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Prosthetic Valve in Chronic Dialysis: a Systematic Review and Meta-Analysis

Emilie Belley-Côté[1], Saurabh Gupta[2], Arjun Pandey[3], Ali Alsagheir[1], Ahmed Makhdoum[4], Graham McClure[1], Brooke Newsome[1], Sophie Gao[5], Matthias Bossard[6], Tetsuya Isayama[7], Yasuhisa Ikuta[7], Michael Walsh[1], Amit Garg[2], Gordon H. Guyatt[1], Richard Whitlock[1], and Kevin Kim[1]

[1]McMaster University Faculty of Health Sciences
[2]McMaster University
[3]McMaster University Michael G DeGroote School of Medicine
[4]University of Toronto
[5]Affiliation not available
[6]Luzerner Kantonsspital
[7]National Center for Child Health and Development

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Abstract

Abstract 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 assessing 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. We evaluated risk of bias using the ROBINS-I tool and certainty in evidence with GRADE. Data were pooled using a random-effects model. Results: We identified 28 observational studies (n=9857; 6680 mechanical and 3717 bioprosthetic) with a median follow-up of 3.45 years. Due to confounding, 22 studies were at "high" and one at "critical" risk of bias. Certainty in evidence for all outcomes, except for bleeding, was very-low. Mechanical valves were associated with reduced mortality at 30 days (RR0.79, 95%CI[0.65,0.97], I2=0, absolute effect 27 fewer deaths per 1000) and at [?] 6 years (mean 9.7 years, RR0.83, 95%CI[0.72,0.96], I2=79%, absolute effect 145 fewer deaths per 1000), but increased bleeding (RR2.46, 95%CI[1.35,4.48], I2=69% absolute effect 113 more events per 1000) and stroke (RR1.53, 95%CI[1.13,2.07], I2=0%, absolute effect 21 more events per 1000). Conclusion: Mechanical valves are associated with reduced mortality, but increased risks of bleeding and stroke. Given very-low certainty for mortality and stroke, patients and clinicians may choose a prosthetic valve based on factors such as bleeding risk and valve longevity.

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Kevin S. Kim, MSc,[1,2], Emilie P. Belley-Côté, MD, PhD,[3,4], Saurabh Gupta MD, MSc,[2,5], Arjun Pandey, BHSc,[1], Ali Alsagheir MBBS, MSc,[2,5], Ahmad Makhdoum, MD, MSc,[2,6], Graham McClure, MD, MSc,[7], Brooke Newsome, BSc,[8], Sophie W. Gao, MD.CM,[5], Matthias Bossard, MD,[9], Tetsuya Isayama, MD, MSc, PhD,[10], Yasuhisa Ikuta, MD,[10], Michael Walsh, MD, PhD,[3,4], Amit X. Garg, MD, PhD,[2,11], Gordon H. Guyatt, MD, MSc,[2,3], Richard P. Whitlock, MD, PhD,[2,4].

Institutions and Affiliations

1. Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Canada
2. Department of Health Research Methodology, Evidence, and Impact, McMaster University, Hamilton, Canada
3. Department of Medicine, McMaster University, Hamilton, Canada
4. Population Health Research Institute, Hamilton, Canada
5. Division of Cardiac Surgery, McMaster University, Hamilton, Canada
6. Division of Cardiac Surgery, The University of Toronto, Toronto, Canada
7. Division of Vascular Surgery, McMaster University, Hamilton, Canada
8. Faculty of Health Sciences, McMaster University, Hamilton, Canada
9. Division of Cardiology, Heart Center Luzerner Kantonsspital, Luzern, Switzerland
10. Division of Neonatology, National Center for Child Health and Development, Tokyo, Japan
11. Department of Medicine, Western University, London, Canada

Corresponding Author

Richard P. Whitlock, MD, PhD

David Braley Cardiac, Vascular and Stroke Research Institute

Room 1C1-5B

237 Barton St. E.,

Hamilton Ontario L8L 2X2

Phone: 905 527 4322 ext.40306

Fax: 905-577-8017

Richard.Whitlock@phri.ca

Data Availability

Data is available based on request to the corresponding author.

