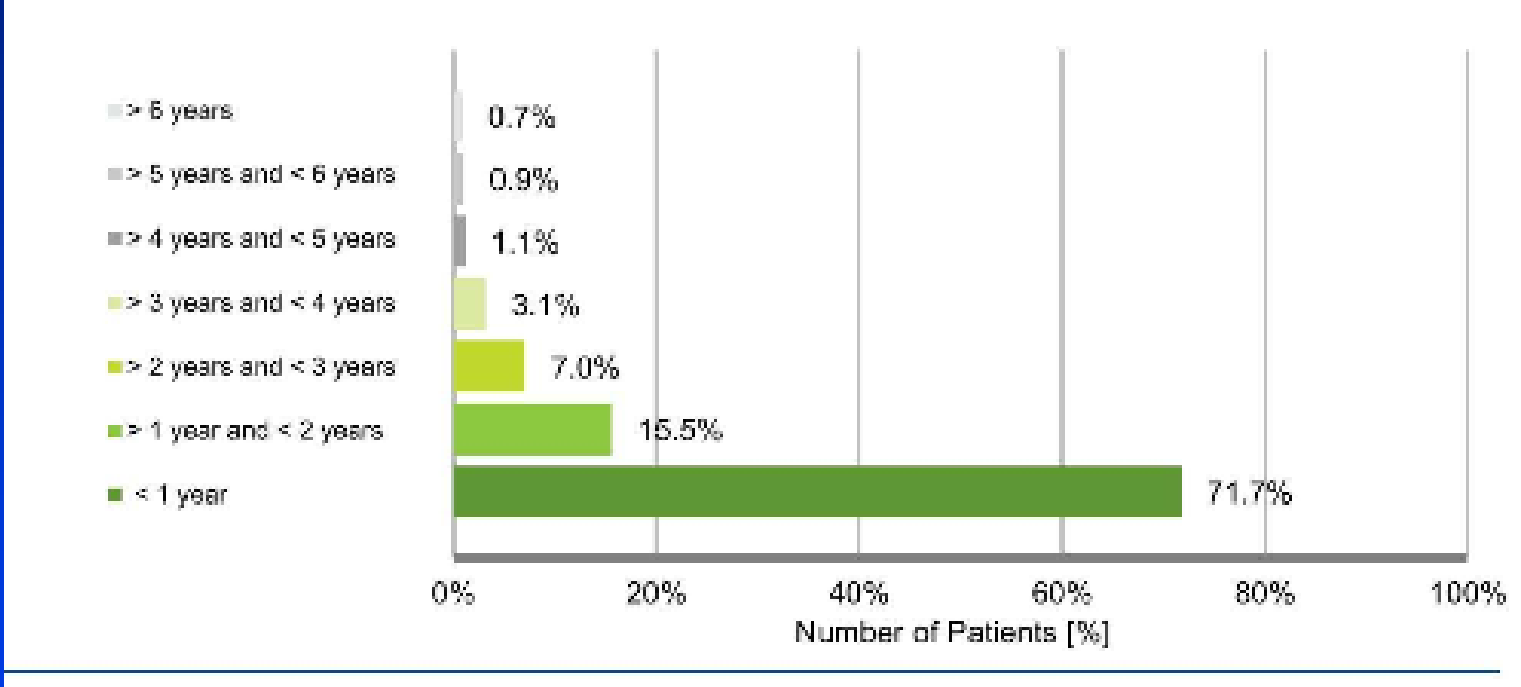
*manufacturers' data, not indep. trial data

Data from: http://www.berlinheart.de/index.

