Ventricular Assist Devices:

The Future is Now

G.M.Wieselthaler

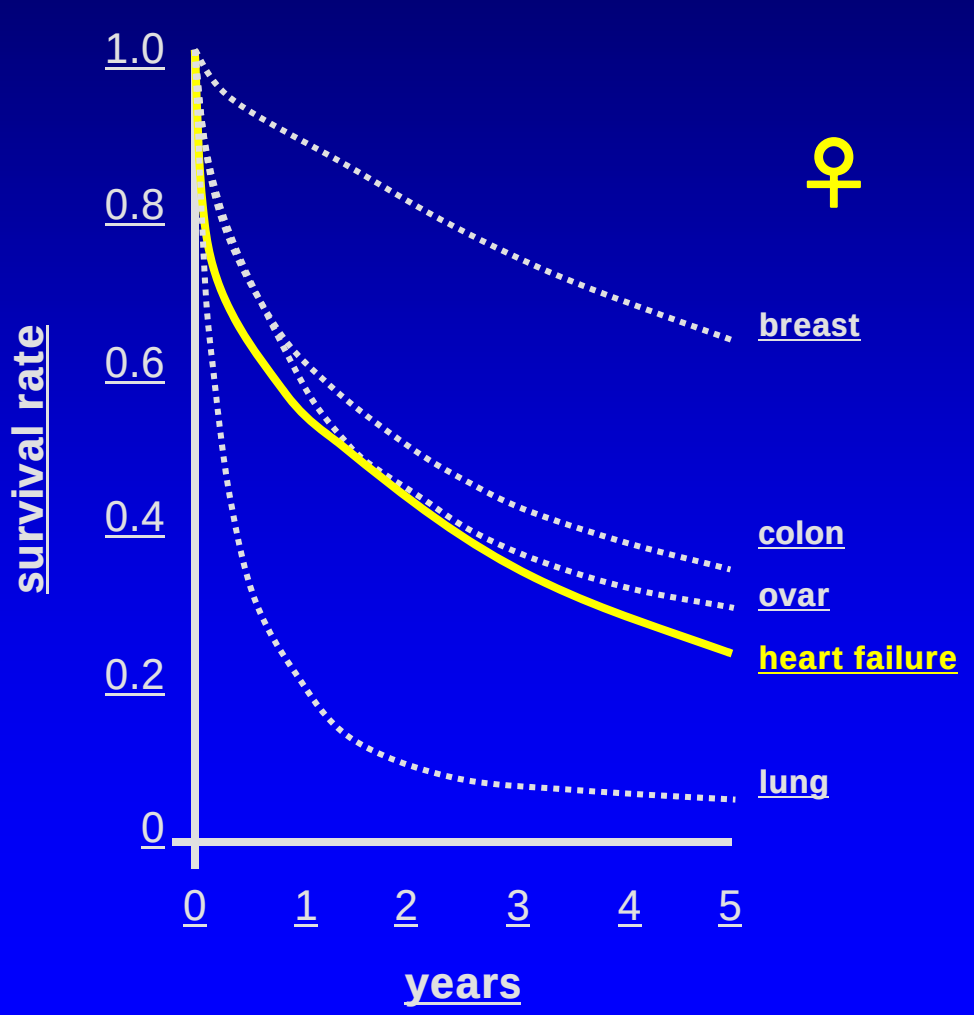
Div. of Cardiothoracic Surgery

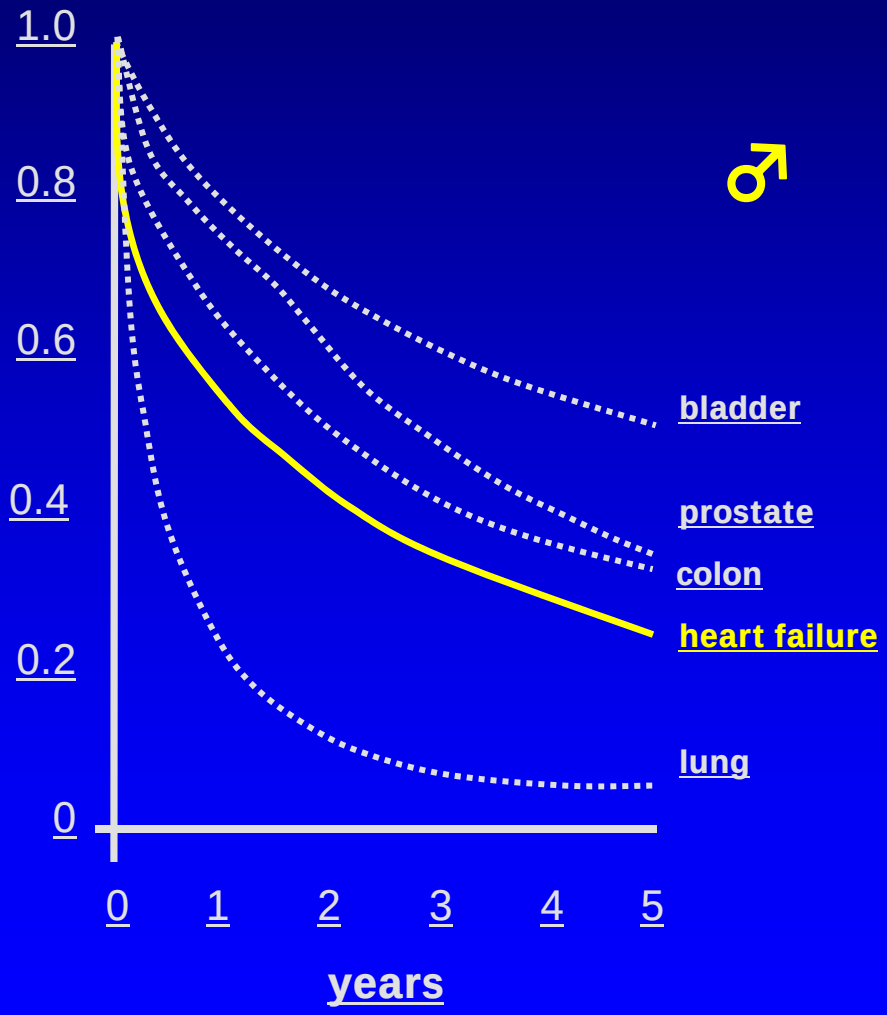
University of California, San Francisco

Exhibit
2024
01/15/2026

heart failure

prognosis vs. malignancies





Stewart S. Eur J Heart Fail 2001;3:315-22

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Increased Incidence of Heart Failure

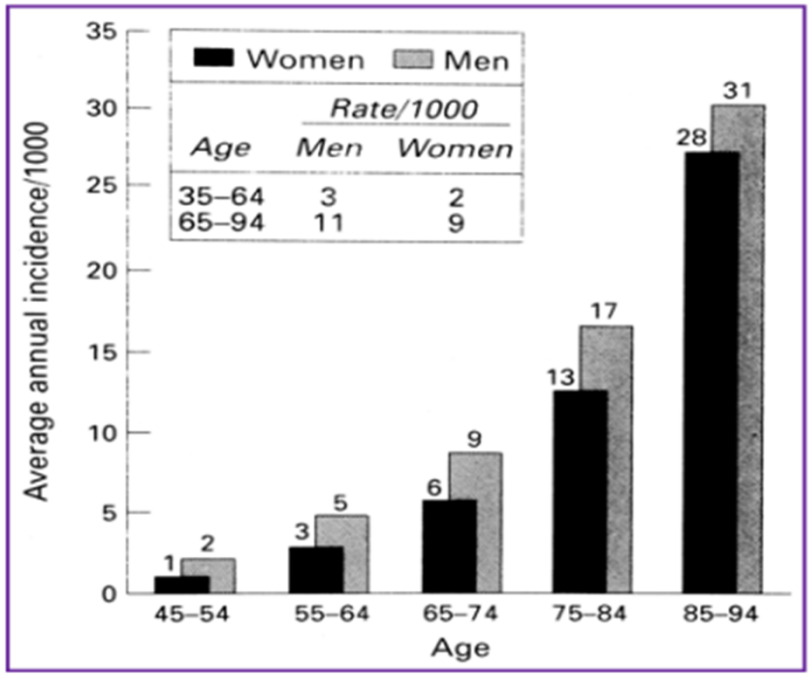


Fig 1. Incidence of heart failure by age and sex from Framingham. (Reproduced from Kannel WB, Ho K, Thom T. Changing epidemiological features of cardiac failure. Br Heart J 1994;72[Suppl 2]:S3–9. With permission from the BMJ Publishing Group.)

2004 **> 5 Mill. Americans** *)

2030 **10 Mill. Americans**

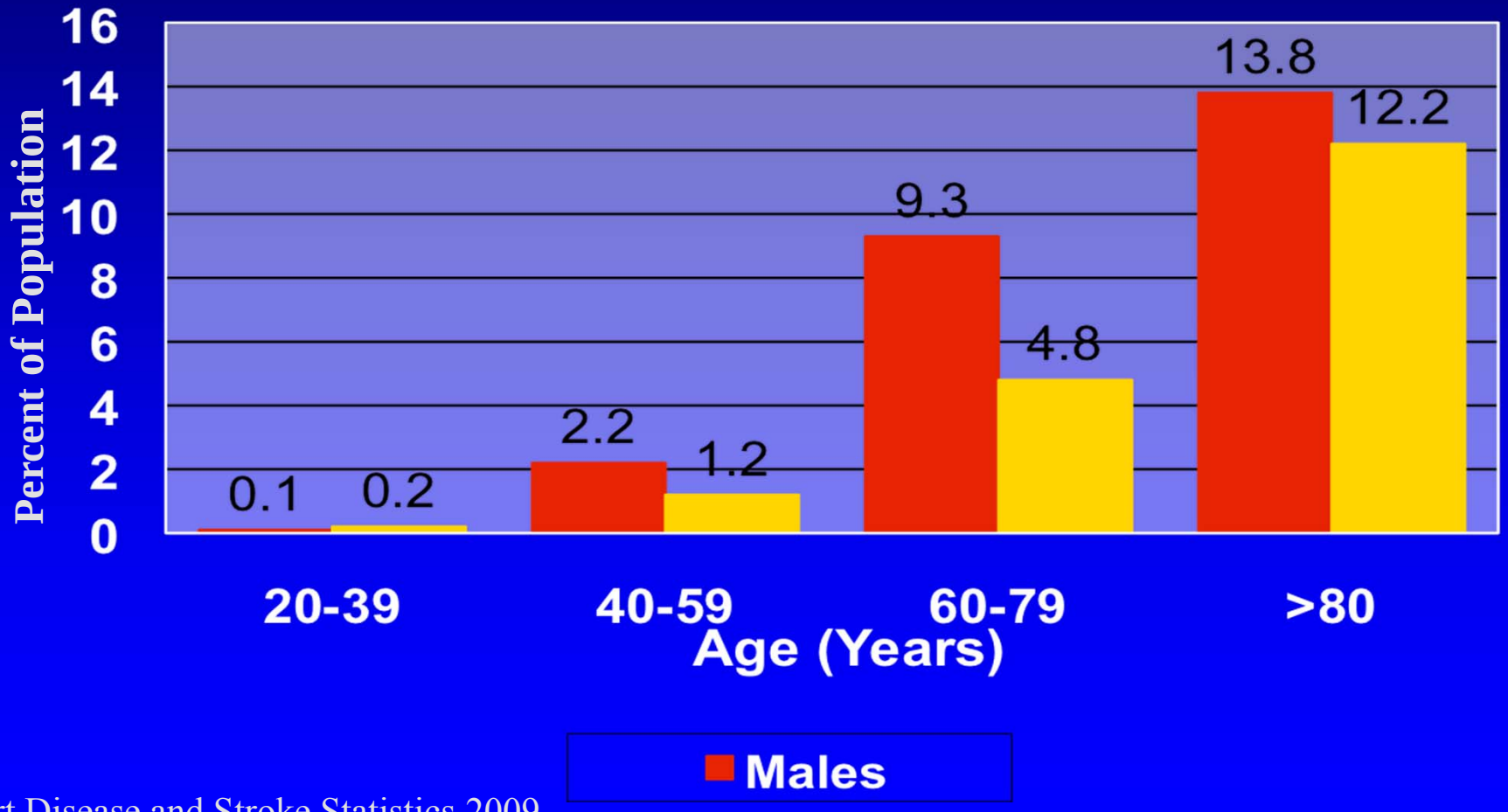
2050 **cardiovascular disease most frequent cause for morbidity worldwide (WHO 1999)**

*) Heart disease and stroke statistics—2004 update. Dallas (Tx): American Heart Association; 2004. p. 24- 5.

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HEART FAILURE
Prevalence by Age & Gender

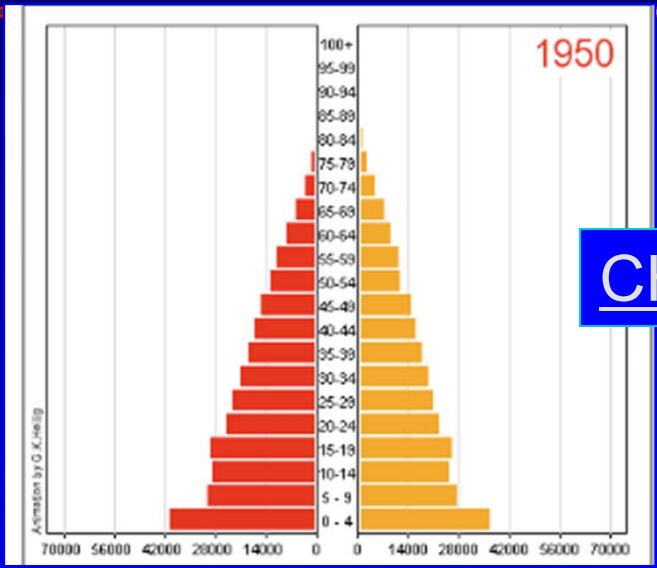
Total = 5.7 million



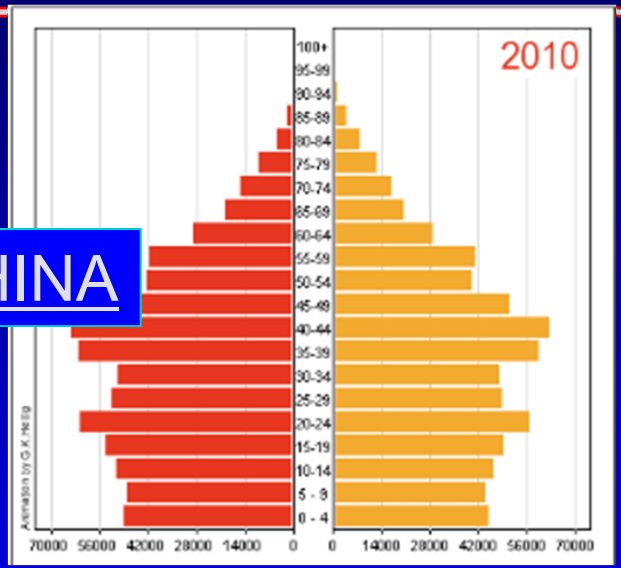
AHA Heart Disease and Stroke Statistics 2009

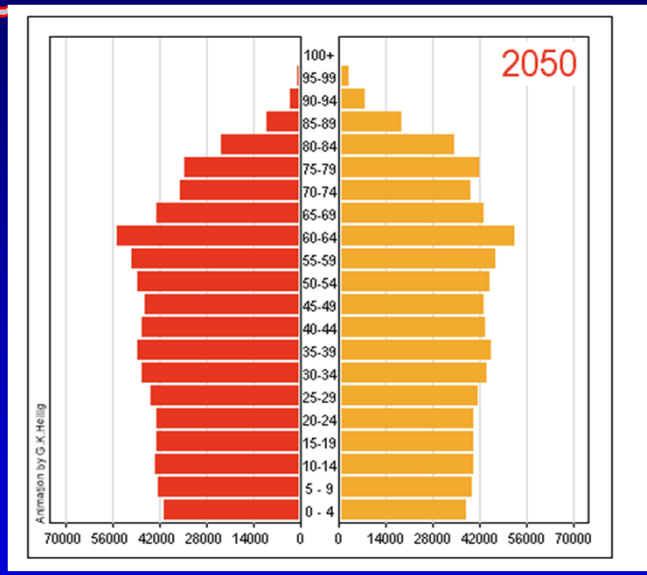
G.M.Wieselthaler

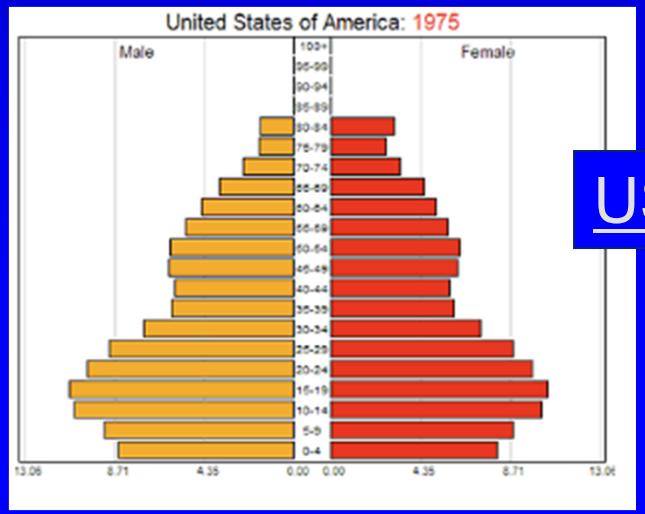
United Nations (1999): World Population Prospects. The 1998 Revision. New York (electronic data files)



