La degenerazione delle bioprotesi.
Esistono dei motivi a priori per “aspettarsi” la degenerazione?
Quando si può attendere e quando si deve reintervenire.
Le opzioni terapeutiche e lo spazio per la TAVI.

Prof. Gino Gerosa

Chief, Division of Cardiac Surgery- University of Padova - Padova - Italy

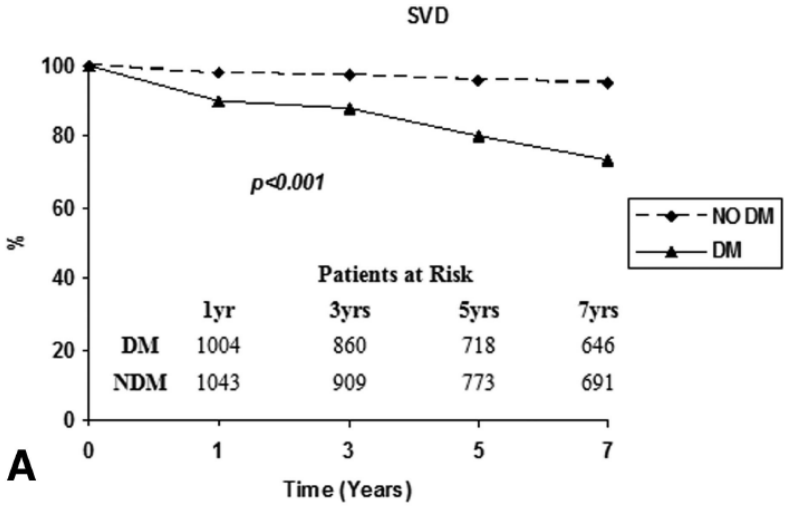
Background

- Degeneration of xenografts depends on
  - Mechanical properties of the valve
  - Host-related immunologic and calcification processes
- Mechanism of calcification
  - Immune-mediated reaction
  - Increased adsorption of proteins related to bone formation
  - Mechanical stress
    - Design of the valve
    - Design of the stent

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
Circulation. 2012;125:604-614

Type 2 Diabetes Mellitus Is Associated With Faster Degeneration of Bioprosthetic Valve : Results From a Propensity Score –Matched Italian Multicenter Study

Roberto Lorusso, Sandro Gelsomino, Fabiana Lucà, Giuseppe De Cicco, Giuseppe Billè, Rocco Carella, Emmanuel Villa, Gianni Troise, Mario Viganò, Carlo Banfi, Carmine Gazzaruso, Pier Gagliardotto, Lorenzo Menicanti, Francesco Formica, Giovanni Paolini, Stefano Benussi, Ottavio Alfieri, Matteo Pastore, Sandro Ferrarese, Giovanni Mariscalco, Germano Di Credico, Cristian Leva, Claudio Russo, Aldo Cannata, Roberto Trevisan, Ugolino Livi, Roberto Scrofani, Carlo Antona, Andrea Sala, Gian Franco Gensini, Jos Maessen and Andrea Giustina



A

Freedom from SVD

Table 4. Multivariate Cox Model*

	HR (95% CI)	*P*
Diabetes	2.39 (2.28–3.52)	<0.001
Age <65 y	1.41 (1.35–2.27)	0.009
Chronic renal failure	1.36 (1.31–2.23)	0.01
Total cholesterol/HDL ≥4	1.19 (1.14–2.00)	0.02
Total cholesterol >200 mg/dL	1.18 (1.12–1.93)	0.02
Triglycerides ≥150 mg/dL	1.16 (1.07–2.03)	0.03
Metabolic syndrome	1.10 (1.02–1.94)	0.08
LDL cholesterol >130 mg/dL	1.05 (0.94–1.75)	0.1
Mitral position	1.00 (0.89–1.70)	0.3
Pericardial bioprosthesis	0.94 (0.81–1.64)	0.6

HR indicates hazard ratio; CI, confidence interval; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

*Model with a robust variance estimate that accounts for clustering within matched pairs.

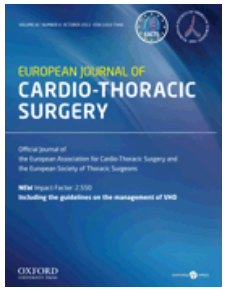
Independent predictors of SVD

Inflammation and calcification mechanisms

- Immune response theory
- Glutaraldehyde intrinsic proinflammatory effect
- Shear stress theory
  - PPM

Post-implantation prosthetic tissue degeneration

Glutaraldehyde treated Heart Valve Bioprostheses (HVBs) in younger patients have been limited by early failures due to the onset of immune response and calcification phenomena which begin after only six years from the implant.

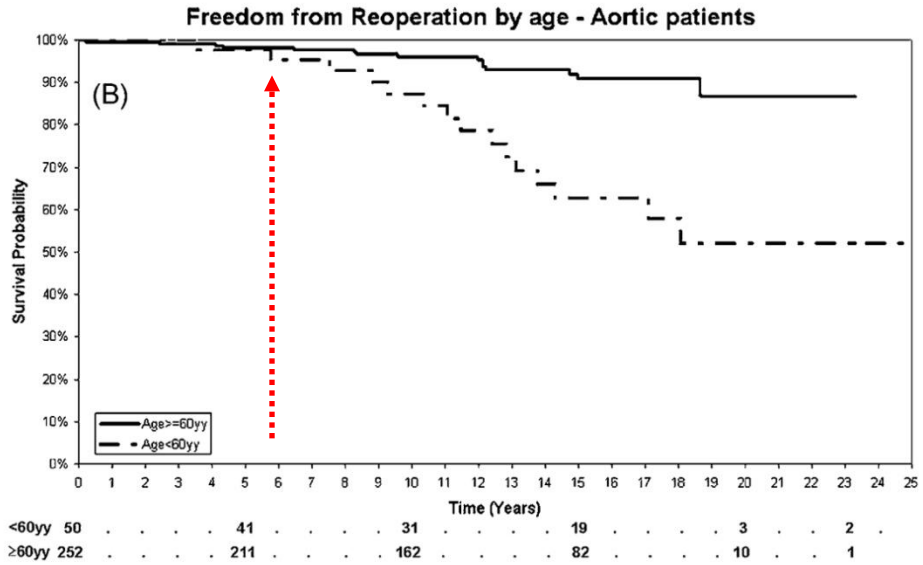


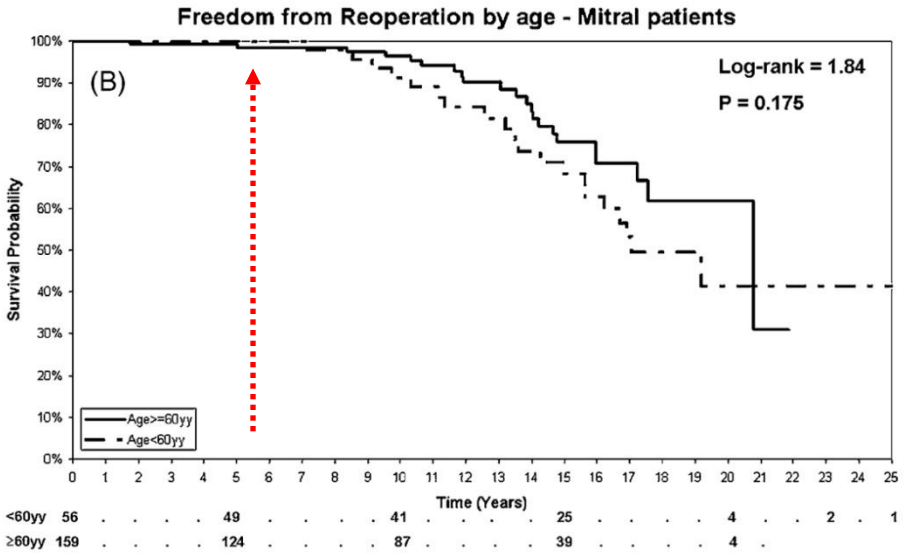
The fate of Hancock II porcine valve recipients 25 years after implant☆

Carlo Valfrè [a,*], Paolo Ius [a], Giuseppe Minniti [a], Loris Salvador [a], Tomaso Bottio [b], Francesco Cesari [a], Giulio Rizzoli [b], Gino Gerosa [b]

