

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

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

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# Background

- Percutaneous pulmonary valve replacement (PPVR) with the Melody valve (Medtronic, Inc., Minneapolis, MN, USA) is used to prolong the durability of degenerated right-ventricle-to-pulmonary-artery (RV–PA) prosthetic conduits.
- PPVR provides an attractive alternative to surgery and can lengthen the time until a patient needs additional open-heart surgery.



# Background

- Since the first procedure was performed in 2000, more than 3000 Melody valves have been implanted worldwide.

Bonhoeffer P, et al. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. *Lancet* 2000;356:1403–5.

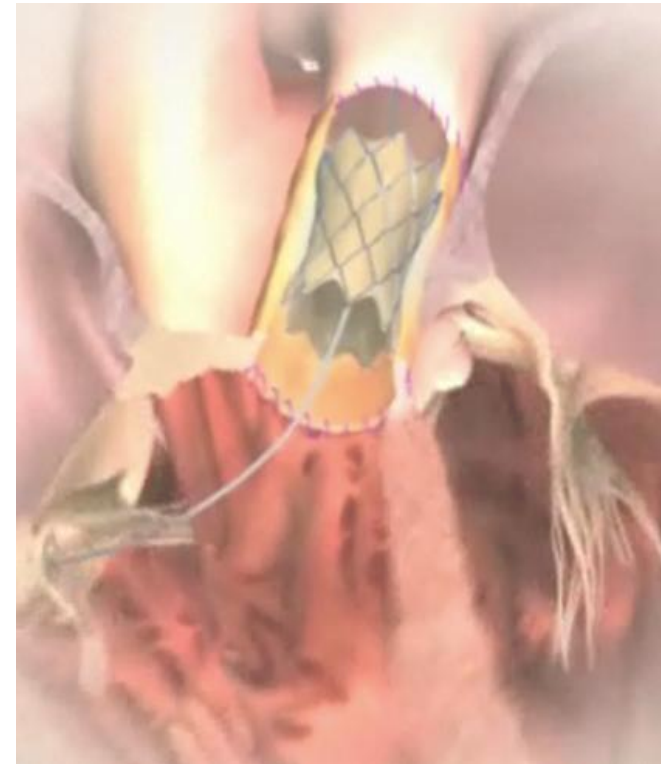
GillespieMJ,etal.Melodyvalveimplantwithinafailedbioprosthetic valves in the pulmonary position: a multicenter experience. *Circ Cardiovasc Interv* Dec 1 2012;5(6):862–70.

- Short-term and intermediate term benefits have been shown in different studies.

Khambadkone S, et al. Percutaneous pulmonary valve implantation in humans: results in 59 consecutive patients. *Circulation* 2005;112:1189–97.

McElhinneyDB, etal.Short-andmedium-termoutcomes after transcatheter pulmonary valve placement in the expanded multicenter US melody valve trial. *Circulation* 2010;122(5):507–16.

Eicken A, et al. Percutaneous pulmonary valve implantation: two-centre experience with more than 100 patients. *Eur Heart J* 2011;32:1260–5.



# Potential complication of Melody Valve: IE

- *Infective endocarditis (IE)* related to the implanted Melody valve was reported, but a few scatter published data about its incidence could be found.
- Moreover, its diagnosis may be challenging because of difficult visualization of the stented valve by TTE and TEE.

Eicken A, Ewert P, Hager A, et al. Percutaneous pulmonary valve implantation: two-centre experience with more than 100 patients. *Eur Heart J* 2011;32:1260–5.

Atamanyukl, Raja SG, Kostolny M, Bartonellahenselaendocarditis of percutaneously implanted pulmonary valve. *J Heart Valve Dis Sep* 2012;21(5):682–5.

Bhat DP, Forbes TJ, Aggarwal S. A case of life-threatening *Staphylococcus aureus* endocarditis involving percutaneous transcatheter prosthetic pulmonary valve. *Congenit Heart Dis Oct* 24 2012.

Butera G, Milanesi O, Spadoni I, et al. Melody transcatheter pulmonary valve implantation. Results from the registry of the Italian Society of Pediatric Cardiology. *Catheter Cardiovasc Interv* 2012;81(2):310–6.

Patel M, Iserin L, Bonnet D, Boudjemline Y. Atypical malignant late infective endocarditis of Melody valve. *J Thorac Cardiovasc Surg* 2012;143(4):e32–5.

Lurz P, Coats L, Khambadkone S, et al. Percutaneous pulmonary valve implantation: impact of evolving technology and learning curve on clinical outcome. *Circulation* 2008;117(15):1964–72.

# Aim of this study

The purpose of this study was to report the **incidence of IE** in patients with Melody valve implantation, and to review **its diagnostic difficulty**.



# Methods

- All patients that undergone PPVR with the Melody valve in a tertiary hospital in Denmark were included retrospectively.
- The electronic medical notes of all eligible patients were reviewed and screened for all suspected and confirmed cases of IE.
- For those documented cases of IE, further detailed information was recorded, including the *underlying diagnosis prior to Melody valve implantation, the indication and the date of the procedure, date and precipitating symptoms of suspected endocarditis, microbiological findings, echocardiographic findings, treatment and outcome.*

# Results

- From November 2006 to November 2012, 43 Melody valve implantations were performed in 42 patients (mean age 25, 6–67 years).
- At a median follow-up of 27 months (2–66 months), 6 *patients were suspected for IE.*
- The median duration between the date of Melody valve implantation and the date of symptom onset of infection was 18 months (9–40 months) .



