










## SYSTEMATIC REVIEW AND META-ANALYSIS

# Valve-in-Valve Transcatheter Aortic Valve Replacement Versus Redo Surgical Aortic Valve Replacement for Failed Surgical Aortic Bioprostheses: A Systematic Review and Meta-Analysis

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**BACKGROUND:** In the absence of randomized controlled trials, reports from nonrandomized studies comparing valve-in-valve implantation (ViV) to redo surgical aortic valve replacement (rAVR) have shown inconsistent results.

**METHODS AND RESULTS:** PubMed/MEDLINE, Google Scholar, and CENTRAL (Cochrane Central Register of Controlled Trials) were searched through December 2021. Meta-Analysis of Observational Studies in Epidemiology guidelines were followed. The protocol was registered at the International Prospective Register of Systematic Reviews. Random effects models were applied. The primary outcomes of interest were short-term and midterm mortality. Secondary outcomes included stroke, myocardial infarction, acute renal failure, and permanent pacemaker implantation, as well as prosthetic aortic valve regurgitation, mean transvalvular gradient, and severe prosthesis-patient mismatch. Of 8881 patients included in 15 studies, 4458 (50.2%) underwent ViV and 4423 (49.8%) rAVR. Short-term mortality was 2.8% in patients undergoing ViV compared with 5.0% in patients undergoing rAVR (risk ratio [RR] 0.55 [95% CI, 0.34–0.91],  $P=0.02$ ). Midterm mortality did not differ in patients undergoing ViV compared with patients undergoing rAVR (hazard ratio, 1.27 [95% CI, 0.72–2.25]). The rate of acute kidney failure was lower following ViV, (RR, 0.54 [95% CI, 0.33–0.88],  $P=0.02$ ), whereas prosthetic aortic valve regurgitation (RR, 4.18 [95% CI, 1.88–9.3],  $P=0.003$ ) as well as severe patient–prosthesis mismatch (RR, 3.12 [95% CI, 2.35–4.1],  $P<0.001$ ) occurred more frequently. The mean transvalvular gradient was higher following ViV (standard mean difference, 0.44 [95% CI, 0.15–0.72],  $P=0.008$ ). There were no significant differences between groups with respect to stroke ( $P=0.26$ ), myocardial infarction ( $P=0.93$ ), or pacemaker implantation ( $P=0.21$ ).

**CONCLUSIONS:** Results of this meta-analysis demonstrate better short-term mortality after ViV compared with rAVR. Midterm mortality was similar between groups. Given the likely selection bias in these individual reports, an adequately powered multicenter randomized clinical trial with sufficiently long follow-up in patients with low-to-intermediate surgical risk is warranted.

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**Key Words:** aortic stenosis ■ failed surgical aortic bioprosthesis ■ redo surgical aortic valve replacement, valve-in-valve transcatheter aortic valve replacement

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## CLINICAL PERSPECTIVE

### What Is New?

- In this meta-analysis of 15 observational studies including 8881 patients with failed surgical bioprosthetic aortic valves, redo surgical aortic valve replacement was associated with similar midterm mortality as compared with valve-in-valve transcatheter aortic valve replacement (ViV) despite a decreased short-term mortality of ViV.
- The mean transvalvular gradient was higher in patients who underwent ViV and prosthetic aortic valve regurgitation as well as severe patient-prosthesis mismatch occurred more frequently following ViV.
- There were no significant differences between groups with respect to stroke, myocardial infarction, or pacemaker implantation, whereas the rate of acute kidney failure was lower following ViV.

### What Are the Clinical Implications?

- ViV is a safe procedure with good clinical short-term outcomes, whereas redo surgical aortic valve replacement leads to better hemodynamic performance.
- The early safety advantages of ViV should be weighed against a potential midterm benefit of redo surgical aortic valve replacement.
- In the absence of randomized controlled trials, patients with failed surgical bioprosthetic aortic valves should be treated at heart valve centers with a multidisciplinary heart team approach discussing the best treatment option for the individual patient.

## Nonstandard Abbreviations and Acronyms

<b>AS</b>	aortic stenosis
<b>rAVR</b>	redo aortic valve replacement
<b>ViV</b>	transcatheter valve-in-valve implantation

**A**ortic stenosis (AS) is the most common valvular heart disease in the Western world.<sup>1</sup> Aortic valve replacement, with conventional surgical or transcatheter techniques, is the only effective treatment option in symptomatic patients.<sup>2,3</sup> The vast majority of patients undergoing surgical valve replacement currently receive a bioprosthesis, with an increasing number of bioprostheses being implanted in younger patients.<sup>4</sup> Structural valve deterioration leading to restenosis or regurgitation or both is the main limitation of bioprosthetic valves, particularly in younger patients.<sup>5,6</sup>

Two options currently exist to treat failed surgical aortic bioprostheses: transcatheter valve-in-valve implantation (ViV) or redo surgical aortic valve replacement (rAVR). In the absence of randomized controlled trials, reports from nonrandomized studies comparing ViV to rAVR and previous meta-analyses have shown inconsistent results, and thus evidence supporting one strategy over the other is lacking.<sup>7–22</sup> Therefore, the aim of this systematic review and meta-analysis is to provide a comprehensive review of current evidence focusing on the comparison of ViV to rAVR in patients presenting with failed surgical bioprosthetic aortic valves.

## METHODS

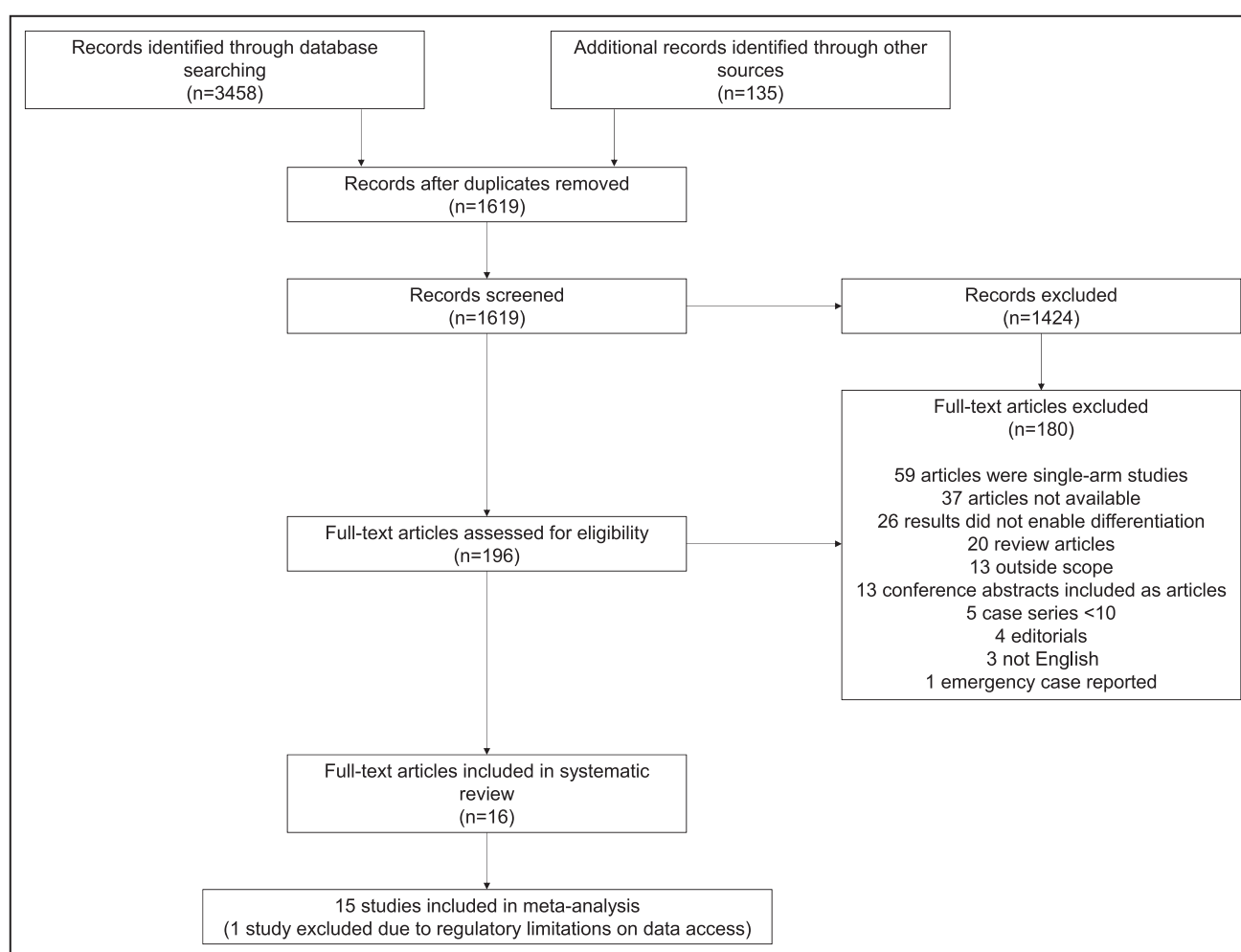
The analysis can be accessed as an R Markdown document from the first author upon request.

