

# INNOVATION IN THORACIC “TRANSPLANTATION”

NVIC Intensivistendagen 2023

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Head Department of Cardiothoracic Surgery Utrecht  
President Dutch Transplant Society

# DISCLOSURE

|   |  |
|---|--|
| Geen (potentiële) belangenverstremgeling  |  |
| <b>Voor bijeenkomst mogelijk relevante relaties</b>   | <b>Bedrijfsnamen</b>   |
| <ul style="list-style-type: none"><li>• Sponsoring of onderzoeksgeld</li><li>• Honorarium of andere (financiële) vergoeding</li></ul> | <ul style="list-style-type: none"><li>• XVIVO Perfusion XB</li><li>• XVIVO Perfusion XB</li><li>• Abbott</li><li>• Astellas Pharma</li><li>• Chiesi Pharma</li></ul> |

# SURGICAL TREATMENT OF....

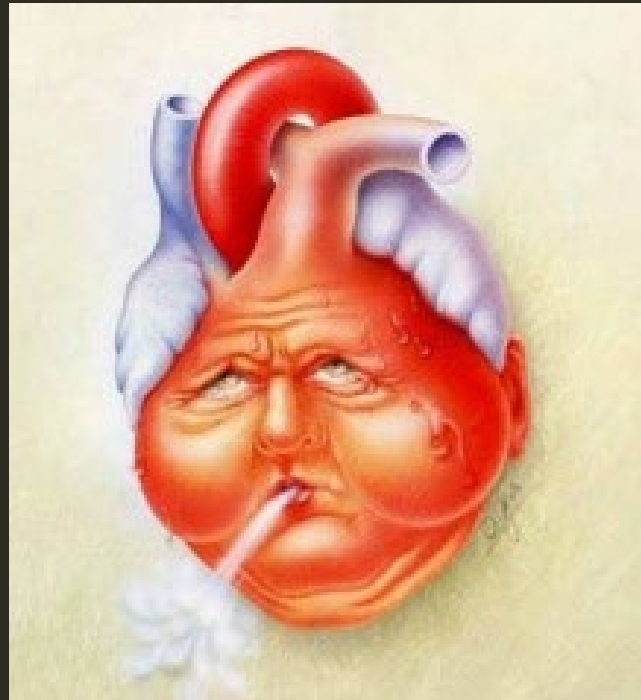
**Advanced lung failure**



**Advanced heart failure**



# Advanced heart failure



# CLINICAL PERSPECTIVE **HEART FAILURE EPIDEMIC** THE NETHERLANDS

~250.000 patients with **diagnosed** heart failure

~250.000 patients with **undiagnosed** heart failure

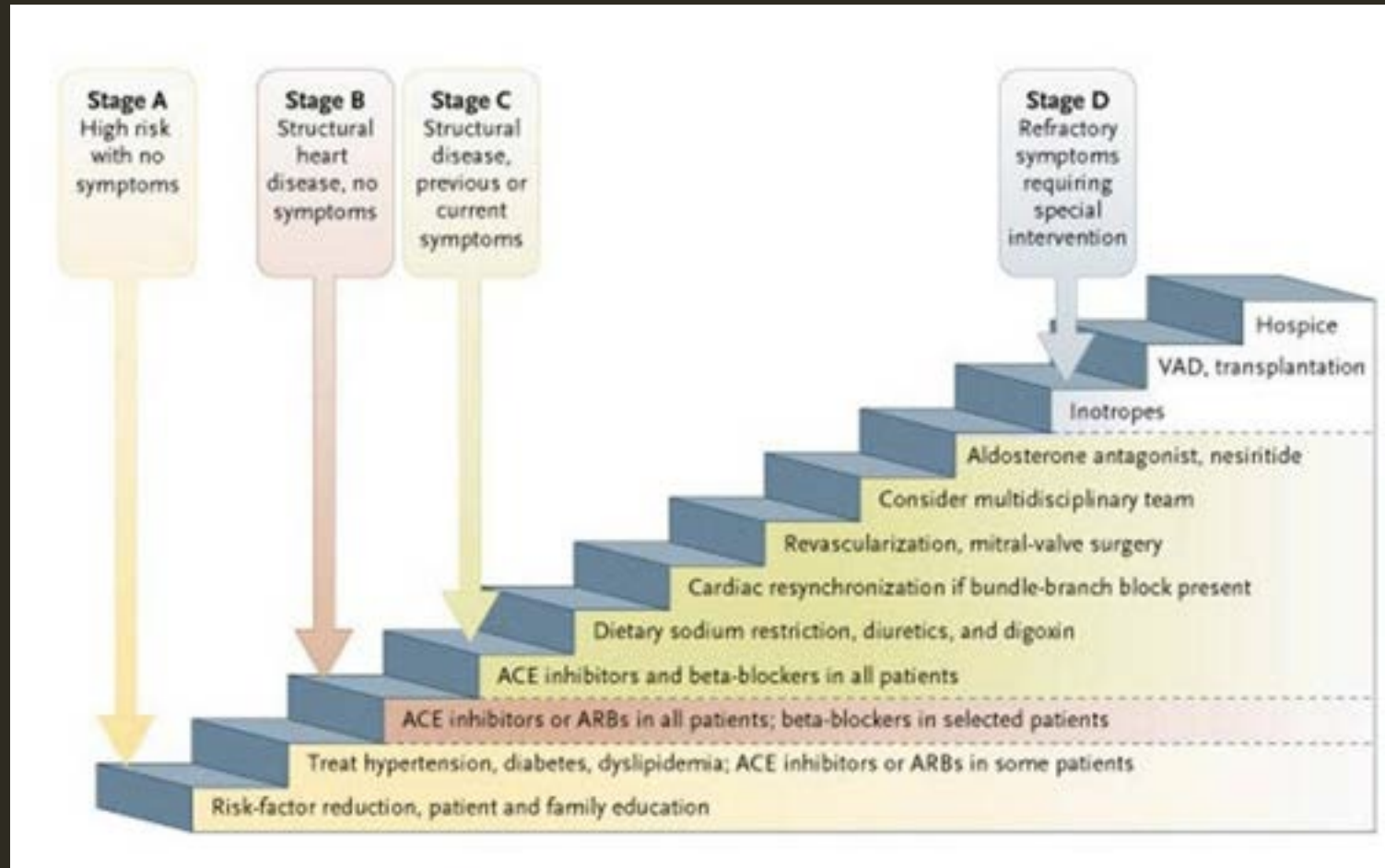
~10% **advanced** heart failure (50.000 patients)



# ADVANCED HEART FAILURE

Definition: Refractory symptoms requiring special intervention

1 year mortality: 25-75%



Circulation

**AHA/ACC/HFSA CLINICAL PRACTICE GUIDELINE**

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

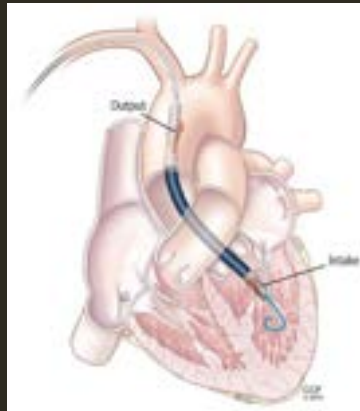
# ADVANCED HEART FAILURE TREATMENT OPTIONS

Heart Transplantation



Brain death Htx  
Circulatory death Htx  
Xenotransplantation

Short term MCS



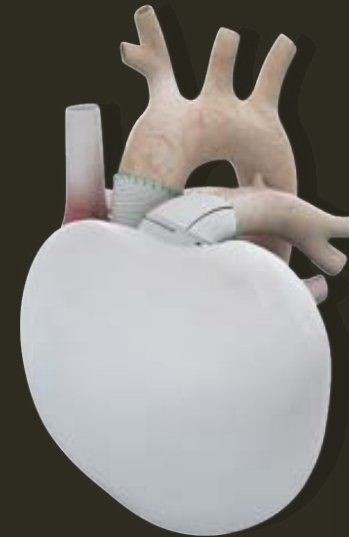
Impella  
ECLS

Long term MCS



LVAD  
• Destination therapy  
• Bridge to transplant

Total artificial heart



CARMAT  
• Destination therapy  
• Bridge to transplant  
candidacy

Regeneration



Experimental  
Pre clinical

# ADVANCED HEART FAILURE TREATMENT OPTIONS

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# CHALLENGES ORGAN TRANSPLANTATION



