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Clinical outcomes for transcatheter valve-in-valve in treating surgical bioprosthetic dysfunction: A meta-analysis

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Over the last 10 years, the use of bioprosthetic valves increased to 78.4% of total valves used, whereas the mechanical valve use declined to 20.5% [1]. However, bioprosthetic valves have limited durability. An increasing number of patients are presenting with symptoms secondary to prosthetic degeneration. Traditionally, redo surgical valve replacement has been performed to treat bioprosthetic valve degeneration. More recently, transcatheter valve-in-valve implantation has emerged as a feasible, minimally invasive alternative approach for failing bioprosthetic valves [2]. The present meta-analysis aimed to assess the successful rate the clinical outcomes of transcatheter valve-in-valve in treating surgical bioprosthetic dysfunction.

We searched MEDLINE for articles published up to December 4, 2015, using the following free text terms: "valve-in-valve", "prosthesis", "bioprosthetic", "dysfunction", and "failure". We included studies which reported the early and late clinical outcomes for transcatheter valve-in-valve in treating surgical prosthetic dysfunction. Publications were excluded if they comprised review, editorials, or letters. Data were recorded on a standard data-extraction form. We extracted the following: first author, publication year, location of study, enroll year, sample size, patients' age and gender distribution, dysfunction valve position (aortic or mitral), LVEF, implanted valve type (SAPIEN, CoreValve, or others), access site (transapical, transfemoral or others), successful rate, follow-up rate, early outcomes (30-day mortality, major stroke rate, renal failure rate, major bleeding rate, permanent pacemaker implantation rate), and late outcome (1-year mortality). Titles and abstracts identified by electronic searches were examined independently by 2 researchers on-screen. The full text articles were obtained and reviewed if the extracted information were not included in titles and abstracts. Any disagreement was resolved by discussion between the authors. We calculated the pooled successful rate, pooled 30-day mortality, major stroke rate, renal failure rate, major bleeding rate, permanent pacemaker implantation rate, and pooled 1-year mortality by meta-analysis. Heterogeneity of effects across studies was assessed by I^2 and z test. If the z test was not significant or an I^2 value more than 50%, the fixed effects methods were used, otherwise the random effects were used. We checked for the publication bias by the Begg's funnel plots and the Egger's test. We also performed subgroup analyses by dysfunction valve position (aortic or mitral). All analyses were conducted using StatsDirect Version 3.0.161. (StatsDirect Ltd., from England).

Our initial database search retrieved 256 citations, of which 231 were excluded because they did not meet our inclusion criteria. Finally, a total of 25 studies with 976 patients met our inclusion criteria and were included in the final analysis. The studies were conducted worldwide. Five studies were multi-center studies, 7 studies came from Germany, 4 studies came from Canada, 2 studies came from Italy, 2 came from United Kingdom, 2 came from France, the other 3 came from USA, Australia, and Brazil. Most of the studies were conducted after 2007. The sample size ranged from 3 to 459. Fifteen studies investigated the aortic valve dysfunction, 8 studies investigated the mitral valve dysfunction, and the other 2 studies investigated aortic and mitral valve dysfunction. General characteristics of the included articles are listed in Table 1.

Twenty-five studies [3–28] reported successful rate of transcatheter valve-in-valve in treating surgical prosthetic dysfunction. The successful rate ranged from 80% to 100%. There was no significant heterogeneity between studies ($I^2 = 18.2\%$, $P = 0.2004$). The pooled successful rate was 95.7% (95% CI 94.4%–96.9%) by fixed effects model (Supplementary Fig. 1A). The Egger test showed no evidence of publication bias ($t = 0.420$, $P = 0.1989$). Subgroup analyses showed the pooled successful rate was 95.4% (95% CI 93.9%–96.7%) for aortic valve-in-valve by random effects model (Supplementary Fig. 1B), and 97.8% (95% CI 94.4%–99.6%) for mitral valve-in-valve by fixed effects model (Supplementary Fig. 1C).

For early clinical outcomes, 25 studies reported the 30-day mortality. The 30-day mortality ranged from 0% to 33.3%. The pooled 30-day mortality was 6.5% (95% CI 4.3%–9.2%) by random effects model (Supplementary Fig. 2A). The Egger test showed no evidence of publication

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Table 1
Summary of studies investigating clinical outcomes for transcatheter valve-in-valve in treating surgical prosthetic dysfunction.