# Table 1

Patient	Year of birth	Sex	Diagnosis before the Melody valve implantation	Date of the Melody valve implantation (mm.yyyy)	Endocarditis, according to the modified Duke's criteria [11] (before ICE examination)	Endocarditis, according to the modified Duke's criteria [11] (after ICE examination)
1	1981	Male	AS s/p Ross operation	11.2006	Possible (1 major + 2 minor)	Possible (1 major + 2 minor)
2	1996	Male	TA	01.2009	Possible (3 minor)	Possible (3 minor)
3	1991	Male	TGA	01.2009	Possible (3 minor)	Possible (3 minor)
4	1984	Male	AS s/p Ross operation	10.2009	Possible (3 minor)	Definite (1 major + 3 minor)
5	1996	Male	TOF/PA	05.2011	Possible (1 major + 2 minor)	Possible (1 major + 2 minor)
6	1990	Male	TGA	08.2011	Possible (1 major + 2 minor)	Definite (2 major)

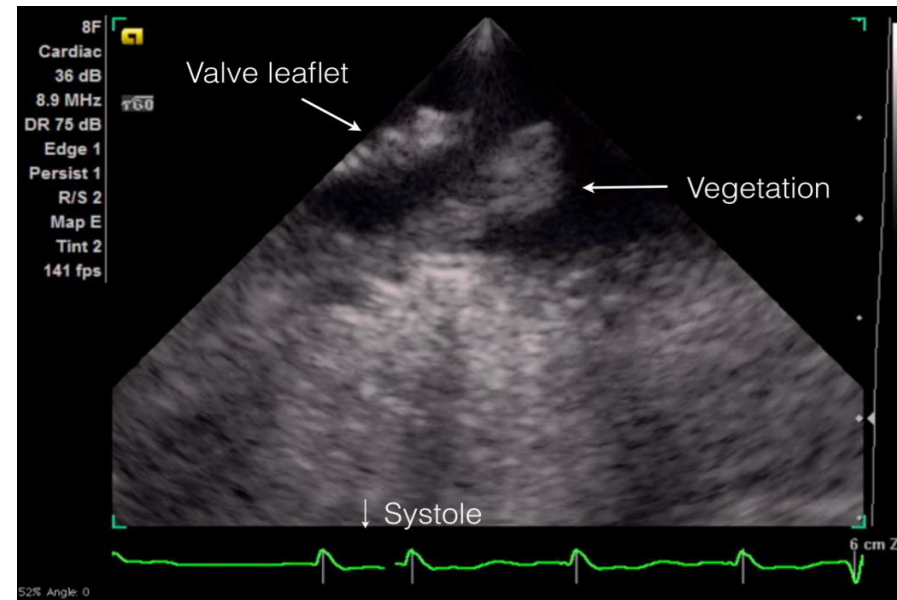
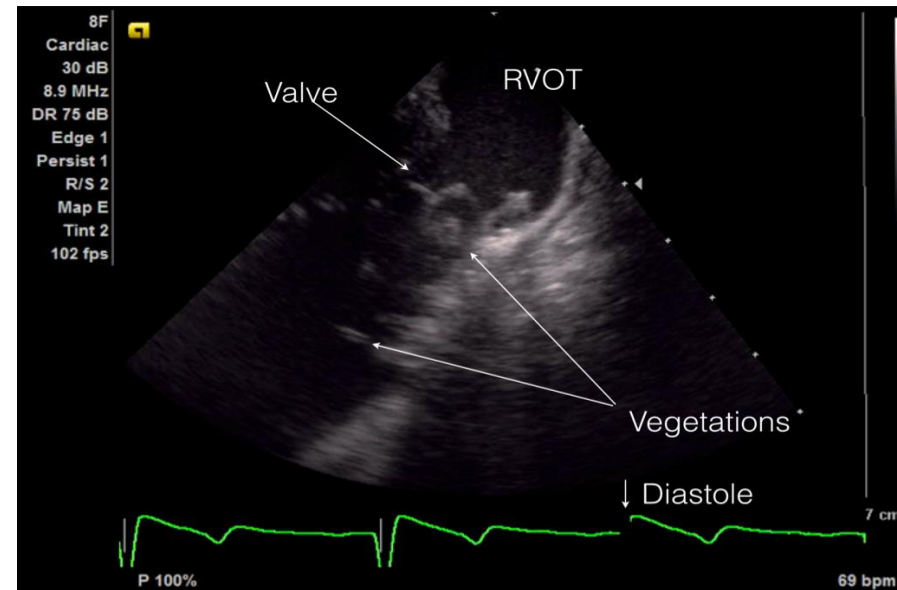
AS, aortic stenosis. TA, truncus arteriosus. TGA, transposition of the great arteries. TOF, tetralogy of Fallot. PA, pulmonary atresia.

