

Mechanical versus bioprosthetic valves in chronic dialysis: a systematic review and meta-analysis

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Background: Many patients with end-stage kidney disease (ESKD) have valvular heart disease requiring surgery. The optimal prosthetic valve is not established in this population. We performed a systematic review and meta-analysis to assess outcomes of patients with dialysis-dependent ESKD who received mechanical or bioprosthetic valves.

Methods: We searched Cochrane Central, Medline and Embase from inception to January 2020. We performed screening, full-text assessment, risk of bias and data collection, independently and in duplicate. Data were pooled using a random-effects model.

Results: We identified 28 observational studies ($n = 9857$ patients, including 6680 with mechanical valves and 3177 with bioprosthetic valves) with a median follow-up of 3.45 years. Twenty-two studies were at high risk of bias and 1 was at critical risk of bias from confounding. Certainty in evidence was very low for all outcomes except bleeding. Mechanical valves were associated with reduced mortality at 30 days (relative risk [RR] 0.79, 95% confidence interval [CI] 0.65–0.97, $P = 0$, absolute effect 27 fewer deaths per 1000) and at 6 or more years (mean 9.7 yr, RR 0.83, 95% CI 0.72–0.96, $P = 79\%$, absolute effect 145 fewer deaths per 1000), but increased bleeding (incidence rate ratio [IRR] 2.46, 95% CI 1.41–4.27, $P = 59\%$, absolute effect 91 more events per 1000) and stroke (IRR 1.63, 95% CI 1.21–2.20, $P = 0\%$, absolute effect 25 more events per 1000).

Conclusion: Mechanical valves were associated with reduced mortality, but increased rate of bleeding and stroke. Given very low certainty for evidence of mortality and stroke outcomes, patients and clinicians may choose prosthetic valves based on factors such as bleeding risk and valve longevity. **Study registration:** PROSPERO no. CRD42017081863

Contexte : De nombreux patients souffrant d'insuffisance rénale terminale (IRT) présentent une valvulopathie nécessitant une intervention chirurgicale. On ignore quelle est la valve prothétique optimale chez cette population. Nous avons effectué un examen systématique et une méta-analyse pour évaluer les résultats des patients atteints d'IRT dialysés ayant reçu une valvule mécanique ou une bioprothèse valvulaire.

Méthodes : Nous avons interrogé les bases de données Cochrane Central, Medline et Embase, de leur date de création jusqu'à janvier 2020. Nous avons procédé à la sélection, à l'évaluation des textes intégraux, à l'évaluation des risques de biais et à la collecte de données, indépendamment et en double. Les données ont été regroupées à l'aide d'un modèle à effets aléatoires.

Résultats : Nous avons ciblé 28 études d'observation ($n = 9857$ patients, dont 6680 avec une valvule mécanique et 3177 avec une bioprothèse valvulaire), avec un suivi d'une durée médiane de 3,45 ans. Vingt-deux études présentaient un risque élevé de biais et 1 étude présentait un risque critique de biais résultant de variables de confusion. La certitude des données était très faible pour tous les résultats, à l'exception des hémorragies. Les valvules mécaniques ont été associées à une réduction de la mortalité à 30 jours (risque relatif [RR] de 0,79, intervalle de confiance [IC] de 95 % 0,65–0,97, $P = 0$, effet absolu de 27 décès de moins pour 1000 patients) et à 6 ans ou plus (moyenne de 9,7 ans, RR de 0,83, IC de 95 % 0,72–0,96, $P = 79\%$, effet absolu de 145 décès de moins pour 1000 patients), mais également à une augmentation des hémorragies (rapport des taux d'incidence [RTI] de 2,46, IC de 95 % 1,41–4,27, $P = 59\%$, effet absolu de 91 événements supplémentaires pour 1000 patients) et des AVC (IRR de 1,63, IC de 95 % 1,21–2,20, $P = 0\%$, effet absolu de 25 événements supplémentaires pour 1000 patients).

Conclusion : Les valvules mécaniques ont été associées à une réduction de la mortalité, mais à une augmentation du taux d'événements hémorragiques et d'AVC. Compte tenu du très faible degré de certitude des données sur la mortalité et les AVC, les patients et les cliniciens peuvent choisir les bioprothèses valvulaires selon des facteurs comme le risque d'hémorragie et la durabilité de la prothèse. **Numéro d'enregistrement de la recherche :** PROSPERO no CRD42017081863

In 2010, more than 2.6 million people worldwide were receiving dialysis for end-stage kidney disease (ESKD), a prevalence that is likely to increase to more than 5.4 million people by 2030.¹ Cardiovascular disease is the leading cause of death in patients with ESKD, responsible for 39% of deaths.² One in 3 patients with ESKD has valvular heart disease.³ In this population, valvular heart disease is diagnosed at a rate 4–5 times higher than the general population and progresses at double the rate.^{2–4}