First author, year	Country	Enroll year	Patients number	Age (year)	Gender (M/F)	Dysfunction valve position	LVEF (%)	Implanted valve type
Erlebach M, 2015 [13]	Canada	2001–2014	50	78.1 ± 6.7	27/23	Aortic	49.8 ± 13.1	SAPIEN/CoreValve/JenaValve
Camboni D, 2015 [6]	Germany	Since 2009	31	77.8 ± 6.3	NR	Aortic	55.6 ± 8	SAPIEN/CoreValve/others
Kliger C, 2015 [17]	France	2012	5	72.6	NR	Mitral	54	Melody
Ye J, 2015 [28]	Canada	2007–2013	42	80.5 ± 9.8	28/24	Aortic	57.5 (47–65)	SAPIEN
Ye J, 2015 [28]	Canada	2007–2013	31	78.7 ± 8.8	13/18	Mitral	60 (40–65)	SAPIEN
Mukherjee C, 2015 [20]	Germany	2009–2013	13	75	NR	Mitral	NR	SAPIEN
Duncan A, 2015 [10]	United Kingdom	2009–2014	22	74 ± 14	14/8	Aortic	NR	CoreValve
Subban V, 2014 [25]	Australia	2009–2014	12	78.5 ± 7.0	9/3	Aortic	NR	SAPIEN/CoreValve
Wilbring M, 2014 [27]	Germany	Since 2008	10	75.0 ± 5.0	6/4	Mitral	44.5 ± 17.4	SAPIEN
Schafer U, 2014 [22]	France	NR	8	69.1	NR	Mitral	NR	SAPIEN
Dvir D, 2014 [11]	55 centers	2007–2013	459	77.6 ± 9.8	257/202	Aortic	50.3 ± 13.1	58.9% SAPIEN and CoreValve
Ihlberg L, 2013 [15]	11 centers in Nordic countries	2008–2012	45	80.6 (61–91)	26/19	Aortic	46.3 ± 12.8	SAPIEN and CoreValve
Cullen MW, 2013 [9]	USA	2011–2012	9	74.8 ± 10.9	4/5	Mitral	50.0 ± 18.0	Melody
Cheung A, 2013 [8]	Canada	2007–2012	23	81 ± 6	9/14	Mitral	54.5 ± 12.3	SAPIEN
Linke A, 2012 [19]	Germany	NR	27	74.8 ± 8	19/8	Aortic	NR	CoreValve
Bapat V, 2012 [3]	United Kingdom	2009–2011	23	76.9 ± 14.4	13/10	Aortic	48.0 ± 12.4	SAPIEN
Seiffert M, 2012 [23]	Germany	2008–2011	11	79.1 ± 6.3	9/2	Aortic	Mean 47.0–52.5	SAPIEN
Latib A, 2012 [18]	Italy	NR	18	75.0 ± 12.6	12/5	Aortic	52.9 ± 10.8	SAPIEN
Seiffert M, 2012 [24]	Germany	2009–2011	6	74.7 ± 14.6	0/6	Mitral	55.8 ± 3.8	SAPIEN
Gaia DF, 2012 [14]	Brazil	2008–2011	14	69.8	7/7	Aortic	51.0 ± 15.9	Braile Inovare
Cerillo AG, 2011 [7]	Italy	Since 2009	3	68.5 ± 17.1	NR	Mitral	NR	SAPIEN
Pasic M, 2011 [21]	Germany	Since 2008	14	73.3 ± 13.1	9/5	Aortic	45 ± 13	SAPIEN
Eggebrecht H, 2011 [12]	Germany and Switzerland	2005–2010	47	79.8 ± 7.1	28/19	Aortic	52 ± 12	SAPIEN and CoreValve
Bedogni F, 2011 [4]	8 Italian centers	NR	25	82.4 ± 3.2	10/15	Aortic	56.5 ± 12.5	CoreValve
Webb JG, 2010 [26]	Canada and Kingdom	NR	10	79.6 ± 4.1	NR	Aortic	55.0 ± 12.0	SAPIEN
Webb JG, 2010 [26]	Canada and Kingdom	NR	7	82.1 ± 5.9	NR	Mitral	62.9 ± 6.4	SAPIEN
Kempfert J, 2010 [16]	Germany	2007–2009	11	78 ± 6	7/4	Aortic	52.8 ± 7.7	SAPIEN

LVEF = left ventricular ejection fraction; NR = not reported; TA = transapical; TAO = transaortic; TAx = transaxillary; TF = transfemoral; TS = transseptal.