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Conflict of Interest

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Co-author e-mails

Kevin Kim:kims95@mcmaster.ca

Emilie Belley-Cote:ebelleycote@me.com

Saurabh Gupta:saurabh.gupta@medportal.ca

Arjun Pandey:pandea6@mcmaster.ca

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Ali Alsagheir:ali.alsagheir@medportal.ca

Ahmed makhdoum:ahmed.makhdoum88@gmail.com

Graham McClure:graham.mcclure@medportal.ca

Brooke Newsome:brooke_6_newsome@hotmail.com

Sophie Gao:sophie.gao@medportal.ca

Matthias Bossard:bossard.matthias@medportal.ca

TETSUYA ISAYAMA:isayamt@mcmaster.ca

Yasuhisa Ikuta:ikuta-y@ncchd.go.jp

Mike Walsh: lastwalsh1975@gmail.com

Amit Garg:amit.garg@lhsc.on.ca

Gordon Guyatt:guyatt@mcmaster.ca

Richard Whitlock:richard.whitlock@phri.ca

Abstract

Abstract

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 assessing 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. We evaluated risk of bias using the ROBINS-I tool and certainty in evidence with GRADE. Data were pooled using a random-effects model.

Results:

We identified 28 observational studies (n=9857; 6680 mechanical and 3717 bioprosthetic) with a median follow-up of 3.45 years. Due to confounding, 22 studies were at "high" and one at "critical" risk of bias. Certainty in evidence for all outcomes, except for bleeding, was very-low. Mechanical valves were associated with reduced mortality at 30 days (RR0.79, 95%CI[0.65,0.97], I^2=0, absolute effect 27 fewer deaths per 1000) and at [?] 6 years (mean 9.7 years, RR0.83, 95%CI[0.72,0.96], I^2=79%, absolute effect 145 fewer deaths per 1000), but increased bleeding (RR2.46, 95%CI[1.35,4.48], I^2=69% absolute effect 113 more events per 1000) and stroke (RR1.53, 95%CI[1.13,2.07], I^2=0%, absolute effect 21 more events per 1000).

Conclusion:

Mechanical valves are associated with reduced mortality, but increased risks of bleeding and stroke. Given very-low certainty for mortality and stroke, patients and clinicians may choose a prosthetic valve based on factors such as bleeding risk and valve longevity.

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Introduction

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In 2010, over 2.6 million people worldwide were receiving dialysis due to end-stage kidney disease (ESKD), a prevalence that is likely to increase to over 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 three patients with ESKD[3] has valvular heart disease (VHD). VHD is diagnosed at a rate four to five times higher than the general population and progresses at double the rate[2–4].

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

Mechanical valves are more durable than bioprosthetic valves, but require life-long anticoagulation with vitamin K antagonists (VKA)[5]. VKA therapy in dialysis patients is associated with a three to ten-fold increased bleeding risk compared to the general population[10,11]. Bioprosthetic valves do not require life-long anticoagulation[5], but are less durable, with case reports describing dysfunction as early as four 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 comparing the morbidity and mortality associated with mechanical and bioprosthetic valves in this population.

Patients and Methods

We registered our protocol on PROSPERO, registration number CRD42017081863[18]. Ethics approval nor informed consent were required as data were collected from published studies, and not individual patients records.

Identification of studies:

In collaboration with a medical librarian, we developed a broad search strategy (Appendix A). We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE from inception to January 2020 for randomized controlled trials (RCTs) and observational studies. We reviewed trial registries (ISRCTN, WHO ICTP, and clinicaltrials.gov), proceedings of key conferences for the past two 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.

Study inclusion and selection:

We included RCTs or observational studies comparing outcomes of mechanical or bioprosthetic valves in the aortic or mitral position for dialysis-dependent adults with ESKD. We performed title and abstract, and full-text screening in duplicate and independently using Covidence[19]. 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 one, we contacted the corresponding author for further information. If multiples references reported the same outcome from the same cohort, we only included the study with the longest follow-up.

Data collection:

Reviewers conducted data extraction independently and in duplicate using Covidence[19]. We recorded study characteristics, demographic data, details of procedure, and outcomes and resolved disagreements through discussion and, if needed, consulted a third reviewer. For missing data, we contacted corresponding authors twice over a two-week period requesting additional information. If we did not receive a response, we deemed the data unavailable.

Outcomes

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Outcomes of interest included: mortality at 30-days, 1, 3, 5-year, or [?] 6 years after surgery, valve-related complications (valve thrombosis, systemic thromboembolism, and valve deterioration), reoperation, major gastrointestinal bleeding, myocardial infarction, post-operative and non-gastrointestinal bleeding, and 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. Appendix B presents the forest plot for outcomes not reported in results.