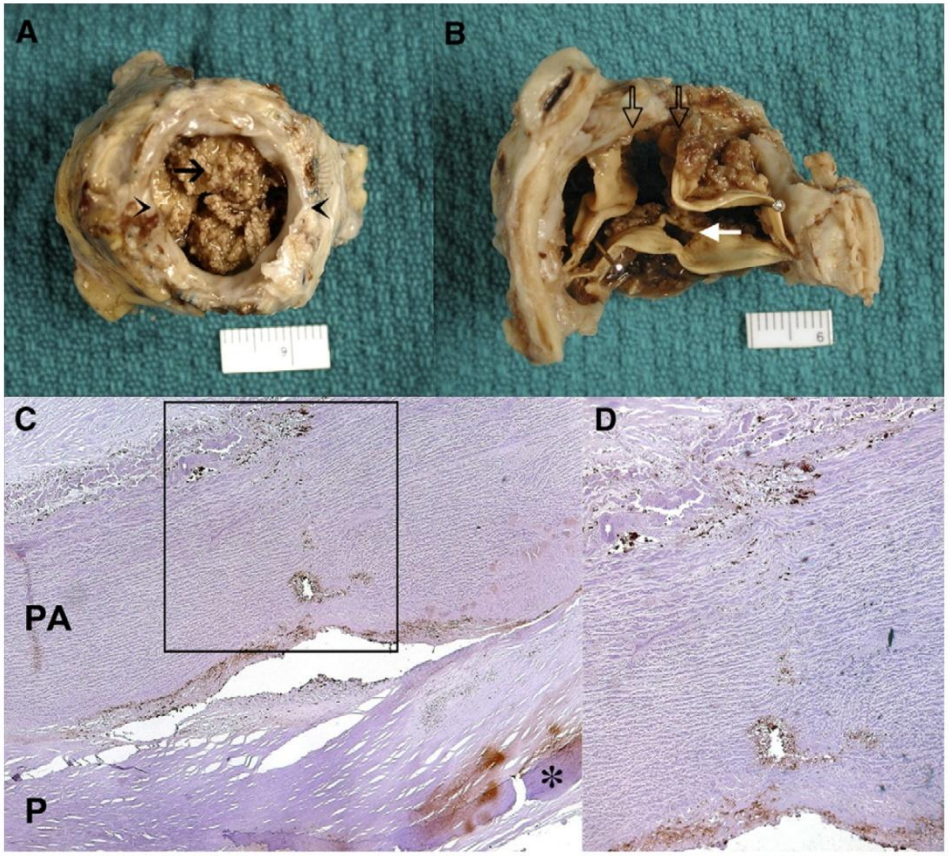
[a] *Cardiovascular Surgery Department, Cà Foncello Hospital, Treviso, Italy*
[b] *Department of Cardiothoracic and Vascular Surgery, University Hospital, Padova, Italy*

Eur J Cardiothorac Surg. 2010 Aug;38(2):141-146.



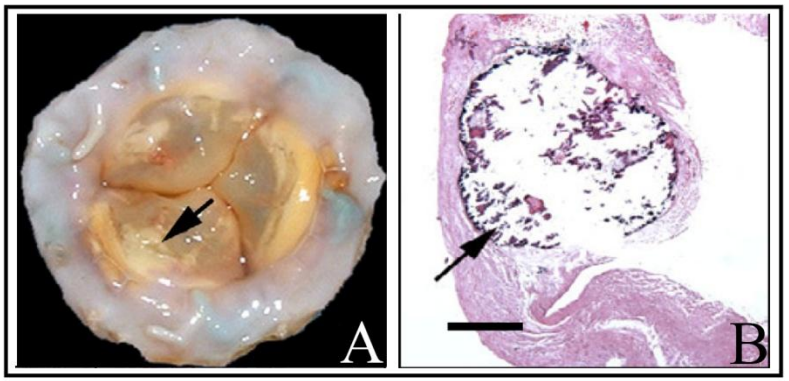


Inflammatory cells and distrophic calcification



A and B – Tissue pannus formation, tears and diffuse nodular calcification of all three cusps;
C - CD68 immunohistochemistry in porcine aorta (PA) with calcification process in pannus (P, asterisk).
Magnification 200X;
D – Higher magnification (400X) of boxed area from panel C;

J.Butany et al. Cardiovascular Pathology 2007;16:258-267

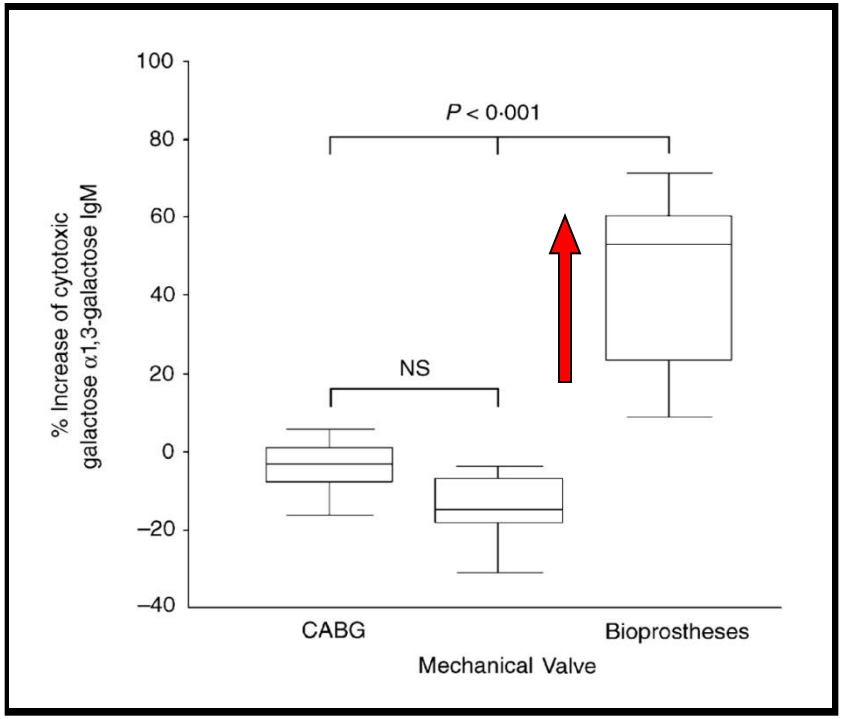


A – Cacific deposit on all three leaflets
B – Von Kossa staining. Bar=100 um

Connolly et al. Ann Thorac Surg 2011;92:858-865

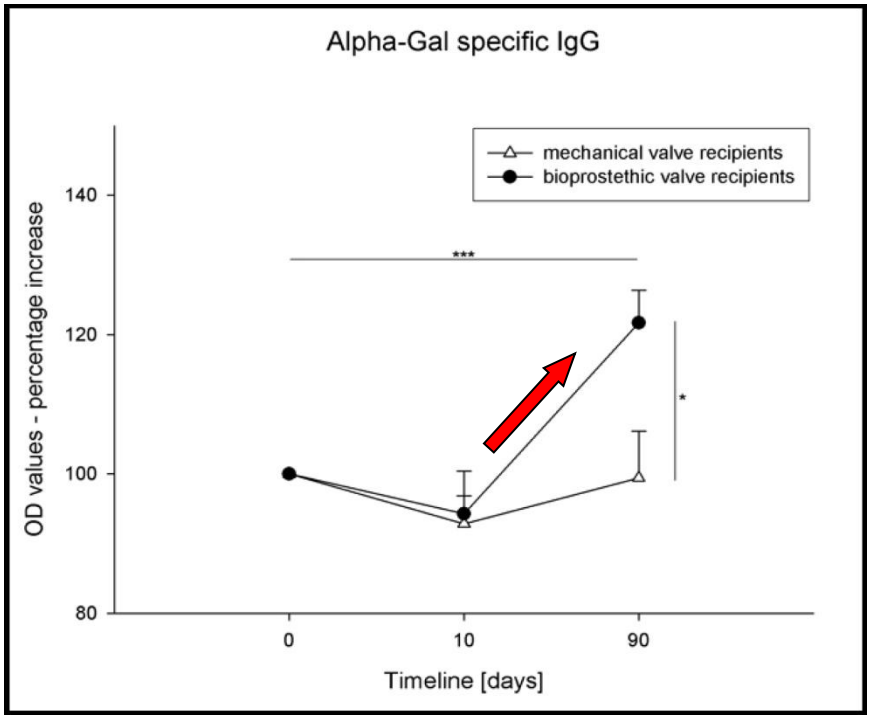
Increasing of specific

α–Gal immune response



Significant increasing of a1,3-galactose IgM antibodies in sera of recipients of bioprosthesis(n=12), mechanical prosthesis (n=12) and coronary artery bypass grafting (CABG, n=12) within 10 days of surgery.

Eur J Clin Invest. 2005 Jan;35(1):17-23.



Evaluation of alpha-Gal specific IgGrevealed a significant increase three months after bio-valve implantation.

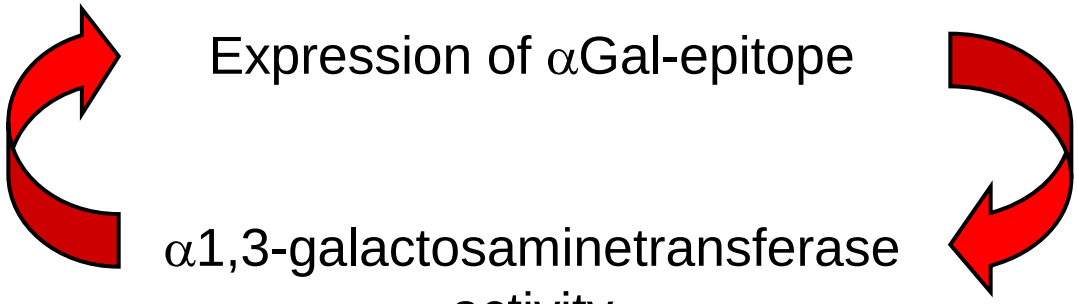
Mangold A et al. Thorac Cardiovasc Surg. 2009;57(4):191-5.

