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Review

# The risk of infective endocarditis following interventional pulmonary valve implantation: A meta-analysis

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ABSTRACT

*Background:* Interventional percutaneous pulmonary valve implantation (PPVI) was first reported in 2000. Today, two different valves are certified for this procedure [i.e. Medtronic Melody® valve (Medtronic, Dublin, Ireland) and Edwards Sapien™ valve (Edwards Lifesciences, Irvine, CA, USA)]. For a decade, studies have reported an increasing risk of infective endocarditis (IE) after PPVI; as patients for PPVI are usually younger, even a low annual incidence of IE is important. However, the overall incidence and potential differences between the valves remain unclear.

*Methods:* A systematic literature search was performed in the databases Medline, Cochrane Library, and Embase including the clinical trials register. The aim was to summarize and compare the cumulative incidence of IE after PPVI. Using a sensitivity analysis we set the incidence rates of the two valve types in ratio with a normal population.

*Results:* A total of 967 publications were identified searching for "pulmonary valve implantation," "PPVI," and 47 publications were used for final analysis. A total 3616 patients with Melody® valves and 501 with Sapien™ valves were included. IE after PPVI occurred in 214 patients with Melody® valves and in 5 patients only with Sapien™ valves. The pooled incidence for Melody® and Sapien™ valves was 4.9% (95% CI: 3.6–6.2) and 1.3% (95% CI: 0.3–2.3), respectively. Chi-square test was significant. The sensitivity analysis showed that the incidence rate ratio was 252.1 (95% CI: 187.6–338.6) for Melody® valves and for Sapien™ valves 2.7 (95% CI: 0.8–9.2).

*Conclusions:* At present, there is an important difference for the risk of IE after PPVI. To reduce the risk of post PPVI endocarditis, a careful valve selection in favor of the Sapien™ valves seems to be beneficial.



**Contents**



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## Introduction

In 2000, Philipp Bonhoeffer implanted the first pulmonary heart valve (Melody® valve, Medtronic, Dublin, Ireland) in a child via cardiac catheterization in France [1]. According to the manufacturer, more than 12,000 Melody® pulmonary valves have since then been implanted worldwide up to the end of 2017 [2]. It is well known that cardiac catheterization is less invasive than open-heart surgery, which requires a thoracotomy and cardiopulmonary bypass. Therefore, this intervention is an attractive alternative to surgery for patients with a dysfunctional pulmonary valve [3]. Most patients with right ventricular outflow tract pathology require multiple interventions or surgeries during their lifetime due to the limited long-term function of the biological valve systems. Percutaneous pulmonary valve implantation (PPVI) is therefore considered to be one of the greatest achievements in pediatric cardiology and for treatment of congenital heart disease [4].

Currently, two percutaneous pulmonary valve systems are commonly available and approved for interventional PPVI in the USA (Food and Drug Administration) and Europe (CE): the Melody® valve and the Edwards Sapien™ valves (Edwards Lifesciences, Irvine, CA) (Fig. 1). The Melody® valve has been used in Europe since September 2006 with restricted access and was commonly available from 2010 onwards. The Sapien™ valve has been CE certified and has been available since May 2010.

Patients with the indication of PPVI are recruited from the group of congenital heart defects such as tetralogy of Fallot, pulmonary atresia, truncus arteriosus, and after Rastelli-type surgery or after Ross operation for aortic valve replacement. These patient cohorts continue to have an increased risk for infective endocarditis (IE) due to the underlying heart defects, previous operations, and the implanted biological valve material and therefore require a prophylaxis against IE with a given indication [5]. In addition, the pulmonary valves are mostly implanted in a relatively young group of patients, who have a correspondingly high cumulative risk of IE due to their expected lifespan.

The aim of the study was to determine the incidence of IE after PPVI, to analyze data from a meta-analysis, and, if possible, to detect differences between the two approved types of valves.

## Materials and methods

### *Material*

The Melody® and Sapien™ valves are implanted today predominantly by using a generally accepted and uniform technique. The Melody® valve is technically designed to achieve a final inside diameter of 18, 20, and 22 mm. The Sapien™ valves have outer diameters of 20, 23, 26, and 29 mm (Fig. 1) [6].

### *Search strategy and study selection*

We searched for the search term combination “pulmonary valve implantation” or “PPVI” in the Embase, MEDLINE, and Cochrane libraries and using the clinical trials register. In addition, we performed a manual search in the bibliography. The period was between 01/2000 and 12/2018. The study selection was carried out by three scientists, who decided on the inclusion of the study according to the defined study population.

### *Definition of the study population*

This review included intervention and cohort studies when reporting target IE and PPVI using the Melody® valve and/or Sapien™ valve. Excluded were narrative reviews and case reports ($n < 5$ cases) that did not allow an estimate of the incidence or reported the use of the valves in mitral, tricuspid, and aortic positions.