Minority accepted for the  
transplant waiting list

**0,28%** patients with  
advanced heart failure



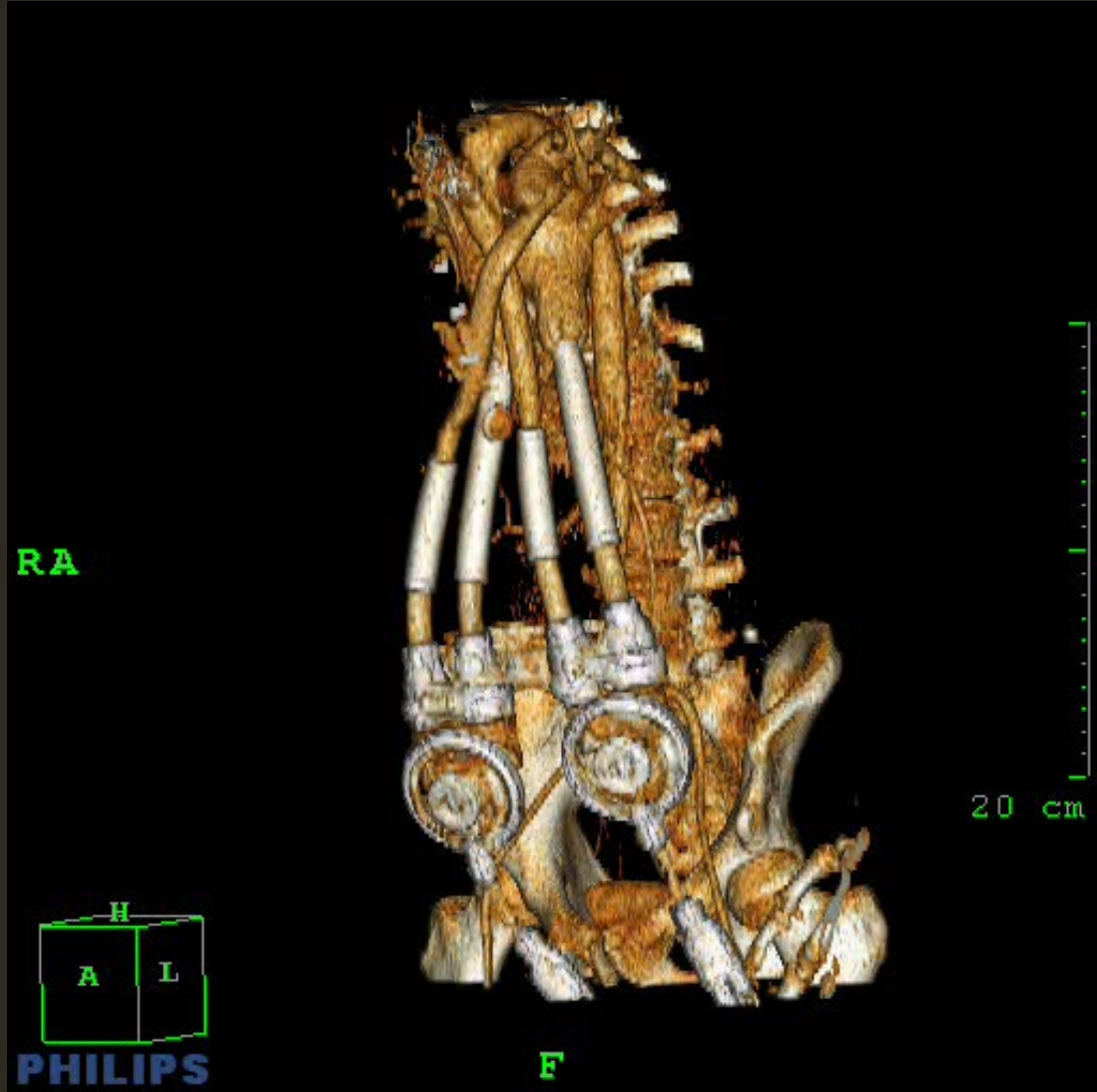
Long waiting times



Relatively high removal  
rates on waiting list

# TRANSPLANT WAITING LIST

# VENTRICULAR ASSIST DEVICE



# INNOVATION LVAD & TOTAL ARTIFICIAL HEART

**1995**



**Paracorporeal  
(external) PVAD  
Pulsatile**

**2008**



**Heartmate II  
Continuous & Axial**

**2010**



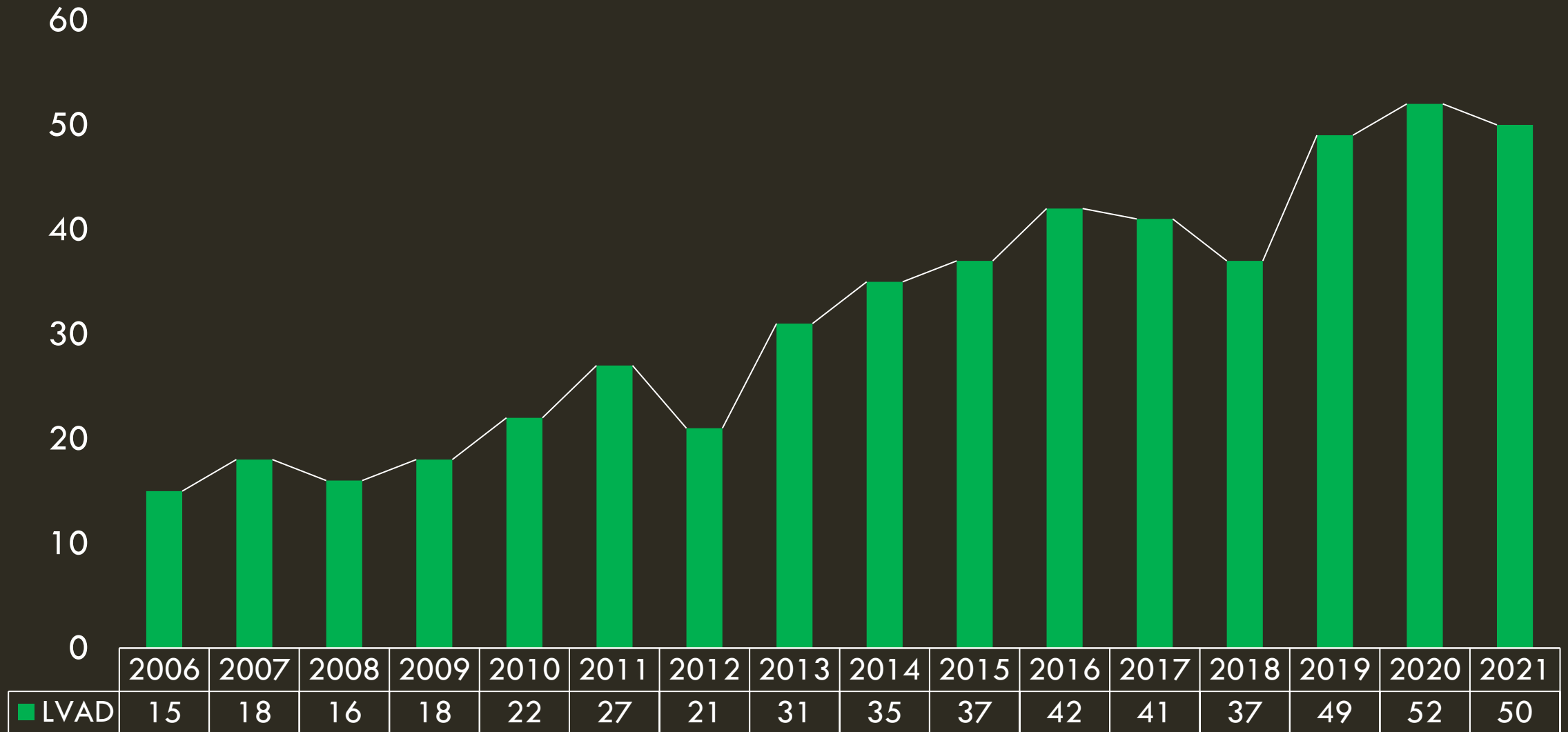
**HVAD  
Continuous and  
Centrifugal**

**2015**



**Heartmate III  
Continuous and  
Centrifugal**

# NUMBER OF LVAD IMPLANTATIONS UTRECHT (START 1993)



**Advanced heart failure stage D**

**Mechanical circulatory support**

**HTX**



Direct transplantation (primo)



LVAD bridge to transplantation



LVAD destination therapy



TAH bridge to transplantation



TAH destination therapy

Advanced heart failure stage D

Mechanical circulatory support

HTX



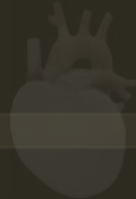
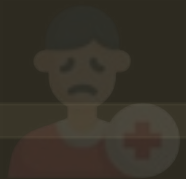
Direct transplantation (primo)



LVAD bridge to transplantation



LVAD destination therapy



TAH bridge to transplantation



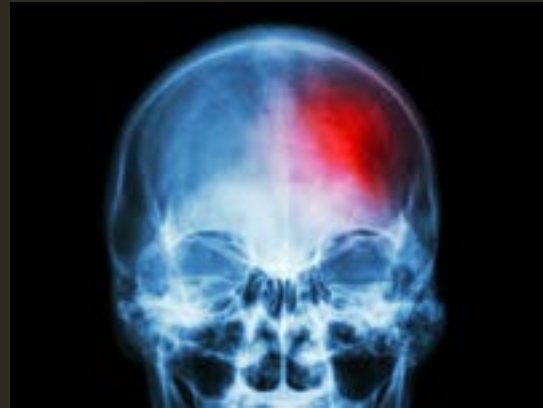
TAH destination therapy

# LVAD & ARTIFICIAL HEART RELATED COMPLICATIONS

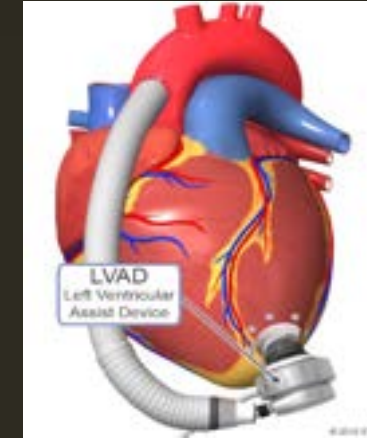
**Driveline infection**



**Stroke**



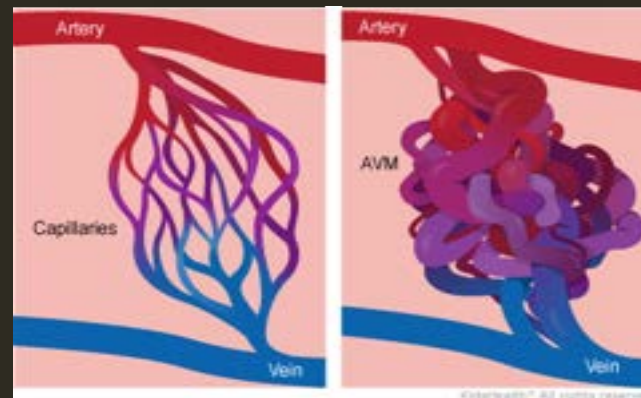
**No support of the right ventricle**



**Pump thrombosis**



**AV malformation**



**Technical failure**



# TRANSPLANT WAITING LIST

# TRANSPLANT WAITING LIST



Significant shortage of organ donors

# HOW TO INCREASE NUMBER OF DONORS

Change donor law

DCD program

Increase acceptance rate

- Donor management
- Machine Perfusion
- Go out to assess
- Liberal acceptance criteria



# HOW TO INCREASE NUMBER OF DONORS

Change donor law

DCD program

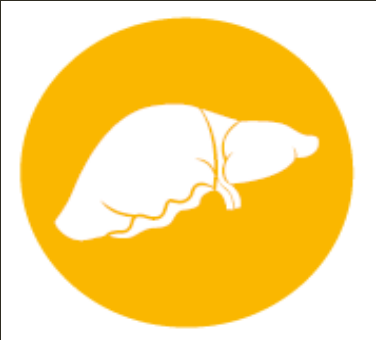
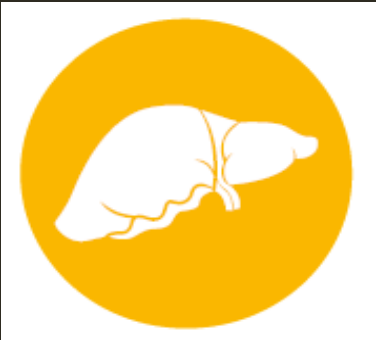
Increase acceptance rate

- Donor management
- Machine Perfusion
- Go out to assess
- Liberal acceptance criteria



**DBD = Donation after Brain Death**

**DCD = Donation after Circulatory Death**



# 03-12-1967 FIRST HEART TRANSPLANTATION: DCD DONOR!



*Fig. 1. Louis Washkansky, the first human-to-human heart transplant patient on 3 December 1967, seen here a few days after the operation. (Photo from the Heart of Cape Town Museum.)*



*Fig. 2. Christiaan Barnard.*

# DCD HEART DONATION CRITERIA

## Exclusion Absolute

- DCD donor type 1,2, or 4
- Previous cardiac surgery
- Previous midline sternotomy
- Known congenital heart disease
- Known coronary artery disease
- Myocardial infarction
- Insulin dependent DM
- Malignancy in the past 5 years (Except BCC)
- Melanoma in history
- Hepatitis B/C positive
- Secondary intracerebral tumours
- HIV
- Intracerebral lymphoma
- Creutzfeld Jacob
- TBC
- Donor weight <50 kg

## Exclusion relative

- Level above maximum inotropic score depending on epinephrine, dopamine or dobutamine infusion
- Norepinephrine > 0.3 ug/kg/min

## Inclusion

- None of the exclusion criteria
- DCD donor type 3
- Age < 58 years old
- Consent
- Normal TTE (TEE)/ECG
- Normal CAG/Coronary CT
- Expected death within 2 hours after WLST
- Donor weight > 50 kg
- Haematocrit donor > 0,30 l/l

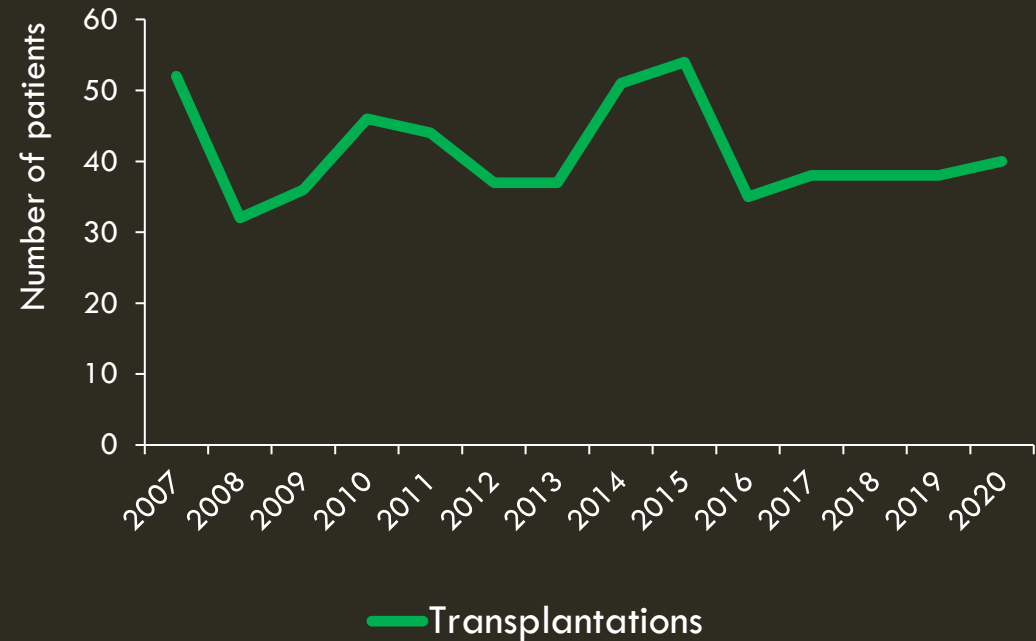
# DCD HEART DONATION DUTCH POTENTIAL

2013 t/m 2017 1006 DCDs

Exclusion criteria



201 potential donors in 5 years  
=  
40 donors per year



Waiting list mortality and the potential of donation after circulatory death heart transplantations in the Netherlands

