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Experience in children, Melody valve and more

Marc Gewillig
Leuven, Belgium

Disclosure Information

Marc Gewillig

The following relationships exist related to this presentation:

Marc Gewillig is proctor for
- Medtronic ®
- **Edwards ®**
- **Numed ®**

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IE after PPVI

- PPVI technical aspects
- incidence
- treatment
- prevention

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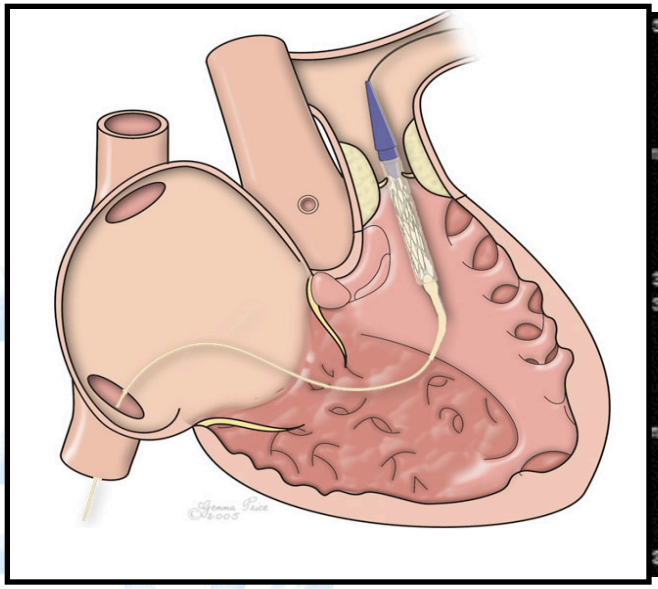
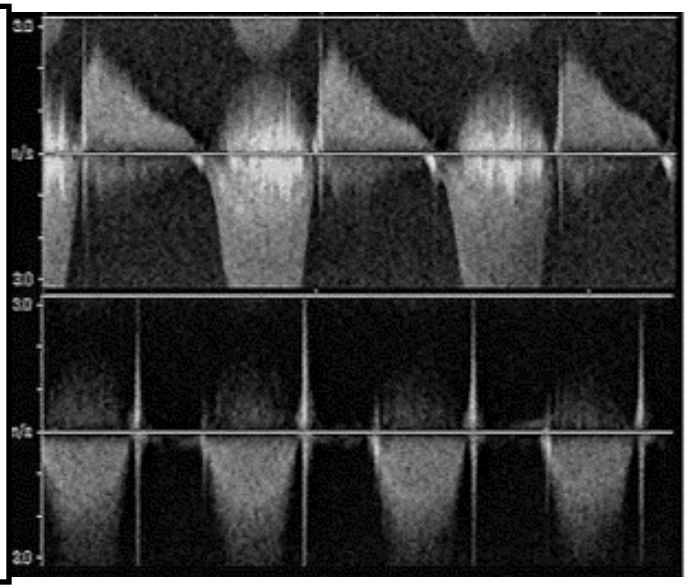
September 2000

Early report

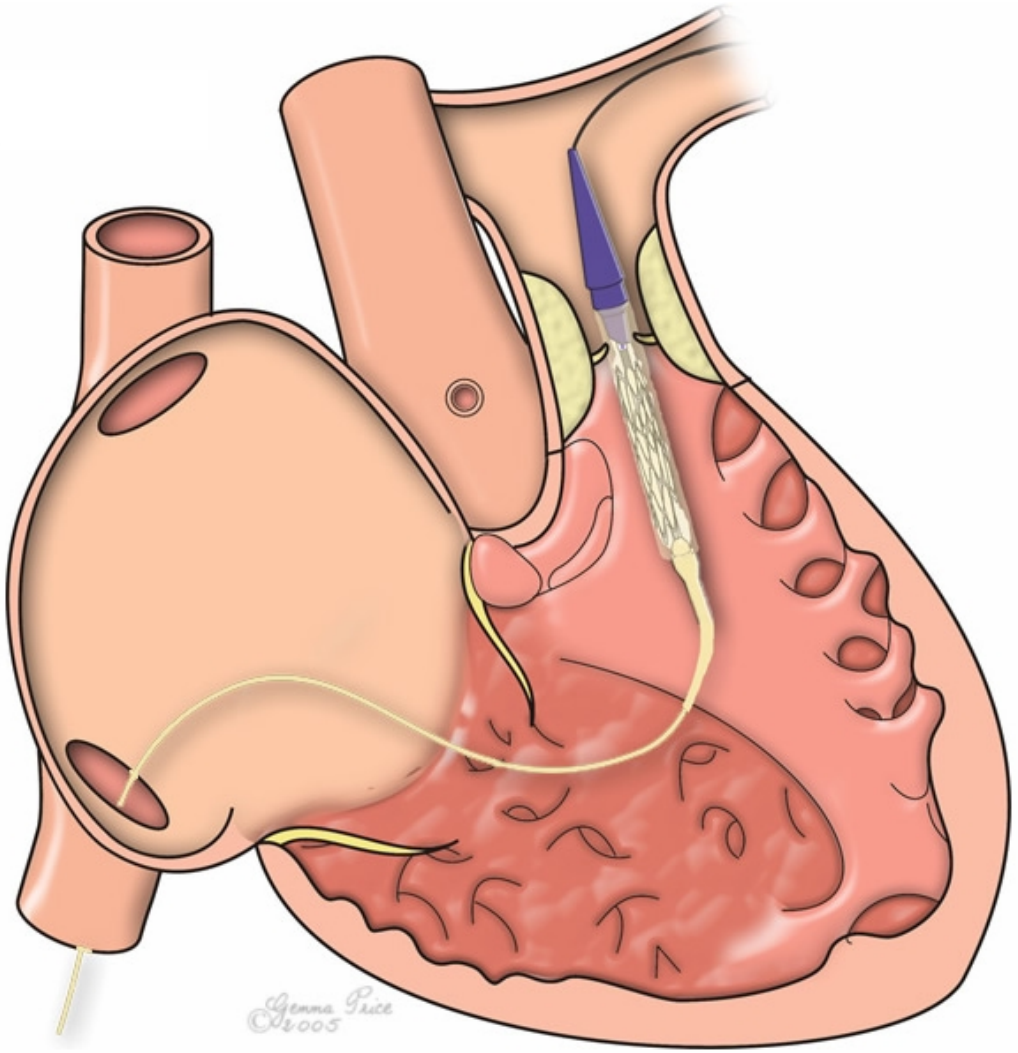
THE LANCET

Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction





PPVI: technique



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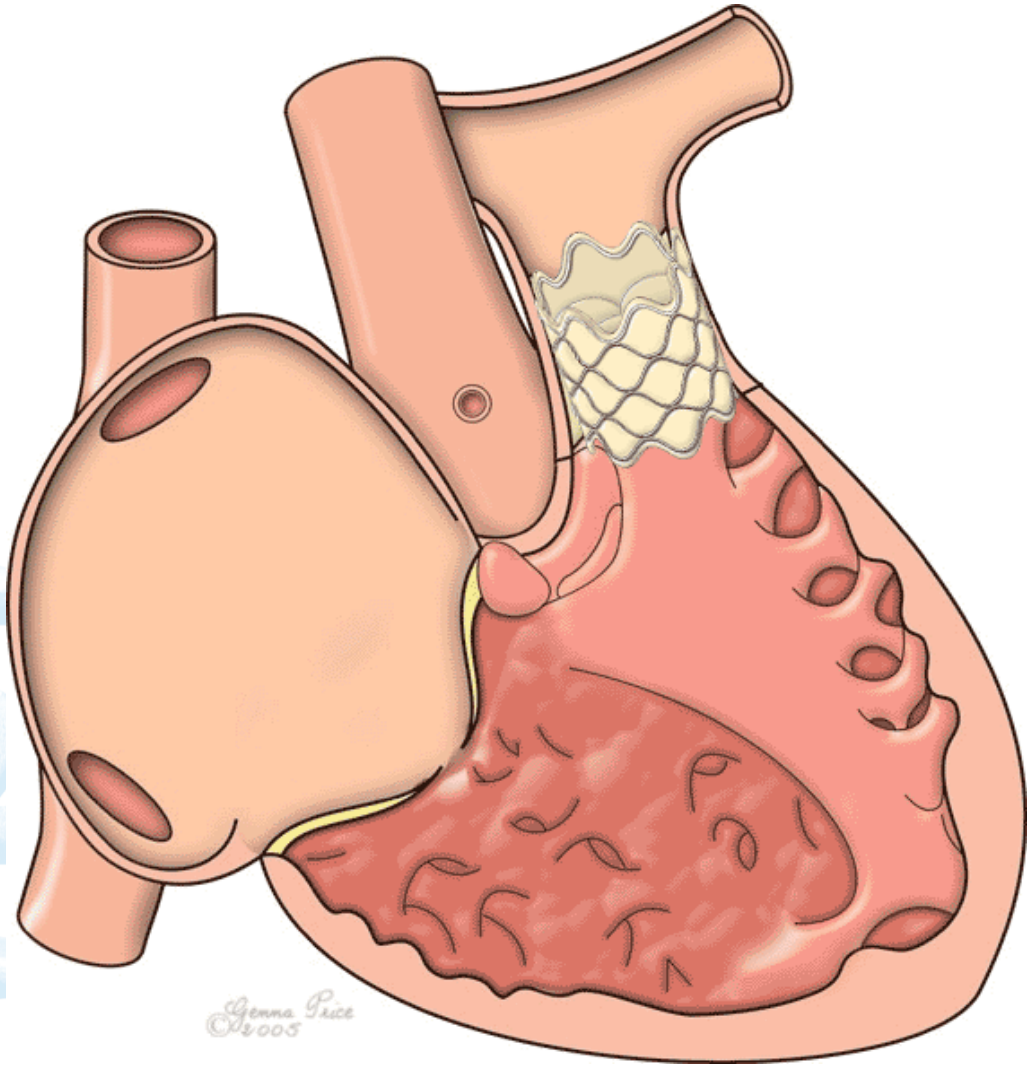
PPVI : technique



2000 – 2019:
N = ± 18.000

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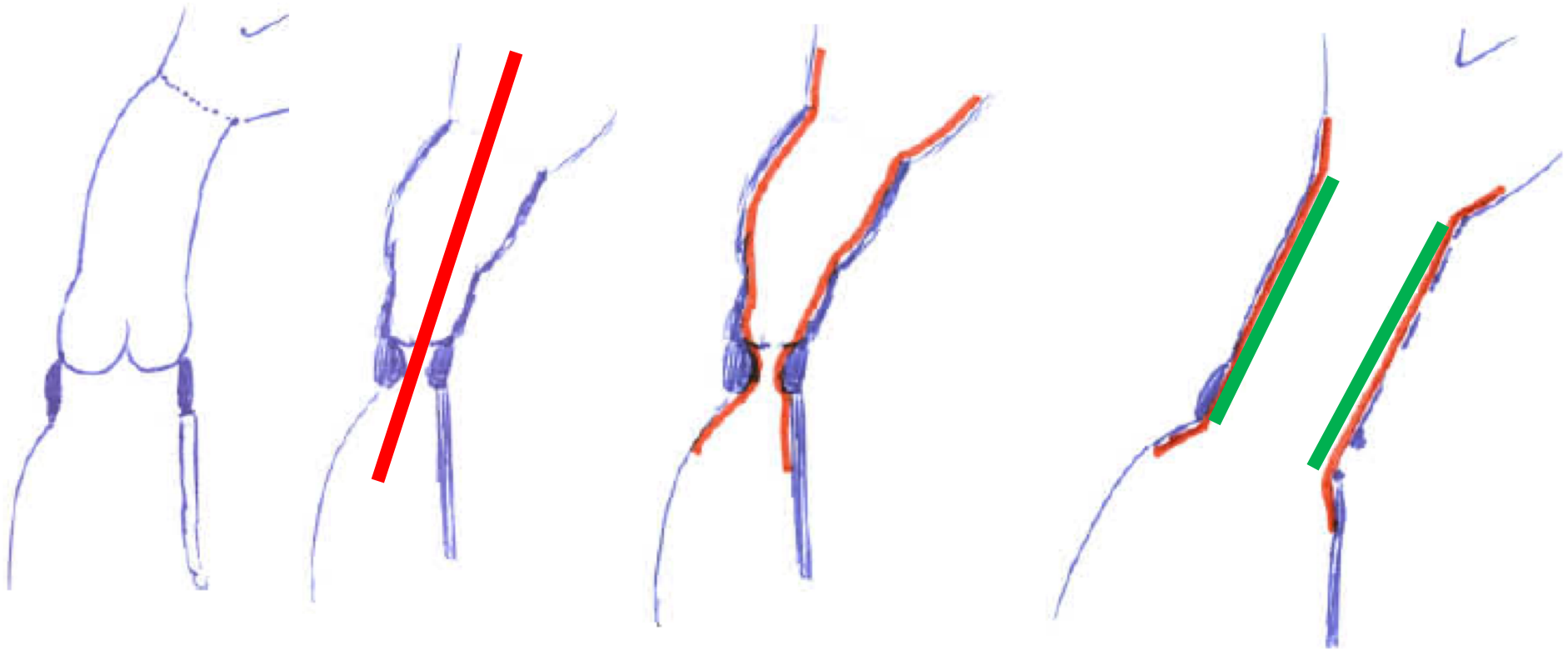
Conduit rupture – prevention extravasation