INCOR Berlin Heart

Clinical update information- May 2013

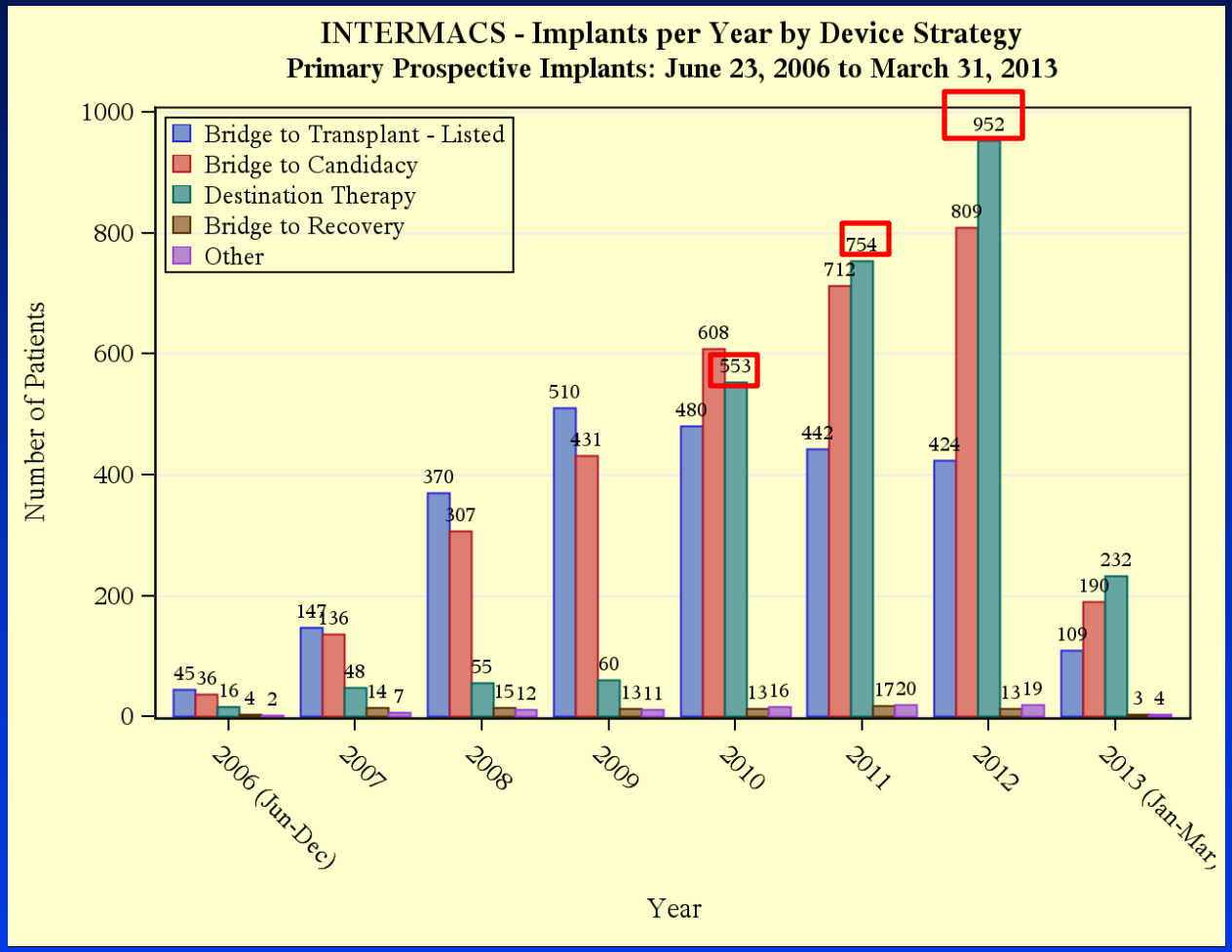
- data from BerlinHeart database (N=646)