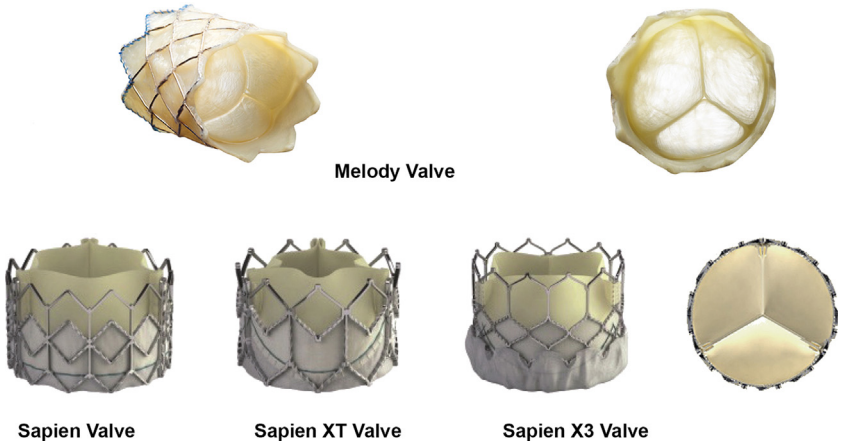


**Fig. 1.** Illustration of different Melody® and Sapien™ valves [67,68].

*Data extraction*

From each study, first author, publication year, country, median age, time period, follow-up time, perspective, and case number were extracted into a table. The methodology is based on the established recommendations for systematic reviews and meta-analysis: PRISMA (Preferred Reporting and Meta-Analysis) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) [7,8].

*Statistical analysis*

The effect sizes were measured with cumulative incidences and relative risks. We calculated pooled risk proportions and the 95% confidence intervals (CI). The cumulative incidence was determined as the ratio between new IE and the number of patients after interventional pulmonary valve implantation. In the case of zero events, a correction of 0.5 was added to observed events. The extent of heterogeneity was examined using $I^2$ statistics. A random effects model was chosen because study populations differ in terms of number of participants and follow-up periods [9].

For the sensitivity analysis we multiplied the number of months of follow-up by the sample size for the Melody® and Sapien™ valves to obtain the total number of person-months of follow-up. The study-specific rate of events per person-month for each valve was then the total number of events divided by the total number of person-months of observation for each arm [10]. At 0 events a distribution was assumed as in the normal population. To get relative risks this annual incidence rate was then multiplied by 100,000 and compared to the IE incidences in the general population reported from the Danish registry [11].