Covered stent : technique



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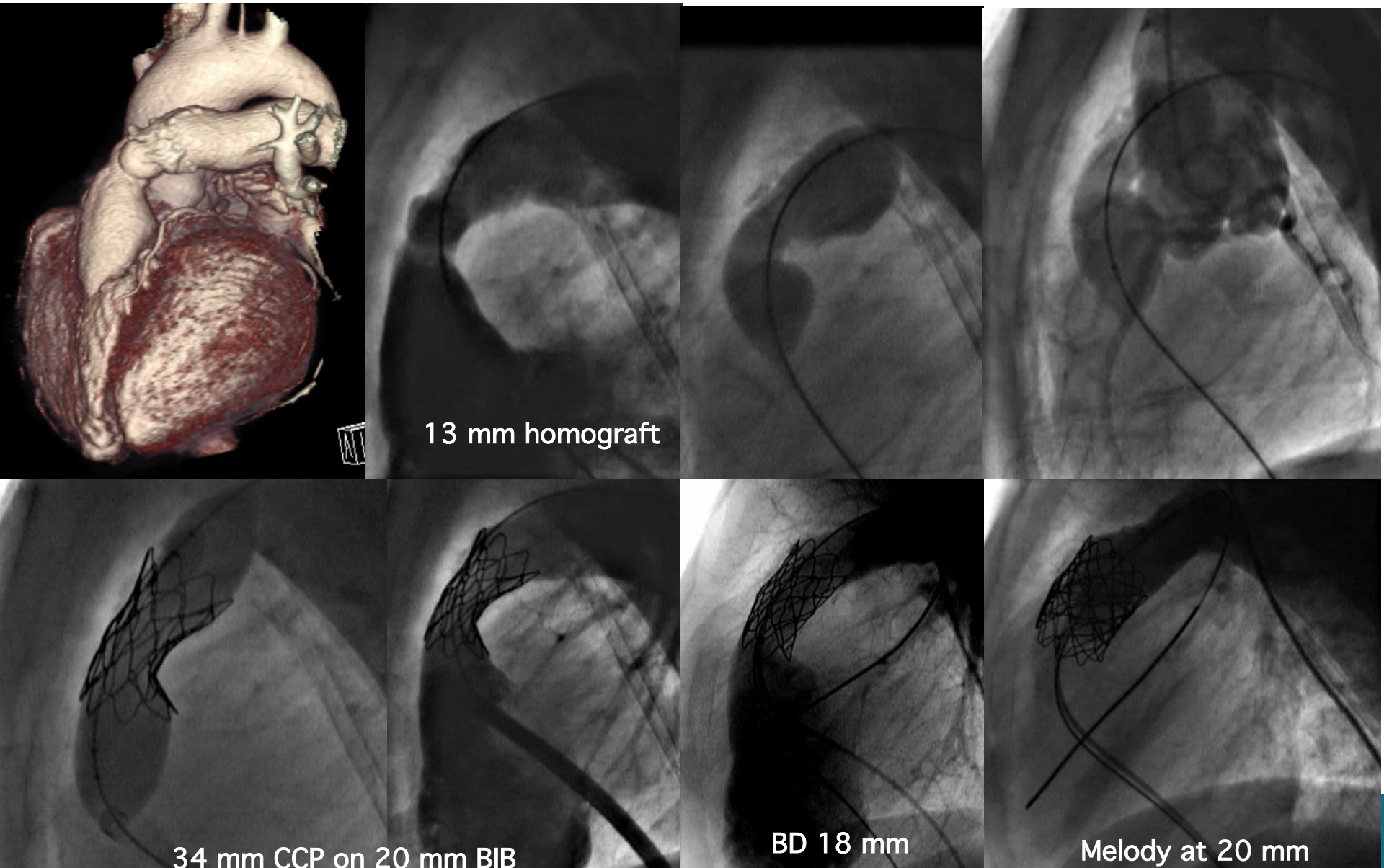
Stent expansion : 13 mm graft < 20 mm Melody



PPVI:

- Previous connection RVOT
  - Patched, conduit free
  - Tube graft: homograft, allograft, PTFE, valve
  - Secondary changes: retraction, Ca, IE, ..
- Preparation of landing zone
  - Multiple stents (1 – 6) : bare, covered
- Valved stent
  - Stent
  - Tube covering: PTFE, tissue, …
  - Leaflets: flow profile, redundancy, stress, ..

Revalvulation RVOT
Melody™ Transcatheter Pulmonary Valve

- 16-18mm Contegra bovine jugular vein with valve
- NuMed Platinum Iridium Stent CP stent
  - 28 mm length
  - crimped down to 6mm, re-expanded 18mm up to 22mm

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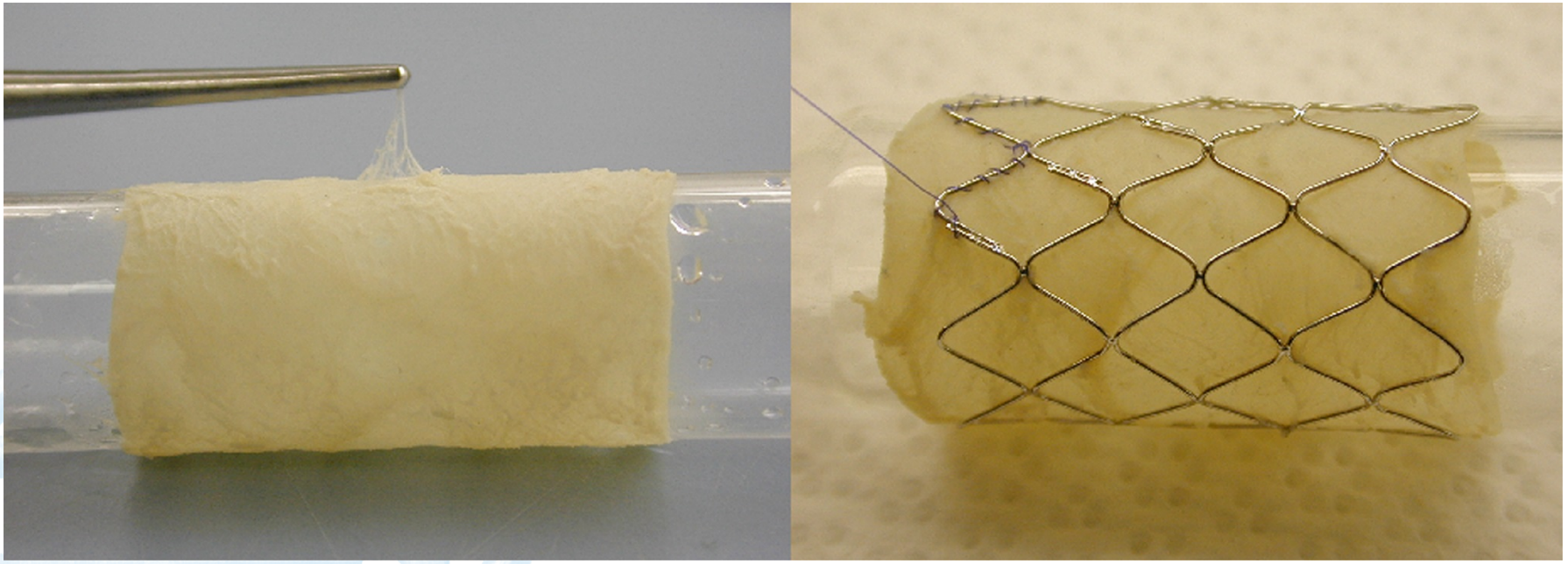
Melody™ : manufacturing



Bovine jugular vein (Venpro graft Medtronic®)
on CP stent (NUMED)

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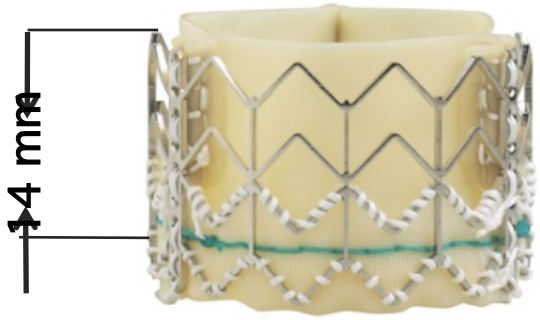
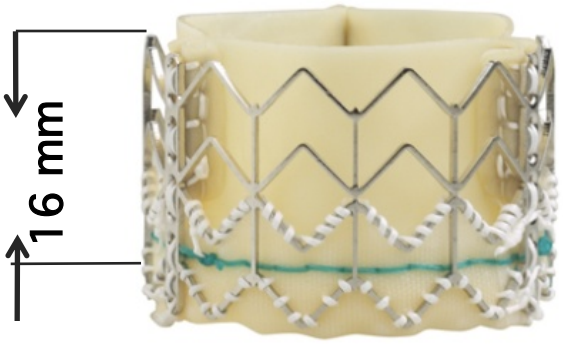
The Edwards SAPIEN Valve



23 mm SAPIEN



26 mm SAPIEN

29 mm SAPIEN XT

29 mm

Tube PTFE; leaflets processed bovine pericardium

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Large self-expandable valve: Venus P-valve

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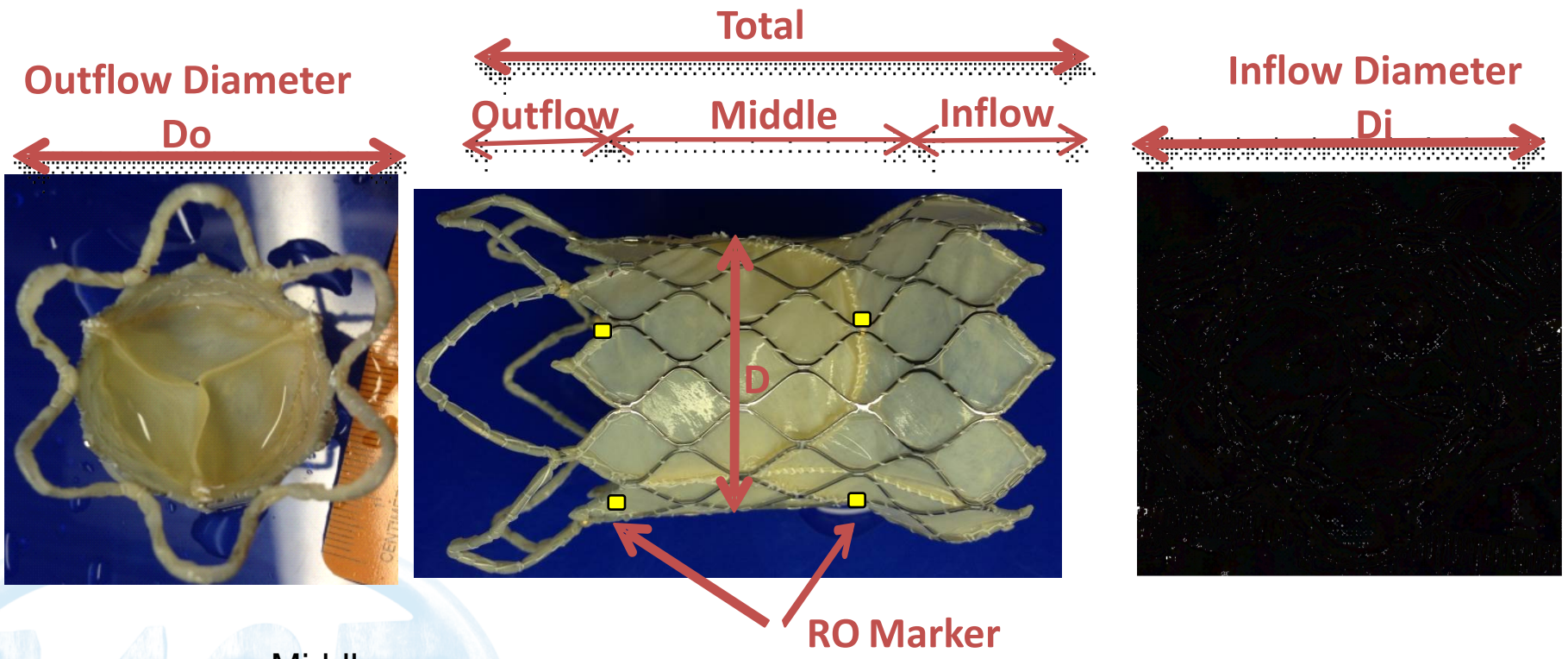
Venus P-Valve Sizes



Middle

- Diameter: 16 – 32 mm by increments of 2 mm
- Length : 20 – 35 mm by increments of 5 mm

In- & outflow:

• Diameter :	middle	+ 10 mm
• Length :	inflow	12-14 mm
•	outflow	10 – 12 mm

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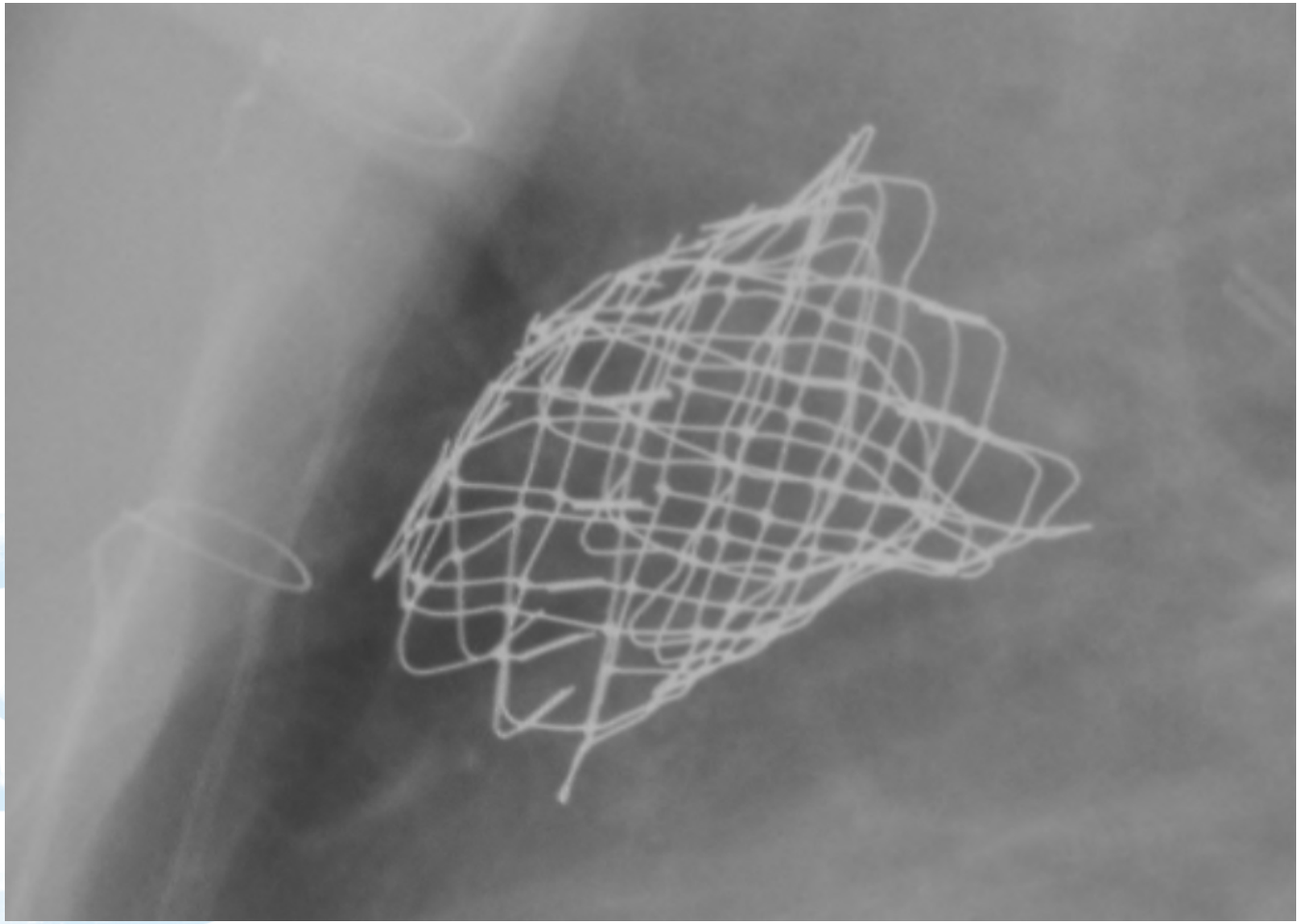
Melody: stent fractures



