Department of Cardiac Surgery

Instituto de Neurologia e Cardiologia de Curitiba (INC-Cardio)

Decellularization of Aortic Homografts: South American and European Current Experience

Francisco Diniz Affonso da Costa

Human Tissue Bank – PUCPR - Brazil

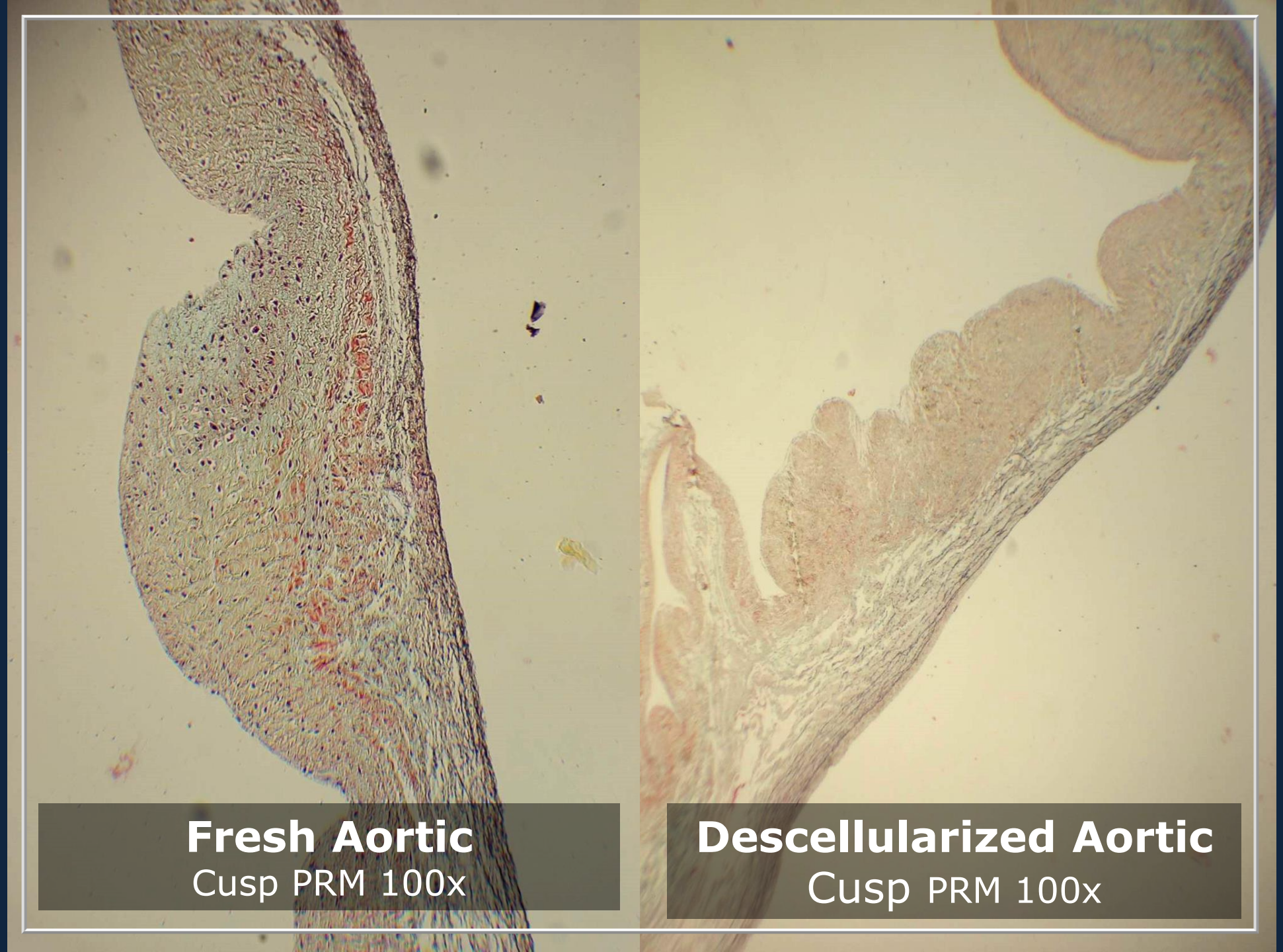
DISCLOSURES

- ✓ Ownership and patent license of the SDS decellularization technique *(d-CELL Allograft)*
- ✓ Consultant and Member of the Advisory Board Tissue Regenix Ltd – England

DECELLULARIZED HEART VALVE

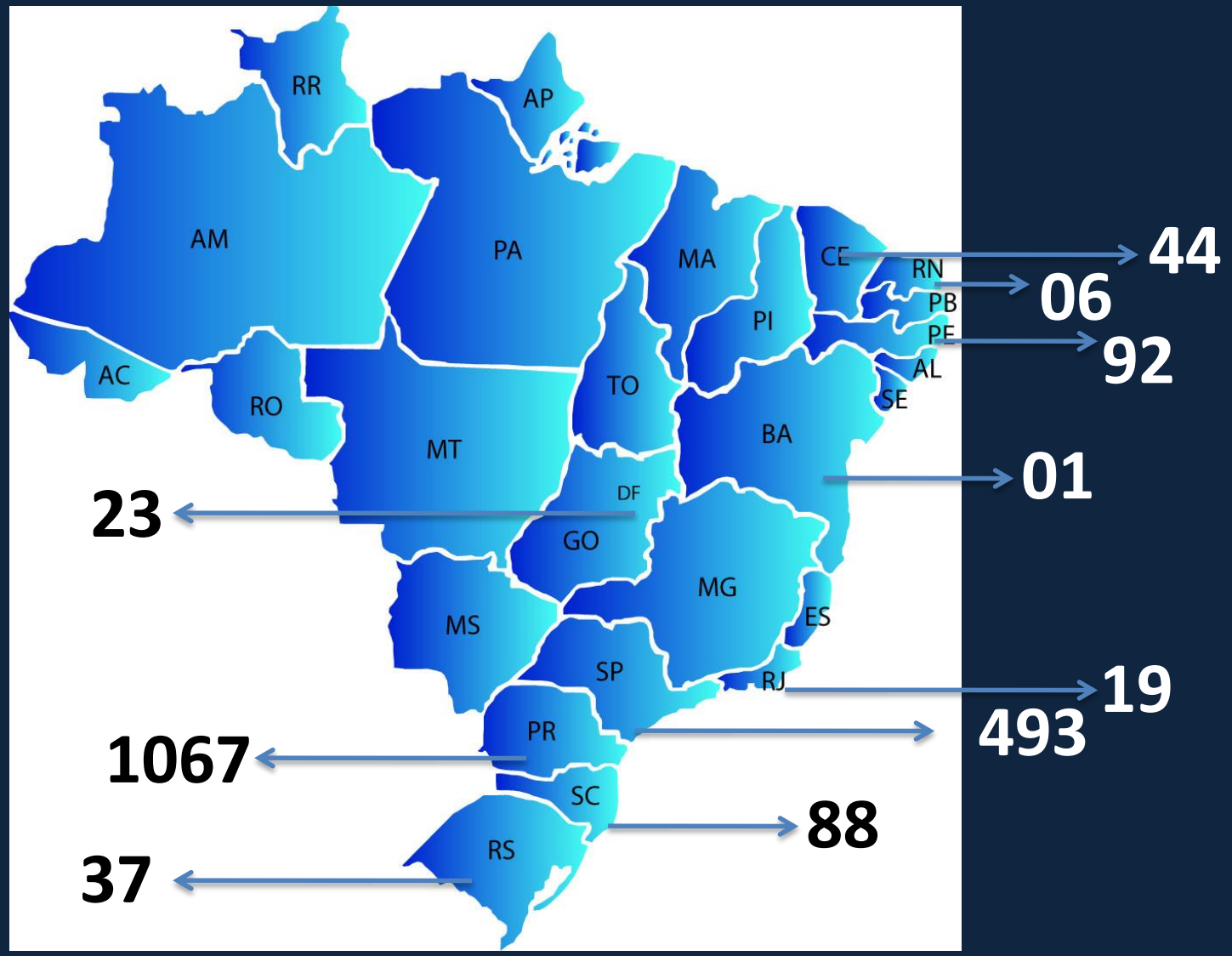
dCELL Technology

- ✓ Decellularization Technique
- ✓ Fresh Allografts, no cryopreservation
- ✓ Storage at 4º C for up to 6 months


Fresh Aortic
Cusp PRM 100x
Descellularized Aortic
Cusp PRM 100x

Decellularized Heart Valves Brazilian Experience (2005-2018)

Number of Implants = 1870 cases



Cryolife aortic valve replacement

BRIEF RESEARCH REPORT

Late durability of decellularized allografts for aortic valve replacement: A word of caution

Meghana R. K. Helder, MD,[a] Nicholas T. Kouchoukos, MD,[b] Kenton Zehr, MD,[c] Joseph A. Dearani, MD,[a] Joseph J. Maleszewski, MD,[d] Charles Leduc, MD,[d] Courtney N. Heins, BS,[e] and Hartzell V. Schaff, MD,[a] Rochester, Minn; St Louis, Mo; and Baltimore, Md

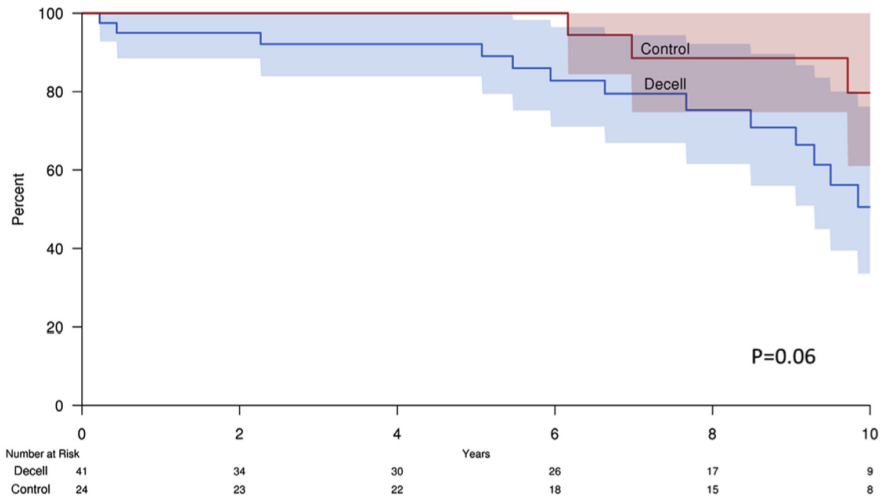


FIGURE 2. Kaplan-Meier curves for freedom from reoperation. Patients implanted with a DAVA had a 92% (95% CI, 84%-100%) freedom from reoperation at 5 years postimplantation, compared with 100% in the control group. Freedom from reoperation at 10 years postoperatively was 51% (95% CI, 34%-76%) in patients receiving a DAVA, compared with 80% (95% CI, 60%-100%) in the control group ($P = .06$).

