Mechanické srdeční podpory v léčbě pokročilého srdečního selhání

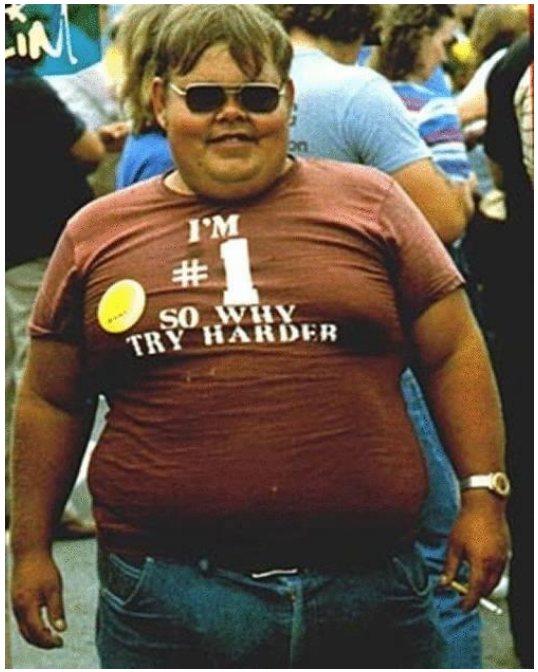
Jiří Malý

Kardiocentrum
Institut klinické a experimentální medicíny

Praha

IKEM

Facts about Chronic Heart Failure



Occurrence of chronical heart failure in EU and US:

2-3% of adult population, Czech Republic: **over 200,000 patients**

Third Millennium Phenomenon

EU estimate:

2010: 14 Million patients

2020: 30 Million patients

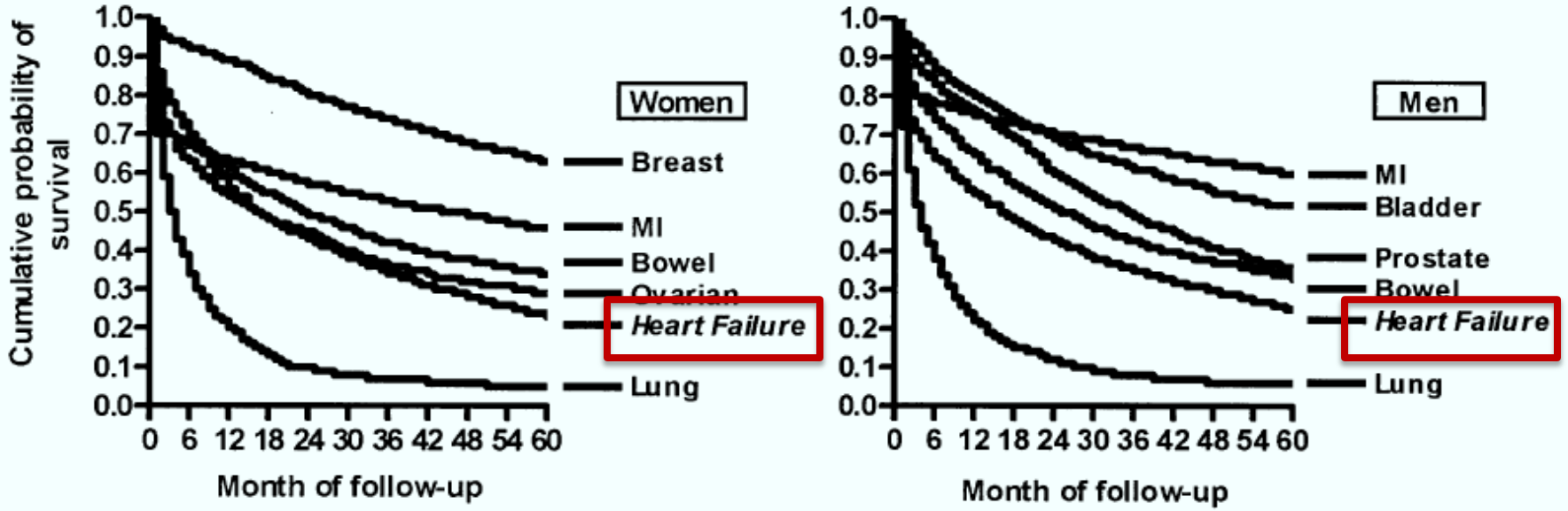
According to the prediction, this number will increase by 25% by 2030

Future prediction: Every 5th person in his/her 40s and every 3rd person in his/her 50s will suffer from heart failure during their lives

in courtesy of Melenovsky V

Heart Failure: No. 2 Killer!

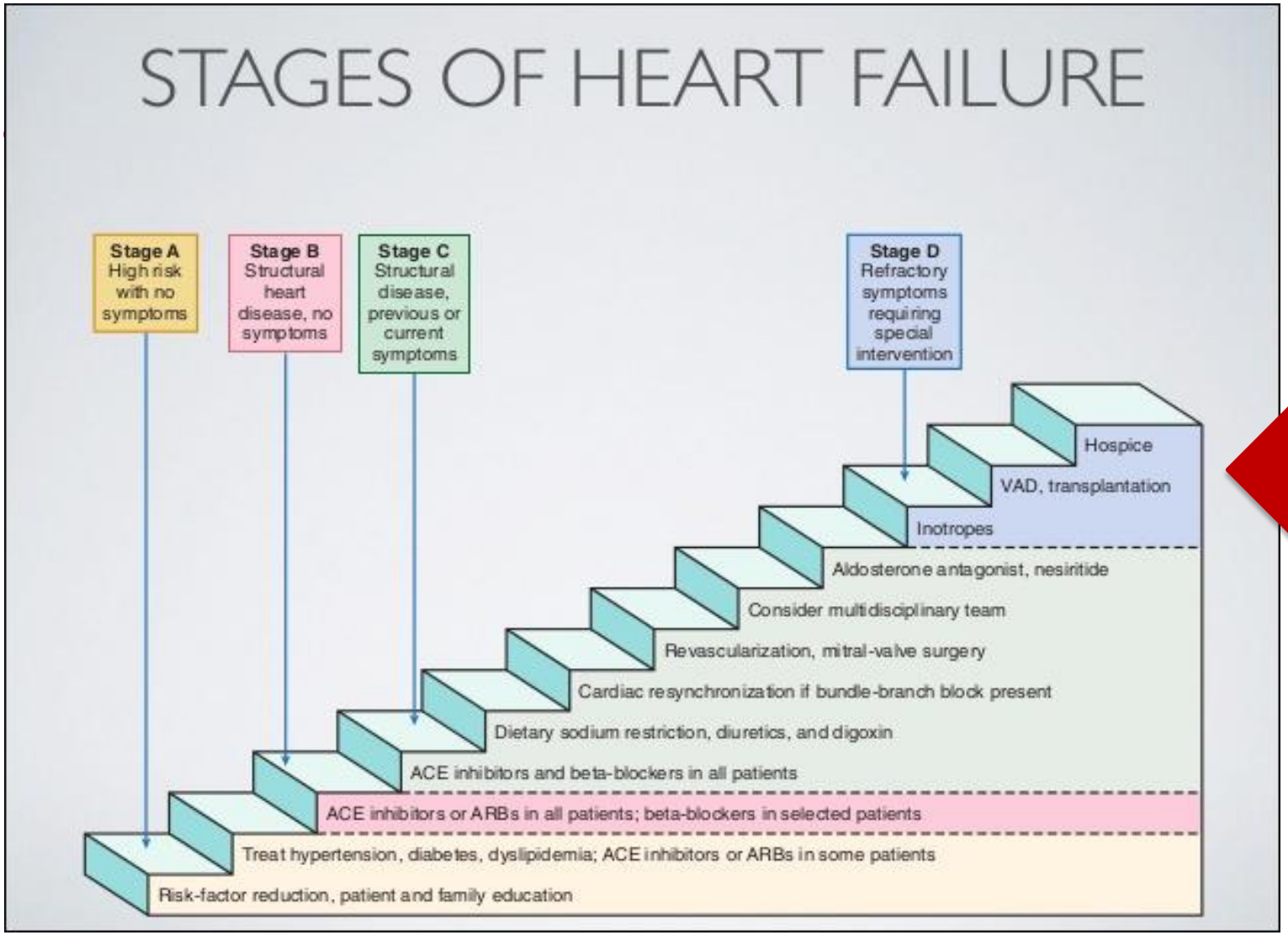
5-year survival since the first hospitalization for chronic heart failure compared to tumors:
Scotland 1991 (n = 3 241)



Most of cancerous diseases have better prognosis than heart failure

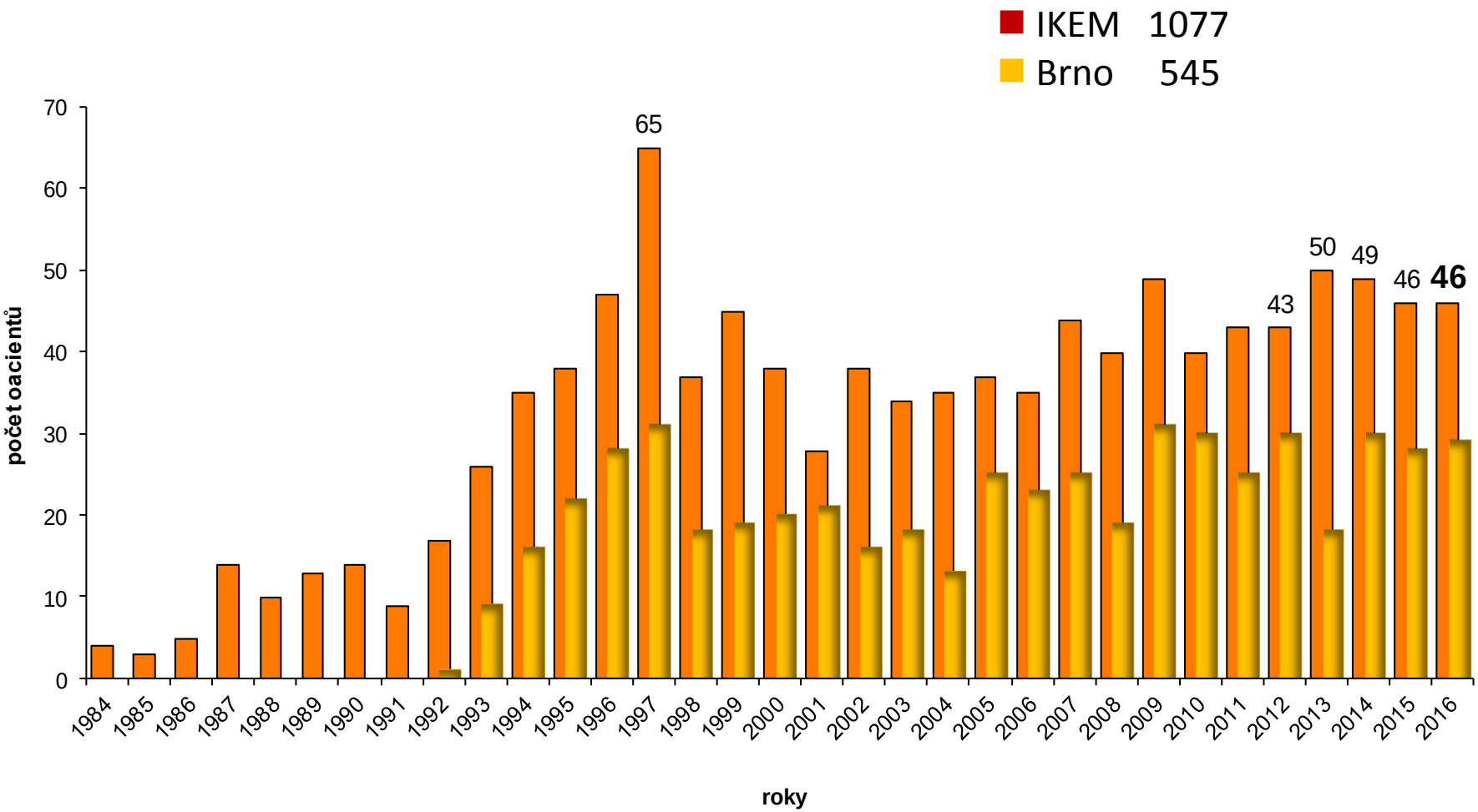
50 – 60% of patients die before 5 years of the first hospitalization

in courtesy of Melenovsky V



Braunwald E. Braunwald's Heart Disease 9th ed. Philadelphia: Elsevier, 2012. p. 548