Covered stent CP Numed

If extravasation expected – observed: covered stent prior Melody

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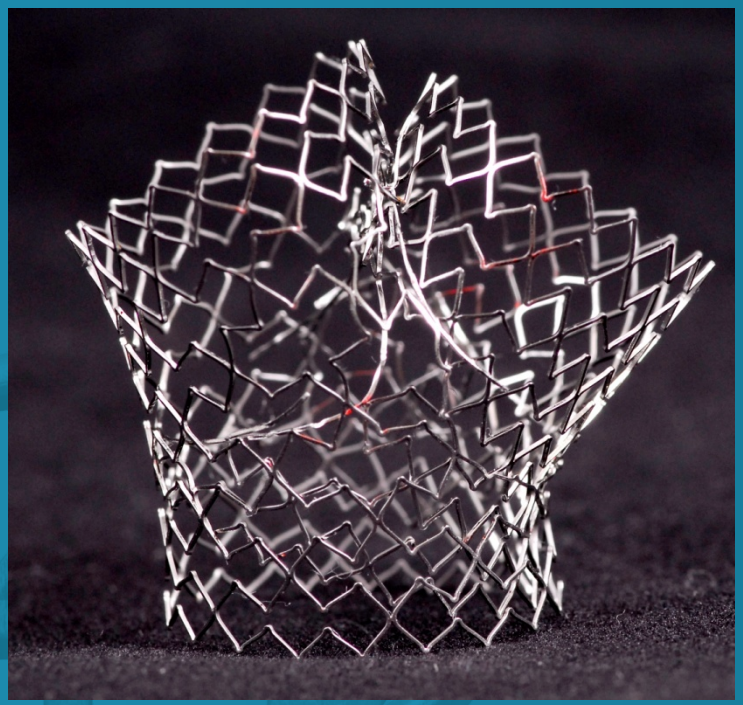
Balloon expandable Y-Stent

Pulmonary Bifurcation Plasty with Stents



individually tailorable

Courtesy P. Ewert

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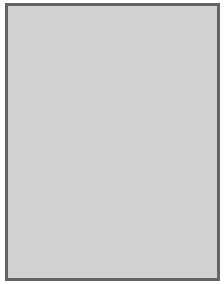
Up to 11 years of experience with the Melody valved stent in the right ventricular outflow tract



Bjorn Cools[1,2], MD; Steven Brown[1,2,3], MD, PhD; Werner Budts[2,4], MD, PhD; Ruth Heying[1,2], MD, PhD; Els Troost[2,4], MD; Derize Boshoff[1,2], MD, PhD; Benedicte Eyskens[1,2], MD, PhD; Marc Gewillig[1,2]*, MD, PhD

1. Division of Pediatric and Congenital Cardiology, University Hospitals Leuven, Leuven, Belgium; 2. Department of Cardiovascular Sciences, Catholic University Leuven, Leuven, Belgium; 3. Division of Pediatric and Congenital Cardiology, University of the Free State, Bloemfontein, South Africa; 4. Division of Adult Congenital Cardiology, University Hospitals Leuven, Leuven, Belgium

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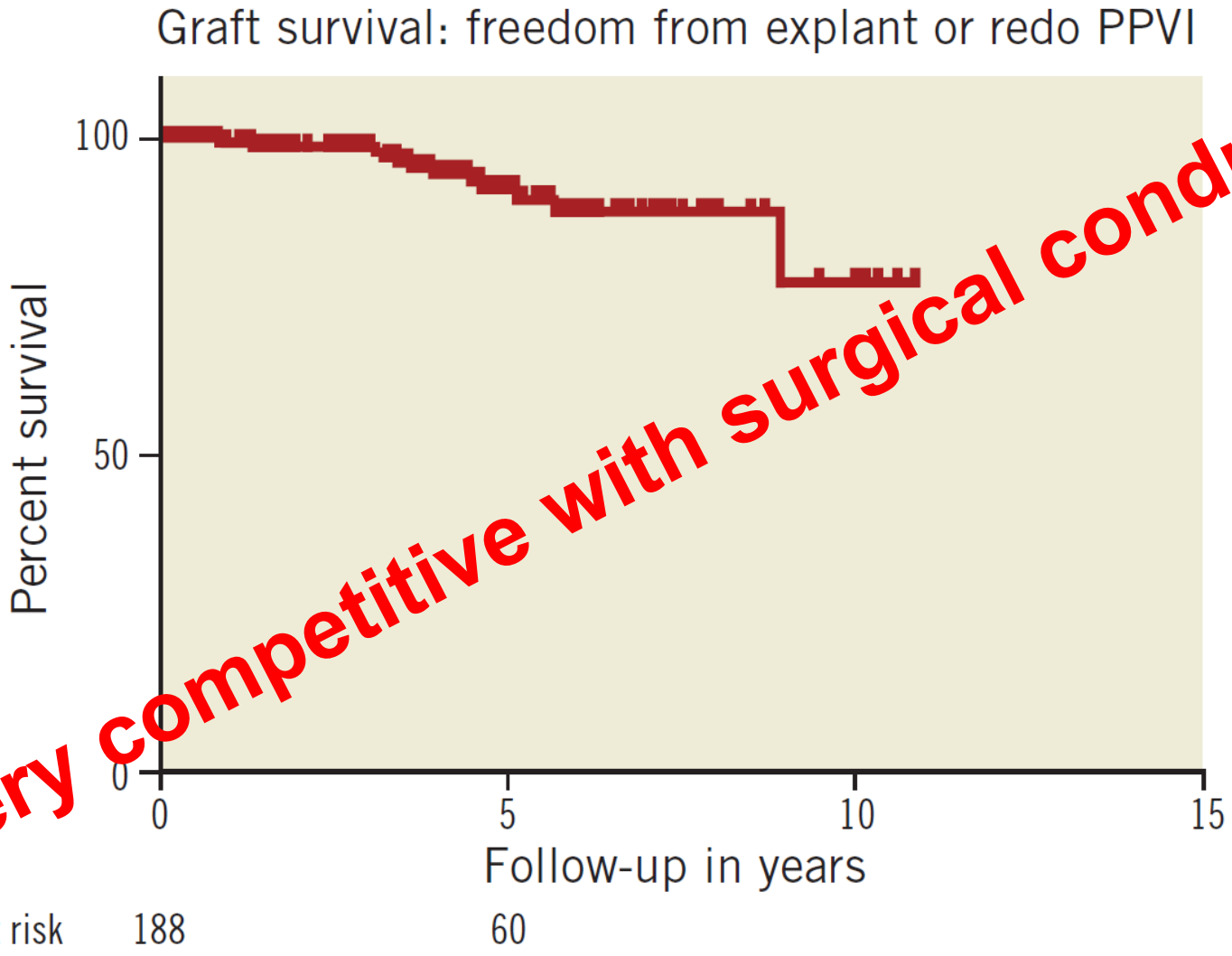
Melody: the Leuven experience 2006-2017



PPVI very competitive with surgical conduits

Cools, Gewillig EuroIntervention 2018

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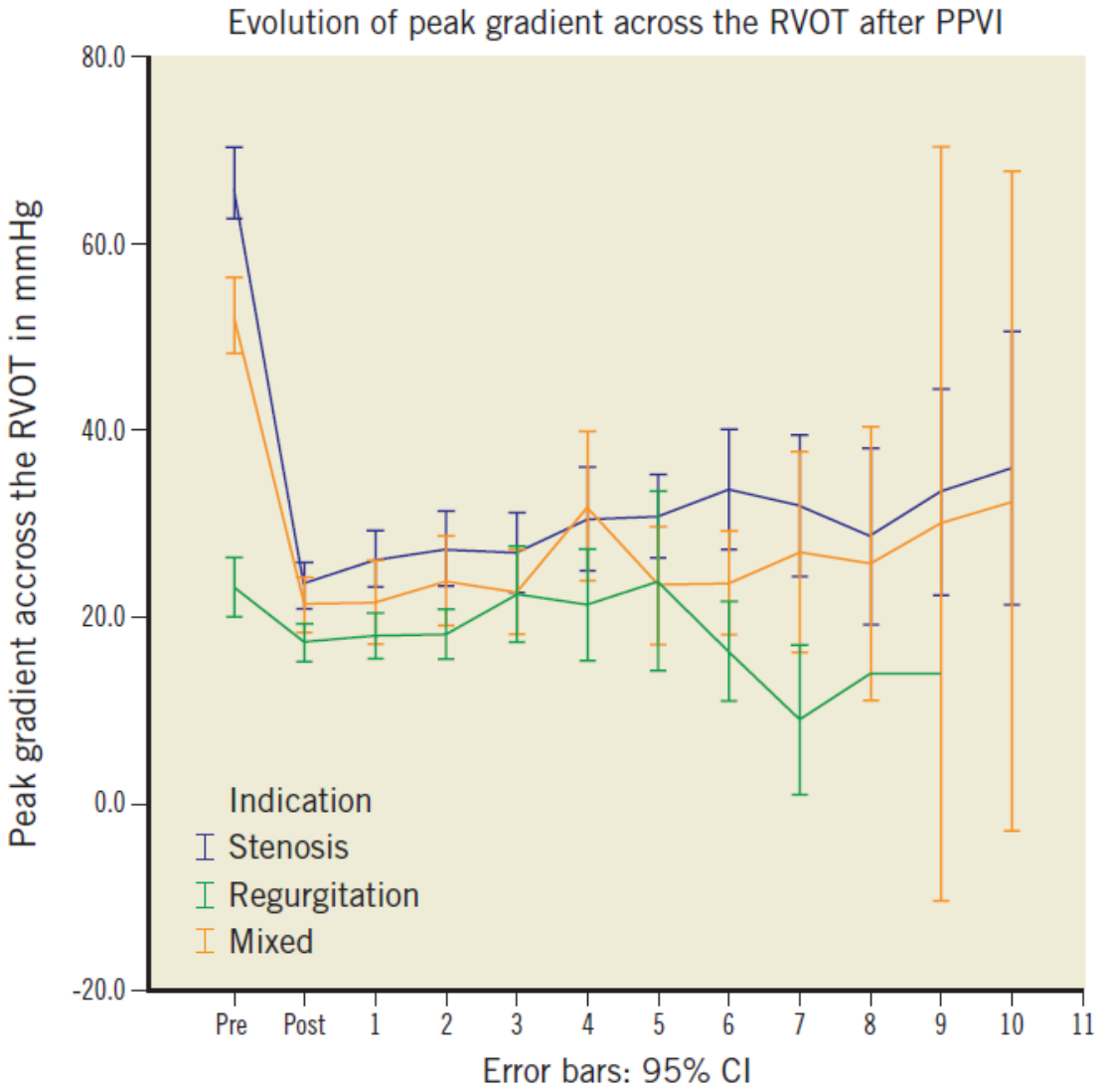
Melody: the Leuven experience 2006-2017



Cools, Gewillig EuroIntervention 2018

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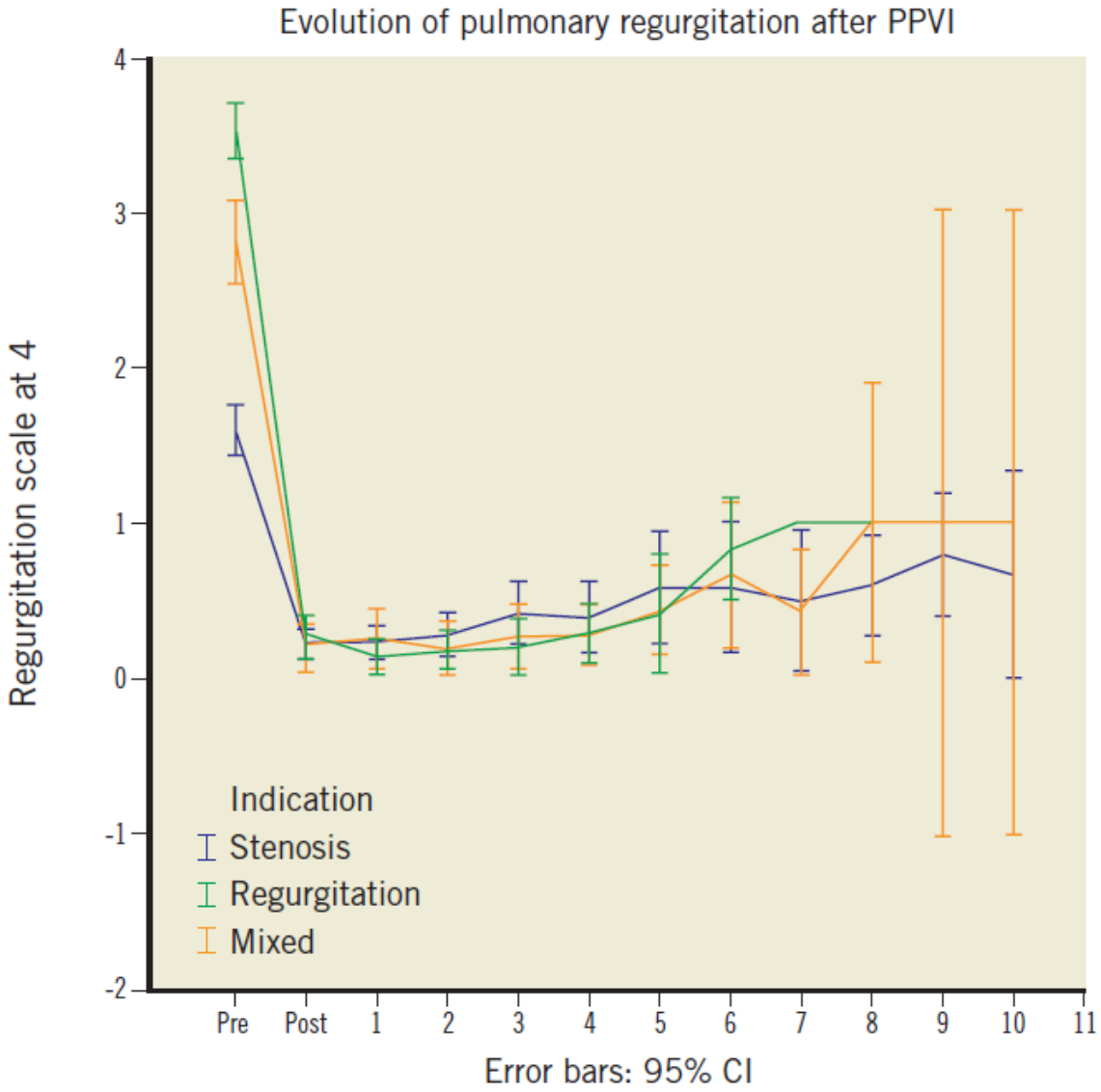
Melody: the Leuven experience 2006-2017