Gal α1 – 3Galβ1 – 4GlcNAc - R

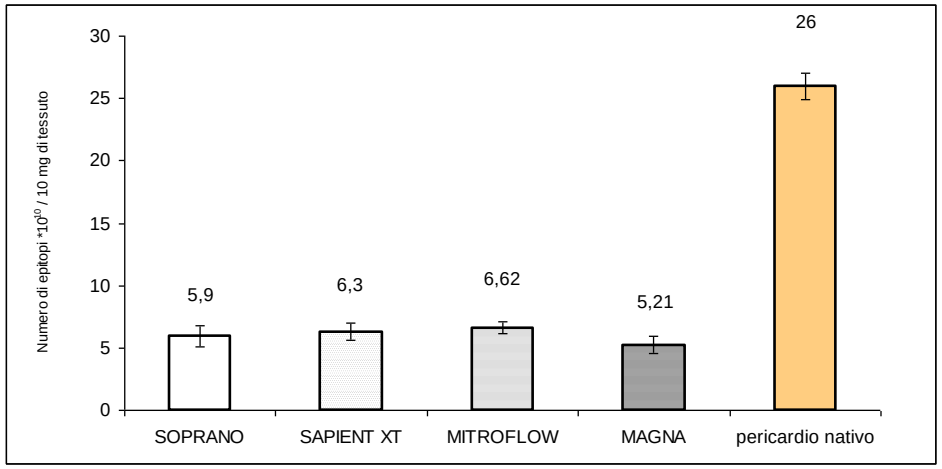
Expression of α-gal epitopes, α1,3galactosyltransferase (α1,3GT) and anti-Gal in mammals

Mammals	α-gal epitope expression	α1,3GT activity	Anti-Gal production
Marsupials	+	+	–
Non-primate mammals	+	+	–
Prosimians	+	+	–
New World monkeys	+	+	–
Old World monkeys	–	–	+
Apes	–	–	+
Humans	–	–	+

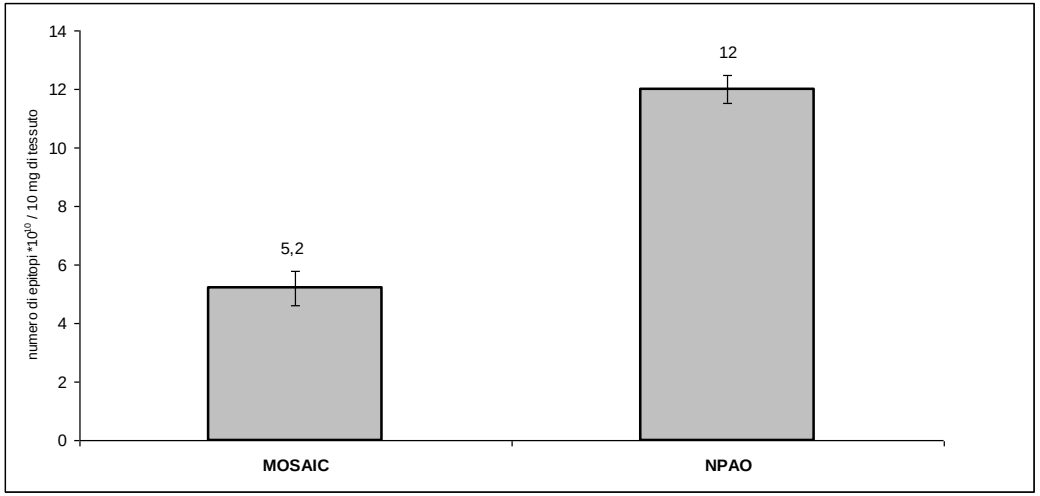
2007 Biochimica et Biophysica Acta – Galili *et al.*



Alpha-gal in commercially available bioprostheses



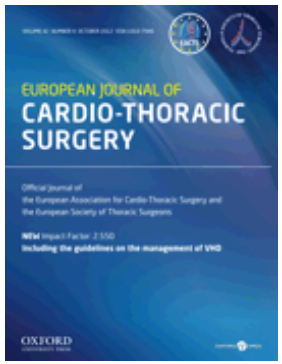
2012, Unpublished data



Alpha-gal e degenerazione bioprotesi

- In pazienti sottoposti ad AVR con bioprotesi si è riscontrato un aumento del titolo anticorpale diretto contro l'epitopo Alpha-gal
- L'aumento anticorpale nel siero dei pazienti è correlabile ad una effettiva presenza dell'epitopo nel tessuto della bioprotesi
- Si instaura una debole ma costante risposta infiammatoria che, associata ad una predisposizione alla calcificazione ed alla citotossicità della glutaraldeide, può essere implicata significativamente nella degenerazione protesica.
- Il "network" di legami tra glutaraldeide e tessuto, responsabile della tolleranza antigenica (parziale) risulta instabile nel tempo (basi di Schiff). Questo comporta un lento rilascio di residui glutaraldeideidici in circolo ed un conseguente rilassamento della copertura con la possibile esposizione di epitopi precedentemente mascherati

ESC/EACTS GUIDELINES



Guidelines on the management of valvular heart disease (version 2012)

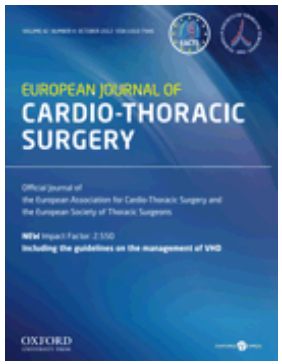
The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

- Reoperation is recommended in symptomatic patients with a significant increase in trans-prosthetic gradient or severe regurgitation (recommendation class I, level of evidence C)

- Reoperation should be considered in asymptomatic patients with any significant prosthetic dysfunction, provided they are at low risk for reoperation (recommendation class IIa, level of evidence C).

ESC/EACTS GUIDELINES

European Heart Journal (2012) **33**, 2451–2496
European Journal of Cardio-Thoracic Surgery 42 (2012) S1–S44



Guidelines on the management of valvular heart disease (version 2012)

The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

- Prophylactic replacement of a bioprosthesis implanted 10 years ago, without structural deterioration, may be considered during an intervention on another valve or on the coronary arteries (recommendation class IIb, level of evidence C).

- Treating bioprosthetic failure by transcatheter valve-in-valve implantation has been shown to be feasible. Current evidence is limited, therefore it cannot be considered as a valid alternative to surgery except in inoperable or high-risk patients as assessed by a ‘heart team’

Reoperation is not an independent predictor of mortality during aortic valve surgery

J Thorac Cardiovasc Surg 2006;131:329-35

Piroze M. Davierwala, MD, Michael A. Borger, MD, PhD, Tirone E. David, MD, Vivek Rao, MD, PhD, Manjula Maganti, MSc, and Terrence M. Yau, MD, MSc

TABLE 3. Distribution of postoperative outcomes

Variable	Primary AVR	Redo AVR	Bentall-after-AVR	*P* value
Mortality (%)	2.3	4.6	2.4	.1
Low output syndrome (%)	5.7	4.6	7.3	.7
Postoperative MI (%)	1.6	0.9	0	.4
Postoperative stroke (%)	2.4	4.6	2.4	.1
Postoperative renal failure (%)	2.1	4.2	4.9	.04
Pacemaker insertion (%)	5.6	14	26	<.0001
Reopening for bleeding (%)	4.3	6.9	9.8	.02
Duration of ventilation (h)	19 ± 41	25 ± 52	26 ± 77	.1
Duration of ICU stay (h)	54 ± 71	61 ± 63	74 ± 106	.02
Postoperative hospital stay (d)	10 ± 7.4	11 ± 8.1	12 ± 9.4	.02

AVR, Aortic valve replacement; *MI*, myocardial infarction; *ICU*, intensive care unit.

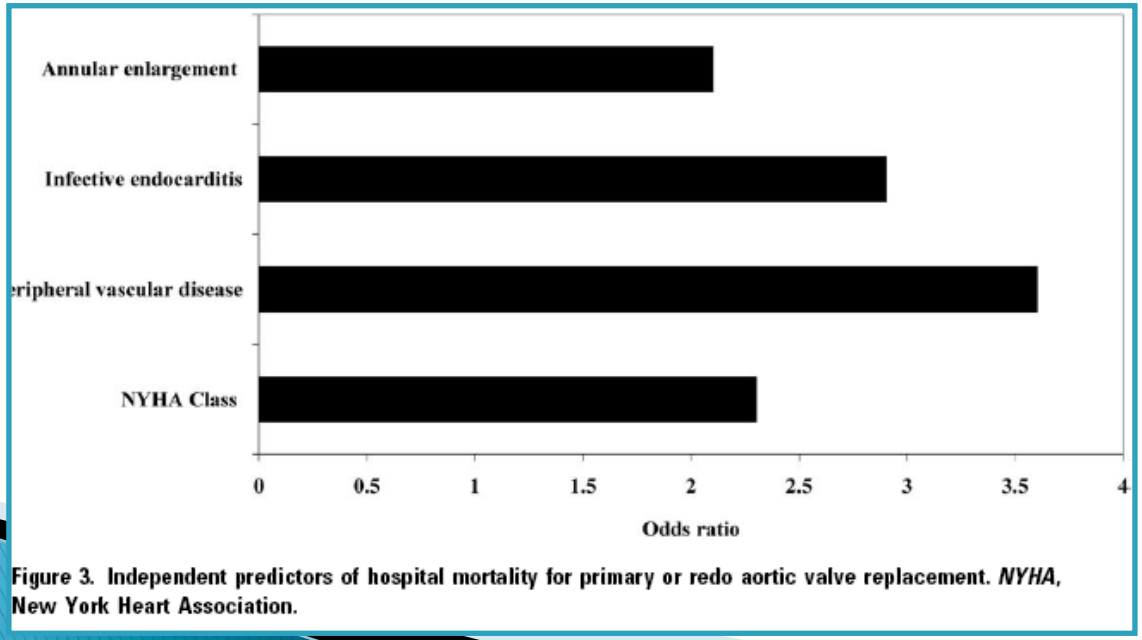


Figure 3. Independent predictors of hospital mortality for primary or redo aortic valve replacement. *NYHA*, New York Heart Association.