Synergraft aortic homograft study

- Reasons for reoperation in DAVA:
  - endocarditis 26 %
  - aortic stenosis 29 %
  - aortic regurgitation 31 %

- Only 10 DAVA were available for histological analysis
  - in 7 edematous degeneration and calcifications were found
  - in 3 valves mild recellularisation was found
  - adventitial fibrosis and neointimal fibrosis were identified in all 10 specimens

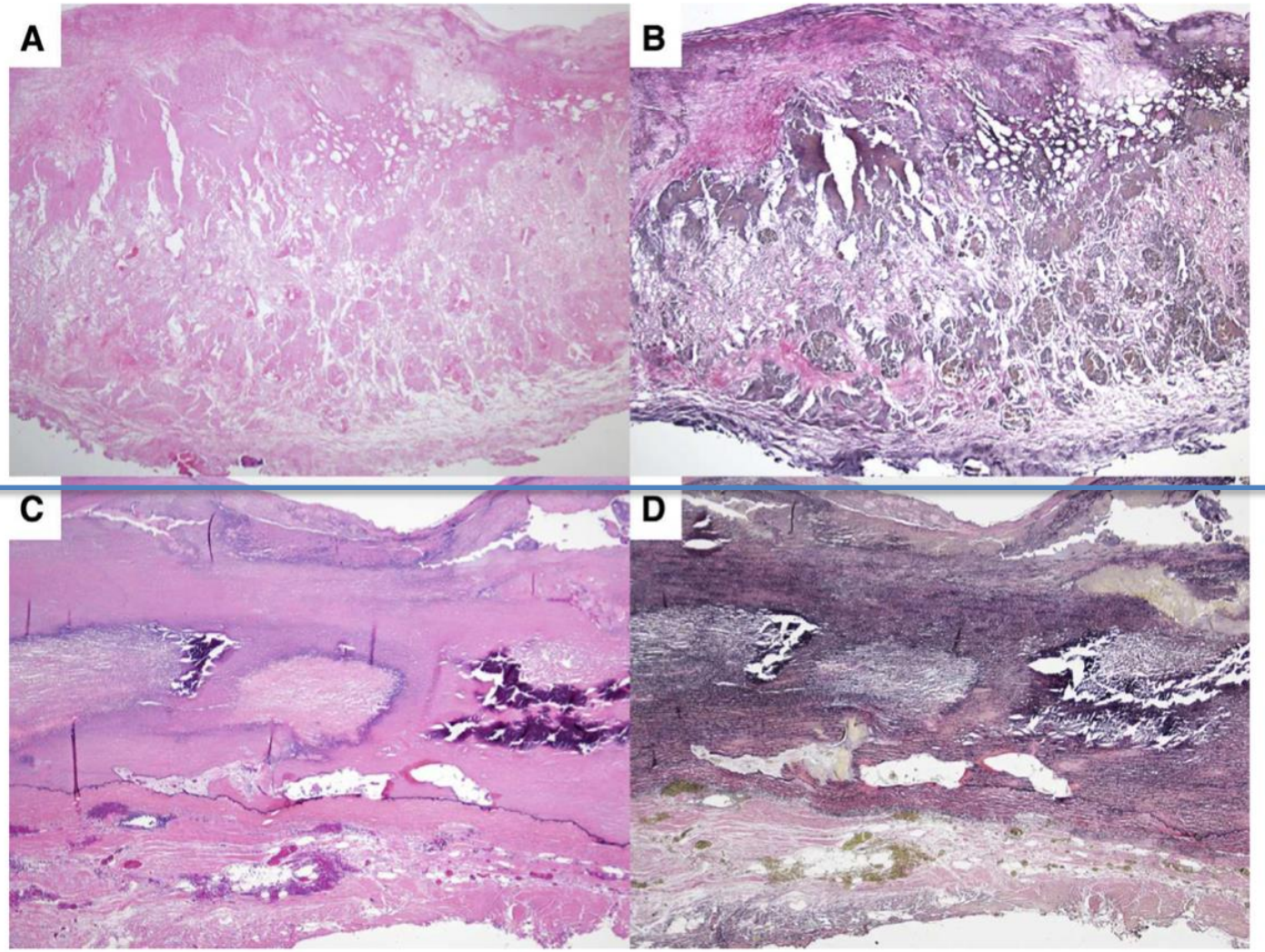


FIGURE 1. Histopathologic findings of DAVAs in tissue sections stained with hematoxylin and eosin (*left* column) and corresponding Verhoeff-Van Gieson elastic (*right* column) stains, showing (A and B) full-thickness degeneration of the valve cusp and (C and D) marked calcification of the tubular component of the graft. (Original magnification, 40×.)

CryoLife homograft processing

- Proprietary technique, details unknown such as strength testing after processing

- Homografts in the Helder report have been cryopreserved and radiated before implantation. Both of these procedures have been demonstrated to impact the ultrastructure.
- Sarathchandra P, Smolenski RT, Yuen AH, Chester AH, Goldstein S, Heacox AE, Yacoub MH, Taylor PM. Impact of γ-irradiation on extracellular matrix of porcine pulmonary valves. J Surg Res. 2012 Aug;176(2):376-85.
- In contrast, the ARISE trial is evaluating fresh, non-cryopreserved and non-radiated DAH for AVR.