Cools, Gewillig EuroIntervention 2018

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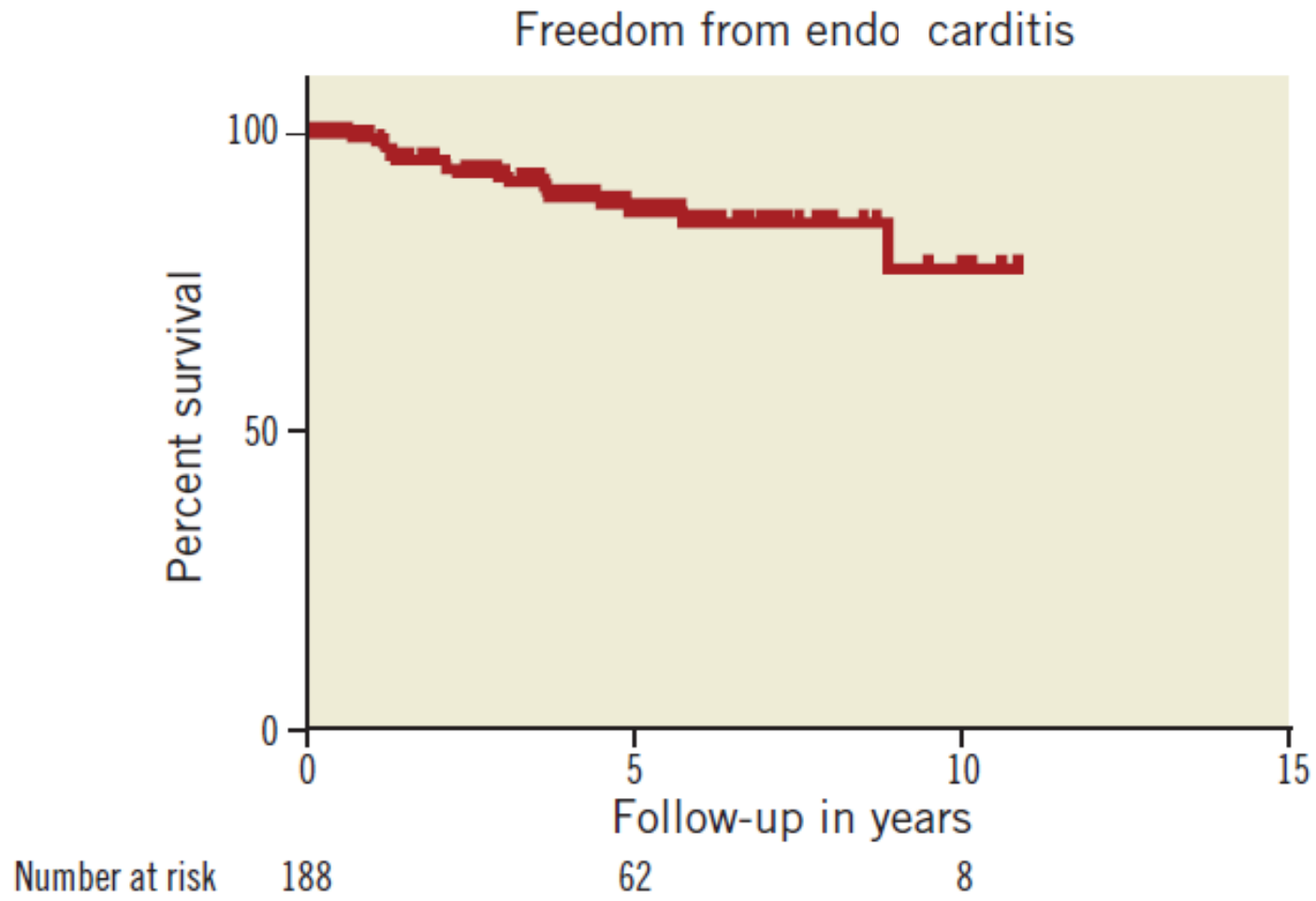
Melody: the Leuven experience 2006-2017



IE after PPVI

- PPVI technical aspects
- incidence
- treatment
- prevention

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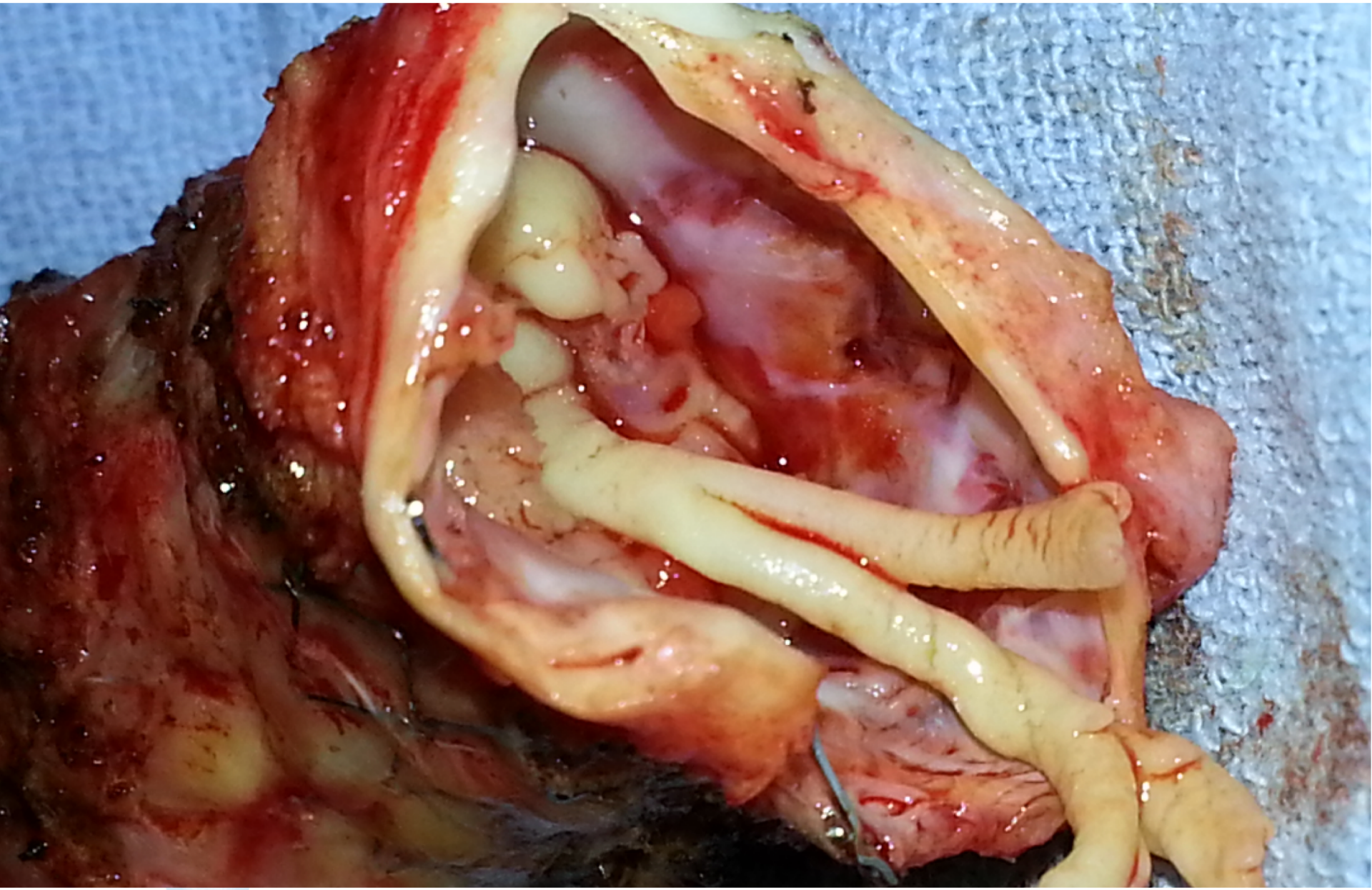

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Background IE

Epidemiology

Incidence: 0.3 - 0.7 per 100.000 children/year

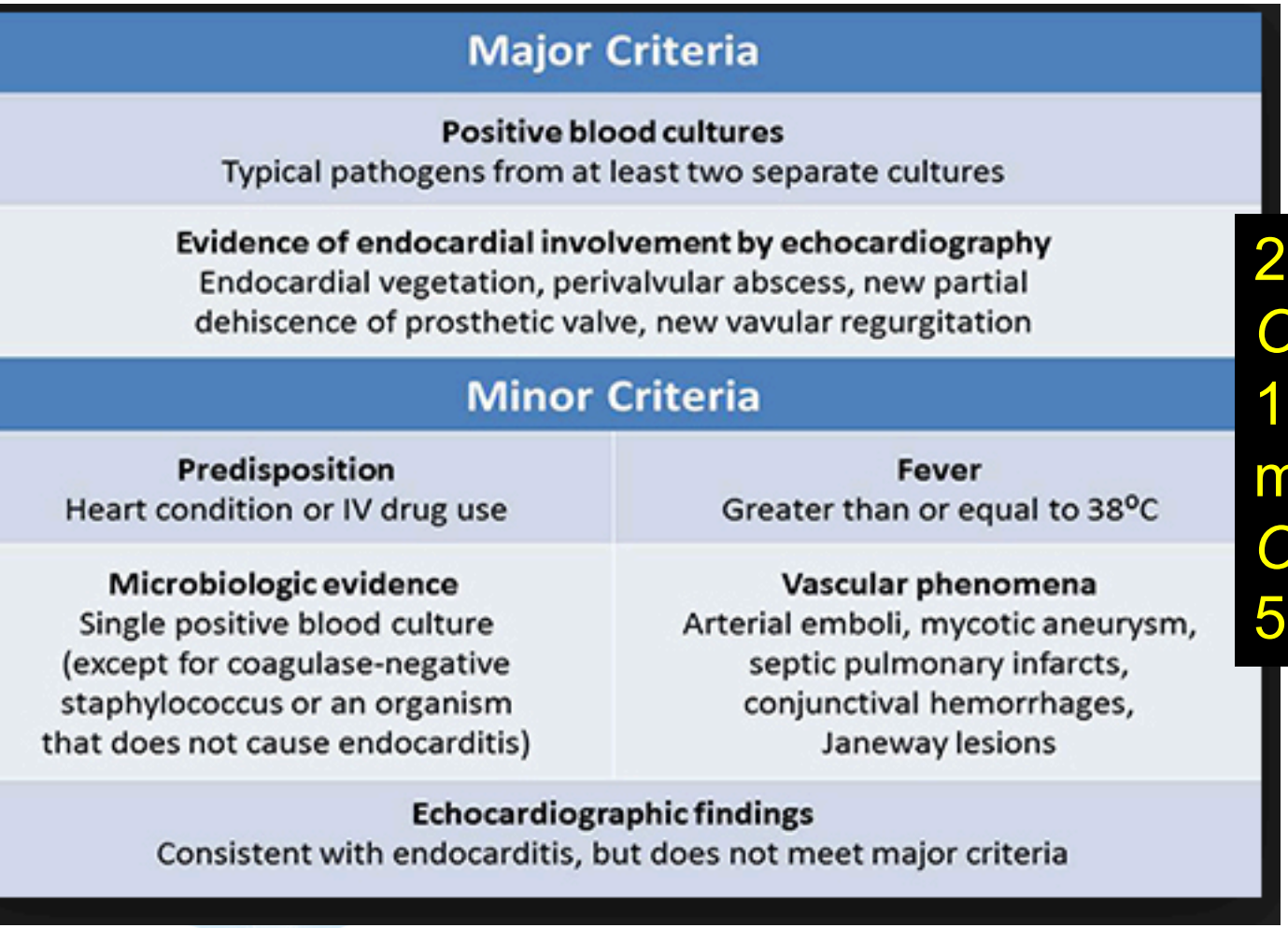
right sided IE: 60-70 % cases in pediatric population

High risk: children with valve conduits (40 %)

Mean diagnostic delay is 29 ± 35 days

Knirsch et al; Eur J Pediatr:170(9):1111-27, 2011
Di Filippo: Arch Cardiovasc Dis:105(8-9):454-60, 2012
Rushani et al; Circulation: 24;128(13):1412-9, 2013
Kelchtermans et al; Ped Inf Dis J: 38(5): 453-458, 2018

The Duke Criteria for Diagnosing BE



Major Criteria	
Positive blood cultures Typical pathogens from at least two separate cultures	
Evidence of endocardial involvement by echocardiography Endocardial vegetation, perivalvular abscess, new partial dehiscence of prosthetic valve, new vavular regurgitation	
Minor Criteria	
Predisposition Heart condition or IV drug use	**Fever** Greater than or equal to 38°C
Microbiologic evidence Single positive blood culture (except for coagulase-negative staphylococcus or an organism that does not cause endocarditis)	**Vascular phenomena** Arterial emboli, mycotic aneurysm, septic pulmonary infarcts, conjunctival hemorrhages, Janeway lesions
Echocardiographic findings Consistent with endocarditis, but does not meet major criteria	

2 major
Or
1 major and 3 minor
Or
5 minor

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Echo Imaging and The RVOT

Contents lists available at ScienceDirect

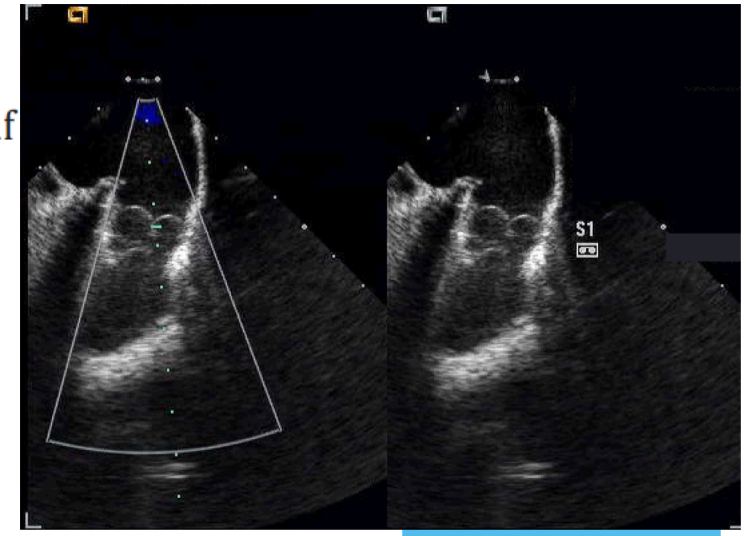
International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Infective endocarditis following percutaneous pulmonary valve replacement: Diagnostic challenges and application of intra-cardiac echocardiography

Gary Cheung, Niels Vejlstrup, Nikolaj Ihlemann, Samer Arnous, Olaf Henning Bundgaard, Lars Søndergaard *

Department of Cardiology, Rigshospitalet, Copenhagen, Denmark



Diagnosis of IE: Modified Duke Criteria

Major criteria

1. Positive blood culture with typical IE microorganism
(viridans group *streptococci,* HAECK, *S. aureus*, community acquired *Enterococci)*

2. Imaging positive for IE

a. Echocardiogram positive for IE:
- Vegetation;
- Abscess, pseudoaneurysm, intracardiac fistula;
- Valvular perforation or aneurysm;
- New partial dehiscence of prosthetic valve.

b. Abnormal activity around the site of prosthetic valve implantation detected by ^{18}F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT.

c. Definite paravalvular lesions by cardiac CT.