CURRENT RESULTS FOR AVR IN REDO: PADUA-EXPERIENCE (GEN 2003 – APR 2011)

DEMOGRAPHICS

Total	78 pts
Mean age (yrs)	62.2 ± 15.5
	(min 23.2 – max 88.9)
Emergency	3.8%
Hypertension	52.5%
AMI	8.9%
STROKE	7.6%
COPD	16.6%
CRF	21.7%
PVP	16.6%
EF < 40%	14.1%
Pulmonary hyp	25.6%
NYHA III-IV	44,8%

RESULTS

In hospital mortality	7.6% (6 pts)
IABP	5.1%
AMI	5.1%
ARF	17.9%
STROKE	1.2%
BAV + PM	6.4%
Respiratory failure	7.6%
AF	23%
Mean ICU stay (dys)	2.5 ± 2.9
	Median: 2

CURRENT RESULTS FOR AVR IN REDO AVR:

PADUA EXPERIENCE

(GEN 2003 – APR 2011)

DEMOGRAPHICS

Total	40 pts
Mean age (yrs)	60,4 ± 13,7 (min 29.5 – max 82,9)
Emergency	5%
Hypertension	47.5%
AMI	5%
STROKE	2.5%
COPD	22.5%
CRF	20%
PVD	7.5%
EF < 40%	12.5%
Pulmonary hyp	17.5%
NYHA III-IV	42.5%

RESULTS

In hospital mortality	5% (2 pts)
IABP	0%
AMI	2.5%
ARF	7.5%
STROKE	0%
BAV + PM	12.5%
Respiratory failure	5%
AF	25%
Mean ICU stay (dys)	2.3 ± 3 Median: 2

Italian registry of Trans-Apical aortic valve implantation (I-TA)

- Spontaneous
- Independent
- Prospective
- Multicenter
- Includes all TA-TAVI performed in Italy since this procedure became available in 2008

Participating study sites

- Clinica Montevergine, Mercogliano
- Centro Cardiologico Monzino, Milan
- San Bortolo Hospital, Vicenza
- San Camillo Hospital, Rome
- University of Padova
- University of Turin
- Humanitas Gavazzeni Hosp., Bergamo
- G. Pasquinucci Heart Hospital, Massa
- University of Bologna
- San Raffaele Hospital, Milan
- Ospedale Dell'Angelo, Venice-Mestre
- University of Pavia
- Ospedale Mauriziano Umberto I, Turin
- S. Maria Misericordia Hospital, Udine
- S. Croce e Carle Hospital, Cuneo
- Clinica S. Anna, Catanzaro
- Ospedali Riuniti, TriesteUniversity of Parma
- Hesperia Hospital, Modena
- University of Verona

Aim of the study

- Aim of this study was to evaluate the impact of a previous cardiac operation in high risk or inoperable patients undergoing TA-TAVI, on early and mid-term clinical outcomes in terms of mortality, morbidity and operative complications

European Journal of Cardio-Thoracic Surgery Advance Access published February 20, 2012

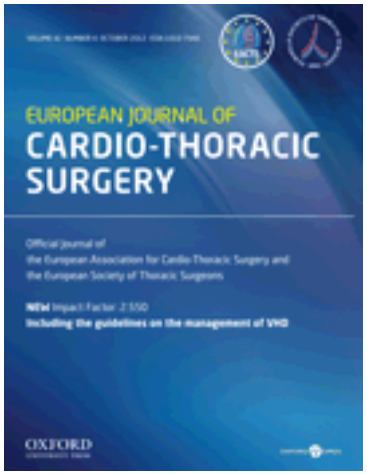
European Journal of Cardio-Thoracic Surgery 0 (2012) 1–6
doi:10.1093/ejcts/ezs027

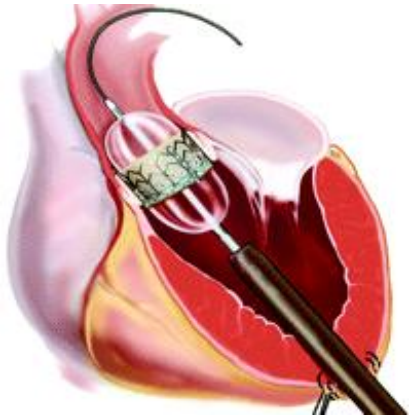
ORIGINAL ARTICLE

Impact of previous cardiac operations on patients undergoing transapical aortic valve implantation: results from the Italian Registry of Transapical Aortic Valve Implantation†

Augusto D'Onofrio[a,*], Paolo Rubino[b], Melissa Fusari[c], Francesco Musumeci[d], Mauro Rinaldi[e], Ottavio Alfieri[f] and Gino Gerosa[a], on behalf of the I-TA investigators

[a] Division of Cardiac Surgery, Centro Gallucci, University of Padova Medical School, Padova, Italy
[b] Invasive Cardiology Laboratory, Cardiology Division, Clinica Montevergine, Mercogliano, Italy
[c] Department of Cardiovascular Sciences, Centro Cardiologico Monzino, IRCCS, University of Milan, Milan, Italy
[d] Department of Cardiac Surgery, San Camillo Hospital, Rome, Italy
[e] Division of Cardiac Surgery, University of Turin, Turin, Italy
[f] Department of Cardiac Surgery, San Raffaele University Hospital, Milan, Italy





Patients

- April 2008 – May 2011

- 566 patients
  - **Group F (first cardiac procedure): 456 (80.6%)**
  - **Group R (at least 1 cardiac operation): 110 (19.4%)**
    - CABG: 66 (60%)
    - Mitral valve surgery: 20 (18.2%)
      - Repair: 13
      - Replacement: 7
    - AVR: 6 (5.5%)
    - AVR+CABG: 3 (2.7%)
    - Other: 15 (13.6%)

Results – All cause 30-day mortality

30-day mortality	Overall (n=566)	Group F (n=456)	Group R (n=110)	P value (F vs. R)
Total 30-day mortality, n(%)	**44 (7.8)**	**36 (7.9)**	**8 (7.3)**	**0.82**
CS/MOF, n(%)	17 (3)	14 (3.1)	3 (2.7)	0.85
Sepsis, n(%)	8 (1.4)	6 (1.3)	2 (1.8)	0.66
Major ventricular arrhythmias, n(%)	5 (0.9)	5 (1.1)	0 (0.0)	0.59
Mesenteric ischemia, n(%)	6 (1.1)	5 (1.1)	1 (0.9)	0.86
Stroke, n(%)	6 (1.1)	5 (1.1)	1 (0.9)	0.86
Bleeding, n(%)	2 (0.4)	1 (0.2)	1 (0.9)	0.35

Results – Operative complications

Operative Complications	Overall (n=566)	Group F (n=456)	Group R (n=110)	P value (F vs. R)
Total operative complications, n(%)	**41 (7.2)**	**31 (6.8)**	**10 (9)**	**0.40**
Need for CPB/ECMO, n(%)	19 (3.3)	15 (3.3)	4 (3.6)	0.85
CPR, n(%)	10 (1.8)	7 (1.5)	3 (2.7)	0.39
PCI, n(%)	8 (1.4)	6 (1.3)	2 (1.8)	0.68
Life threatening or disabling bleeding, n(%)	4 (0.7)	3 (0.7)	1 (0.9)	0.77