Courtesy of Prof Samir Sarikouch - Hannover

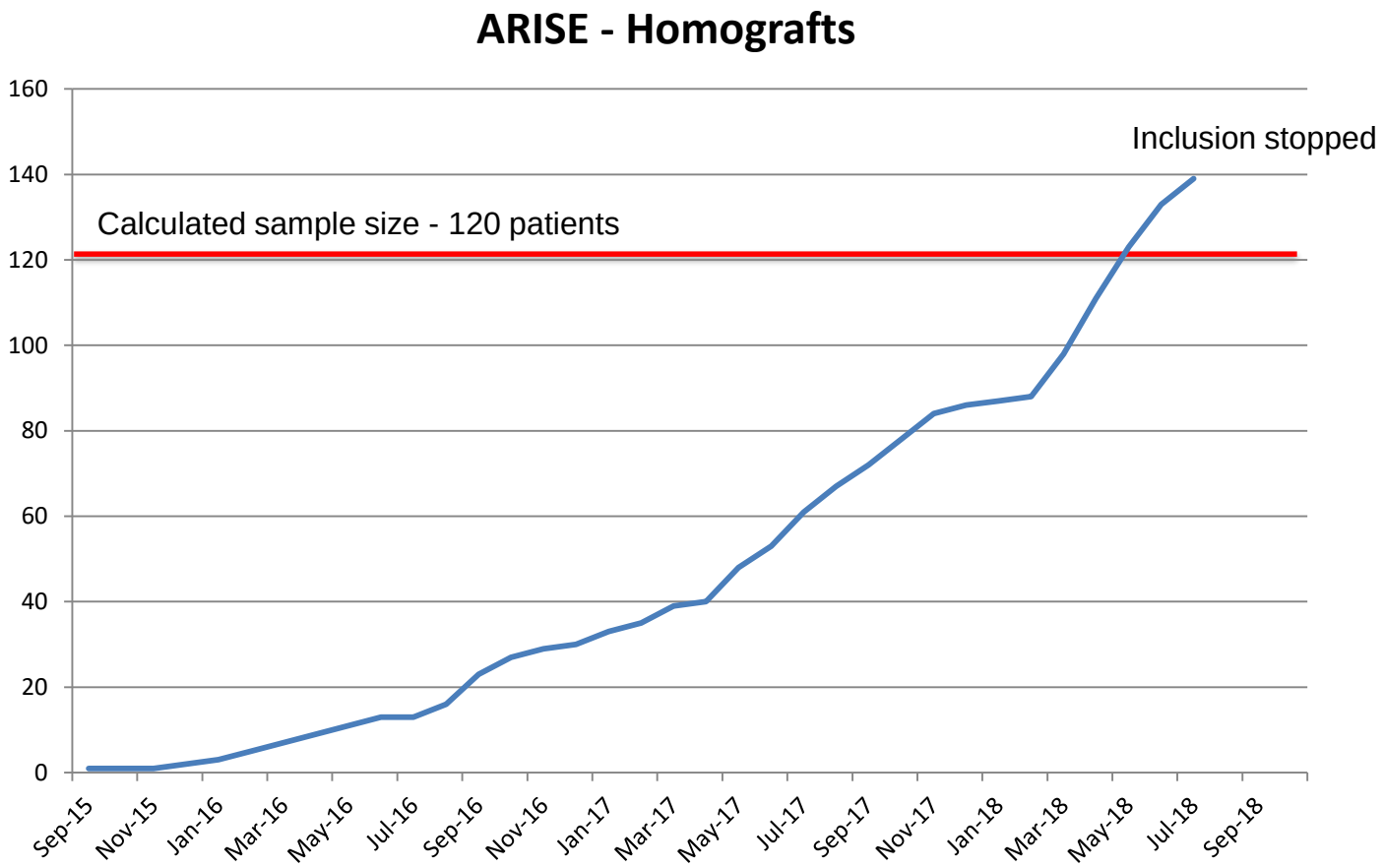
The ARISE Study Group

ARISE

Horizon 2020 Programme

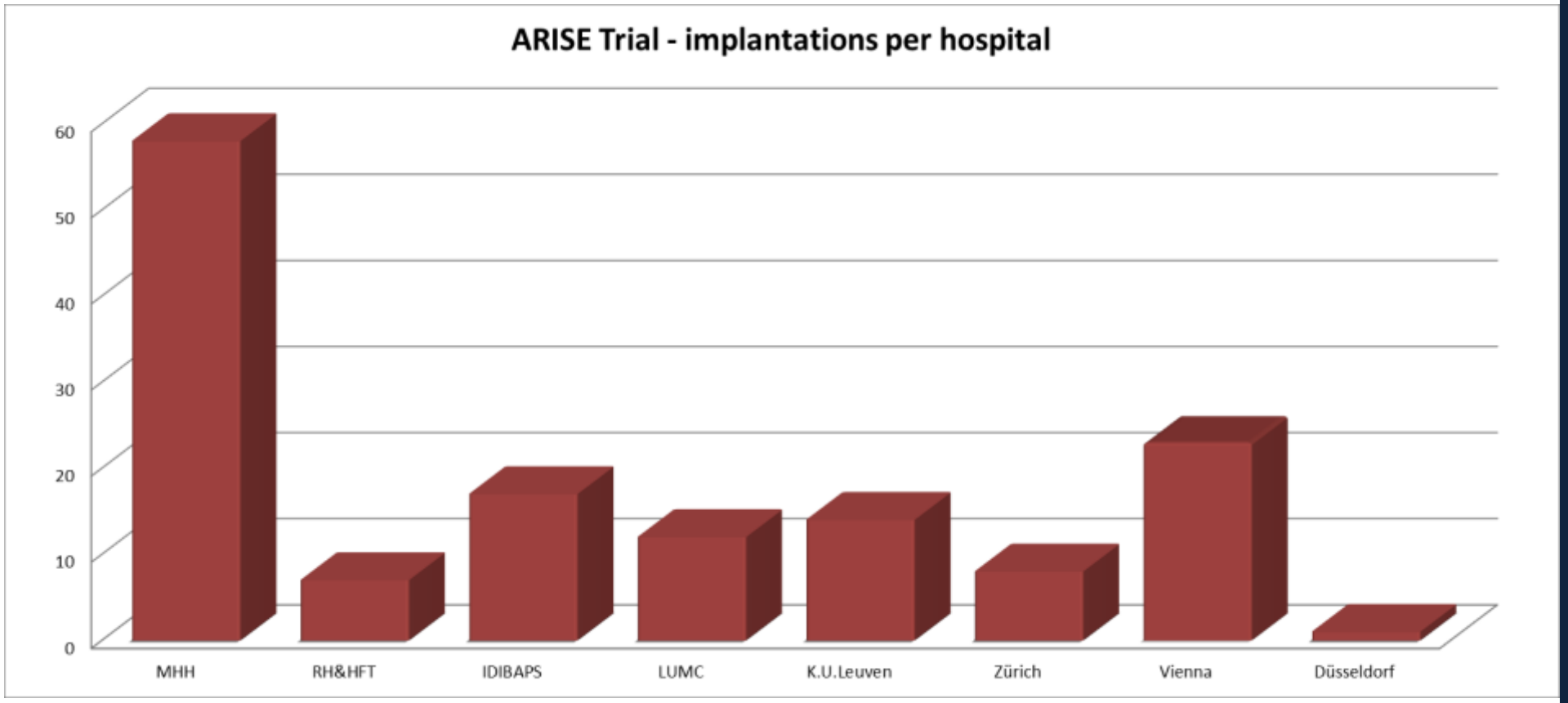
Courtesy of Prof Samir Sarikouch - Hannover

Current status clinical trial



Courtesy of Prof Samir Sarikouch - Hannover

Current status clinical trial



Courtesy of Prof Samir Sarikouch - Hannover

European Journal of Cardio-Thoracic Surgery Advance Access published February 18, 2016

European Journal of Cardio-Thoracic Surgery (2016) 1–9
doi:10.1093/ejcts/ezw013

ORIGINAL ARTICLE

Cite this article as: Tudorache I, Horke A, Cebotari S, Sarikouch S, Boethig D, Breymann T et al. Decellularized aortic homografts for aortic valve and aorta ascendens replacement. Eur J Cardiothorac Surg 2016; doi:10.1093/ejcts/ezw013.

Decellularized aortic homografts for aortic valve and aorta ascendens replacement†

Igor Tudorache[a,‡*], Alexander Horke[a,‡], Serghei Cebotari[a], Samir Sarikouch[a], Dietmar Boethig[a], Thomas Breymann[a], Philipp Beerbaum[a], Harald Bertram[a], Mechthild Westhoff-Bleck[a], Karolina Theodoridis[a], Dmitry Bobylev[a], Eduard Cheptanaru[b], Anatol Ciubotaru[a,b] and Axel Haverich[a]

[a] Department of Cardiac-, Thoracic-, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany
[b] State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

* Corresponding author. Department of Cardiac-, Thoracic-, Transplantation and Vascular Surgery, Hannover Medical School, Carl-Neuberg Str. 1, 30625 Hannover, Germany. Tel: +49-5115322125; fax: +49-5115325404; e-mail: tudorache.igor@mh-hannover.de (I. Tudorache).

Received 23 September 2015; received in revised form 8 December 2015; accepted 11 December 2015

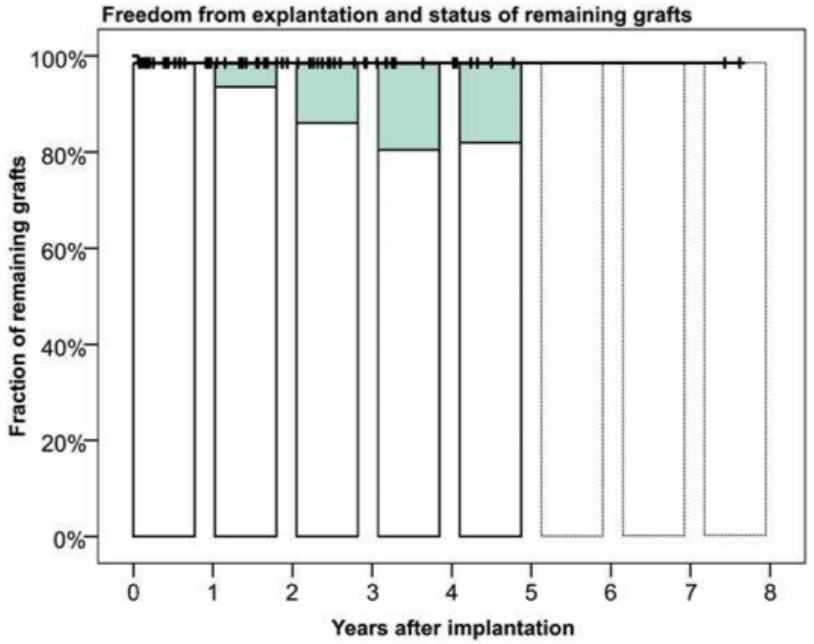


Figure 3: Freedom from explantation including the percentage of conduits with degeneration signs for the DAH (peak gradient >49 mmHg and/or at least moderate regurgitation). For 3 Moldavian patients, only clinical follow-up was available.

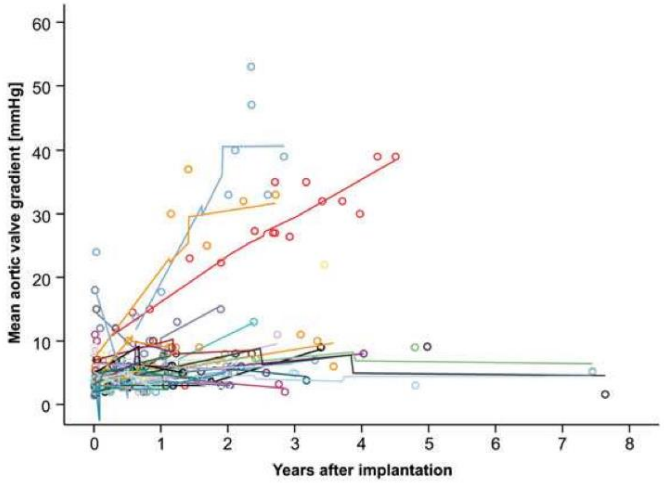


Figure 1: Echocardiographic mean gradient over time in the DAH. Different colours represent different patients; loess-smoothed lines are interpolated between the measurements for each individual. Some individuals show gradients that decrease over time.