## Table 2

Patient	Blood culture	Echocardiographic result	Treatment	Outcome
1	<i>Staphylococcus aureus</i>	Negative TTE and TEE examination	Medical	Alive
2	<i>Streptococcus pneumoniae</i>	Negative TTE and TEE examination	Medical	Alive
3	Non-haemolytic <i>Streptococci</i>	Negative TTE and TEE examination	Medical	Alive
4	<i>Staphylococcus epidermidis</i>	Negative TTE and TEE examination; ICE showed two mobile mass attached to the Melody valve	Surgical + medical	Dead two years after IE
5	<i>Streptococcus gordonii</i>	Negative TTE and TEE examination	Medical	Alive
6	<i>Staphylococcus aureus</i>	Negative TTE and TEE examination; ICE showed a 8 × 8mm large mass attached to the Melody valve	Surgical + medical	Alive

# Two patients did not response well medically

- Intra-cardiac echocardiography (AcuNav, Siemens Medical, Mountain View, CA) examinations was performed through a 9-Fr sheath over femoral vein under local anaesthesia.
- ICE demonstrated the presence of vegetations, so changed their modified Duke's classification to definite case of IE!



# Discussion



# Incidence of IE in our cohort of 42 patients

- Two definite IE cases involving the Melody valve, giving an incidence of 4.7%. With a total of 155 FU patient-year, the incidence of definite IE was 1.3% per patient-year.
- If additional four possible cases are included, the incidence will be 14.3%, corresponding to 3.9% per patient-year.
- Another published study on IE after PPVR cited that the incidence of IE was 5.1%. The annualized rate was 2.4% per patient-year.

McElhinney DB, Benson LN, Eicken A, Kreutzer J, Padera RF, Zahn EM. Infective endocarditis after transcatheter pulmonary valve replacement using the Melody valve: combined results of 3 prospective North American and European studies. *Circ Cardiovasc Interv* Jun 1 2013;6(3):292–300.

# Incidence of IE

- Since the median FU in that study and our study was just 27 and 29 months, the true incidence of IE may not really reflect in these kind of duration of time.
- *A prospective randomized controlled study comparing PPVR and surgical valve replacement over a long time period could truly reflect any significant difference in the incidence of IE.*

# Limitation of TTE/TEE for PV lesions

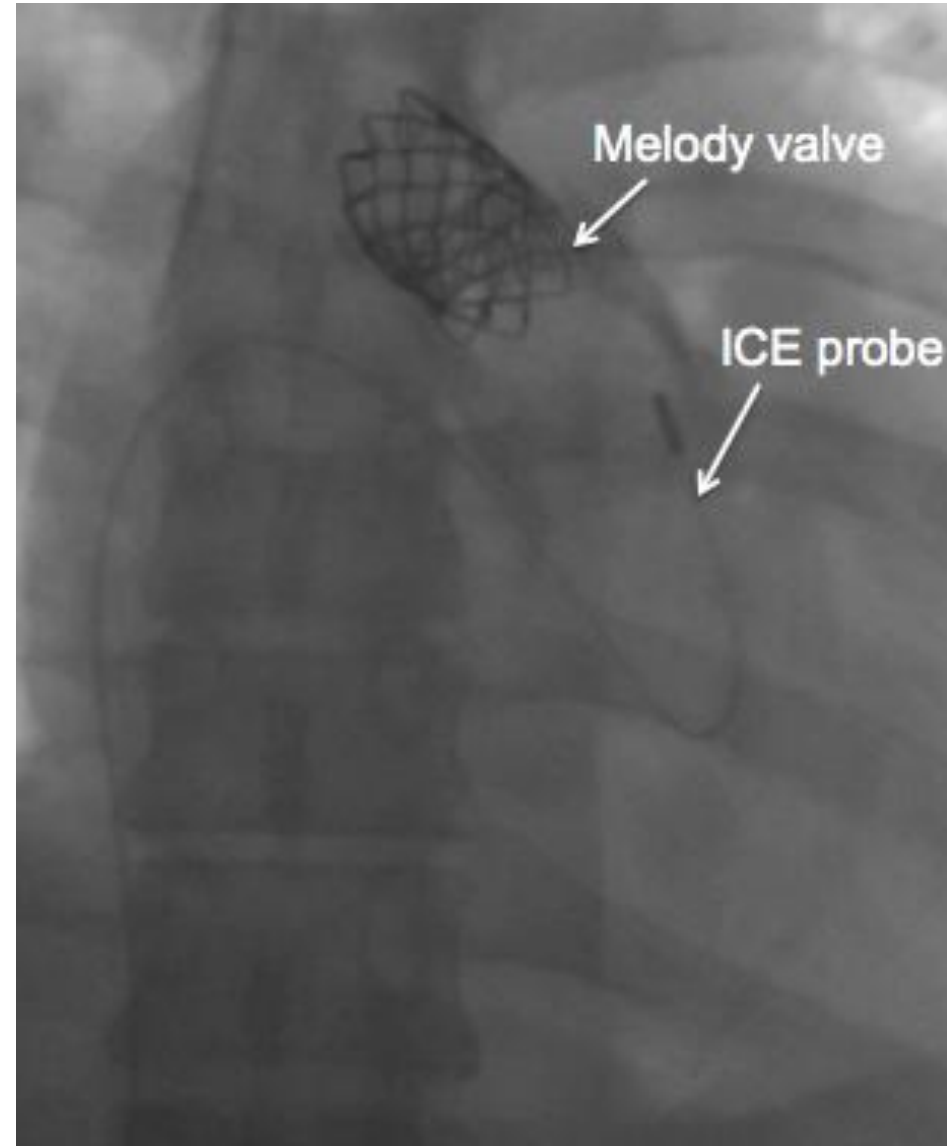
- The sensitivity of detection of IE in all native valves by TTE ranged from 40 to 63% and that of TEE from 90 to 100%.
- However, imaging is more challenging in IE involving prosthesis.
- For prosthetic IE, TTE has shown only 36–69% sensitivity in detection of vegetations, while the sensitivity of TEE was 86–94%.