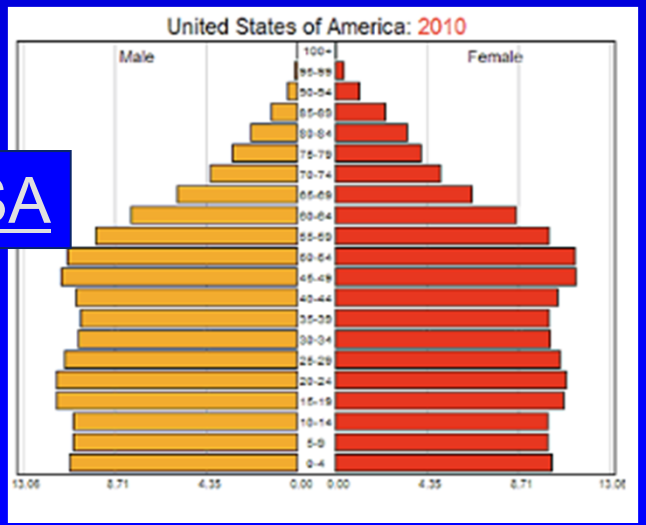
CHINA

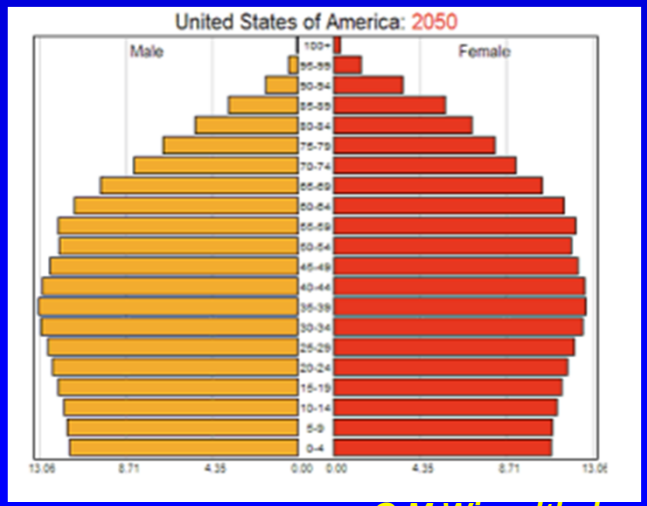






USA

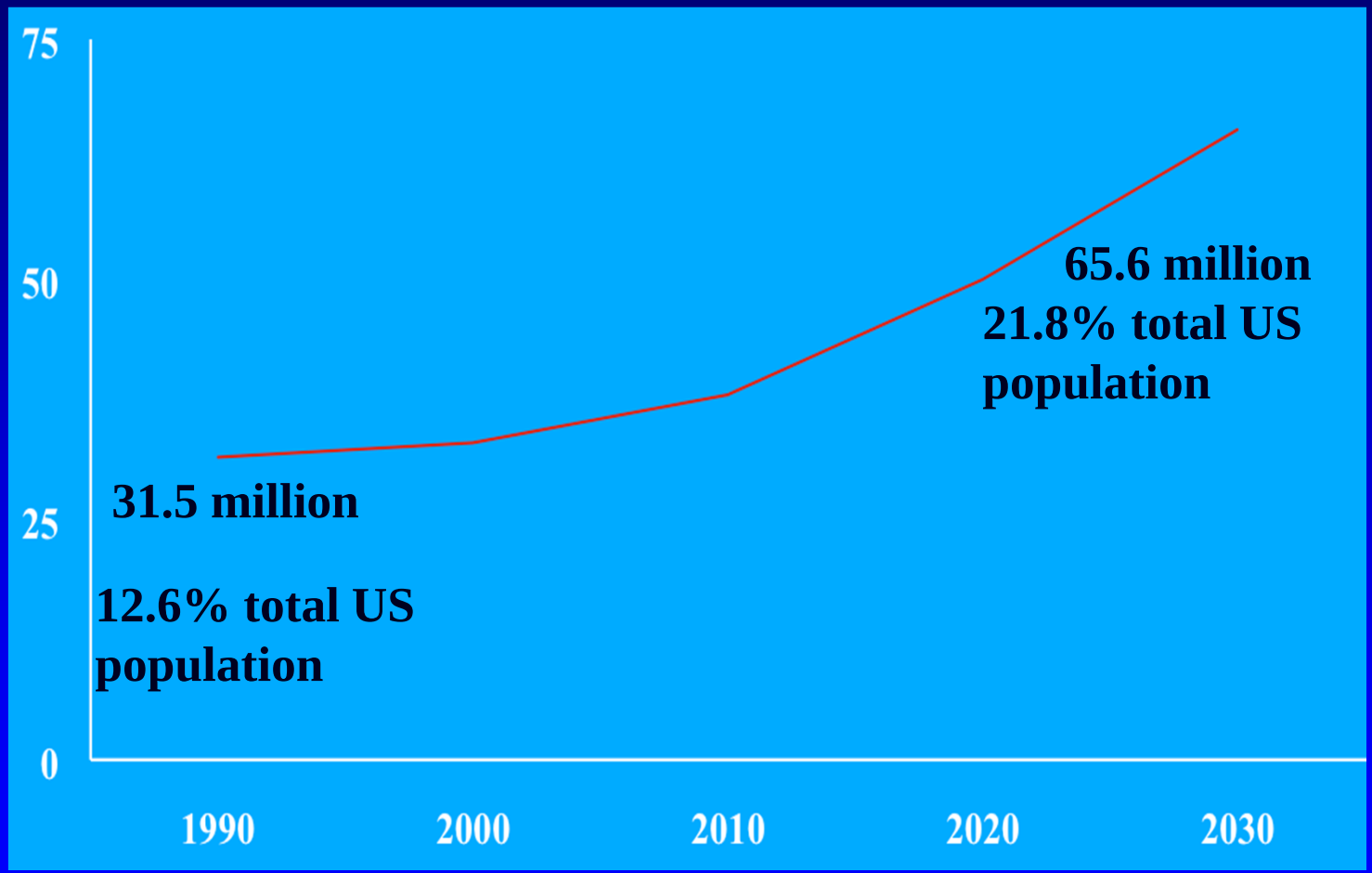




G.M.Wieselthaler

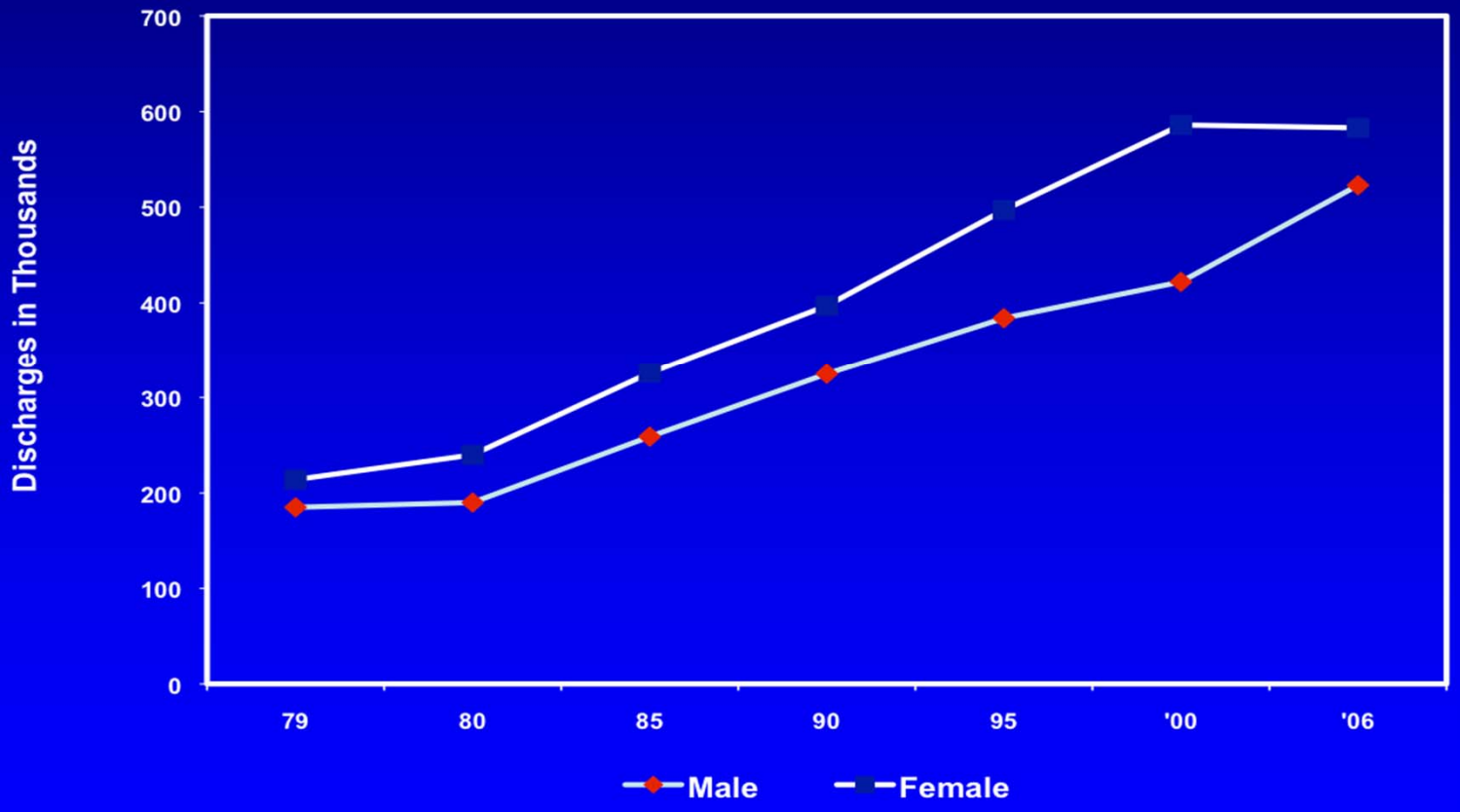
USA Demographic Trends

Projected Elderly Population Age 65+ (millions)



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USA Hospitalization for Heart Failure



* American Heart Association. Heart Disease and Stroke Statistics – 2009 Update.

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Therapy Options For Chronic Heart Failure

- advanced pharmacological therapy (levosimendan,.....)
- CRT, optimizer, …..
- experimental therapies (Angio-neogenesis, stemcell Tx.....)
- conventional cardiac surgery (high risk bypass- & valve-surgery)
- specific cardiac surgery (Dor-,Batista-procedure, Cardiomyoplasty,...)
- mechanical support (IABP, ECMO, VAD, TAH)
- orthotopic Tx (HTx, HLTx)

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Therapy Options For Chronic Heart Failure

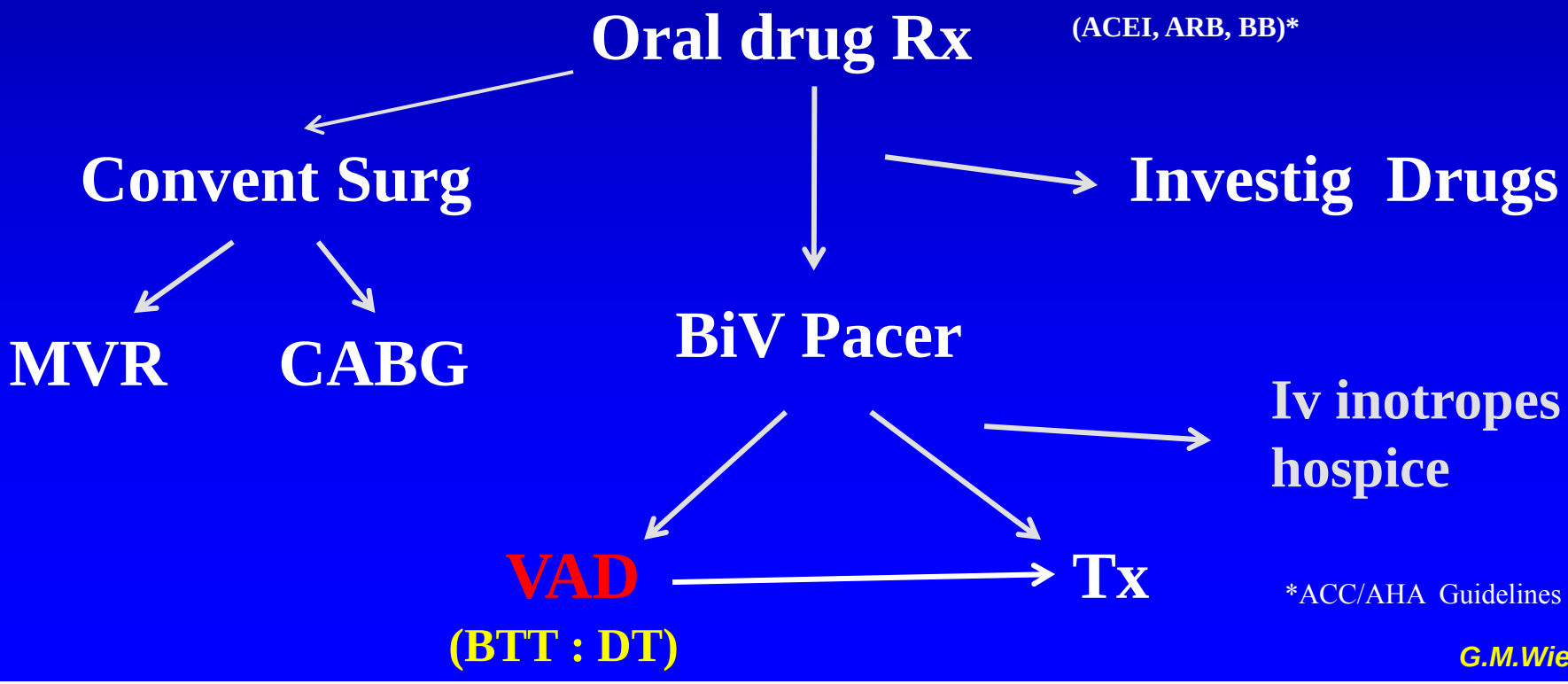
- advanced pharmacological therapy (levosimendan,.....)
- CRT, optimizer, …..
- experimental therapies (Angio-neogenesis, stemcell Tx.....)
- conventional cardiac surgery (high risk bypass- & valve-surgery)
- specific cardiac surgery (Dor-,Batista-procedure, Cardiomyoplasty,...)
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Miracor Ex. 2024, p. 9 of 64

Our Approach to Patients with Advanced HF

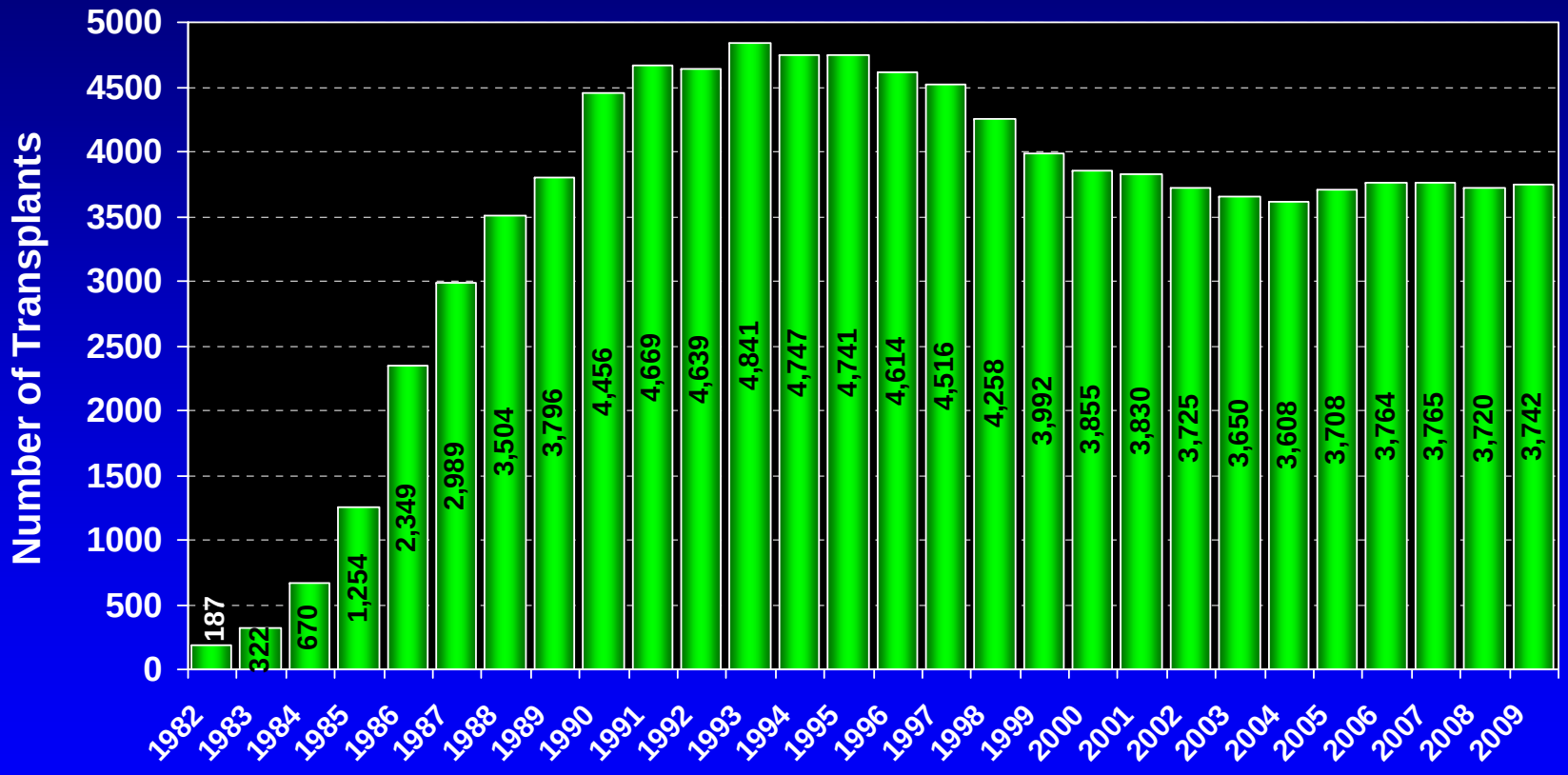
Interdisciplinary Surgical Heart Failure Outpatient Clinic



*ACC/AHA Guidelines

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"The Golden Standard"
but
lack of resources (donors)



NOTE: This figure includes only the heart transplants that are reported to the ISHLT Transplant Registry. As such, the presented data may not mirror the changes in the number of heart transplants performed worldwide

ISHLT

2011

J Heart Lung Transplant. 2011 Oct; 30 (10): 1071-1132

Increased Incidence of Heart Failure

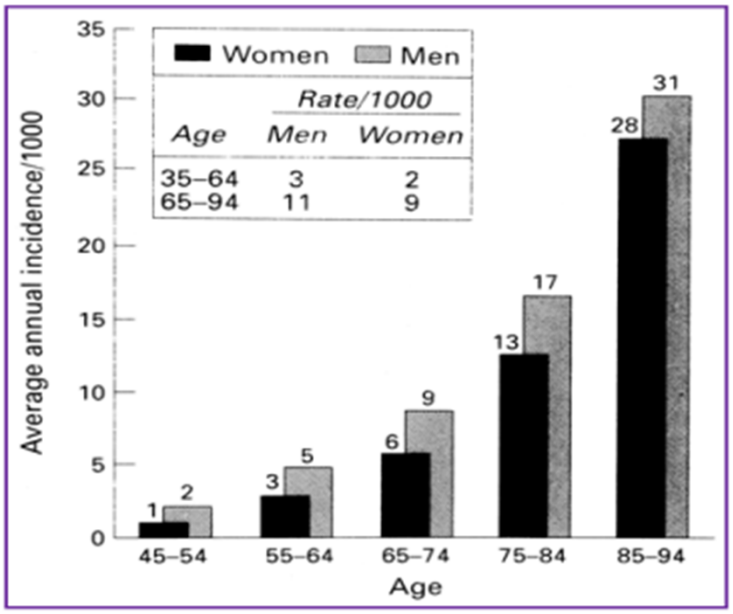


Fig 1. Incidence of heart failure by age and sex from Framingham. (Reproduced from Kannel WB, Ho K, Thom T. Changing epidemiological features of cardiac failure. Br Heart J 1994;72[Suppl 2]:S3–9. With permission from the BMJ Publishing Group.)