S. Roest · S. E. Kafka genaamd Dengler · V. van Suylen · N. P. van der Kaaij · K. Damman · L. W. van Laake · J. A. Bekkers · M. Dallinghaus · M. E. Erasmus · O. C. Manintveld

x2

# DCD TRANSPLANTATION EUROTRANSPLANT REGION



DBD : DCD (2021)

Austria

96% : 4%

Belgium

57% : 43%

Croatia

Germany

Hungary

Luxembourg

The Netherlands

37% : 63%

Slovenia

# DCD organ procurement

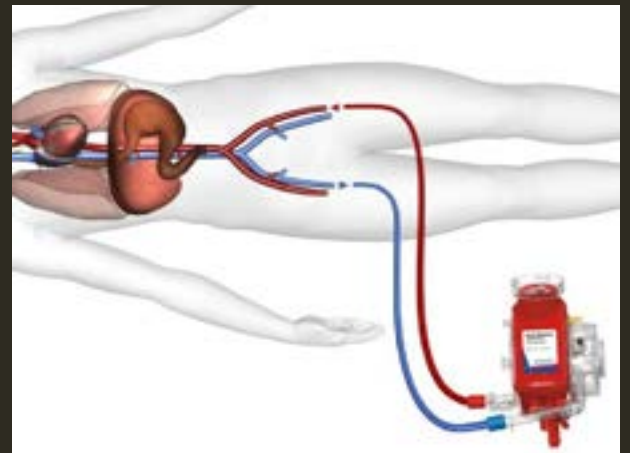
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Static Cold Storage  
(SCS)



Direct Procurement  
and Perfusion (DPP)



Normothermic Regional  
Perfusion (NRP)

# DCD organ procurement

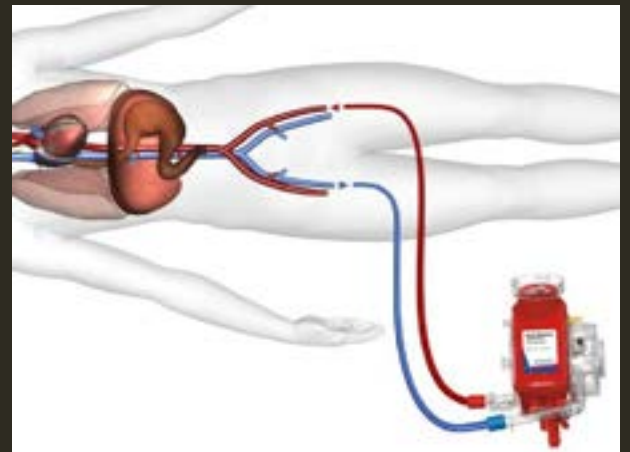
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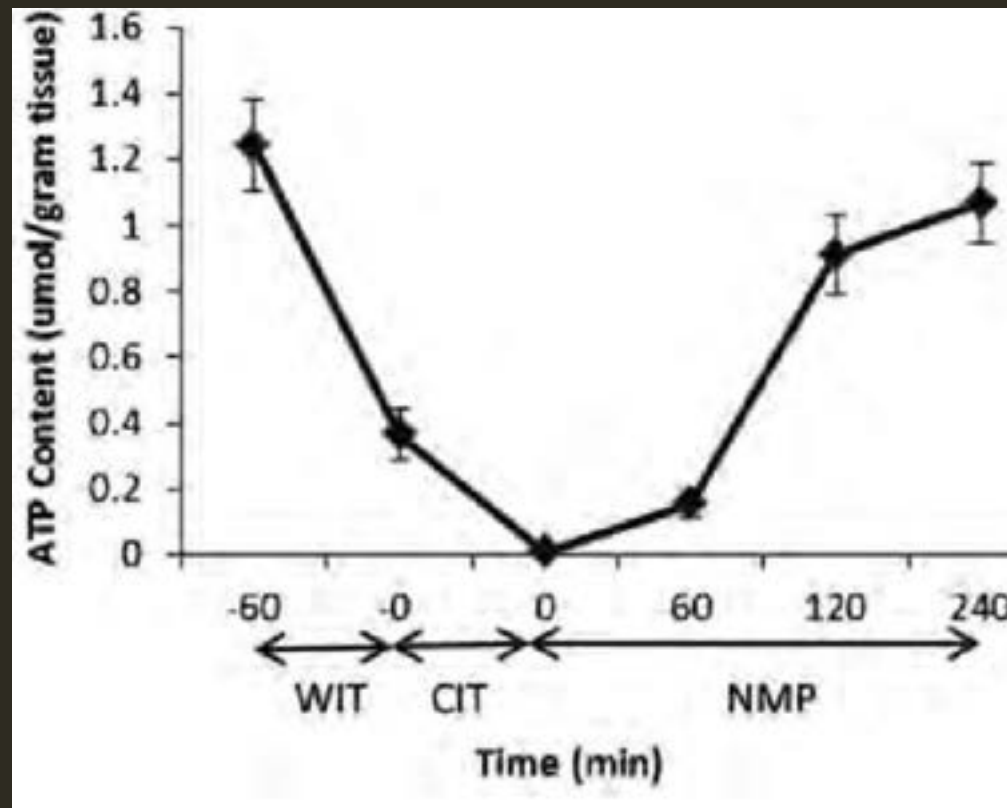
Static Cold Storage (SCS)



Direct Procurement and Perfusion (DPP)



Normothermic Regional Perfusion (NRP)



# DCD organ procurement

.....



Static Cold Storage  
(SCS)



Direct Procurement  
and Perfusion (DPP)



Normothermic Regional  
Perfusion (NRP)

# DCD DEAD DONOR RULE

PERSPECTIVE

THE DEAD DONOR RULE AND ORGAN TRANSPLANTATION

## The Dead Donor Rule and Organ Transplantation

Robert D. Truog, M.D., and Franklin G. Miller, Ph.D.

“Over the past few years, our reliance on the dead donor rule has again been challenged, this time by the emergence of donation after cardiac death as a pathway for organ donation. Under protocols for this type of donation, patients who are not brain-dead but who are undergoing an orchestrated withdrawal of life support are monitored for the onset of cardiac arrest. In typical protocols, patients are pronounced dead 2 to 5 minutes after the onset of asystole (on the basis of cardiac criteria), and their organs are expeditiously removed for transplantation. Although everyone agrees that many patients could be resuscitated after an interval of 2 to 5 minutes, advocates of this approach to donation say that these patients can be regarded as dead because a decision has been made not to attempt resuscitation.”

## DCD organ procurement

.....



Direct Procurement  
and Perfusion (DPP)