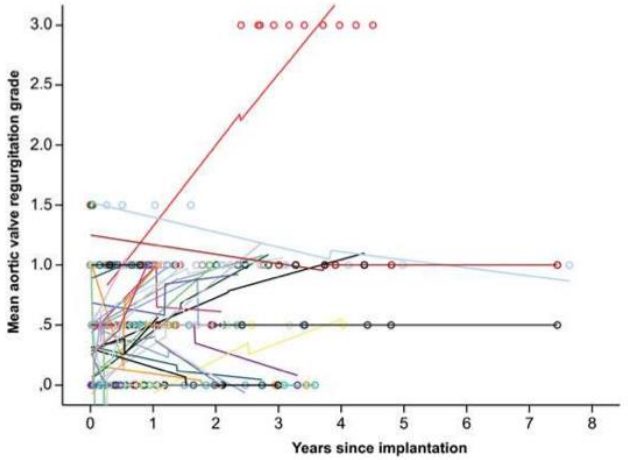


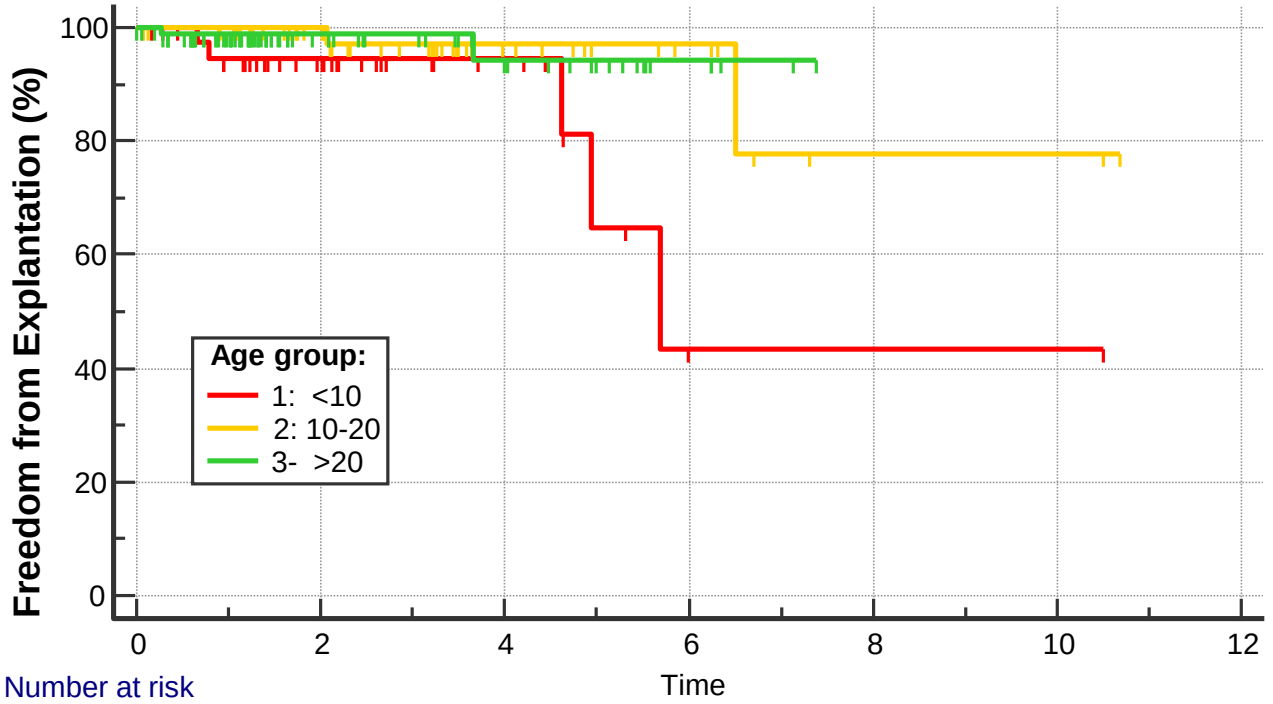
Figure 2: Valvular regurgitation over time in DAH (0 = none, 0.5 = trace, 1 = mild, 1.5 = mild to moderate, 2 = moderate, 2.5 = moderate to severe and 3 = severe). This figure shows the individual aortic valve insufficiency development and loess-smoothed interpolation lines. The decrease of insufficiency is not uncommon.

Overview cell-free homografts 9/2018

	Aortic valve
Period	02/2008-09/2018
Diameter	22.4 ± 3.0 mm
Patients	180 (210 total)
Mean age	27.0 ± 20.0 yrs., (in >40 % as a redo operation)
Age range	0.2-74.4 yrs.
Follow-up	100% (1313 exams)
Patient years total	348.0
Mean follow-up years	2.0 ± 2.1 (max. 9.5)
Max. gradient (mmHg)	16.2 ± 18.0
Regurgitation (Grad 0-3)	0.5 ± 0.6
Freedom from explantation	94.3 % (n=12/210)

Courtesy of Prof Samir Sarikouch - Hannover

Freedom from explantation



Number at risk

Group: 1: <10						
40	23	11	1	1	1	0
Group: 2:10-20						
52	36	15	8	2	2	0
Group: 3- >20						
88	32	20	6	0	0	0

Courtesy of Prof Samir Sarikouch - Hannover

The Early and Midterm Function of Decellularized Aortic Valve Allografts

Francisco D. A. da Costa, MD, Ana Claudia B. A. Costa, Roberta Prestes, Ana Carolina Domanski, MD, Eduardo Mendel Balbi, MD, Andreia D. A. Ferreira, MD, and Sergio Veiga Lopes, MD

Department of Cardiac Surgery, Santa Casa de Curitiba, Pontificia Universidade Catolica do Parana, and Institute of Neurology and Cardiology of Curitiba, Curitiba, Paraná, Brazil

Conclusions. The early and midterm results with DAVA demonstrated stable structural integrity, low rate of calcification, and adequate hemodynamics. Although longer periods of observation are necessary, DAVA appears to be a promising alternative for aortic valve replacement in selected patients.

(Ann Thorac Surg 2010;90:1854–61)

CLINICAL DATA

- **Study Period:** **Nov 2005 – Sep 2018**
- **Patients:** **n= 125 (High Risk Profile]**
- **Age:** **47 ± 18,6 (min=0,1 – max=81)**
- **Sex:** **Males = 82, Females =43**
    - 27 Concomitant Mitral Valve Disease (Multiple Reoperations]
    - 20 Ascending Aorta / Hemiarch Aneurysm
    - 27 Bacterial Endocarditis
    - 8 Coronary Artery Disease

Data	n	%
Valvular Lesion		
Aortic Stenosis	46	36,8
Aortic Insufficiency	50	40
Mixed Lesion	29	23,2
Etiology		
Rheumatic	18	14,4
Congenital	32	25,6
Degenerative	24	19,2
Prosthetic Valve Dysfunction	21	16,8
Endocarditis	28	22,4
Acute Aortic Dissection	1	0,8
Unknown	1	0,8
NYHA Classe Funcional		
I	9	7,2
II	69	55,2
III	39	31,2
IV	8	6,4
Operation		
Primary	70	56
Reoperation	55	44

OPERATIVE DATA

- **Surgical Technique**
  Aortic Root Replacement in all patients

- **Allograft Diameter**
  21,6 ±2,5 mm (min=6, max=28)

- **Cross-Clamp Time**
  110,7±26,1min (min=60, max=215)

- **Extracorporeal Circulation Time**
  141,4±45,4min (min=80, max=270)

POSTOPERATIVE EVALUATION

- Clinical Examination

- Echocardiography
  - Before hospital discharge
  - 6/12 months PO, annualy thereafter
  - CT Scan
  - MRI

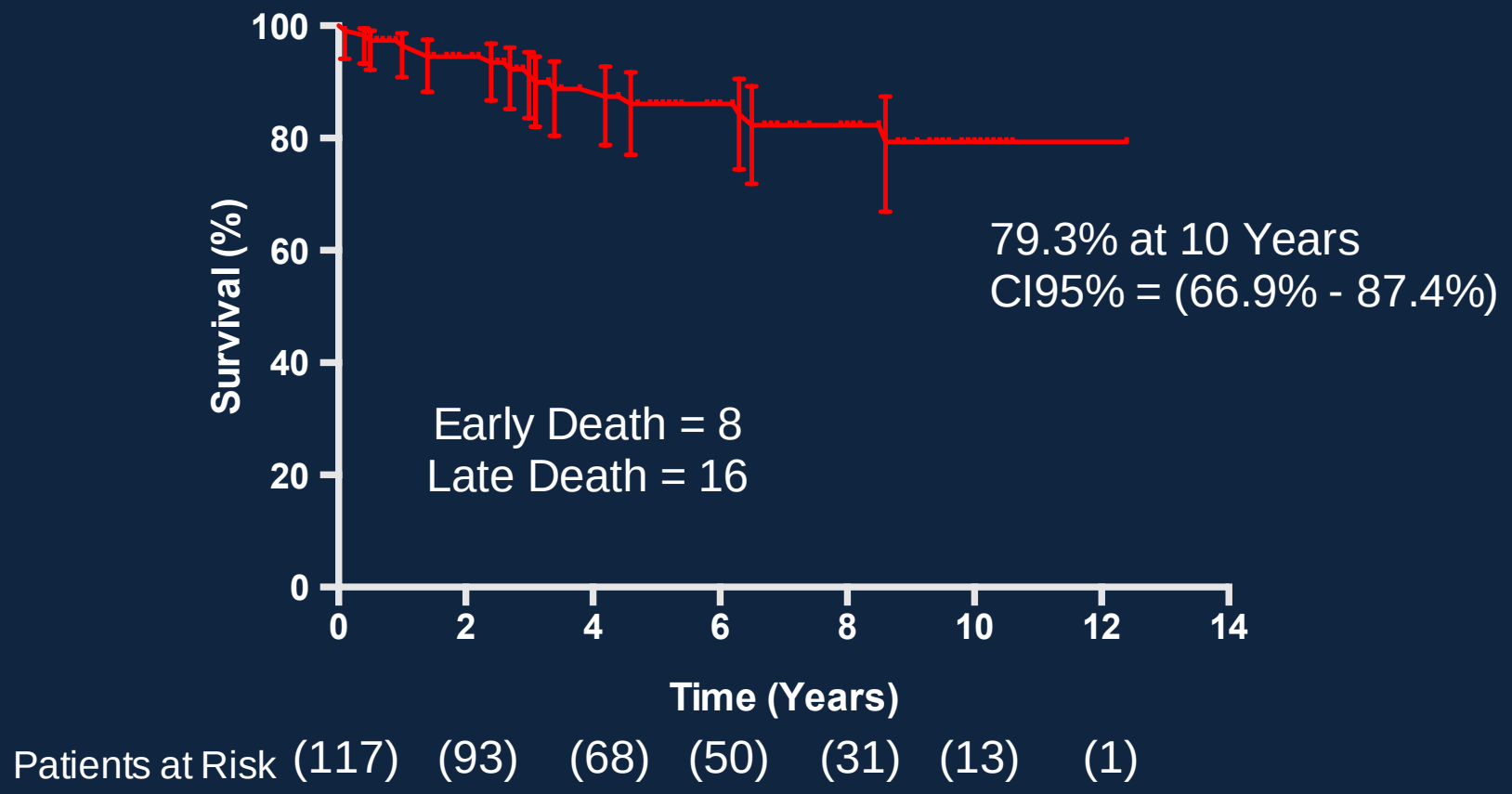
- Follow-up
  - Clinical Follow-up – 106 patients (90,1% complete)
  - Mean clinical follow-up time = 4,9 years (0,1 – 12,4)