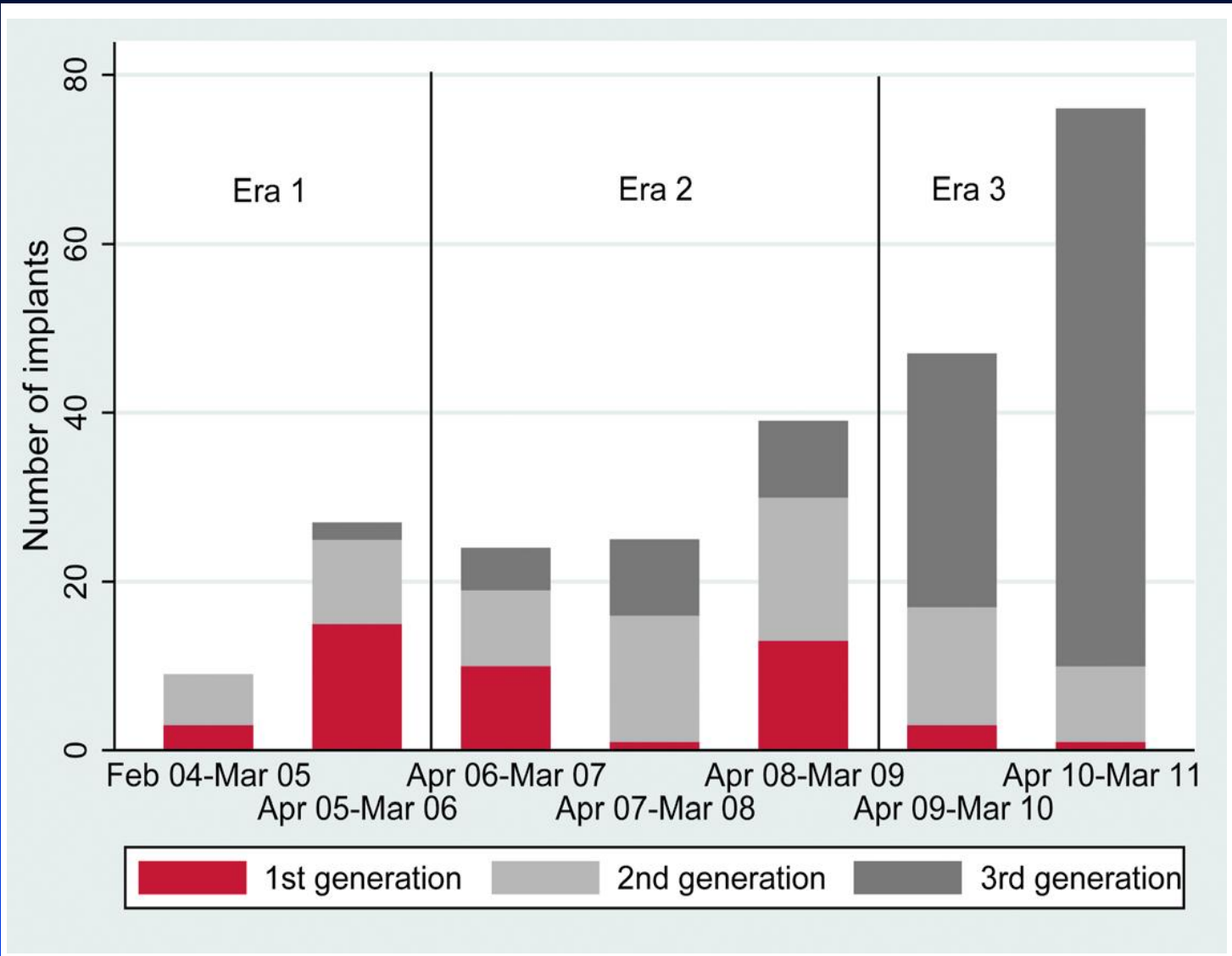
Data from: http://www.berlinheart.de/index.