Results–Postoperative complications

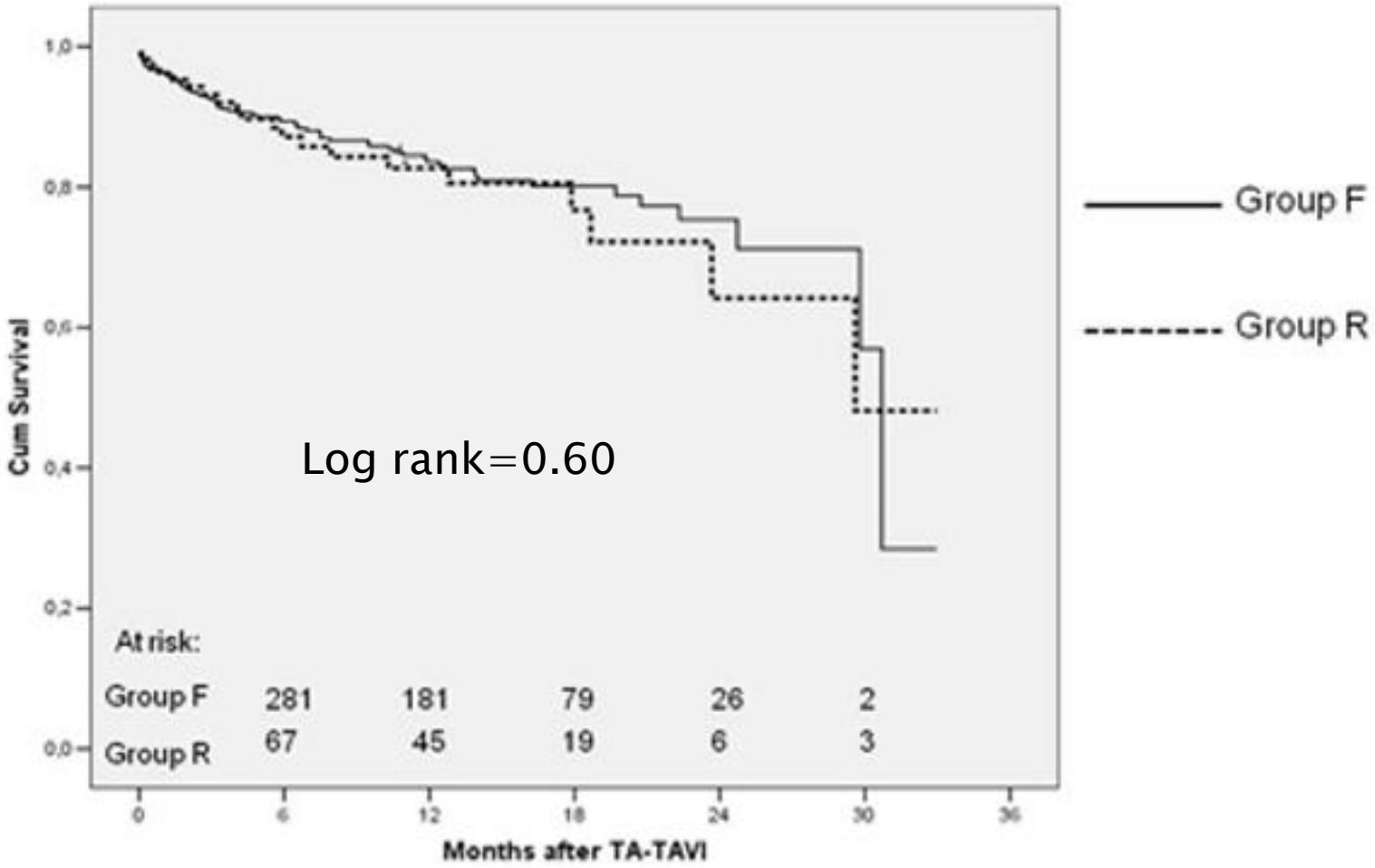
Postoperative complications	Overall (n=566)	Group F (n=456)	Group R (n=110)	P value (F vs. R)
Total post-operative complications, n(%)	**91 (16.1%)**	**71 (15.6)**	**20 (18.2)**	**0.56**
Major stroke, n(%)	18 (3.2)	12 (2.6)	6 (5.5)	0.13
PM implantation, n(%)	30 (5.3)	24 (5.3)	6 (5.5)	0.94
AKI, n(%)	33 (5.8)	28 (6.1)	5 (4.5)	0.65
AMI (Periprocedural and spontaneous) , n(%)	10 (1.8)	7 (1.5)	3 (2.7)	0.41

Group R
Risk factors for 30-day mortality

- Univariate analysis
  - Arterial hypertension
  - Logistic Euroscore
  - Porcelain aorta
  - LVEF
  - Previous PCI

- Multivariate analysis
  - Porcelain aorta (OR: 3.48; 95%CI:1.04-11.68; $p<0.05$)
  - LVEF (OR:0.94; 95%CI:0.89-0.99; $p<0.05$)

Survival in groups F and R



The "valve-in-valve" concept

The Journal of
Thoracic and Cardiovascular Surgery

Transapical aortic valve implantation after previous aortic valve replacement: Clinical proof of the "valve-in-valve" concept

Miralem Pasic, MD, PhD, Axel Unbehaun, MD, Stephan Dreysse, MD, Semih Buz, MD, Thorsten Drews, MD, Marian Kukucka, MD, and Roland Hetzer, MD, PhD

TABLE 3. Data of previous aortic valve replacement and new implanted Edwards SAPIEN transcatheter heart valves

Patients	Time (y)	Prosthesis (type)	Size of old valve (mm)	Stentless	Size of new TAVI valve (Edwards SAPIEN) (mm)	Follow up (mo)
Patient 1	12.0	Homograft	23	+	26	20
Patient 2	8.6	Hancock (Medtronic Inc, Minneapolis, Minn)	23	–	23	19
Patient 3	12.7	Homograft	28	+	26	19
Patient 4	3.6	Hancock (Medtronic Inc)	23	–	23	18
Patient 5	0.9	SAPIEN (Edwards SAPIEN, Edwards Lifesciences, Irvine, Calif)	26	–	26	17
Patient 6	13.9	Freestyle (Medtronic Inc)	23	+	23	17
Patient 7*	6.9	Carpentier-Edwards	21	–	23	3*
Patient 8*	9.3	Mosaic (Medtronic Inc)	23	–	23	5*
Patient 9	14.0	Hancock (Medtronic Inc)	21	–	23	13
Patient 10	13.4	Carpentier-Edwards (after previous homograft)	21	–	23	13
Patient 11	2.7	Hancock ultra (Medtronic Inc)	21	–	23	11
Patient 12	2.1	Hancock ultra	23	–	23	10
Patient 13	9.8	Carpentier-Edwards	23	–	23	3
Patient 14	14.3	Homograft	25	+	26	2

TAVI, Transapical aortic valve implantation. *Patient died during follow-up.

"Valve-in-valve" basic concepts and technical issues

- Previously implanted valve
  - Sizing
  - Patient-prosthesis mismatch
  - Stented/Stentless
  - Pericardial/Porcine
  - Distance from coronary ostia
- Screening
  - Exclude endocarditis
  - Exclude paravalvular leak
- Reduced rate of PM implantation
- Durability
  - Leaflets folding for incomplete opening
  - "Bridge to redo"
- No balloon dilatation before TAVI deployment
  - Embolization
  - Severe aortic regurgitation
- Reduced use of contrast medium

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

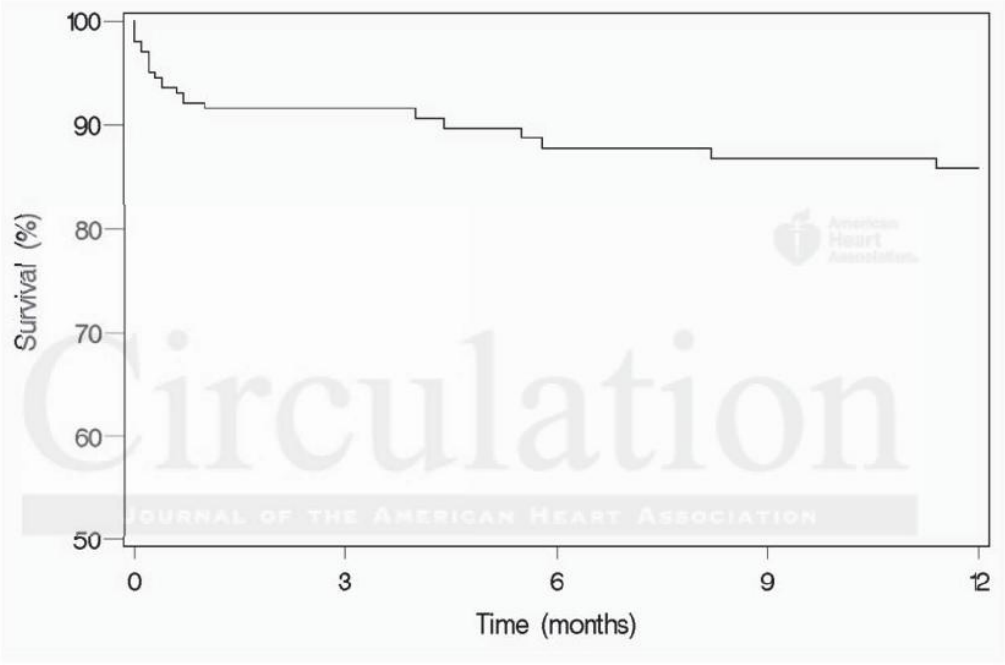
American Heart Association

Circulation. published online October 10, 2012

Transcatheter Aortic Valve Replacement for Degenerative Bioprosthetic Surgical Valves: Results from the Global Valve-in-Valve Registry

Danny Dvir, John Webb, Stephen Brecker, Sabine Bleiziffer, David Hildick-Smith, Antonio Colombo, Fleur Descoutures, Christian Hengstenberg, Neil E. Moat, Raffi Bekeredjian, Massimo Napodano, Luca Testa, Thierry Lefevre, Victor Guetta, Henrik Nissen, José-María Hernández, David Roy, Rui C. Teles, Amit Segev, Nicolas Dumonteil, Claudia Fiorina, Michael Gotzmann, Didier Tchetche, Mohamed Abdel-Wahab, Federico De Marco, Andreas Baumbach, Jean-Claude Laborde and Ran Kornowski

Thirty-day outcome
Death
Major stroke‡
Death or major stroke
Major vascular complication‡
Need for a permanent pacemake
Aortic Valve maximal gradients (mmHg)
Aortic Valve mean gradients (mmHg)
Aortic regurgitation (≥ +2)



Patient at risk:	**202**	**163**	**129**	**102**	**87**
Survival (%):	**100**	**91.5**	**87.7**	**86.7**	**85.8**

valve procedures
iate analysis

		idence Interval	p Value
		9 – 0.94	0.001
		7 – 4.43	0.02
		7 – 1.02	0.83
		7 – 1.06	0.13
		9 – 2.17	0.93
Stented bioprosthesis	1.42	0.61 – 3.31	0.42
Small bioprostheses (ID < 20 mm)	1.40	0.63 – 3.10	0.35
Pre-implantation valvuloplasty	1.67	0.93 – 2.91	0.08
Using small TAVR device†	2.85	0.41 – 17.32	0.84
Post-implantation valvuloplasty	1.57	0.62 – 3.81	0.38