Do the Math !!!

2004 **> 5 Mill. Americans *)**

5% of 5,000,000 Americans with HF stage D

= 250,000 patients with advanced HF

2200 Tx / year
1300 VAD/year ***= 3500 patients !!!!!***

USA ~ 246,500 patients with advanced HF and no life saving therapeutic option

Majority elderly patients > 70!!

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Therapy Options For Chronic Heart Failure

"…..mechanical support of the failing heart is today an established therapy option for terminal, end-stage heart failure patients"

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MECHANICAL SUPPORT OF THE FAILING HEART

Intention to Treat:

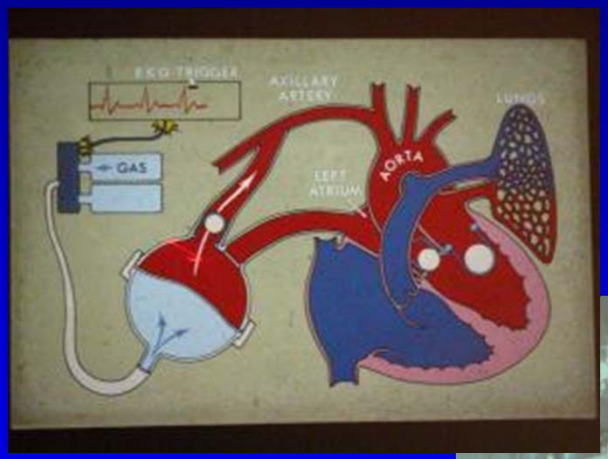
-- Bridge to Recovery
-- Bridge to Decision
-- Bridge to Bridge
-- Bridge to Transplantation
-- chronic implant, destination therapy (alternative to Tx)

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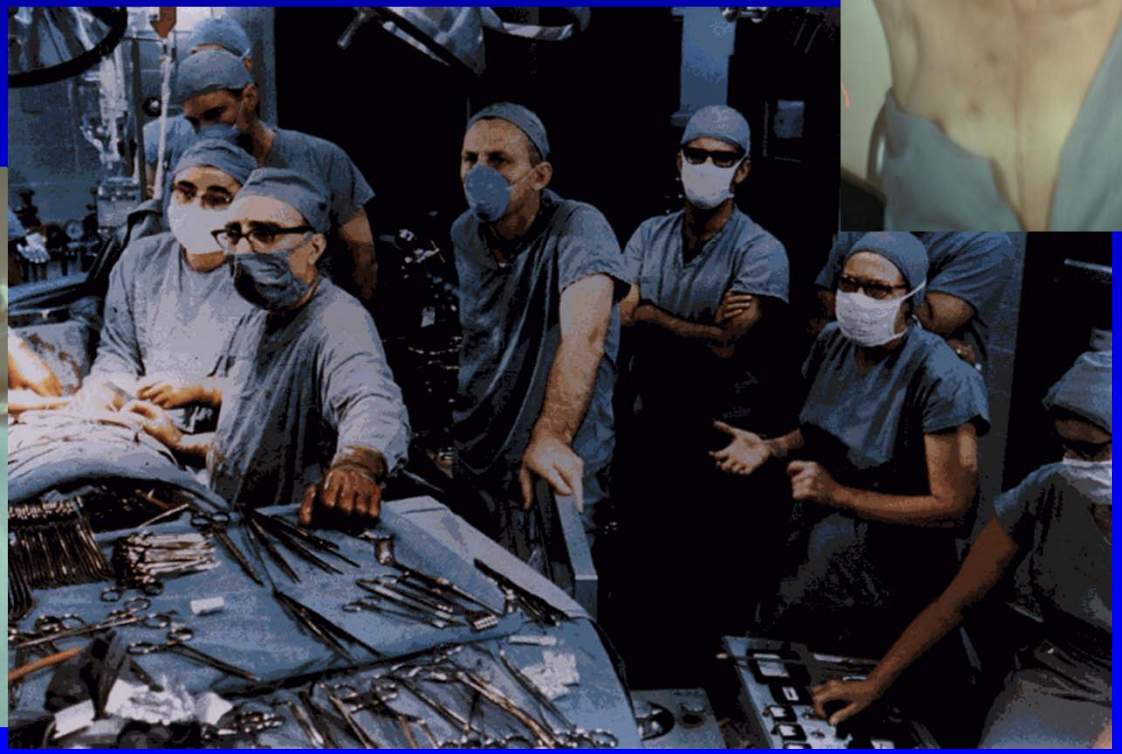
History of Mechanical Circulatory Support

First Successful LVAD Implantation

M.E.DeBakey, Baylor College, Houston,Tx 1966



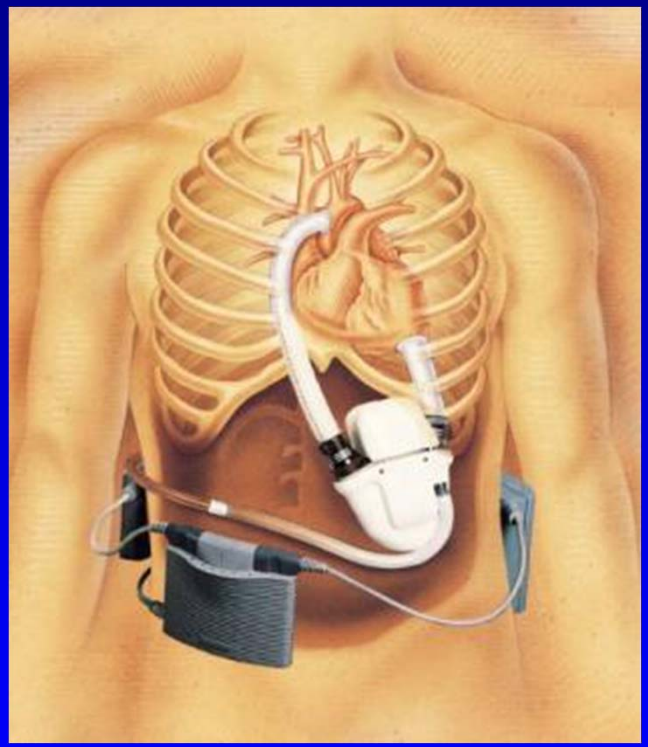






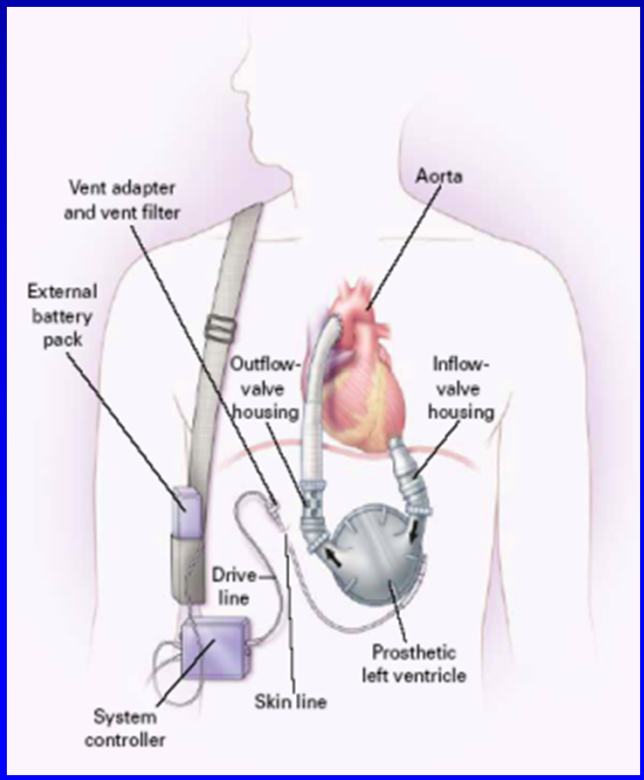
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Implantable, electro-mechanically driven displacement pumps



Novacor LVAS

Thoratec HeartMate I



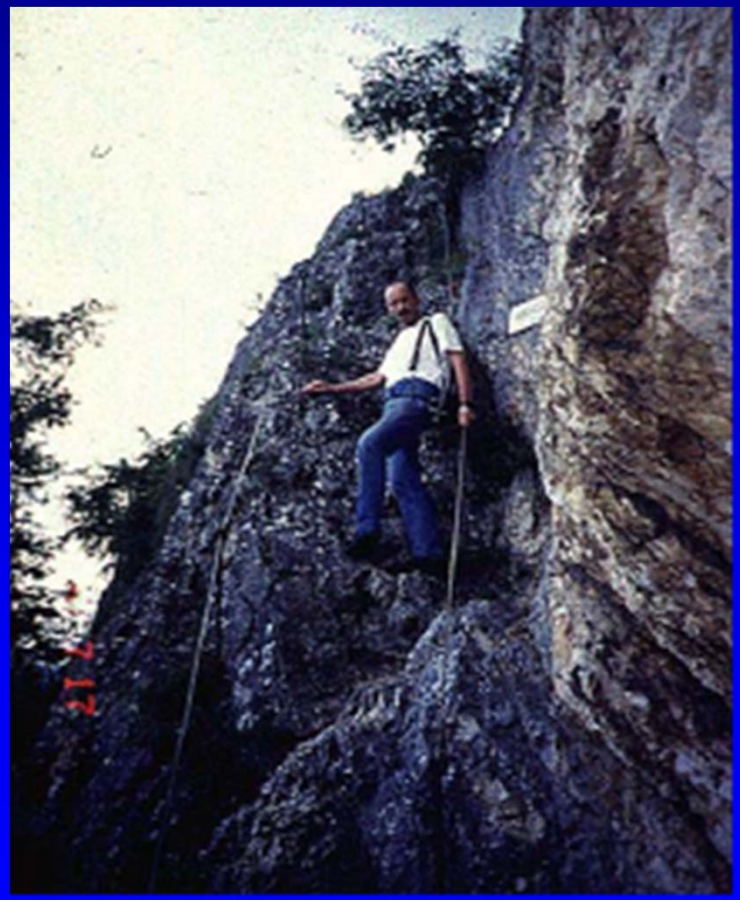
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Mechanical Circulatory Support

Implantable, electro-mechanically driven displacement pumps

Quality of Life





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Implantable, electro-mechanically driven displacement pumps

Exit-Site Wound Care









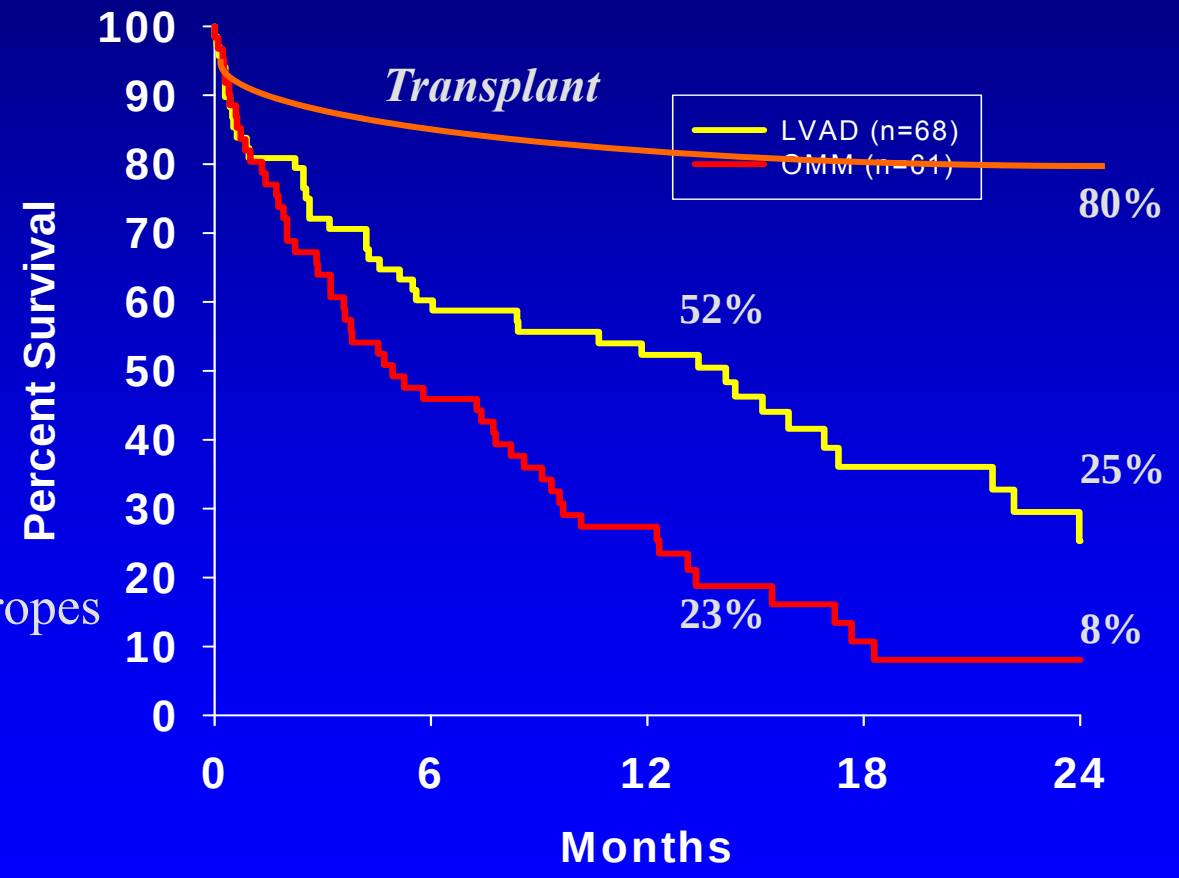


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REMATCH (2001)

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

- Randomized clinical trial
  - optimal medical therapy vs. pulsatile flow LVAD
- Non-transplant candidates (n=129)
  - EF ≤ 25%,
  - peak VO2 < 12 ml/kg/min,
  - or continuous infusion inotropes



N Engl J Med 2001; 345:1435-43

Second generation nonpulsatile rotary blood pumps



axial flow pumps **centrifugal pumps**

40 years of mechanical circulatory support in Vienna

1998

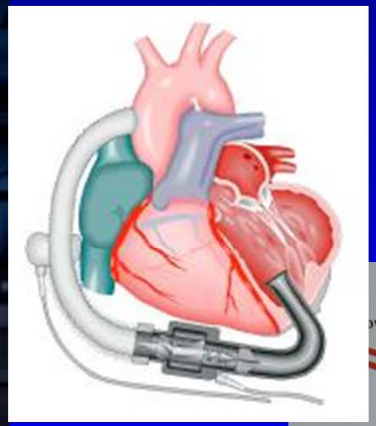


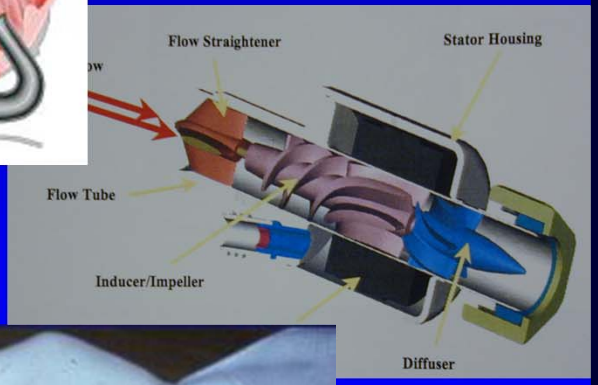
diameter 30,5 mm

length 76,2 mm

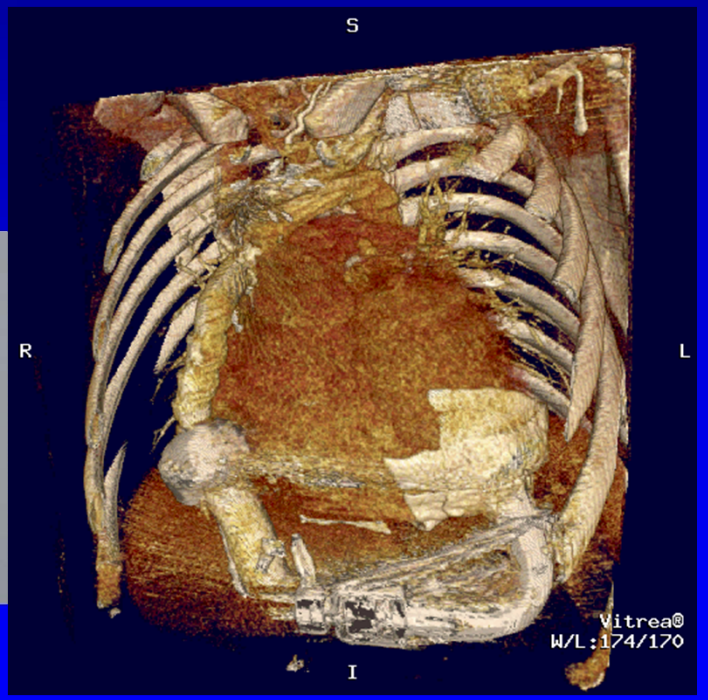
weigth 93 g

MicroMed –DeBakey VAD: 2nd generation nonpulsatile pump









First, full implantable, miniaturized axial flow pump

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Mechanical Circulatory Support

Advantages of Miniaturized Rotary Blood Pumps:

-- **small size**	**(small incisions, easy implantation, less bleeding)**
-- **no compliance chamber**	**(thin, flexible powercable, less infections)**
-- **small, miniaturized controller**	**(maximal freedom to move, quality of life)**
-- **no noise**	**(quality of life)**
-- **adequate high pump-output**	**(optimal tissue perfusion, high exercise capacity)**
-- **discharge to home**	**(quality of life, costs)**

Abbott v. Miracor, IPR2025-00115
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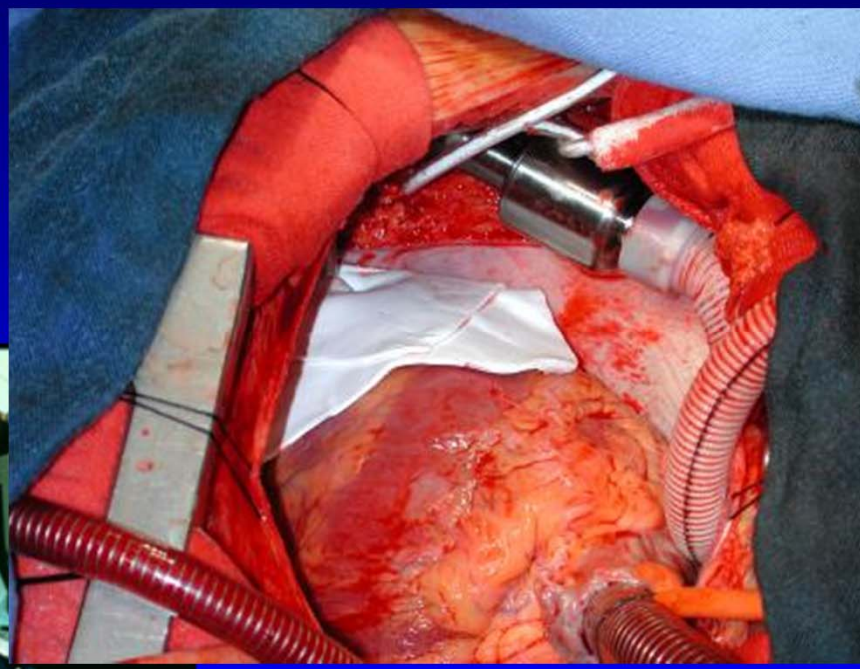
Mechanical Circulatory Support