Based on guidelines for conducting Meta-Analysis of Observational Studies in Epidemiology, three investigators (M.R., P.T.B., D.K.) searched medical literature databases of PubMed/Medline, CENTRAL (Cochrane Central Register of Controlled Trials), and Google Scholar through December 2021, using the Medical Subject Headings terms *Aortic Valve/abnormalities*, *Aortic Valve/therapy*, *Heart Valve Prosthesis/adverse effects*, *Reoperation/adverse effects*, *Reoperation/methods*, *Reoperation/therapeutic use*, *Reoperation/therapy*, *Bioprosthesis/therapy*, and *Transcatheter Aortic Valve Replacement*.<sup>23</sup> Added search terms in either title or abstract or keyword fields were (*failure or degeneration*) and (*valve-in-valve or reoperation or rAVR*), and *aortic valve AND valve-in-valve OR reoperation OR redo surgery*. Key words used were *aortic valve*, *degeneration*, *failure*, *heart*, *prosthesis*, *redo*, *reoperation*, and *valve-in-valve*. Reference lists from review articles and eligible studies were further checked to identify additional citations. Studies eligible for inclusion compared ViV to rAVR in patients with failed surgical bioprostheses and reported at least all-cause mortality at  $\leq 30$  days. No restrictions on publication date and language were applied (Figure 1). Risk of overlapping groups of patients was present in 4 studies.<sup>9,10,16,20</sup>

## Data Acquisition and Outcome Measures

Data were independently extracted by 2 investigators (M.R. and S.dW-T.) using a standardized Microsoft Excel spreadsheet. This included study characteristics, baseline information, and outcome data. Discrepancies between researchers were resolved by consensus.

The primary outcomes of interest were (1) short-term mortality defined as operative, in-hospital, or 30-day all-cause mortality; and (2) midterm mortality defined as all-cause mortality at the longest follow-up



**Figure 1.** Flow diagram of the study selection process.

available. Secondary outcomes of interest included procedural outcome measures including stroke, myocardial infarction, acute renal failure, and permanent pacemaker implantation, as well as hemodynamic outcome including prosthetic aortic valve regurgitation, mean transvalvular gradient, and severe prosthesis-patient mismatch (defined as indexed effective orifice area  $<0.65 \text{ cm}^2/\text{m}^2$ ). If a study performed propensity score matching, data of the matched cohorts were included for further analysis. Clinical events were analyzed according to study-specific definitions.

## Statistical Analysis

Baseline characteristics containing demographics and medical history were tabulated by treatment group for each study. Continuous variables were summarized as mean and SD or median and interquartile range as they were reported originally for each study. Binary outcomes were captured by calculating risk ratios (RR) and 95% CIs. A treatment arm continuity correction

was applied in studies with zero cell frequencies.<sup>24</sup> Mean transvalvular gradient was captured by calculating the standard mean difference using Hedges'  $g$ . The Sidik-Jonkman estimator was used to estimate the between-study variance  $\tau^2$  and the Q-profile method for CI of  $\tau^2$  and  $\tau$ .<sup>25,26</sup> A random effects meta-analysis was conducted with the Hartung-Knapp method to adjust test statistics and CIs. Heterogeneity was analyzed using Cochran's Q-test and the  $I^2$  statistics. In addition, heterogeneity was assessed using both outlier analysis and analysis of influential cases. Studies with 95% CI outside the 95% CI of the pooled effect size were defined as outliers. Analysis of influential cases was conducted using the Leave-One-Out method and Baujat plots. Possible publication bias was evaluated using Egger's test for funnel plot asymmetry as well as Duval and Tweedie's trim-and-fill-method. Risk of bias was summarized for observational studies as recommended.<sup>27</sup> Univariable meta-regressions were performed using mixed effects considering

relevant baseline patients characteristics. An alpha of  $<0.1$  was considered significant. Midterm survival was evaluated using hazard ratios (HR) and 95% CIs, which were estimated using methods by Parmar et al (1998) if not reported in publications.<sup>28</sup>

Statistical analysis was performed using base R functions (R version 3.6.3) within RStudio (version 1.2.1153) as well as the following R packages: *meta*, *dmetar*, *metafor*, *robvis*, *tidyverse*, *knitr*, and *rmarkdown*.

## RESULTS

### Characteristics of the Included Studies

In the absence of randomized trials, 16 observational studies published between 2015 and 2020 were identified.<sup>7–22</sup> Ten studies reported midterm mortality as Kaplan–Meier estimates. One study was excluded owing to limited presentation of outcome data to the observed absolute risk reduction in ViV versus rAVR, and no further information on the actual event rates could be obtained following contact with the corresponding author because of local data privacy policies.<sup>22</sup> Consequently, 15 studies were included in the meta-analysis (Figure 1). Characteristics of each study are depicted in Table. Five studies were multicenter analyses and 10 studies enrolled all patients at a single institution. Six studies performed propensity score matching. Risk ratios were calculated for binary outcomes from the number of events and sample sizes from adjusted or unadjusted data, depending on whether propensity score matching was applied in the individual report. HRs used were adjusted or unadjusted, depending on whether the *P* values were derived from the log-rank tests originating from propensity score matched cohorts.

A total of 8881 patients were included with 4458 (50.2%) undergoing ViV and 4423 (49.8%) who underwent rAVR. Mean age was  $77 \pm 2.5$  years in patients with ViV and  $70 \pm 6.0$  years in patients with rAVR. Baseline characteristics of the individual studies are displayed in Table S1. Outcome definitions of individual studies are listed in Table S2. The overall risk of bias was moderate (Figure S1).

### Mortality

Short-term mortality was assessed at 30 days in 10 studies, whereas 5 studies reported operative/interventional or in-hospital mortality (Table S2). Short-term mortality was lower in patients undergoing ViV versus those undergoing rAVR (2.8% versus 5.0%; RR, 0.55 [95% CI, 0.34–0.91],  $P=0.02$ , Figure 2A). The prediction interval for the result of a future trial ranged from 0.10 to 3.01 and the probability to observe a beneficial effect in patients undergoing ViV was 78%.

Data on midterm mortality were reported in 10 studies, of which 1 could not be included because of a

log-rank *P* value of 1.0.<sup>14</sup> The 9 studies analyzed consisted of 2773 patients, with a maximum follow-up duration of 5 years (Table S2). Midterm mortality was not different in patients with ViV as compared with rAVR (HR, 1.27 [95% CI, 0.72–2.2],  $P=0.37$ ; Figure 2B). The prediction interval for the result of a future trial ranged from 0.24 to 6.69 and the probability to observe a beneficial effect in patients undergoing ViV was 37%.

### Procedural Outcomes

Acute kidney injury occurred less frequently following ViV as compared with rAVR (RR, 0.54 [95% CI, 0.33–0.88],  $P=0.01$ ; Figure 3A). The reported incidence of stroke was low for both groups, without significant differences in patients undergoing ViV as compared with those treated by rAVR (RR, 0.73 [95% CI, 0.41–1.3],  $P=0.26$ ; Figure S2A). Similarly, the rate of myocardial infarction (1.0% versus 1.1%, RR, 0.98 [95% CI, 0.55–1.70],  $P=0.93$ ; Figure S2B), and permanent pacemaker implantation (RR, 0.76 [95% CI, 0.48–1.19],  $P=0.21$ ; Figure S2C) did not differ between groups. Exclusion of the influential study by Deharo et al resulted in lower rates of pacemaker implantation in patients who had ViV (RR, 0.64 [95% CI, 0.43–0.95],  $P=0.03$ ).<sup>10</sup>

### Hemodynamic Outcomes

At least mild prosthetic aortic valve regurgitation (RR, 4.18 [95% CI, 1.88–9.3],  $P=0.003$ ; Figure 3B) and severe patient–prosthesis mismatch (RR, 3.12 [95% CI, 2.35–4.1],  $P<0.001$ ; Figure 3C) occurred more frequently in patients with ViV compared with rAVR. The mean aortic valve gradient was higher following ViV as compared with rAVR (standard mean difference, 0.44 [95% CI, 0.15–0.72],  $P=0.008$ ; Figure 3D).

### Propensity Score Matched Analyses

In 6 studies, propensity score matching was performed resulting in 7476 matched patients. Analyses limited to matched cohorts confirmed the results with respect to mortality. Short-term mortality was 2.6% in patients who underwent ViV versus 5.5% in patients with rAVR (RR, 0.45 [95% CI, 0.29–0.69],  $P=0.005$ , Figure S3A). Data on midterm mortality in matched patients were available for 3 studies. Midterm mortality did not differ between groups (HR, 1.04 [95% CI, 0.5–2.2],  $P=0.82$ ), (Figure S3B).