Left untreated, valvular heart disease leads to cardiac dysfunction, heart failure and death.⁵ Valve replacement can prevent these complications, but the choice of a prosthetic valve for patients with dialysis-dependent ESKD is uncertain. This uncertainty is reflected by the lack of guideline recommendations for valvular heart disease in patients with kidney failure.^{6–9}

Mechanical valves are more durable than bioprosthetic valves but require life-long anticoagulation with vitamin K antagonists.⁵ Use of vitamin K antagonists in patients on dialysis is associated with a 3- to 10-fold increased risk of bleeding compared with the general population.^{10,11} Bioprosthetic valves do not require lifelong anticoagulation,⁵ but are less durable, with case reports describing dysfunction as early as 4 months after surgery.^{12,13}

Four systematic reviews exist but are limited by language restrictions, number of databases searched and narrow search strategies.^{14–17} Given these limitations, we performed a systematic review and meta-analysis to address the following question: in adult patients with a history of ESKD and chronic dialysis who undergo valve replacement surgery, what is the frequency of major adverse outcomes, comparing mechanical and bioprosthetic valves?

METHODS

We registered our protocol on PROSPERO, registration number CRD42017081863.¹⁸ Appendix 1, Section 1, available at www.canjsurg.ca/lookup/doi/10.1503/cjs.001121/tab-related-content, presents the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist.

Search strategy

In collaboration with a medical librarian, we developed a broad search strategy (Appendix 1, Section 2). We searched the Cochrane Central Register of Controlled Trials, Medline, and Embase from inception to January 2020, for randomized controlled trials (RCTs) and observational studies. We reviewed trial registries (ISRCTN, World Health Organization International Clinical Trial Registry Platform, clinicaltrials.gov), proceedings of key conferences for

the past 2 years (American Heart Association Scientific Session, European Society Cardiology Congress, Canadian Cardiovascular Conference, American Association Thoracic Surgery Annual Meeting, The Society of Thoracic Surgeons Annual Meeting), references of included studies and relevant systematic reviews for eligible studies.

Inclusion criteria

We included RCTs or observational studies that compared outcomes of mechanical or bioprosthetic valves in the aortic or mitral position for patients with dialysis-dependent ESKD. We performed screening of titles and abstracts and of full texts in duplicate and independently using Covidence online software. We recorded reasons for study exclusion after full-text review. Through discussion, reviewers resolved disagreements regarding eligibility, consulting a third reviewer when they could not reach consensus. If all criteria were met for inclusion except for 1, reviewers contacted the corresponding author for further information. If multiple references reported the same outcome from the same cohort, we included only the study with the longest follow-up.

Data collection

Reviewers conducted data extraction independently and in duplicate using Covidence software. We recorded study characteristics, demographic data, details of procedure and outcomes. We resolved disagreements through discussion and, if needed, consulted a third reviewer. For missing data, we contacted corresponding authors twice over a 2-week period, requesting additional information. If we did not receive a response, we deemed the data unavailable.

Outcomes

Outcomes of interest included mortality at 30 days, 1 year, 3 years, 5 years and 6 or more years after surgery; valve-related complications, including valve thrombosis, systemic thromboembolism and valve deterioration; reoperation; major gastrointestinal bleeding; myocardial infarction; postoperative and nongastrointestinal bleeding; stroke (composite of hemorrhagic and ischemic); and health-related quality of life, as reported by any validated instrument. We used indirect evidence to estimate the bleeding risk in patients on dialysis. Appendix 1, Section 3 presents the forest plot for outcomes not reported in results.

Assessment of risk of bias

As our search did not yield eligible RCTs, we discuss only assessment of the risk of bias for observational studies. Two independent reviewers assessed the risk of bias of each included study using the Risk Of Bias In Non-randomized

Studies – Interventions (ROBINS-I) tool.¹⁹ Reviewers evaluated the risk of bias as either low, moderate, serious or critical for each outcome of interest and study. The ROBINS-I tool includes 7 domains, assessing bias from confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported results.

Overall risk of bias for each study was low if all domains were rated as low and was moderate if 1 domain was rated as moderate without any other domain deemed as serious or critical. If at least 1 domain was deemed serious, without another other domain deemed critical, the study's risk of bias was serious. If at least 1 domain was deemed critical, the overall risk of bias was critical.

Assessment of confidence in pooled effect estimates

We used Grading of Recommendations Assessment, Development and Evaluation (GRADE) to evaluate the certainty in evidence.²⁰ We rated each pooled outcome and its body of evidence as high, moderate, low or very low. Outcomes started at high-quality evidence but could be rated down based on the following 5 criteria: limitations in detailed study design and execution (i.e., risk of bias), the applicability of evidence to the patient population of interest (i.e., directness), heterogeneity between study data in the pooled estimate (i.e., inconsistency), confidence intervals of pooled estimates (i.e., imprecision) and publication bias. Quality of evidence could be rated up if there was a dose–response gradient or a large (relative risk [RR] ≥ 2) or very large (RR ≥ 5) effect estimate.