Transplantace srdce v ČR



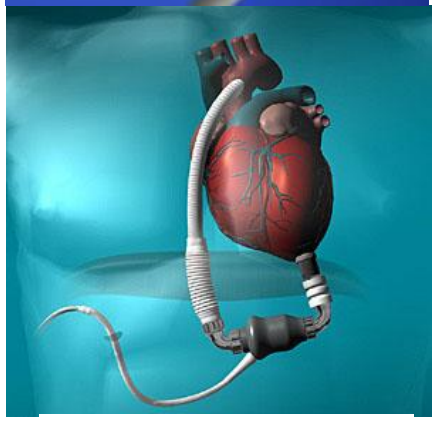
MSP v terapii srdečního selhání

- Přemostění k transplantaci
- Permanentní terapie
- Momentum 3 studie

Technologický vývoj MSP

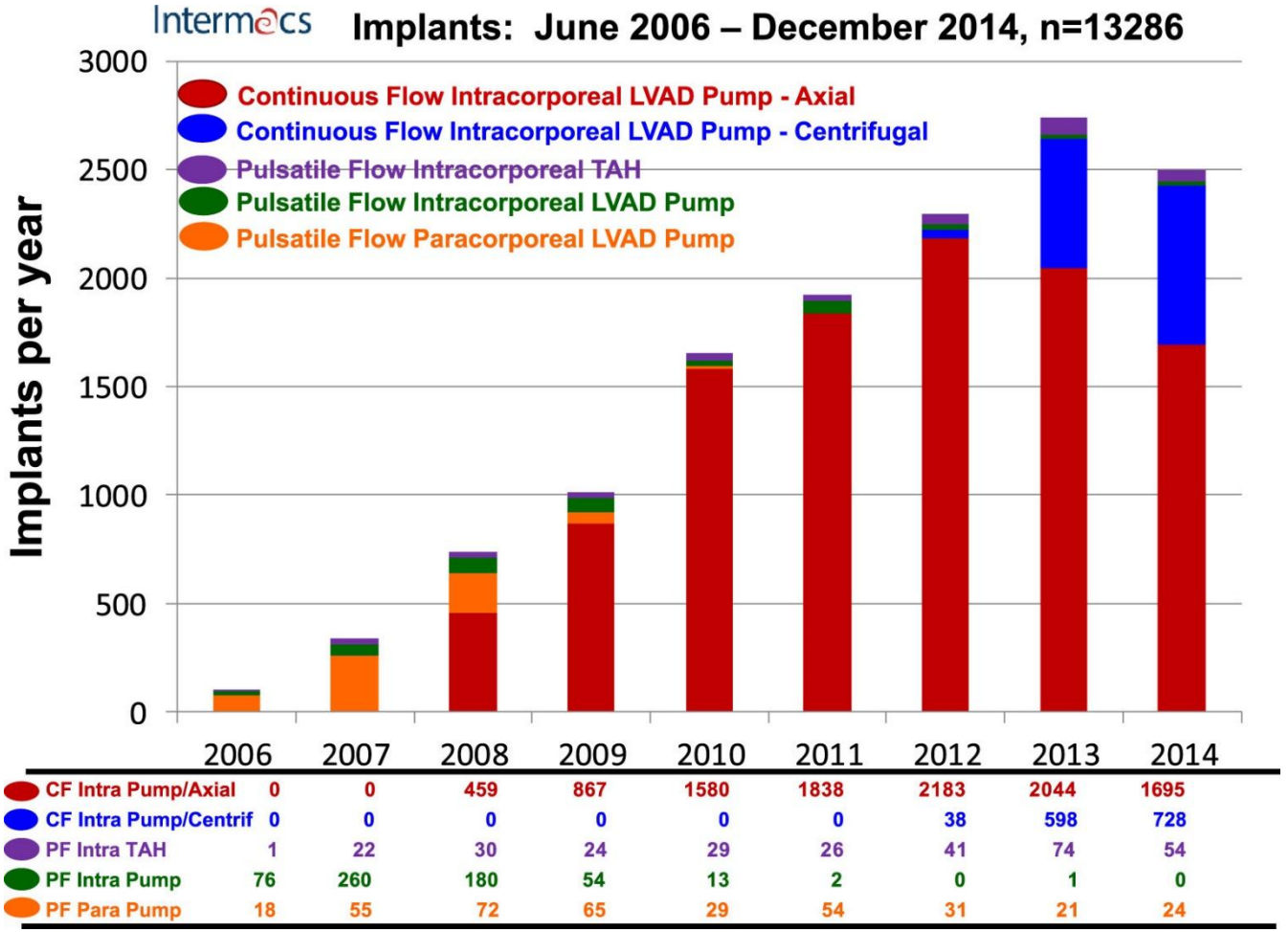
- **Pulsatilní pumpy (1. generace)**
- Thoratec PVAD
- HeartMate I
- Novacor

- **Axiální pumpy (2. generace)**
- HeartMate II
- Jarvik 2000
- MicroMed DeBakey