Vienna Gen Hospital

19.Nov.1998



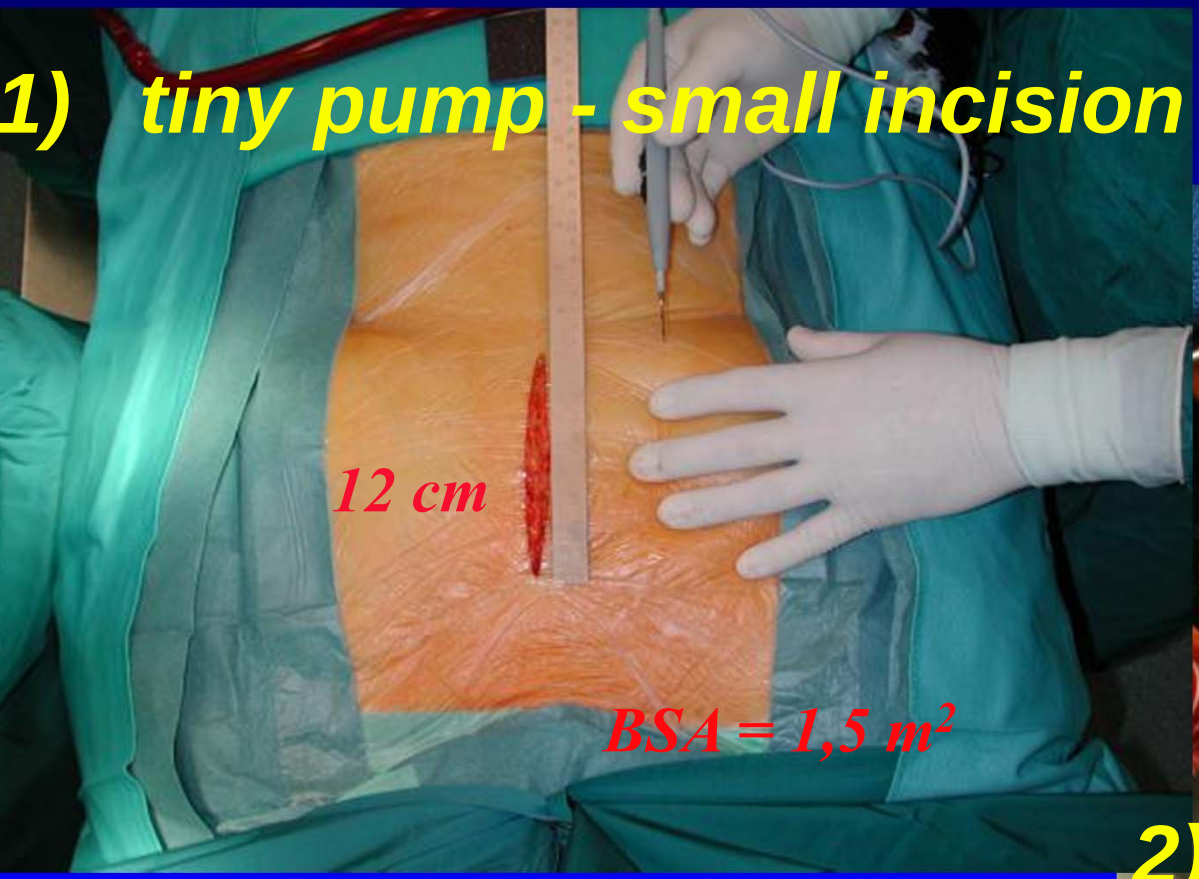


MicroMed DeBakey VAD

G.M.Wieselthaler

Abbott v. Miracor, IPR2025-00115
Miracor Ex. 2024, p. 23 of 64

Mechanical Circulatory Support

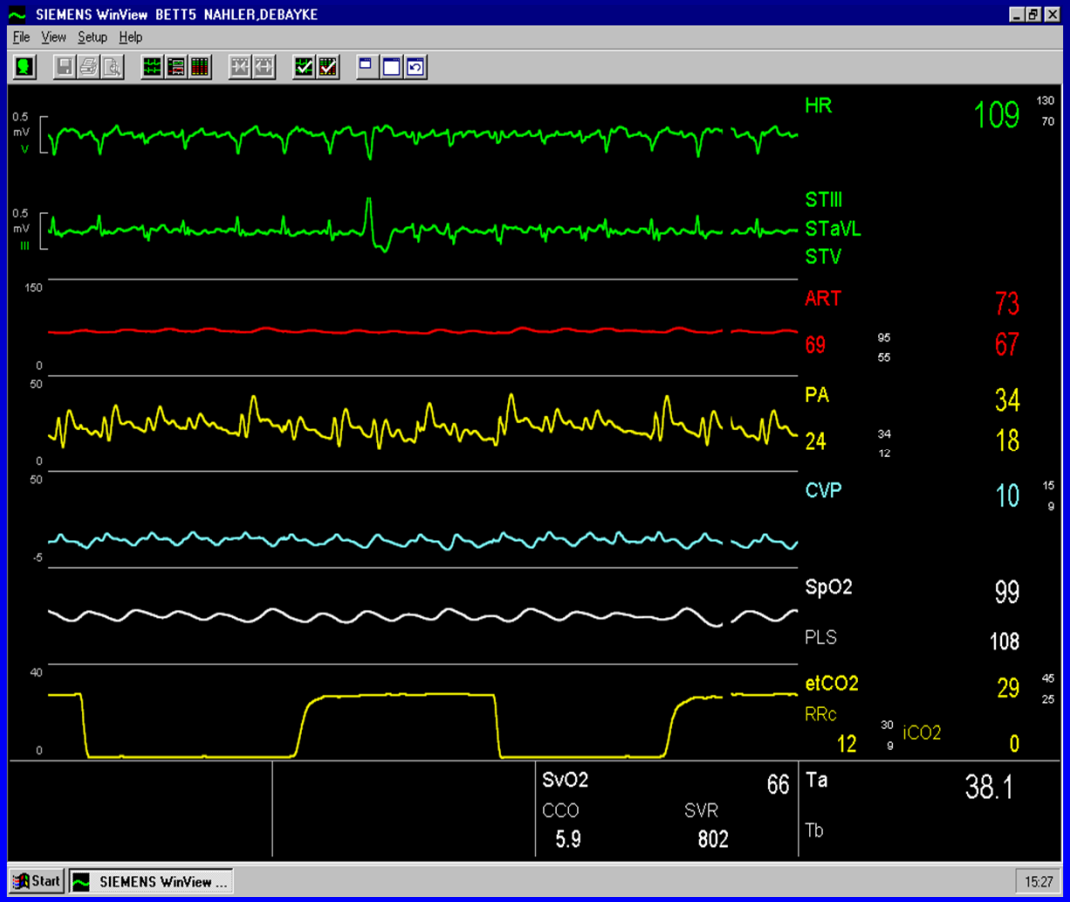




MicroMed DeBakey VAD

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Pathophysiology of Non-Pulsatile Flow



nonpulsatile flow in early postoperative period

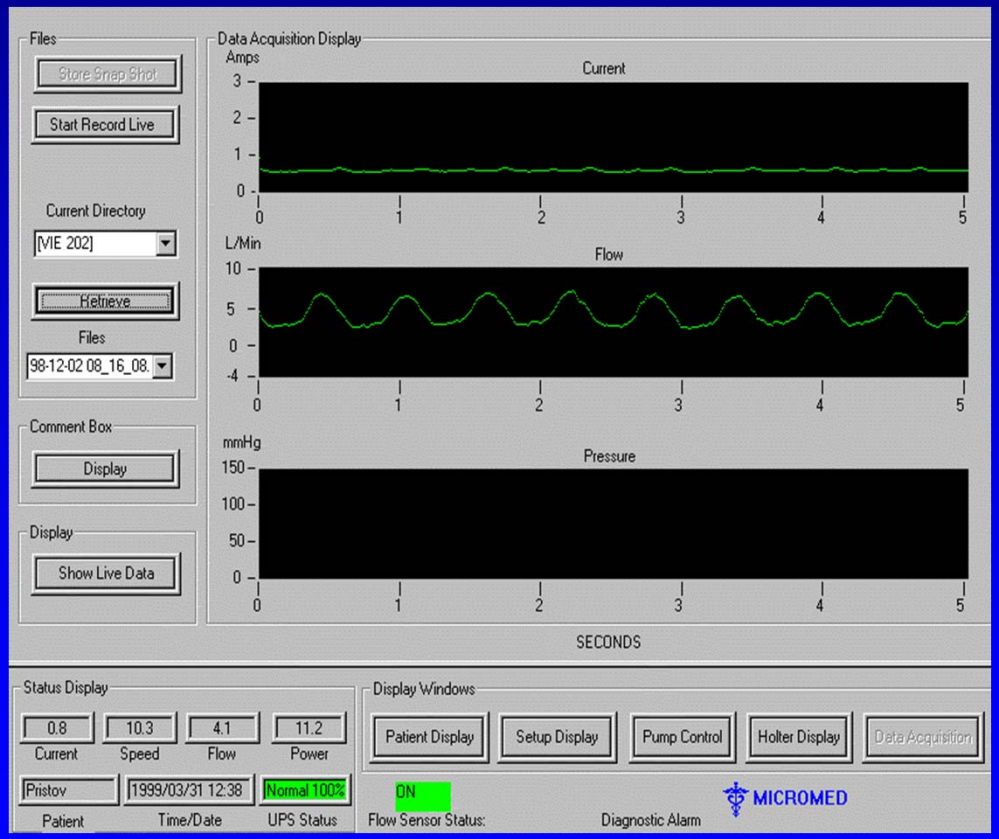
Clinical impact:

-- None (as long as good tissue perfusion is obtained, $SVO_2 \geq 60$ %)

-- AOP measurement with invasive arterial line during this early postop period

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Pathophysiology of ~~Non~~- Low Pulsatile Flow



low pulsatility of blood flow occurs with recovery of native left heart function

Clinical impact:

-- *no nonpulsatile flow anymore*

-- *AOP measurement with regular RR-method in many cases not possible (ΔAOP ≤ 5 - 10 mm Hg)*

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Mechanical Circulatory Support



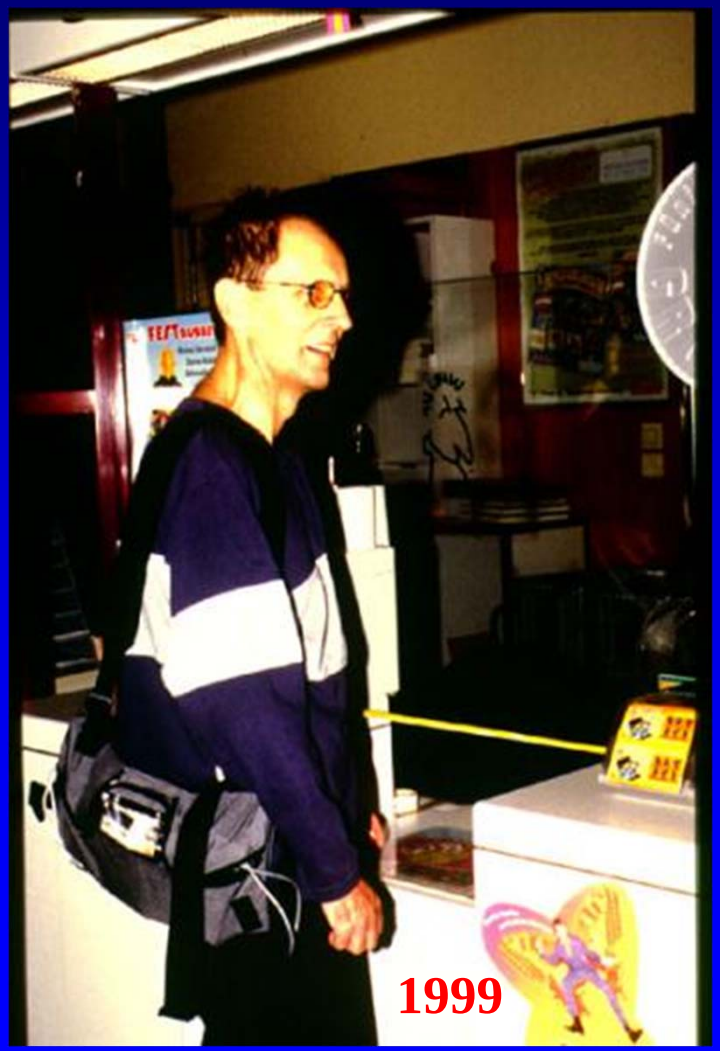




Jan. 1999

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Mechanical Circulatory Support





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Pathophysiology of Low Pulsatile Flow

“Living without Pulse“

pulsepressure: 5 - 15 mm Hg







- development of a flow-Doppler AOP measurement device

- in future: automatic device

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Pathophysiology of Low Pulsatile Flow

“ daily ergometer-training “







- weekly spiro-ergometry

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Pathophysiology of Low Pulsatile Flow



„Quality of Life with VAD“









.....343 steps to the top of St. Stephans .....

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Pathophysiology of Low Pulsatile Flow

First Clinical Experience With the DeBakey VAD Continuous-Axial-Flow Pump for Bridge to Transplantation

Georg M. Wieselthaler, MD; Heinrich Schima, PhD; Michael Hiesmayr, MD; Richard Pacher, MD; Günther Laufer, MD; George P. Noon, MD; Michael DeBakey, MD; Ernst Wolner, MD

Background—A shortage of donor organs and increased numbers of deaths of patients on the waiting list for cardiac transplantation make mechanical circulatory support for a bridge to transplantation a standard clinical procedure. Continuous-flow rotary blood pumps offer exciting new perspectives.

Methods and Results—Two male patients (ages 44 and 65 years) suffering from end-stage left heart failure were implanted with a DeBakey VAD axial-flow pump for use as a bridge to transplant. In the initial postoperative period, the mean pump flow was 3.9±0.5 L/min, which equals a mean cardiac index (CI) of 2.3±0.2 $L \cdot min^{-1} \cdot m^{-2}$. In both patients, the early postoperative phase was characterized by a completely nonpulsatile flow profile. However, with the recovery of heart function 8 to 12 days after implantation, increasing pulse pressures became evident, and net flow rose to 4.5±0.6 L/min, causing an increase of mean CI up to 2.7±0.2 $L \cdot min^{-1} \cdot m^{-2}$. Patients were mobilized and put through regular physical training. Hemolysis stayed in the physiological range and increased only slightly from 2.1±0.8 mg/dL before surgery to 3.3±1.8 mg/dL 6 weeks after implantation.

Conclusions—The first clinical implants of the DeBakey VAD axial-flow pump have demonstrated the device to be a promising measure of bridge-to-transplant mechanical support. (***Circulation*. 2000;101:356-359.)**

Key Words: heart failure ■ heart-assist device ■ DeBakey VAD

G.M.Wieselthaler

Pathophysiology of Low Pulsatile Flow

Endocrine function is not impaired in patients with a continuous MicroMed–DeBakey axial flow pump

Georg M. Wieselthaler, MD,[a,d] Michaela Riedl, MD,[b] Heinrich Schima, PhD,[a,d] Oswald Wagner, MD,[c] Werner Waldhäusl, MD,[b] Ernst Wolner, MD,[a,d] Anton Luger, MD,[b] and Martin Clodi, MD[b]

Objectives: Pulsatile blood flow has been regarded to be of importance for the regulation of endocrine organs. A new generation of continuous flow mechanical blood pumps is now available for clinical application. Patients with implanted MicroMed-DeBakey axial pumps show nonphysiologic low-pulsatile blood flow profiles, and therefore it appeared to be of interest to evaluate their possible effect on the endocrine system.

J Thorac Cardiovasc Surg 2007;133:2-6

G.M.Wieselthaler

Pathophysiology of Low Pulsatile Flow

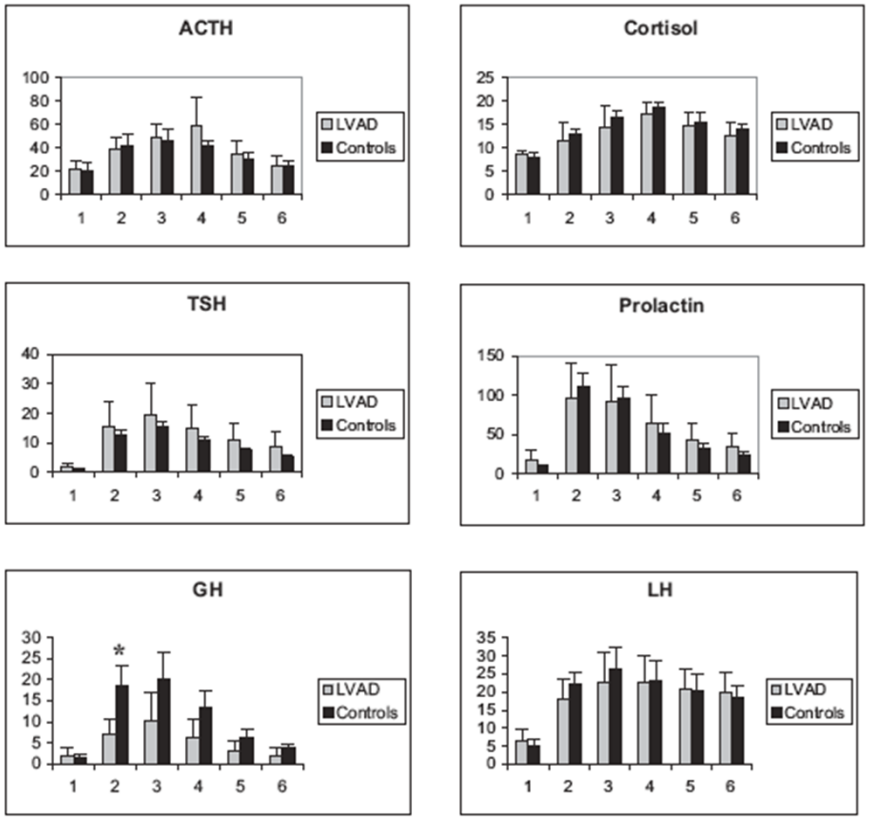


Figure 1. Adrenocorticotropic hormone (*ACTH*; in picograms per milliliter) and cortisol (in micrograms per deciliter) responses after 100 μg corticotropin-releasing hormone are shown. Thyroid-stimulating hormone (*TSH*; in milliunits per liter [TSH = μU/mL]) and prolactin responses to 200 μg of thyreotropin-releasing hormone are shown. Growth hormone (*GH*; in nanograms per milliliter) response to 100 μg of growth hormone–releasing hormone and luteinizing hormone (*LH*; in units per liter) response to 100 μg of luteinizing hormone–releasing hormone are shown. Patients receiving a left ventricular assist device (*LVAD*) are indicated by *shaded gray bars*, and control subjects are indicated by *filled bars*. *1*, Zero minutes; *2*, 15 minutes; *3*, 30 minutes; *4*, 60 minutes; *5*, 90 minutes; and *6*, 120 minutes.