Rozich JD, Edwards WD, Hanna RD, et al. Mechanical prosthetic valve associated strands: pathologic correlates to transesophageal echocardiography. *J Am Soc Echocardiogr* 2003;16:97–100.

- Even with the use of TEE, the lesions within the PV stent may not be visualized well as the valve is located anterior, and thus not in proximity to the TEE probe.
- The shadowing artefacts by the more echogenic nature of the stented valve will affect the accuracy of echo detection of vegetations, and/or other more subtle IE changes.

# Usage of ICE in prosthetic PV

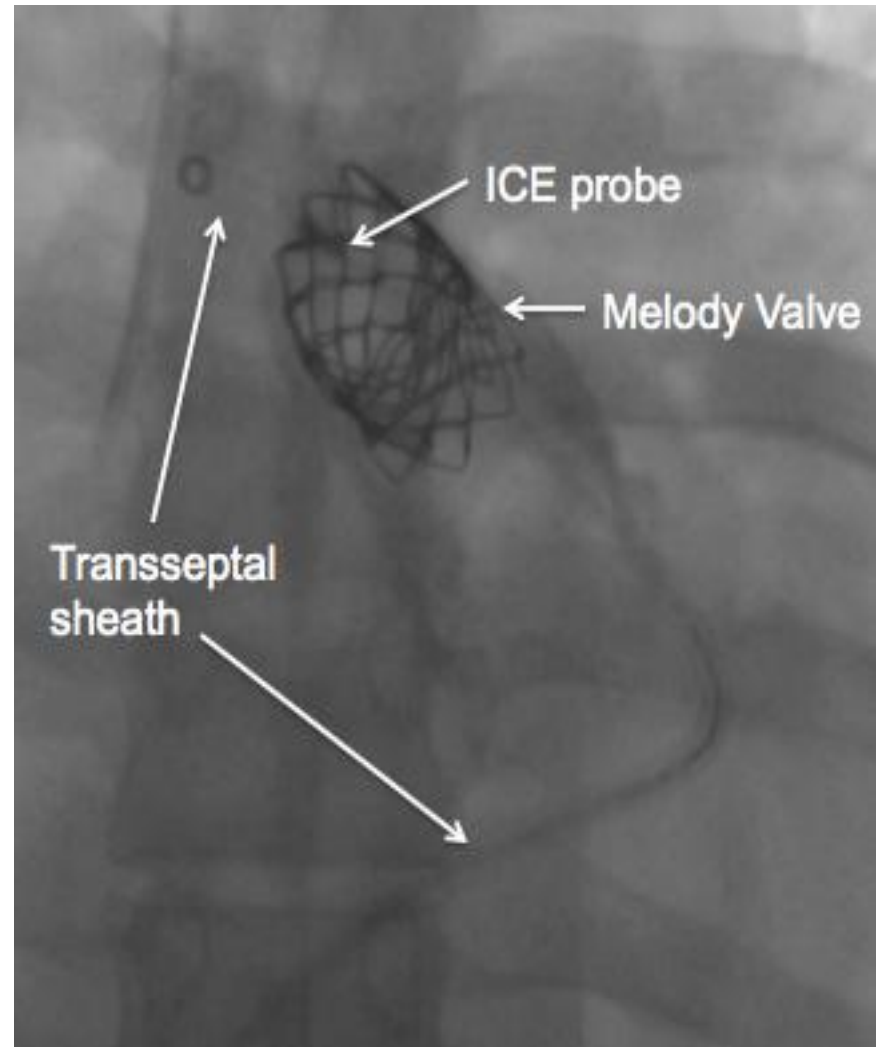
- ICE is increasingly being used in percutaneous heart interventions, and it allows for close-up examination of a prosthetic PV.
- ICE probe may not pass into the PV prosthesis easily, and can get caught in the proximal part of the stent.
- To overcome that problem, a multi-purpose catheter and hydrophilic guidewire were used to pass through the PPVR prosthesis and into PA.





# Usage of ICE in prosthetic PV

- After exchange to a stiff wire, a long 9-Fr transseptal sheath was inserted, in which the ICE probe advanced into the Melody valve without risk of embolization of dislodged vegetations to PA.
- Meticulous manipulation of the transseptal sheath and guidewire is strongly recommended since this also imposes a risk of embolization.