### Metaregression on Short-Term Mortality

Using univariable metaregression including a detailed set of baseline parameters (Table S3), only the percentage of patients with rAVR and prior myocardial infarction (coefficient of beta =  $-0.0624$ ,  $P=0.056$ ; *P* value of residual heterogeneity = 0.15) and the year of publication (coefficient of beta =  $-0.2868$ ,  $P=0.047$ ; *P* value

**Table. Characteristics of the Included Studies**

Study	Year of publication	Center	Country	Design	Enrollment period	Number of patients according to treatment strategy n (%)	
						ViV	rAVR
Cizmic et al <sup>7</sup>	2021	Single center	Germany	Nonmatched	2009–2019	73/90 (81)	17/90 (19)
Dokollari et al <sup>8</sup>	2021	Single center	Canada	Nonmatched	2010–2018	31/88 (37)	57/88 (63)
Hirji et al <sup>9</sup>	2020	Multicenter	United States*	PMS	2012–2016	2181/4362 (50)	2181/4362 (50)
Deharo et al <sup>10</sup>	2020	Multicenter	France†	PMS	2010–2019	717/1434 (50)	717/1434 (50)
Malik et al <sup>11</sup>	2020	Multicenter	United States‡	PMS	2012–2016	710/1420 (50)	710/1420 (50)
Patel et al <sup>12</sup>	2020	Single center	United States	Nonmatched	2012–2019	187/273 (69)	86/273 (31)
Woitek et al <sup>13</sup>	2020	Single center	Germany	No-matched	2006–2017	147/258 (57)	111/258 (43)
Stankowski et al <sup>14</sup>	2020	Single center	Germany	PMS	2003–2018	30/60 (50)	30/60 (50)
Sedeek et al <sup>15</sup>	2019	Single center	United States	Nonmatched	2008–2018	90/350 (26)	260/350 (74)
Spaziano et al <sup>16</sup>	2017	Multicenter	Canada and Europe§	PMS	2007–2015	78/156 (50)	78/156 (50)
Grubitzsch et al <sup>17</sup>	2017	Single center	Germany	Nonmatched	2010–2015	27/52 (52)	25/52 (48)
Silaschi et al <sup>18</sup>	2016	Multicenter	Germany and United Kingdom	Nonmatched	2002 (rAVR)/2008 (ViV)–2015	71/130 (55)	59/130 (45)
Ejiofor et al <sup>19</sup>	2016	Single center	United States	PMS	2002–2015	22/44 (50)	22/44 (50)
Erlebach et al <sup>20</sup>	2015	Single center	Germany	Nonmatched	2001–2014	50/102 (49)	52/102 (51)
Santarpino et al <sup>21</sup>	2016	Single center	Germany	Nonmatched	2010–not reported	6/14 (43)	8/14 (57)

PMS indicates propensity-score matching; rAVR, redo aortic valve replacement; and ViV, transcatheter valve-in-valve implantation.

\*Nationwide based on National Readmission Database.

†French Programme de Médicalisation des Systèmes d'Information (Mandatory Administrative Database).

‡National Inpatient Sample Database.

§Antwerp, Belgium; Catania, Italy; Munich, Germany; Lille, France; Copenhagen, Denmark; Montreal, Canada; Bonn, Germany.

||London, United Kingdom; Hamburg, Germany.

of residual heterogeneity=0.37) remained inversely associated with the effect size considering short-term mortality. The coefficients did not change much in a metaregression considering both covariables.

## DISCUSSION

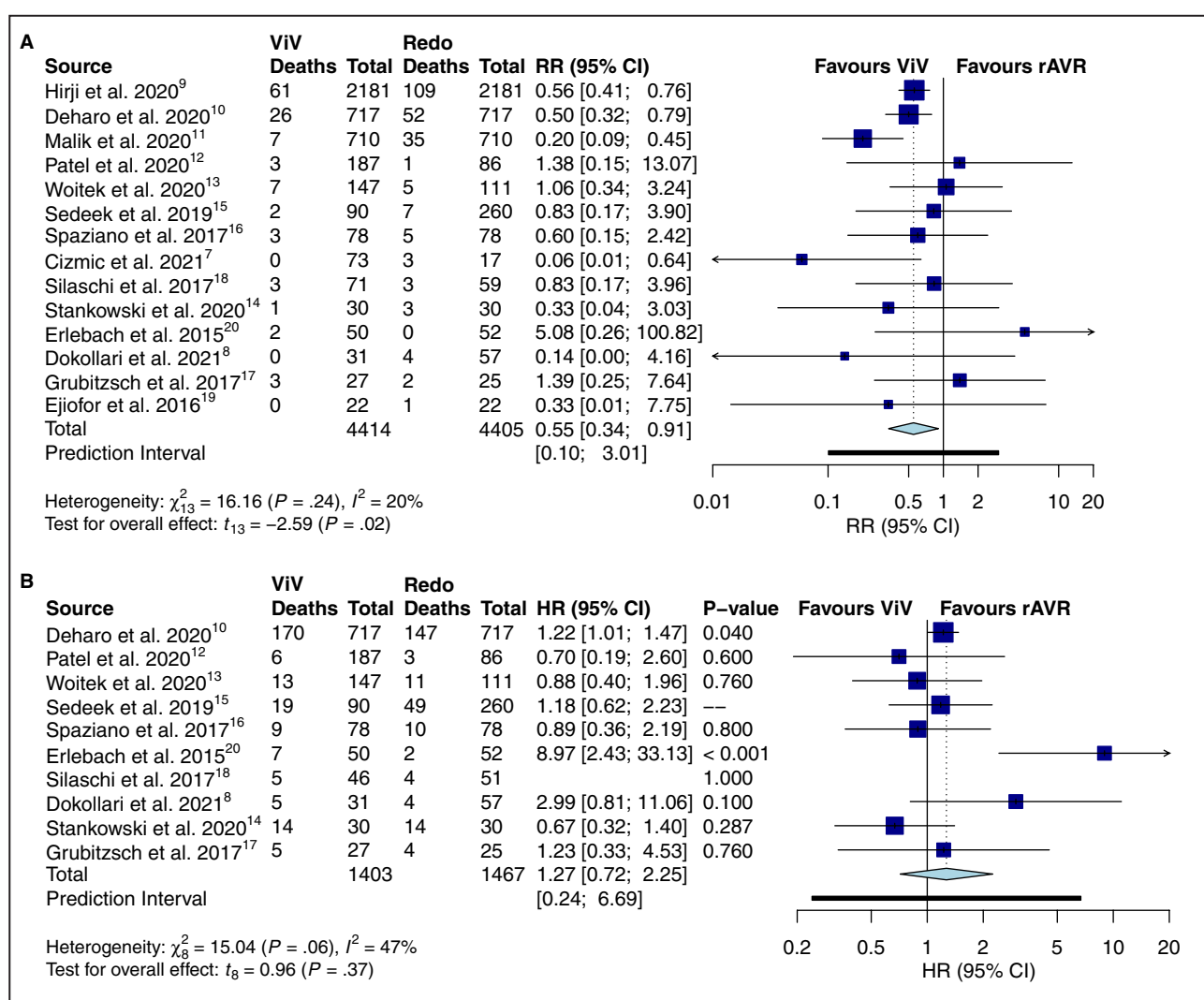
Our meta-analysis of 15 cohort studies investigating clinical outcome of ViV versus rAVR in patients with failed surgical bioprosthetic aortic valves indicates lower short-term mortality following ViV versus rAVR. The incidence of acute renal failure was also lower in patients who underwent ViV, whereas postinterventional aortic valve regurgitation and severe patient-prosthesis mismatch occurred more frequently, and mean aortic valve gradients were higher, in the group with ViV. No differences with respect to stroke, myocardial infarction, and pacemaker implantation were observed. Despite the decreased short-term mortality, midterm survival did not differ.

AS is the most common *valvular disease* in developed countries.<sup>1</sup> Because of the rising age of the population, the incidence of AS is increasing. If left untreated,

the prognosis of patients with symptomatic severe AS is dismal.<sup>29</sup> Therefore, current guidelines recommend surgical or transcatheter aortic valve replacement using mechanical or bioprosthetic valves in symptomatic patients, as well as asymptomatic patients with specific risk factors.<sup>2,3</sup> Each type of valve prosthesis has associated risks and benefits. Mechanical valves require lifelong anticoagulation, which increases the risk of hemorrhage and thromboembolism, whereas bioprosthetic valves are associated with a higher risk of severe hemodynamic valve dysfunction due to structural valve deterioration.<sup>30</sup>

Based on reports of improved durability of biological prostheses and changing patient preferences, the treatment of AS has shifted favoring bioprostheses. The majority of patients undergoing surgical valve replacement in developed countries currently receives a bioprosthesis, with limited prosthesis durability.<sup>31,32</sup> In addition, the largest growth in bioprosthetic use has been observed in younger patients, who are at increased risk of subsequent structural valve deterioration.<sup>31,33</sup> Finally, quoted bioprosthetic structural valve deterioration rates historically obtained from