TABLE 1. Baseline concentrations of hormones and sexual hormone binding globulin

	Patients with LVADs	Normal range
Urinary epinephrine excretion (24 h)	5.3 ± 2.0	<20 μg/24 hours
Urinary norepinephrine excretion (24 h)	60.8 ± 15.8	23-105 μg/24 h
Urinary dopamine excretion (24 h)	419 ± 123	190-450 μg/24 h
TSH	2.0 ± 1.3	<4 U/L
Thyroxine	90 ± 15	50-120
Triiodothyronine	1.4 ± 0.2	0.6-2.0
Sexual hormone–binding globulin	72.8 ± 11.7	16-76 nmol/L
Testosterone	5.7 ± 1.3	2.7-10.7 ng/mL
IGF-I	205.7 ± 91	105-330 ng/mL

LVADs, Left ventricular assist devices; *TSH*, thyroid-stimulating hormone; *IGF-I*, insulin-like growth factor I.

Conclusions: Implantation of a continuous flow axial pump with low-pulsatile blood flow profile appears to have no major effect on the hypothalamic-pituitary-endorgan system and sympathoadrenal functions. This finding is reassuring for the growing number of patients treated with this convenient new pump and could contribute considerably to their prognosis and quality of life.

J Thorac Cardiovasc Surg 2007;133:2-6

G.M.Wieselthaler

Mechanical Circulatory Support

Left ventricular assist devices decrease fixed pulmonary hypertension in cardiac transplant candidates

Daniel Zimpfer, MD,[a] Philipp Zrunek, MS,[b] Wilfried Roethy, MD,[a] Martin Czerny, MD,[a] Heinz Schima, PhD,[b] Leopold Huber, PhD,[b] Michael Grimm, MD,[a] Angela Rajek, MD,[c] Ernst Wolner, MD, PhD,[a] and Georg Wieselthaler, MD[a]

Objective: Fixed pulmonary hypertension is a contraindication for cardiac transplantation because of the increased risk of donor heart failure. We sought to determine whether left ventricular assist devices improve fixed pulmonary hypertension in cardiac transplant candidates to enable safe cardiac transplantation.

Methods: Thirty-five consecutive cardiac transplant candidates (age 56 ± 6 years, 88.5% were men) with fixed pulmonary hypertension (5.1 ± 2.6 Wood units) resistant to medical treatment received a left ventricular assist device as a bridge to transplantation. Three left ventricular assist device systems were used (pulsatile blood flow: Novacor [World Heart Inc, Oakland, Calif] n = 8; continuous blood flow: MicroMed DeBakey [MicroMed Technology Inc, Houston, Tex] n = 24, DuraHeart [Terumo Heart Inc, Ann Arbor, Mich] n = 3). Right-sided heart catheter data were obtained before left ventricular assist device implantation at 3-day and 6-week follow-ups. Clinical data and complications were recorded.

J Thorac Cardiovasc Surg. 2007 Mar;133(3):689-95.

COPY

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fixed pulmonary hypertension and LVAD

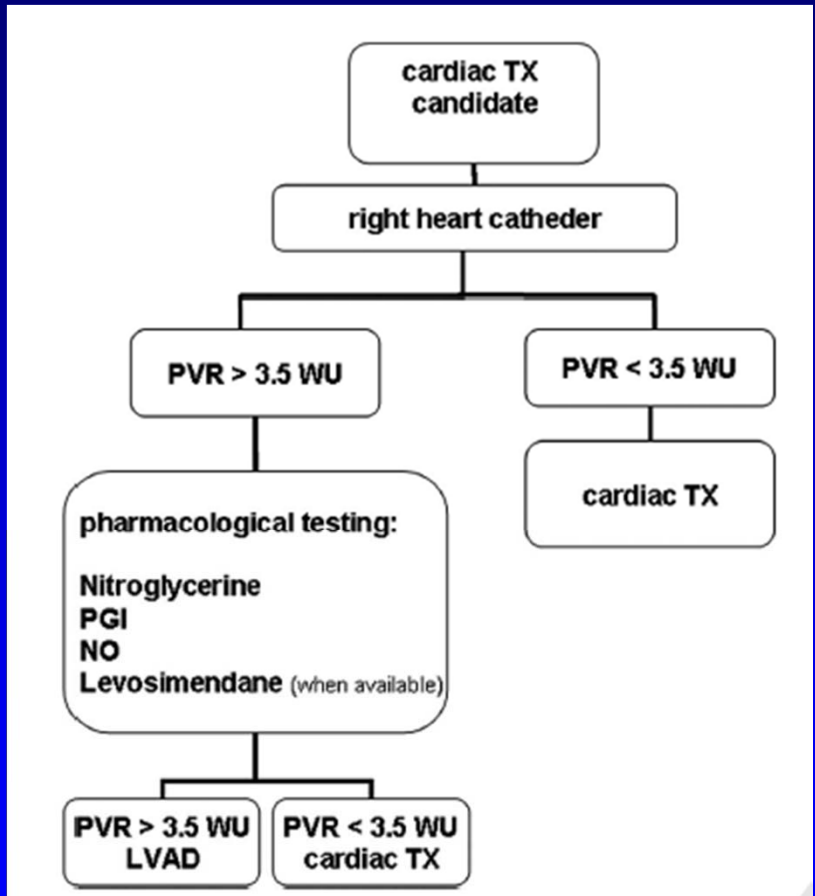


Figure 1. Pharmacologic testing: decision-making tree. *TX*, Transplant; *PVR*, pulmonary vascular resistance; *WU*, Wood units; *PG*, prostaglandin; *NO*, nitric oxide; *LVAD*, left ventricular assist device.

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fixed pulmonary hypertension and LVAD

TABLE 2. Data from right-sided heart catheterization

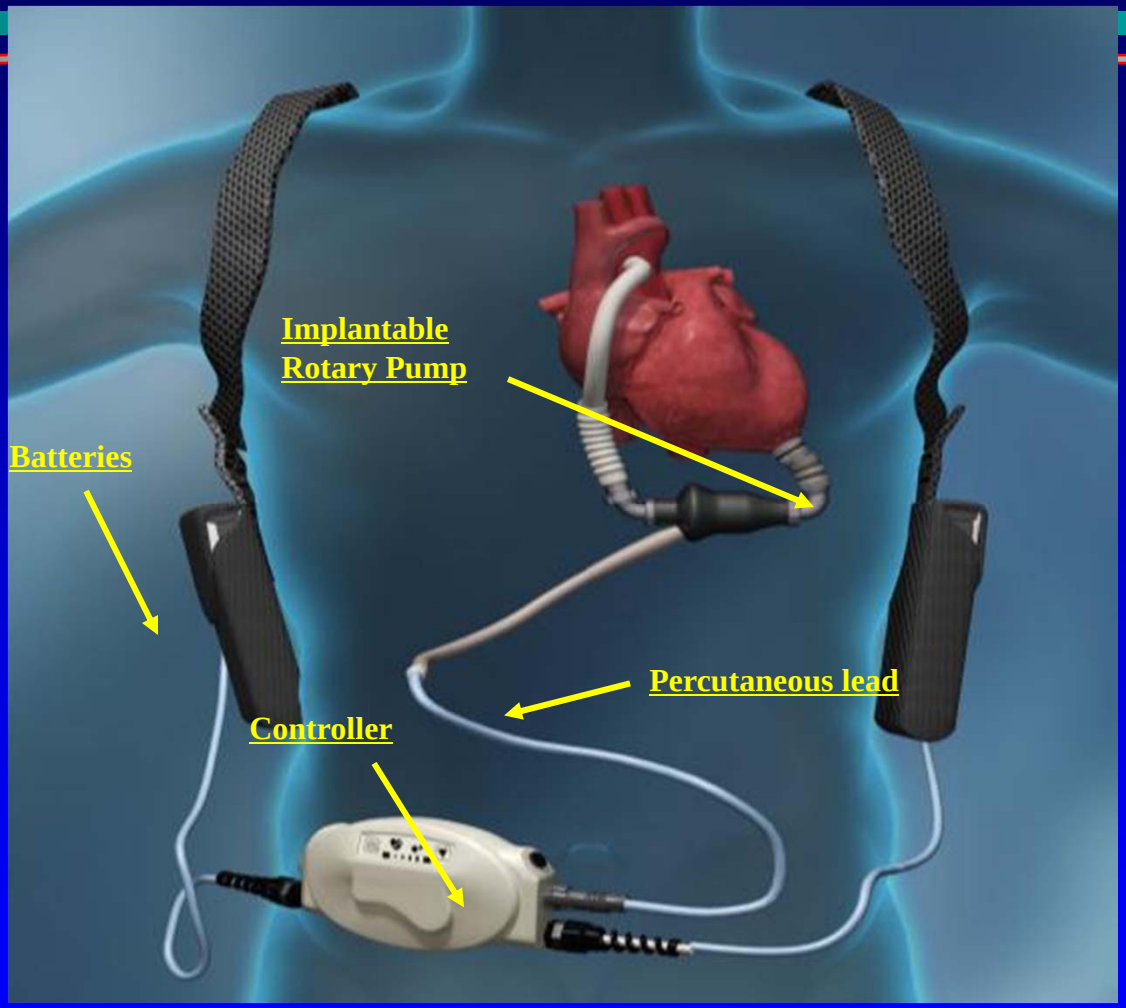
Variable	All patients	*P* value*	Continuous flow†	Pulsatile flow‡	*P* value§
N	35		27	8	
PVR					
Baseline	5.1 ± 2.6	—	5.3 ± 2.7	5.1 ± 3.5	.976
3-d FUP	2.9 ± 1.3	<.0001	2.7 ± 1.2	3.2 ± 1.3	.310
6-wk FUP	2.0 ± 0.8	<.0001	2.1 ± 0.8	1.9 ± 0.9	.905
After testing	4.5 ± 2.1	—	—	—	—
PAsyst					
Baseline	63.2 ± 9.3	—	65.2 ± 13.0	65.3 ± 10	.976
3-d FUP	39.6 ± 10.6	<.0001	37.6 ± 9.4	43.4 ± 12.5	.175
6-wk FUP	26.7 ± 3.6	<.0001	29.6 ± 6.5	28.1 ± 7.5	.236
After testing	36 ± 10.2	—	—	—	—
PAmean					
Baseline	44.0 ± 6.2	—	45.5 ± 6.8	43.0 ± 8.4	.397
3-d FUP	28.6 ± 7.3	<.0001	28.1 ± 7.5	29.6 ± 6.5	.604
6-wk FUP	18.4 ± 4.3	<.0001	19.0 ± 4.2	17.8 ± 5.1	.571
After testing	30.2 ± 6.8	—	—	—	—
PCWP					
Baseline	28.1 ± 6.0	—	29.0 ± 5.7	27.1 ± 7.0	.439
3-d FUP	12.0 ± 5.7	<.0001	11.9 ± 4.4	13.0 ± 8.3	.641
6-wk FUP	10.0 ± 3.6	<.0001	10.1 ± 13.7	9.1 ± 3.7	.572
After testing	15.8 ± 1.9	—	—	—	—
CO					
Baseline	3.1 ± 0.8	—	3.0 ± 0.6	2.6 ± 0.7	.601
3-y FUP	5.7 ± 0.7	<.0001	6.2 ± 1.1	5.1 ± 0.8	.375
6-wk FUP	4.0 ± 0.9	.002	4.2 ± 0.8	4.6 ± 0.4	.453
After testing	3.2 ± 7	—	—	—	—

PVR, Pulmonary vascular resistance (WU); *FUP*, follow-up; *PAsyst*, systolic pulmonary artery pressure (mm Hg); *PAmean*, mean pulmonary artery pressure (mm Hg); *PCWP*, pulmonary capillary wedge pressure (mm Hg); *CO*, cardiac output (lxmin^{-1}). *P value: compared with before LVAD implantation. †Patients treated with continuous flow LVADs. ‡Patients treated with pulsatile flow LVADs. §P value: continuous flow LVADs versus pulsatile flow LVADs. Baseline: hemodynamic data immediately before LVAD implantation. After testing: hemodynamic data after pharmacologic testing.

ACCEPTED PROOF

Abbott v. Miracor, IPR2025-00115
Miracor Ex. 2024, p. 37 of 64

HeartMate II Left Ventricular Assist System

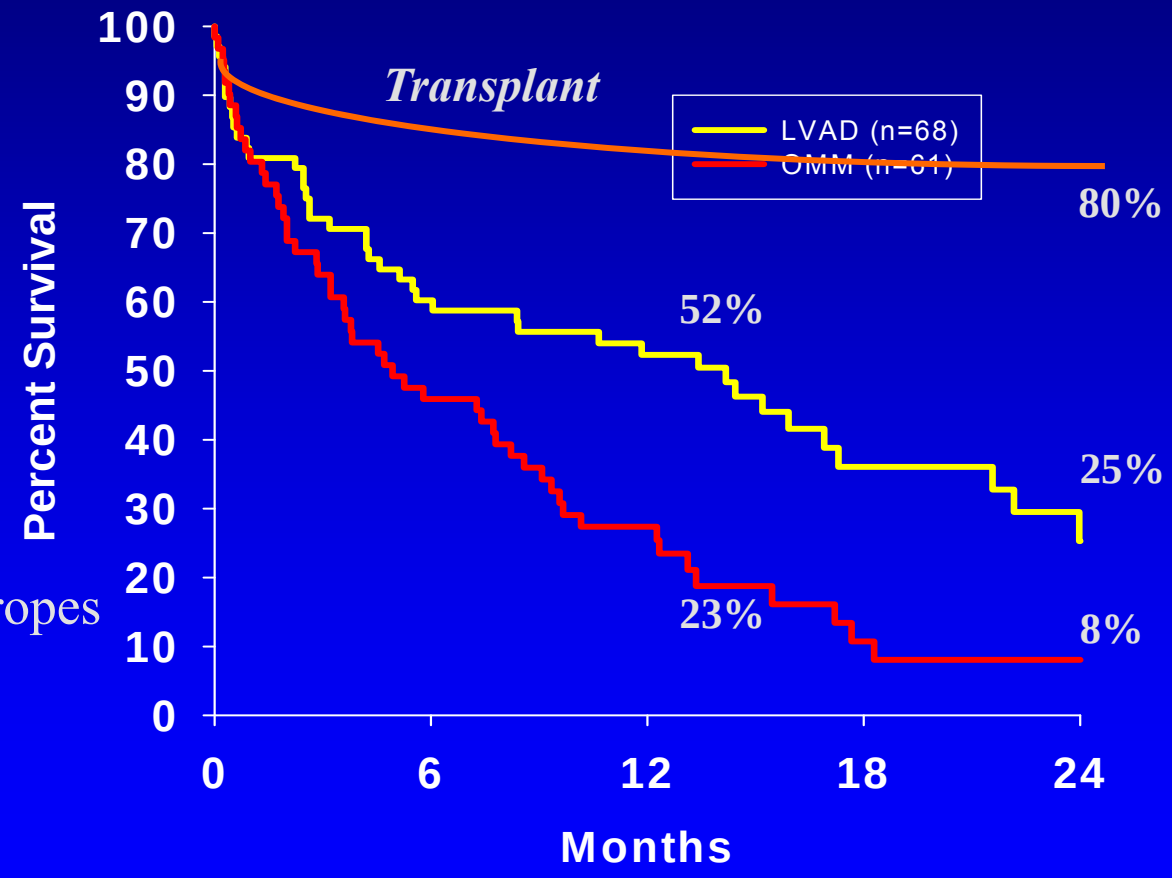


12.000 implants worldwide !!