# Usefulness of ICE

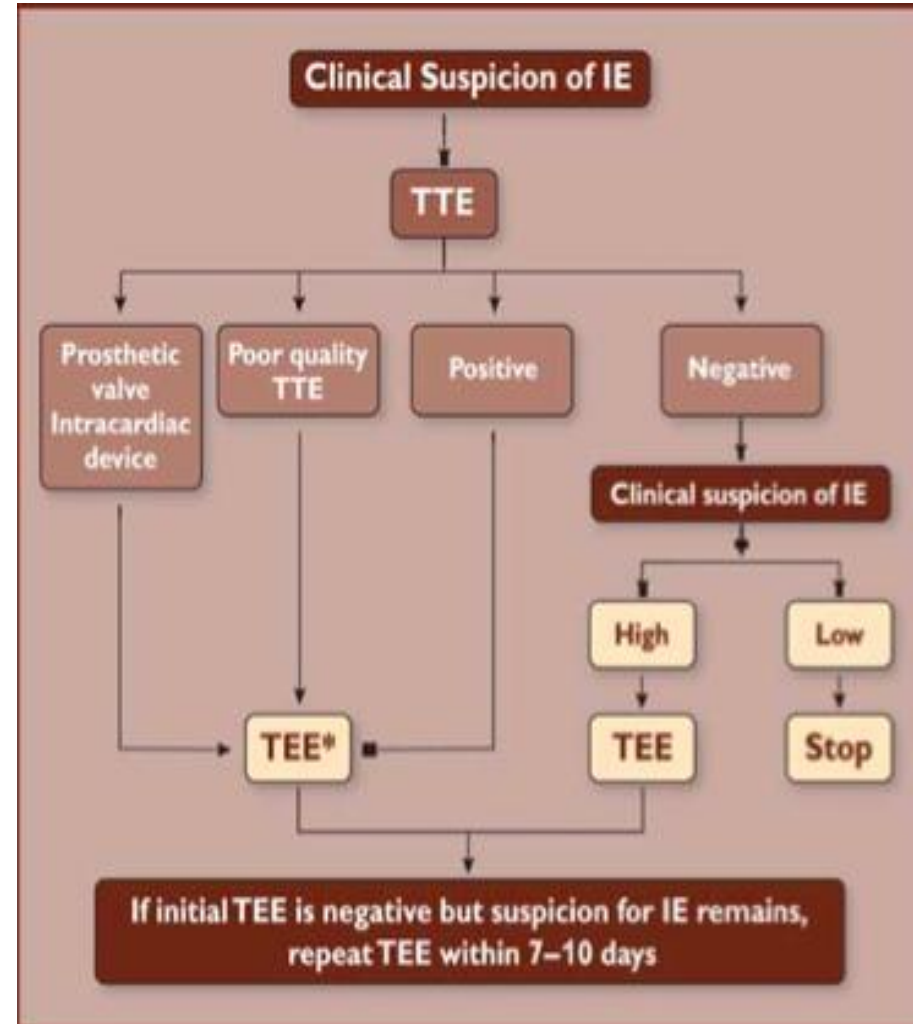
The background of the slide features a medical device, specifically an ICE (Intracardiac Echocardiography) catheter. It consists of a long, thin, flexible black tube that is coiled. At the end of the tube is a white, cylindrical probe with a blue sensor tip. A control unit, which is a white and blue handheld device with a dial and buttons, is connected to the catheter. The entire setup is laid out on a light blue surface.

- Two cases in our series demonstrated the usefulness of ICE in making a firm diagnosis and subsequent management of IE.
- If no echocardiographic evidence of IE by ICE, those two cases could not be classified as definite cases by the modified Duke's criteria.
- Moreover, surgical intervention might not have been performed so promptly without the convincing evidence from ICE.

# European Society of Cardiology (ESC)

## Guidelines on IE

- In the latest version of the ESC guideline on prevention, diagnosis, and treatment of IE, no any recommendation or even description of the role for ICE in diagnosing IE.
- The guideline recommends repeating TEE within 7–10 days after an initially negative examination, but persistently high clinical suspicion of IE.
- No additional suggestion of imaging modalities if repeated TEE is still negative and no other focus of infection is found.



] Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J* 2009;30:2369–413.

# Benefits of ICE



- This study reported how ICE could diagnose IE, when repeated TTE and TEE were inconclusive.
- Thus, ICE may be considered in all suspected cases of IE in PPVR prosthesis with negative TTE and TEE results; otherwise patients could be at risk during prolonged course of antibiotics without having IE.