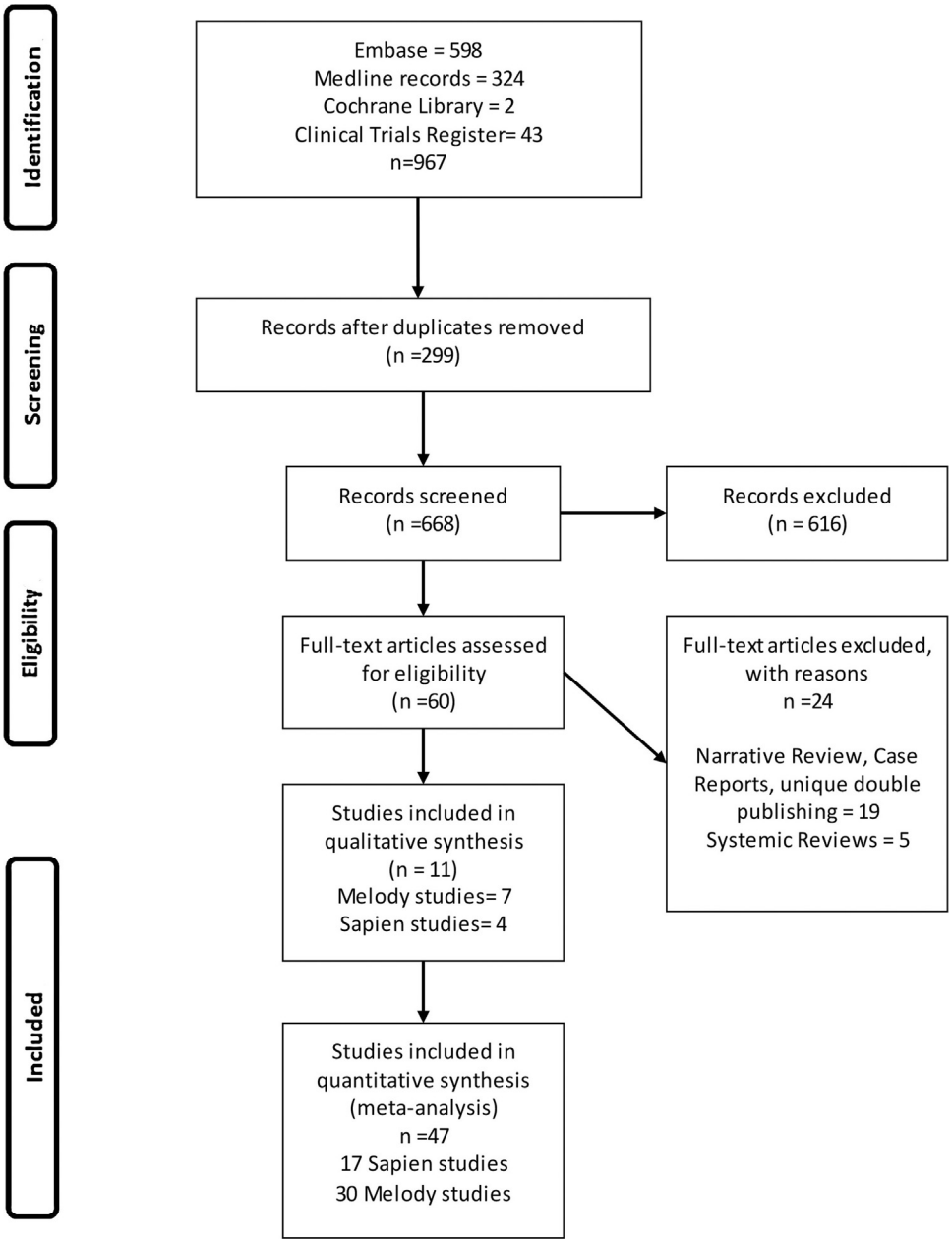


**Fig. 2.** Process of the systematic literature search.

**Table 1**
Included cohort studies.

| First author (year) [reference] | Country | Age | Period | Time (month) | Perspective | *n* | PY | IR/100,000 PY | Events | Time to IE | Severity stage | Microorganism |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Melody valve exposure | | | | | | | | | | | | |
| Armstrong 2014 [13] | USA | 20 | 2007–2010 | 12 | Pro | 100 | 100 | 3000 | 3 | 3 | ABX = 2, OP = 1 | *S. aureus* = 2, GN = 1 |
| Bensemlali 2017 [14] | France | 16 | 2000–2015 | 46 | Pro | 11 | 42 | 7115 | 3 | | ABX = 1, OP = 2 | – |
| Biernacka 2015 [15] | Poland | 25 | 2008–2012 | 20 | Pro | 26 | 43 | 9231 | 4 | – | OP = 4, D = 1 | – |
| Borik 2015 [16] | Canada | 20 | 2005–2011 | 54 | Pro | 51 | 230 | 436 | 1 | 60 | OP = 1 | GP = 1 |
| Buber 2013 [17] | USA | 19 | 2007–2012 | 19 | Retro | 147 | 233 | 1719 | 4 | 13 | ABX = 3, OP = 1, D = 2 | Staph = 1, Strep = 2, HACEK = 1 |
| Butera 2013 [18] | Italy | 24 | 2007–2010 | 30 | Pro | 61 | 153 | 1311 | 2 | 2,5 | OP = 2 | *S. aureus* = 2 |
| Cheatham 2015 [19] | USA | 19 | 2007–2014 | 54 | Pro | 150 | 675 | 2074 | 14 | | ABX = 6, CC = 8, D = 1 | – |
| Cheung 2013 [20] | Denmark | 25 | 2006–2012 | 27 | Retro | 42 | 95 | 6349 | 6 | 18 | ABX = 4, OP = 2, D = 1 | Staph = 1, *S. aureus* = 2, Strep = 3 |
| Cools 2015 [21] | Belgium | 19 | 2006–2014 | 12 | Retro | 112 | 112 | 7143 | 8 | 16 | ABX = 6, CC = 2, OP = 2 | *S. aureus* = 1, Strep = 3, GP = 1, HACEK = 3 |
| Eicken 2011 [22] | Germany | 21 | 2006–2010 | 12 | Pro | 102 | 102 | 980 | 1 | 6 | OP = 1 | *S. aureus* = 1 |
| Fiszer 2017 [23] | Poland | 18 | 2009–2016 | 35 | Pro | 44 | 128 | 8 | 0 | | – | – |
| Fraisse 2014 [24] | France | 21 | 2008–2010 | 54 | Pro | 64 | 288 | 1389 | 4 | 26 | OP = 3, D = 2 | Staph = 2, Strep = 1; – |
| Gewillig 2016 [25] | Belgium | 21 | 2006–2015 | 108 | Retro | 206 | 1854 | 755 | 14 | – | OP = 4 | |
| Gillespie 2012 [26] | USA | 26 | 2007–2012 | 12 | Retro | 104 | 104 | 1923 | 2 | 16 | OP = 2 | – |
| Haas 2018 [27] | Germany | 13 | 2010–2015 | 50 | Retro | 29 | 121 | 4966 | 6 | 29 | ABX = 3, CC = 3 | Staph = 2, *S. aureus* = 4 |
| Hascoet 2017 [28] | France | 25 | 2008–2016 | 60 | Retro | 32 | 160 | 5000 | 8 | 22 | ABX = 1, CC = 2, OP = 4, D = 1 | Staph = 1, *S. aureus* = 3, Strep = 1, GP = 2, HACEK = 1 |
| Hascoet 2018 [29] | France | 12 | 2008–2016 | 20 | Retro | 14 | 23 | 8 | 0 | | – | – |
| Hill 2017 [30] | USA | – | 2010–2015 | 54 | Retro | 244 | 1098 | 1548 | 17 | 12 | – | – |
| Khambadkone 2005 [31] | UK | 16 | 2000–2004 | 10 | Retro | 59 | 49 | 2034 | 1 | – | OP = 1 | – |
| Kuo 2017 [32] | USA | 15 | 2012–2015 | 24 | Retro | 19 | 38 | 8 | 0 | | – | – |
| Lurz 2008 [33] | UK | 21 | 2000–2007 | 28 | Retro | 155 | 362 | 1382 | 5 | 5 | ABX = 2, OP = 3 | *S. aureus* = 1, Strep = 1, GP = 3, |