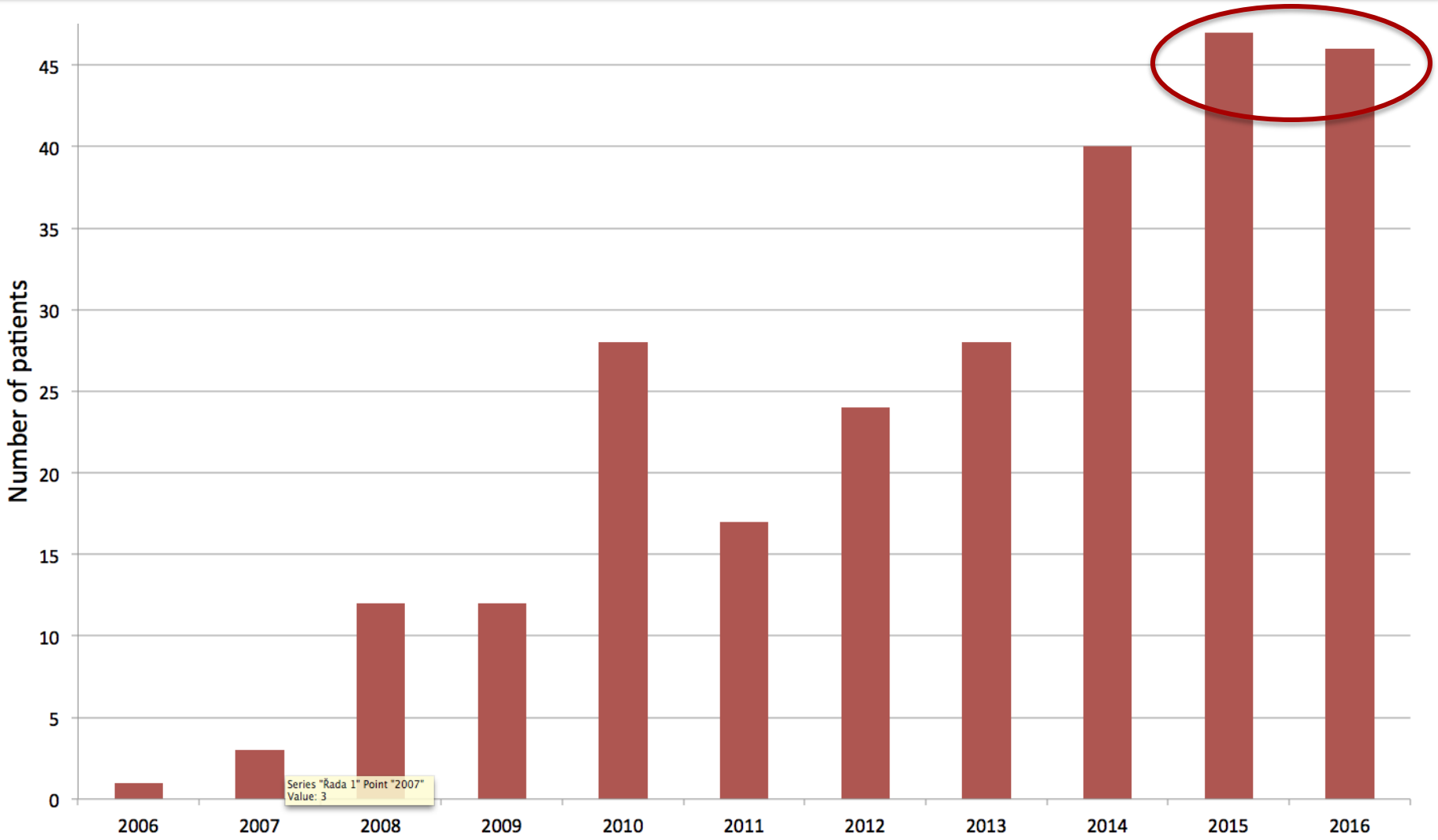


- **Centrifugální pumpy (3. generace)**
- HeartWare HVAD
- HeartMate 3

Registr INTERMACS



Dlouhodobé MSP v IKEM



ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC

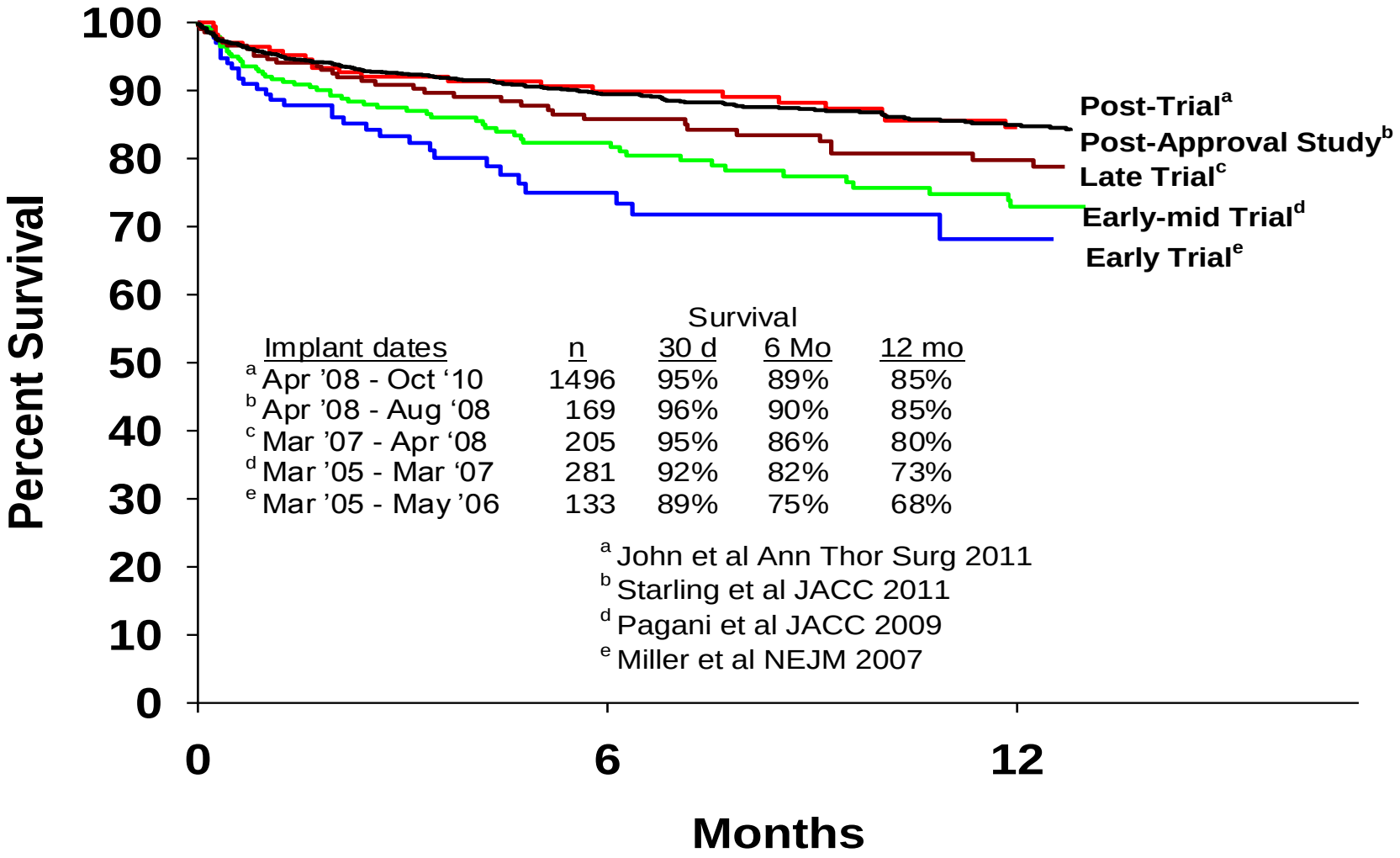
Třída	Stupeň
I	B

Pacienti s výraznými symptomy srdečního selhání > 2 měsíce navzdory optimalizované medikamentózní terapii s >1 z následujících příznaků:

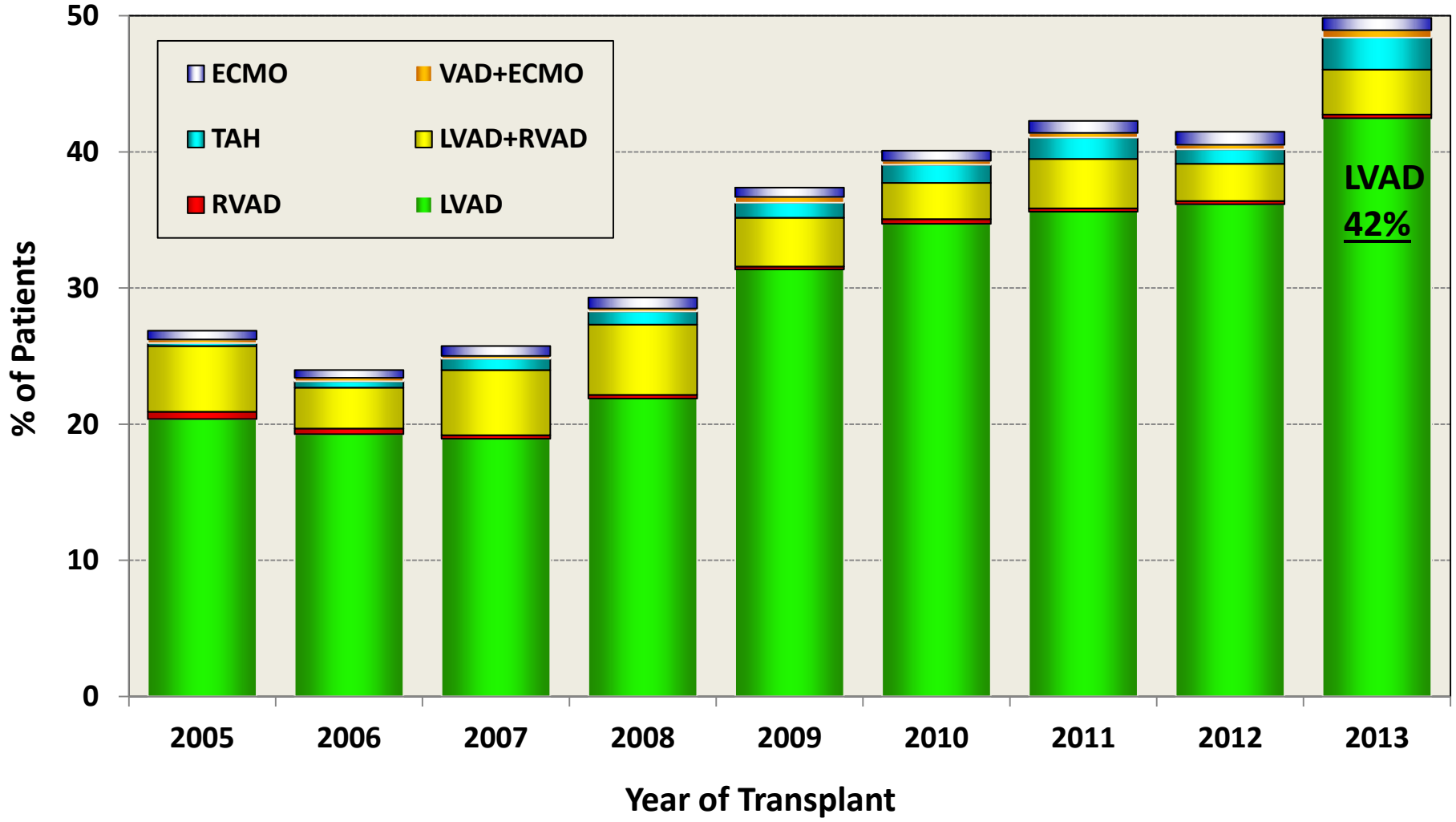
- **EF LK < 25%**
- **> 2 hospitalizace pro srdeční selhání během 1 roku bez jiné vyvolávající příčiny**
- **závislost na i.v. inotropní podpoře**
- **progresivní orgánové selhávání pro sníženou perfúzi a systolickým TK < 80-90 mmHg nebo SI <2,0 l/min/m^2)**
- **zhoršující se funkce pravé komory srdeční**

McMurray J. et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: Eur J Heart Fail. 2012;14(8):803-69.

MSP - přemostění k transplantaci

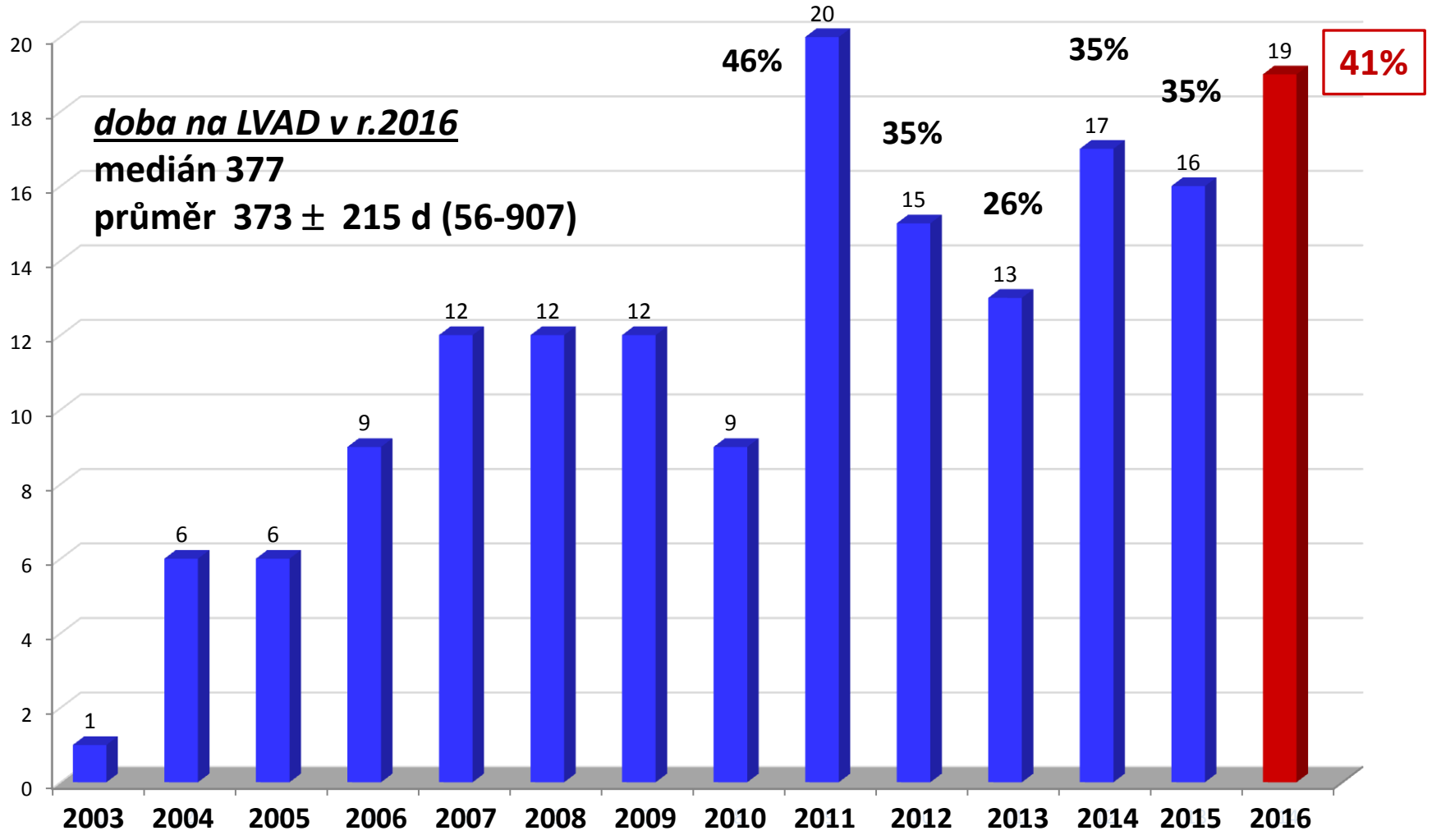


Mechanická podpora v přemostění k TxS



Registry ISHLT J Heart and Lung Transplant 2016; 35: 1158 - 1169

Mechanická srdeční podpora v přemostění k TxS
IKEM (2003 – 2016)