**Figure 2. Risk estimates of mortality for ViV versus rAVR.**

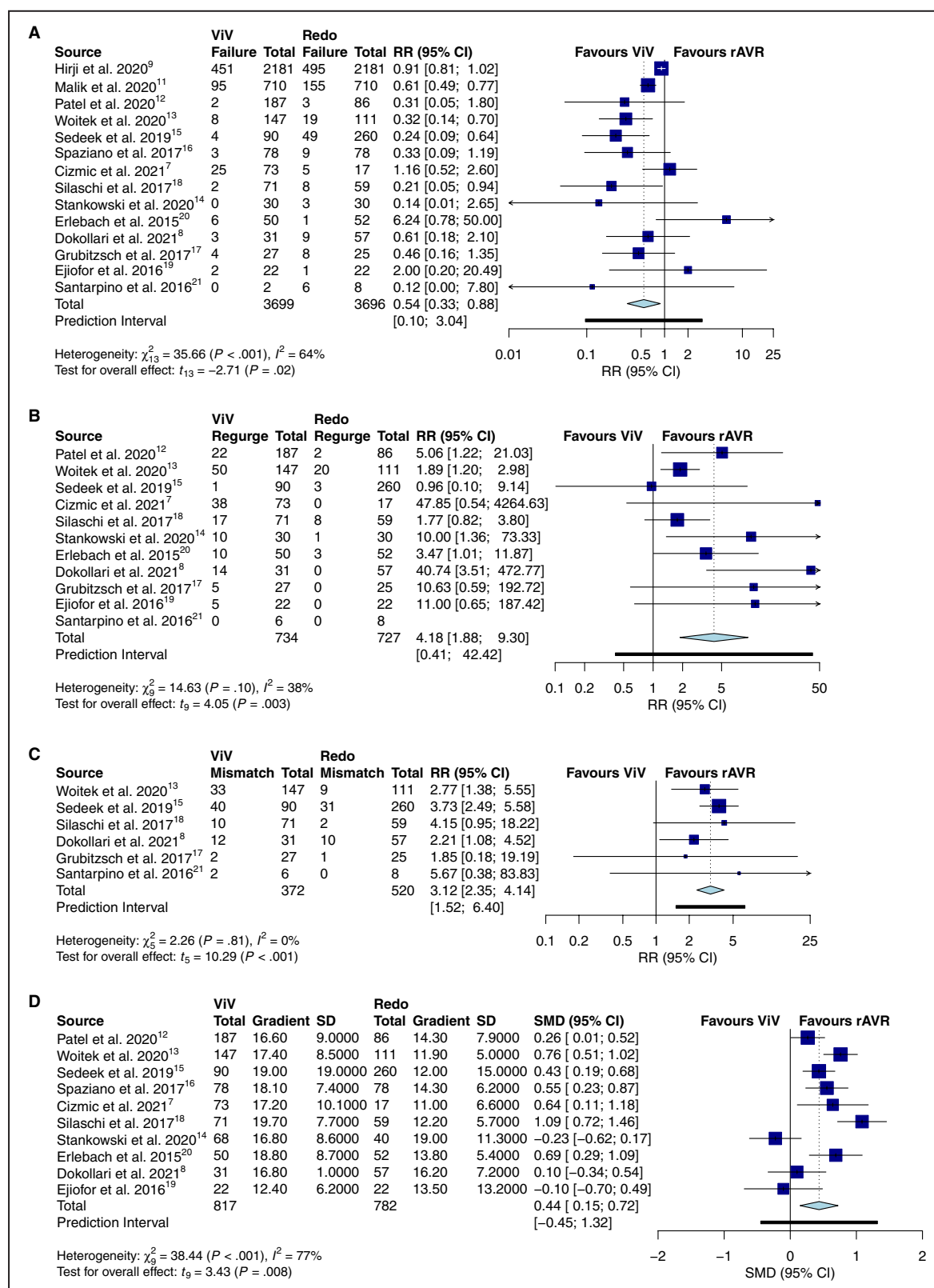
Forest plots show results for short-term (A) and midterm mortality (B). HR indicates hazard ratio; rAVR, redo aortic valve replacement; RR, risk ratio; and ViV, transcatheter valve-in-valve implantation.

retrospective studies may underestimate the true incidence of severe hemodynamic valve failure.<sup>34</sup> Consequently, an increasing number of patients will require rAVR or ViV treatment in the coming years.

Similar to the treatment of native AS, the therapeutic options to replace the failed surgical aortic valve include surgical rAVR as well as the transcatheter-based approach of ViV. Despite the increasing number of ViV procedures that are being performed, evidence with respect to safety and efficacy of ViV versus rAVR in failed surgical aortic bioprostheses is limited to extreme and high surgical risk patients with no surgical option. In the absence of randomized clinical trials, decision making in patients with failed surgical aortic bioprosthesis remains based on local expertise, individual patient and valve characteristics, and shared decision making.<sup>2,3</sup>

The current finding of a lower mortality rate within the first 30 days after ViV was observed even though patients with ViV were older and had a higher prevalence of comorbidities in nonmatched studies. This underlines the safety of the ViV procedure, whereas rAVR has a greater upfront risk owing to the more invasive nature of surgery. The lower rate of acute kidney failure in patients with ViV supports this assumption.

Other periprocedural outcome parameters such as stroke, myocardial infarction, or need for permanent pacemaker implantation did not differ between groups. In contrast, we observed better hemodynamic performance of rAVR as compared with ViV with a more than 2-fold decrease of prosthetic aortic valve regurgitation and a more than 3-fold decrease of severe patient-prosthesis mismatch and significantly lower mean aortic valve gradients in the early peri-interventional period.



**Figure 3. Risk estimates of secondary nonfatal clinical and hemodynamic outcome for ViV versus rAVR.**

Forest plots show results for acute renal failure (A), prosthetic aortic valve regurgitation (B), severe patient-prosthesis mismatch (C), and mean aortic valve gradient (D). rAVR indicates redo aortic valve replacement; RR, risk ratio; SMD, standard mean difference; and ViV, transcatheter valve-in-valve implantation.

This appears to be explained by differing technical approaches: whereas the sewing ring of the failed bioprosthesis is used to anchor the stent of a transcatheter prosthesis, rAVR allows complete explantation of the failed prosthesis including the sewing ring and struts. Theoretically, this could translate into a net benefit with regard to patients' outcomes in the longer term because of the favorable hemodynamic performance of rAVR. We therefore sought to compare midterm mortality following the acute peri-interventional period in the 2 groups of patients.

Here, we observed that survival did not differ between patients, possibly indicating a late catch-up of events. Based on the total hazard ratio, these data demonstrate that it is entirely possible that rAVR may outperform ViV in the longer term. The prediction interval, on the other hand, shows a wide range of potential outcome scenarios, again confirming the lack of high-quality data currently available. The main challenge in comparing these 2 interventions lies in the dissimilarity between the groups, in which higher risk patients—older with more comorbidities—are those who have been considered for ViV. Although propensity score matching was performed in the majority of the latest publications, complete elimination of the inherent selection bias cannot be achieved by any statistical method but a randomized clinical trial.

Another possible explanation may be worse hemodynamic performance associated with ViV procedures. Previous studies have shown an association between prosthetic aortic valve regurgitation as well as severe patient–prosthesis mismatch and late mortality.<sup>35,36</sup> Nevertheless, the duration of follow-up in the current analysis was limited, with half of the included studies reporting follow-up at  $\leq 1$  year, which may not be long enough to observe the full spectrum of late events due to the worse hemodynamic profile in patients with ViV. The largest study giving insight into midterm outcome included 1434 matched patients with an intermediate operative risk (EuroSCORE II 4.7%) and a median follow-up duration of 516 days.<sup>10</sup> At 2 years, the survival curves of patients with ViV and rAVR for all-cause death crossed. This resulted in lower, although statistically nonsignificant, event rates for rAVR at the end of follow-up despite better early outcomes in patients who underwent ViV. The early safety advantages of ViV should therefore be weighed against a potential midterm benefit of rAVR. This is a well-known clinical scenario in cardiovascular care because interventional, less invasive therapeutic strategies tend to be associated with improved short-term outcome, whereas the greater upfront risk of surgical approaches may be attenuated or even converted into a net benefit in the long term. When 2 treatment options with different hazard risk profiles exist, properly

designed randomized clinical trials are warranted in order to guide therapeutic decisions.<sup>37</sup>

Several meta-analyses have been performed comparing ViV with rAVR. The current analysis, however, is the most recent and includes all available data. Further, it demonstrates similar survival at midterm follow-up, possibly indicating a late catch-up of events. If this is because of the worse baseline profile of patients with ViV or also related to impaired hemodynamic performance of ViV remains unclear. We believe that we need a randomized clinical trial before applying ViV as a treatment option in patients with failed aortic bioprostheses at low to intermediate surgical risk.

In contrast to our observations, a recent meta-analysis by Sá et al demonstrated lower rates of stroke and pacemaker implantation in patients who underwent ViV versus rAVR.<sup>38</sup> Further, prosthetic aortic valve regurgitation did not differ between groups. We could not include the analysis of Tam et al owing to local policies at the investigating institution. In addition, we provide a detailed insight into hemodynamic performance of ViV and rAVR (eg, mean aortic valve gradient) as well as clinical outcome (eg, midterm, subanalyses of matched cohorts).

Current international guidelines state that ViV is a reasonable alternative to rAVR in patients with increased surgical risk.<sup>2,3</sup> However, the class of recommendation as well as the level of evidence is moderate (European guidelines IIa C, American guidelines 2a B-NR). Further, it is recommended that these procedures ought to be performed at comprehensive heart valve centers and that a multidisciplinary heart team discusses every patient and chooses the best individualized approach. The current findings support these recommendations. They also emphasize that an adequately powered randomized trial in patients of low-to-intermediate surgical risk with sufficiently long follow-up is warranted.

## Limitations

The current meta-analysis includes nonrandomized retrospective studies and is subject to the inherent weaknesses of observational data. The results should therefore be interpreted with caution. Further, definitions of secondary outcome parameters such as acute renal failure and stroke as well as prosthetic aortic valve regurgitation varied among the individual studies or were not reported. In addition, clinically relevant valve-related factors such as valve size, design, or mode of deterioration were rarely reported and may have influenced the results. There was no adjudication of clinical events by an independent clinical events committee and echocardiographic results were assessed at the local institutions without analyses at core laboratories. Finally, a possible double counting of events by 2 larger studies may affect the interpretation of the



results, especially the conclusion of similar short-term outcomes.<sup>7,9</sup> Regarding both the primary and secondary outcomes of interest, however, the analysis of influential cases (see Methods) did not reveal either study as an influential case, that is, leaving out these studies would not significantly change the results.

## CONCLUSIONS

In patients with failed surgical bioprosthetic aortic valves, ViV is superior to rAVR with respect to short-term clinical outcome. At midterm follow-up, however, survival does not seem to differ, possibly indicating a late catch-up of events following ViV, which could be attributed to better hemodynamic performance of rAVR. A properly designed randomized controlled trial with sufficiently long follow-up comparing these 2 treatment strategies is warranted in lower risk patients with failed aortic bioprostheses.