| Malekzadeh-Milani [34] | France | 40 | 2008–2016 | 43 | Pro | 365 | 1217 | 3534 | 43 | 31 | ABX = 27, CC = 7, OP = 6, D = 3 | Staph = 7, *S. aureus* = 12, Strep = 16, GP = 5, GN = 4 |
| Markham 2017 [35] | Australia | 34 | 2009–2016 | 29 | Retro | 17 | 41 | 8 | | | – | |
| McElhinney 2013 [36] | USA | 19 | 2007–2009 | 24 | Pro | 311 | 622 | 2572 | 16 | 16 | ABX = 8, CC = 2, OP = 4, D = 2 | *S. aureus* = 5, Staph = 5, Strep = 6, GN = 1 |
| Nordmeyer 2014 [37] | Germany | 21 | 2006–2013 | 12 | Retro | 694 | 694 | 2305 | 19 | – | – | – |
| O'Donell 2017 [38] | New Zealand | 18 | 2009–2015 | 36 | Retro | 25 | 75 | 5333 | 4 | 43 | ABX = 1, OP = 3 | *S. aureus* = 1, Staph = 2, Strep = 1 |
| Oechslin 2018 [39] | CH | 28 | 2008–2016 | 43 | Pro | 29 | 104 | 8 | – | – | – | – |
| Solana Gracia [40] | Spain | 13 | 2007–2016 | 4 | Retro | 81 | 196 | 2043 | 4 | 15 | ABX = 1, OP = 3 | Strep = 3, HACEK = 1 |
| Tanase 2018 [41] | Germany | 21 | 2006–2017 | 47 | Retro | 215 | 824 | 2063 | 17 | 33 | ABX = 8, OP = 8, D = 1 | *S. aureus* = 5, Staph = 4, Strep = 4, GP = 2, HACEK = 1, GN = 1 |
| Van Dijck 2015 [42] | Belgium | 14 | 1989–2013 | 78 | Retro | 107 | 696 | 1150 | 8 | 16 | ABX = 2, OP = 6 | *S. aureus* = 1, Strep = 3, GP = 1, HACEK = 3 |
| Sapien valve exposure | | | | | | | | | | | | |
| Biernacka 2015 [15] | Poland | 25 | 2008–2012 | 20 | Pro | 14 | 23 | 8 | – | | | – |
| Boone 2010 [43] | USA | 19 | 2006–2009 | 22 | Retro | 7 | 13 | 8 | – | | | |
| Demkov 2014 [44] | Poland | 28 | 2011–2012 | 2 | Pro | 10 | 2 | 8 | – | | | |
| Gagliardi 2016 [45] | Italy | 18 | 2011–2013 | 18 | Pro | 8 | 12 | 8 | – | | | |
| Haas 2013 [6] | Germany | 22 | 2007–2010 | 6 | Pro | 22 | 11 | 8 | – | | | |
| Haas 2018 I [46] | Germany | 29 | 2014–2016 | 24 | Retro | 46 | 92 | 8 | – | | | |
| Haas 2018 II [27] | Germany | 16 | 2000–2015 | 60 | Pro | 44 | 121 | 8 | – | | | |
| Hascoet 2017 I [28] | France | – | 2011–2016 | 12 | Retro | 47 | 47 | 8 | – | | | |
| 2018 II [47] | France | 28 | 2016–2018 | 17 | Pro | 82 | 18 | 8 | – | | | |
| Kenny 2018 [48] | USA | 27 | 2008–2014 | 36 | Pro | 79 | 237 | 1266 | 3 | 2 | ABX = 3 | Staph = 2, HACEK = 1 |
| Odemis 2013 [49] | Turkey | 14 | 2007–2010 | 30 | Pro | 14 | 35 | 8 | – | | | |
| Oechslin 2018 [39] | CH | 28 | 2008–2016 | 43 | Pro | 4 | 14 | 8 | – | | | |
| Pilati 2011 [50] | Italy | 19 | 2010–2011 | 3 | Pro | 7 | 2 | 8 | – | | | |
| Plessis 2018 [51] | France | 27 | 2011–2017 | 12 | Pro | 71 | 71 | 1408 | 1 | – | OP = 1 | – |
| Tanase 2018 [41] | Germany | 22 | 2006–2017 | 36 | Retro | 11 | 40 | 8 | – | | | |
| Vollroth 2015 [52] | Germany | – | 2011–2017 | – | Retro | 13 | 26 | 3846 | 1 | – | OP = 1 | *S. aureus* = 1 |
| Wilson 2015 [53] | USA | 34 | 2007–2014 | 30 | Retro | 25 | 62 | 8 | – | | | |