DECELLULARIZED AORTIC VALVE ALLOGRAFTS RESULTS

Early Mortality = 6.4% (8/125)

- Low Cardiac Output 4
- Sepsis and Multiorgan Failure.....2
- Cardiogenic Shock 2

AVR WITH DECELLULARIZED AORTIC VALVE ALLOGRAFTS LATE SURVIVAL



DECELLULARIZED AORTIC VALVE ALLOGRAFTS CAUSES OF LATE DEATH (N=16)

Sudden Death 2

Pneumonia 2

Cancer.....2

Brain Stroke 1

Acute Myocardial Infarction 2

Reoperation for CABG 2

DVP– Pulmonary Embolism 1

Trauma.....1

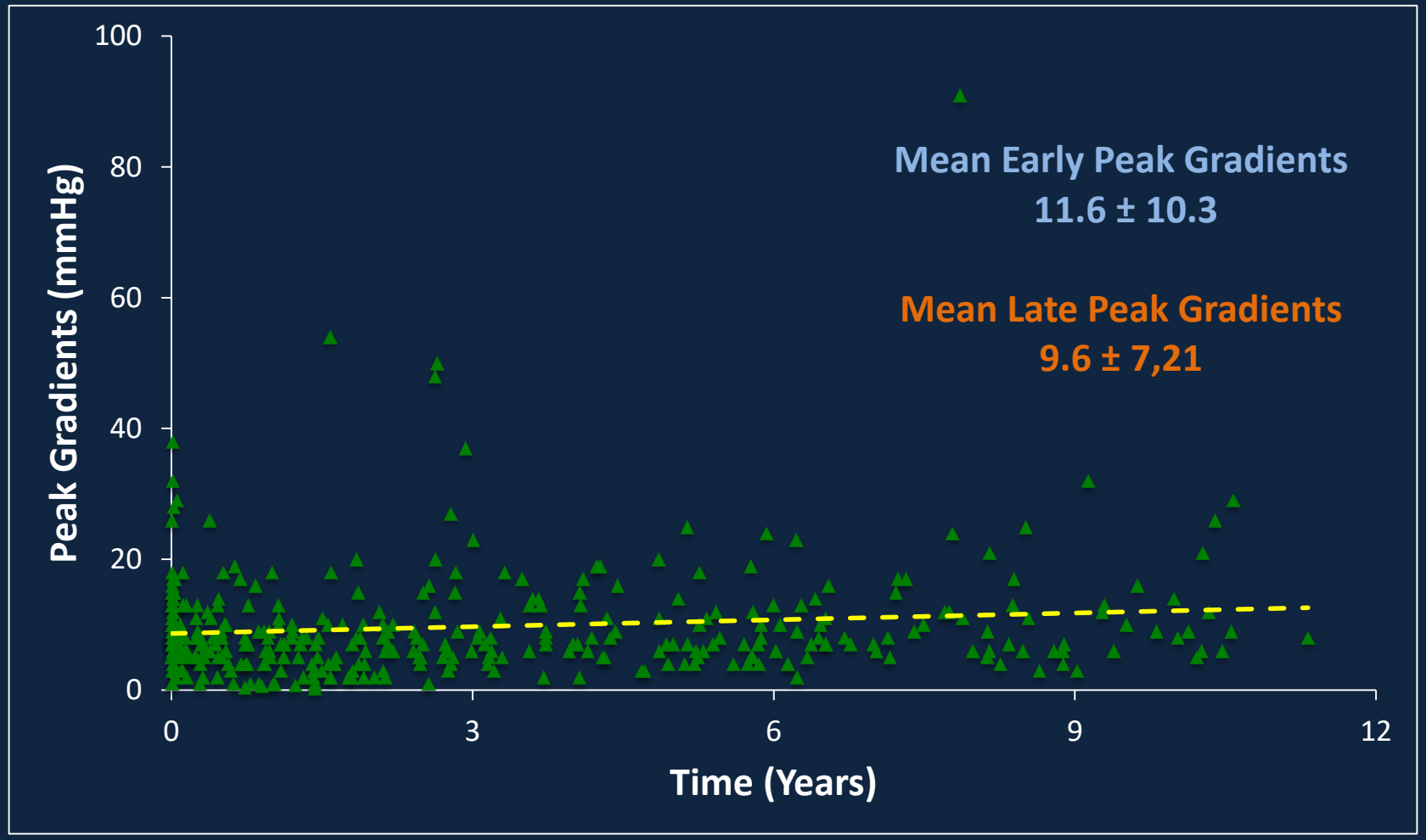
Unknown 3

RESULTS

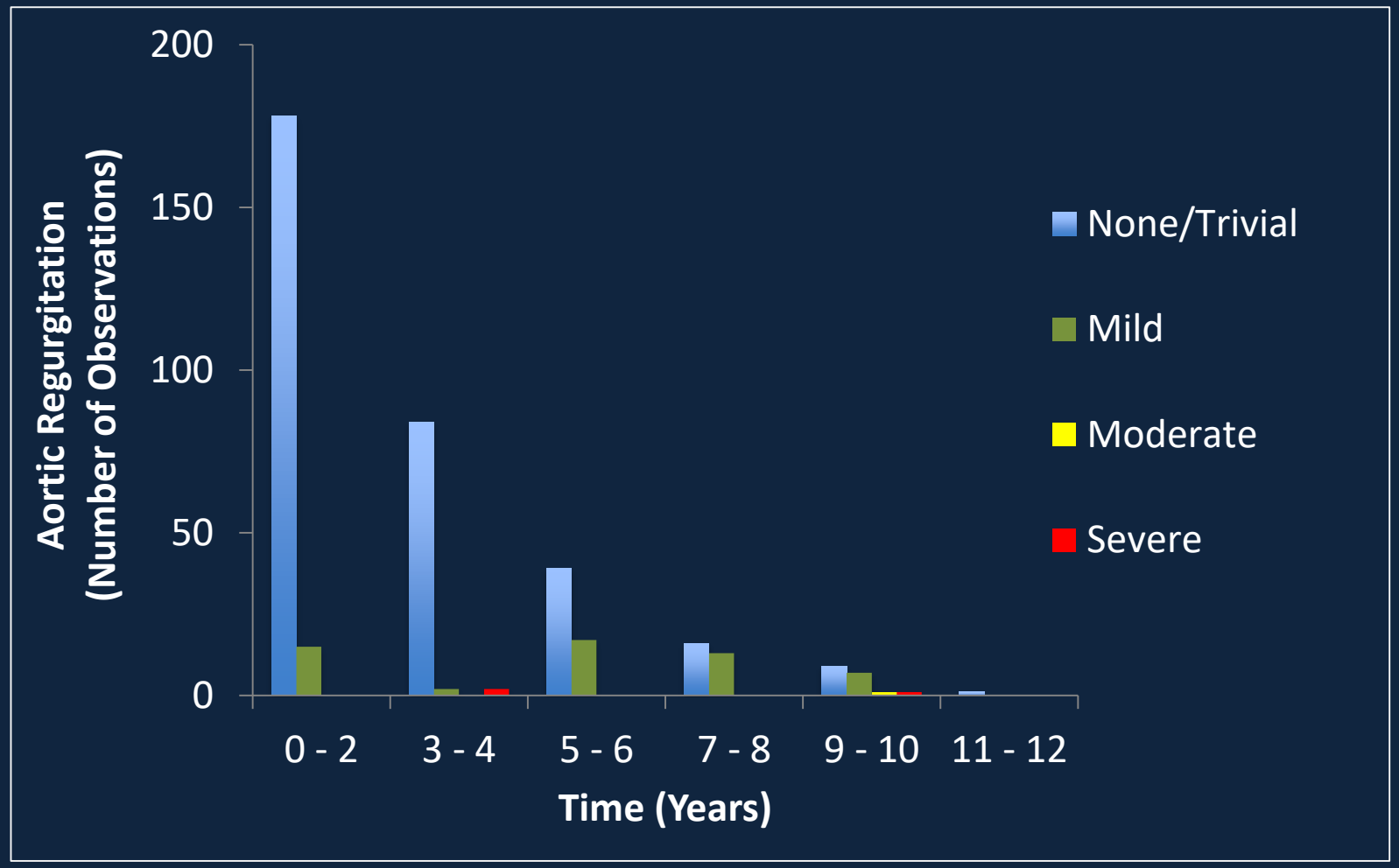
CLINICAL FOLLOW-UP

- Late Functional Status
  - NYHA I - 91 patients
  - NYHA II - 14 patients
  - NYHA III - 1 patient
  - NYHA IV – 0 patient
- 2 cases of Thromboembolism
- No case of Bleeding
- 1 case of Bacterial Endocarditis