Summary measurement of treatment effect and unit of analysis

We analyzed data using Review Manager version 5.3 (RevMan5.3) and R Studio. We examined the clinical and methodological heterogeneity to ensure pooling data were appropriate. Because of variability between studies, we used a random-effects model and weighted studies using the DerSimonian and Laird inverse-variance method.²¹ We also used a mixed-effects Poisson regression model, using the metafor package in R Studio, to pool outcomes at latest follow-up to address variability in study duration.^{22,23} We included studies with outcomes of 0 in both treatment arms in the meta-analysis using the meta package in R Studio. This package uses the continuity correction to estimate individual study outcomes with confidence intervals, and to conduct meta-analysis based on the inverse-variance method. We also used this package to conduct meta-regression, examining the duration of follow-up as a predictor of mortality. All outcomes are dichotomous and presented as an RR or incidence rate ratio (IRR) with 95% confidence intervals (CIs).

Assessment of heterogeneity

We assessed heterogeneity by inspecting the point estimates and confidence intervals in a forest plot. We also used the χ^2 test for homogeneity and the I^2 index.

Where possible, we performed subgroup analyses to explain observed heterogeneity. These included analysis of studies from Asia versus North America, hypothesizing that studies from Asia would favour mechanical (v. bioprosthetic) valve owing to longer life expectancy on dialysis;²⁴ studies evaluating long-term risk of death in patients receiving peritoneal dialysis versus hemodialysis, hypothesizing that patients selected for peritoneal dialysis would be earlier in the ESKD disease process, leading to longer life expectancy on average than patients receiving hemodialysis;^{25–28} patients receiving mitral versus aortic valve replacement, hypothesizing that mitral valve replacement would benefit more from mechanical prostheses owing to accelerated bioprosthesis deterioration in the mitral position; patients undergoing valve replacement only versus valve replacement with concomitant procedure, hypothesizing that patients undergoing concomitant procedure would benefit from the bioprosthetic valve owing to greater comorbidity; patients younger than 50 years versus those 50 years and older, hypothesizing that patients younger than 50 years would benefit from mechanical valves, owing to accelerated valve calcification and longer life expectancy; diabetic status, hypothesizing that patients without diabetes would benefit from mechanical valve owing to fewer comorbidities and complications; studies at low risk of bias versus serious risk of bias, hypothesizing that studies at serious risk of bias would report larger effect sizes.

Publication bias

We assessed outcomes pooled from 10 or more studies for publication bias using funnel plots generated by RevMan 5.3. We confirmed bias using the arcsine test. Appendix 1, Section 3, presents funnel plots.

RESULTS

We screened 9178 references, yielding no RCT but 28 observational studies with a total of 9857 patients, including 6680 with mechanical valves and 3717 with bioprosthetic valves (Figure 1). Follow-up ranged from 30 days to 12 years (median 3.45 years).^{29–57} Six studies included only aortic valves.^{30,32,38,40,41,53} One study included patients with moderate-to-severe renal failure, some not requiring dialysis.³⁰ We included this study as most patients (70%) received dialysis preoperation. We included 2 studies published in Japanese and 2 studies published as abstracts.^{41,49–51} No studies reported functional capacity or health-related quality of life. We emailed 25 authors requesting missing data or additional information. We received 3 initial replies,