# Benefits of ICE



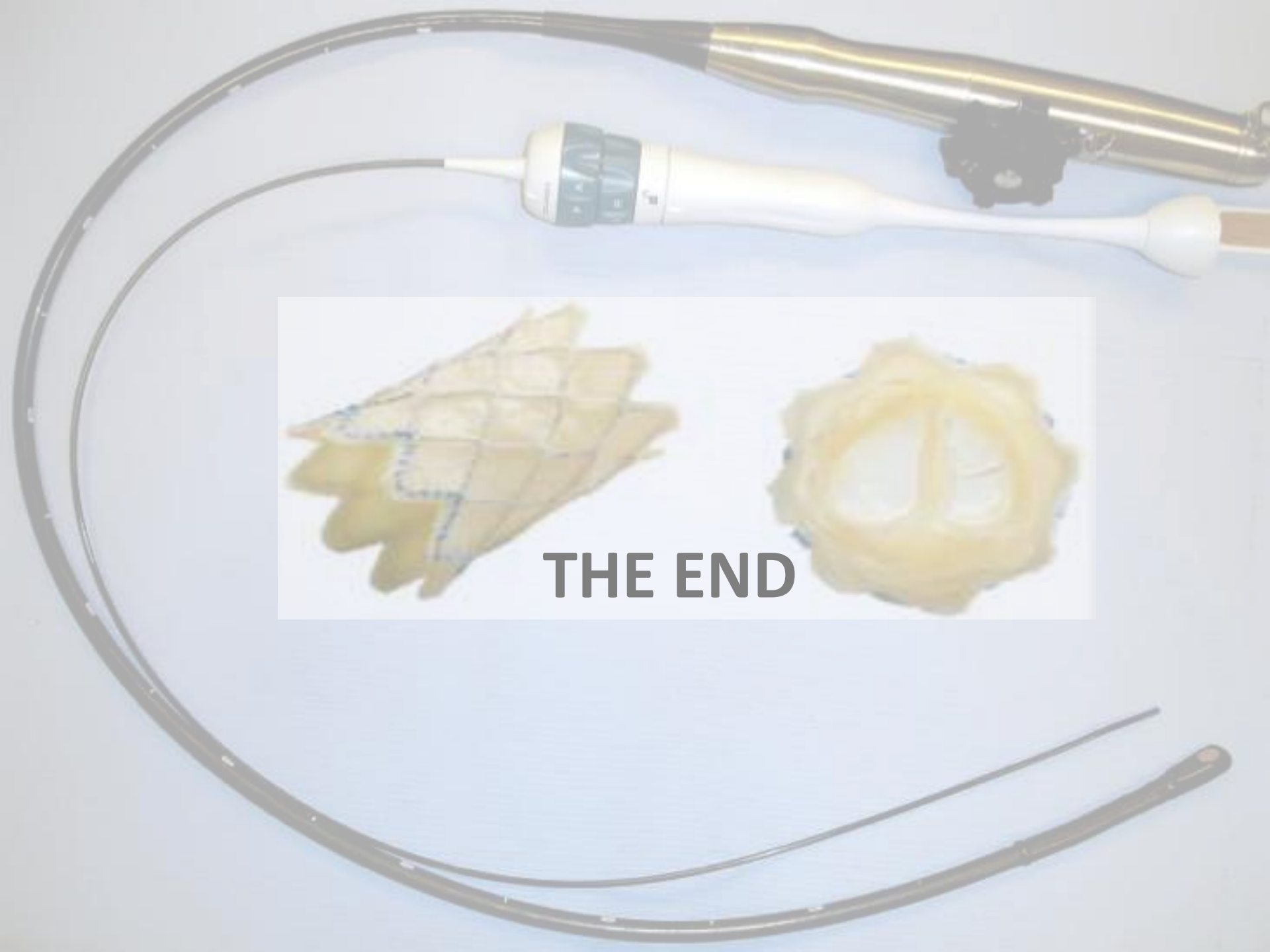
- As the cost and the potential risks due to the invasive nature, the usage of ICE should be considered as a *second-line* addition to TTE and TEE.
- It may avoid prolonged antibiotic treatment in non-IE patients when there is negative ICE; while early surgery could be done in confirmed cases of IE if ICE provides convincing evidence of IE.

# Limitation

- This study is a single centre retrospective data review involving only 42 patients. Large-scale registries involving different centres with PPVR should be recommended.

# Conclusion

- IE is *not an uncommon complication* after percutaneous PV replacement with the Melody valve.  
⇒ Multi-centre registries may help to identify the actual incidence in this group of patients.
- *Diagnostic difficulties* are common especially when TTE and TEE cannot demonstrate vegetations.  
⇒ ICE should be considered in suspected case of IE following percutaneous PV replacement with repeated negative TTE and TEE examinations.
- *Strict antibiotic prophylaxis and good preventive dental care* should be strongly recommended to all these patients.