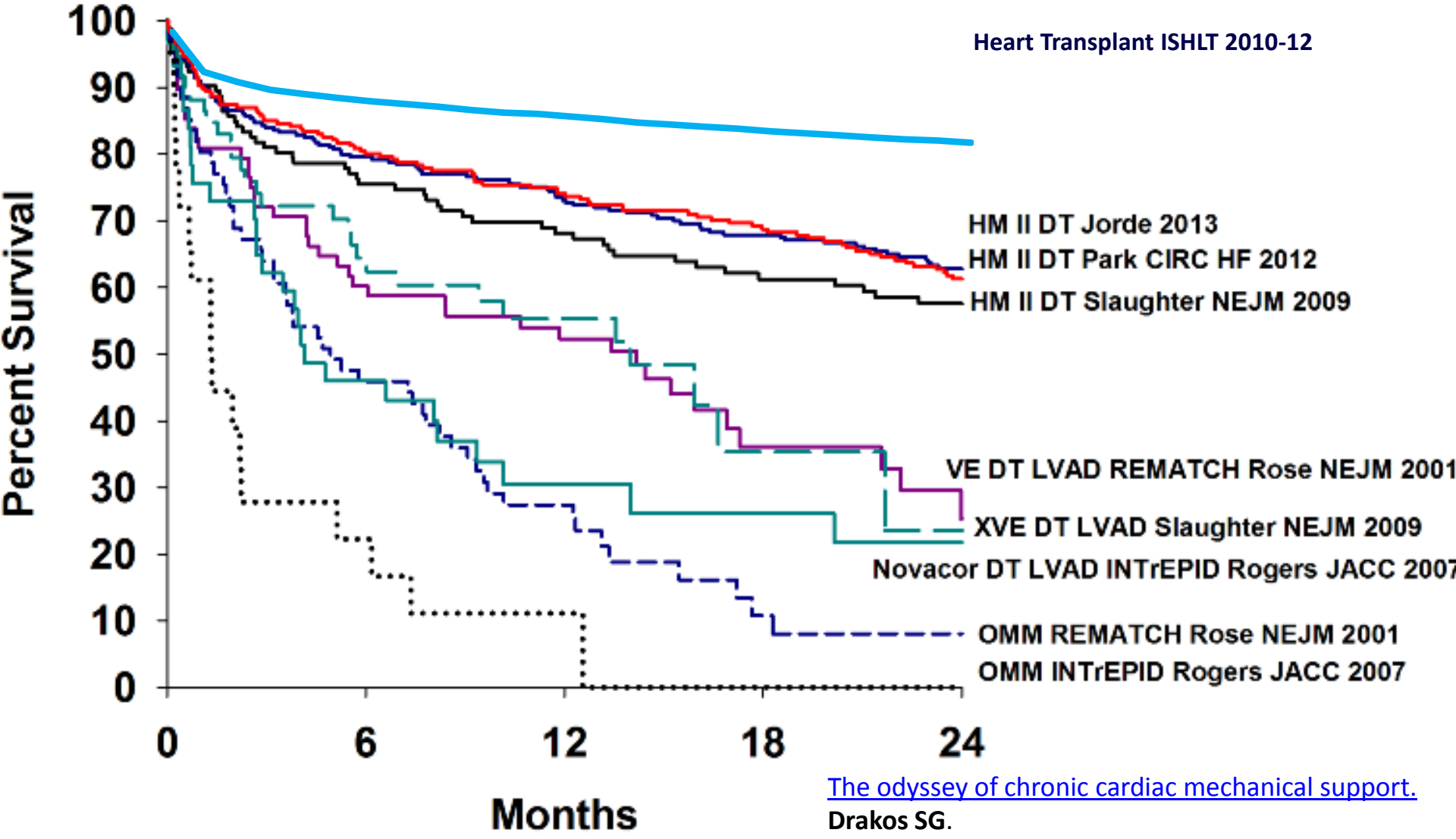


Destinační (permanentní) terapie

Indikace destinační terapie

- Věk pacienta (> 65 let)
- Diabetes mellitus s orgánovými komplikacemi
- Multietážová ateroskleroza
- Těžká obezita
- Excesivní imunosensitizace
- Interval vyléčené malignity < 5let

Pokroky permanentní terapie



The odyssey of chronic cardiac mechanical support.
Drakos SG.
J Am Coll Cardiol. 2014 May 6;63(17):1758-60.

Přežívání pacientů v indikaci permanentní terapie

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Heart Failure

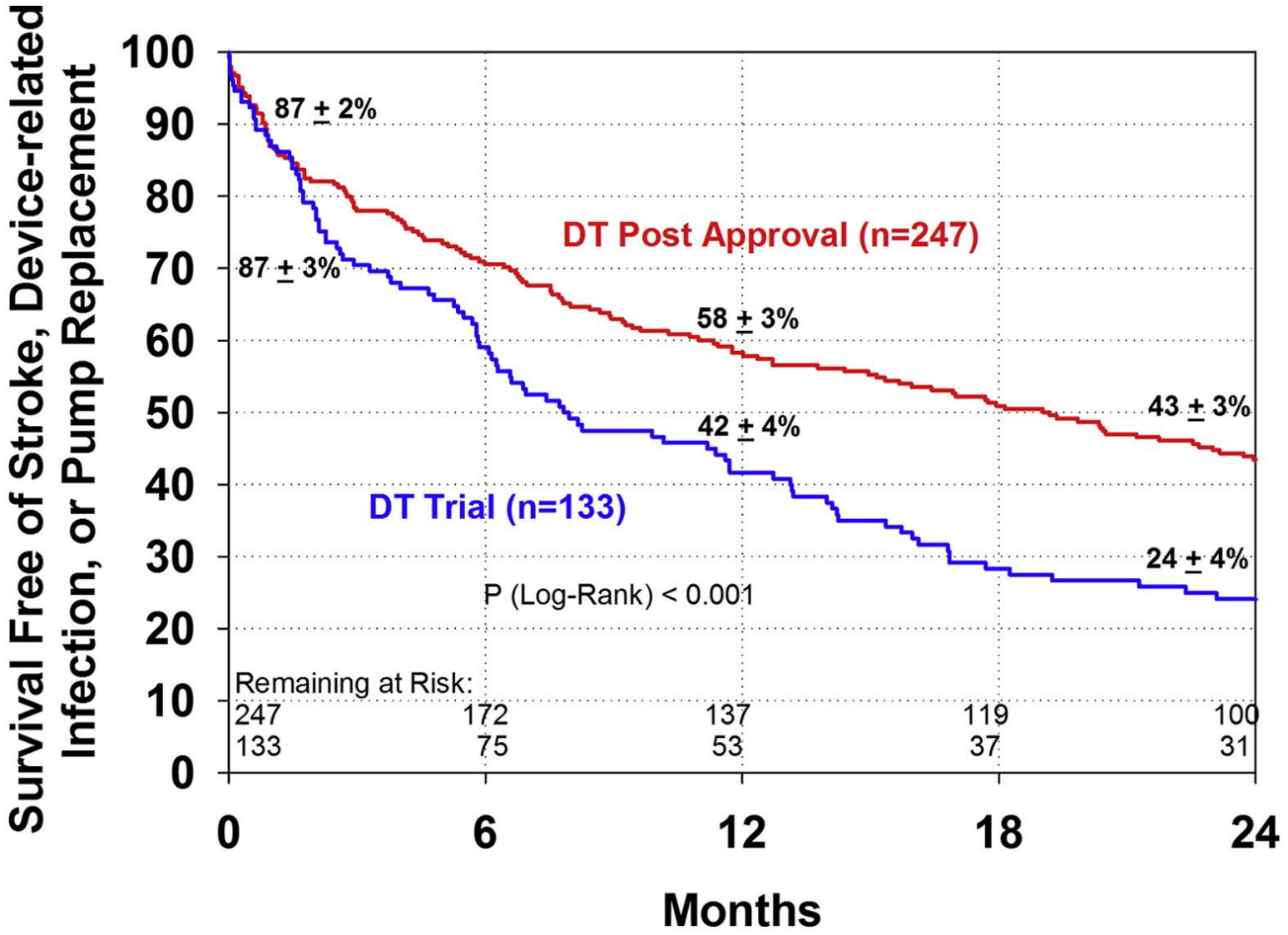
Results of the Destination Therapy Post-Food and Drug Administration Approval Study With a Continuous Flow Left Ventricular Assist Device

A Prospective Study Using the INTERMACS Registry (Interagency Registry for Mechanically Assisted Circulatory Support)

Ulrich P. Jorde, MD,* Sudhir S. Kushwaha, MD,† Antone J. Tatooles, MD,‡ Yoshifumi Naka, MD, PHD,* Geetha Bhat, MD,‡ James W. Long, MD, PHD,§ Douglas A. Horstmanshof, MD,§ Robert L. Kormos, MD,|| Jeffrey J. Teuteberg, MD,|| Mark S. Slaughter, MD,¶ Emma J. Birks, MD,¶ David J. Farrar, PHD,# Soon J. Park, MD,† for the HeartMate II Clinical Investigators

New York, New York; Rochester, Minnesota; Oak Lawn, Illinois; Oklahoma City, Oklahoma; Pittsburgh, Pennsylvania; Louisville, Kentucky; and Pleasanton, California

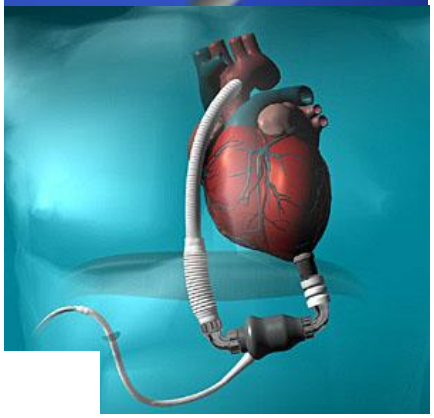
Přežívání pacientů v indikaci permanentní terapie