ABX, only antibiotic treatment; CC, cardiac catheterization; CH, Switzerland; D, death; GN, other Gram-negative bacteria; GP, other Gram-positive bacteria; HACEK, *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; IE, infective endocarditis; OP, explantation by surgery; pro, prospective; retro, retrospective; *S. aureus, Staphylococcus aureus*; Staph, other staphylococcus bacteria; Strep, streptococcus.

Incidence rate ratio (IRR) is the proportion of the IE cases divided by person time and the IE cases in a normal population by person time. The graph of the rate ratios was plotted on a log scale [12]. The analysis was done using Open Meta-Analyst 1.0 software and Microsoft Excel.

## Results

### *Enrollment*

Based on the literature search, 967 (924 databases and 43 clinical trials register) potential relevant references could be identified. After the first sighting 915 (299 duplicates and 616 records) could be excluded. This was followed by the evaluation of the 60 full texts. After hand searches 11 studies were additionally included. A total of 24 reviews were excluded. Of the included studies, 30 studies reported Melody® valves and 17 studies on Sapien™ valves. A total of 47 studies were finally considered relevant for this analysis (Table 1) [13–53] (Fig. 2).

### *Meta-analysis of cohort studies*

In total, 3616 patients were treated with Melody® valves and 501 with Sapien™ valves (Fig. 3). While patients with Melody® valves reported 214 IE cases, those with Sapien™ valves had only 5 cases. The pooled incidence of Melody®-PPVI was 4.9% (95% CI: 3.6–6.2) and 1.3% for Sapien™ valves (95% CI: 0.3–2.3) (Fig. 3). Chi-square test was significant. There was however a notable variation in the reports of IE in the Melody® studies. The largest Incidence of IE was 27%; only 5 studies [15,27,28,39,41] did not observe IE cases.

There are five retrospective studies comparing the Sapien™ and Melody® valves within a well-defined cohort and where complete follow-up samples were compared. Hascoët et al. [28] evaluated 32 Melody® and 47 Sapien™ patients. IE occurred in eight patients who received a Melody® valve. Haas et al. [27] compared 29 Melody® valves with 51 Edwards® valves and could show a significant difference for the risk of IE (6/29 vs. 0/51). Biernacka et al. [15] also described 4 IE cases in 26 implemented Melody® valves. No cases were reported for the 14 Sapien™ valves. Oechslin et al. [39] reported no IE at all. Tanase et al. [41] observed no IE event for Sapien valves but 17 of 215 events for Melody valves.

The sensitivity analysis (figure) showed that the incidence rate ratio was 252.1 (95% CI: 187.6–338.6) for Melody® valves and for Sapien™ valves 2.7 (95% CI: 0.8–9.2).

Regarding the interval period between valve implantation and onset of IE the two valves differed significantly. While the mean interval for the Melody® valves was 20 ± 16 months, the IE in the Sapien® valves occurred after only 2 months. In general, IE after Sapien® implantation appeared within one year. Kenny et al. [48] reported that three events occurred in two patients post-procedure. The time interval to the first IE event following implantation was 25, 51, and 71 days. Plessis [51] and Vollroth [52] gave no information about the time to IE; this may be explained by