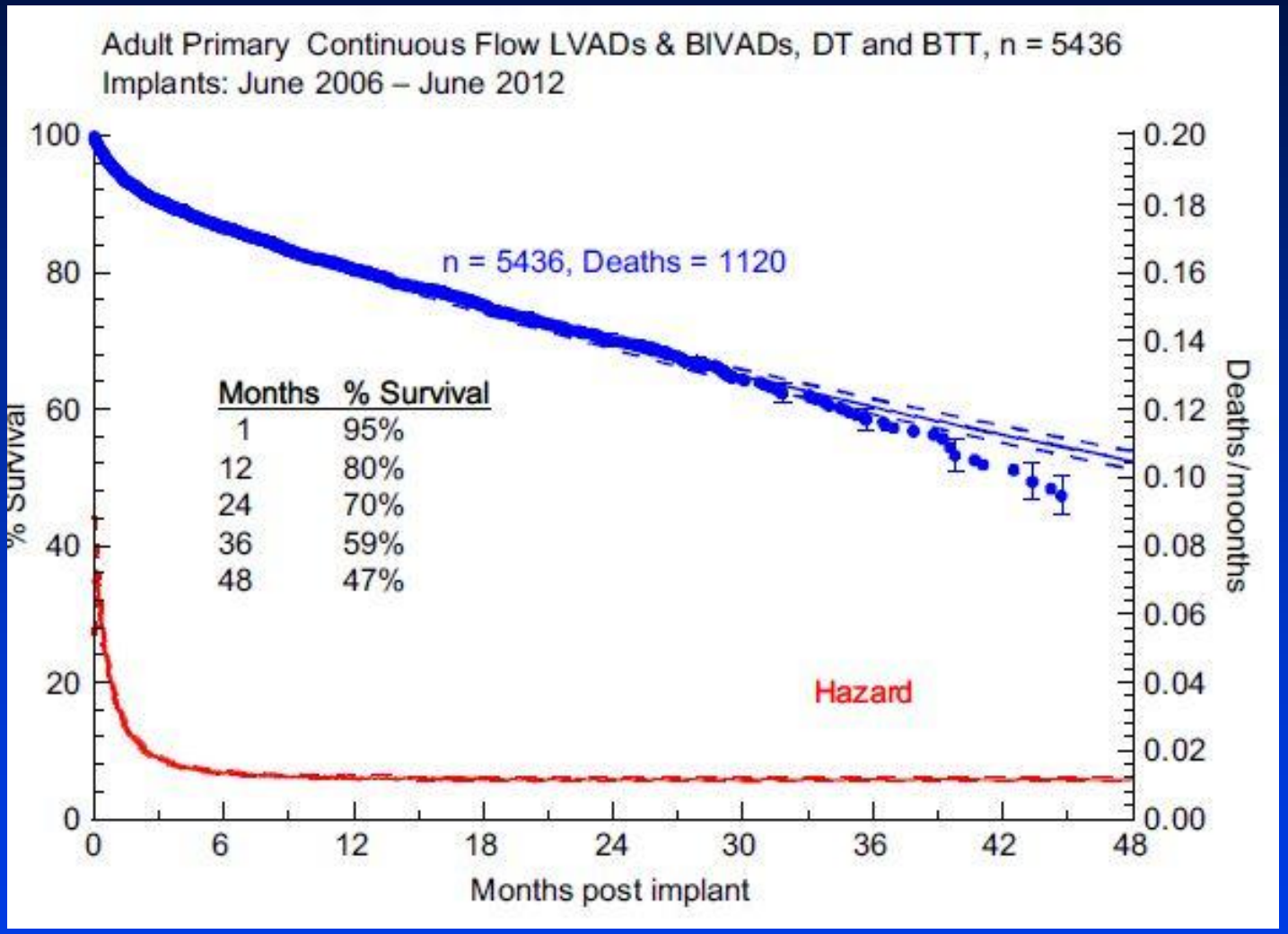
TRENDS

INTERMACS
Implants per year by device strategy



Quarterly Rep


Era 1
Era 2
Era 3
Number of implants
0
20
40
60
80
Feb 04-Mar 05
Apr 05-Mar 06
Apr 06-Mar 07
Apr 07-Mar 08
Apr 08-Mar 09
Apr 09-Mar 10
Apr 10-Mar 11
1st generation
2nd generation
3rd generation