Ministerie van Volksgezondheid,  
Welzijn en Sport



**Eurotransplant**



NEDERLANDSE **TRANSPLANTATIE** VERENIGING



**Universitair Medisch Centrum Groningen**

**Erasmus MC**  
Universitair Medisch Centrum Rotterdam



**UMC Utrecht**

# DCD HEART DONATION AND TRANSPLANTATION MARCH 2021- FEB 2023

63 Donors attended

8 no circulatory arrest within 120 minutes

1 Functional warm ischemic time >30 minutes

54 Hearts mounted on the machine

## 10 Hearts rejected:

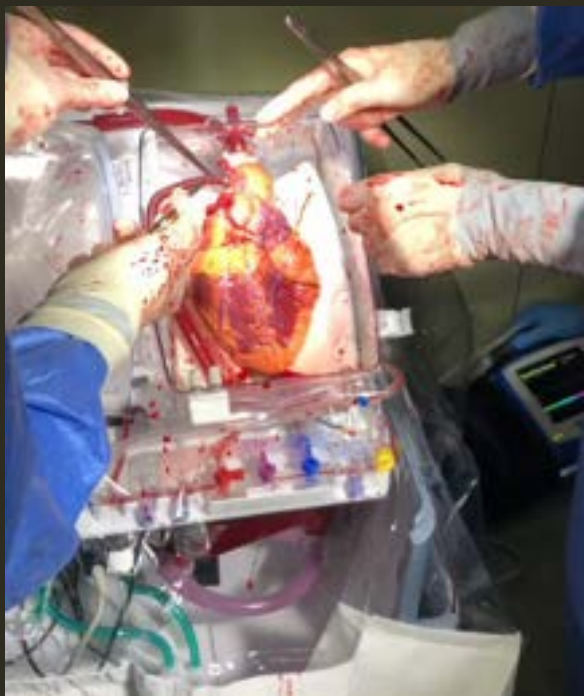
3 technical issues

2 suspicion of abdominal malignancy

1 size mismatch

4 poor quality

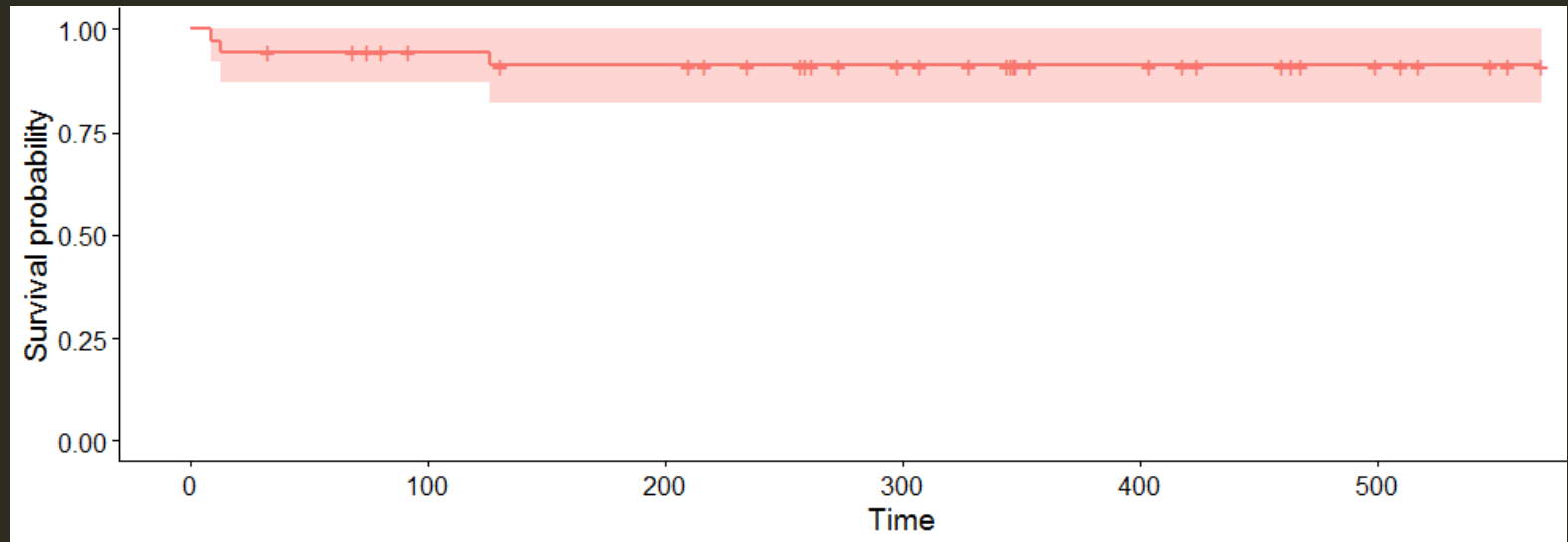
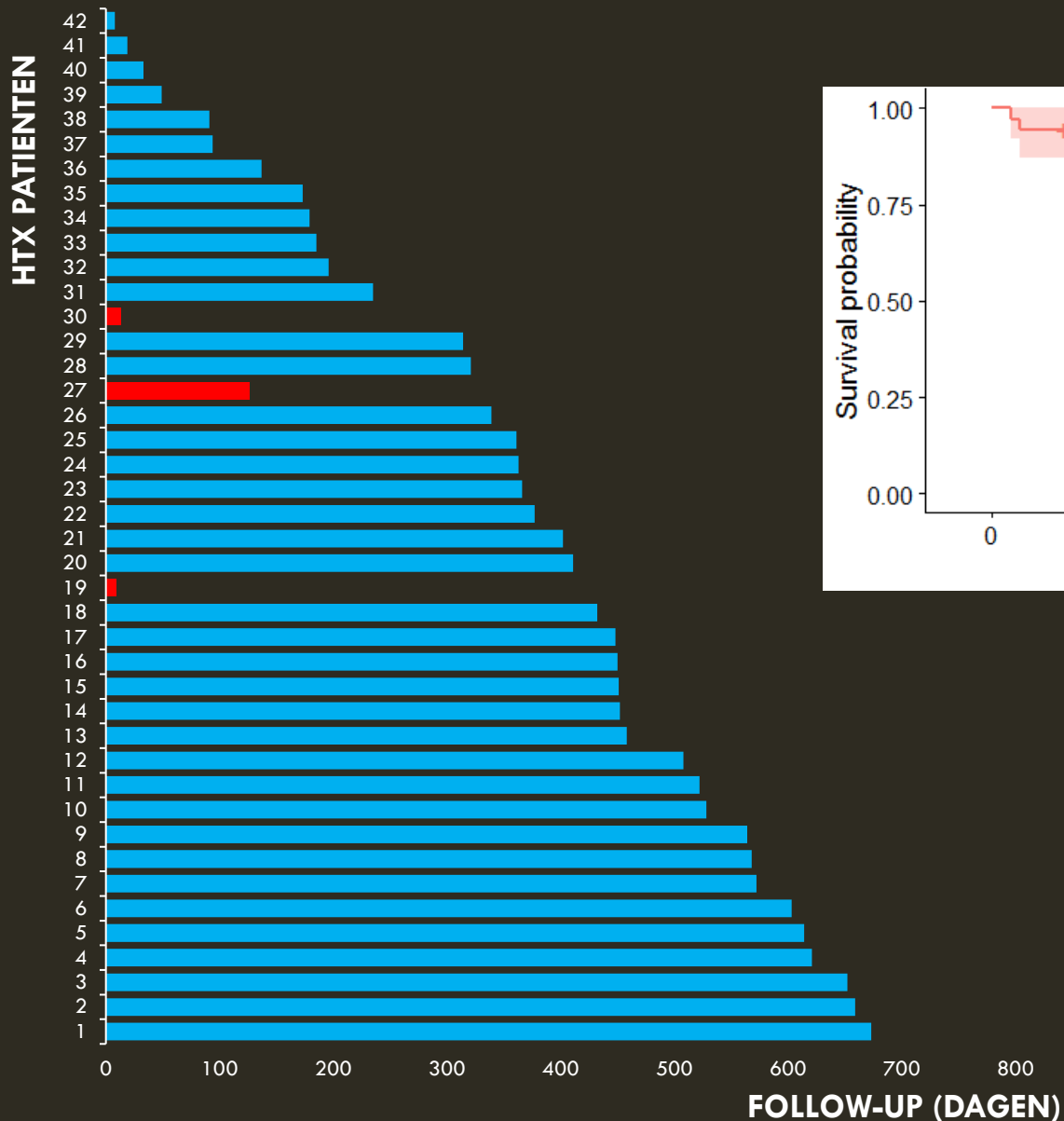
44 Hearts transplanted





# SURVIVAL DCD HEART THE NETHERLANDS

**Survival 92,9%**



**Mortality 7,1%**

- 1 Necrotizing pancreatitis**
- 1 Stroke**
- 1 Surgical complications**



**BBC** NEWS | MUNDO

# ADVANCED HEART FAILURE TREATMENT OPTIONS

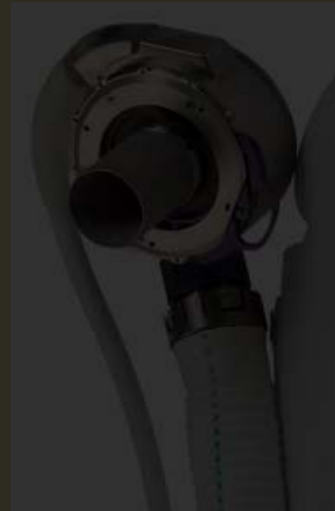
Heart Transplant



Short term MCS



Long term MCS



Total artificial heart



Regeneration



Brain death Htx  
Circulatory death Htx  
**Xenotransplantation**

Impella  
ECLS (VA/VV/VAV)  
RVAD

LVAD  
• Destination therapy  
• Bridge to transplant

CARMAT  
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candidacy

Experimental  
Pre clinical

# HISTORY XENOTRANSPLANTATION

## Human recipient

1964 baboon kidney

1964 Chimpanzee heart

1966 Chimpanzee liver

1977 Baboon heart

**1984 Baboon heart**

1992 Baboon liver

## Outcome

Max 9 month survival

2 hour rejection and death

Max 14 day survival

6 hour rejection and death

**20 day survival**

71 day survival

# BABY FAE


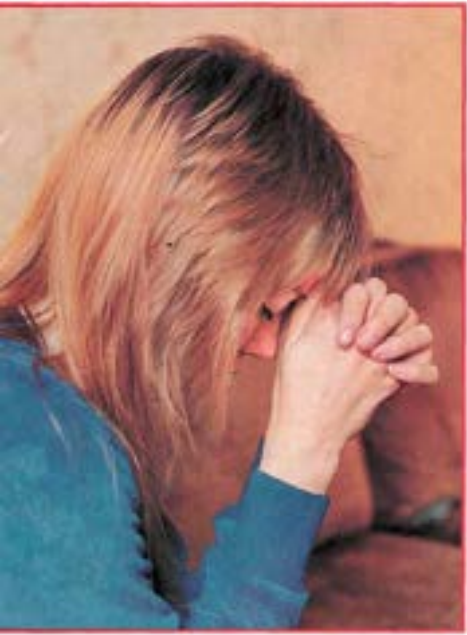
A hair-raising new cure for baldness  
Supergirl: Will she fly?  
Miami Vice's playboy kicks his bad habits

DECEMBER 3, 1984 \$1.25


# People

weekly

## BABY FAE



HER MOTHER AND FATHER TELL HER STORY—AND THEIRS



**A MILLION DOLLAR BONANZA**  
Play Double-Chance Roulette! You could get lucky! See Pages 16 & 17

Manhattan  
\*\*\*\*  
South  
Fulton

# DAILY NEWS

NEW YORK'S PICTURE NEWSPAPER

## BABOON-HEART BABY IS DEAD

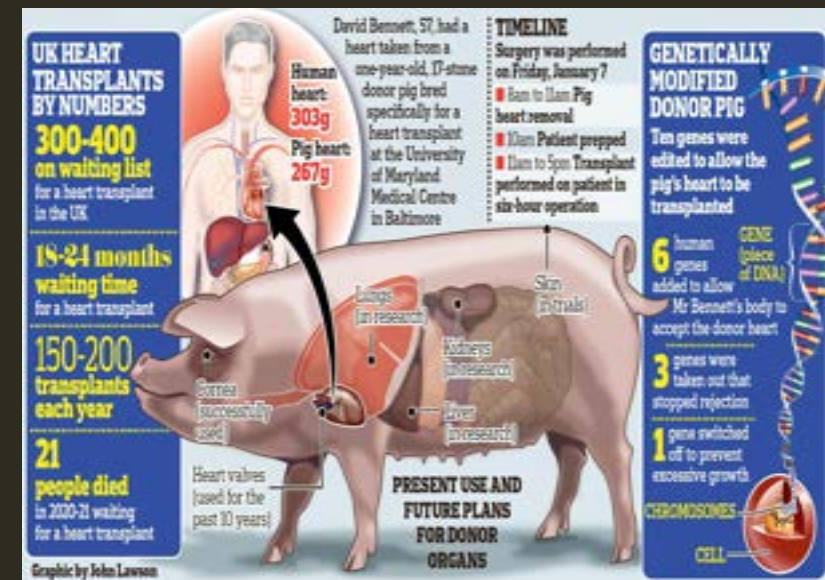


MS

Baby Fae, who received the heart of a baboon in transplant operation three weeks ago, died last night. Stories start page 7

# DEVELOPMENTS LAST DECADE

1. Genetic modification to:
  1. Reduce rejection chance
  2. Prevent left ventricular hypertrophy
2. Pathogen free pigs
3. Ex-situ heart perfusion to prevent or minimize additional injury by ischemia and reperfusion injury



## Pig-to-human heart transplants 'one step closer' after success with baboons

New techniques triple survival rates among baboons requiring the surgery

Harry Cockburn | Wednesday 6 December 2018 10:02 |



Pig and human organs are new source | (The photo)

## CASE DAVID BENNETT (57)

**Day 2** “heart was pumping fantastically and performing like a rock star,” transplant surgeon Bartley Griffith

**Day 20** Cytomegalovirus (CMV) found in blood samples

**Day 43** Viral CMV sepsis → Cidofovir & immunoglobulines

**Day 50** Cardiac edema, heart failure and death

**Conclusion** CMV transmission could have been prevented

> [Sci Rep. 2020 Oct 16;10\(1\):17531. doi: 10.1038/s41598-020-73150-9.](#)

## Impact of porcine cytomegalovirus on long-term orthotopic cardiac xenotransplant survival

Joachim Denner <sup>1</sup>, Matthias Längin <sup>2 3</sup>, Bruno Reichart <sup>3</sup>, Luise Krüger <sup>4</sup>, Uwe Fiebig <sup>4</sup>, Maren Mokolke <sup>3</sup>, Julia Radan <sup>3</sup>, Tanja Mayr <sup>2</sup>, Anastasia Milusev <sup>5</sup>, Fabian Luther <sup>5</sup>, Nicoletta Sorvillo <sup>5</sup>, Robert Rieben <sup>5</sup>, Paolo Brenner <sup>6</sup>, Christoph Walz <sup>7</sup>, Eckhard Wolf <sup>8</sup>, Berit Roshani <sup>9</sup>, Christiane Stahl-Hennig <sup>9</sup>, Jan-Michael Abicht <sup>2 3</sup>

Affiliations + expand

PMID: 33067513 PMCID: [PMC7568528](#) DOI: [10.1038/s41598-020-73150-9](#)

[Free PMC article](#)

Survival after transplant with CMV

Weeks

Survival after transplant without CMV

>6 months

Very high viral concentration in hearts at the end of the experiment

“Since different non-human primate species (cynomolgus monkeys, baboons) showed a similar reduction of the survival time, **it seems very likely that the same may happen in humans.**”

## CASE DAVID BENNETT (57)

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**Day 50** Cardiac edema, heart failure and death

**Conclusion** CMV transmission could have been prevented

→ enough ground for a second case?

Survival after first and second **human** heart transplant was respectively 18 days en 27 hours.....