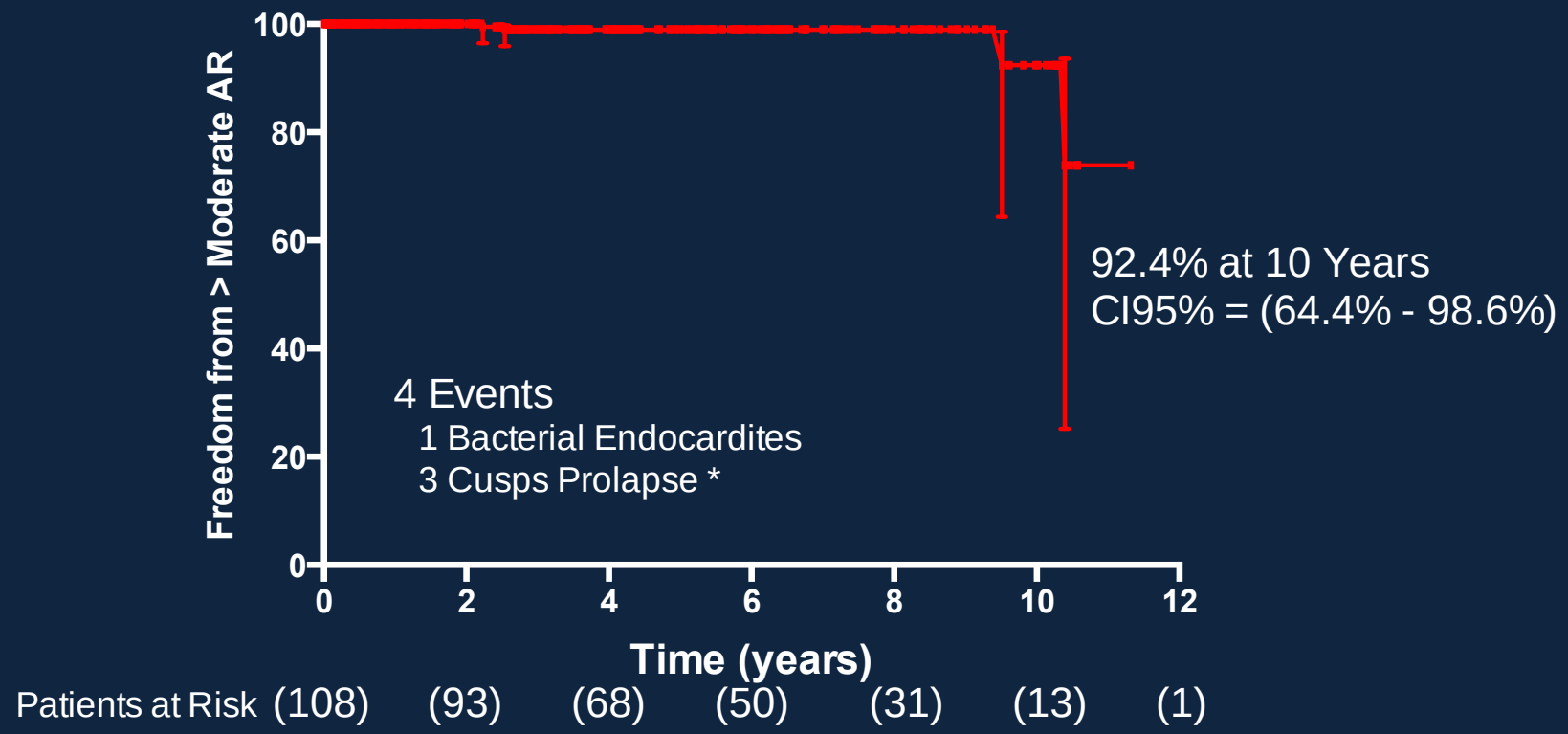
DECELLULARIZED AOTIC VALVE ALLOGRAFTS EARLY AND LATE MAX INSTANTANEOUS GRADIENTS



DECELLULARIZED AORTIC VALVE ALLOGRAFTS
AORTIC REGURGITATION



DECELLULARIZED AORTIC VALVE ALLOGRAFTS
FREEDOM FROM ≥ MODERATE AR

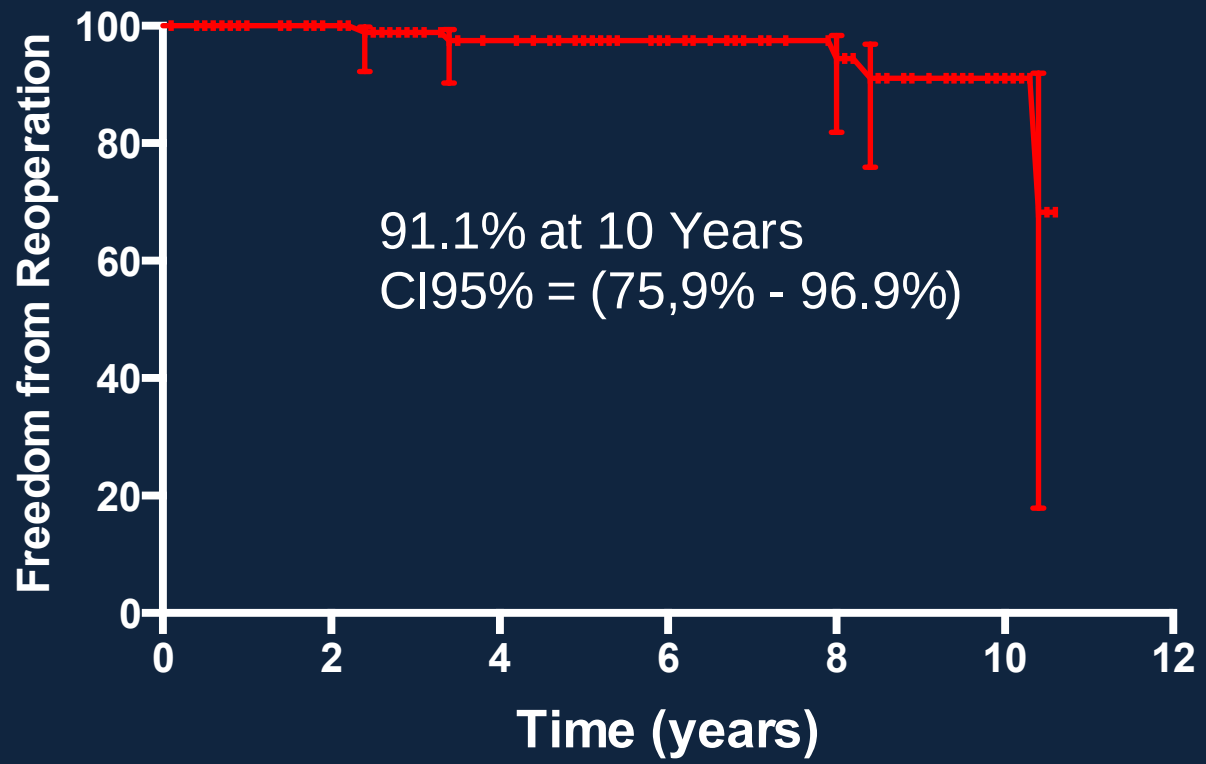


DECELLULARIZED AORTIC VALVE ALLOGRAFTS REOPERATIONS(N=5)

- AR due to Healed Bacterial Endocarditis……1
- Primary Cusp Prolapse * ……..3
- Patient Outgrowth ……1