Technologické inovace MSP

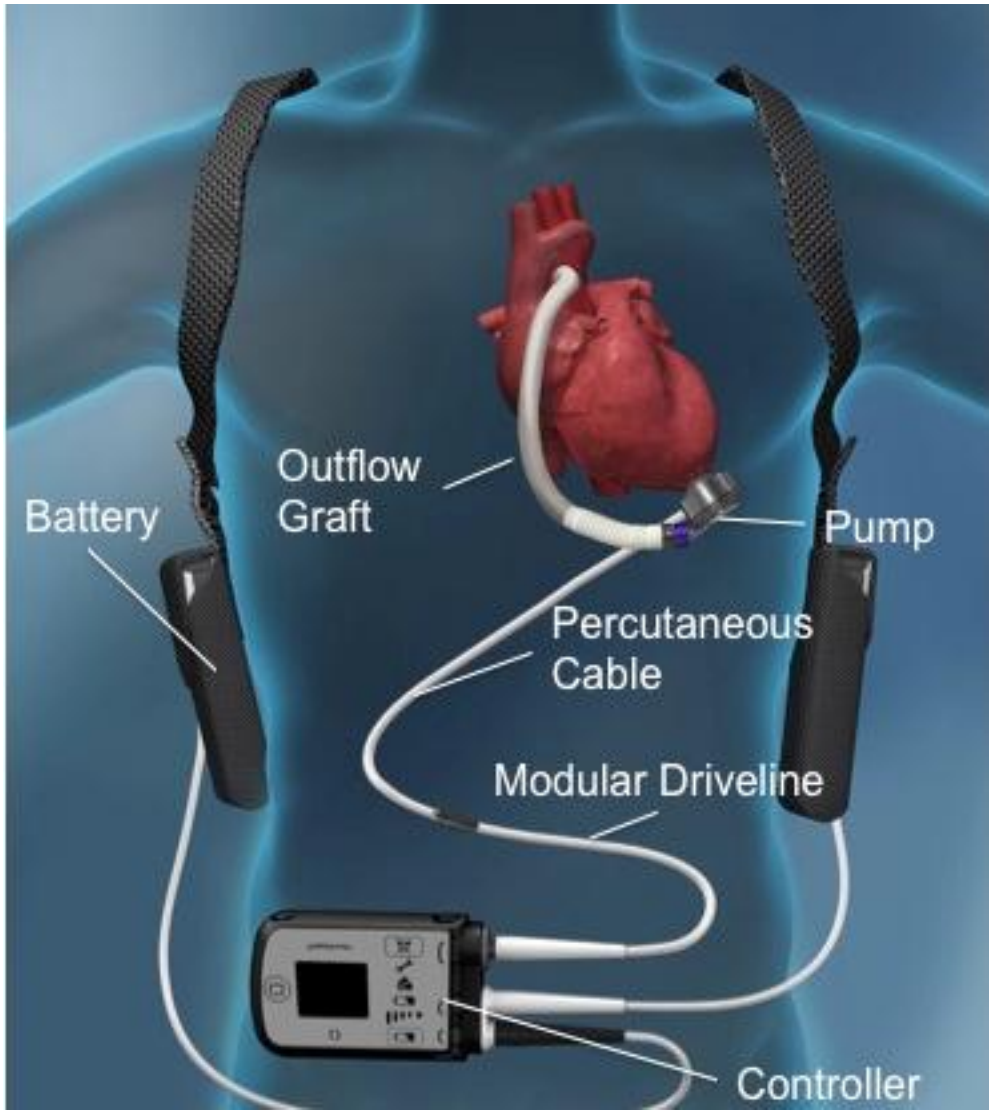
- **Pulsatilní pumpy (1. generace)**
  - Thoratec PVAD
  - HeartMate I
  - Novacor

- **Axiální pumpy (2. generace)**
  - HeartMate II
  - Jarvik 2000
  - MicroMed DeBakey



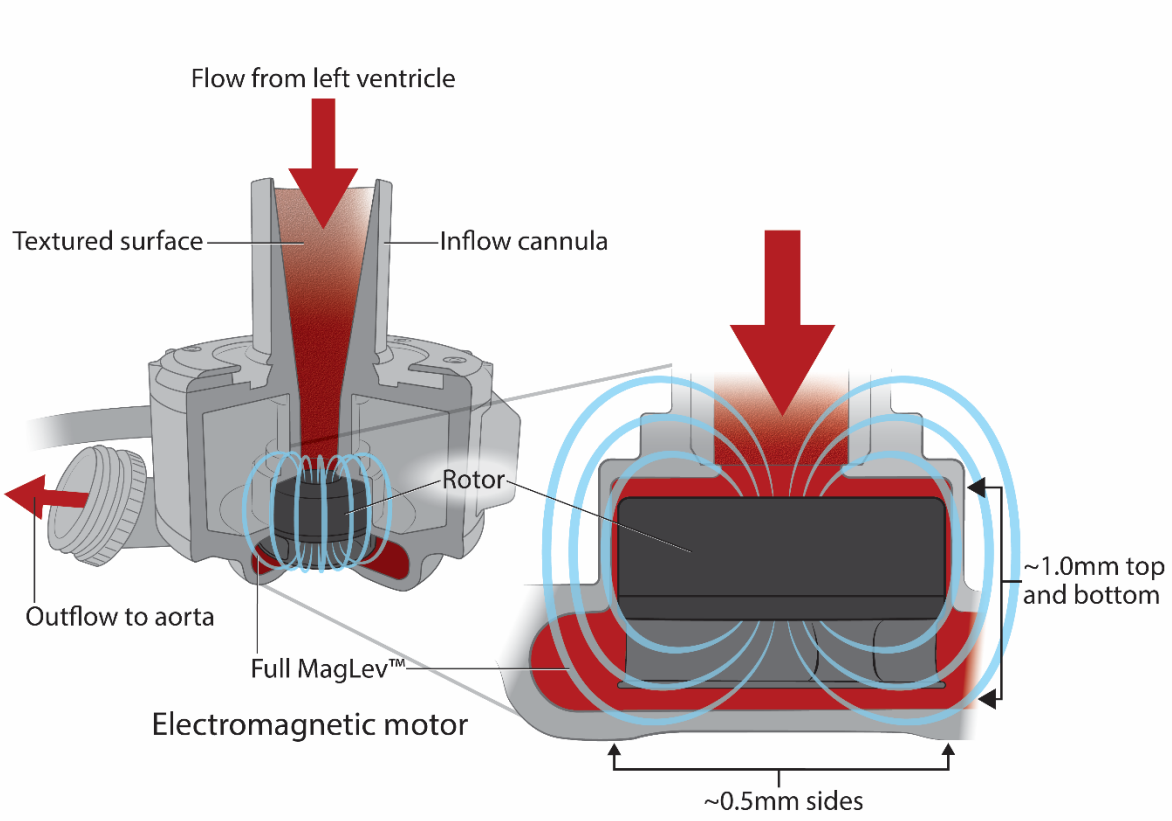
- **Centrifugální pumpy (3. generace)**
  - **HeartWare HVAD**
  - **HeartMate 3**

HeartMate 3


Outflow
Graft
Battery
Pump
Percutaneous
Cable
Modular Driveline
Controller

Magnetická levitace rotoru

HeartMate 3



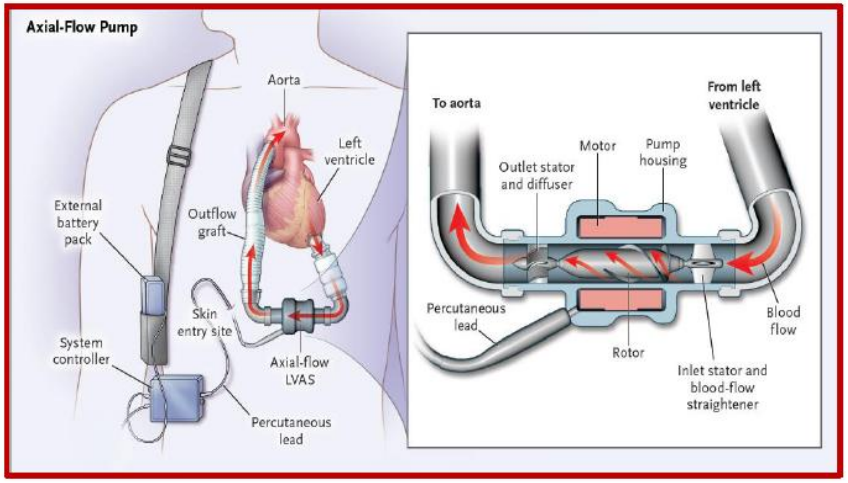
Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3) – Long Term Outcomes

Mandeep R. Mehra, MD, Daniel J. Goldstein, MD, Nir Uriel, MD, Joseph C. Cleveland, Jr., MD,
National Principal Investigators, on behalf of the MOMENTUM 3 Investigators

MOMENTUM 3

Background

- **Continuous-flow Left Ventricular Assist Systems (LVAS) improve survival and quality of life in patients with advanced heart failure refractory to medical therapy[1]**



The HeartMate II LVAS is a mechanical bearing axial continuous-flow blood pump;
An LVAS approved for *both* Bridge-To-Transplant (BTT) and Destination Therapy (DT) patients

MOMENTUM 3

[1]Slaughter et al. Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device. *N Engl J Med*. 2009;361(23):2241-2251.

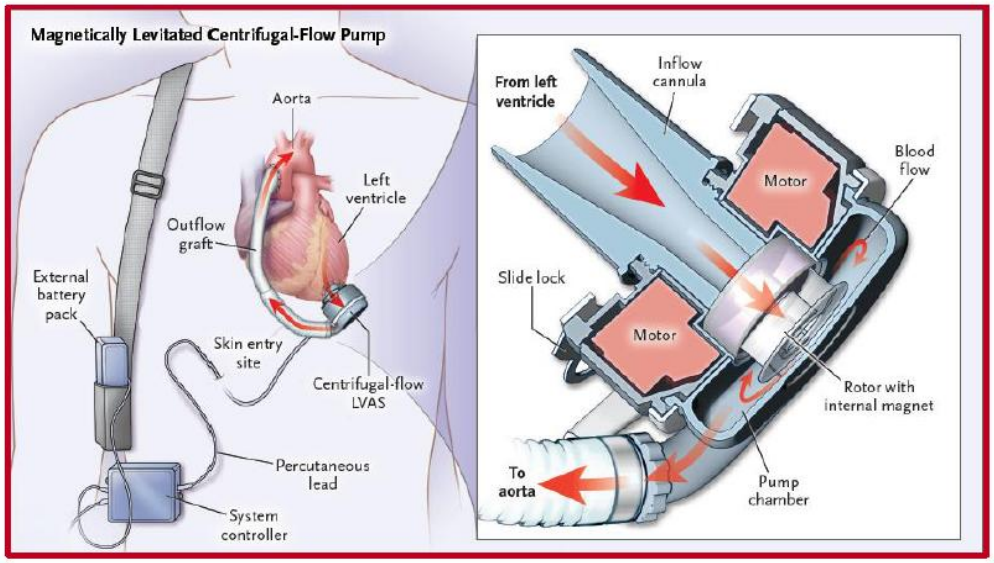
Background

- LVAS, such as the HeartMate II, are associated with significant risk of pump thrombosis requiring pump exchange, limiting long-term durability

- Other major adverse events of concern with LVAS devices include stroke, bleeding and device related infection[1]

[1]Slaughter et al. Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device. *N Engl J Med*. 2009;361(23):2241-2251.