REMATCH (2001)

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

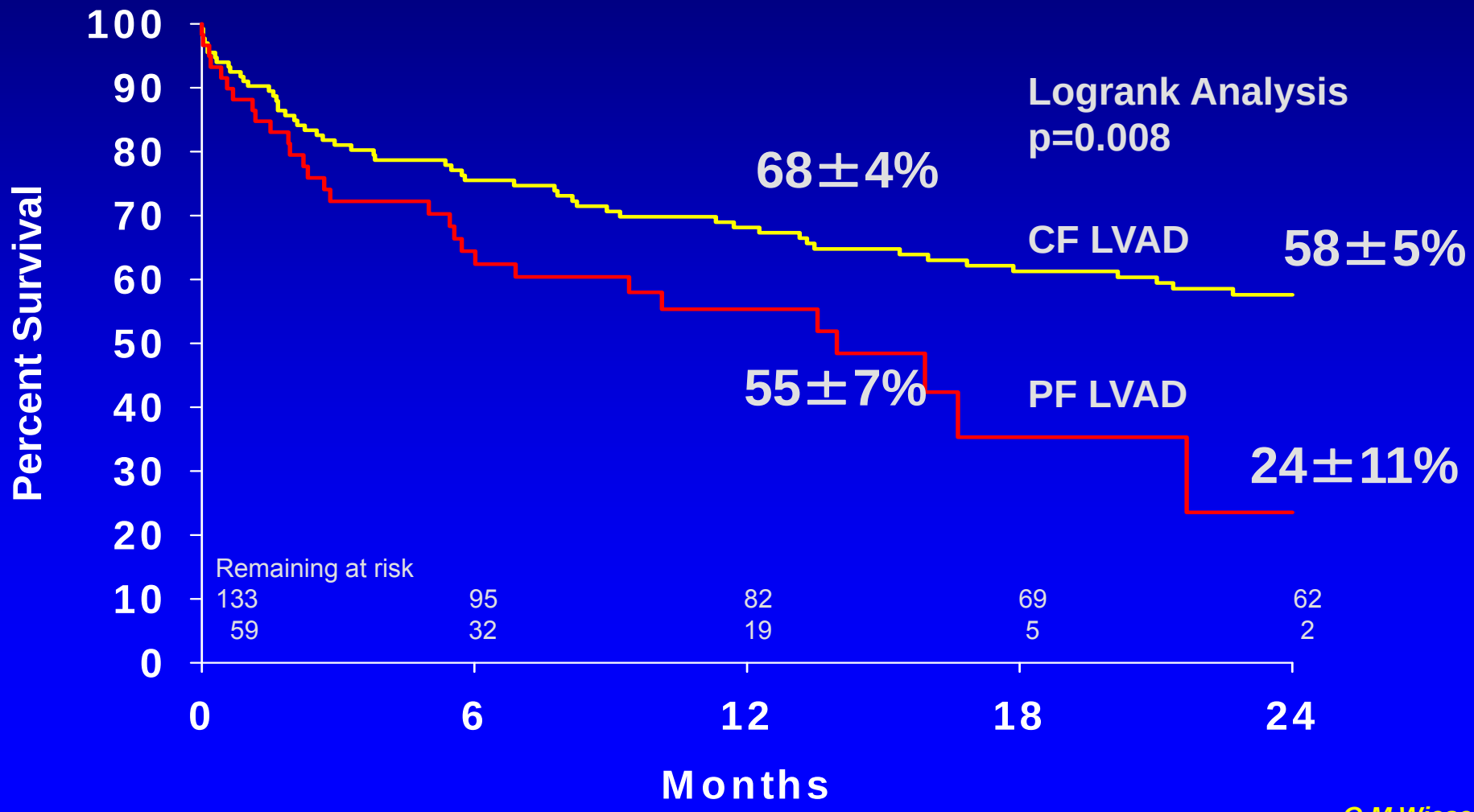
- Randomized clinical trial
  - optimal medical therapy vs. pulsatile flow LVAD
- Non-transplant candidates (n=129)
  - EF ≤ 25%,
  - peak VO2 < 12 ml/kg/min,
  - or continuous infusion inotropes



N Engl J Med 2001; 345:1435-43

Actuarial Survival

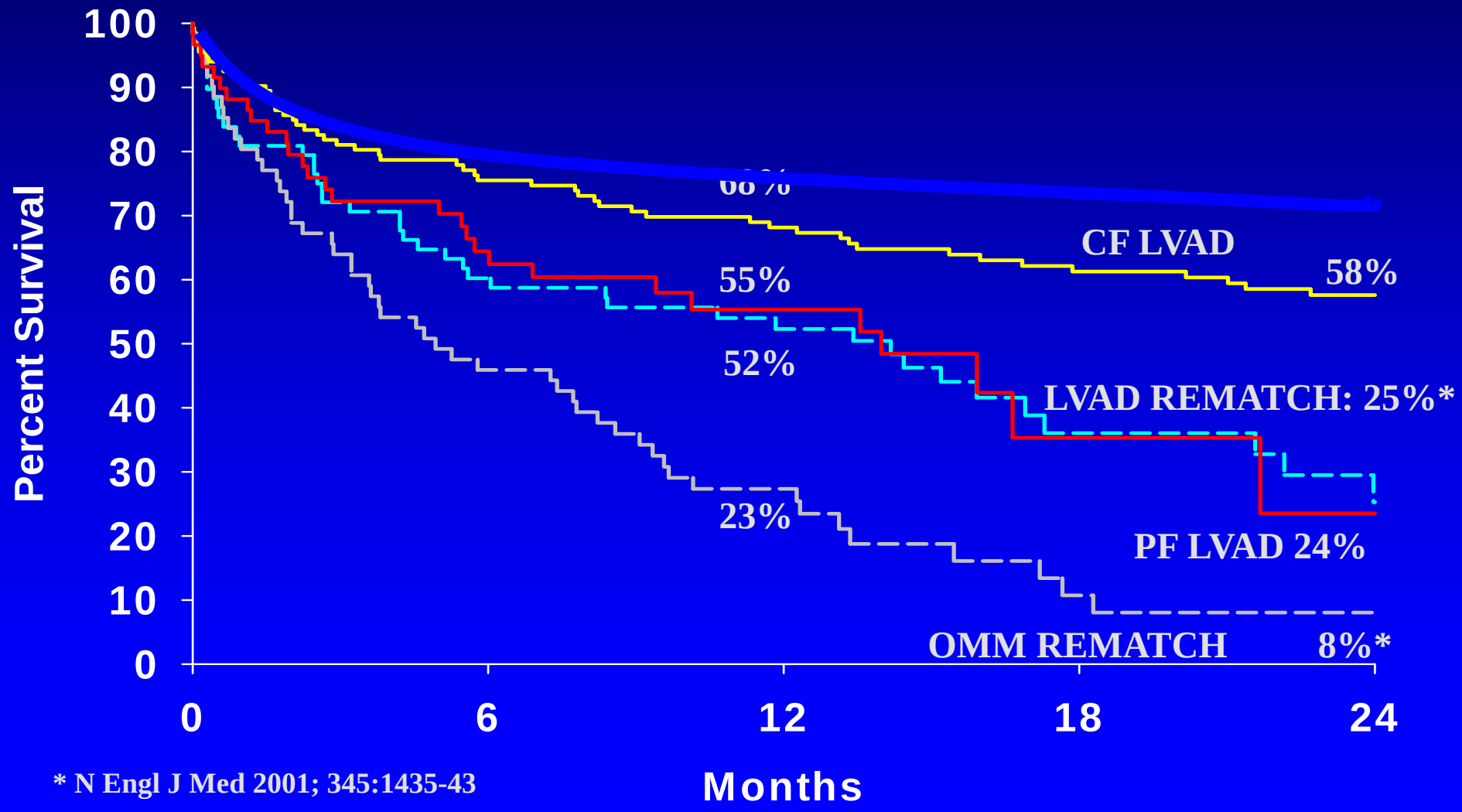
HeartMate II Destination Therapy Trial



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Actuarial Survival vs. REMATCH

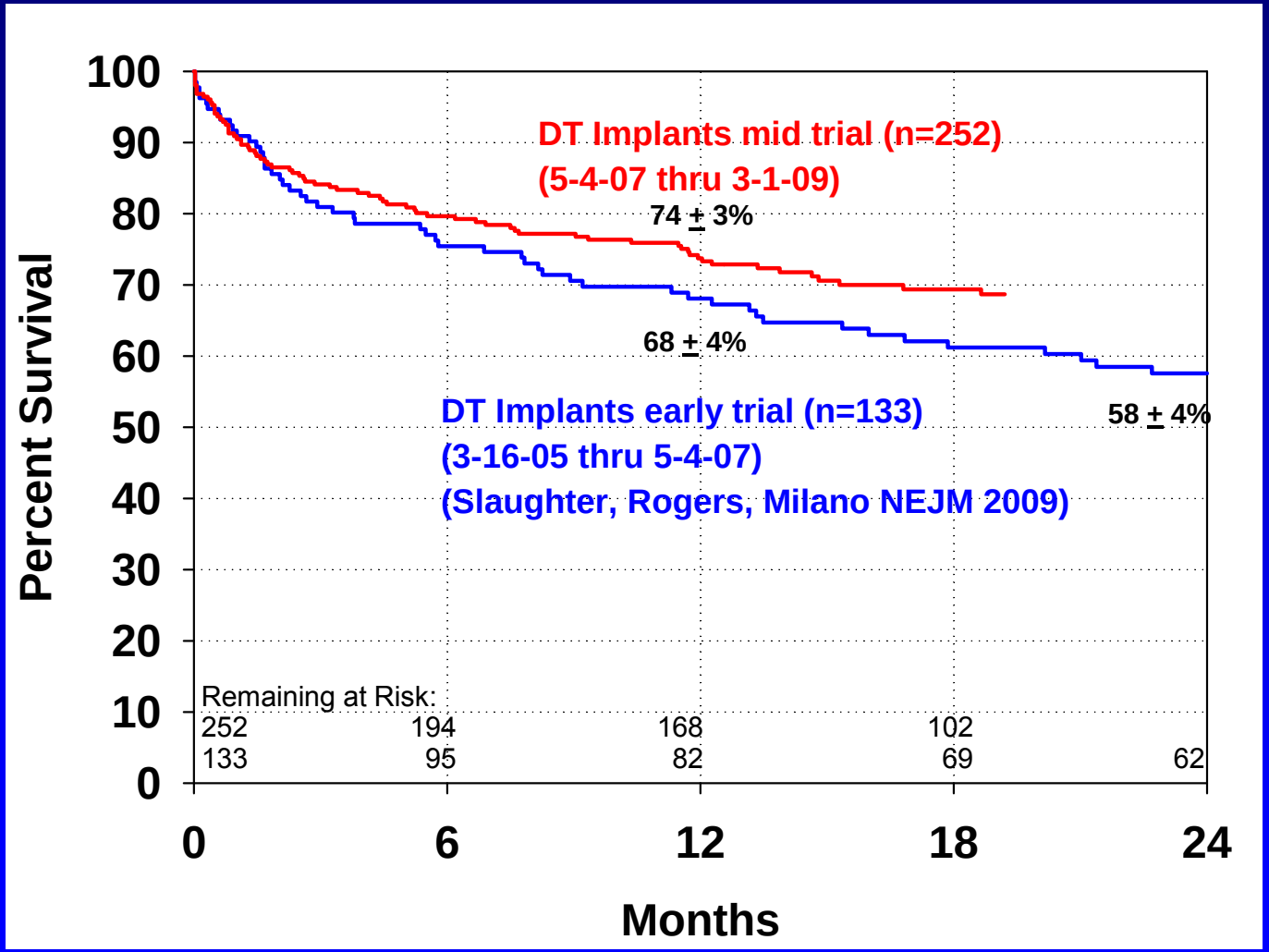
HeartMate II Destination Therapy Trial



* N Engl J Med 2001; 345:1435-43

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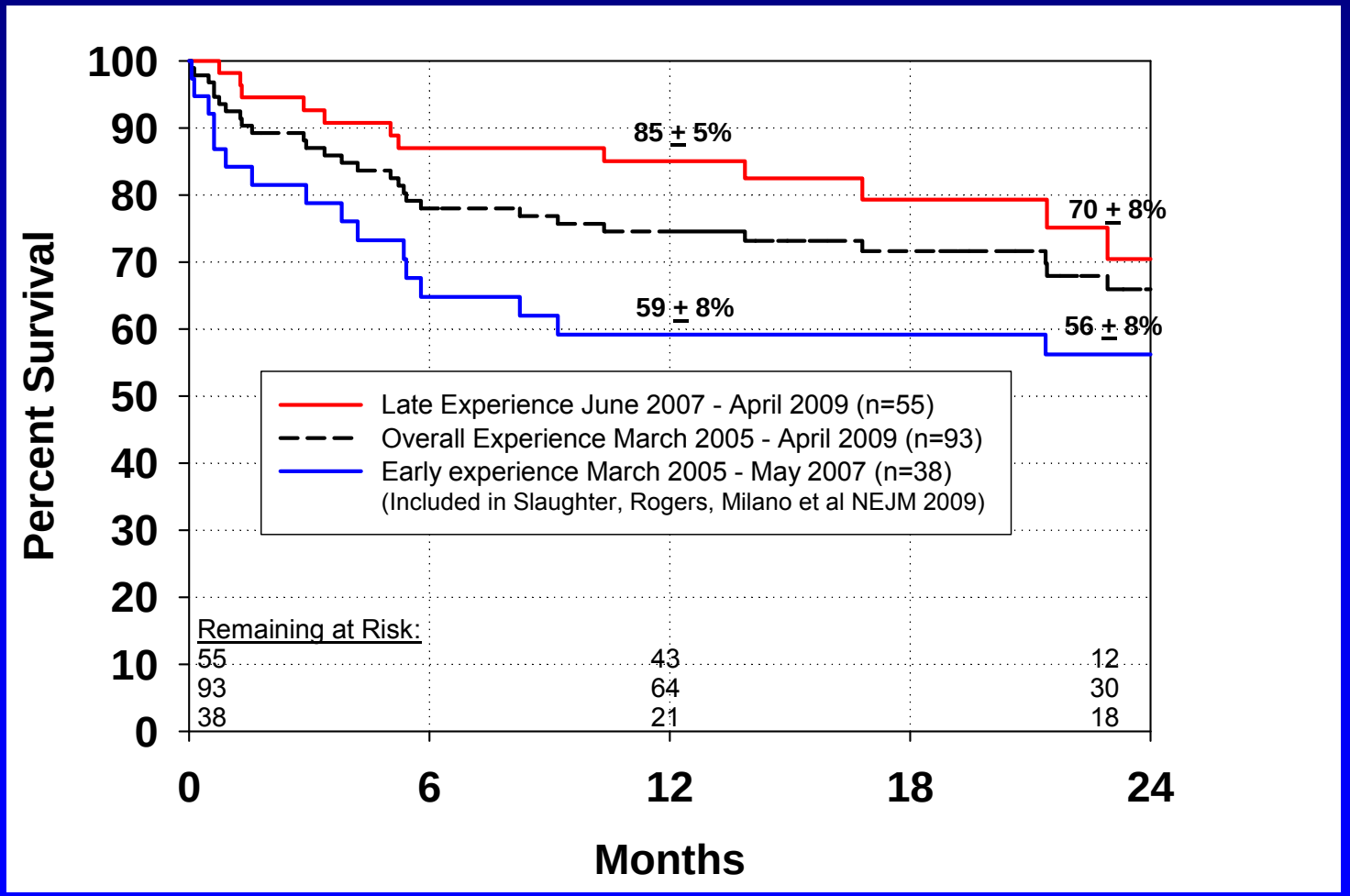
Improving DT Outcomes



G.M.Wieselthaler

Improving DT Outcomes

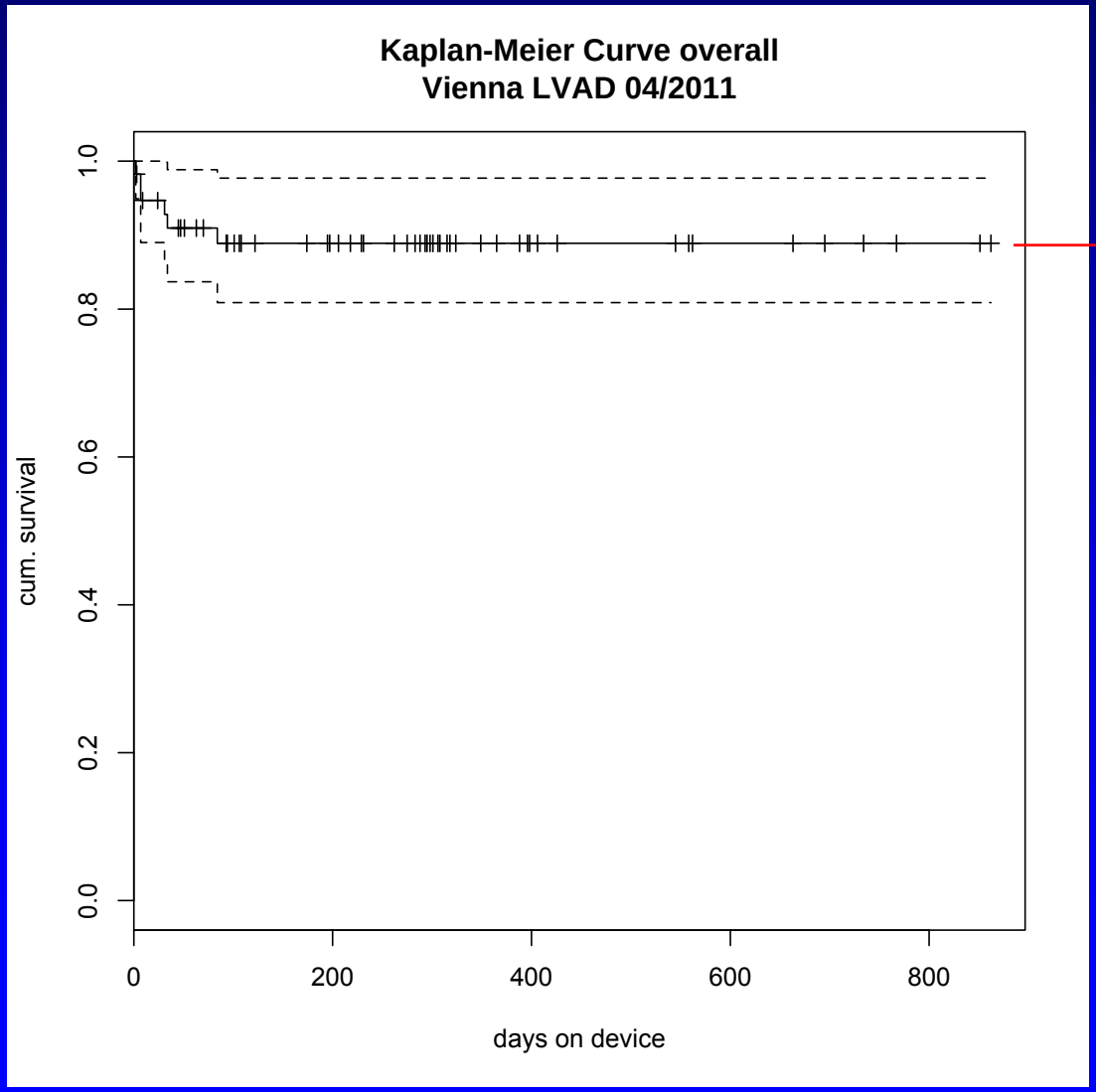
Two Center (Advocate Christ-Duke) Results



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Long-term survival LVAD patients