Kirklin et al. Fifth INTERMACS annual report Feb 2013

10-y Survival, University Hospital Centre Zagreb

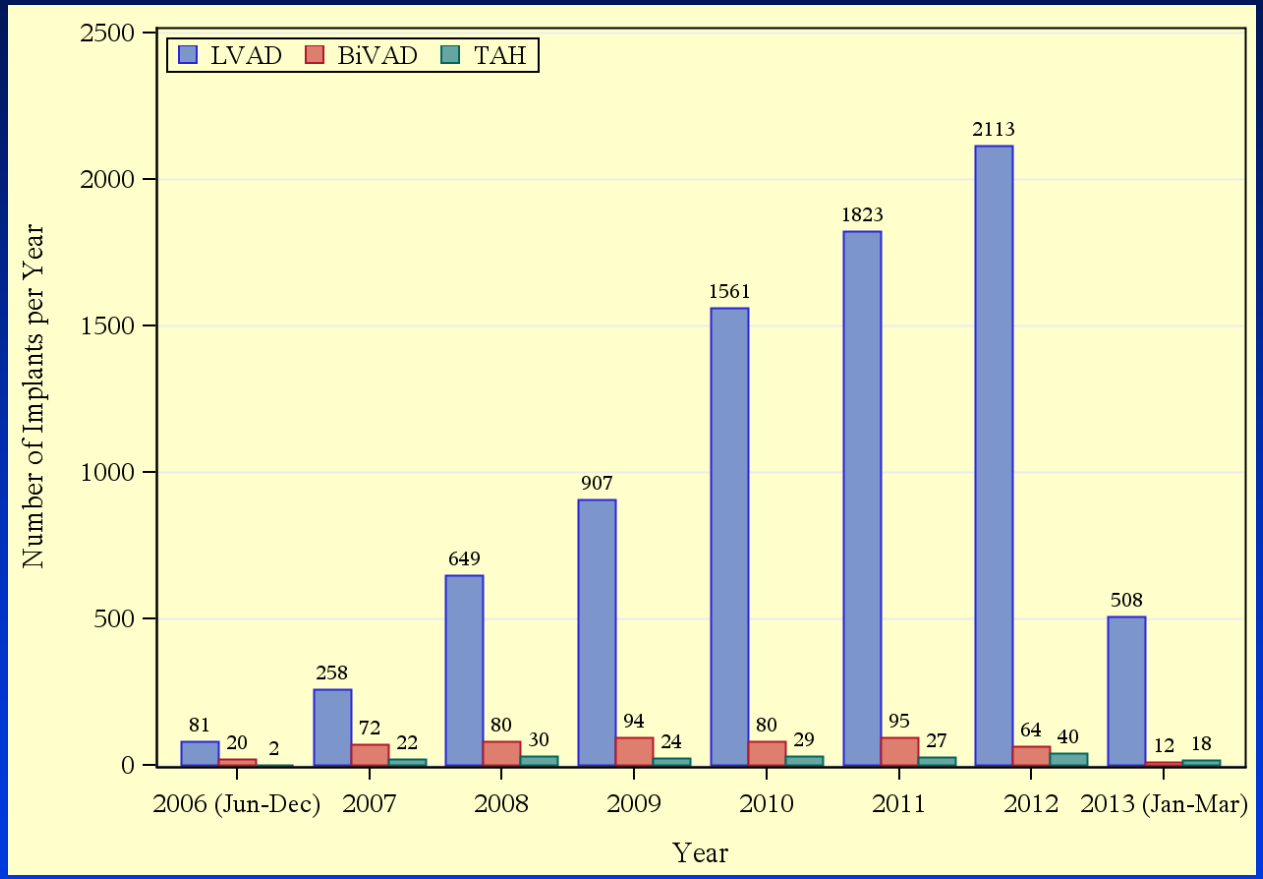
1988-1999

- 30 d: 73%
- 1 y.: 63%
- 5 y.: 49%
- 10 y: 35%

2000-2010

- 30 d: 85%
- 1 y: 80%
- 5 y: 64%
- 9 y: 54%

INTERMACS
Implants per year by device type



Technological improvements

- Fully implantable miniaturized durable VAD with percoutaneously charging batery
- TETS (LionHeart 2000 LVAD; AbioCor TAH)
- Synergy Pocket Micro Pump; partial support up to 4.25 L/min, pacemaker like implantation