HeartMate 3 LVAS



- **Wide** blood-flow passages to reduce shear stress
- **Frictionless** with absence of mechanical bearings
- **Intrinsic Pulse** designed to reduce stasis and avert thrombosis

MOMENTUM 3

Mehra et al. A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. *N Engl J Med* 2017;376(5):440-50.
Bourque et al. Design Rationale and Preclinical Evaluation of the HeartMate 3 Left Ventricular Assist System for Hemocompatibility. *ASAIO J* 2016;62(4):375-83

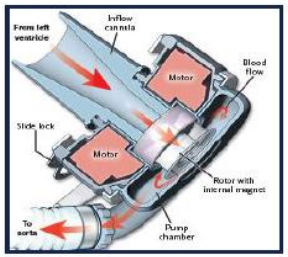
MOMENTUM 3 Target Population

- **Patients with advanced heart failure and severe limitations (NYHA IIIB or IV), refractory to guideline-mandated medical management** and *deemed as necessary candidates for left ventricular assist device implantation*, irrespective of the intended goal of pump support (BTT or DT)

- **Key exclusion criteria** included planned biventricular support, irreversible end-organ dysfunction, or active infection

Heatley et al. Clinical trial design and rationale of the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 (MOMENTUM 3) investigational device exemption clinical study protocol. *J Heart Lung Transplant*. 2016;35(4):528-36.

Study Design



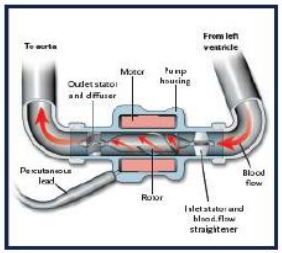
Patient meets MOMENTUM 3 eligibility criteria?

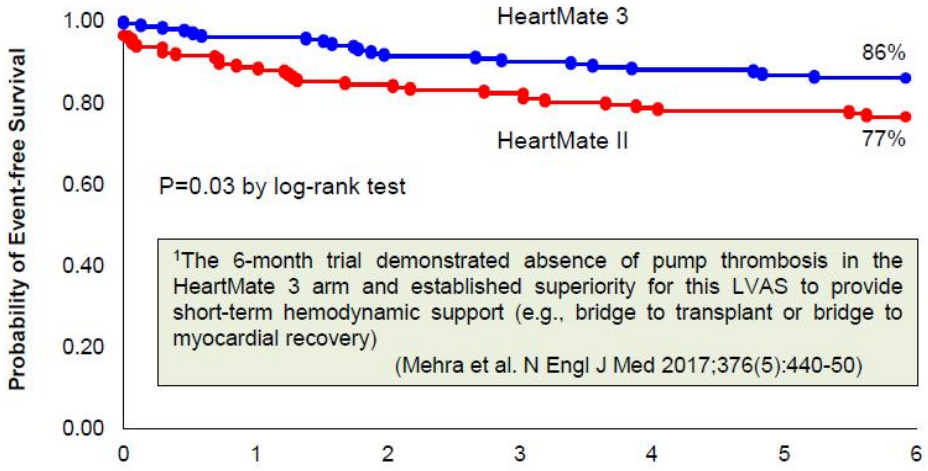
↓

Randomization 1:1

↓

Short Term (ST) Cohort[1]
N=294
6-month follow-up





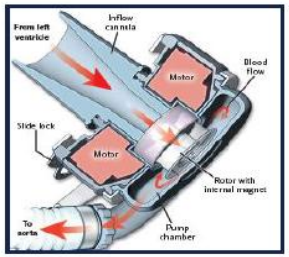
[1]The 6-month trial demonstrated absence of pump thrombosis in the HeartMate 3 arm and established superiority for this LVAS to provide short-term hemodynamic support (e.g., bridge to transplant or bridge to myocardial recovery)

(Mehra et al. N Engl J Med 2017;376(5):440-50)

No. at Risk							
HeartMate 3	152	146	138	135	130	128	127
HeartMate II	142	125	119	116	110	106	103

MOMENTUM 3

Study Design



Patient meets MOMENTUM 3 eligibility criteria?

Randomization 1:1

Short Term (ST) Cohort[1]
N=294
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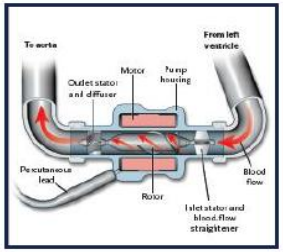


Additional 72 patients enrolled

Long Term (LT) Cohort
N=366
2-year follow-up

Full Cohort
N=1028
2-year follow-up

Intent-to-Treat (ITT) Population
N=366

HeartMate 3 Pump
N=190

HeartMate II Pump
N=176

Withdrawn before implant
N = 1
Death: 1

Withdrawn before implant
N = 4
No LVAD implant: 1
Withdrawal of consent: 1
Transplant: 1
Implanted with non-study LVAD: 1

Per Protocol Population
N=361

Implanted with HeartMate 3
N=189

Implanted with HeartMate II
N=172

MOMENTUM 3

[1]Mehra et al. A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. *N Engl J Med* 2017;376(5):440-50.

Study Aim and Primary Endpoint

Study Aim

- **The long-term (2-year) study** is designed to ascertain success to optimally support patients who wait for extended periods for heart transplantation or are ineligible for heart transplantation (e.g., destination therapy)

Primary Endpoint

- **Survival at 2 years free of disabling stroke (>3 mRS) or reoperation to replace or remove a malfunctioning device**

Baseline Characteristics - 1

Characteristic	HeartMate 3 (n=190)	HeartMate II (n=176)
Age - years		
Mean	61 ± 12	59 ± 12
Median (range)	65 (19-81)	61 (24-84)
Male sex - no. (%)	150 (78.9)	143 (81.2)
Race or ethnic group - no. (%)		
White	127 (66.8)	131 (74.4)
Black or African American	52 (27.4)	32 (18.2)
Other*	11 (5.8)	13 (7.4)
Body surface area - m^2	2.1 ± 0.3	2.1 ± 0.3
Ischemic cause of heart failure - no. (%)	80 (42.1)	88 (50.0)
History of atrial fibrillation - no. (%)	81 (42.6)	83 (47.2)
History of stroke - no. (%)	16 (8.4)	20 (11.4)
Previous cardiac surgical procedure - no. (%)		
Coronary-artery bypass	44 (23.2)	41 (23.3)
History of valve replacement or repair	18 (9.5)	7 (4.0)
Concomitant medication or intervention - no (%)		
Intravenous inotropic agents	167 (87.9)	152 (86.4)
Diuretic	166 (87.4)	165 (93.8)
ACE inhibitor or Angiotensin II-receptor antagonist	58 (30.5)	66 (37.5)
Beta-blocker	111 (58.4)	98 (55.7)
CRT/ CRT-D	75 (39.5)	62 (35.2)
ICD/ CRT-D	122 (64.2)	123 (69.9)
IABP	25 (13.2)	26 (14.8)

There were significant differences between groups for history of valve replacement or repair (P=0.04) and diuretic use (P=0.05).
*Includes Asian, Native Hawaiian or Pacific Islanders, and other. CRT(-D) denotes cardiac resynchronization therapy with or without defibrillator; ICD, implantable cardioverter-defibrillator; IABP, intraaortic balloon pump.

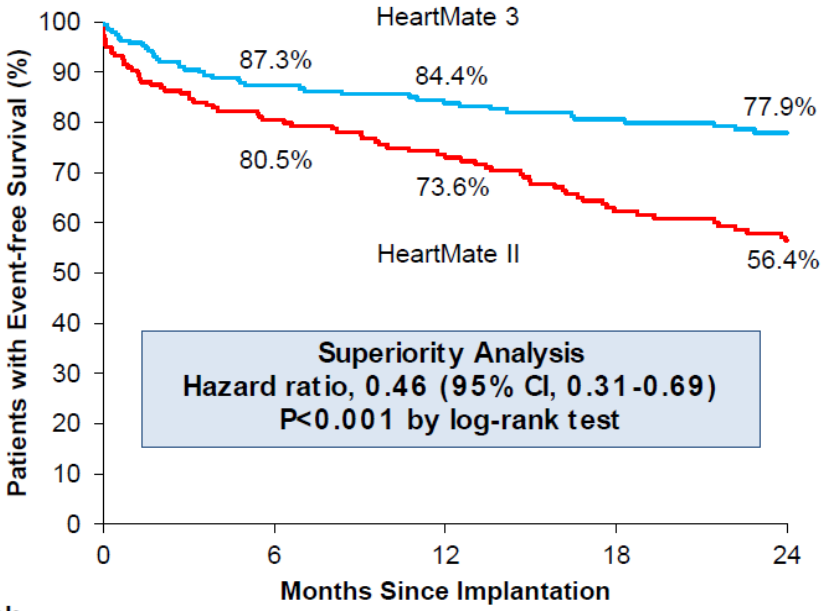
Baseline Characteristics - 2

Characteristic	HeartMate 3 (n=190)	HeartMate II (n=176)
Left ventricular ejection fraction - %	17.2 ± 4.9	17.4 ± 5.0
Arterial blood pressure - mmHg		
Systolic	110.2 ± 15.6	106.3 ± 12.9
Diastolic	67.0 ± 10.8	65.4 ± 10.4
Mean arterial pressure - mmHg	79.5 ± 10.1	78.4 ± 9.8
PCWP - mmHg	23.9 ± 8.6	22.2 ± 9.2
Cardiac index - liters/ min/ m^2 of body-surface area	2.0 ± 0.5	2.0 ± 0.7
PVR - Wood units	3.2 ± 1.7	3.0 ± 1.6
Right atrial pressure - mmHg	11.0 ± 6.5	10.5 ± 6.7
Serum sodium - mmol/ liter	135.5 ± 3.8	135.2 ± 4.1
Serum creatinine - mg/ dl	1.4 ± 0.4	1.4 ± 0.4
INTERMACS profile – no (%)		
1	1 (0.5)	4 (2.3)
2	61 (32.1)	51 (29.0)
3	101 (53.2)	91 (51.7)
4	24 (12.6)	28 (15.9)
5-7 or not provided	3 (1.6)*	2 (1.1)
Intended goal of pump support – no (%)		
Bridge to transplantation (BTT)	49 (25.8)	42 (23.9)
Bridge to candidacy for transplantation	30 (15.8)	28 (15.9)
Destination therapy (DT)	111 (58.4)	106 (60.2)

*One patient died before assessment was performed. There were only significant differences between groups for systolic blood pressure (P=0.01).
PCWP denotes pulmonary-capillary wedge pressure; PVR, pulmonary vascular resistance; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

Primary End Point Analysis (ITT)

Survival at 2 years free of disabling stroke (>3 mRS) or reoperation to replace or remove a malfunctioning device