3. "sudden" increase of gradient

Minor criteria

1. predisposing factor
2. fever >38 °C
3. embolism evidence
4. immunological problems
5. microbiologic evidence (no major criterion)

Gilbert Habib et al. Eur Heart J 2015;36:3075-3128;
adapted from Li *et al.*, Clin Infect Dis 2000, 30: 633-638.

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Boston Children's Hospital
Large Single Center Experience

Structural Heart Disease

Bloodstream Infections Occurring in Patients With Percutaneously Implanted Bioprosthetic Pulmonary Valve

A Single-center Experience

Jonathan Buber, MD; Lisa Bergersen, MD, MPH; James E. Lock, MD; Kimberlee Gauvreau, ScD; Jesse J. Esch, MD; Michael J. Landzberg, MD; Anne Marie Valente, MD; Thomas J. Sandora, MD, MPH; Audrey C. Marshall, MD

Background—Percutaneous pulmonary valve implantation using a stent-based bioprosthetic valve provides an alternative to surgery in select patients. Systemic infections in Melody valve–implanted patients with and without identified valve involvement have been reported, yet the incidence is unknown, and risk factors remain unidentified.

Methods and Results—Between 2007 and 2012, a total of 147 consecutive patients with congenital heart disease underwent Melody percutaneous pulmonary valve implantation at our institution. Demographic and clinical variables were collected at baseline and at follow-up and analyzed as predictors. The occurrence of bloodstream infection (BSI), defined as a bacterial infection treated with ≥4 weeks of antibiotics, served as our primary outcome. The mean age at implantation for the study population was 21.5±11 years, and tetralogy of Fallot was the cardiac condition in 59%. During a median follow-up of 19 months, 14 patients experienced BSI (9.5%; 95% confidence interval, 5.3%–15%). Of these, 4 (2.7%) patients had Melody valve endocarditis. Two patients died during the event, neither of whom had known valve involvement. The median procedure to infection time was 15 months (range, 1–56). In univariate analysis, male sex, previous endocarditis, in situ stents in the right ventricular outflow tract, and presence of outflow tract irregularities at the implant site were associated with BSI occurrence.

Conclusions—In this cohort, 9.5% of patients who underwent Melody percutaneous pulmonary valve implantation experienced subsequent BSI, occurring 1 to 56 months after implant, and 2.7% of patients had prosthetic endocarditis. Our findings suggest that patient and nonvalve anatomic factors may be associated with BSI after percutaneous pulmonary valve implantation. (***Circ Cardiovasc Interv*. 2013;6:301-310.**)

Key Words: congenital cardiac defect ■ infection ■ percutaneous valve implantation

Burber et al, Circ Cardiovasc Interv. 2013

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Necker Hospital for Sick Children, Paris
Large Single Center Experience

CLINICAL RESEARCH

Incidence and predictors of Melody® valve endocarditis: A prospective study

Incidence et facteurs prédictifs d'endocardites sur valve Melody® : une étude prospective

Sophie Malekzadeh-Milani[a], Magalie Ladouceur[a], Mehul Patel[a], Fazia-Marie Boughenou[a], Laurence Iserin[a], Damien Bonnet[a,b], Younes Boudjemline[a,b,*]

[a] *Centre de Référence Malformations Cardiaques Congénitales Complexes (M3C), Necker Hospital for Sick Children—HEGP, AP—HP, Paris, France*
[b] *Université Paris Descartes, Sorbonne Paris Cité, 75006 Paris, France*

Received 7 July 2014; received in revised form 5 September 2014; accepted 5 September 2014

Malekzadeh-Milaniet al, Arch Cardiovasc Dis. 2014

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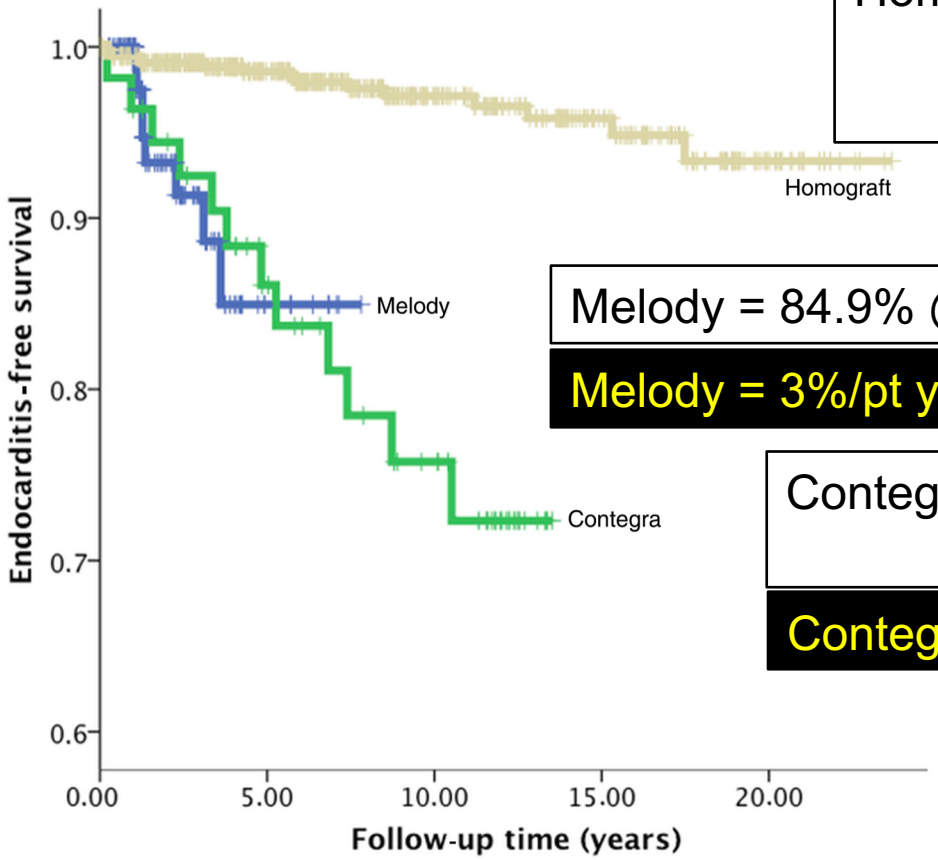
Leuven Comparative Single Center Study

Survival free from BE



Homograft	AR	577	342	180	101	27
	IE	0	6	10	12	14
Contegra	AR	54	37	25		
	IE	0	6	10		
Melody	AR	106	11			
	IE	0	8			

Homograft = 98.7% @ 5 yrs
= 97.3% @10 yrs
= 93.5% @20 yrs

Homograft= 0.8%/pt yr

Melody = 84.9% @ 5 yrs

Melody = 3%/pt yr

Contegra = 87.8 @ 5 yrs
= 77.3% @ 10 yrs

Contegra = 2.7%/pt yr

Van Dijck, et al, Heart, 2014

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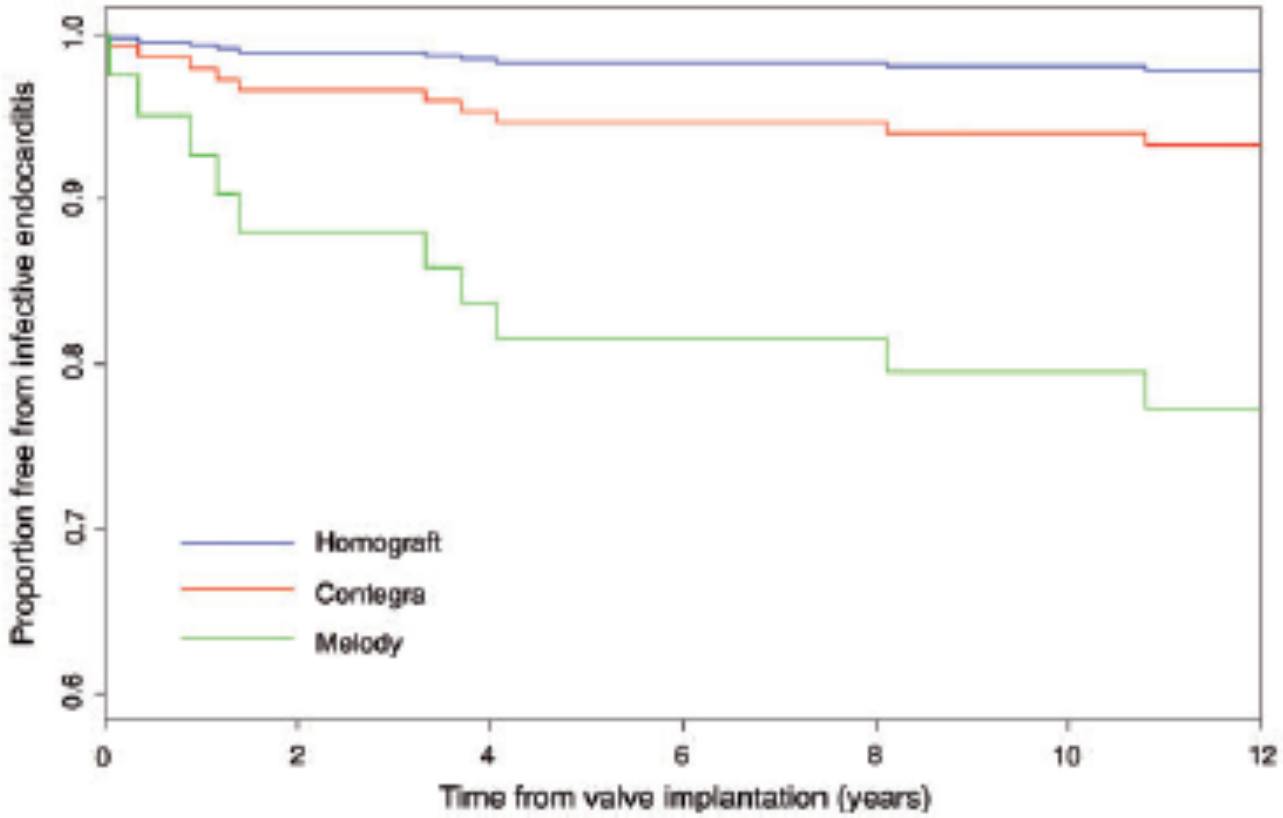
Infective endocarditis in right ventricular outflow tract conduits: a register-based comparison of homografts, Contegra grafts and Melody transcatheter valves

Mathis Gröning[a], Naima Borg Tahri[b], Lars Søndergaard[a], Morten Helvind[b], Mads Kristian Ersbøll[a] and Henrik Ørbæk Andersen[b,*]



Gröning et al, Eur J Cardio Thorac Surg, 2019

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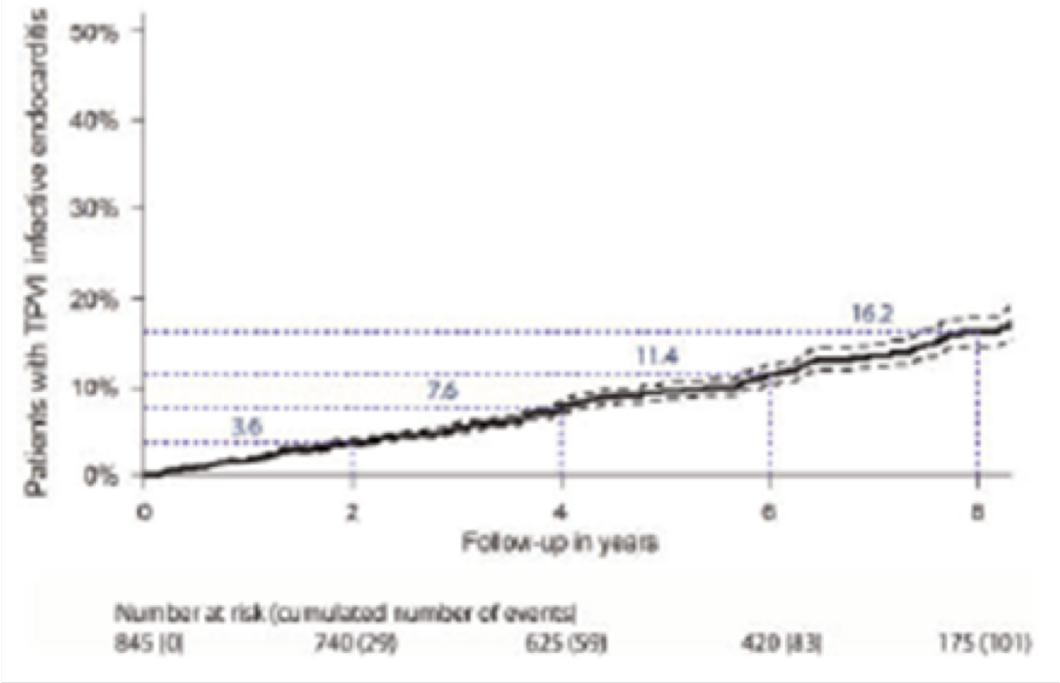
Acute and midterm outcomes of the post-approval MELODY Registry: a multicentre registry of transcatheter pulmonary valve implantation

Johannes Nordmeyer[1]*, Peter Ewert[2,3,4], Marc Gewillig[5], Mansour AlJufan[6], Mario Carminati[7], Oliver Kretschmar[8], Anselm Uebing[9], Ingo Dähnert[10], Robert Röhle[11], Heike Schneider[12], Maarten Witsenburg[13], Lee Benson[14], Roland Gitter[15], Regina Bökenkamp[16], Vaikom Mahadevan[17], and Felix Berger[1,18,19]; on behalf of the MELODY Registry investigators

- 845 pts
- FU median 5.9 years
- re-intervention 4.2 % /p/y

IE 109/845 (12.9 %)