# ADVANCED HEART FAILURE TREATMENT OPTIONS

Heart Transplant



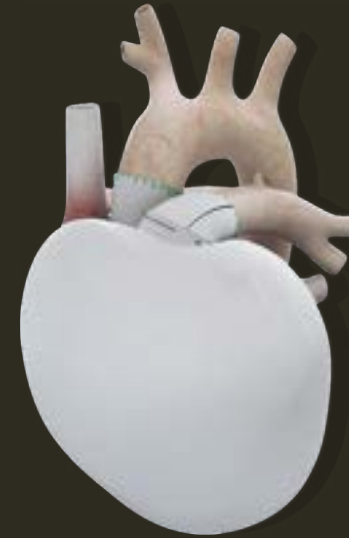
Short term MCS



Long term MCS



Total artificial heart



Regeneration



Brain death Htx  
**Circulatory death Htx**  
Xenotransplantation

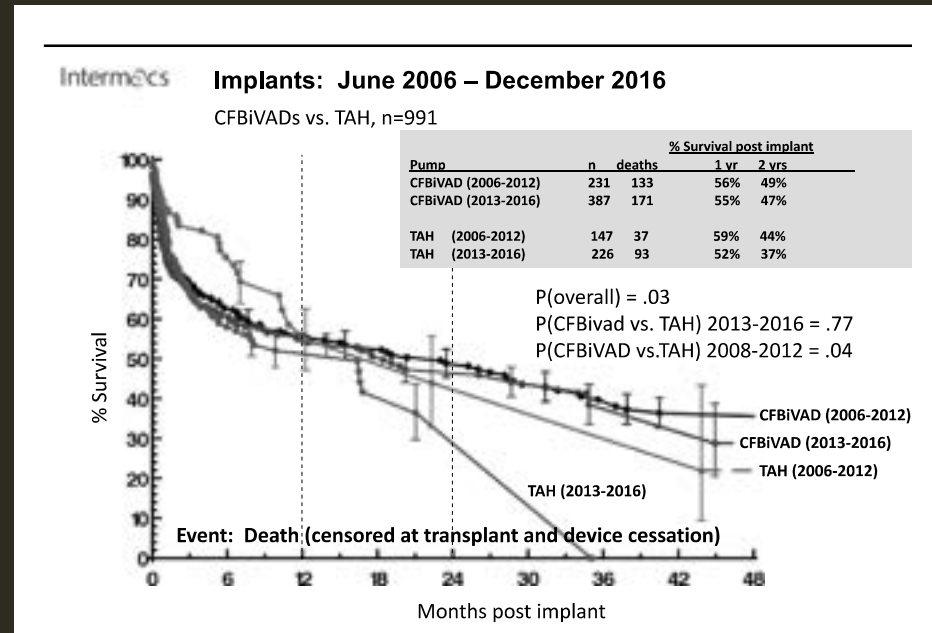
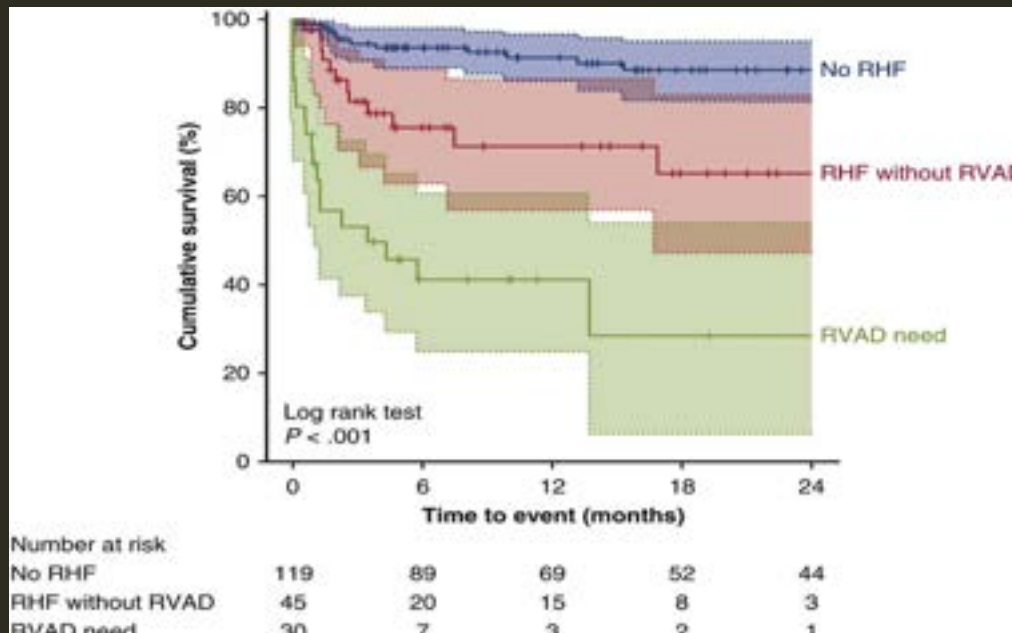
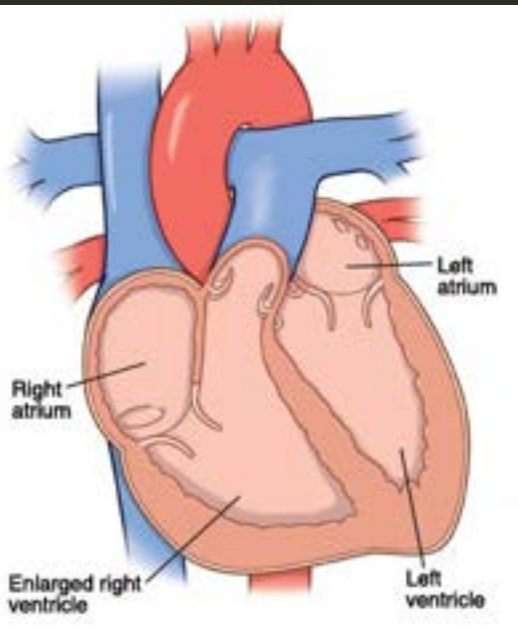
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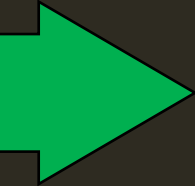
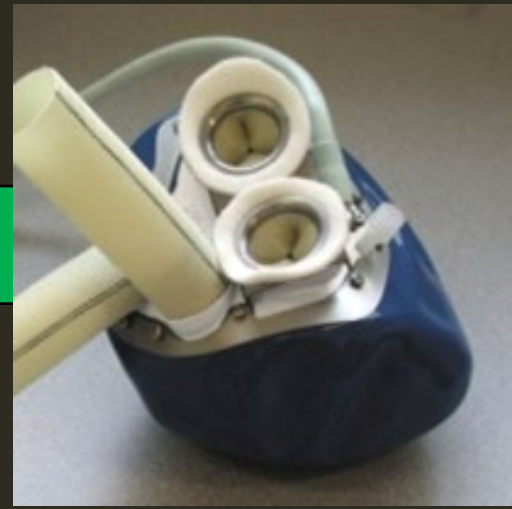
Experimental  
Pre clinical

# TREATMENT OF BIVENTRICULAR END-STAGE HEART FAILURE



# CARMAT — 15-YEAR RESEARCH & DEVELOPMENT

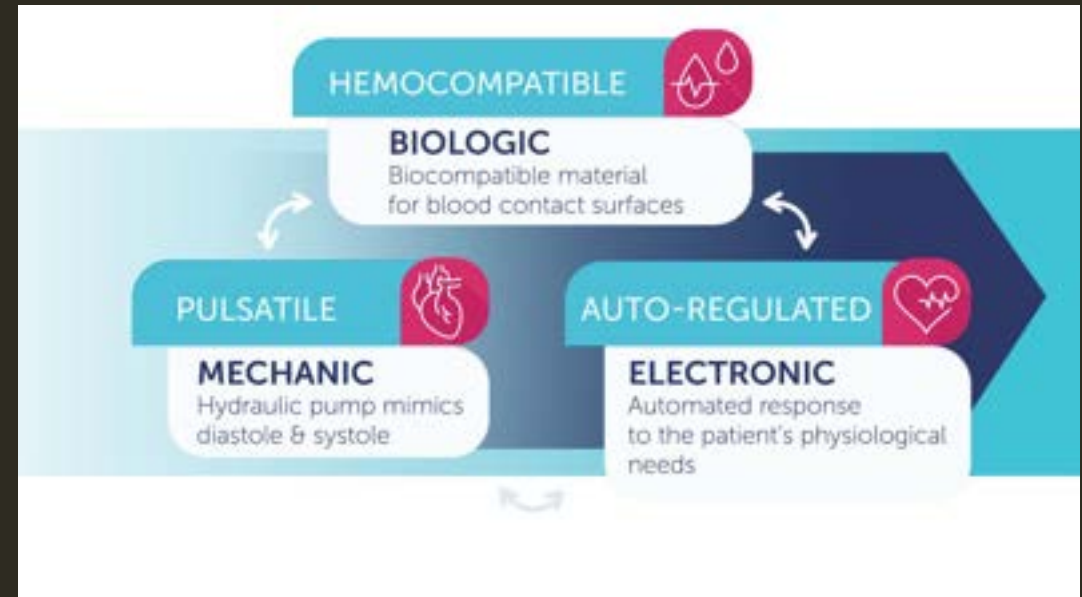
- Airbus group
- Alain Carpentier



# THE PUMP



- Pulsatile flow (2 ventricles & 4 biological valves)
- Independent flow left & right
- Flow adaptation to physiological needs



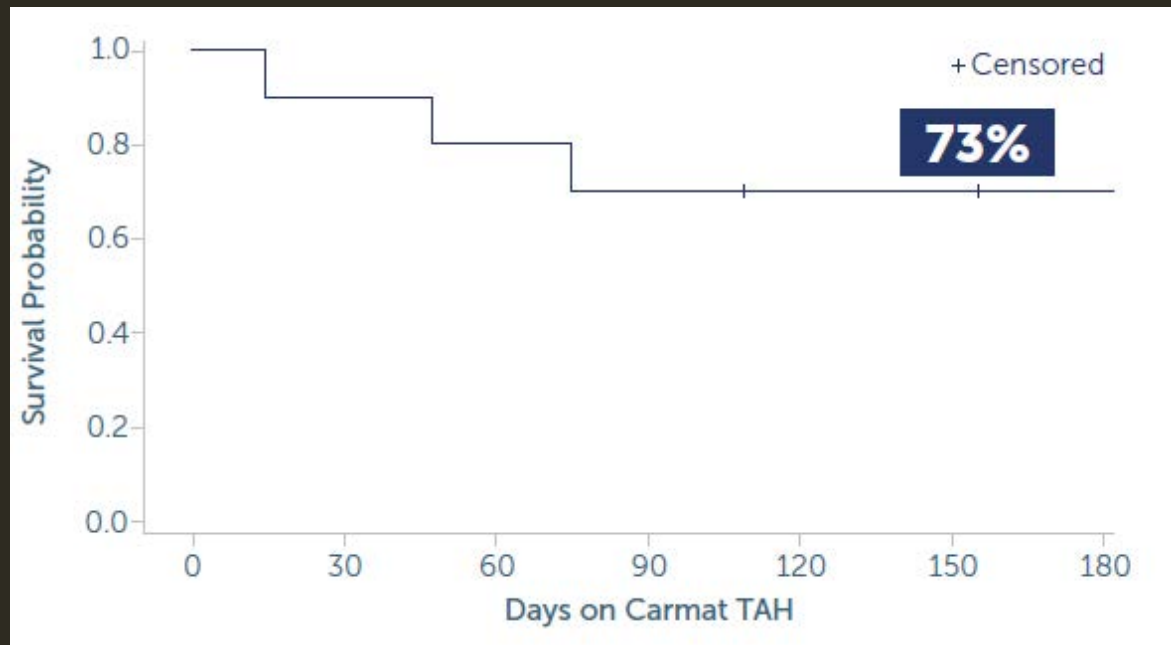
# PIVOTAL (CE-MARK) CARMAT STUDY

17 patients

INTERMACS 2-3 (“sliding on inotropes” or “dependent stability”)

Mean life expectancy 0.8 year based on Seattle Heart Failure Model

Primary endpoint: 6-month survival or succesful transplantation <6 months



*Data on file: clinical evaluation report.*  
*Kirklin JK et al., J Heart Lung Transplant 2018;37:685-691.*  
*Arabia F et al., J Heart Lung Transplant, 2018;37:1304–1312.*  
*Lavee J et al., J Heart Lung Transplant 2018;37:1399–1402.*  
*Arabia F et al., Ann Thorac Surg 2018;105:548–56.*  
*Strueber M et al. J Am Coll Cardiol 2011;57:1375–82.*  
*Netuka I et al., J Am Coll Cardiol 2015;66:2579–89.*

# BIVENTRICULAR FAILURE TREATMENT OPTIONS



**Aeson CARMAT**

**Syncardia TAH**

**BiVAD**

**LVAD + tRVAD**

**LVAD**

Biventricular support



Pulsatility



Autoregulation



Hemocompatibility



# CARMAT IN UTRECHT



NOS NIEUWS • BINNENLAND • VANDAAG, 06:38

## Artsen van UMC Utrecht implanteren succesvol eerste kunsthart in Nederland

Specialisten van het UMC Utrecht hebben voor het eerst in Nederland succesvol een volledig kunsthart bij een patiënt met zeer ernstig hartfalen geïmplantéerd. De operatie is onderdeel van een langdurig en internationaal onderzoeksproject om een betrouwbaar alternatief voor donorharten te vinden.