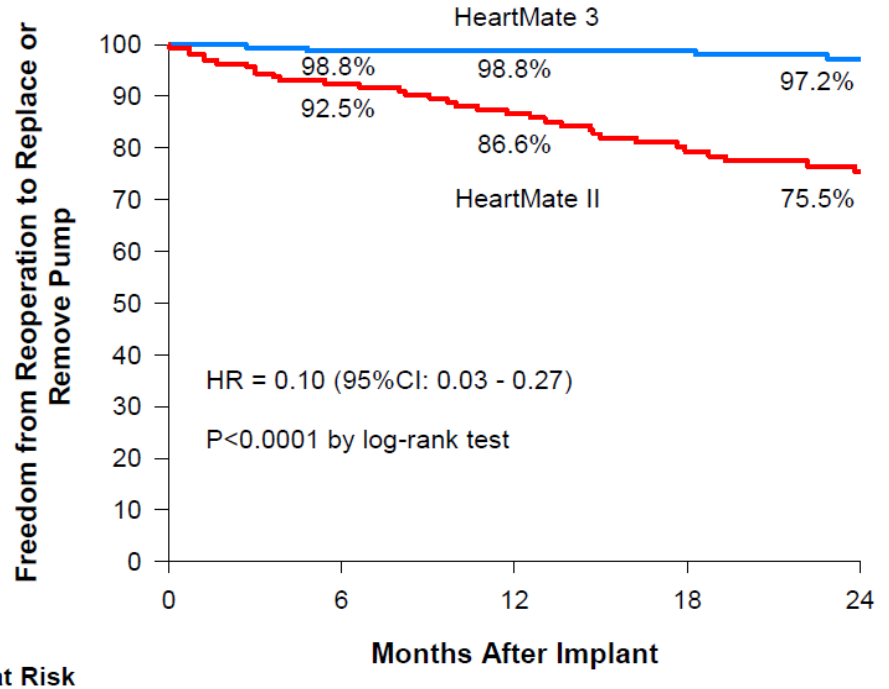
No. at Risk					
HeartMate 3	190	161	141	122	111
HeartMate II	176	134	114	90	75

MOMENTUM 3

mRS denotes modified Rankin Score; CI, confidence interval

Primary Endpoint Component 3

Freedom from Reoperation to Replace or Remove Pump



No. at Risk					
HeartMate 3	189	164	145	126	114
HeartMate II	172	135	114	90	76

- There was a **ten-fold** difference in the reoperation rate between HeartMate II and HeartMate 3
- HeartMate 3 reoperations were due to infection (1), electrical fault (1), and outflow-graft twist (1)
- **2/3rd** of HeartMate II reoperations were due to "pump thrombosis or severe hemolysis"

MOMENTUM 3

HR denotes hazard ratio, CI, confidence interval

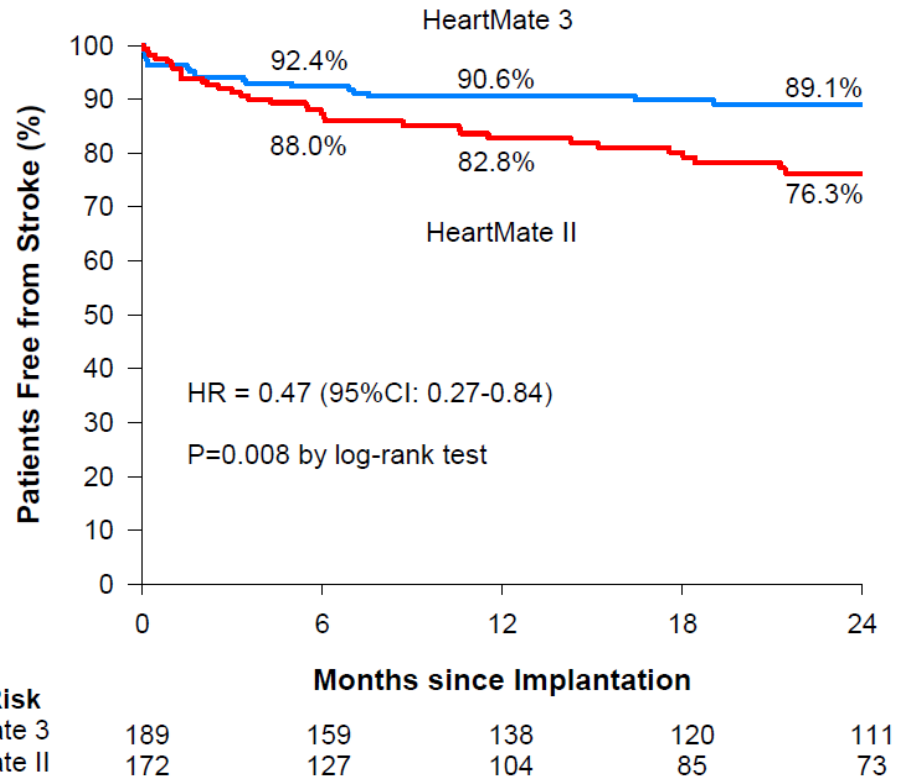
Key Adverse Events

Pump Thrombosis, Neurological Events, Bleeding

	HeartMate 3 (n=189)		HeartMate II (n=172)			
	n (%)	no. of Events	n (%)	no. of Events	HR (95% CI)	P Value*
Suspected or confirmed pump thrombosis	2 (1.1)	2	27 (15.7)	33	0.06 (0.01-0.26)	<0.001
Resulting in reoperation	0 (0)	0	21 (12.2)	25	NA	<0.001
Any stroke	19 (10.1)	22	33 (19.2)	43	0.47 (0.27-0.84)	0.02
Ischemic stroke	12 (6.3)	14	23 (13.4)	26	0.44 (0.22-0.88)	0.03
Hemorrhagic stroke	8 (4.2)	8	16 (9.3)	17	0.42 (0.18-0.98)	0.06
Other neurologic event†	22 (11.6)	25	15 (8.7)	16	1.27 (0.66-2.45)	0.39
Bleeding	81 (42.9)	187	90 (52.3)	206	0.71 (0.53-0.96)	0.07
Bleeding that led to surgery	23 (12.2)	29	30 (17.4)	34	0.66 (0.38-1.13)	0.18
Gastrointestinal bleeding	51 (27.0)	107	47 (27.3)	100	0.92 (0.62-1.37)	1.00

HR denotes hazard ratio; CI, confidence interval
*P values were calculated with the use of Fisher's exact test. †Includes transient ischemic attacks and neurologic events other than stroke

Key Adverse Events
Stroke

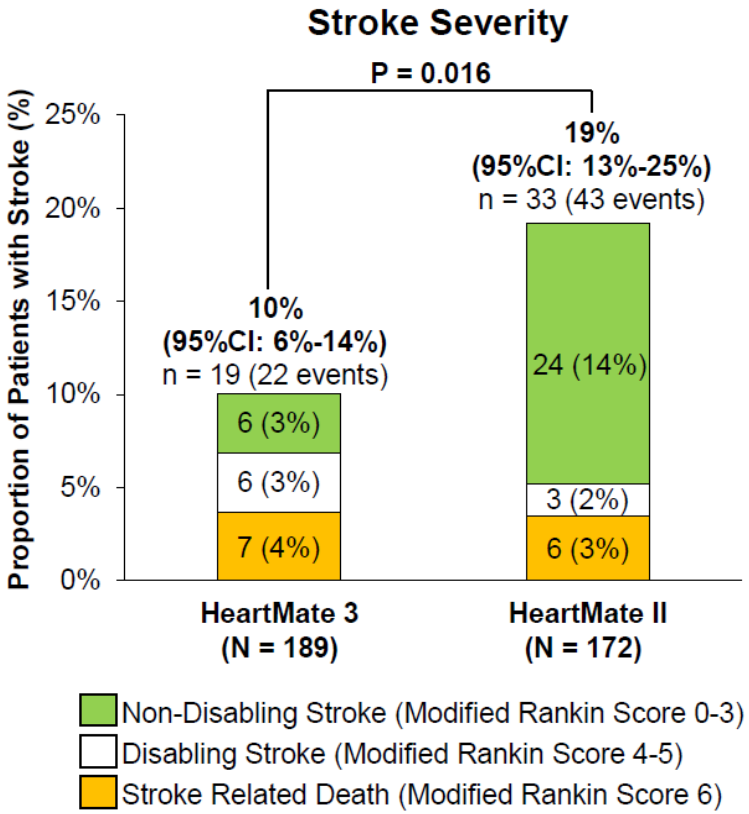


No. at Risk					
HeartMate 3	189	159	138	120	111
HeartMate II	172	127	104	85	73

MOMENTUM 3

HR denotes hazard ratio; CI, confidence interval

Key Adverse Events
Stroke



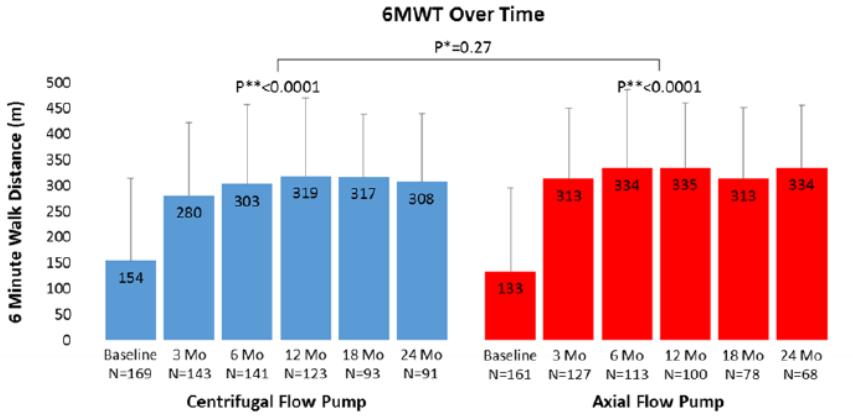
Two HeartMate 3 subjects and 9 HeartMate II subjects had >1 stroke. The score for the most severe stoke is shown. 1.6% of HeartMate 3 subjects (n = 3) and 5.2% of HeartMate II subjects (n = 9) had a modified Rankin score of 0 at 60 days post-stroke. CI denotes confidence interval.