- incidence 2.3 % /p/y



Cummulative incidence for PPVI IE

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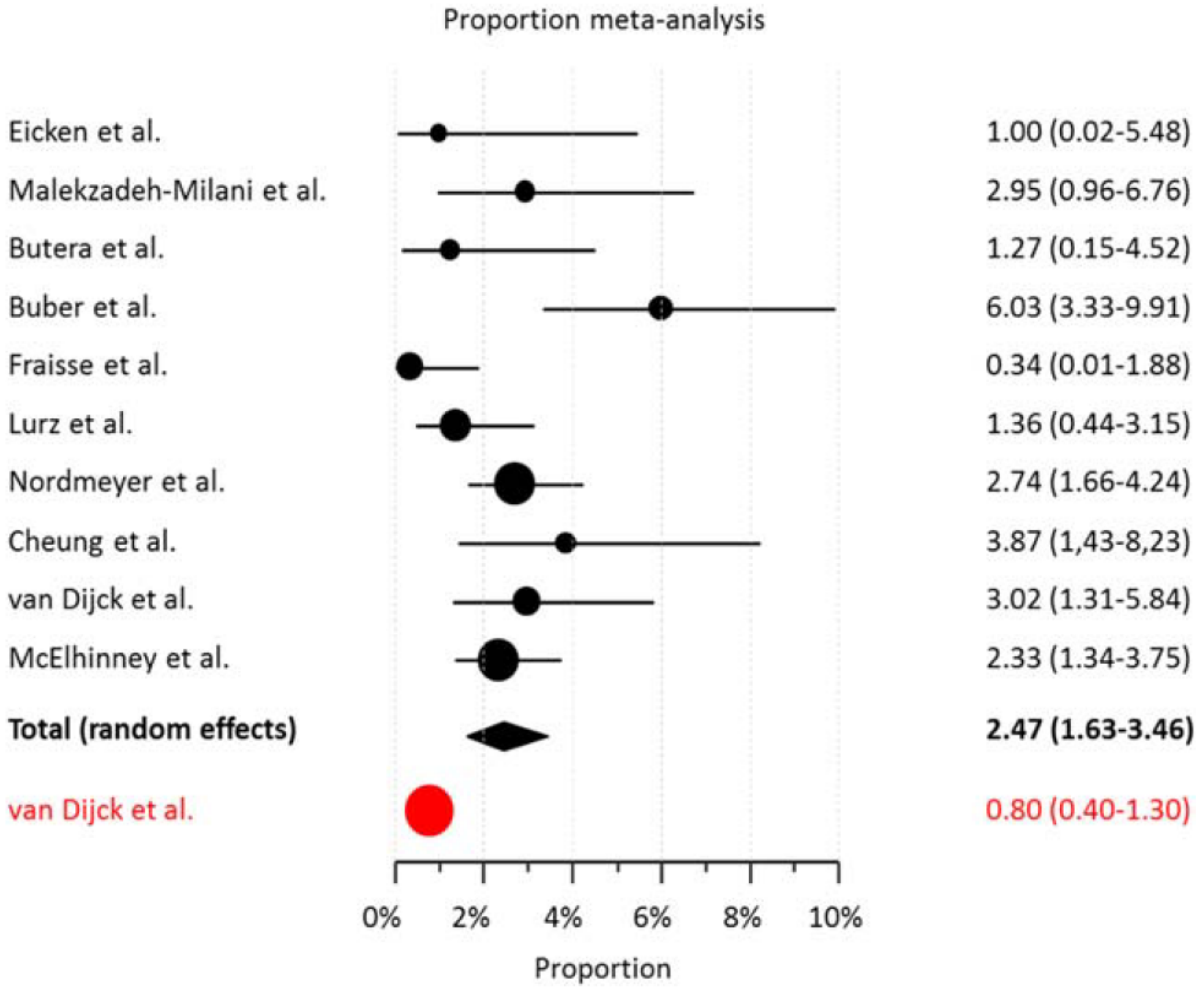
Annual event rate IE after PPVI Melody

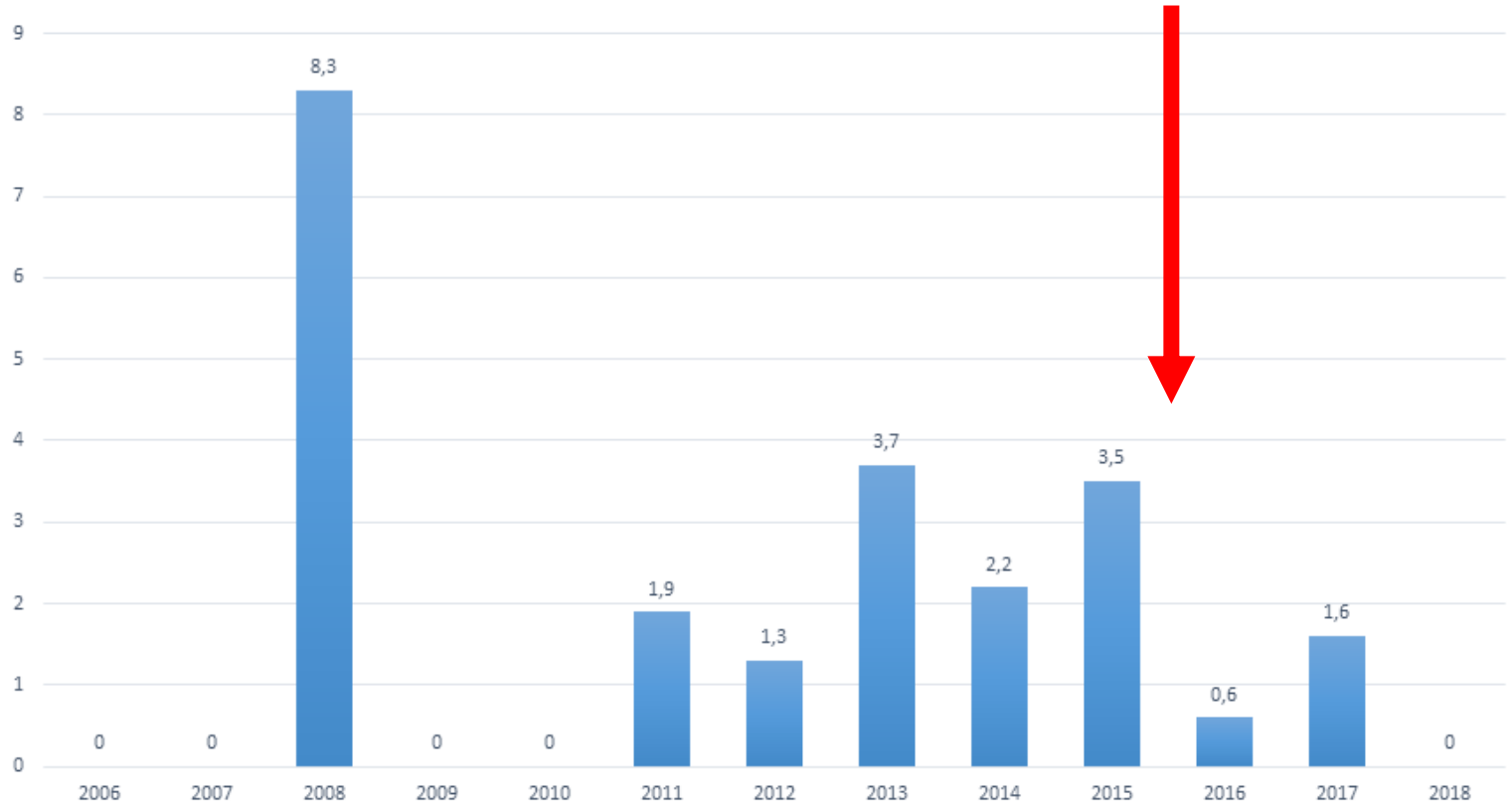


homograft

Uebing, Rigby Heart 2015

Endocarditis: annual incidence

Melody in Leuven 2006 - 2018



Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Valves	3	10	12	21	32	54	78	107	134	142	165	189	215
Endocarditis	0	0	1	0	0	1	1	4	3	5	1	3	0

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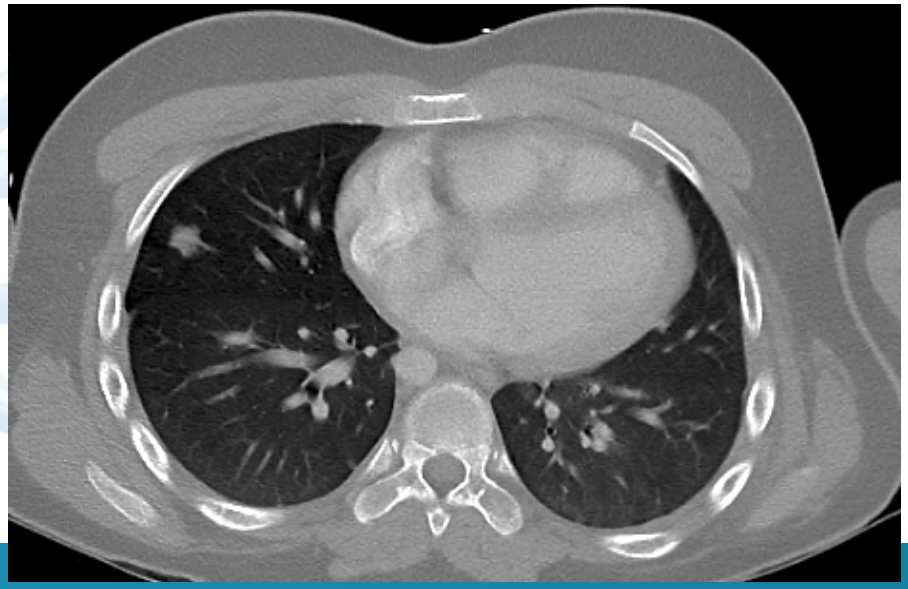
Characteristics of patients with IE in Melody®



- Incidence: 8 / 107 (7,5%)
- Avoidable factors: 7/8
  - oral infections 5
  - poor hygiene 2
  - PM retardation 4/8

    vs 9/99
- Fever at presentation: 7/8
  - Septic lungemboli 2
  - Septic shock 1

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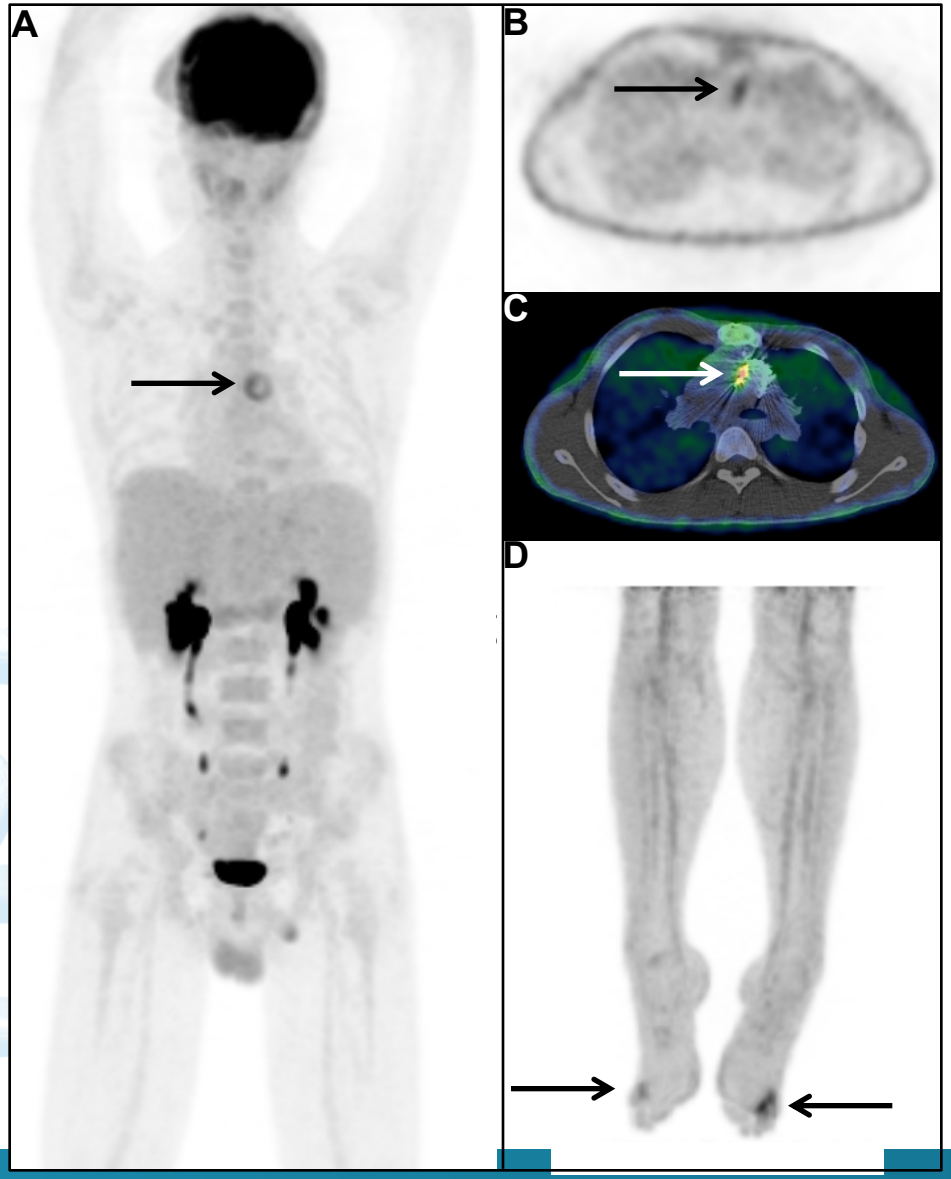
Van Dijck, Gewillig Heart 2015

Melody IE: PET-CT



Van Dijck, Gewillig Heart 2015

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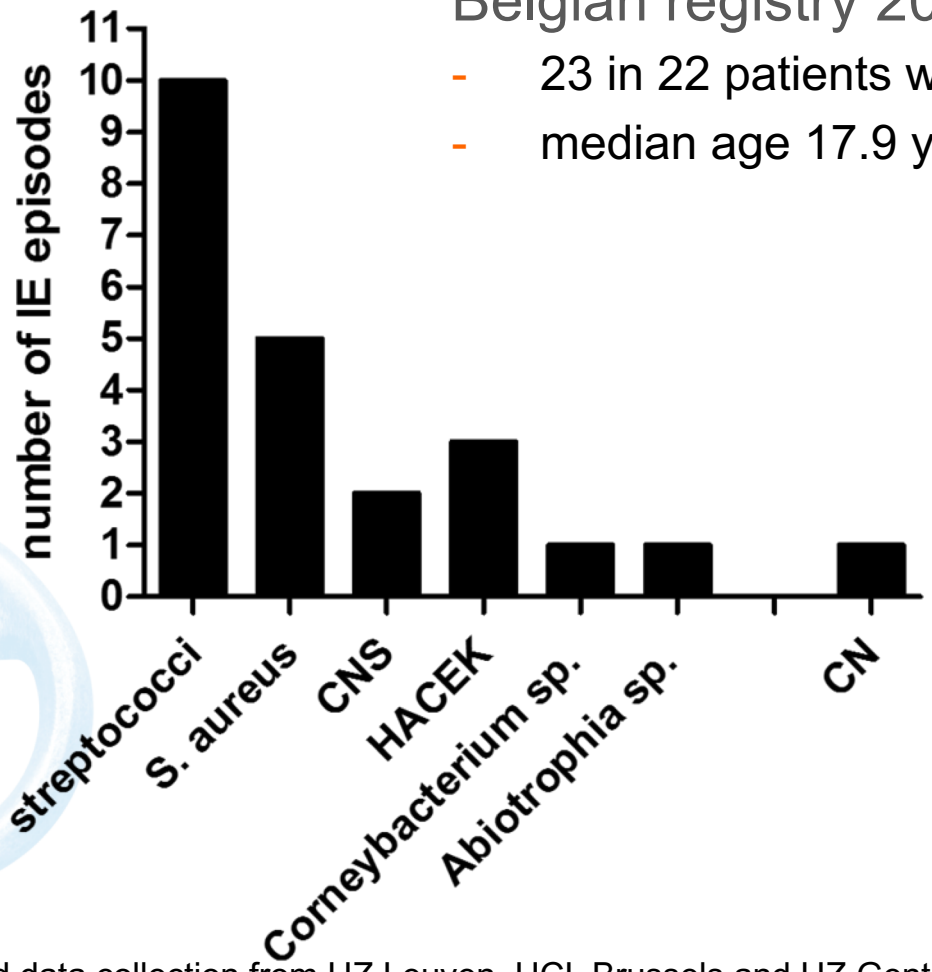
Melody: IE 2006 – 2015 n = 10 / 133