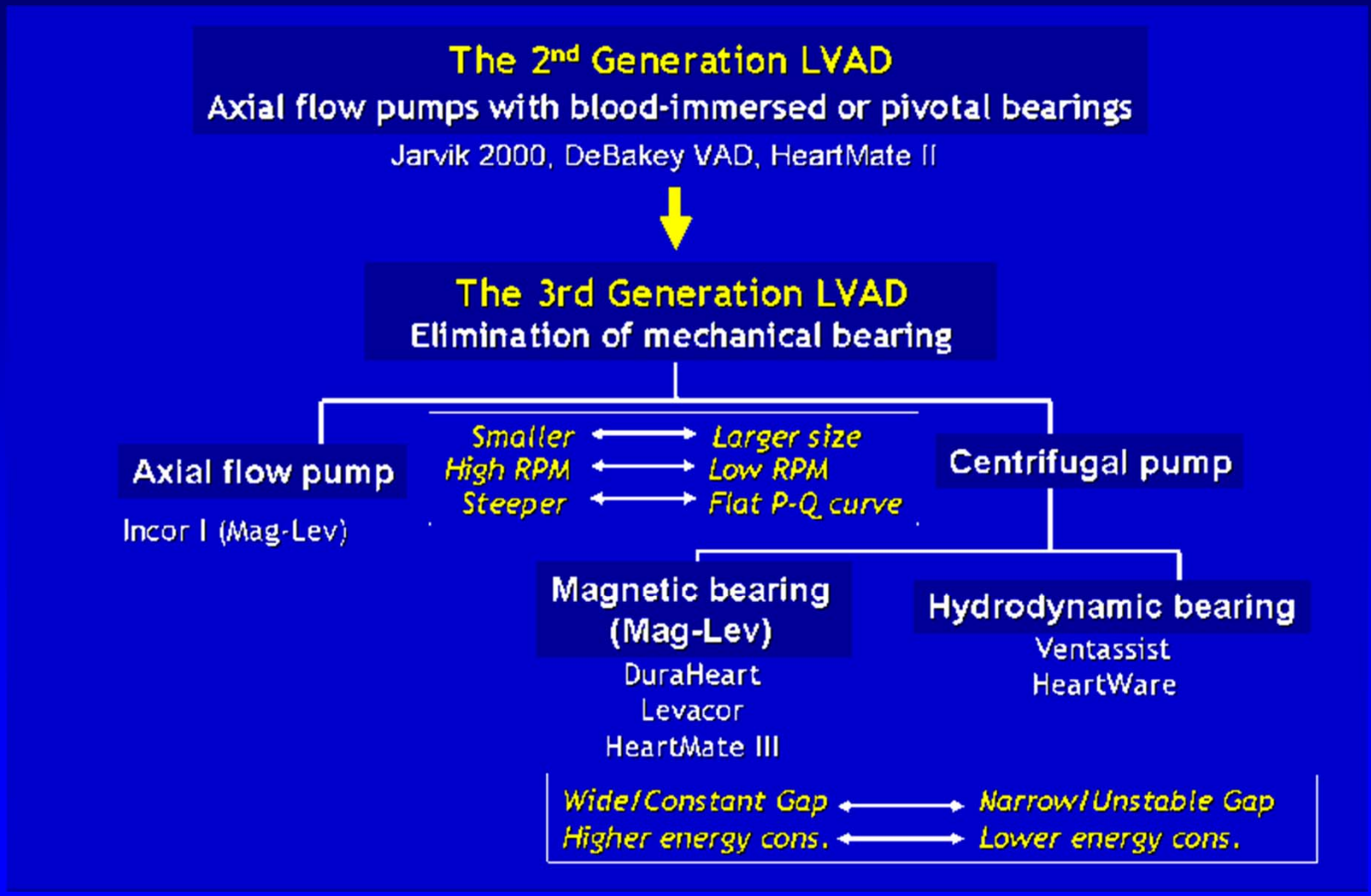
Vienna General Hospital 2007 - 2011



88,9 %

n = 67

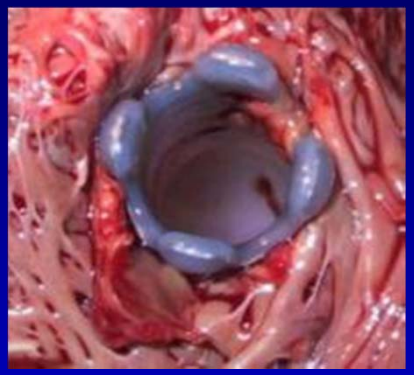
Evolution of Rotary LVAD Technology



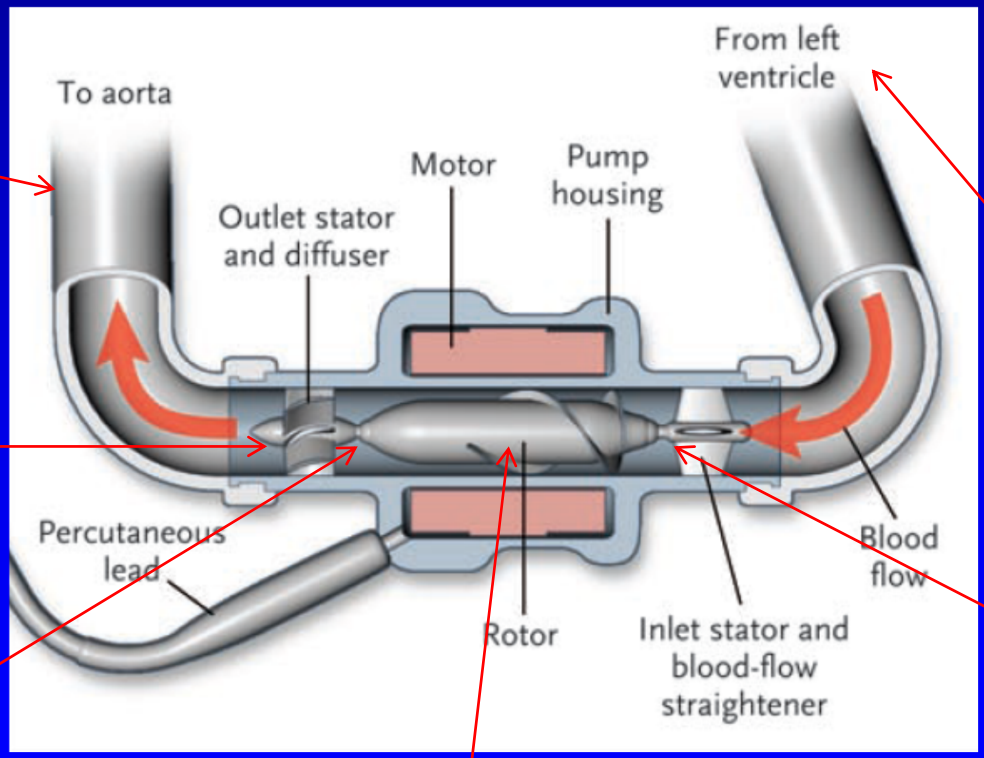
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thrombus formation in MCS

clot formation spots



outflow graft



inflow cannula

Outlet stator / diffusor

rotor bearing outflow

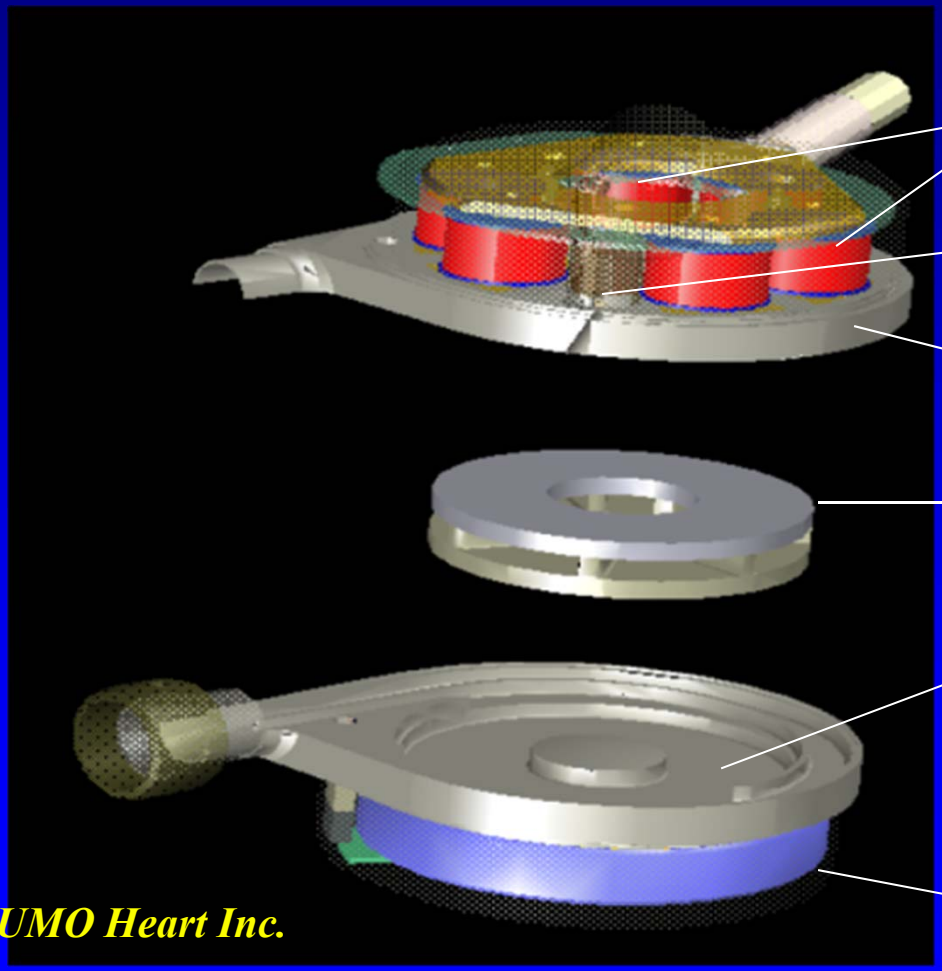
rotor bearing inflow

rotor vanes

Third Generation: rotary blood pumps with magnetically levitated rotors

Third Generation Nonpulsatile Pumps

Major Pump Components



Electromagnets

Position sensors

Upper pump housing half

Magnetically suspended and coupled Impeller

Lower pump half with hydrodynamic bearing

Brushless DC Motor

courtesy of TERUMO Heart Inc.

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TERUMO DuraHeart: Vienna Experience



August 2005

all 5 patients were successfully transplanted after 111 ± 58 days of pump support (202, 81, 96, 128 and 47 days)

total patient days of support: 556

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Abbott v. Miracor, IPR2025-00115
Miracor Ex. 2024, p. 49 of 64

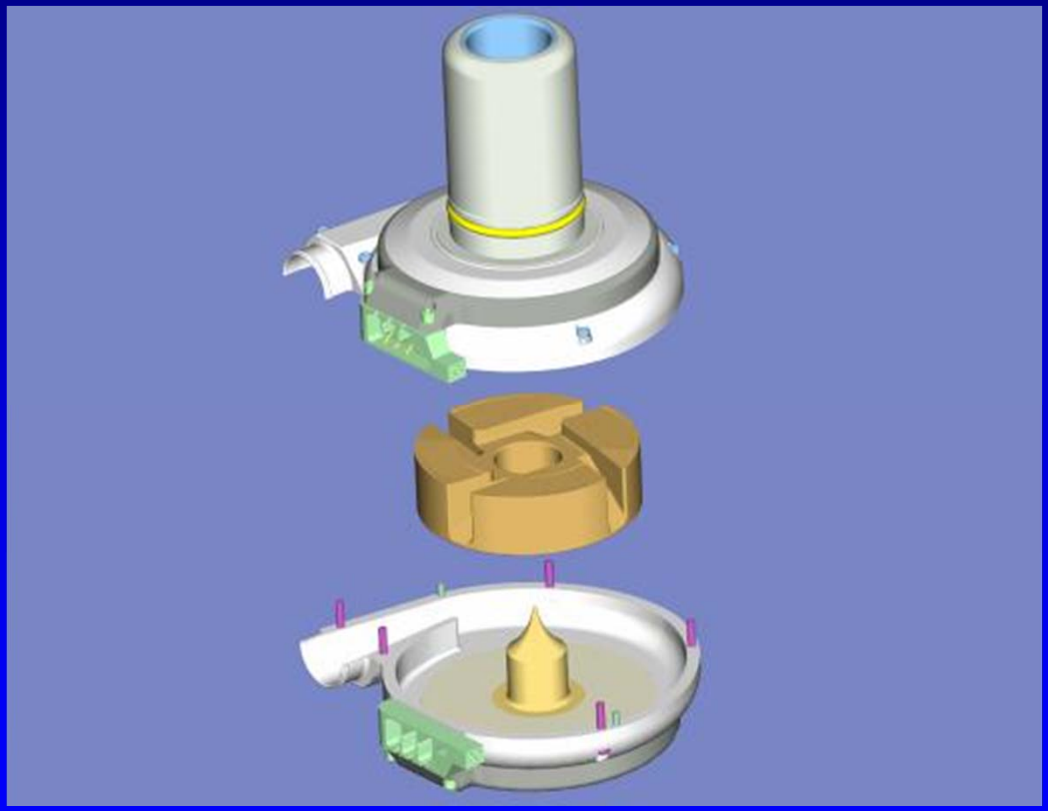
Third Generation Nonpulsatile Pumps

- Small wearless, centrifugal pump, 45cc, 145gms, ~2" outside diameter
- Full output device with up to 10L/min flow capacity
- Only one moving part designed for ≥ 10 years of clinical use
- Integrated inflow cannula allowing pericardial implantation
- High reliability with dual stators, passive impeller suspension
- Small driveline designed to minimize site infections.



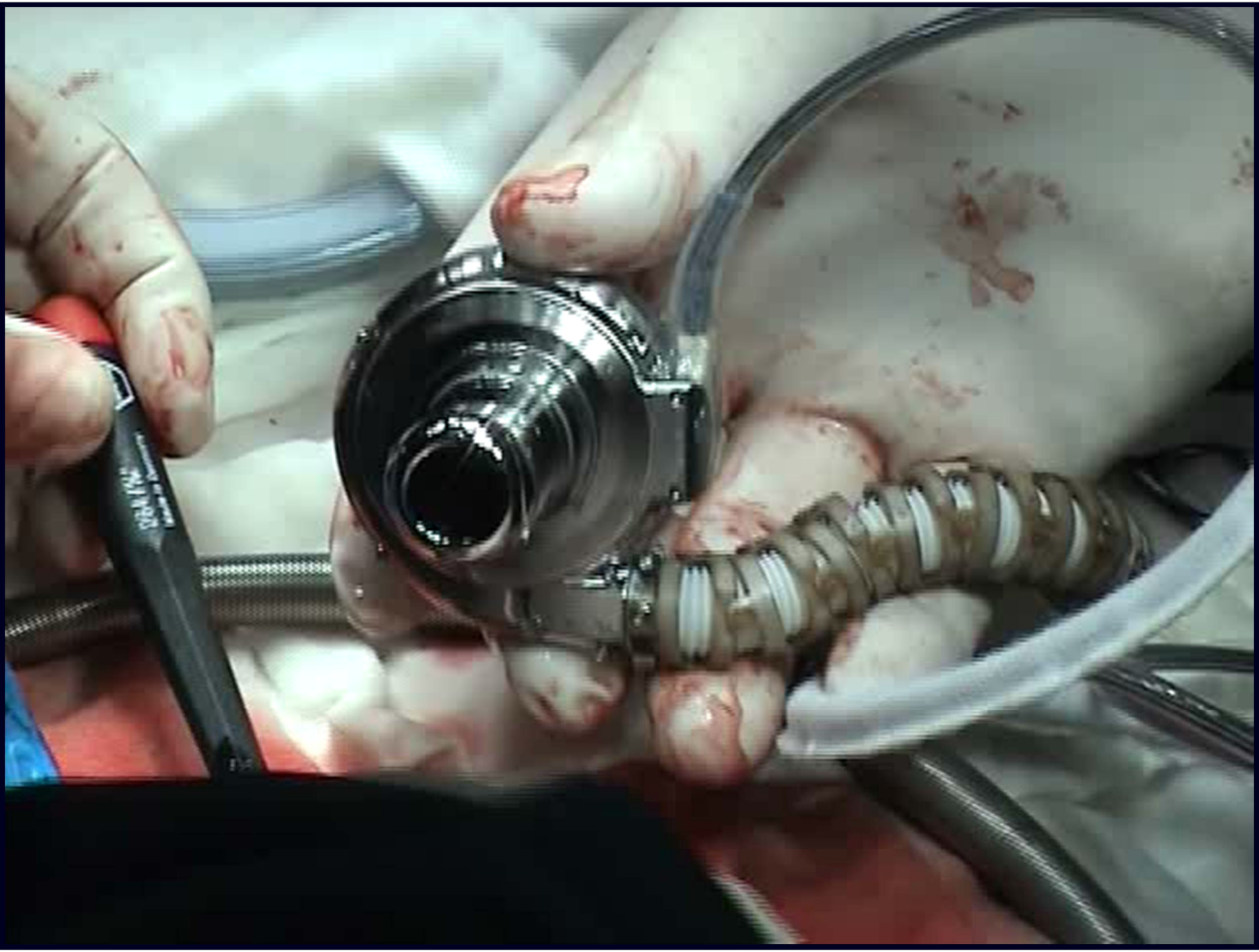
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HeartWare - HVAD





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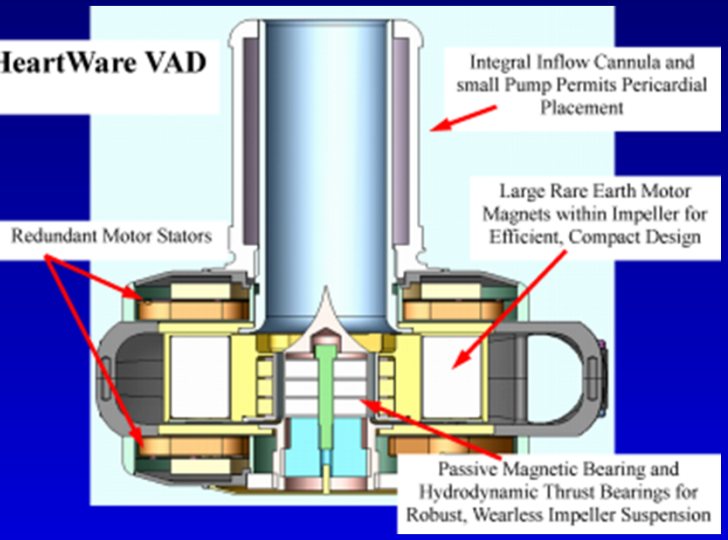
HeartWare - HVAD