* 1 PATIENT REOPERATED ELSEWHERE – NO ECHO AVAILABLE – SURGEON REPORT ONLY

DECELLULARIZED AORTIC VALVE ALLOGRAFTS
FREEDOM FROM REOPERATION ON THE ALLOGRAFT



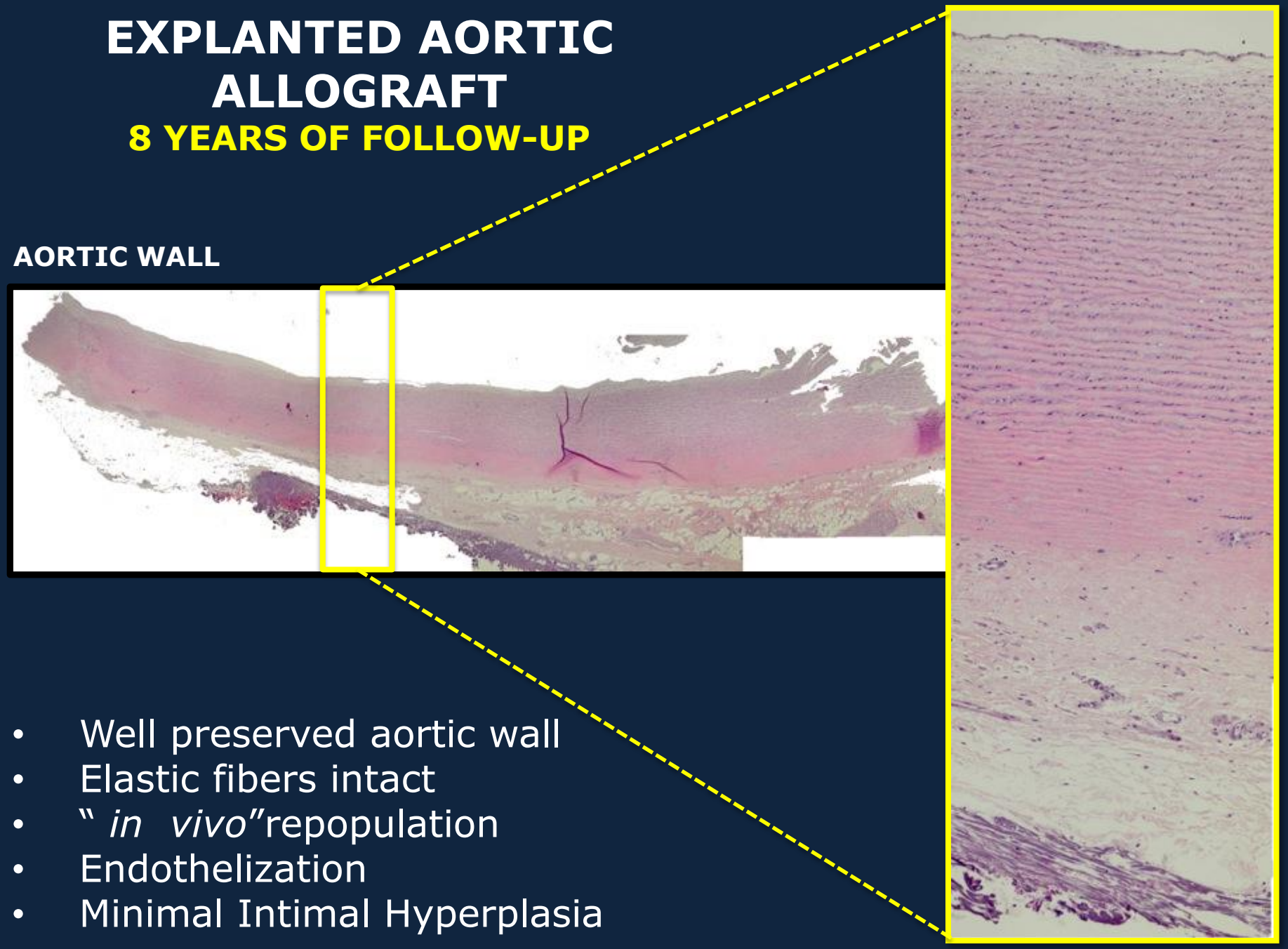
Patients at Risk	(117)	(93)	(68)	(50)	(31)	(13)	(1)


FREITAS, LUCAS
13-09-24-094015
I.N.C
24/9/2013
09:48:14
PHILIPS
Compr = 1,10 cm
A
EMBF
S4-2
MI 1,6
TIS 0,7
H3 Gn 23
232dB/C2
E/2/0
30Hz Zoom
T
P
R
1,9 3,8

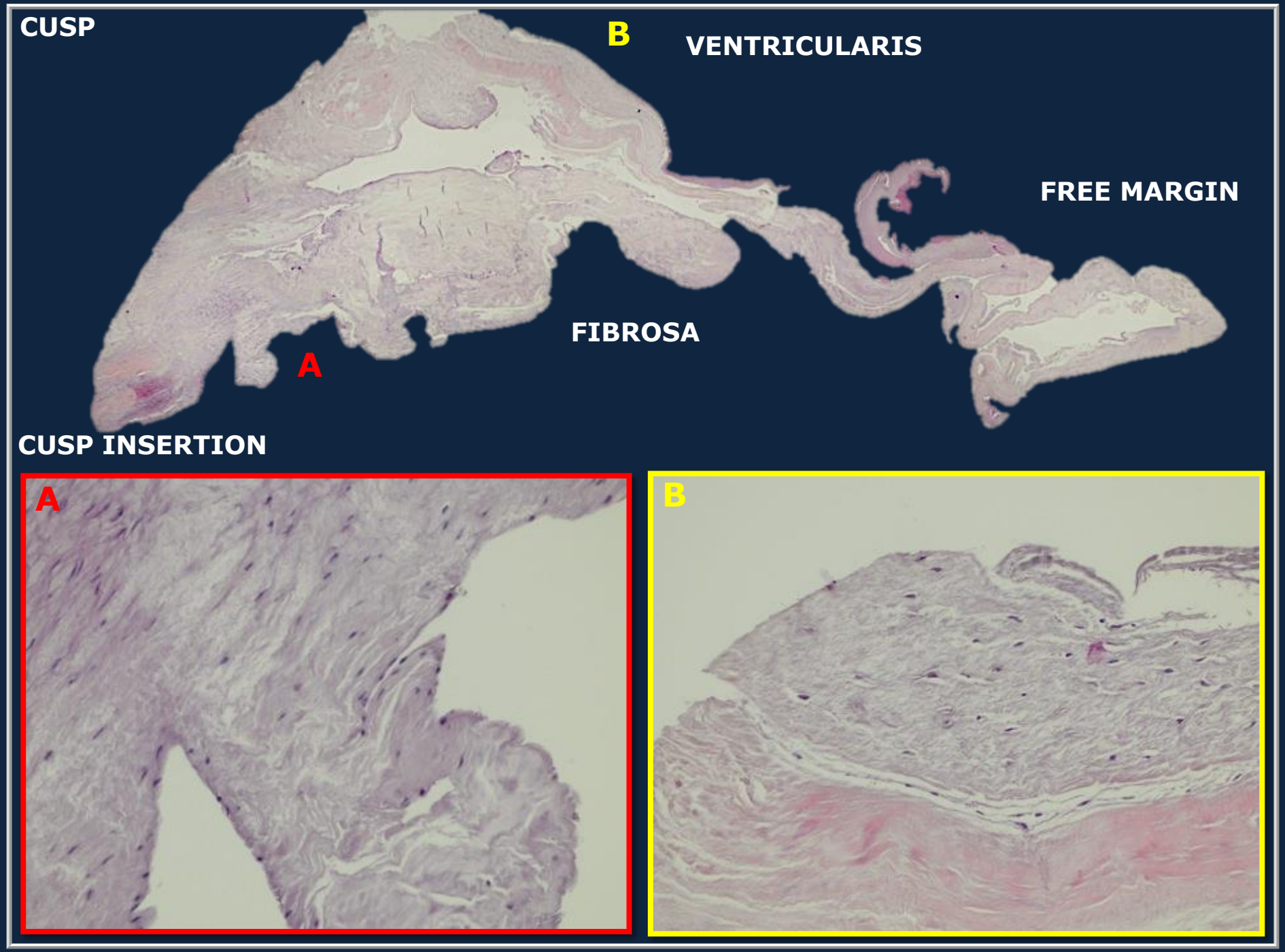
EXPLANTED AORTIC ALLOGRAFT

8 YEARS OF FOLLOW-UP

AORTIC WALL

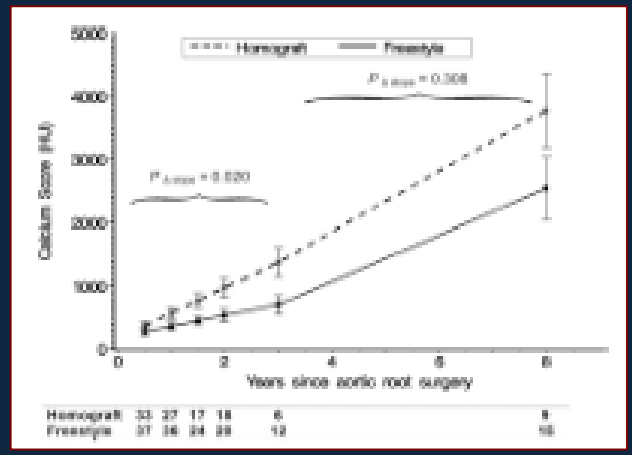


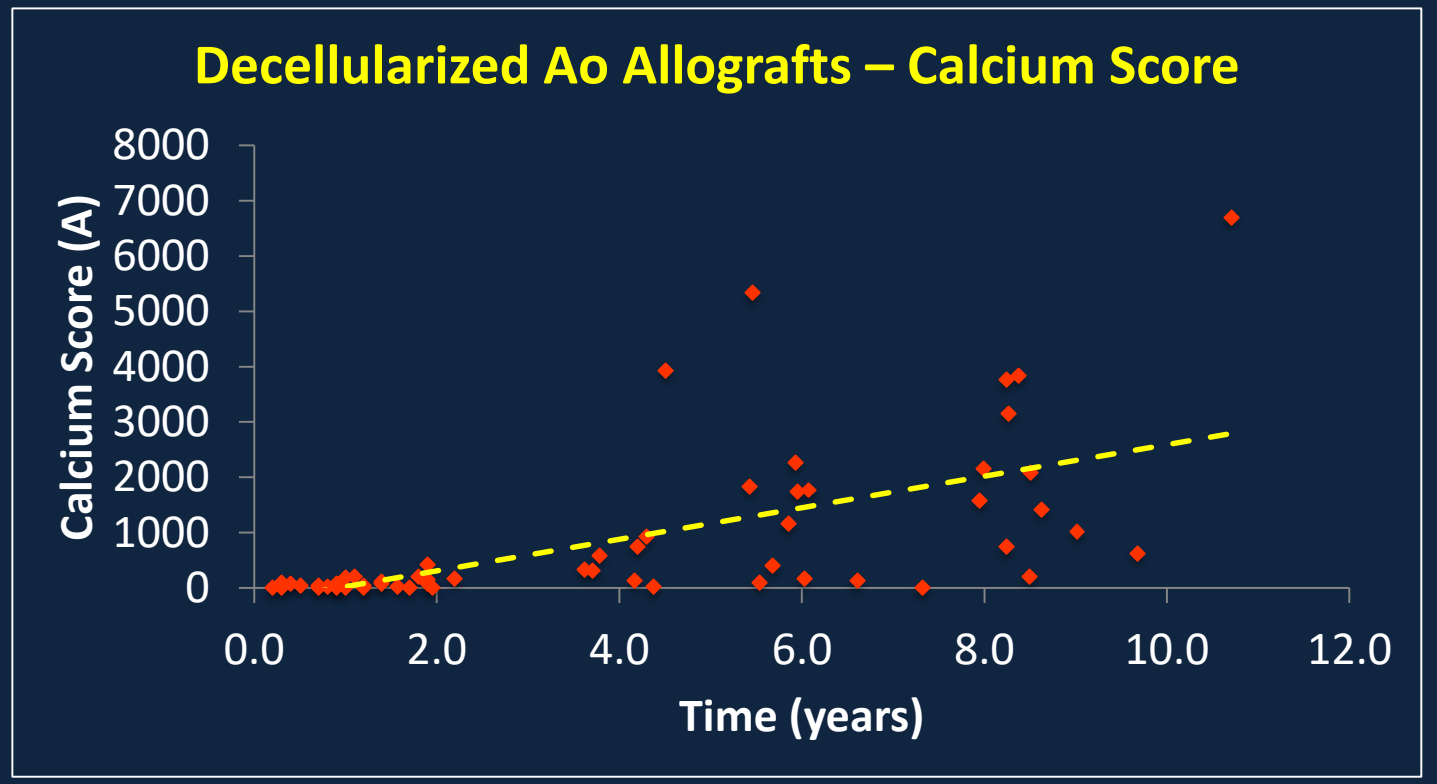
- Well preserved aortic wall
- Elastic fibers intact
- " *in vivo*"repopulation
- Endothelization
- Minimal Intimal Hyperplasia