bias (t = 0.073, P = 0.8381). In aortic valve-in-valve subgroup, the 30-day mortality was 6.9% (95% CI 4.3%–10.0%) (Supplementary Fig. 2B); in mitral valve-in-valve subgroup, the 30-day mortality was 4.7% (95% CI 1.7%–9.2%) (Supplementary Fig. 2C). 19 studies reported the major stroke incidence. The major stroke incidence ranged from 0% to 14.3%. The pooled major stroke incidence was 2.1% (95% CI 1.3%–3.2%) by fixed effects model (Supplementary Fig. 3A). The Egger test showed no evidence of publication bias (t = −0.069, P = 0.9227). In aortic valve-in-valve subgroup, the pooled major stroke incidence was 1.8% (95% CI 1.0%–2.8%) (Supplementary Fig. 3B); in mitral valve-in-valve subgroup, the pooled major stroke incidence was 6.2% (95% CI 2.2%–12.0%) (Supplementary Fig. 3C).19 studies reported the renal failure incidence. The renal failure incidence ranged from 0% to 15.4%. The pooled renal failure incidence was 6.7% (95% CI 5.1%–8.4%) by fixed effects model (Supplementary Fig. 4A). The Egger test showed no evidence of publication bias (t = −0.202, P = 0.7431). In aortic valve-in-valve subgroup, the pooled renal failure incidence was 6.7% (95% CI 5.1%–8.6%) (Supplementary Fig. 4B); in mitral valve-in-valve subgroup, the pooled renal failure incidence was 6.4% (95% CI 2.3%–12.2%) (Supplementary Fig. 4C).18 studies reported the major bleeding incidence. The major bleeding incidence ranged from 0% to 15.4%. The pooled the major bleeding incidence was 5.7% (95% CI 4.2%–7.3%) by fixed effects model (Supplementary Fig. 5A). The Egger test showed no evidence of publication bias (t = −0.202, P = 0.7431). In aortic valve-in-valve subgroup, the pooled major bleeding incidence was 5.5% (95% CI 4.0%–7.2%) (Supplementary Fig. 5B); in mitral valve-in-valve subgroup, the pooled major bleeding incidence was 7.5% (95% CI 3.1%–13.8%) (Supplementary Fig. 5C).19 studies reported the permanent pacemaker rate. The permanent pacemaker rate ranged from 0% to 15.4%. The pooled permanent pacemaker rate was 7.3% (95% CI 5.7%–9.2%) by fixed effects model (Supplementary Fig. 6A). The Egger test showed no evidence of publication bias (t = −0.227, P = 0.589). In aortic valve-in-valve subgroup, the pooled permanent pacemaker rate was 7.6% (95% CI 5.9%–9.6%) (Supplementary Fig. 6B); in mitral valve-in-valve subgroup, the pooled permanent pacemaker rate was 5.2% (95% CI 1.6%–10.7%) (Supplementary Fig. 6C).

For late clinical outcome, 21 studies reported 1-year mortality. The 1-year mortality ranged from 0.0% to 33.3%. The pooled 1-year mortality was 16.4% (95% CI 12.5%–20.6%) by random effects model (Supplementary Fig. 7A). The Egger test showed no evidence of publication bias (t = 0.427, P = 0.3243). In aortic valve-in-valve subgroup, the 1-year mortality was 16.5% (95% CI 12.0%–21.6%) (Supplementary Fig. 7B); in mitral valve-in-valve subgroup, the 1-year mortality was 14.8% (95% CI 8.1%–23.1%) (Supplementary Fig. 7C).

Fig. 1 shows the forest plot of the clinical outcomes for transcatheter valve-in-valve in treating surgical bioprosthetic dysfunction.

Our meta-analysis has some limitations. First, substantial heterogeneity was found between studies in many outcomes. Many risk factors can affect the success rate and clinical outcomes, such as patients' age, gender distribution, disease severity, valve position, implanted valve type, and access site. We only did subgroup analysis by valve position. However, heterogeneity was still found. The heterogeneity will result to some degrees of measurement bias. Second, the sample sizes of the studies were small, which ranged from 3 to 459 patients; and most of the studies were only follow-up of 1-year or less. Transcatheter valve-in-valve used for bioprosthetic dysfunction only has 10 years of history. It seems further studies with large sample and longer follow-up are needed.

In summary, our meta-analysis demonstrated that transcatheter valve-in-valve can be safely performed with a high success rate, minimal early and late mortality, and low early complications. Transcatheter valve-in-valve is an acceptable alternative therapy for failed aortic or mitral bioprostheses. Our meta-analysis also provided a useful benchmark for physicians involved in the management of patients with surgical bioprosthetic dysfunction.