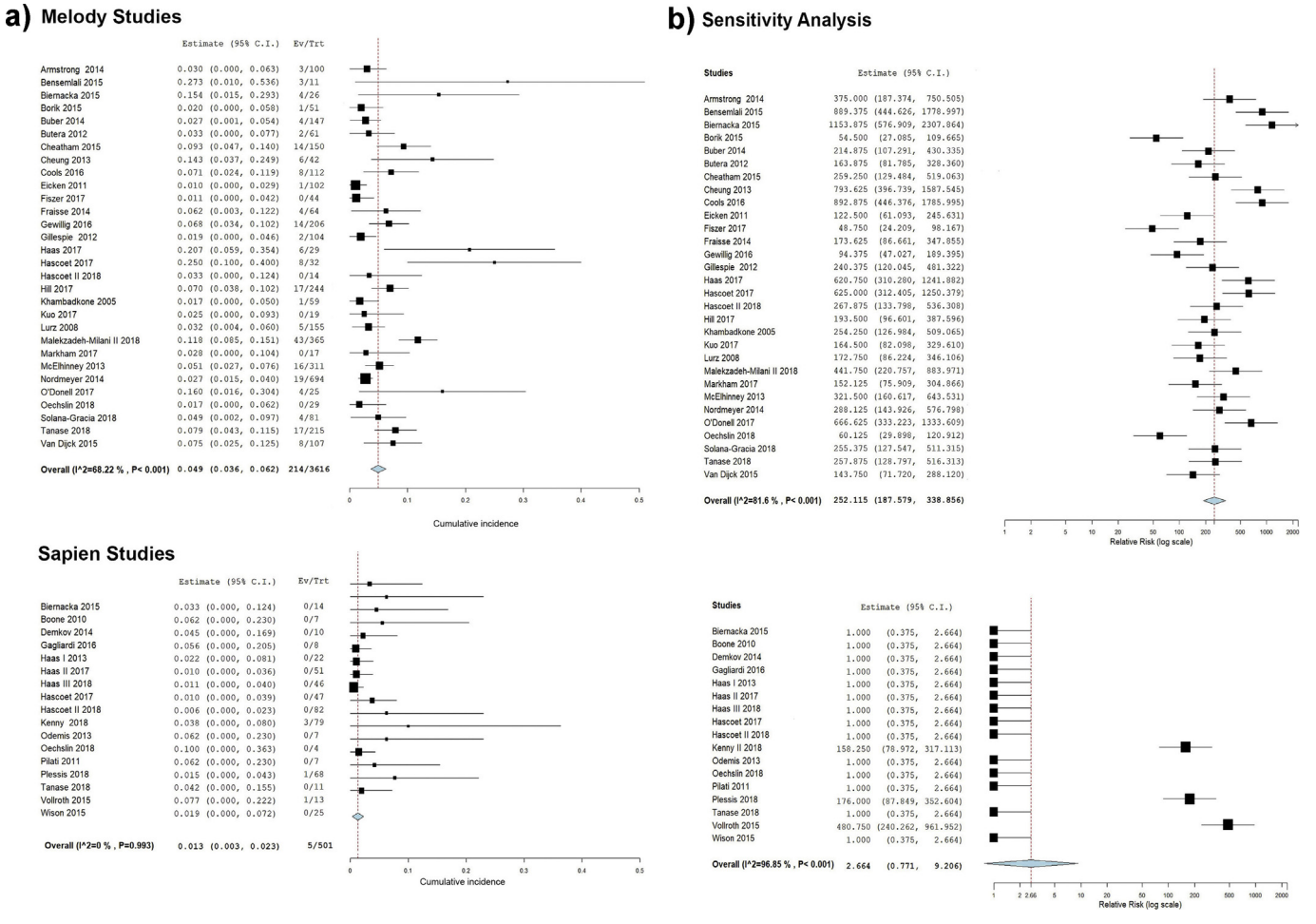


**Fig. 3.** (a) Forest plots of endocarditis incidence after Melody and Sapien™ pulmonary valve implantation. With a correction of 0.5 in studies with zero events. (b) Forest plots of the comparison of incidence rates after Melody and Sapien™ pulmonary valve implantation with a general population reported from the Danish registry [11].

**Table 2**
Patient characteristics.

| | Melody ($n=3616$) | Sapien ($n=501$) |
|---|---|---|
| Mean age | 21 ± 6 | 23 ± 5 |
| Mean Follow up | 35 ± 22 months | 23 ± 16 months |
| IE events (cumulative incidence) | 214 (4.9%) | 5 (1.3%) |
| | $n=155$ | $n=2$ |
| Time to IE | 20 ± 16 months | 2 ± 0 months |
| Severity stage of IE patients | $n=176$ | $n=5$ |
| Only antibiotic treatment | 43% | 60% |
| Cardiac catheterization | 15% | – |
| Explantation by surgery | 34% | 40% |
| Death | 8% | – |
| Types of bacteria | $n=141$ | $n=4$ |
| *Staphylococcus aureus* | 28% | 25% |
| Other Staphylococcus | 18% | 50% |
| Streptococcus | 31% | – |
| HACEK | 7% | 25% |
| Other Gram-positive bacteria | 11% | – |
| Other Gram-negative bacteria | 5% | – |

IE, infective endocarditis.

the fact that the infection after Sapien® implantation could be caused during the implantation process whilst the IE in Melody® valves could be caused by bloodstream infections and a specific susceptibility of this valve type later on.

In 43% of IE cases after Melody® procedure, antibiotics were sufficient. In one-third (34%) an explantation was required by surgery, in 15% by an interventional heart catheter. Eight percent of the IE patients died. Regarding the Sapien® valves in only three events information is provided. These IE patients were managed by antibiotic therapy only after Sapien® procedure, suggesting a mild degree of severity [48].