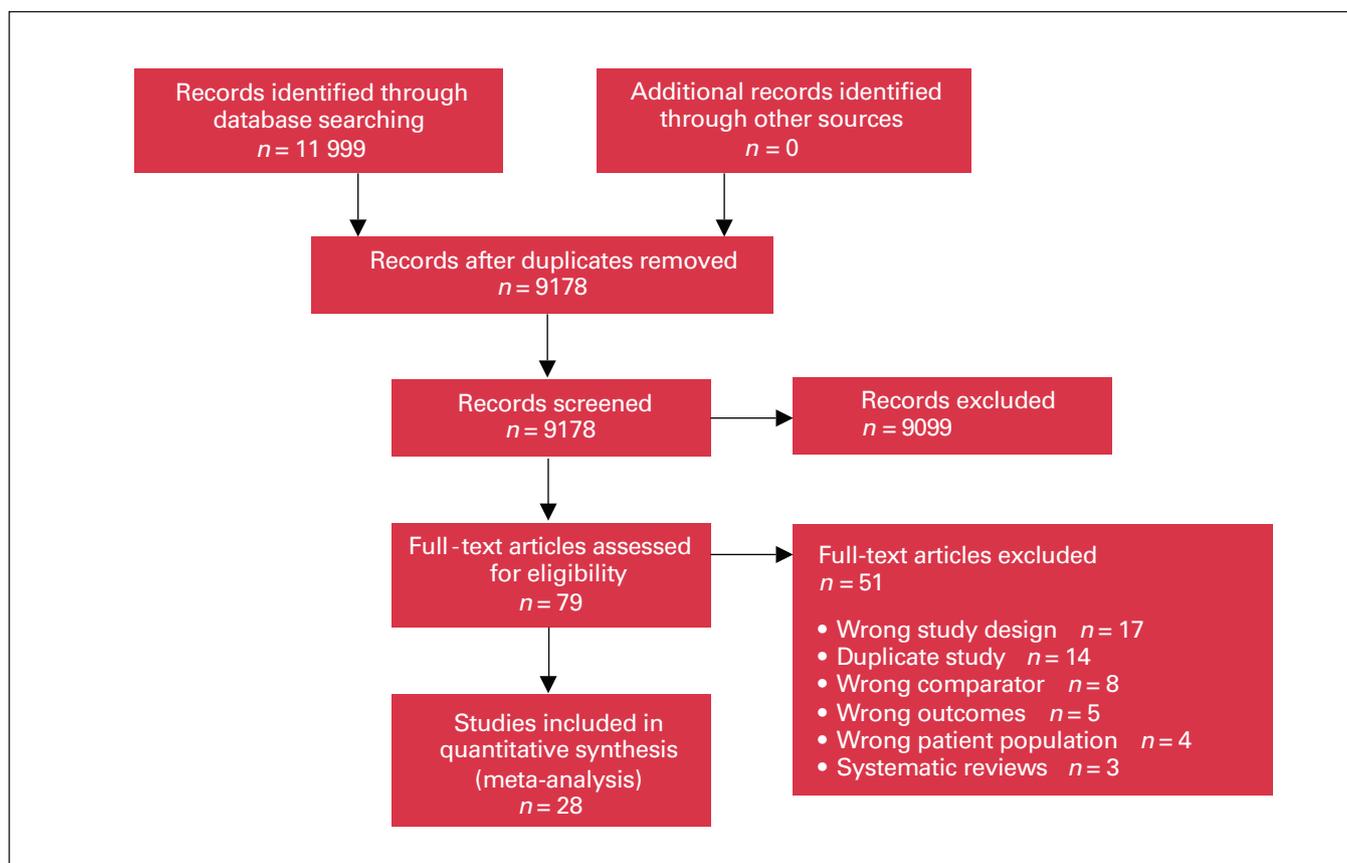


Fig. 1. Prisma flow diagram.

Table 1. Patient characteristics of included studies

Characteristic	Bioprosthetic valve		Mechanical valve		Overall	
	No. (%) of patients*	Total no. of patients (no. of studies)	No. (%) of patients*	Total no. of patients (no. of studies)	No. (%) of patients*	Total no. of patients (no. of studies)
Age, yr, mean	64	2499 (20)	64	1506 (20)	65	3271 (21)
Duration of dialysis, yr, mean	10	658 (7)	13	418 (7)	10	763 (10)
Coronary artery disease or previous myocardial infarction	318 (16.2)	1962 (11)	164 (13.4)	1225 (11)	552 (16.5)	3353 (14)
Congestive heart failure	572 (43.3)	1322 (7)	390 (43.3)	901 (7)	958 (43.1)	2223 (7)
Left ventricular ejection fraction < 30%	120 (8.3)	1441 (5)	78 (8.1)	956 (5)	198 (8.3)	2397 (5)
Left ventricular ejection fraction, %, mean	51.5	944 (9)	54.2	418 (9)	51.7	947 (9)
Cerebral vascular attack	326 (18.0)	1814 (8)	205 (18.1)	1134 (8)	533 (17.8)	2992 (9)
Peripheral vascular disease	512 (22.7)	2253 (12)	257 (19.3)	1316 (12)	785 (23.0)	3658 (13)
Peritoneal dialysis	8 (8.8)	91 (3)	10 (9.5)	105 (3)	18 (9.4)	192 (3)
Hemodialysis	1253 (85.4)	1467 (8)	4241 (79.2)	5358 (8)	5508 (80.6)	6834 (8)
Diabetes	774 (36.6)	2114 (13)	409 (32.0)	1327 (14)	2319 (24.5)	9484 (18)
Hypertension	1605 (67.8)	2368 (15)	911 (64.0)	1423 (16)	4348 (44.3)	9824 (20)
History of endocarditis	185 (20.3)	910 (9)	64 (13.4)	474 (10)	291 (18.0)	1616 (13)

*Unless indicated otherwise.

but none to subsequent emails and deemed the data unavailable. Table 1 presents patient characteristics of included studies and Appendix 1, Supplemental Table S1, presents other study characteristics. We pooled baseline patient characteristics (Table 1) using weighted means.

Five studies were considered at moderate risk of bias owing to selection of reported results; they lacked a pre-registered protocol or statistical analysis plan.^{29,41,52} Twenty-two studies were at serious risk of bias owing to confounding; statistical adjustment was nonexistent or insufficient.