"In Nederland is een groot tekort aan donorharten",

# LVAD&ARTIFICIAL HEART RELATED COMPLICATIONS

Driveline infection



Stroke



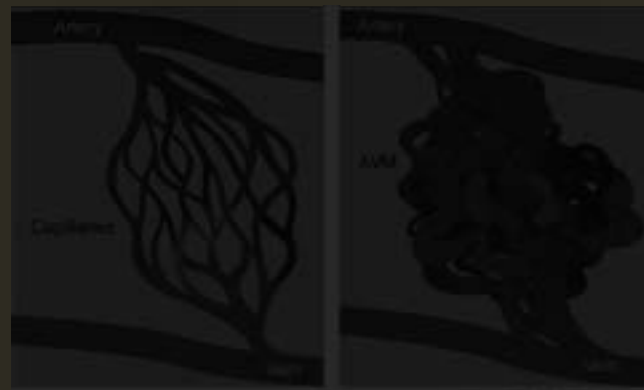
No support of the right ventricle



Pump thrombosis



AV malformation



Technical failure



# THORACIC “TRANSPLANTATION”, TREATMENT OF....

## Advanced lung failure



# CHALLENGES LUNG TRANSPLANTATION

Increase  
number of  
organ donors



Improve the  
outcome after  
transplantation

# HOW TO INCREASE NUMBER OF LUNG DONORS

Change donor law

DCD program

Increase acceptance rate



# HOW TO INCREASE NUMBER OF LUNG DONORS

Change donor law

DCD program

Increase acceptance rate





Mmmmmm:  
I don't know



Perfect:  
Accept



Poor:  
However.....

Poor:  
Reject



Perfect:  
But not now  
(or me)



# INCREASE ACCEPTANCE RATE

## **Donor management**

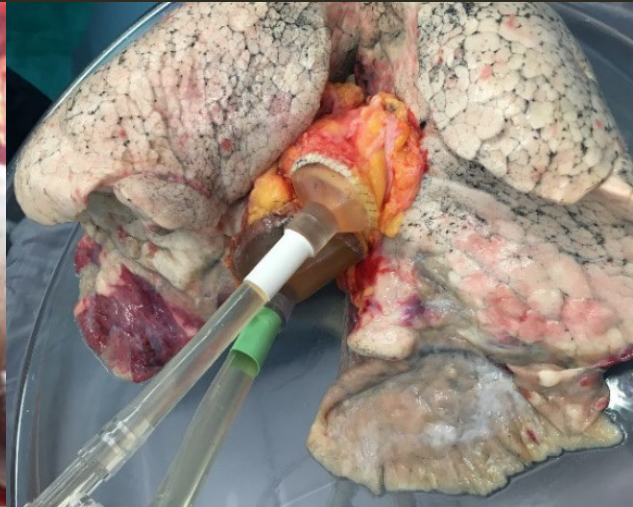
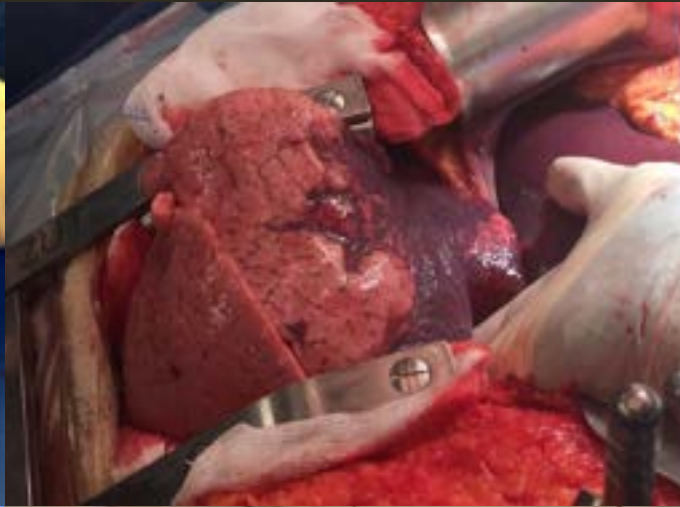
Type of ventilation

Position of the patient

Medical treatment

.....

# DONOR LUNG....



# INCREASE ACCEPTANCE RATE

## Donor management

Type of ventilation

Position of the patient

Medical treatment

.....

## Ex Vivo Lung Perfusion



# EX VIVO LONG PERFUSIE (EVLV)

**Platform:**

To Test

Mmmmmmm:  
I don't know

To Regenerate

Poor:  
However.....

To Preserve

Perfect:  
But not now  
(or me)



# EX VIVO LONG PERFUSIE (EVLP)



# EX VIVO LONG PERFUSIE (EVLVP)

Platform:

To Test

Mmmmmmm:  
I don't know

To Regenerate

Poor:  
However.....

To Preserve

Perfect:  
But not now  
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# PREVENTION BY TESTING | DOUBT AT PROCUREMENT

55-year old man

195 cm, 140 kg

Stroke

Donation after Circulatory Death

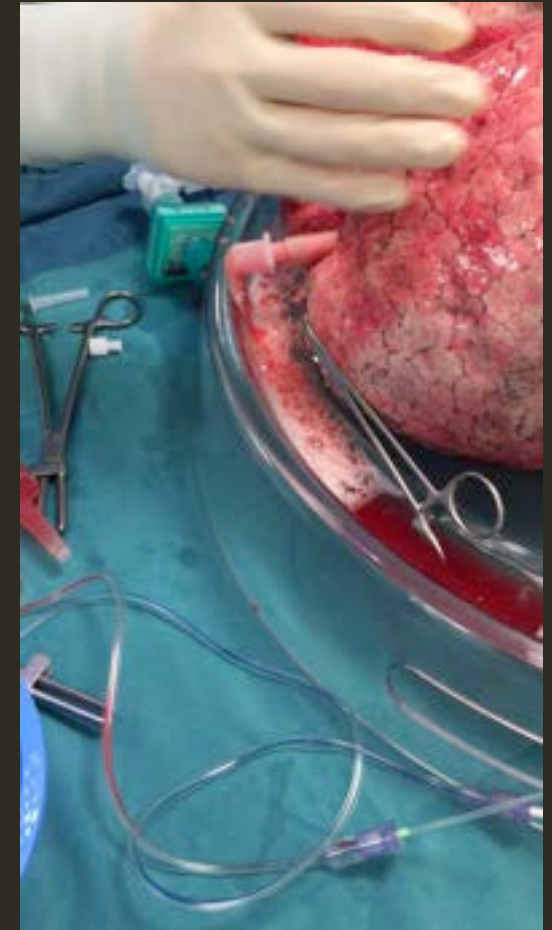
$\text{PaO}_2/\text{FiO}_2$  ratio  $> 300$  mmHg

Clear bronchoscopy

Clear chest X-ray

Died within 30 minutes after switch off

At harvest heavy lungs with diminished compliance



# EX VIVO LONG PERFUSIE (EVLV)

**Platform:**

To Test

Mmmmmmm:  
I don't know

**To Regenerate**

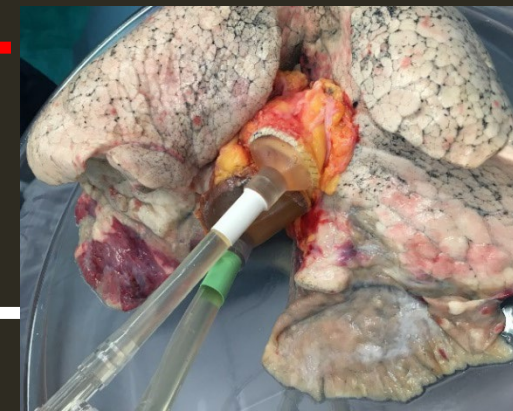
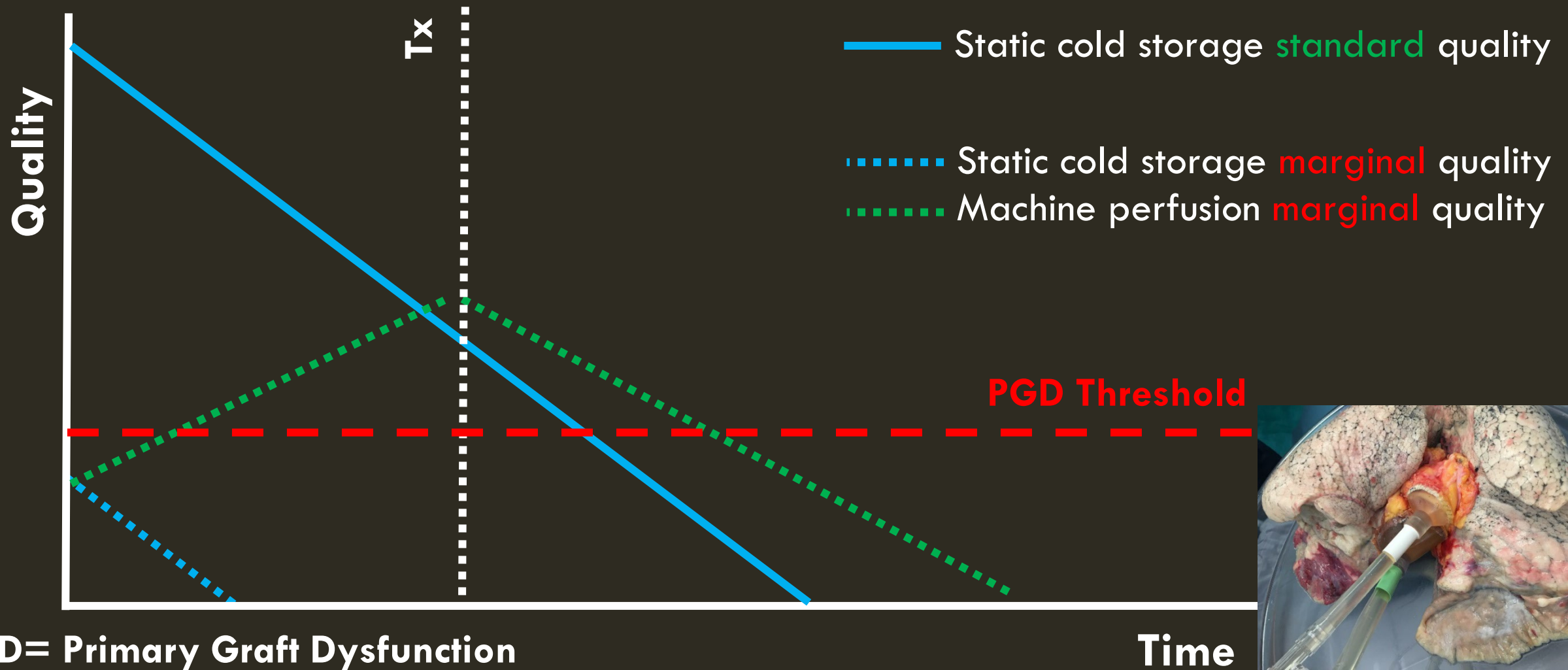
Poor:  
However.....