New indications

- VADs in less sick patients e.g. stabile NYHA III patients/ambulatory patients
- Ongoing studies:

- ROADMAP (HM II) – ending Dec. 2015
- REVIVE-IT (HVAD) – ending Jan. 2016

Conclusion

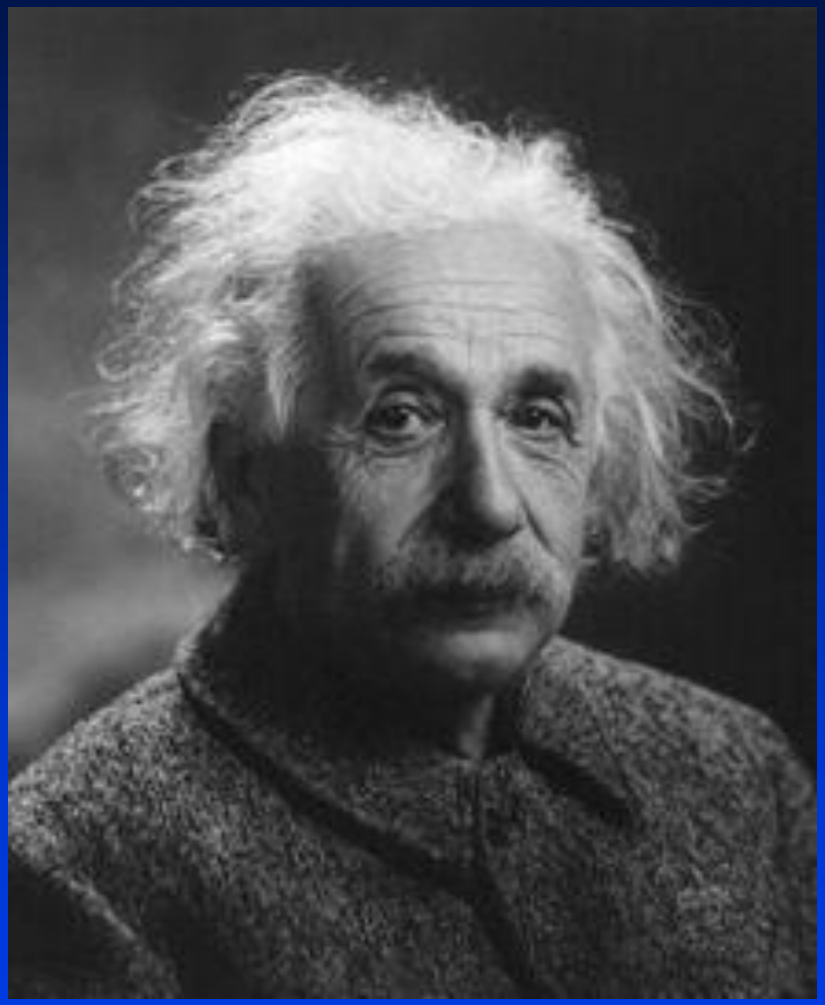
- LVADs of 2nd and 3rd generation are an accapted long term BTT and for DT for patients with advanced HF not eligible for HTx
- As the need for HTx constantly increases and HTx rates do not increase, LVAD can be an acceptable alternative to HTx
- Adequate RVAD and BVAD still remains an unsolved issue