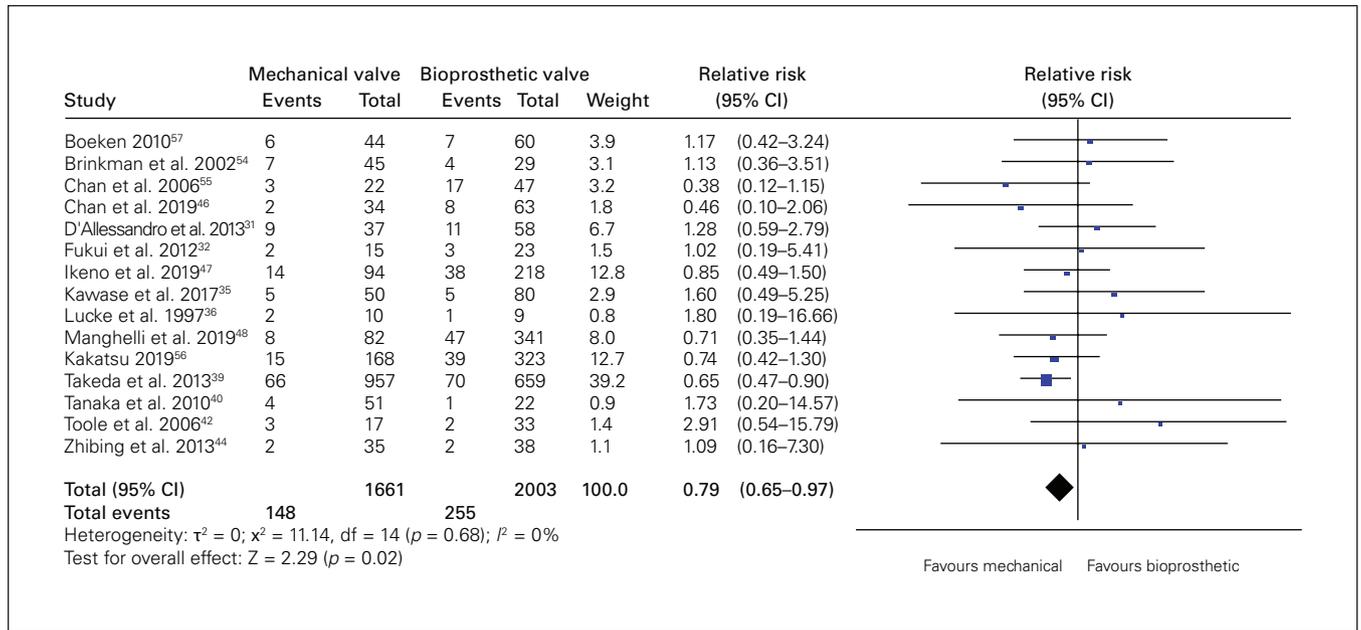


Fig. 2. Forest plot for 30-day mortality. Note: CI = confidence interval.