To Preserve

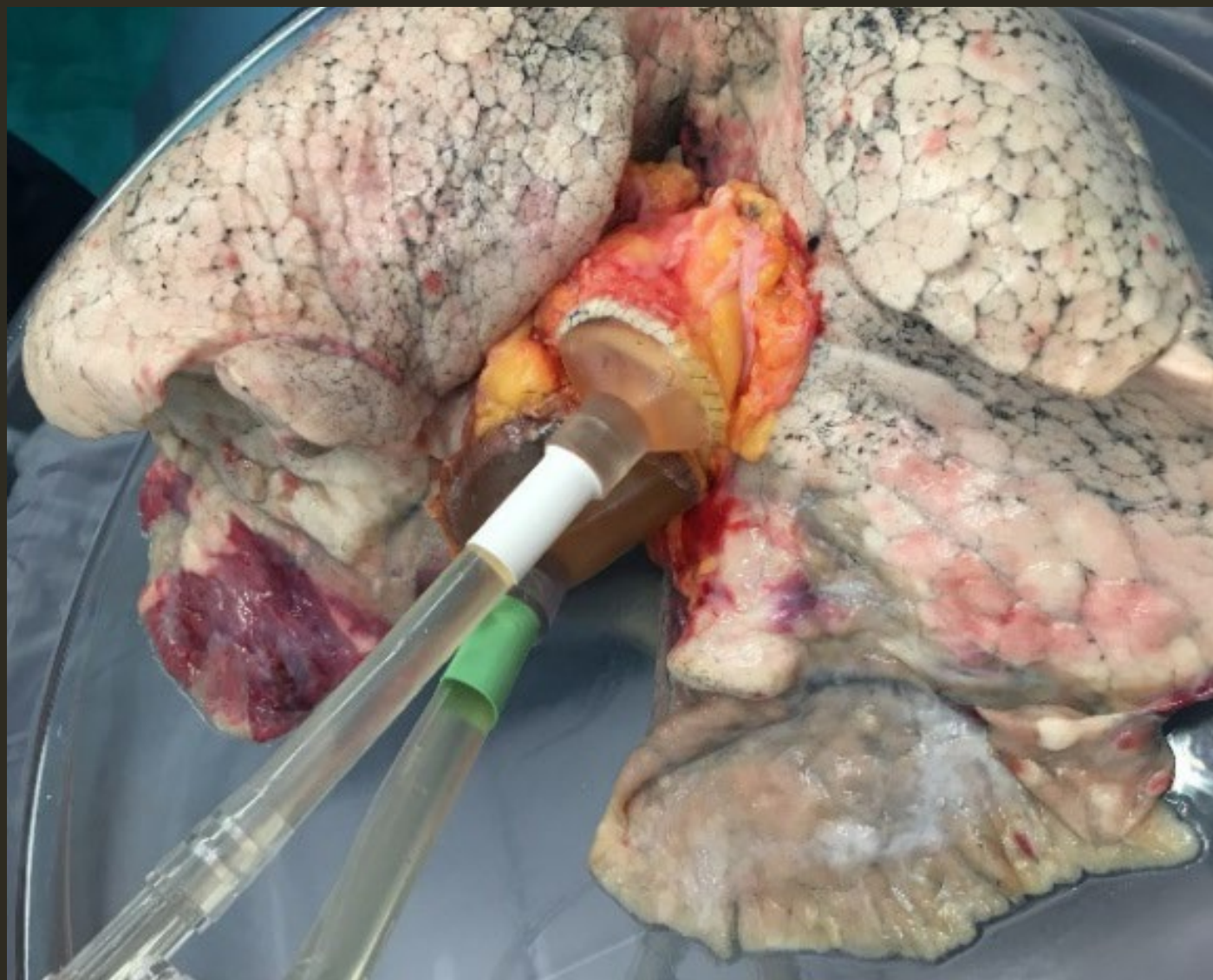
Perfect:  
But not now  
(or me)



# EVLP AS A TOOL TO IMPROVE INJURED LUNGS



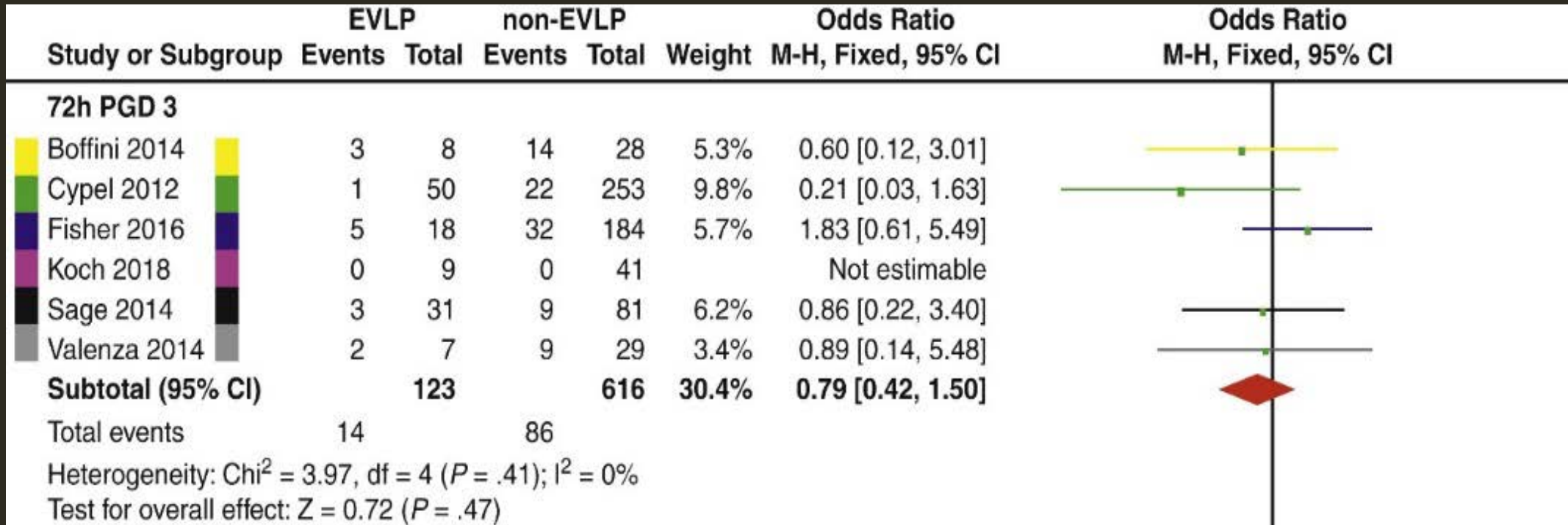
# EVLP INDICATION INJURED LUNGS



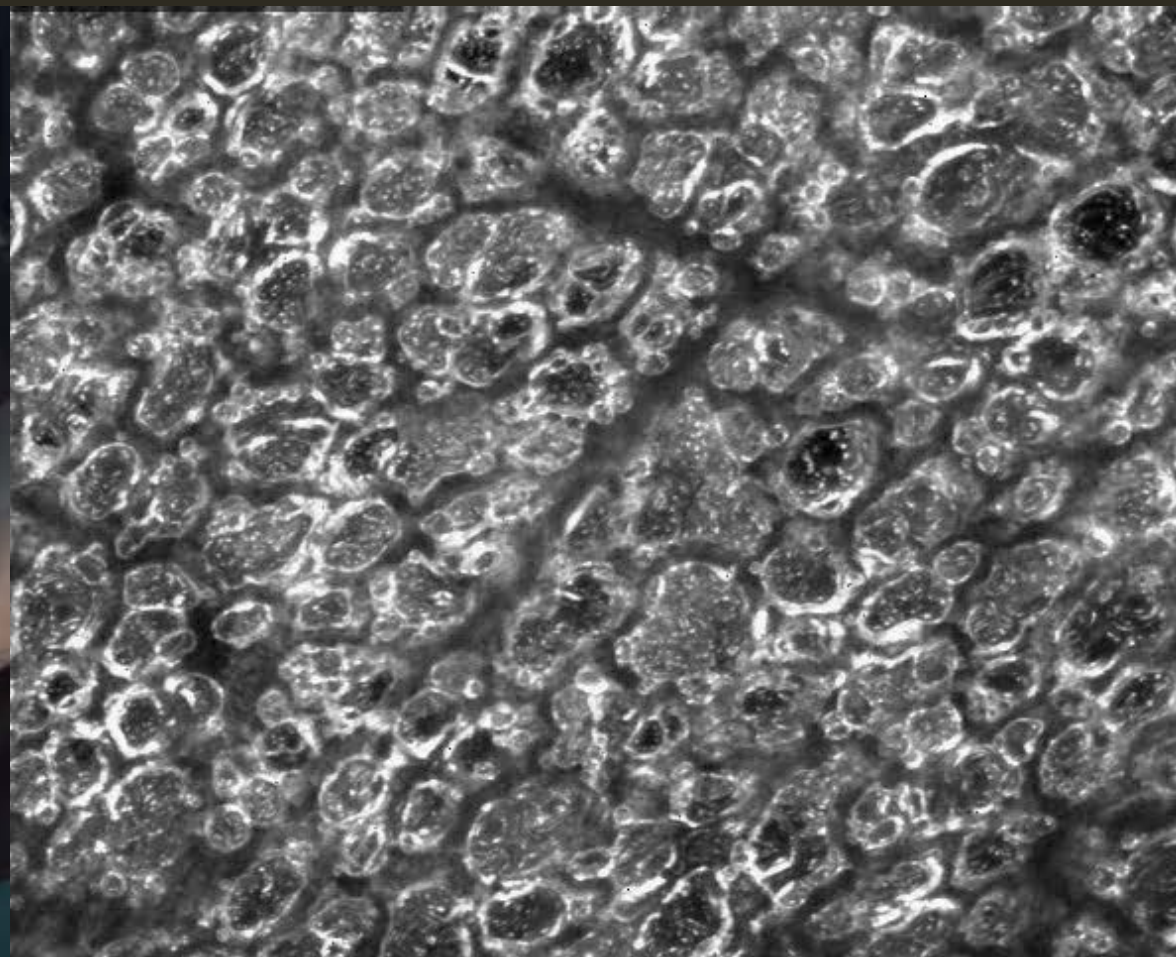
# EVLP & PGD META-ANALYSIS

## Outcomes of marginal donors for lung transplantation after ex vivo lung perfusion: A systematic review and meta-analysis

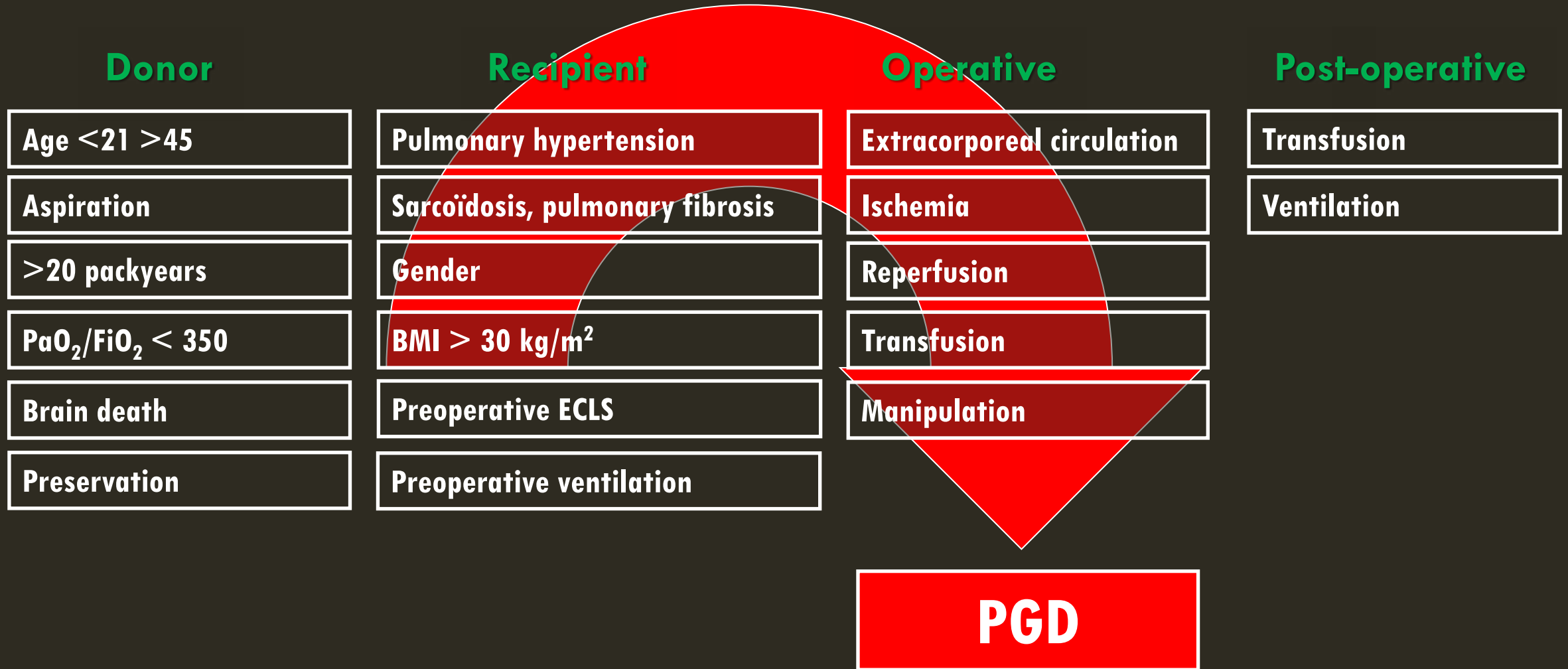
Dong Tian, MD,<sup>1,2,3,4</sup> Yu Wang, MD,<sup>2</sup> Haruhiko Shiiya, MD,<sup>3,4</sup> Chang-Bo Sun, MD,<sup>4</sup> Yukari Uemura, MD, PhD,<sup>1</sup> Masaaki Sato, MD, PhD,<sup>2</sup> and Jun Nakajima, MD, PhD<sup>1</sup>