**THE END**



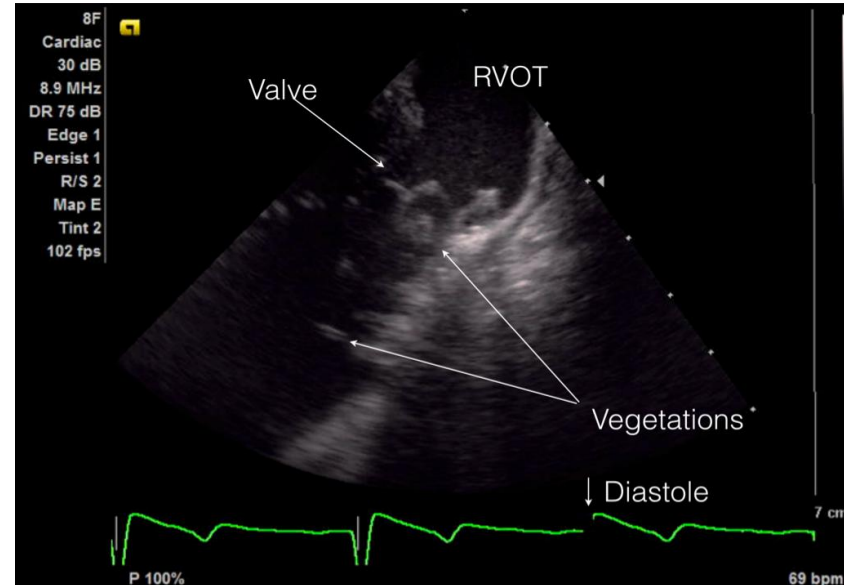
Supplement slides

# Case 4

- A 27-year-old man, with a previous Ross operation for severe aortic stenosis, underwent PPVR with a Melody valve due to stenosis of a pulmonary Contegra graft.
- As a co-morbid and predisposing factor, he required chronic haemodialysis, from the age of 19 years old, for end-stage renal failure due to Goodpasture's syndrome.
- He presented with a febrile episode 9 months after PPVR, and growth of *S. epidermidis* was found in four sets of blood cultures.
- Initial TTE and TEE showed no vegetations or signs of abscess formation on the Melody valve. He was classified as possible case of IE according to the modified Duke's criteria.
- The patient was treated with a complete course of antibiotics for 6 weeks carefully guided by culture and resistance pattern.
- However, the patient was re-admitted with asymptomatic septicaemia two months later, due to persistent growth of *S. epidermidis* from surveillance blood culture samples.

# Case 4

- As repeated TTE and TEE again failed to demonstrate vegetation, ICE was performed and showed two mobile vegetations inside the Melody valve.
- The definite case of IE could then be confirmed according to the modified Duke's criteria.
- Surgical biological valve replacement was performed, and a further 6-week course of antibiotic treatment was completed.
- Careful clinical work-up did not reveal any primary focus for the IE.
- He passed away two years after the surgical valve replacement due to sudden cardiac death.
- Before his death, surveillance blood culture showed no evidence of recurrence of infection.

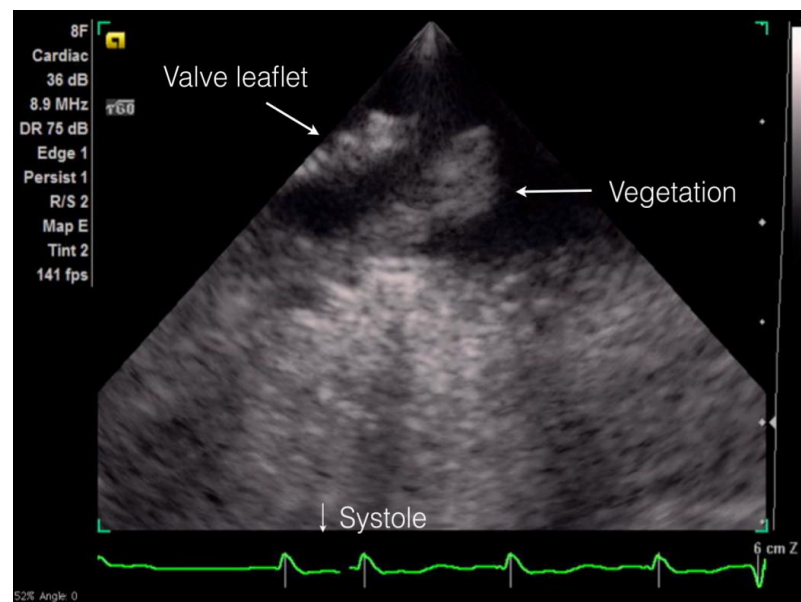


# Case 6

- A 21-year-old man was born with transposition of the great arteries, ventricular septal defect and pulmonary stenosis.
- He had received multiple palliative surgeries in infancy and he had radical surgery at 3 years old (Rastelli operation, VSD closure and RV–PA homograft).
- The homograft was replaced when he was 14 years old, with a 21 mm pulmonary homograft.
- Due to significant stenosis in the new homograft implant, he underwent Melody valve implantation at age 21.
- Fourteen months after PPVR, he presented with febrile illness, and blood cultures showed the growth of *S. aureus*.
- He was classified as possible case of IE according to the modified Duke's criteria.
- There was no clinical improvement after adequate antibiotic treatment for four weeks.

# Case 6

- Due to repeated negative TTE and TEE results, ICE was arranged which showed an 8 × 8 mm large mobile mass inside the Melody valve.
- The diagnosis was then changed to definite case of IE according to the modified Duke's criteria and surgical explantation was decided.
- Intraoperatively, there was pus in a fibrous pocket around the valve, and a new homograft was inserted after removal of the Melody valve.
- Cultures of the pericardium showed the growth of *S. aureus*.
- Careful clinical work-up did not reveal any primary focus for the IE.
- After 6 week postoperative antibiotic treatment, the patient was asymptomatic and he was clinically stable at the most recent follow-up 6 months after surgery.