The analysis of causative microorganisms demonstrates that the infection with *Staphylococcus aureus* pathogen is widespread. A total of 141 events reported causative microorganisms. Almost half (46.1%) of IE after Melody® implantation was triggered by staphylococci. Of these, 40 pathogens (28.4%) were *S. aureus*. One third (44/31.2%) of these events were due to streptococci.

Regarding the pathogen after Sapien® implantation, it should be noted that four bacteria were identified. Vollroth [52] reported a case of *S. aureus*. Kenny [48] identified two staphylococci, and one HACEK bacteria. Plessis does not provide any information regarding the causative microorganism (Table 2).

## Discussion

To the best of our knowledge, this review is the most comprehensive meta-analysis on this important topic published so far. Based on the data analysis reviewed here, there was a clear evidence to suggest that IE after PPVI was less common with Sapien™ valves than after implantation of a Melody® valve.

The estimated incidence of 4.9% after Melody®-PPVI is consistent with the increasing number of other published reviews. The observation time for Sapien™ valves is more than seven years and 501 reported treatments have been identified. In general there was only sparse information about IE in patients with Sapien™ valves, the general incidence was very low and only five cases are published so far [48,51,52]. In order to determine the highest possible incidence of IE for Sapien™ valves, all available study registries were also searched and may therefore even overestimate the incidence as compared to the Melody® valves. This low incidence may further support the results of this meta-analysis to carefully select the type of valve and to avoid IE cases.

Unfortunately, little updated population-based evidence exists for the incidence of IE in the general population, and the existing data report conflicting results with incidence rates ranging between 1.4 and 16 per 100,000 person years [11]. The Italian population-based study by Fedeli et al. including 1873 subjects hospitalized for IE reported an increased incidence rate of IE of 4.9 per 100,000 person-years in 2011 [54].

The dates of Erichsen et al. [11] are most recent and are derived from a European registry. As most of the reports cited here are from Europe or a comparable medical setting, we have used these data in our sensitivity analysis.

These results are particularly relevant, as the cumulative risk of IE is especially important with increasing age of younger patients in addition to the individual exposure.

### *Possible explantations*

To date, the causes of this accumulation of IE or a possible increased susceptibility of one valve in contrast to the other is unclear. As the general implantation technique does not differ for both valves, this influence can be omitted.

In both valves, the biological substitutes are fixed into a stent and the biological valve portion of both pulmonary valves is derived from bovine material. While the Melody® valve is harvested from a calf's vein and then preserved almost untreated (see Contegra® Graft), the leaflets of the Sapien™ valves are manufactured from bovine pericardium and treated with a special descaling and denaturing technique [53]. This treatment method could cause a general reduction in the susceptibility of bacteria to colonize this valve.

Some studies have already shown that the bovine Contegra® graft has an increased IE risk compared to other surgical implants [55,56]. Van Dijck et al. [42] found in a large national cohort study an increased risk of IE for the same biological substrate (Contegra® Conduit and Melody® valve) when related to homografts. Haas et al. [27] could demonstrate a significantly increased IE risk for Contegra® conduits and Melody® valves when compared to other biological pulmonary valve substrates (i.e. homografts, Sapien™ valves, and Hancock valves). Jalal et al. [57] compared in vitro the bacterial adherence of different bacterial species to the biological substrates of the Melody® valve versus the Sapien™ valve; in this study a significant difference was found in favor of the Sapien™ valve material. Thus, the biological substrate of the Melody® valve appears to be more susceptible to IE than other materials [58].

Another possible reason for IE might be varying blood flow patterns, as observed by Malekzadeh-Milani et al. [34]. The authors were able to relate IE in Melody® valves to a discontinuation of aspirin and consecutive thrombosis formation. It may be speculated that with the larger diameters of the Sapien™ valves there may be less turbulence and therefore a lower risk of thrombosis; maximal flow velocities measured by ultrasound and published so far do however not differ; therefore it seems unlikely that the size difference plays a role in the occurrence of IE.

The Melody® valve design has remained unchanged since its introduction (Fig. 1). The Sapien™ valves have changed their external design based on the requirements of the aortic valve market. The biological material however remained the same. Initially, the Sapien™ valve was introduced into the market, followed by the Sapien XT™ with modified stent material, and finally the Sapien X3™ valve with additionally modified stent design and outer design. Sapien™ and Sapien XT™ are approved

for pulmonary use; today the Sapien 3™ is increasingly used on an off-label basis for PPVI; CE registration was expected in 2018.

*Evaluation of the quality of the included studies*

In general, the validity of observational studies may be judged limited. There are particular shortcomings due to the retrospective and one-arm study designs. Randomized-controlled studies are considered the gold standard and would therefore be important for the future. In this analysis, only seven multi-arm studies were identified in the literature search [15,27,28,34,39,41,42].