## ARTICLE INFORMATION

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M.A.B. declares that his hospital receives speakers' honoraria and/or consulting fees on his behalf from Edwards Lifesciences, Medtronic, Abbott, and CryoLife (ie, modest relationship). M.A.W. declares that his hospital receives speakers' honoraria and/or consulting fees on his behalf from Edwards Lifesciences, Medtronic, Abbott, and CryoLife (ie, modest relationship). R.M. has received grant support from Edwards Lifesciences; has served as a consultant for Abbott Vascular, Cordis, and Medtronic; and owns equity in Entourage Medical. The remaining authors have no disclosures to report. Dr Makkar has received grant support from Edwards Lifesciences; has served as a consultant for Abbott Vascular, Cordis, and Medtronic; and owns equity in Entourage Medical.

### Supplemental Material

Tables S1–S3  
Figures S1–S3

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# SUPPLEMENTAL MATERIAL

TABLES

Table S1 Baseline characteristics according to treatment strategy reported in the individual studies

	Hirji et al. <sup>9</sup>			Deharo et al. <sup>10</sup>			Malik et al. <sup>11</sup>			Patel et al. <sup>12</sup>			Woitek et al. <sup>13</sup>		
	ViV	rSAVR	p	ViV	rSAVR	p	ViV	rSAVR	p	ViV	rSAVR	p	ViV	rSAVR	p
Age, years	78.0±8	77.4±5	0.58	74.9±9.7	74.5±8.2	0.33	73.7±10.4	73.3±8.6	0.73	73±13.1	61.3±14.8	<0.0001	76.2±8.0	58.5±14.4	<0.05
Male gender, %	50	56	0.52	56.1	57.7	0.52	52.8	54.9	0.71	67.9	66.3	0.79	62.6	59.9	>0.05
Cardiovascular risk factors															
Arterial Hypertension, %	72	73	1.00	79.4	77.8	0.48	83.1	78.2	0.26	93.6	83.7	0.01	98.0	86.5	>0.05
Hyperlipidaemia, %	-	-	-	54.1	52.9	0.63	-	-	-	-	-	-	-	-	-
Diabetes Mellitus, %	19	15	0.67	31.7	30.3	0.57	32.4	33.1	0.9	39	34.9	0.51	36.1	16.2	<0.05
Current Smoking, %	-	-	-	13.8	15.2	0.45	-	-	-	-	-	-	-	-	-
BMI, kg/m <sup>2</sup>	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical history															
Prior stroke, %	9	12	0.79	5.3	5	0.81	-	-	-	-	-	-	8.8	7.2	<0.05
Prior PCI, %	-	-	-	14.4	13.5	0.65	-	-	-	-	-	-	14.3	6.3	-
Prior CABG, %	31	23	0.37	24.8	22.3	0.26	-	-	-	-	-	-	32.7	9.9	<0.05
Renal insufficiency, %	-	-	-	15.9	15.2	0.72	26.8	26.8	>0.999	5.9	3.5	0.56	26.6	7.2	<0.05
LV ejection fraction, %	-	-	-	-	-	-	-	-	-	-	-	-	54.5±13.9	57.4±10.2	>0.05
Risk scores															
Log EuroSCORE	22.1±16	22.1±18.3	0.99	-	-	-	-	-	-	-	-	-	-	-	-
EuroScore II	-	-	-	4.7±1	4.7±1	0.46	-	-	-	-	-	-	-	-	-
STS PROM score	7.2±4.9	5.8±4.6	0.09	-	-	-	-	-	-	8.4±7.6	5.5±4.6	0.005	8.3±6.1	2.8±2.1	<0.05
Procedural characteristics															
Transfemoral access, %	54	-	-	-	-	-	-	-	-	84	-	-	100	-	-
Transapical access, %	31	-	-	-	-	-	-	-	-	6	-	-	0	-	-
Transaortic access, %	-	-	-	-	-	-	-	-	-	1	-	-	0	-	-
Subclavian access, %	-	-	-	-	-	-	-	-	-	-	-	-	0	-	-
Procedure duration, min	-	-	-	-	-	-	-	-	-	-	145±42	-	-	-	-
CPB time, min	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cross clamp time, min	-	-	-	-	-	-	-	-	-	-	105±29	-	-	-	-

BMI=body mass index; CABG=coronary artery bypass grafting; CPB=cardiopulmonary bypass; LV=left ventricular; PCI=percutaneous coronary intervention; rAVR=redo aortic valve replacement; STS-PROM=Society of Thoracic Surgeons – Predicted Risk of Mortality; ViV=transcatheter valve-in-valve implantation.

**Table S1 Baseline characteristics according to treatment strategy reported in the individual studies (continued)**

	Sedeek et al. <sup>15</sup>			Spaziano et al. <sup>16</sup>			Silaschi et al. <sup>18</sup>			Erlebach et al. <sup>20</sup>		
	ViV	rSAVR	p	ViV	rSAVR	p	ViV	rSAVR	p	ViV	rSAVR	p
Age, years	79 (76-83)	72 (63-77)	<0.001	78.0±8	77.4±5	0.58	78.6±7.5	72.9±6.6	0.06	78.1±6.7	66.2±13.1	<0.001
Male gender, %	73 (81)	177 (68)	0.02	50	56	0.52	57.7	61.0	0.44	54	73	0.06
Arterial Hypertension, %	79 (88)	191 (73)	0.005	72	73	1.00	-	-	-	82	73	0.35
Hyperlipidaemia, %	-	-	-	-	-	-	-	-	-	-	-	-
Diabetes Mellitus, %	25 (28)	57 (22)	0.258	19	15	0.67	11.3	10.2	1.0	20	10	0.17
Current Smoking, %	-	-	-	-	-	-	-	-	-	-	-	-
BMI, kg/m <sup>2</sup>	28 (25-33)	28 (25-32)	0.37	-	-	-	-	-	-	-	-	-
Prior stroke, %	30 (33)	48 (18)	0.004	9	12	0.79	14.1	10.1	0.6	8	0	0.05
Prior PCI, %	-	-	-	-	-	-	-	-	-	-	-	-
Prior CABG, %	43 (48)	75 (29)	0.001	31	23	0.37	-	-	-	40	12	<0.001
Renal insufficiency, %	-	-	-	-	-	-	-	-	-	-	-	-
LV ejection fraction, %	56 (45-62)	62 (55-66)	<0.001	50.7±13.5	49.5±13.4	0.58	-	-	-	49.8±13.1	56.7±15.8	0.02
Log EuroSCORE	-	-	-	22.1±16	22.1±18.3	0.99	25.1±18.9	16.8±9.3	<0.01	27.4±18.7	14.4±10	<0.001
EuroScore II	-	-	-	-	-	-	-	-	-	-	-	-
STS PROM score	7.5 (4.9-10.7)	3 (2.1-5.3)	<0.001	7.2±4.9	5.8±4.6	0.09	-	-	-	-	-	-
Transfemoral access, %	79 (88)	-	-	54	-	-	49.3	-	-	36	-	-
Transapical access, %	10 (11)	-	-	31	-	-	46.5	-	-	54	-	-
Transaortic access, %	-	-	-	-	-	-	4.2	-	-	8	-	-
Subclavian access, %	-	-	-	-	-	-	-	-	-	2	-	-
Procedure duration, min	-	-	-	-	-	-	100±48	270±77	<0.01	101±46	251±76	<0.001
CPB time, min	-	-	-	-	-	-	-	126±57	-	-	110±29	-
Cross clamp time, min	-	-	-	-	-	-	-	79±25	-	-	79±19	-

BMI=body mass index; CABG=coronary artery bypass grafting; CPB=cardiopulmonary bypass; LV=left ventricular; PCI=percutaneous coronary intervention; rAVR=redo aortic valve replacement; STS-PROM=Society of Thoracic Surgeons – Predicted Risk of Mortality; ViV=transcatheter valve-in-valve implantation.



Table S1 Baseline characteristics according to treatment strategy reported in the individual studies (continued)