Circulation
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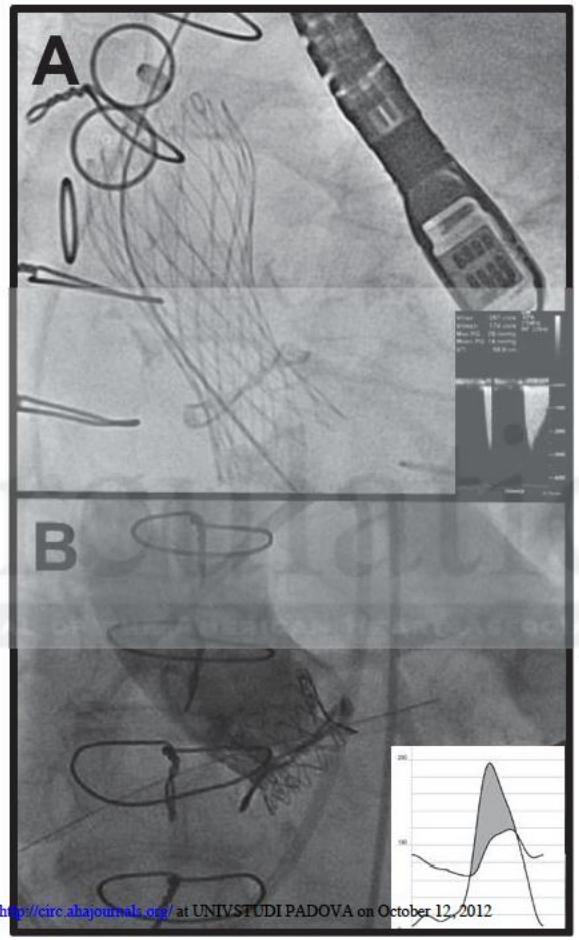
American Heart Association.

Transcatheter Aortic Valve Replacement for Degenerative Bioprosthetic Surgical Valves: Results from the Global Valve-in-Valve Registry

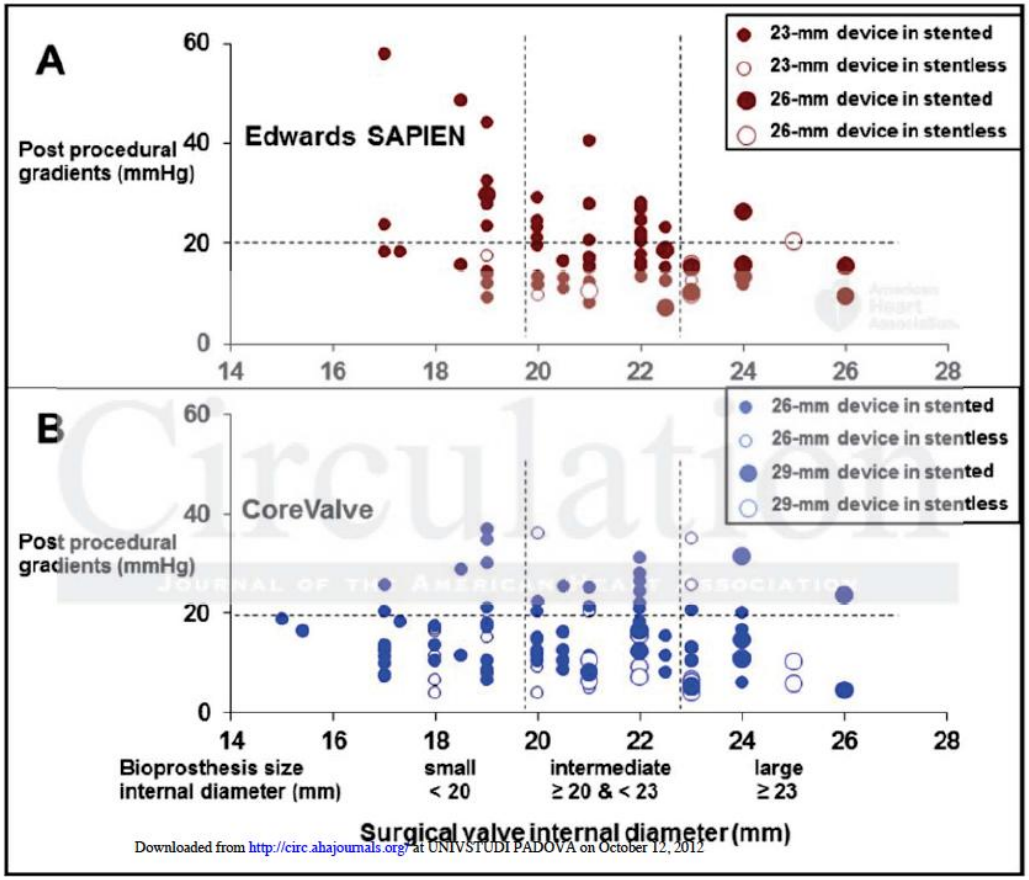
Danny Dvir, John Webb, Stephen Brecker, Sabine Bleiziffer, David Hildick-Smith, Antonio Colombo, Fleur Descoutures, Christian Hengstenberg, Neil E. Moat, Raffi Bekeredjian, Massimo Napodano, Luca Testa, Thierry Lefevre, Victor Guetta, Henrik Nissen, José-María Hernández, David Roy, Rui C. Teles, Amit Segev, Nicolas Dumonteil, Claudia Fiorina, Michael Gotzmann, Didier Tchetche, Mohamed Abdel-Wahab, Federico De Marco, Andreas Baumbach, Jean-Claude Laborde and Ran Kornowski