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HeartWare - HVAD



Touch screen Hospital Monitor with pump parameters & flow waveforms



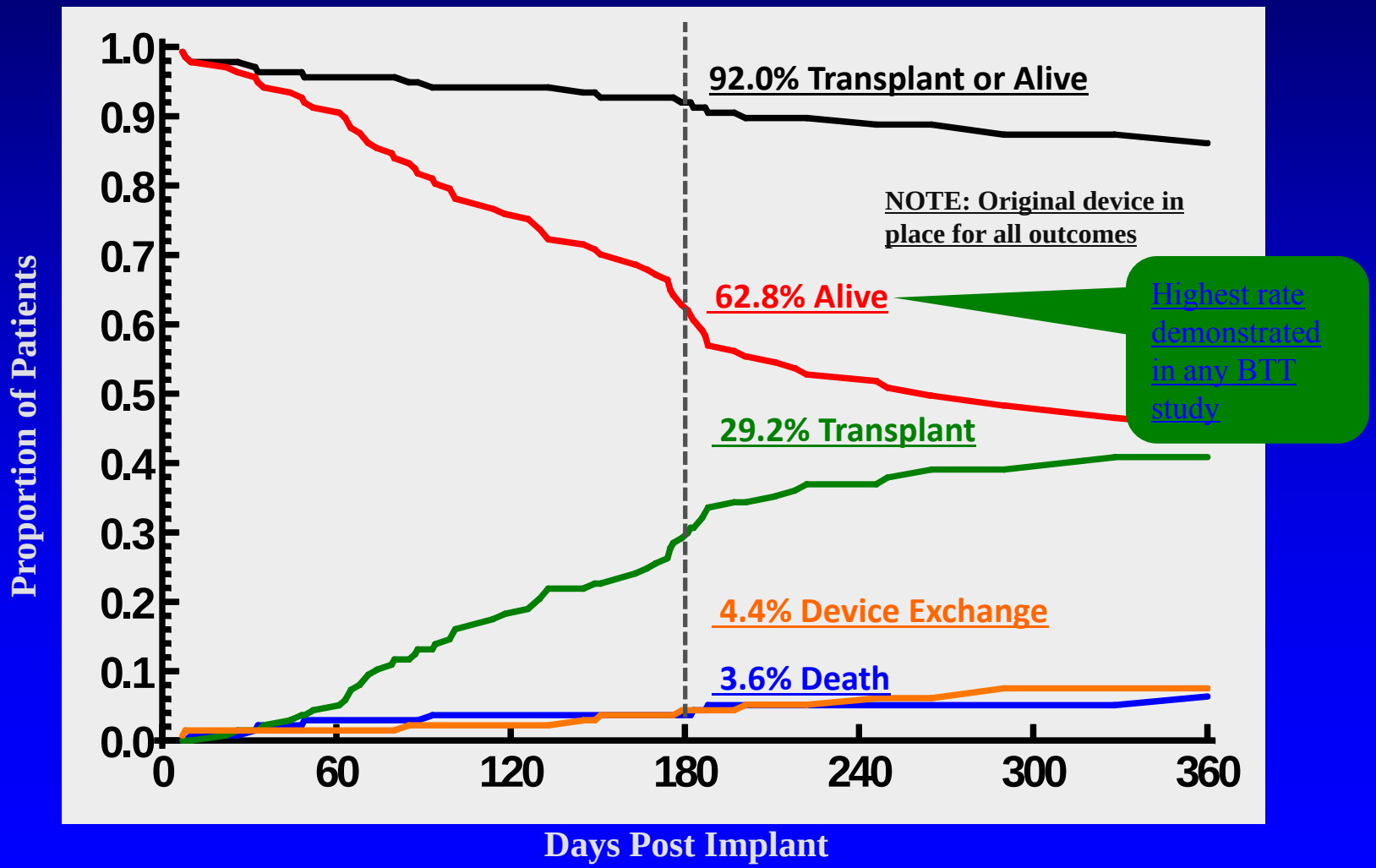


Controller with LCD display, audible alarms and 30 day data storage

2 small, Lithium ION Batteries last 12 hours

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ADVANCE Trial Treatment Group Outcomes
92% probability of success at 180 days

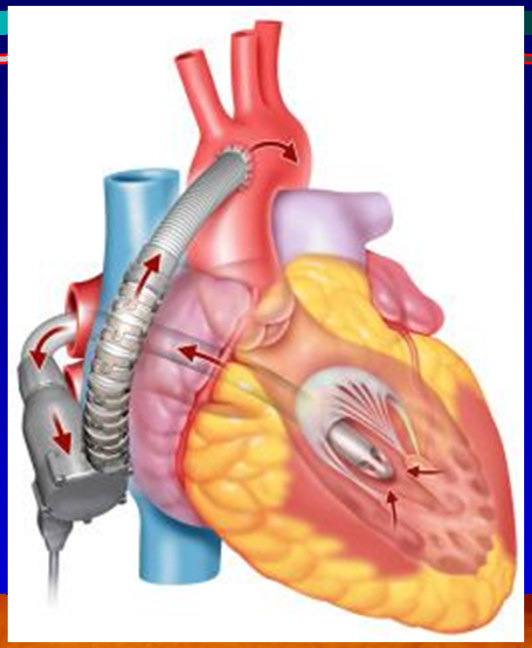


3rd Generation HeartWare: MVAD

Minimal invasive LVAD Implantation



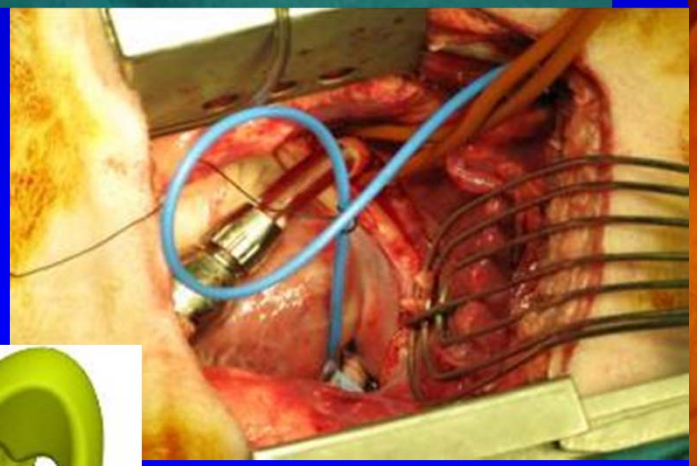


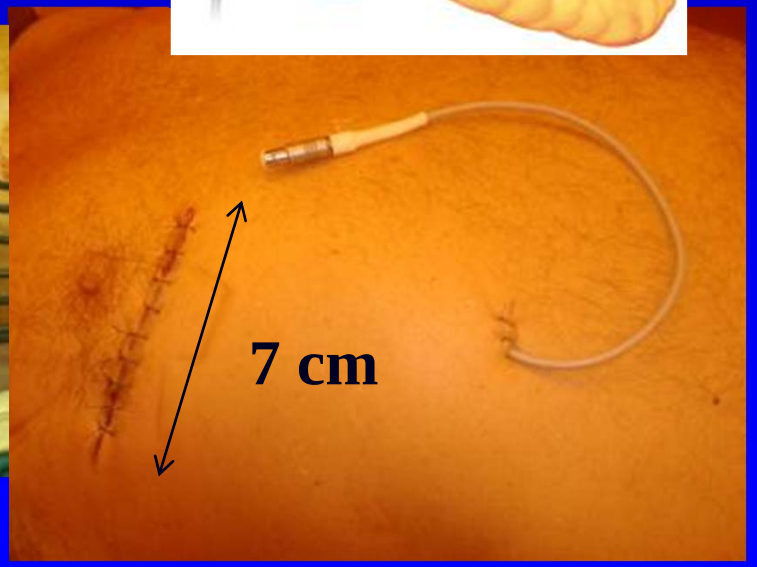




Tip design: minimization of suction *and* recirculation areas (patent filed)





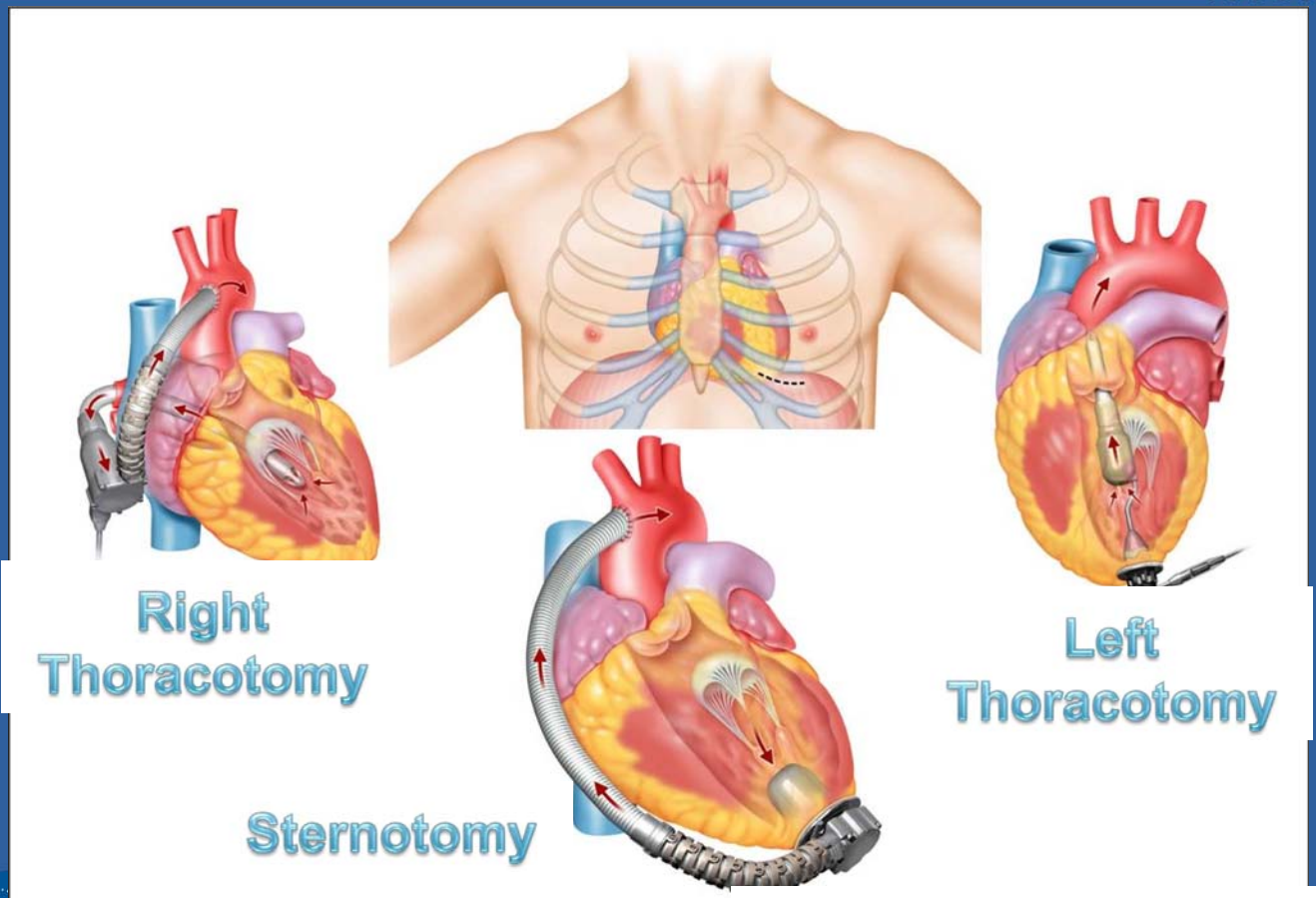


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3rd Generation HeartWare: MVAD

Minimal invasive LVAD Implantation

Left Ventricle Implantation Methods



HeartWare

RVAD's, BiVADs, and TAH

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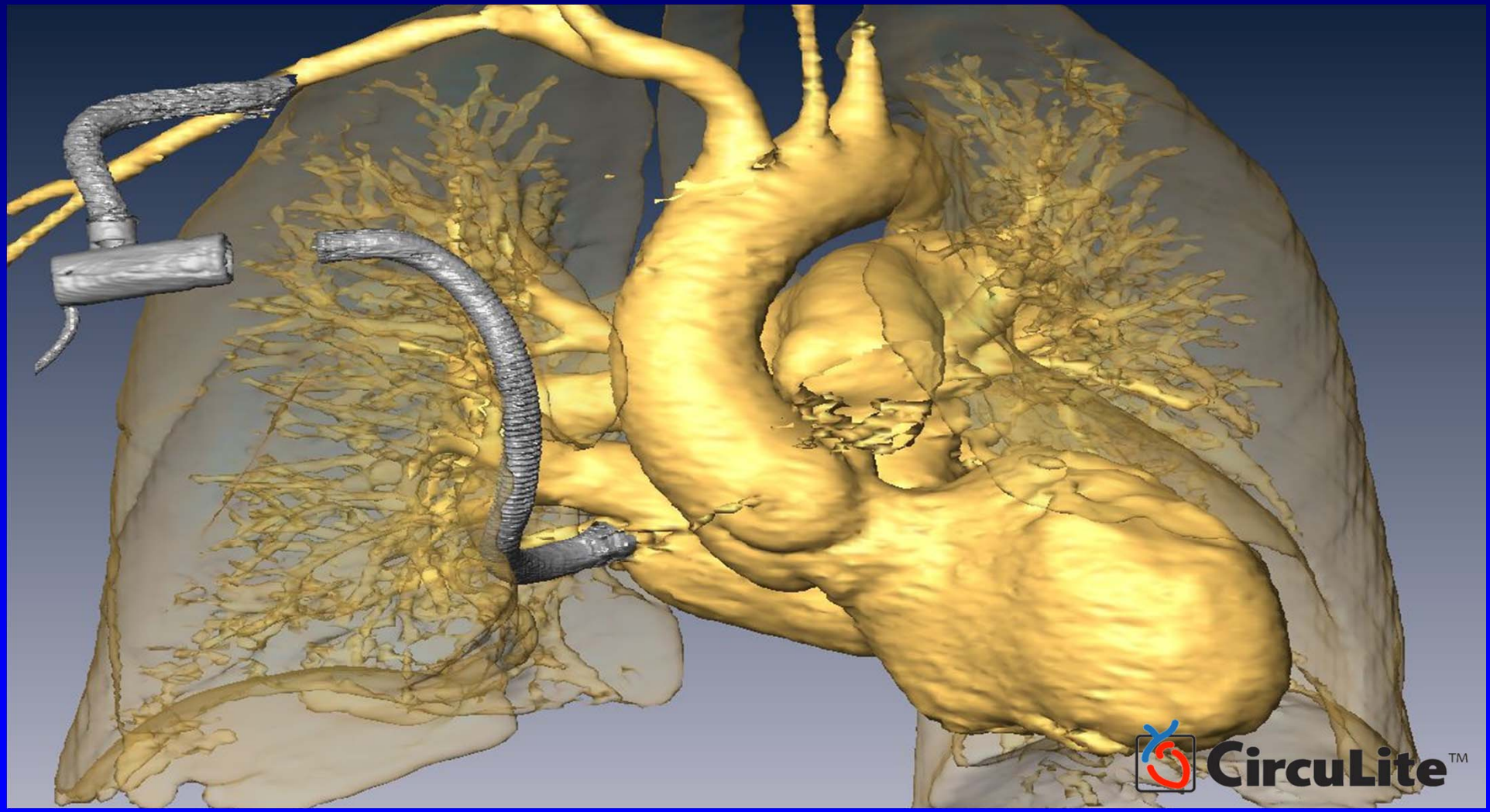
Synergy Micro-Pump Technology

- Smallest implantable blood pump
- Miniature size allows superficial pacer-like “pocket” placement
- Provides partial support: up to 3L/minute of blood flow
- Designed for long-term support
- Protected by six exclusive patents



CircuLite™

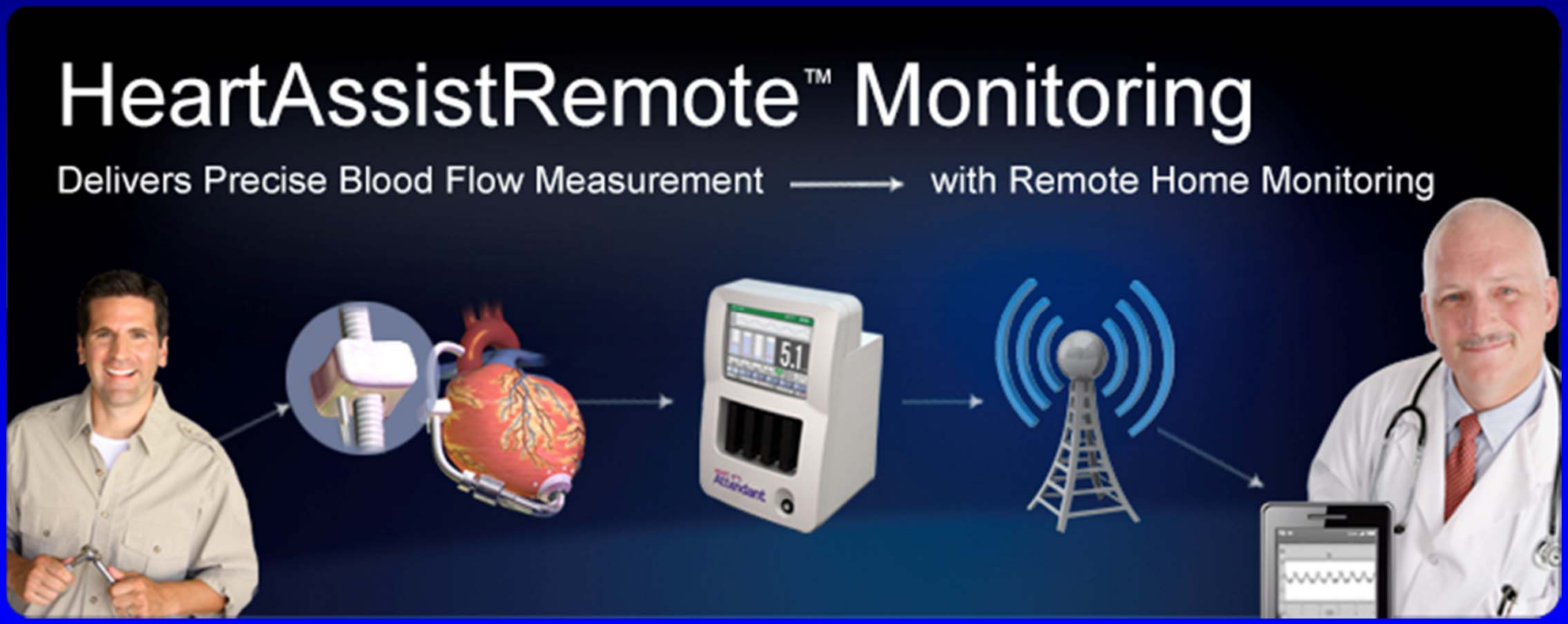
Implanted Synergy System: 3D CT Scan



NOTE: Non-reinforced section of the inflow cannula (at micro-pump connection) is not visible on CT Scan

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Future of Mechanical Circulatory Support



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Future of Mechanical Circulatory Support

Batteries for VAD support

- Smart phones = 4 Whr → ~30 minutes
- Power tools = 54 Whr → ~7 hours
- Tesla Roadster = 56kWh → ~48 weeks











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Future of Mechanical Circulatory Support

What about Transcutaneous Energy Transfer?



Consortium working on international standard for wireless charging



Increasingly popular in low power consumer market



HeartWare

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Future of Mechanical Circulatory Support

"Your focus determines your reality." Qui-Gon Jinn of Star Wars: Episode I

VAD-therapy today:

-- **final therapy for terminal heart insufficiency patients**
-- **due to growing experience favorable outcome**
-- **sophisticated technology provides excellent long-term results**
-- **still - individual pump-types for individual patients**

What can we expect ??

-- **next 2 - 3 yrs minimal invasive pump concepts in clinical application**
-- **next generation pump is predominantly further miniaturized rotary pump**
-- **great usability of pump externals– easy to use technology**
-- **competition and up-scaled use will bring prizes down (PM, AICD, Dialysis, …)**
-- **very durable VADs for chronic implants with TET-systems**
-- **true alternative to clinical heart transplantation – QOL ↑↑↑**

G.M.Wieselthaler

Transplantation & MCS is a Team Effort



Cardiology Team:

T. DeMarco
D. McGlothlin
L. Klein

CT-Surgery Team:

G.Wieselthaler
G. Al-Dossari
Tx-fellow

Anaesthesia/Intensive Care Team

G.M.Wieselthaler