	Stankowski et al. <sup>14</sup> (intermediate risk)			Stankowski et al. <sup>14</sup> (high risk)			Ejiofor et al. <sup>19</sup>			Grubitzsch et al. <sup>17</sup>			Santarpino et al. <sup>21</sup>		
	ViV	rSAVR	p	ViV	rSAVR	p	ViV	rSAVR	p	ViV	rSAVR	p	ViV	rSAVR	p
Age, years	75.7±4.4	75.8±4.3	0.97	75.8±3.6	75.8±3.6	0.32	75±9.6	74.5±10.4	0.75	75.3±9.9	60±8.6	0.06	80.2±2.3	78.8±3	0.35
Male gender, %	40	70	0.06	30	50	0.36	63.6	59.1	1.00	-	-	-	66.7	25	0.16
Cardiovascular risk factors															
Arterial Hypertension, %	90	95	0.55	90	90	1.0	95.5	90.9	1.0	-	-	-	-	-	-
Hyperlipidaemia, %	80	75	0.705	90	60	0.12	-	-	-	-	-	-	-	-	-
Diabetes Mellitus, %	20	35	0.29	70	70	1.0	45.5	22.7	0.2	-	-	-	83.3	62.5	0.41
Current Smoking, %	10	5	0.55	10	10	1.0	-	-	-	-	-	-	-	-	-
BMI, kg/m <sup>2</sup>	27.3±4.6	28.5±4.5	0.86	29.8	28.9	0.60	25.9±4.4	28.1±6.3	0.05	-	-	-	-	-	-
Medical history															
Prior stroke, %	10	5	0.55	30	10	0.26	8	0	0.05	-	-	-	-	-	-
Prior PCI, %	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prior CABG, %	40	20	0.17	70	30	0.07	40	12	<0.001	-	-	-	-	-	-
Renal insufficiency, %	85	65	0.14	10	10	1.0	-	-	-	59	16	0.006	33.3	37.5	0.66
LV ejection fraction, %	56.2±8.7	58.0±7.1	0.48	45.3±14.7	52.7±12	0.23	49.8±13.1	56.7±15.8	0.02	-	-	-	53±13	58±20	0.57
Risk scores															
Log EuroSCORE	-	-	-	-	-	-	27.4±18.7	14.4±10	<0.001	51	52	0.75	33.8±13.8	36.4±24.1	0.81
EuroScore II	5.8±1.5	5.8±1.4	0.93	15.8±5.3	13.6±3.6	0.3	-	-	-	13.0±10.4	8.9±6.5	0.05	-	-	-
STS PROM score	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Procedural characteristics															
Transfemoral access, %	100	-	-	100	-	-	36	-	-	93	-	-	-	-	-
Transapical access, %	0	-	-	0	-	-	54	-	-	7	-	-	-	-	-
Transaortic access, %	0	-	-	0	-	-	8	-	-	-	-	-	-	-	-
Subclavian access, %	0	-	-	0	-	-	2	-	-	-	-	-	-	-	-
Procedure duration, min	64±54	210±74	<0.001	63±34	194±53	<0.001	101±46	251±76	<0.001	92±29	212±59	-	-	-	-
CPB time, min	-	99±45	-	-	78±26	-	-	110±29	-	-	125±36	-	-	-	-
Cross clamp time, min	-	89±35	-	-	64±15	-	-	79±19	-	-	101±25	-	-	-	-

BMI=body mass index; CABG=coronary artery bypass grafting; CPB=cardiopulmonary bypass; LV=left ventricular; PCI=percutaneous coronary intervention; rAVR=redo aortic valve replacement; STS-PROM=Society of Thoracic Surgeons – Predicted Risk of Mortality; ViV=transcatheter valve-in-valve implantation.

**Table S1** Baseline characteristics according to treatment strategy reported in the individual studies (continued)

	Dokollari et al. <sup>8</sup>			Cizmiz et al. <sup>7</sup>		
	ViV	rSAVR	p	ViV	rSAVR	p
Age, years	79.06±7.4	67.2±14.1	<0.01	78.0±7.4	62.1±16.2	0.01
Male gender, %	43.8	64.7	0.12	56.1	57.7	0.52
<b>Cardiovascular risk factors</b>						
Arterial Hypertension, %	90.3	82.5	0.49	95.9	52.7	<0.001
Hyperlipidaemia, %	87.1	73.7	0.23	65.8	29.4	0.006
Diabetes Mellitus, %	22.6	28.1	0.79	42.5	11.8	0.02
Current Smoking, %	22.6	40.4	0.14	9.6	23.5	0.11
BMI, kg/m <sup>2</sup>	27.3±4.9	27.7±6.3	0.45	27.0±5.0	25.9±5.0	0.43
<b>Medical history</b>						
Prior stroke, %	16.1	31.6	0.18	12.3	0	0.13
Prior PCI, %	-	-	-	-	-	-
Prior CABG, %	32.3	17.5	0.19	-	-	-
Renal insufficiency, %	-	-	-	53.4	23.5	0.03
LV ejection fraction, %	49.0±14.0	50.1±12.8	0.62	51.4±12.0	51.1±12.0	0.22
<b>Risk scores</b>						
Log EuroSCORE	-	-	-	-	-	-
EuroScore II	9.5±7.3	11.0±9.3	0.42	-	-	-
STS PROM score	-	-	-	6.4±3.1	6.4±3.2	-
<b>Procedural characteristics</b>						
Transfemoral access, %	83.1	5.2	<0.01	84.9	-	-
Transapical access, %	9.7	0	0.01	9.6	-	-
Transaortic access, %	3.2	0	0.75	5.5	-	-
Subclavian access, %	3.2	3.5	1.00	-	-	-
Procedure duration, min	85±25	251±81	<0.01	91±35	221±47	-
CPB time, min	-	110±41	-	-	118±36	-
Cross clamp time, min	-	88±34	-	-	72±18	-

BMI=body mass index; CABG=coronary artery bypass grafting; CPB=cardiopulmonary bypass; LV=left ventricular; PCI=percutaneous coronary intervention; rAVR=redo aortic valve replacement; STS-PROM=Society of Thoracic Surgeons – Predicted Risk of Mortality; ViV=transcatheter valve-in-valve implantation.

**Table S2**      **Reported outcomes and definitions**

	Dokollari et al. <sup>8</sup>	Cizmiz et al. <sup>7</sup>	Hirji et al. <sup>9</sup>	Deharo et al. <sup>10</sup>	Malik et al. <sup>11</sup>	Patel et al. <sup>12</sup>	Woitek et al. <sup>13</sup>	Stankowski et al. <sup>14</sup>
<b>Short-term mortality</b>	+	+	+	+	+	+	+	+
	(30 days)	(in-hospital)	(30 days)	(30 days)	(in-hospital)	(in-hospital or within 30 days)	(30 days)	(30 days)
<b>Long-term mortality</b>	+	-	-	+	-	+	+	+
	(mean 3 years)			(760±795 days)		(1.2±1.8 years for rAVR 1.4±1.5 years for ViV)	(1 year)	(5 years)
<b>Stroke</b>	+	+	+	+	-	+	+	+
	(definition not reported)	(VARC-2)	(stroke and TIA based on ICD-9-CM and ICD-10-CM)	(all-cause, VARC-2)		(definition not reported)	(VARC-2)	(VARC-2)
<b>Myocardial infarction</b>	-	-	-	+	+	+	+	+
				(VARC-2)	(ICD-9, ICD-10)	(definition not reported)	(VARC-2)	(VARC-2)
<b>Pacemaker implantation</b>	+	+	+	+	+	+	+	+
					(ICD-9, ICD-10)			
<b>Renal failure</b>	+	+	+	-	+	+	+	+
	(acute kidney injury I-III)	(acute kidney injury I-III)	(based on ICD-9-CM and ICD-10-CM codes)		(ICD-9, ICD-10)	(dialysis)	(acute kidney injury II-III)	(dialysis)
<b>Aortic regurgitation</b>	+	+	-	-	-	+	+	+
	(mild, moderate, severe)	(mild, moderate, severe)				(mild, moderate, severe)	(mild, moderate, severe)	(mild, moderate, severe)
<b>Severe patient-prosthesis mismatch</b>	+	-	-	-	-	-	+	-
	(iEOA ≤0.65 cm <sup>2</sup> /m <sup>2</sup> )						(VARC-2)	

ICD=International Classification of Diseases; iEOA=indexed effective orifice area; rAVR= redo aortic valve replacement; RIFLE=Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; STS-PROM=Society of Thoracic Surgeons – Predicted Risk of Mortality; TIA=transient ischemic attack; VARC=Valve Academic Research Consortium; ViV=transcatheter valve-in-valve implantation.

**Table S2      Reported outcomes and definitions (continued)**

	Sedeek et al. <sup>15</sup>	Spaziano et al. <sup>16</sup>	Grubitzsch et al. <sup>17</sup>	Silaschi et al. <sup>18</sup>	Ejiofor et al. <sup>19</sup>	Erlebach et al. <sup>20</sup>	Santarpino et al. <sup>21</sup>
<b>Short-term mortality</b>	+	+	+	+	+	+	+
	(operative)	(30 days)	(30 days)	(30 days)	(operative)	(30 days)	(in-hospital)
<b>Long-term mortality</b>	+	+	+	+	-	+	+
	(2.1 years, IQR 1.2-4.2)	(1 year)	(1 year)	(180 days)	(data inconclusive)	(1 year)	(21±13 months)
<b>Stroke</b>	+	+	+	+	+	+	+
	(definition not reported)	(VARC-2)	(VARC-2)	(VARC-2, disabling)	(definition not reported)	(VARC-2)	(definition not reported)
<b>Myocardial infarction</b>	-	+	+	+	-	+	+
		(VARC-2)	(VARC-2)	(VARC-2)		(VARC-2)	(definition not reported)
<b>Pacemaker implantation</b>	+	+	+	+	+	+	+
<b>Renal failure</b>	+	+	+	+	+	+	+
	(RIFLE I-III)	(dialysis)	(acute kidney injury II-III)	(acute kidney injury II-III)	(definition not reported)	(dialysis)	(dialysis)
<b>Aortic regurgitation</b>	+	-	+	+	+	+	+
	(moderate or severe)		(mild, moderate, severe)	(mild, moderate, severe)	(mild, moderate, severe)	(mild, moderate, severe)	(mild, moderate, severe)
<b>Severe patient-prosthesis mismatch</b>	+	-	+	+	-	-	+
	(iEOA ≤0.65 cm <sup>2</sup> /m <sup>2</sup> )		(iEOA ≤0.65 cm <sup>2</sup> /m <sup>2</sup> )	(iEOA ≤0.65 cm <sup>2</sup> /m <sup>2</sup> )			(iEOA ≤0.65 cm <sup>2</sup> /m <sup>2</sup> )

ICD=International Classification of Diseases; iEOA=indexed effective orifice area; rAVR= redo aortic valve replacement; RIFLE=Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; STS-PROM=Society of Thoracic Surgeons – Predicted Risk of Mortality; TIA=transient ischemic attack; VARC=Valve Academic Research Consortium; ViV=transcatheter valve-in-valve implantation.