CV 26 mm in Mitroflow 19

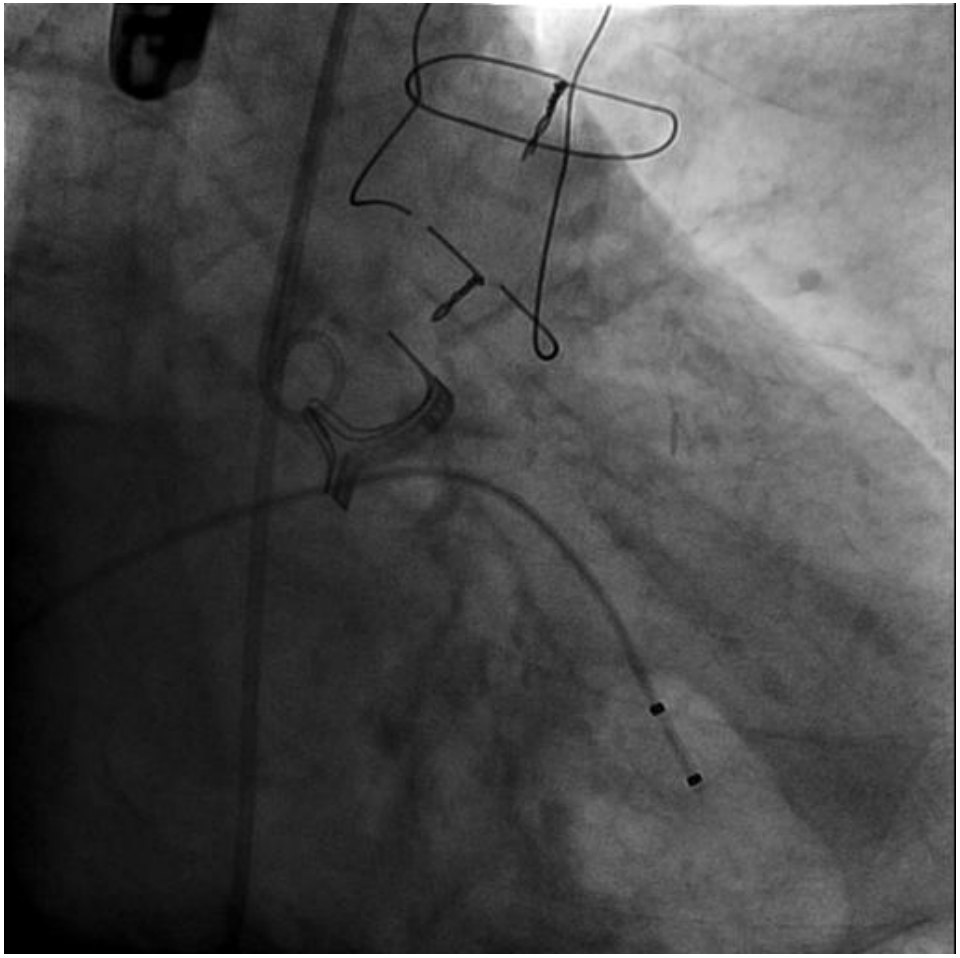


ΔP: 29/14 mmHg

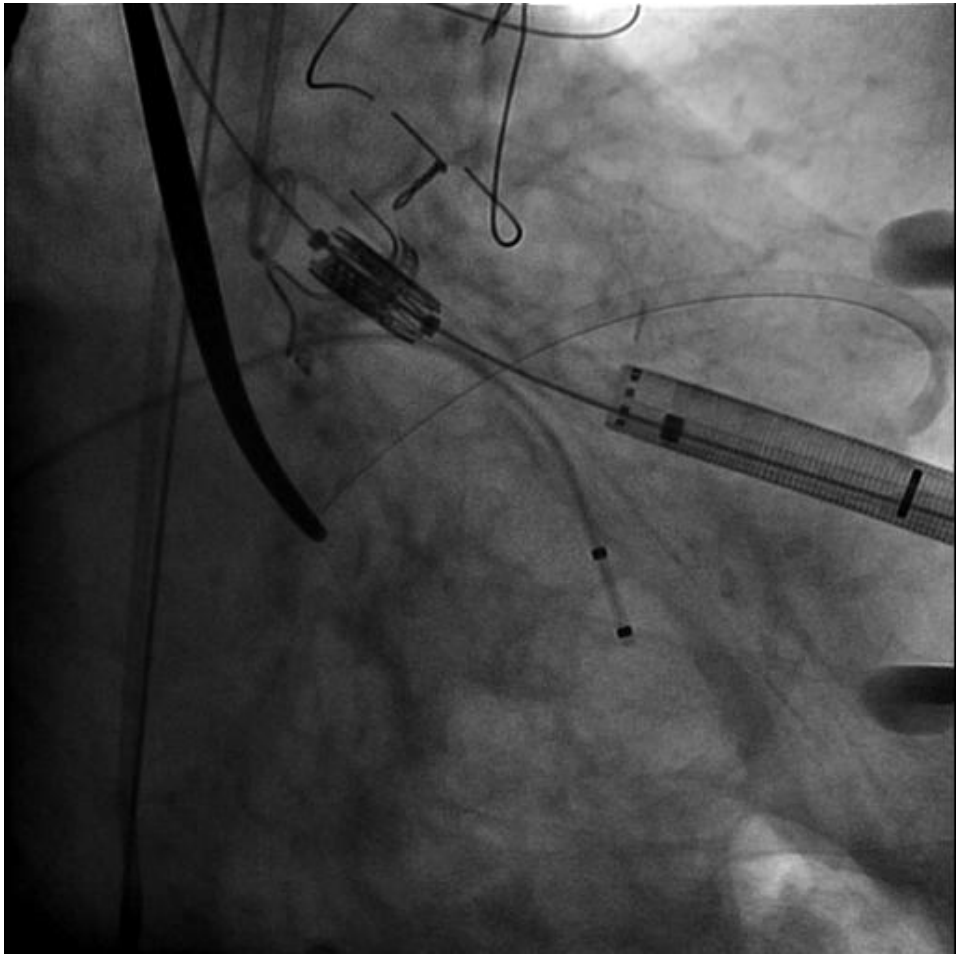
Sapien 23 in Mitroflow 21
ΔP: 88/58 mmHg



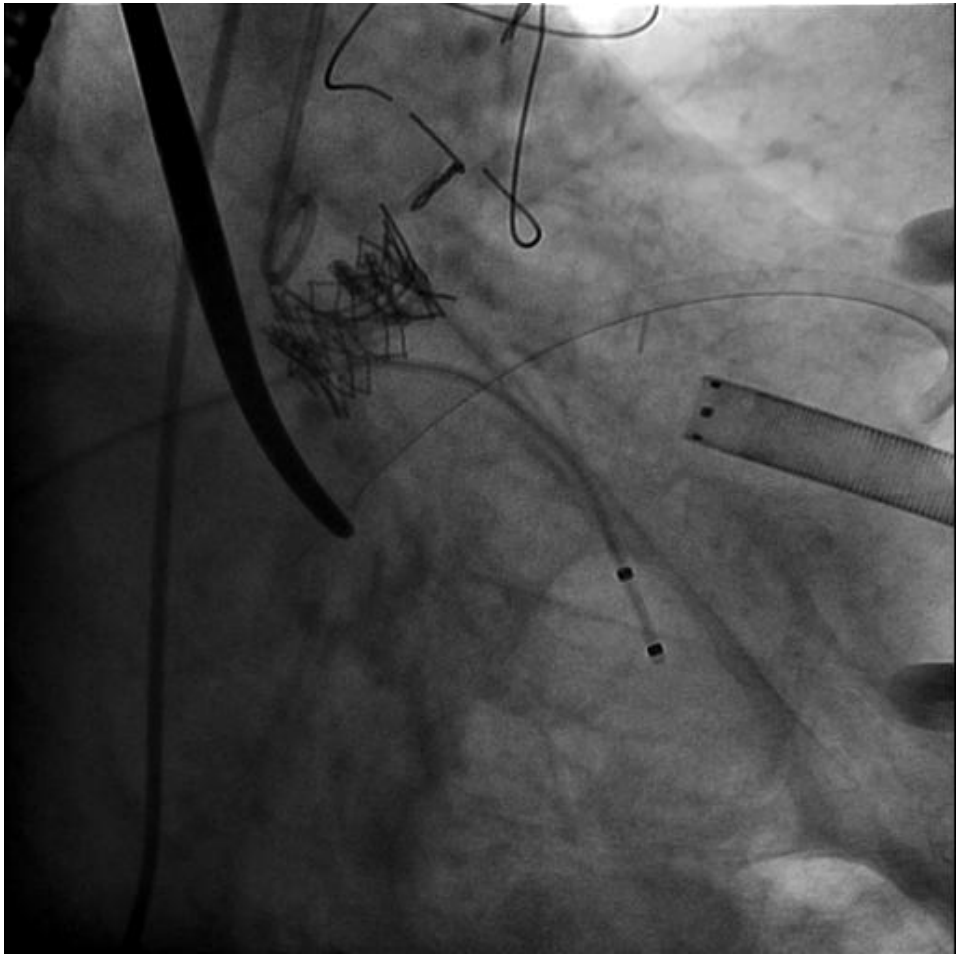
“Valve-in-valve” procedure – preop. angiogram