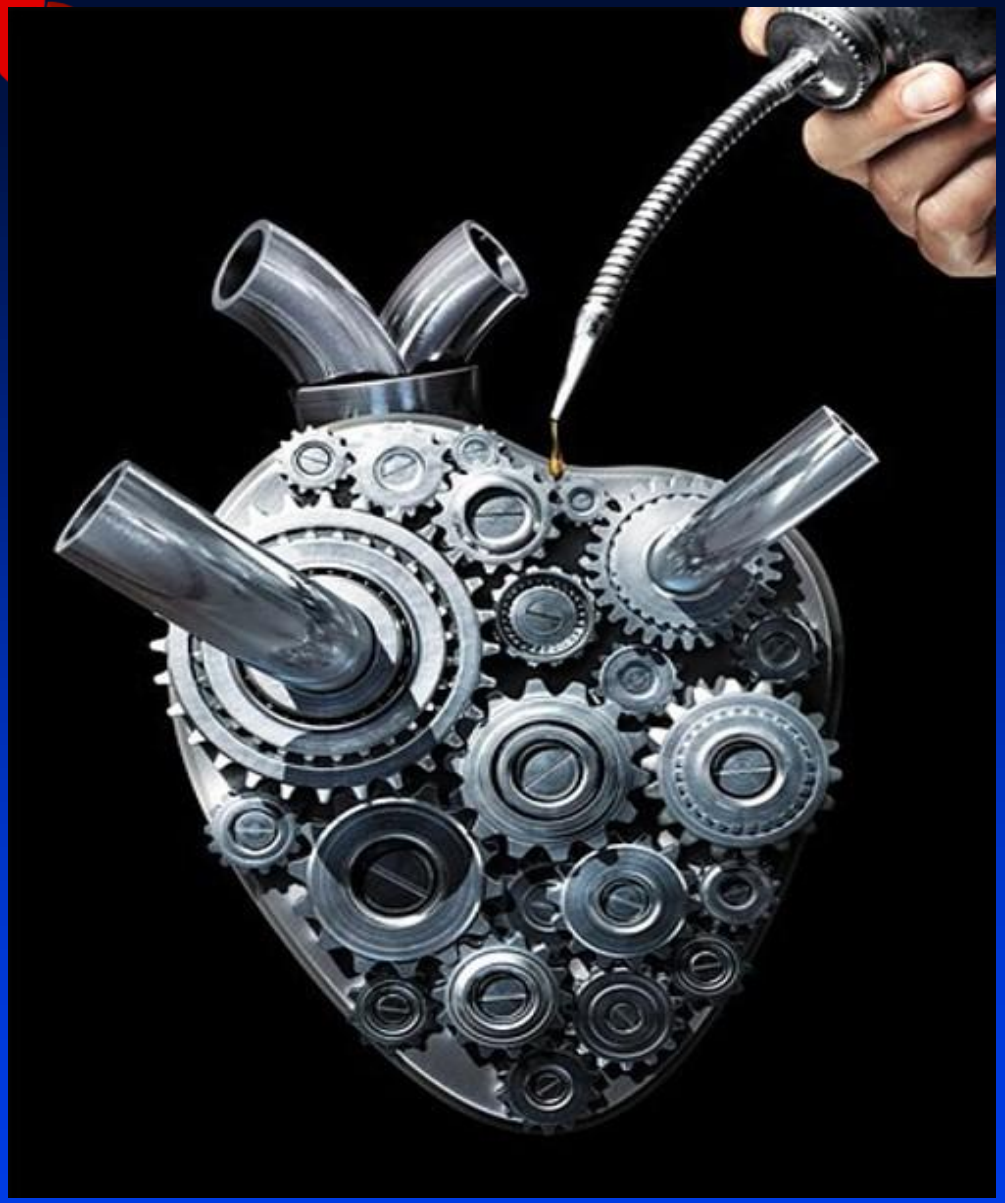
Conclusion (cont.)

- New technological development will bring TETS and less invasive implantation strategies
- VADs are going to be tested against OMT and CRT in less sick patients
- The need for VADs will exponentially grow and require lowering prices and high volume production

- I never think of the Future. It comes soon enough.

Albert Einstein,
(1930)





Thank you!