- Outcome:

○ Explantation		
• Urgent	0	
• Early	3	
○ Obstruction		
• Overstented & re-revalvation	2	5/10
○ Remaining		
• PS < 25 mmHg	5	
• PR < 2/4	5	

Van Dijck, Gewillig Heart 2015

Underlying microorganisms



Belgian registry 2006-2017

- 23 in 22 patients with IE (19 male)
- median age 17.9 years

David Bos et al, unpublished data collection from UZ Leuven, UCL Brussels and UZ Gent

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IE after PPVI

- PPVI technical aspects
- incidence
- treatment
- prevention

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Recommendations for treatment

After Diagnosis of BE

Determine Which Presentation Type

Hemodynamically Stable (87%)

Fulminant Disease RVOT Obstruction (13%)

- Early institution of broad spectrum IV abx
- Emergent RVOTO relief
  - Catheter intervention: BMS
  - Surgical removal

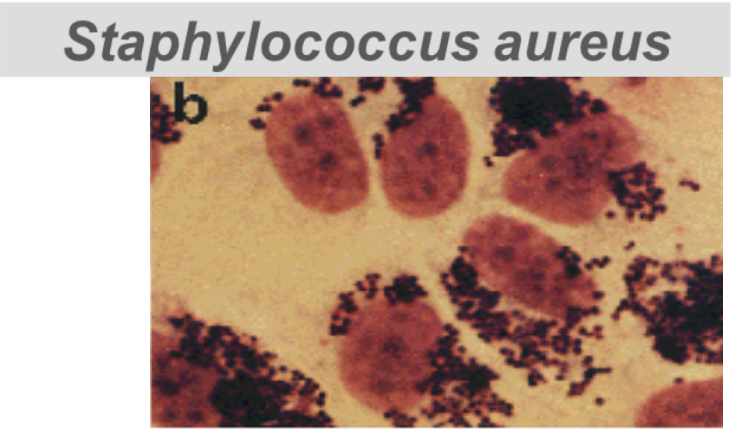
Reasonable Recommendations to Consider:

Acute Treatment

Hemodynamically Stable

- Early institution of broad spectrum IV abx
- Close in-house observation
- Serial evaluation of RVOT for obstruction
  - ? Advanced imaging
- Consider surgical removal if
  - Persistent fever
  - Persistent lung emboli
  - Increasing gradient
  - Other adverse evolution

S. aureus and outcome



- Staphylococci sp.: 42-46%
- Death: 8 - 11%
  - 80 – 90 % *staph.sp.*

Doff B and McElhinney, 2017, Nordmeyer et al, 2017; Abdelghani et al, 2017

IE after PPVI

- PPVI technical aspects
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- treatment
- prevention

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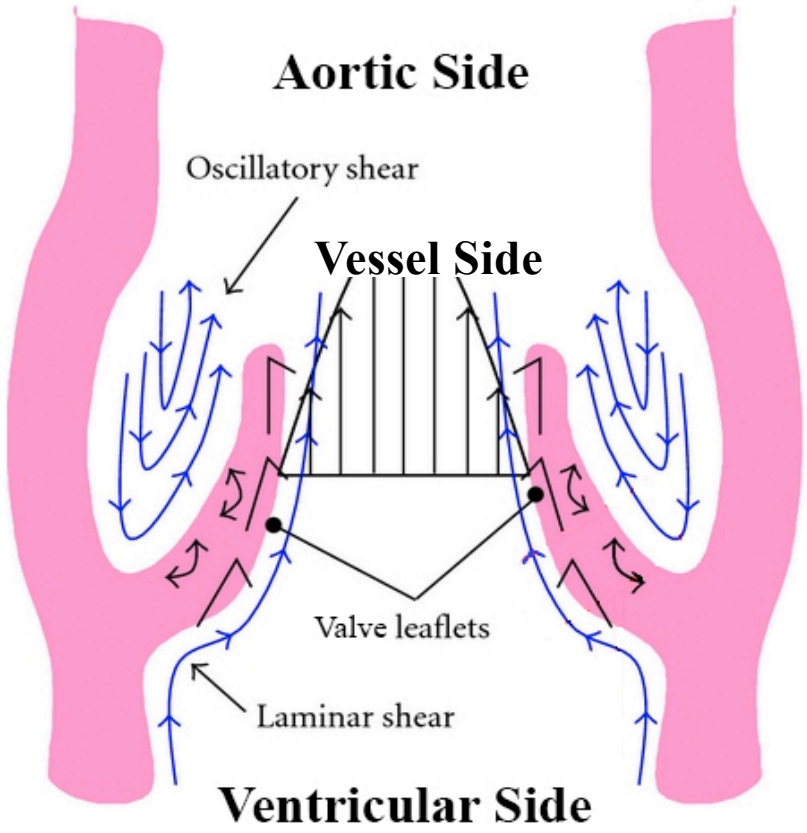
IE : ? risk factors

- life style: skin – mucosal care (male pubers, PM)
  - avoidance of entry ports for bacteria
- antibiotics in case of predictable high level bacteremia
- avoidance of high energy turbulence by adequate pre-stenting of the RVOT
- micro-thrombi, BP
- blood stasis in and around the conduit
- pockets due to incomplete apposition
- tissue surface characteristics
- leaflet motion and redundancy, flow profile
- immunologic interaction

Hemodynamic profile

Recirculations

- high shear stress laminar flow on the ventricular side
- recirculating shear stress present on vessel side



Balachandran et al; Int J Inflam, 2011

Risk of IE after PPVI

Retrospective studies comparing occurrence of IE

	Sapien™ valve	Melody® valve
Meta analysis:	17 studies	30 studies
Lehner et al:	5/501 pts	214/3,616 pts
Estimated implants	2,500	14,000

Future: longer FU will contribute to higher conclusiveness of data

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IE after PPVI: differences in valves

- RVOT
  - Size, turbulence, shear stress
  - Microclots
- Patient
  - Age, size
  - Skin & dental care
- Valved stent
  - Tube graft
  - Leaflet material
  - Flow patterns
  - Size valve, delivery system

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Boston Children's Hospital
Anatomic Examination of Risk Factors
pockets & irregularities

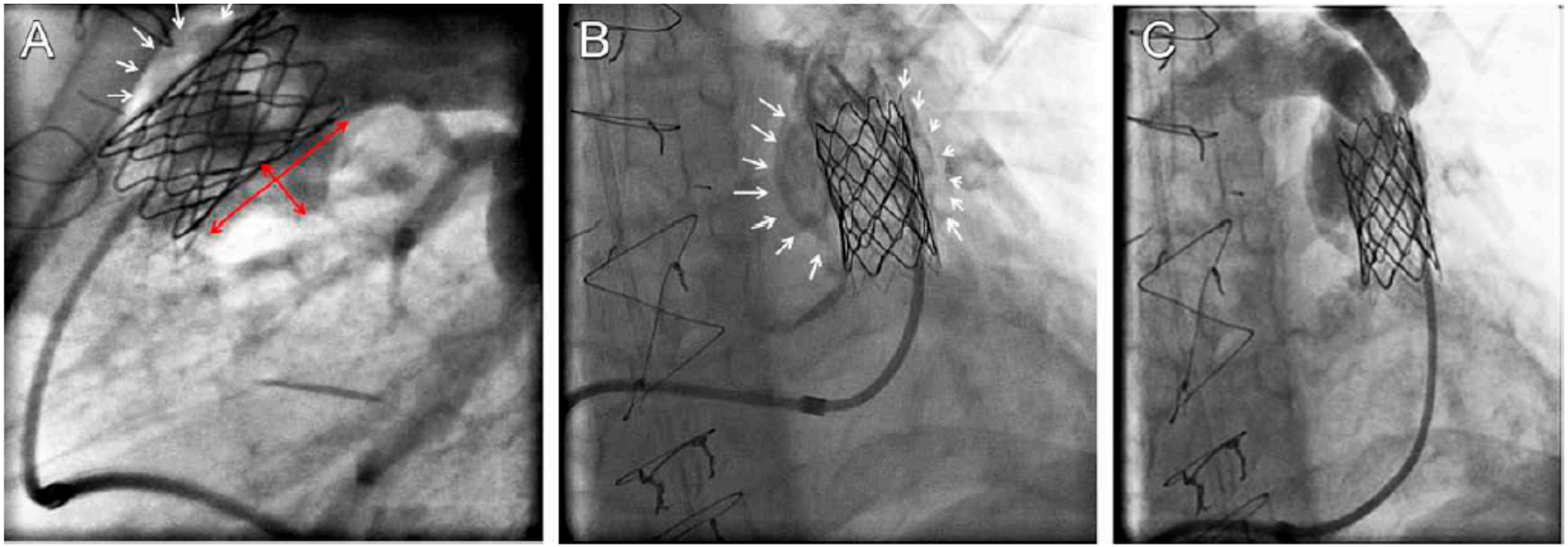


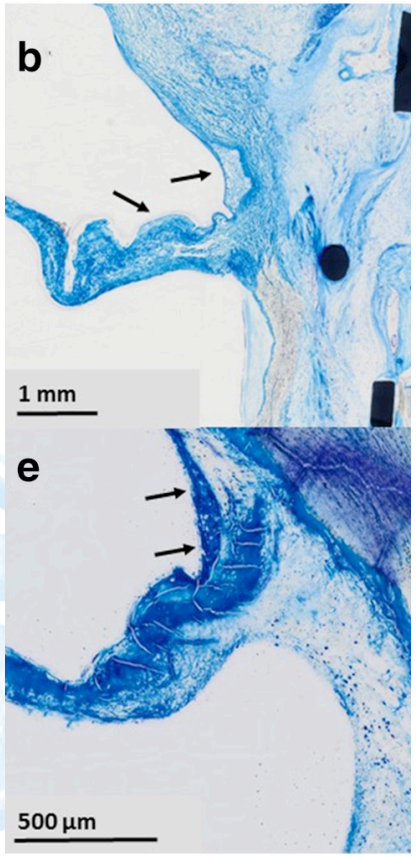
Figure 1. Lateral (**A**, with arrows showing length and depth measurements) and anterior-posterior (white arrows delineate the outer border of the outflow tract, **B**) angiographic projections demonstrating right ventricular outflow tract irregularities after percutaneous pulmonary valve implantation in a patient with a previously implanted 22-mm homograft who developed severe regurgitation. Presence of contrast inside the irregularities indicates direct communication with the conduit lumen (**C**). Irregularities were observed in both sides of the outflow tract in both projections, yielding a circumference score of 4.

Burber et al, Circ Cardiovasc Interv. 2013

Subclinical thrombus formation in bioprosthetic pulmonary valve conduits

Philipp Jewgenow [a,b], Heike Schneider [a], Regina Bökenkamp [c], Jürgen Hörer [d], Julie Cleuziou [d], Rudi Foth [a], Alexander Paul Horke [e], Andreas Eicken [f], Thomas Paul [a], Matthias Sigler [a,*]

Fibrin deposition in the valvular sinus
(Brown Hopps staining)



? predisposition for bacterial and platelet adhesion ?

? facilitation of endothelialisation

? time ?

Jewgenow et al., Int J Cardiol 281: 113-118; 2019

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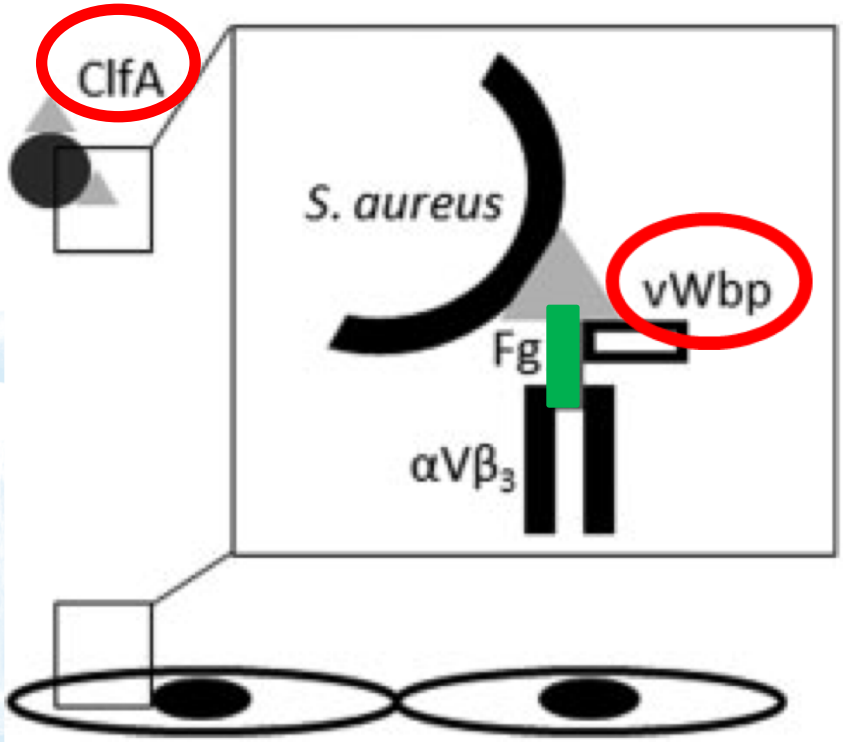
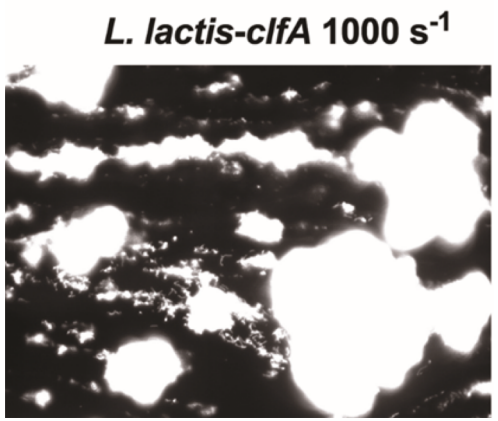
IE & fibrinogen