“Valve-in-valve” procedure – valve deployment

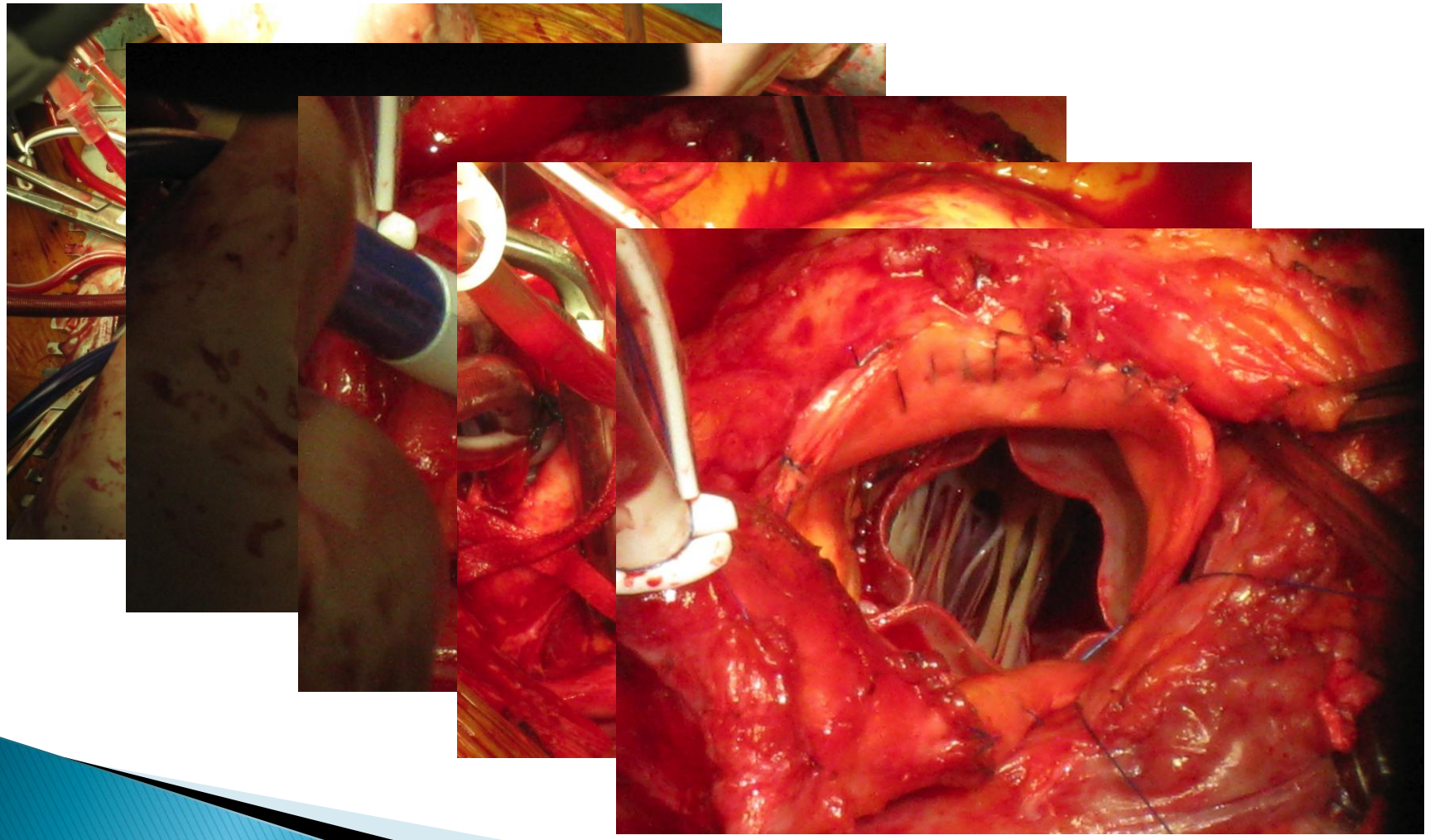


“Valve-in-valve” procedure – postop. angiogram



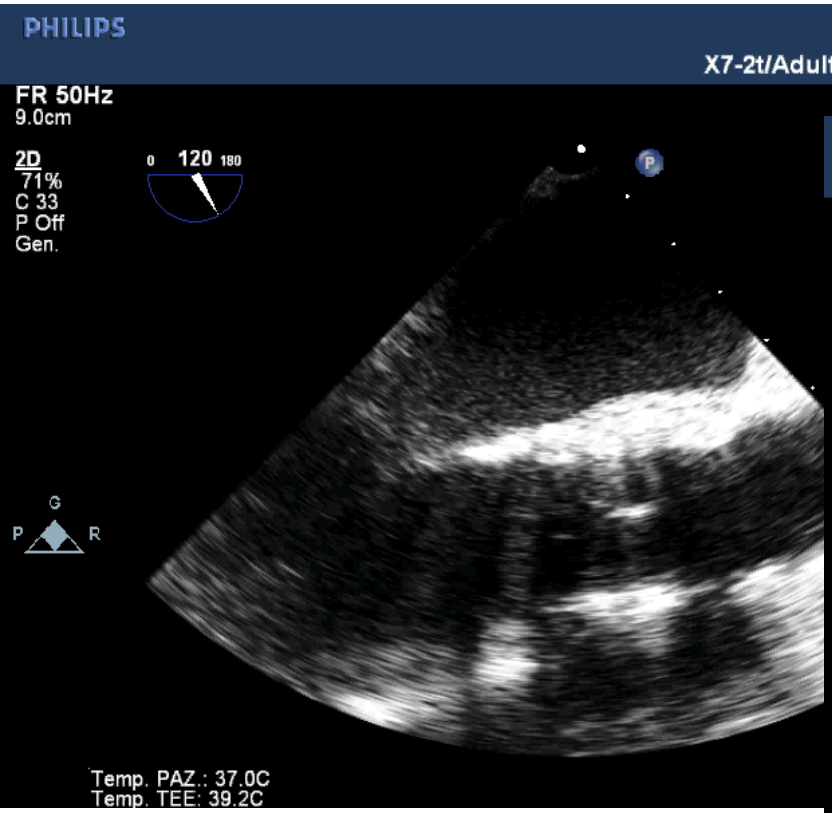
“Open-Heart” Valve in Valve

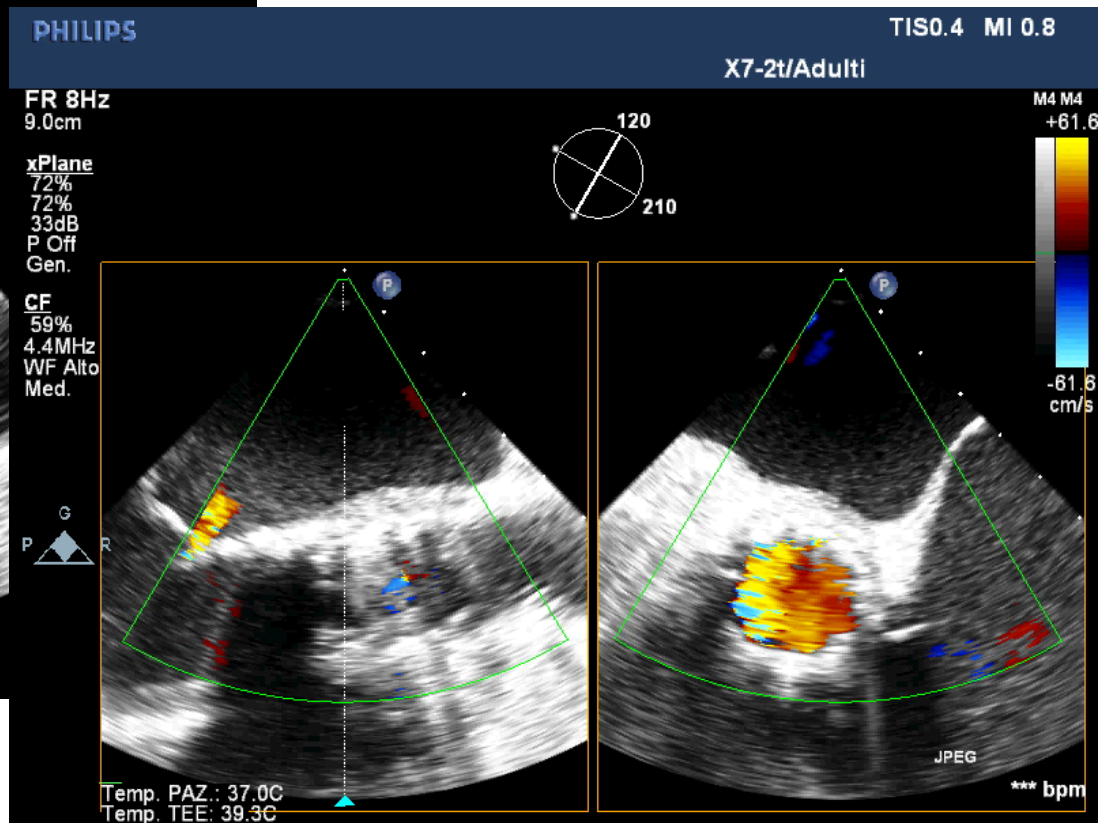
- “Bail-out” for hostile aortic root



“Open-Heart” Valve in Valve

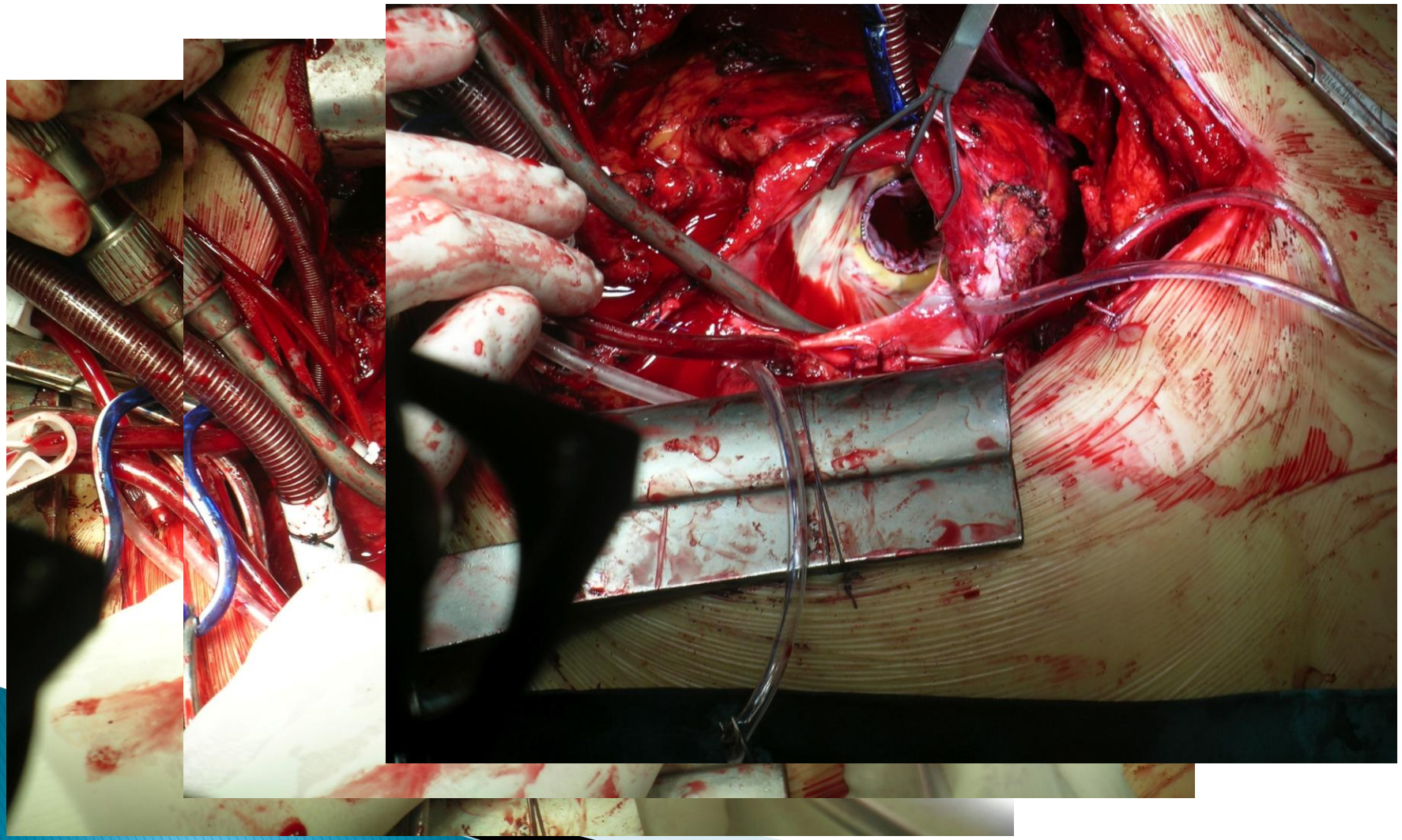
- “Bail-out” for hostile aortic root





“Open-Heart” Valve in Valve

- Tricuspid valve-in-valve



“Open-Heart” Valve in Valve

- Tricuspid valve-in-valve