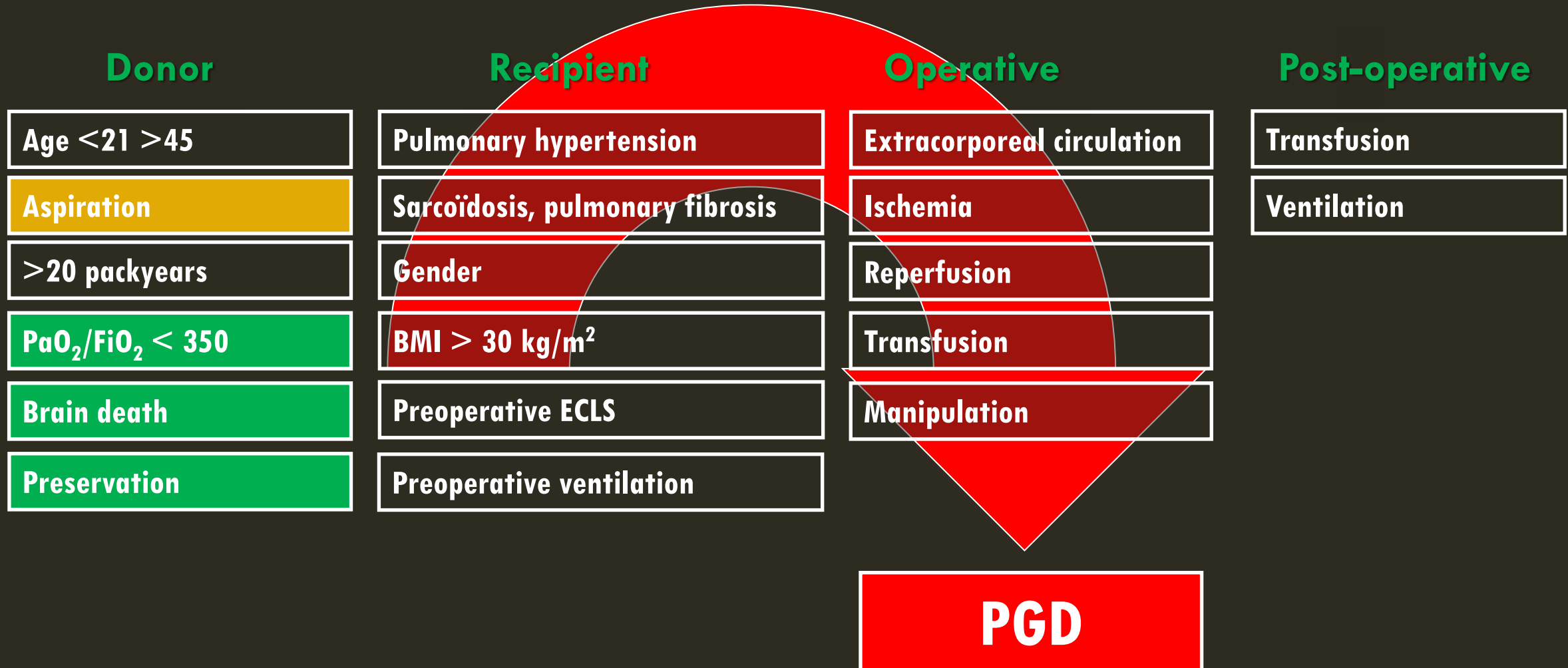
EVLP in marginal lungs is an adequate tool to optimize the graft for transplant resulting in comparable outcomes with standard lung transplantation



# PGD RISK FACTORS



# EVLP INFLUENCE ON PGD RISK FACTORS



## HOW TO OPTIMIZE OUTCOME

**Test lung with  
EVLP when in  
doubt**

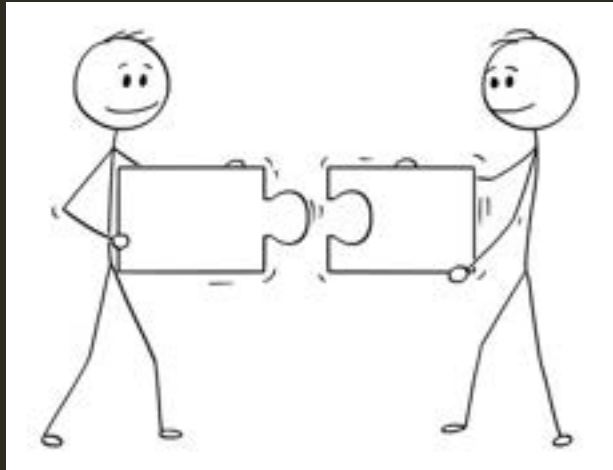
**Optimize donor  
lung quality**

**Matching**

**Recipient  
selection**

**Tailormade  
treatment pre-  
peri and  
postoperative**

**MARGINAL  
DONOR**



**MARGINAL  
RECIPIENT**

**=**

**MARGINAL  
OUTCOME**

# MARGINAL DONOR LUNG...FOR WHICH RECIPIENT



# MARGINAL LUNG AND HIGH RISK RECIPIENT

## Donor PGD risk factors

Age <21

Aspiration

>20 packyears

$\text{PaO}_2/\text{FiO}_2 < 300$

Brain death

Preservation

## Recipient PGD risk factors

Pulmonary hypertension

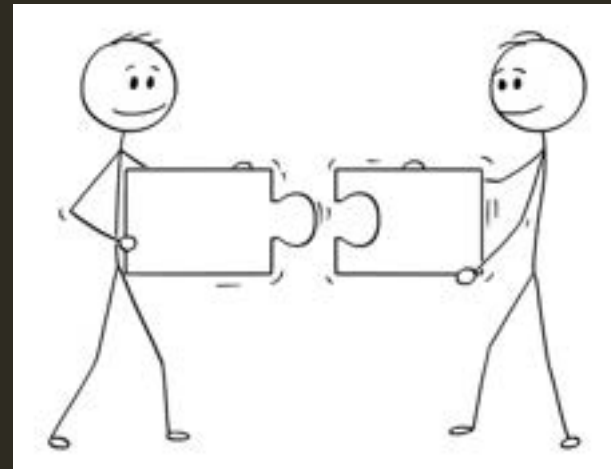
Pulmonary fibrosis

Gender

$\text{BMI} > 30 \text{ kg/m}^2$

Preoperative ECLS

Preoperative ventilation



**PGD= Primary Graft Dysfunction**

# MARGINAL LUNG AND LOW RISK RECIPIENT

## Donor PGD risk factors

Age <21

Aspiration

>20 packyears

$PaO_2/FiO_2 < 300$

Brain death

Preservation

## Recipient PGD risk factors

Pulmonary hypertension

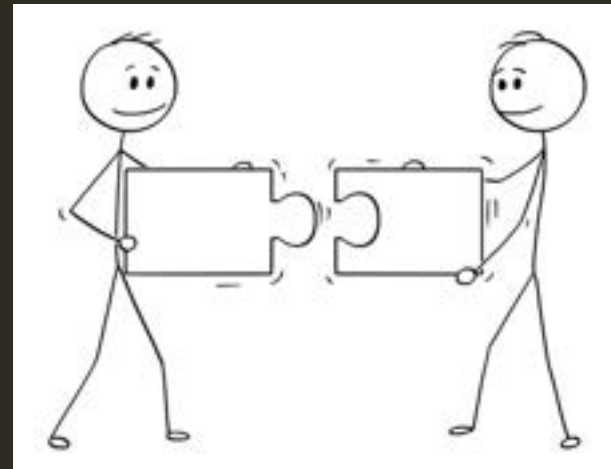
Sarcoidosis, pulmonary fibrosis

Gender

BMI > 30 kg/m<sup>2</sup>

Preoperative ECLS

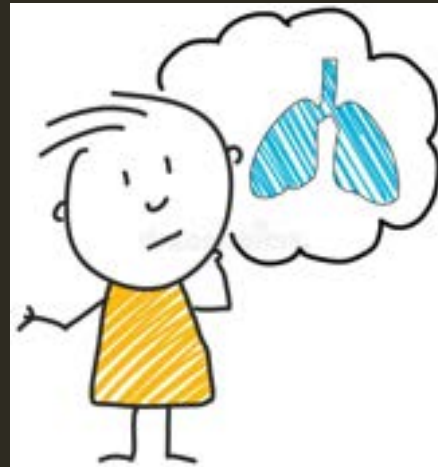
Preoperative ventilation



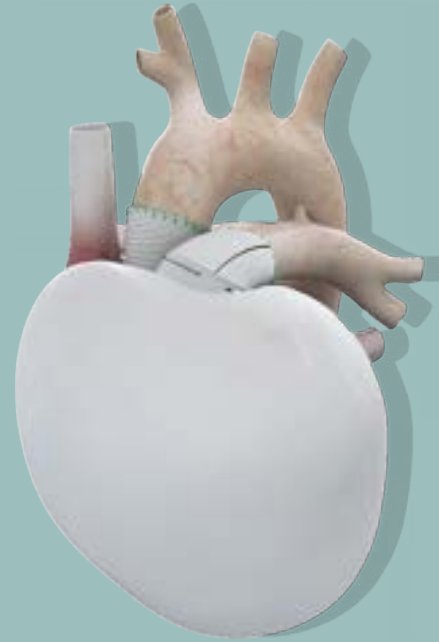
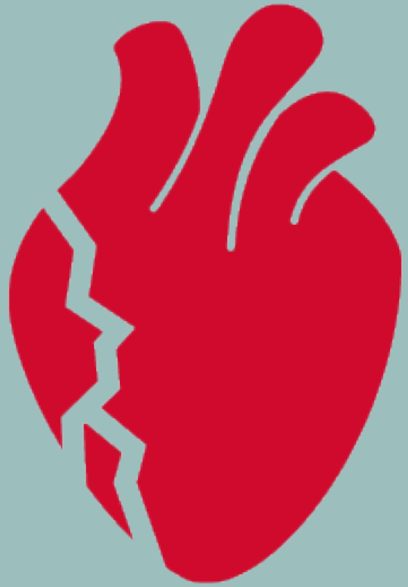
**PGD= Primary Graft Dysfunction**

# EVLP LUNG ON STOCK

**IN STOCK**







# INNOVATION IN THORACIC “TRANSPLANTATION”

NVIC Intensivistendagen 2023

Niels van der Kaaij

Head Department of Cardiothoracic Surgery Utrecht  
President Dutch Transplant Society