Fg mediates bacteria & platelet binding



shear stress dependent pathways



Claes, Ditkowski *et al. Thromb Haem* 2018
Ditkowski et al, unpublished data

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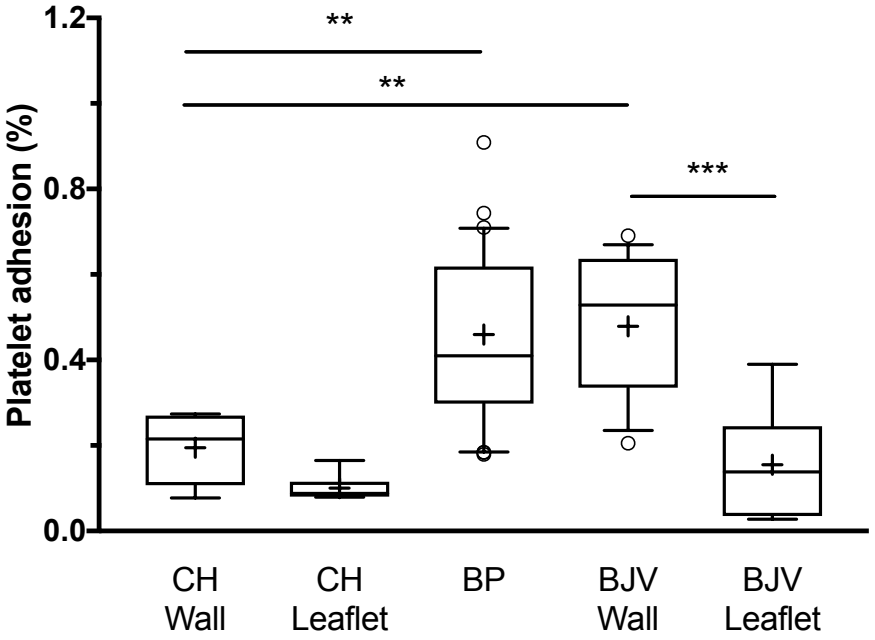
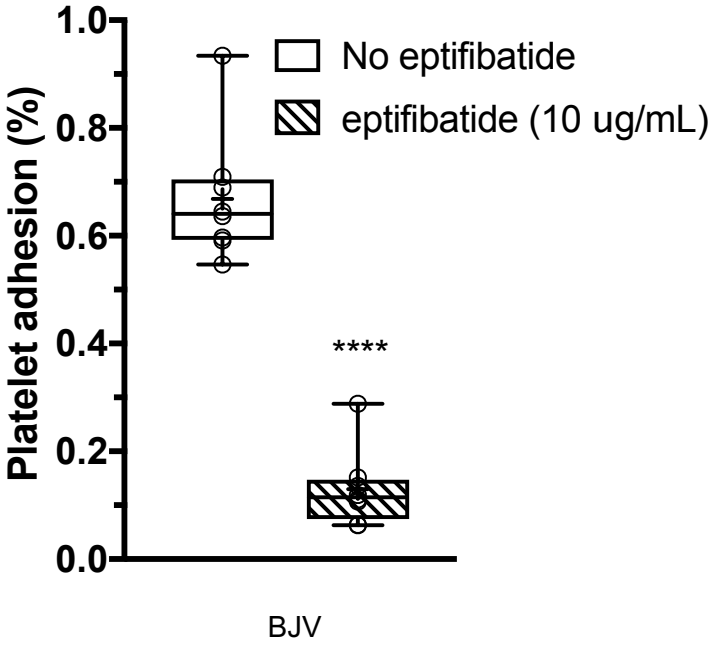
Platelet adhesion to RVOT tissues





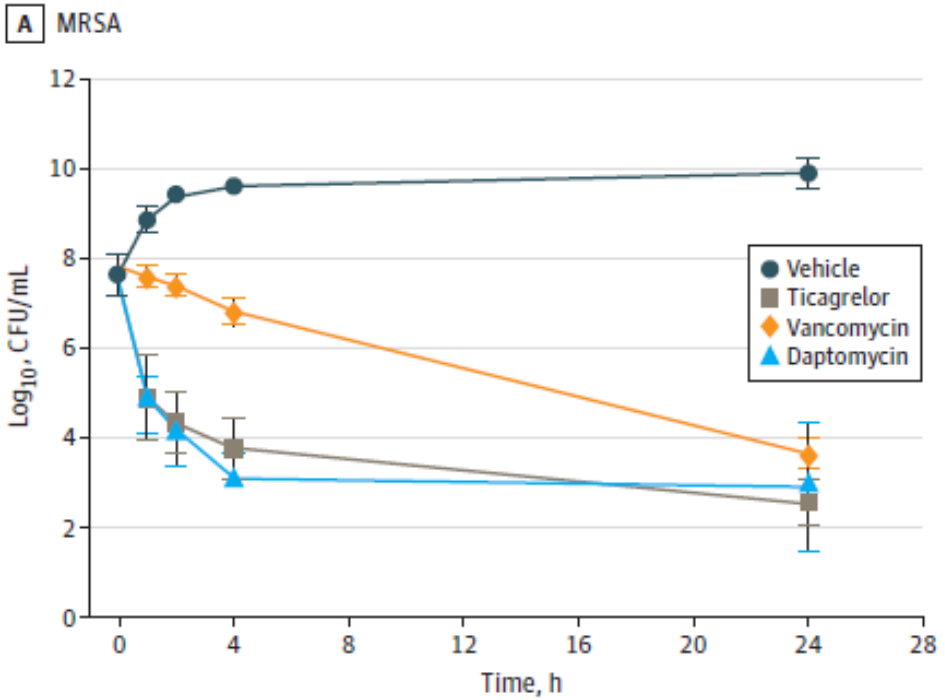
Ditkowski et al, unpublished data

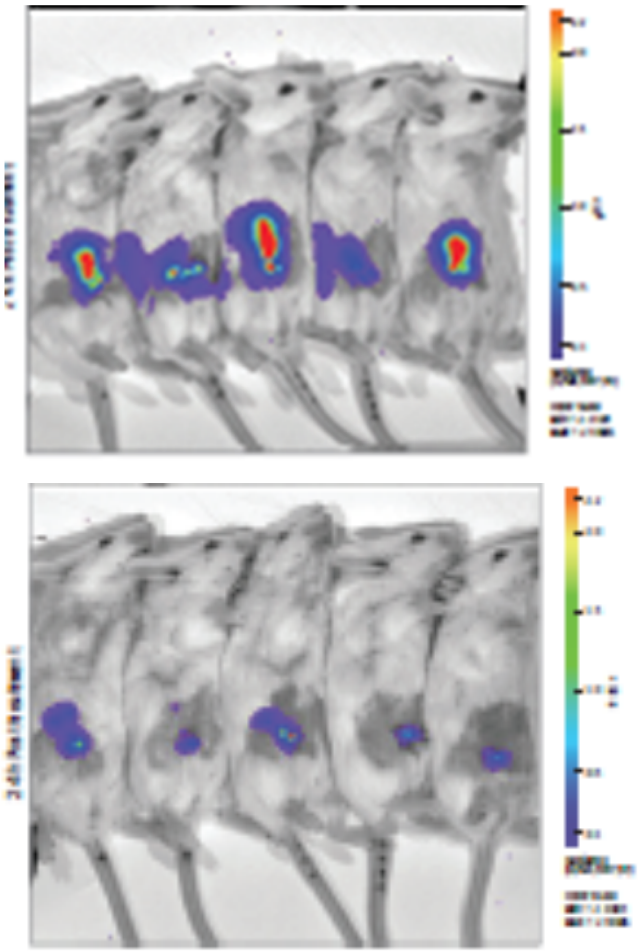
JAMA Cardiol. 2019 May 8. doi: 10.1001/jamacardio.2019.1189. [Epub ahead of print]

Antibacterial Activity of Ticagrelor in Conventional Antiplatelet Dosages Against Antibiotic-Resistant Gram-Positive Bacteria.

Lancellotti P[1,2], Musumeci L[1], Jacques N[1], Servais L[1], Goffin E[1,3], Pirotte B[3], Oury C[1].

Figure 1. In vitro Characterization of Bactericidal and Anti-Biofilm Activity





Bioluminescent signals of *in vivo* bactericidal activity

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Current guidelines

2002

- Société Française de Cardiologie (SFC)
- Heart Journal, 30, 2369-2413

- American Heart Association (AHA)

2014 revised guidelines, JACC 63:2438-88

- National Institute for Health and Care Excellence (NICE), United Kingdom

2016 revised guidelines, Br Dent J, 221(3), 112-114

- European Society of Cardiology (ESC)

2015 revised guidelines, European Heart Journal, 36, 3075-3123

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Knowledge on IE

Are adults with congenital heart disease informed about their risk for infective endocarditis and treated in accordance to current guidelines?

Ulrike M.M. Bauer [a,g,1], Paul C. Helm [a,g,1], Gerhard-Paul Diller [b,g,1], Boulos Asfour [a,c,g,1], Christian Schlensak [d,g,1], Katharina Schmitt [e,g,1], Peter Ewert [f,g,1], Oktay Tutarel [f,g,*,1]

insufficient knowledge on
IE prevention and oral hygiene

„A nationwide survey of French dentists´knowledge“

- 12000 dentists in France
- 34.5 % good knowledge of actual guidelines

Bauer et al, Int J Cardiol, 245, 105-108, 2017
Cloitre et el, Oral Surg Oral Med Oral Pathol Oral Radiol. **2017**
Koerdt et el, Clin Oral Invest, 2017

Non-specific prevention measures

ESC guidelines 2015

These measures should ideally be applied to the general population and particularly reinforced in high-risk patients:
• Strict dental and cutaneous hygiene. Dental follow-up should be performed twice a year in high-risk patients and yearly in the others.
• Disinfection of wounds.
• Eradication or decrease of chronic bacterial carriage: skin, urine.
• Curative antibiotics for any focus of bacterial infection.
• No self-medication with antibiotics.
• Strict infection control measures for any at-risk procedure.
• Discourage piercing and tattooing.

Gilbert Habib et al. Eur Heart J 2015;36:3075-3128

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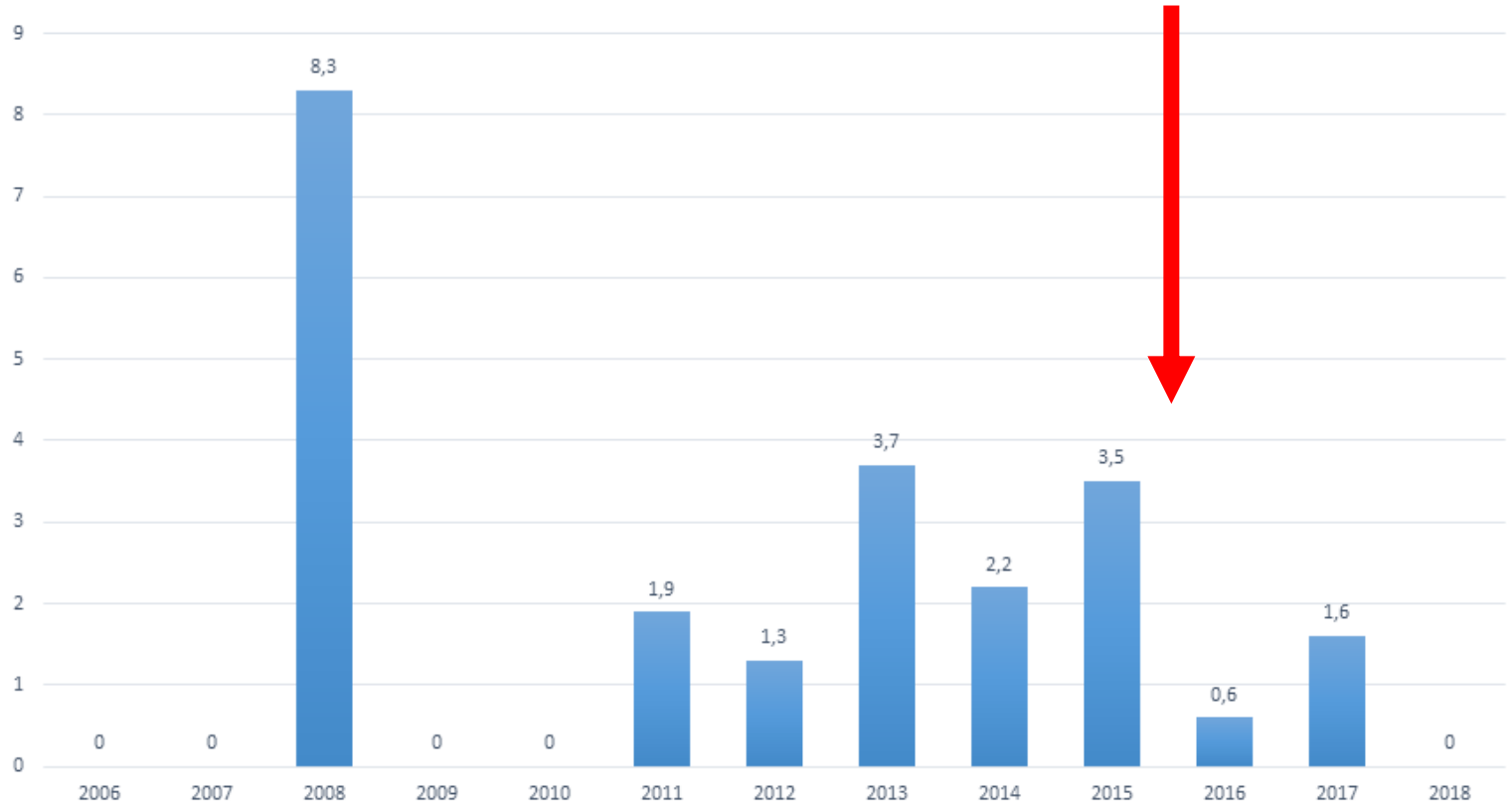
Endocarditis: annual incidence



Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Valves	3	10	12	21	32	54	78	107	134	142	165	189	215
Endocarditis	0	0	1	0	0	1	1	4	3	5	1	3	0

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Conclusion: prevention IE after PPVI

Multifactorial

- Valve: design, material
- Patient selection
- Implantation technique:
  - size, gradient, turbulence, ...
- Education
  - Patient
  - Health professional
- Clotting – BP – immunology

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Experience in children, Melody valve and more

Marc Gewillig
Leuven, Belgium