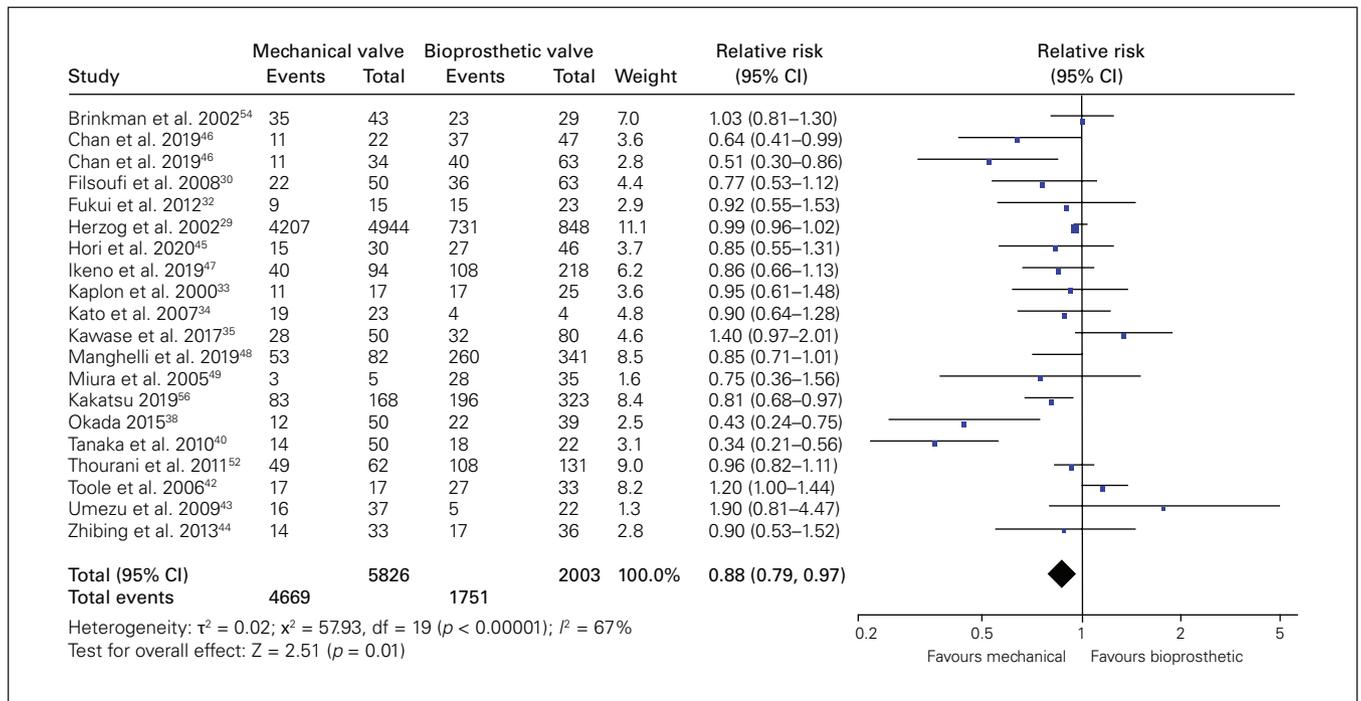


Fig. 3. Forest plot for 5-year mortality. Note: CI = confidence interval.

One study was at critical risk of bias as the authors did not report baseline variables, making controlling confounding infeasible.⁴⁹ We could not conduct a sensitivity analysis because of the overall serious risk of bias of included studies. We conducted post hoc sensitivity analyses for key outcomes based on year of publication to explore time-bias, comparing effect estimates of studies published 2010 and earlier to studies published after 2010. We detected no difference based on year of publication for mortality at

30 days, mortality at 6 or more years, stroke and reoperation. We also conducted post hoc sensitivity analyses for these key outcomes based on risk of bias (moderate v. high). We found a significant difference for mortality at 6 or more years (p for interaction = 0.01), but no difference for others. Appendix 1 presents a risk of bias table for each study, and a summary table of our post hoc sensitivity analysis (Appendix 1, Supplemental Tables S2, S6, S7). We detected asymmetry in funnel plots for all outcomes and

further examined possible publication bias using the arcsine test. Results of the arcsine test are reported for each outcome.

Mortality

Fifteen studies ($n = 3664$ patients) reported 30-day mortality. Mortality was 8.9% (148/1661) in the mechanical group and was 12.7% (255/2003) in the bioprosthetic group (RR 0.79, 95% CI 0.65–0.97, $p = 0.02$, $I^2 = 0\%$, very low quality) (Figure 2). We rated down the quality of evidence for very serious risk of bias and imprecision. On visual inspection, we suspected publication bias, but the arcsine test did not confirm this ($p = 0.06$).

Twenty studies ($n = 8274$ patients) reported 1-year mortality. Mortality in the mechanical group was 42.8% (2508/5856) and was 35.9% (868/2418) in the bioprosthetic group (RR 0.97, 95% CI 0.83–1.12, $p = 0.67$, $I^2 = 31\%$, very low quality). We rated down the quality of evidence for very serious risk of bias and imprecision. The arcsine test did not detect publication bias ($p = 0.97$).

Nineteen studies ($n = 8187$ patients) reported 3-year mortality, suggesting no significant difference (RR 0.97, 95% CI 0.90–1.06, $p = 0.52$, $I^2 = 17\%$, very low quality). We rated down the quality of evidence for risk of bias and imprecision. The arcsine test did not detect publication bias ($p = 0.60$).

Twenty studies ($n = 8254$ patients) reported 5-year mortality; it was 80.1% (4669/5826) with mechanical valves and 72.1% (1751/2428) with bioprosthetic valves (RR 0.88, 95% CI 0.79–0.97, $p = 0.01$, $I^2 = 67\%$, very low quality) (Figure 3). We rated down the quality of evidence for risk of bias, inconsistency and imprecision. We did not detect publication bias using the arcsine test ($p = 0.20$).

Ten studies ($n = 6369$ patients) reported mortality at 6 or more years (mean 9.7 yr); mortality was 92.7% (4972/5361) with mechanical valves and 85.3% (1214/1423) with bioprostheses (RR 0.83, 95% CI 0.72–0.96, $p = 0.01$, $I^2 = 79\%$, very low quality). We rated down the quality of evidence for very serious risk of bias and inconsistency. We suspected publication bias from the funnel plot; smaller studies favouring bioprosthetic valves were missing. We confirmed publication bias using the arcsine test ($p = 0.02$). We conducted a meta-regression to assess duration of follow-up as a predictor of mortality; it was not significant ($\beta = -0.0001$, $p = 0.98$). Appendix 1, Supplemental Figure 1 presents the plot of the meta-regression. We also conducted a post hoc sensitivity analysis based on risk of bias. Comparing studies at moderate risk of bias to those at high risk of bias, we found no significant difference between mechanical and bioprosthetic valves for mortality at 6 or more years (RR 1.01, 95% CI 0.99–1.03, $p = 0.22$, $I^2 = 0\%$).

Postoperative and nongastrointestinal bleeding at latest follow-up

Sixteen studies ($n = 3548$ patients) reported on bleeding (median follow-up 2.8 yr), occurring in 8.7% (144/1650) of patients in the mechanical group and 6.2% (118/1898) of patients in the bioprosthetic group (IRR 2.46, 95% CI 1.41–4.27, $p < 0.01$, $I^2 = 59\%$, very low quality). Small studies favouring mechanical valves were missing in the funnel plot, creating asymmetry. The arcsine test confirmed publication bias ($p = 0.001$). We rated down the quality of evidence for serious risk of bias and publication bias.