In the included studies a recall bias is possible in which cases may have been overlooked or forgotten, especially as some studies are based on a retrospective study design. This seems however unlikely as PPVI is a relatively new treatment strategy that usually attracts special attention and documentation.

While no cases of IE were reported in 14 out of 17 included Sapien™ studies, only 5 out of 30 Melody® trials did not detect IE. There are limitations in these studies due to the small samples of 14, 17, 19, 29, and 44 participants [23,29,32,34,39]. This limitation also applies to some of the Sapien™ studies. The three included studies by Haas et al. [6,27,46] are not considered to be duplicate publications as different Sapien™ valve types and patient cohorts were described.

Although the review finds clear evidence that an increased number of IE cases is associated with Melody® valves, the statement is nevertheless based on heterogeneous observational studies with sometimes only small samples. So, although the difference between Sapien™ and Melody® valves in terms of IE is statistically significant and reflects clinically important results, the meta-analysis results are not yet comprehensive enough to evaluate all safety-related areas. To obtain a differentiated picture of the effectiveness and side effects of the two valves, multi-arm studies would be necessary.

*Further reviews*

Other reviews also show an increasing number of IE cases for the Melody® valves [59,60]. In 2015, Amat-Santos et al. [61] estimated the pooled annual incidence of IE at 2.2%, and it was calculated by Uebing and Rigby [62] at 2.5%. In 2015, Cardoso et al. [63] estimated the pooled incidence at 2.9%. One year later, Chatterjee et al. [64] published an incidence of 3.1% and Sharma et al. [65] 7.5%.

The research groups also compared percutaneous to surgically implanted pulmonary valves. Cardoso et al. [63] identified stent fractures as one of the most common complications of Melody®-PPVI. The authors estimated this risk at 12.9%. Surgical repair, however, became necessary in just 1.5%. Re-interventions were necessary in 10% in percutaneous procedures and surgical explantations in 4.6% of implantations. For the authors the benefits of percutaneous procedures outweigh these potential risks. Amat-Santos et al. [61] concluded with regard to IE that although the aseptic conditions are less strict than in surgical procedures, the incidence in PPVI is similar to that seen in surgical procedures. According to Chatterjee et al. [64] implantations of percutaneous pulmonary valves are judged to be safe. The incidence of potential complications was estimated at 8.8%.

Due to the high number of IE cases, however, much more is reported about Melody® valves than for Sapien® valves. Abdelghani et al. [66] calculated similar results about the time to IE or the causative microorganism after Melody valve implantation. Their distribution of the main bacteria was staphylococci (42%) and streptococci (30%). Abdelghani et al. [66] also confirmed that there is a significant difference for the risk of IE after PPVI especially using Melody® valves; hence, their statement that the use of Sapien™ valves seems to be beneficial.

*Evaluation of other safety-relevant target variables*

The quality of the previously published reviews is however limited because the literature was partly selectively researched. Nevertheless, the reviews report pooled incidences and are therefore presented here.

Another limitation of the previous reviews is that there is not always a distinction between Melody® and Sapien™ pulmonary valves. Accordingly, a detailed subgroup analysis is lacking. Statements about the differences between other safety-relevant outcomes such as re-intervention, stent breakage, and mortality are therefore not conclusive.

*Evidence-based recommendation for PPVI*

There is no consensus in the guidelines on the type of valve that should be used for PPVI [3,60]. Based on experience and general agreement, only biological valves are used as primary choice in pulmonary position. If the implantation of these valve systems is technically possible, percutaneous pulmonary valves are today an alternative to surgical pulmonary valve implantation, and they are increasingly being used. However, the current guideline of the German Society for Pediatric Cardiology (DGPK) points out that the risk of IE after implantation of these valve systems may be higher than after surgical pulmonary artery implantation with e.g. a homograft [3]. Thus, besides concerns about the overall longevity of catheter-based valves, there is also criticism due to the potentially increased IE risk. Nevertheless, surgical reoperations or multiple reoperations are generally associated with an increased morbidity and mortality risk.

Compared to surgical procedures, minimally invasive cardiac catheterization offers many advantages. This includes a shorter recovery time, or the reduction of the number of cardiopulmonary bypass procedures. The studies on IE after PPVI published in recent years now clearly show a positive trend toward Sapien™ valves when compared to Melody® valves [27,28].

## Conclusions

PPVI is the treatment of choice wherever feasible in patients with a relevant pathology of the right ventricular outflow tract. Since all biological valves have a limited lifespan, re-operations or subsequent interventions are foreseeable. Due to the relatively young age of the majority of patients, the cumulative risk of IE is of particular importance. Based on the data presented here, one of the two catheter valves currently available on the market appears to be superior to the other with regard to the risk of IE. The reason for this is unclear, but it seems likely that the different biological material as well as the mode of preparation may influence this outcome.

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## Conflicts of interest

There is no conflict of interest by any of the authors regarding this report. NA Haas has worked as proctor for Edwards as well as Medtronic for training of PPVI.

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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