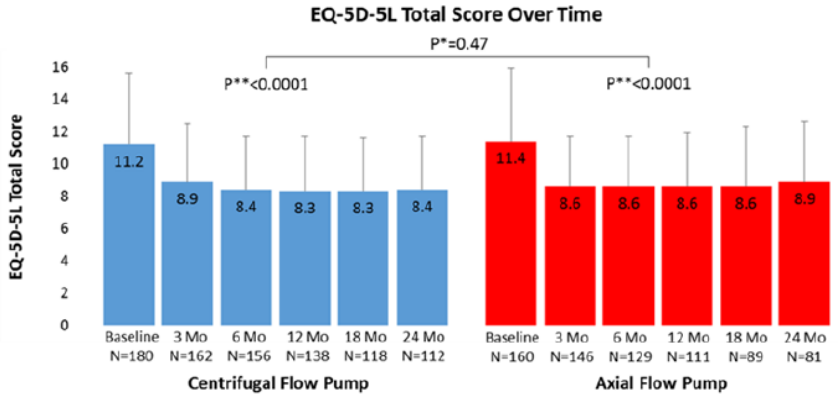
Other Adverse Events

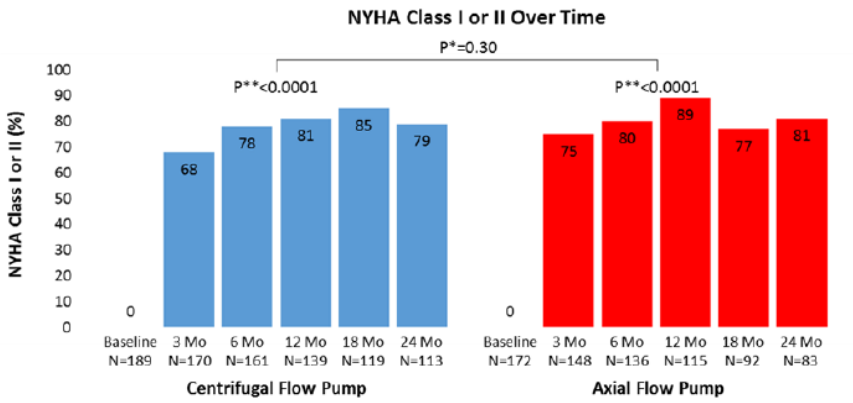
	HeartMate 3 (n=189)		HeartMate II (n=172)			
	n (%)	no. of Events	n (%)	no. of Events	HR (95% CI)	P Value
Sepsis	26 (13.8)	37	24 (14.0)	28	0.95 (0.55-1.66)	1.00
LVAS drive-line infection	45 (23.8)	68	34 (19.8)	59	1.15 (0.73-1.79)	0.37
Local non-LVAS infection	70 (37.0)	108	60 (34.9)	114	1.00 (0.71-1.42)	0.74
Right heart failure	60 (31.7)	73	48 (27.9)	53	1.12 (0.77-1.64)	0.49
Managed with RVAS	6 (3.2)	6	8 (4.7)	8	0.67 (0.23-1.94)	0.59
Cardiac arrhythmia	71 (37.6)	108	70 (40.7)	105	0.88 (0.63-1.23)	0.59
Ventricular	45 (23.8)	67	39 (22.7)	64	1.04 (0.67-1.59)	0.80
Supraventricular	33 (17.5)	40	36 (20.9)	37	0.79 (0.49-1.26)	0.42
Respiratory failure	45 (23.8)	61	39 (22.7)	46	1.04 (0.68-1.59)	0.80
Renal Dysfunction	25 (13.2)	29	18 (10.5)	18	1.23 (0.67-2.25)	0.52
Hepatic dysfunction	8 (4.2)	8	7 (4.1)	7	0.98 (0.36-2.71)	1.00

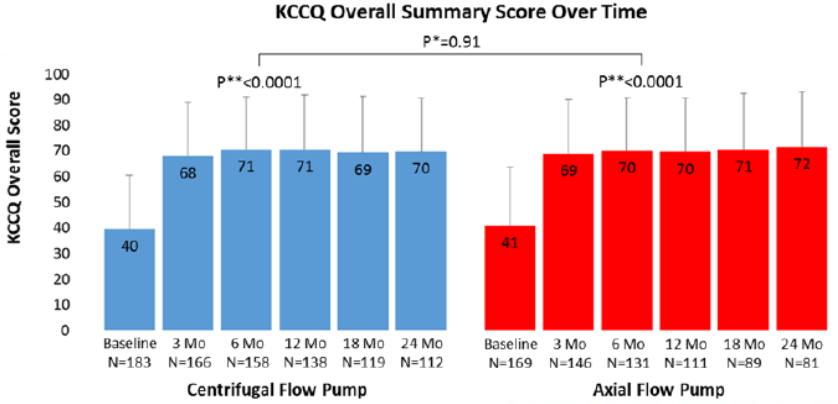
LVAS denotes Left Ventricular Assist System, RVAD, Right Ventricular Assist Device, HR, Hazard Ratio, and CI, confidence interval.

Functional Status and Quality of Life









*P-value between treatment arms over time
**P-value for treatment over time

MOMENTUM 3

Conclusions

- The HeartMate 3 LVAS is **clinically superior** when compared to the HeartMate II axial-flow pump, at 2-years

- These benefits were primarily driven by a **lower reoperation rate** in the HeartMate 3 arm
  - largely due to excess device malfunctions resulting from **pump thrombosis** in the HeartMate II LVAS

- Importantly, we observed a markedly **lower rate of stroke** with the HeartMate 3 LVAS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two-Year Outcomes of a Magnetically Levitated Cardiac Pump in Heart Failure

M.R. Mehra, D.J. Goldstein, N. Uriel, J.C. Cleveland, Jr., M. Yuzefpolskaya, C. Salerno, M.N. Walsh, C.A. Milano, C.B. Patel, G.A. Ewald, A. Itoh, D. Dean, A. Krishnamoorthy, W.G. Cotts, A.J. Tatooles, U.P. Jorde, B.A. Bruckner, J.D. Estep, V. Jeevanandam, G. Sayer, D. Horstmanshof, J.W. Long, S. Gulati, E.R. Skipper, J.B. O'Connell, G. Heatley, P. Sood, and Y. Naka, for the MOMENTUM 3 Investigators*

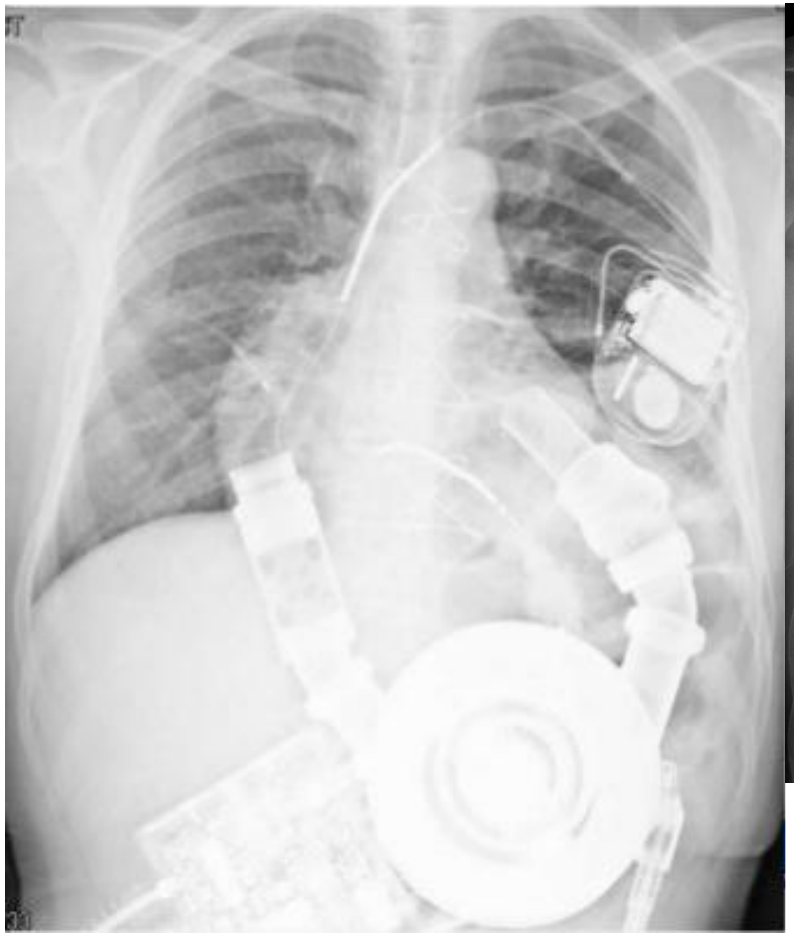
Available now on www.nejm.org

Závěry

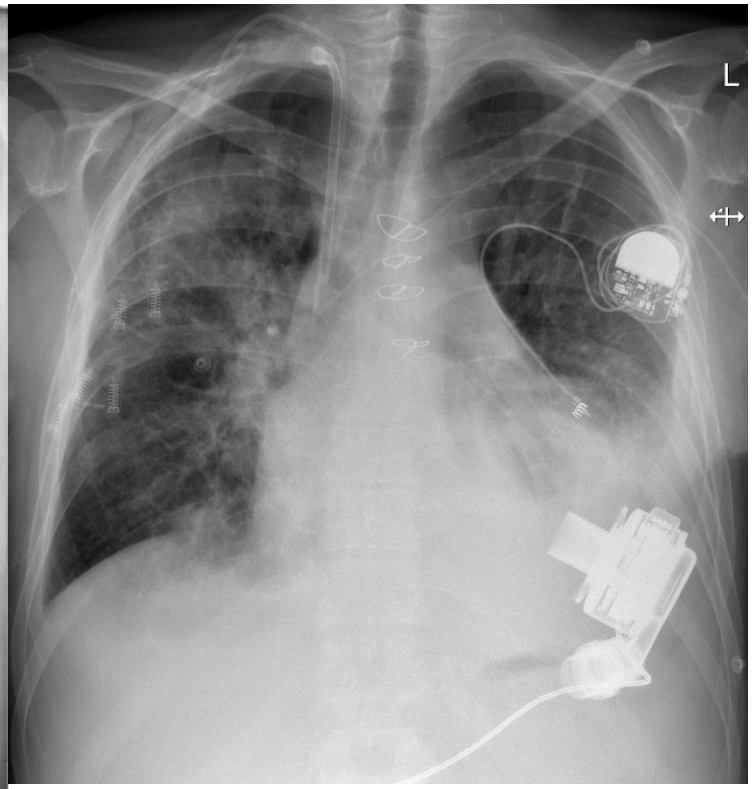
- Nedílná součást programu transplantace srdce
- Alternativa pro nemocné za hranicí indikace k transplantaci
- Technologické inovace snižují výskyt klíčových komplikací
- Včasná komplexní indikace

Děkuji za pozornost

HeartMate XVE



HeartMate 3



Blízká budoucnost

Journal of the American College of Cardiology

Published by Elsevier Inc.

EDITORIAL COMMENT

The Odyssey of Chronic Cardiac Mechanical Support*

Stavros G. [illegible]
Salt Lake C

Table 1 Future Targets Critical for Progress of Long-Term MCS

Technological advances: smaller device size, wireless energy transfer (infections, strokes, and/or quality of life), flow autoregulation
Patient selection: multidisciplinary team approach, benefit-to-risk ratio research
Patient management and/or understanding of biological consequences of MCS: end organs, hematological system, immune system, skeletal muscles, myocardium/bridge-to-recovery research
Cost reduction: device cost, complications, patient support system, cost-benefit research

MCS = mechanical circulatory support.

Patient management

A Safety and Feasibility Study of Low-intensity Anticoagulation With HeartMate 3 LVAS: A Single Center Prospective Controlled Study (**MAGENTUM 1**)

Watch-only System – Wireless Technology