Given the very low certainty in evidence among patients with dialysis-dependent ESKD, we conducted a meta-analysis, whereby we pooled bleeding reported from 5 RCTs ($n = 2786$ patients) comparing warfarin to placebo in the general population (IRR 2.99, 95% CI 1.46–6.13, $p < 0.01$, $I^2 = 74\%$, moderate quality).^{58–62} We rated down the quality of evidence for serious indirectness. Appendix 1 details how we assessed the risk of bias for the 5 RCTs (Appendix 1, Supplemental Table S3).

Gastrointestinal bleeding at latest follow-up

We pooled 11 studies ($n = 2475$ patients) that reported gastrointestinal bleeding (median follow-up 3.2 yr). Gastrointestinal bleeding occurred in 6.4% (84/1314) of patients with mechanical valves and 6.3% (73/1161) of patients with bioprosthetic valves (IRR 1.45, 95% CI 0.79–2.64, $p = 0.23$, $I^2 = 27\%$, very low quality). We rated down the quality of evidence owing to risk of bias and imprecision. The arcsine test confirmed publication bias ($p = 0.03$).

Stroke

Seventeen studies ($n = 2870$ patients) reported stroke at a median of 2.6 years; it occurred more frequently in patients with mechanical valves (6.0%, 103/1718) than in those with bioprosthetic valves (3.9%, 81/2060) for an IRR of 1.63 (95% CI 1.21–2.20, $p < 0.01$, $I^2 = 0\%$, very low quality). We rated down the quality of evidence for serious risk of bias and publication bias ($p = 0.01$).

Reoperation

Sixteen studies ($n = 3602$ patients) reported on reoperation at a median 3.6 years of follow-up. The rate of reoperation with mechanical valves was 5.7% (93/1627) and was 4.8% (95/1975) with bioprosthetic valves (IRR 0.93, 95% CI 0.69–1.26, $p = 0.65$, $I^2 = 0\%$, very low quality). The arcsine test did not detect publication bias ($p = 0.90$). We rated down the quality of evidence for risk of bias and imprecision.

Table 2. Meta-analysis of valve-related complications (bioprosthetic valve as reference)

Outcome	No. of studies	No. of patients	RR or IRR* (95% CI)	p value	β , %	Quality of evidence
Endocarditis	12	1318	1.59 (0.91–2.79)	0.11	0	Very low
Myocardial infarction	4	848	3.08 (1.14–8.30)	0.02	0	Very low
Valve thrombosis	3	408	2.87 (0.34–24.52)	0.33	23	Very low
Systemic thromboembolism	8	1067	2.20 (1.15–4.22)	0.01	10	Very low
Valve deterioration	13	1385	0.60 (0.23–1.54)	0.28	0	Very low
Composite of valve-related complications	13	1385	1.44 (0.71–2.91)	0.32	24	Very low

CI = confidence interval; IRR = incident rate ratio; RR = relative risk.

*Relative risk is the effect estimate for outcomes of valve deterioration and the composite of valve-related complications. All other outcomes use incidental rate ratios as the effect estimate.

Valve-related complications

Table 2 summarizes the results for valve-related complications. We found significant difference for myocardial infarction and systemic thromboembolism in favour of the bioprosthetic valve, and no significant difference for endocarditis, valve thrombosis, valve deterioration and a composite of valve-related complications (i.e., valve thrombosis, systemic thromboembolism and valve deterioration). The quality of evidence for all outcomes was very low. Appendix 1, Section 3, includes the forest plots and funnel plots for each outcome within valve-related complications. Appendix 1, Supplemental Tables S4 and S5, include the GRADE summary of findings for all outcomes in this review.

DISCUSSION

In patients with dialysis-dependent ESKD who underwent valve replacement, the current evidence provides little confidence in differentiating outcomes between bioprosthetic and mechanical valves, though risk of death appears lower in patients who receive mechanical valves. Measuring mortality at 30 days, 27 (95% CI 4–45) fewer deaths per 1000 occurred in patients with mechanical valves than in those with bioprosthetic valves. At follow-up approaching 10 years, 145 (95% CI 34–239) fewer deaths per 1000 occurred in patients with mechanical valves than in those with bioprosthetic valves. However, mechanical valves are associated with significantly increased rates of stroke and bleeding. The certainty of evidence ranged from very low to moderate; all outcomes from direct evidence were rated down for very serious risk of bias and imprecision.

We found 4 previously published systematic review and meta-analyses on the topic. The most recent systematic review found a long-term survival benefit for patients who received mechanical valves, similar to findings in this review.¹⁷ Despite this similarity, our review has several strengths. Our review includes 4 additional studies than the most recent review. We attribute this to our comprehensive search strategy, allowing the inclusion of 2 studies in Japanese and conference abstracts.^{41,49–51} We report mortality at specific time points rather than early or late mortality.^{14–17} Specific time points are critical for 2 reasons.