# Literature review for IE in PV

- Incidence of IE in isolated native PV is very rare, but it has previously been reported to account for **1.5% to 2%** of hospital admissions for IE in children.

Johnson DH, Rosenthal A, Nadas AS. A forty-year review of bacterial endocarditis in infancy and childhood. *Circulation* 1975;51(4):581–8.

Cremieux AC, Witchitz S, Malergue MC, et al. Clinical and echocardiographic observations in pulmonary valve endocarditis. *Am J Cardiol* 1985;56(10):610–3.

- The literature from 1960 to 1999 identified only 36 reported cases of PV IE in structurally normal hearts with alcoholism, sepsis, IV drug abuse, and infection from central venous catheter or pacemaker as predisposing factors.

Ramadan FB, Beanlands DS, Burwash IG. Isolated pulmonic valve endocarditis in healthy hearts: a case report and review of the literature. *Can J Cardiol* 2000;16:1282–8.

- IE in surgically implanted RV–PA conduit has even more rarely been reported.
- In a study of 72 children with congenital heart disease who developed IE between 1992 and 2004, 7 patients (**9.7%**) developed IE in surgically implanted RV–PA conduits over a 12- year FU period.

Rosenthal LB, Feja KN, Levasseur SM, Alba LR, Gersony W, Saiman L. The changing epidemiology of pediatric endocarditis at a children's hospital over seven decades. *Pediatr Cardiol* 2010;31:813–20.

# What's the possible reasons in development of IE in PPVR?

## 1. the nature of the repeat procedure?

- In patients receiving PPVR it will almost always be a repeat procedure of a previously surgically replaced/corrected pulmonary valve.
- Repeat procedures always carry a higher risk of infections as is also seen in pacemaker endocarditis.

Johansen JB, Jørgensen OD, Møller M, Arnsbo P, Mortensen PT, Nielsen JC. Infection after pacemaker implantation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. Eur Heart J 2011 Apr;32(8):991–8.

## 2. the anatomy of the stented valve might carry a higher risk of infection?

- A 28 mm long stent, like in the Melody valve, could likely be more prone to pick up microbes from the circulation than a surgical homograft.

=> Much is unknown at present due to the small number of reported IE cases in both left and right sided transcatheter implanted valves, and probably partly due to underreporting of complicating infections.

# Duke's criteria is enough?

- The majority of the published IE cases involving PPVR were classified as definite by the modified Duke's criteria, and also required surgical explantation like the two definite IE cases we hereby report.
- However, whether the Duke's criteria, which are developed to diagnose IE in native valve, are applicable in heart valve prosthesis can be questioned.
- However, reported cases usually had complicated course of treatment, and also ended up by pathological confirmation from explanted materials.
- Thus, it is reasonable to comment that much more possible IE cases were not published, and just treated them as the definite cases by a course of antibiotic without doing further test to confirm or exclude the diagnosis if there's good clinical response by medical treatment.
- On the other hand, these patients may be suffering from bacteraemia only, but not IE. In this situation, ICE may prevent non-IE patients from a prolonged antibiotic treatment.



# Any beneficial effects of antiplatelet therapy among patients in prevention of IE ?

- In our cohort, the mean duration between the termination of antiplatelet therapy and the date of symptom onset of infection was 12 months.
- The beneficial effects of antiplatelet therapy among patients in prevention of IE remain controversial.
- One animal experiment demonstrated the efficacy of antiplatelet drugs in reducing vegetation size and bacterial titres within vegetations, due to reduction of the adherence of *S. aureus* cells to sterile vegetations, platelets, fibrin matrices and fibrin–platelet matrices.

Kupferwasser LI, Yeaman MR, Shapiro SM, et al. Acetylsalicylic acid reduces vegetation bacterial density, hematogenous bacterial dissemination, and frequency of embolic events in experimental *Staphylococcus aureus* endocarditis through antiplatelet and antibacterial effects. *Circulation* 1999;99:2791–7.

- A randomized study failed to show the benefit of aspirin (325 mg daily), but it was introduced after the diagnosis of IE.

Chan KL, Dumesnil JG, Cujec B, et al. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. *J Am Coll Cardiol* 2003;42:775–80.

# Any beneficial effects of antiplatelet therapy among patients in prevention of IE ?

- On the other hand, a retrospective study demonstrated that use of antiplatelet drugs before the onset of IE was associated with a lower risk of embolism.

Anavekar NS, Tleyjeh IM, Anavekar NS, et al. Impact of prior antiplatelet therapy on risk of embolism in infective endocarditis. *Clin Infect Dis* 2007;44:1180–6.

- Another retrospective study showed that chronic antiplatelet therapy was associated with lower mortality among patients with IE.

Pepin J, Tremblay V, Becharad D, et al. Chronic antiplatelet therapy and mortality among patients with infective endocarditis. *Clin Microbiol Infect* Feb 2009;15(2):193–9.

- Before the long-term antiplatelet therapy should be considered for all patients implanted with Melody valve, potential increases of bleeding episodes due to antiplatelet therapy should not be underestimated, especially majority of these patients are children and young adults.
- More adequately powered multi-centre randomized controlled trial should be conducted for the answer.