**Table S3 List of Variables Included in Meta-Regression**

1. Year of publication
  2. N in experimental group
  3. N<100 in experimental group
  4. Average age of patients undergoing ViV
  5. Average age of patients undergoing rAVR
  6. Percentage of patients with hypertension in patients undergoing ViV
  7. Percentage of patients with hypertension in patients undergoing rAVR
  8. Percentage of patients with diabetes mellitus in patients undergoing ViV
  9. Percentage of patients with diabetes mellitus in patients undergoing rAVR
  10. Percentage of patients with chronic kidney disease in patients undergoing ViV
  11. Percentage of patients with chronic kidney disease in patients undergoing rAVR
  12. Percentage of patients with peripheral vascular disease in patients undergoing ViV
  13. Percentage of patients with peripheral vascular disease in patients undergoing rAVR
  14. Percentage of patients with atrial fibrillation in patients undergoing ViV
  15. Percentage of patients with atrial fibrillation in patients undergoing rAVR
  16. Percentage of patients with prior pacemaker in patients undergoing ViV
  17. Percentage of patients with prior pacemaker in patients undergoing rAVR
  18. Percentage of patients with coronary artery disease in patients undergoing ViV
  19. Percentage of patients with coronary artery disease in patients undergoing rAVR
  20. Percentage of patients with prior myocardial infarction in patients undergoing ViV
  21. Percentage of patients with prior myocardial infarction in patients undergoing rAVR
  22. Percentage of patients with prior stroke in patients undergoing ViV
  23. Percentage of patients with prior stroke in patients undergoing rAVR
  24. Percentage of patients with prior coronary artery bypass graft in patients undergoing ViV
  25. Percentage of patients with prior coronary artery bypass graft in patients undergoing rAVR
  26. Percentage of patients with prosthesis stenosis in patients undergoing ViV
  27. Percentage of patients with prosthesis stenosis in patients undergoing rAVR
  28. Percentage of patients with prosthesis regurgitation in patients undergoing ViV
  29. Percentage of patients with prosthesis regurgitation in patients undergoing rAVR
  30. Percentage of patients with combined prosthesis dysfunction in patients undergoing ViV
  31. Percentage of patients with combined prosthesis dysfunction in patients undergoing rAVR
  32. Average LV-EF in patients undergoing ViV
  33. Average LV-EF in patients undergoing rAVR
  34. Percentage of females in patients undergoing ViV
  35. Percentage of females in patients undergoing rAVR
- LV-EF=left ventricular ejection fraction; rAVR= redo aortic valve replacement; ViV=transcatheter valve-in-valve implantation.



## FIGURE LEGENDS

**Figure S1 Risk of bias assessment**

**Figure S2 Risk estimates of secondary non-fatal clinical endpoints for ViV versus rAVR**

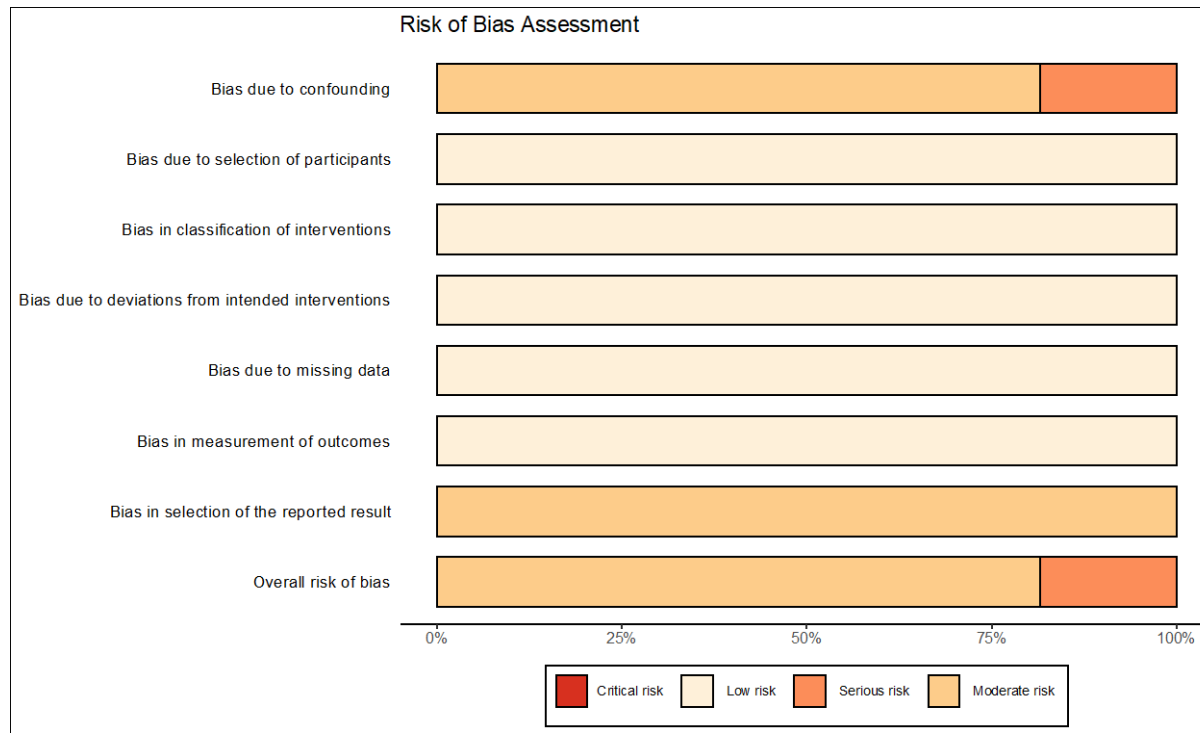
Forest plots show results for stroke (A), myocardial infarction (B), and need for pacemaker implantation (C).

ViV = transcatheter valve-in-valve implantation; rAVR = redo aortic valve replacement; RR = risk ratio; CI = confidence interval.

**Figure S3 Risk estimates of short-term and Mid-term mortality for ViV versus rAVR in studies with propensity score matching**

Forest plots show results for short-term mortality (A) and mid-term mortality (B).

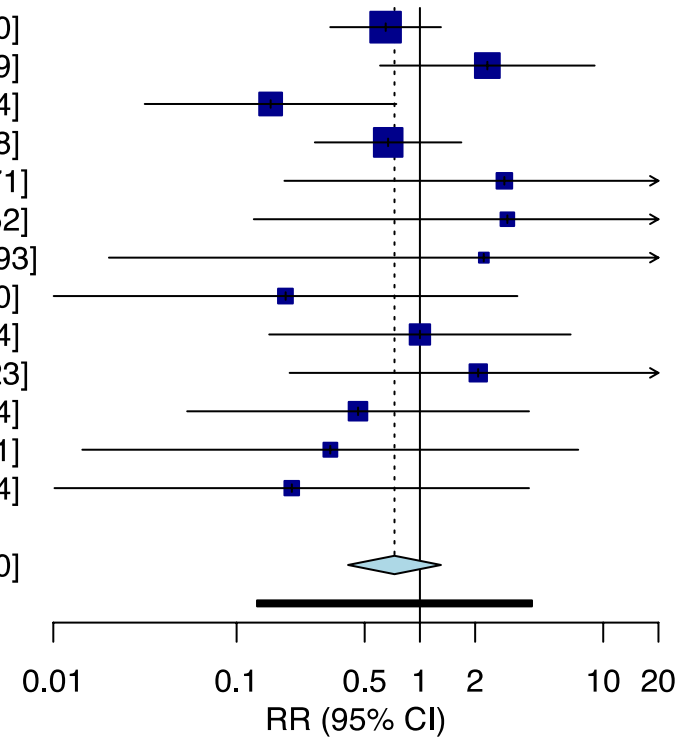
ViV = transcatheter valve-in-valve implantation; rAVR = redo aortic valve replacement; RR = risk ratio; CI = confidence interval.



**Figure S1**

Hirji et al. 2020 <sup>9</sup>	13	2181	20	2181	0.65 [0.32; 1.30]
Deharo et al. 2020 <sup>10</sup>	7	717	3	717	2.33 [0.61; 8.99]
Patel et al. 2020 <sup>12</sup>	2	187	6	86	0.15 [0.03; 0.74]
Woitek et al. 2020 <sup>13</sup>	8	147	9	111	0.67 [0.27; 1.68]
Sedeeq et al. 2019 <sup>15</sup>	1	90	1	260	2.89 [0.18; 45.71]
Spaziano et al. 2017 <sup>16</sup>	1	78	0	78	3.00 [0.12; 72.52]
Cizmici et al. 2021 <sup>7</sup>	1	73	0	17	2.23 [0.02; 247.93]
Silaschi et al. 2017 <sup>18</sup>	0	71	2	59	0.18 [0.01; 3.40]
Stankowski et al. 2020 <sup>14</sup>	2	30	2	30	1.00 [0.15; 6.64]
Erlebach et al. 2015 <sup>20</sup>	2	50	1	52	2.08 [0.19; 22.23]
Dokollari et al. 2021 <sup>8</sup>	1	31	4	57	0.46 [0.05; 3.94]
Grubitzsch et al. 2017 <sup>17</sup>	0	27	1	25	0.32 [0.01; 7.31]
Ejiofor et al. 2016 <sup>19</sup>	0	22	2	22	0.20 [0.01; 3.94]
Santarpino et al. 2016 <sup>21</sup>	0	6	0	8	
Total		3710		3703	0.73 [0.41; 1.30]
Prediction Interval					[0.13; 4.09]