First, prognosis in patients with dialysis-dependent ESKD can vary widely depending on variables not measured (e.g., kidney transplantation) and, second, the length of follow-up between studies varies greatly (30 d to 12 yr).

We report pooled analysis of stroke and gastrointestinal bleeding. Both of these outcomes are important in all patients starting vitamin K antagonist therapy but are especially important in patients with ESKD who are at an increased risk of bleeding at baseline. We also provide a comprehensive estimate of valve deterioration. Previous reviews have qualitatively described valve deterioration and the most recent review pooled 2 studies.^{14–17} We pooled 13 studies using the continuity correction, which allowed us to include studies with 0 outcomes in both groups.⁶³ Finally, we applied the GRADE framework to provide clinical practice recommendations for choosing a prosthetic valve for patients with dialysis-dependent ESKD. With the GRADE framework, we used indirect evidence to evaluate risk of bleeding with greater certainty. We identified 5 RCTs from a systematic review that compared warfarin to placebo in the general population.⁶⁴ We believe that the pooled effect estimate underestimates the true risk of bleeding in patients with dialysis-dependent ESKD, who are at an increased risk of bleeding than the general population. Therefore, we rated down for serious indirectness.

This systematic review shows the paucity of evidence to guide clinicians who must choose a prosthetic valve for patients with dialysis-dependent ESKD. These patients were excluded in previous RCTs that compared outcomes of mechanical and bioprosthetic valves.^{65–67} Most included studies were underpowered and presented unadjusted results.

Although we found a significantly lower mortality on short- and long-term follow-up with mechanical valves, we did not find an RCT that informed the question. Most included studies did not address confounding or did not appropriately adjust for known confounding variables. This prevents causal inferences; differences in outcomes may be owing to differences in baseline characteristics and residual confounding. For example, bioprosthetic valves may more likely be selected for frail patients with lower life expectancies, while mechanical prostheses may more likely be selected for patients with better overall health or who are

awaiting renal transplant, which significantly improves life expectancy.⁶⁸ Despite this, age and comorbidities did not differ substantially between recipients of bioprosthetic and mechanical valve in this review.

Lower mortality with mechanical valves may also be attributed to survivor bias. Traditionally, structural valve deterioration is defined as a requirement for reoperation.^{69,70} Patients on dialysis may not be offered reoperation owing to their comorbidities. Among the bioprosthetic valve group, this may result in increased risk of death, decreased reoperation rates and decreased reporting of structural valve deterioration. Studies included in this systematic review reported reoperation, with a median of 3.6 years of follow-up. This length of follow-up is likely insufficient to produce a meaningful result. Another key issue with the literature is publication bias. We suspected publication bias when inspecting funnel plots of 30-day mortality, 1-year mortality, 3-year mortality, 5-year mortality, gastrointestinal bleeding, stroke, postoperative bleeding and endocarditis. We showed publication bias with the arcsine test for gastrointestinal bleeding, stroke and postoperative bleeding. For these outcomes, small studies favouring mechanical valves were missing.

In light of our results, variability in physician practice is expected. Large observational studies with appropriate adjustment or RCTs are required to inform practice. Until higher quality evidence is available, prosthesis choice should be based on discussions of the pros and cons of each prosthetic valve with the patients as well as their values and preferences.

Limitations

We used PlotDigitizer software to extract mortality at specific time points from survival curves. We calculated the proportion deceased from the difference of those who survived at a specific time point and the total sample, assuming that patients on dialysis were unlikely to be lost to follow-up after surgery. We also included studies with 0 events in both groups in the meta-analysis of all outcomes providing conservative and generalizable estimates of infrequent outcomes.⁶ We used the ROBINS-I tool for transparent and detailed risk of bias assessment¹⁹ and GRADE to assess the quality of evidence.²⁰ Despite these strengths, this study also has several limitations. We identified only observational studies with substantial confounding, resulting in very low-to-low quality of evidence. We were also unable to conduct sensitivity and subgroup analyses because of the high risk of bias and lack of reported characteristics. We contacted authors of studies with missing data but were unable to gain additional data needed to perform subgroup analyses. Patients in this review may not reflect the general dialysis population. The average duration of preoperative dialysis was 10 years, but the average 5-year survival rate for ESKD ranges from 42% to 52%.² Limited data exist to

inform the durability of the bioprosthetic valve in the dialysis population. A disadvantage of the bioprosthetic valve in the general population is durability at 10 years. With a median follow-up of 3.45 years, we cannot reliably assess durability in the dialysis population.

CONCLUSION

Based on very low-quality evidence, risk of death is lower with mechanical valves, but at the cost of increased risk of bleeding and stroke. Residual confounding related to selection bias may account for the association between mechanical valves and death. To further inform clinical practice, future studies should be large enough to allow for adjusted analyses and to generate narrow confidence intervals. Until high-quality evidence is generated, patient values and preferences should guide decisions.

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