CUSP
B
VENTRICULARIS
FREE MARGIN
FIBROSA
A
CUSP INSERTION
A
B

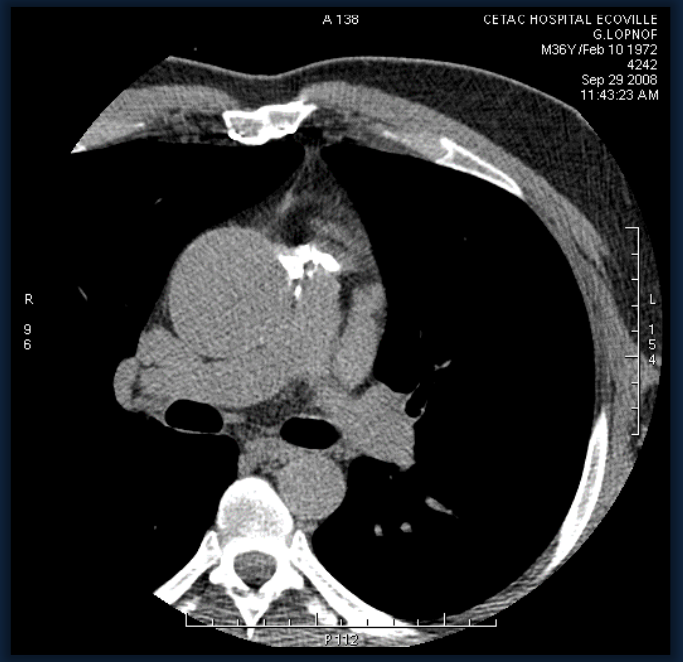
The Early and Midterm Function of Decellularized Aortic Valve Allografts

Francisco D. A. da Costa, MD, Ana Claudia B. A. Costa, Roberta Prestes, Ana Carolina Domanski, MD, Eduardo Mendel Balbi, MD, Andreia D. A. Ferreira, MD, and Sergio Veiga Lopes, MD



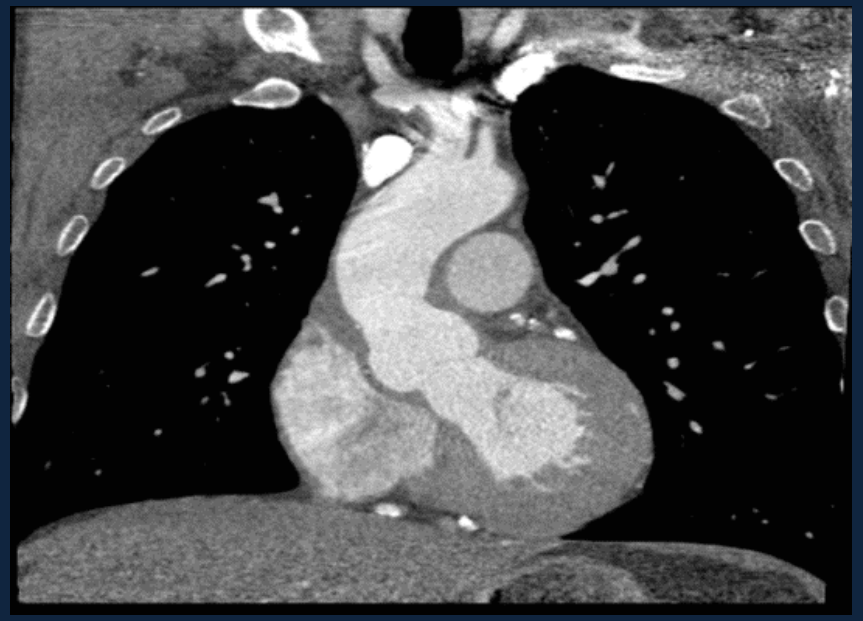


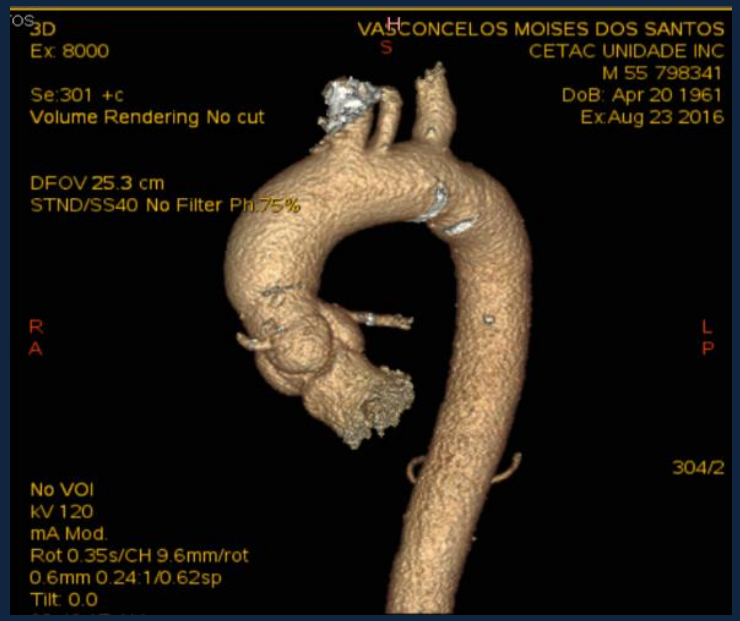
CT SCAN EVALUATION – CALCIUM SCORES -



ABSENT OR MINIMAL CALCIFICATION ON CUSPS AND CONDUITS AT 8 YEARS OF FOLLOW-UP !!!!!

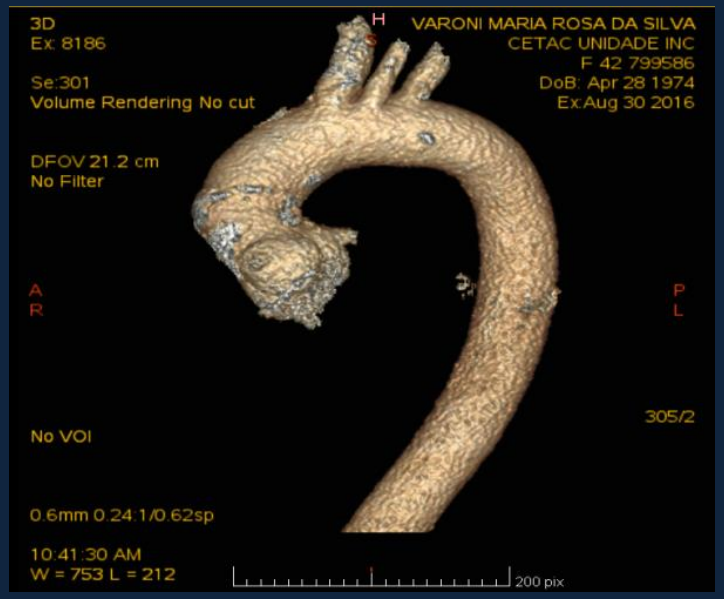
CT SCAN EVALUATION – CALCIUM SCORES -





ABSENT OR MINIMAL CALCIFICATION ON CUSPS AND CONDUITS AT 7 YEARS OF FOLLOW-UP !!!!!

CT SCAN EVALUATION – CALCIUM SCORES -



More Intense Calcification on the Aortic Wall Only at 9Years of Follow-up

CONCLUSIONS

Decellularized Allografts have shown very promising results up to 12 years of follow-up. They are well incorporated to the host, with minimal inflammation and negligible immune reaction. They do not retract in the pulmonary circulation and do not dilate in the systemic side. Occasional biopsies have demonstrated partial repopulation of these grafts and minimal or absent calcification, even in children under the age of 12 years. These data demonstrate that decellularized allografts have, at least up to 10 years, better performance than conventional cryopreserved allografts and they are currently our graft of choice for patients at any age.

Contact:

Francisco Diniz Affonso da Costa

E-mail:

fcosta13@me.com

Phone:

(55) 41-32411200 / (55) 41-32411209