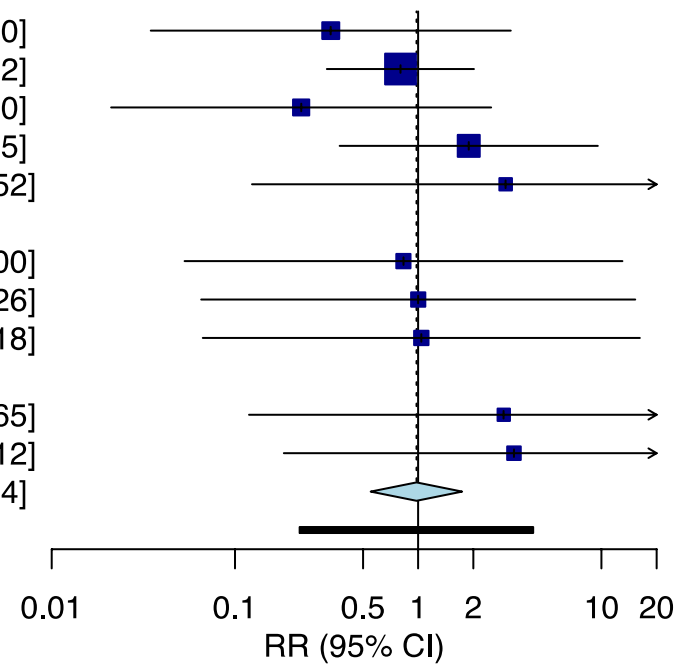
Heterogeneity:  $\chi^2_{12} = 11.52$  ( $P = .49$ ),  $I^2 = 0\%$   
Test for overall effect:  $Z = -1.19$  ( $P = .26$ )



**Figure S2A**

Deharo et al. 2020 <sup>10</sup>	1	717	3	717	0.33 [0.03; 3.20]
Malik et al. 2020 <sup>11</sup>	8	710	10	710	0.80 [0.32; 2.02]
Patel et al. 2020 <sup>12</sup>	1	187	2	86	0.23 [0.02; 2.50]
Woitek et al. 2020 <sup>13</sup>	5	147	2	111	1.89 [0.37; 9.55]
Spaziano et al. 2017 <sup>16</sup>	1	78	0	78	3.00 [0.12; 72.52]
Cizmic et al. 2021 <sup>7</sup>	.	.	.	.	
Silaschi et al. 2017 <sup>18</sup>	1	71	1	59	0.83 [0.05; 13.00]
Stankowski et al. 2020 <sup>14</sup>	1	30	1	30	1.00 [0.07; 15.26]
Erlebach et al. 2015 <sup>20</sup>	1	50	1	52	1.04 [0.07; 16.18]
Dokollari et al. 2021 <sup>8</sup>	.	.	.	.	
Grubitzsch et al. 2017 <sup>17</sup>	1	27	0	25	2.93 [0.12; 71.65]
Santarpino et al. 2016 <sup>21</sup>	1	6	0	8	3.33 [0.18; 60.12]
Total		2023		1876	0.98 [0.55; 1.74]
Prediction Interval					[0.23; 4.24]

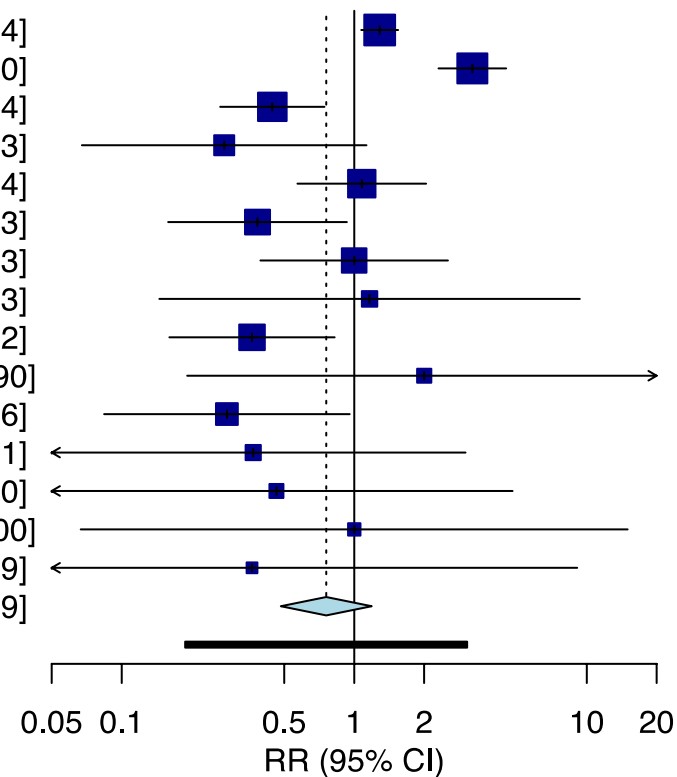
Heterogeneity:  $\chi^2_9 = 4.72$  ( $P = .86$ ),  $I^2 = 0\%$   
 Test for overall effect:  $Z = -0.09$  ( $P = .93$ )



**Figure S2B**

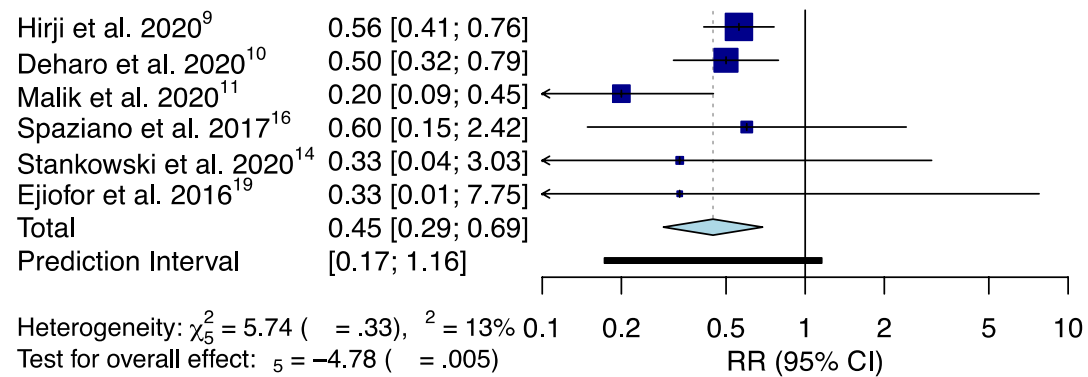
Hirji et al. 2020 <sup>9</sup>	238	2181	185	2181	1.29 [1.07; 1.54]
Deharo et al. 2020 <sup>10</sup>	132	717	41	717	3.22 [2.30; 4.50]
Malik et al. 2020 <sup>11</sup>	20	710	45	710	0.44 [0.27; 0.74]
Patel et al. 2020 <sup>12</sup>	3	187	5	86	0.28 [0.07; 1.13]
Woitek et al. 2020 <sup>13</sup>	20	147	14	111	1.08 [0.57; 2.04]
Sedeeq et al. 2019 <sup>15</sup>	5	69	44	233	0.38 [0.16; 0.93]
Spaziano et al. 2017 <sup>16</sup>	8	78	8	78	1.00 [0.40; 2.53]
Cizmic et al. 2021 <sup>7</sup>	5	73	1	17	1.16 [0.15; 9.33]
Silaschi et al. 2017 <sup>18</sup>	7	71	16	59	0.36 [0.16; 0.82]
Stankowski et al. 2020 <sup>14</sup>	2	30	1	30	2.00 [0.19; 20.90]
Erlebach et al. 2015 <sup>20</sup>	3	50	11	52	0.28 [0.08; 0.96]
Dokollari et al. 2021 <sup>8</sup>	1	31	5	57	0.37 [0.04; 3.01]
Grubitzsch et al. 2017 <sup>17</sup>	1	27	2	25	0.46 [0.04; 4.80]
Ejiofor et al. 2016 <sup>19</sup>	1	22	1	22	1.00 [0.07; 15.00]
Santarpino et al. 2016 <sup>21</sup>	0	6	1	8	0.36 [0.01; 9.09]
Total		4399		4386	0.76 [0.48; 1.19]
Prediction Interval					[0.19; 3.06]

Heterogeneity:  $\chi^2_{14} = 75.02$  ( $p < .001$ ),  $I^2 = 81\%$   
 Test for overall effect:  $Z_{14} = -1.32$  ( $p = .21$ )

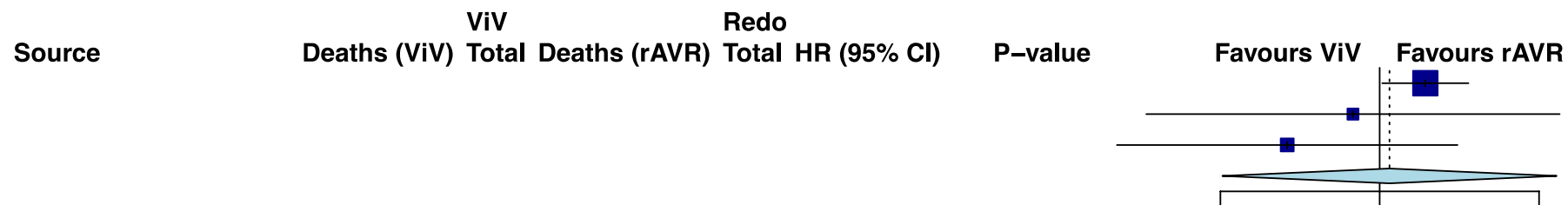


**Figure S2C**





**Figure S3A**



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Figure S3B