Assessment of risk of bias

As our search did not yield eligible RCTs, we only discuss the risk of bias (RoB) assessment for observational studies. Two independent reviewers assessed the RoB of each included study using the Risk Of Bias In Non-randomized Studies – Interventions (ROBINS-I) tool[20]. Reviewers evaluated the RoB as either "low", "moderate", "serious", or "critical" for each outcome of interest and study. ROBINS-I includes seven domains assessing bias due to: 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 RoB for each study was "low" if all domains were "low", "moderate" if one domain was "moderate" without any other domain deemed as "serious" or "critical". If at least one domain was deemed "serious" without another other domain deemed "critical", it was "serious". If at least one domain was deemed "critical", the overall RoB was "critical".

Assessment of confidence in pooled effect estimates

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to evaluate the certainty in evidence[21]. 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 five criteria: 1) limitations in detailed study design and execution (i.e. risk of bias), 2) the applicability of evidence to the patient population of interest (i.e. directness), 3) heterogeneity between study data in the pooled estimate (i.e. inconsistency), 4) confidence intervals of pooled estimates (i.e. imprecision), and 5) publication bias.

Summary measurement of treatment effect and unit of analysis

We analyzed data using Review Manager version 5.3 (RevMan5.3) and R Studio[22,23]. 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 DerSimonian and Laird's inverse-variance method[24]. We included studies with zero-outcomes in both treatment arms in the meta-analysis using the "meta" package in R Studio[23,25]. This package uses the continuity correction to estimate individual study outcomes with confidence intervals, and conducts meta-analysis using the inverse-variance method[26]. 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 relative risk (RR) with 95% confidence interval (CI).

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^2index. We planned subgroup analyses to explain observed heterogeneity. These are outlined in our PROSPERO protocol[18].

Publication Bias

We assessed outcomes pooled from [?]10 studies for publication bias using funnel plots and confirmed bias using the arcsine test. Appendix B presents funnel plots.

Table 1. Patient Characteristics of Included Studies

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	Bioprosthetic	Mechanical	Overall
Age (mean)	64 years (20 studies, 2499 patients)	64 years (20 studies, 1506 patients)	65 years (21 studies, 3271 patients)
Duration of dialysis in years	10 years (7 studies, 658 patients)	13 years (7 studies, 418 patients)	10 years (10 studies, 763 people)
Coronary artery disease or previous myocardial infarction	318 (16.2%) (11 studies, 1962 patients)	164 (13.4%) (11 studies, 1225 patients)	552 (16.5%) (14 studies, 3353 patients)
Congestive Heart Failure	572 (43.3%) (7 studies, 1322 patients)	390 (43.3%) (7 studies, 901 patients)	958 (43.1%) (7 studies, 2223 patients)
Left ventricular ejection fraction (LVEF) < 30%	120 (8.3%) (5 studies, 1441 patients)	78 (8.1%) (5 studies, 956 patients)	198 (8.3%) (5 studies, 2397 patients)
Mean LVEF (%)	51.5% (9 studies, 944 patients)	54.2% (9 studies, 418 patients)	51.7% (9 studies, 947 patients)
Cerebral vascular attack	326 (18.0%) (8 studies, 1814 patients)	205 (18.1%) (8 studies, 1134 patients)	533 (17.8%) (9 studies, 2992 patients)
Peripheral vascular disease	512 (22.7%) (12 studies, 2253 patients)	257 (19.3%) (12 studies, 1316 patients)	785 (23.0%) (13 studies, 3658 patients)
Peritoneal dialysis	8 (8.8%) (3 studies, 91 patients)	10 (9.5%) (3 studies, 105 patients)	18 (9.4%) (3 studies, 192 patients)
Hemodialysis	1253 (85.4%) (8 studies, 1467 patients)	4241 (79.2%) (8 studies, 5358 patients)	5508 (80.6%) (8 studies, 6834 patients)
Diabetes	774 (36.6%) (13 studies, 2114 patients)	409 (32.0%) (14 studies, 1327 patients)	2319 (24.5%) (18 studies, 9484 patients)
Hypertension	1605 (67.8%) (15 studies, 2368 patients)	911 (64.0%) (16 studies, 1423 patients)	4348 (44.3%) (20 studies, 9824 patients)
History of endocarditis	185 (20.3%) (9 studies, 910 patients)	64 (13.4%) (10 studies, 474 patients)	291 (18.0%) (13 studies, 1616 patients)

Results

We screened 9178 references, yielding no RCT but 28 observational studies with a total of 9857 patients (Fig. 1). Follow-up ranged from 30 days to 12 years[27–53]. Six studies included only aortic valves[28,30,36,38,39,51]. One study included patients with moderate to severe renal failure, some not requiring dialysis[28]. We included this study as a majority (70%) received dialysis pre-operation. We included two studies published in Japanese, and two studies published as abstracts[39,47–49]. No studies reported functional capacity or health-related quality of life. We e-mailed 25 authors requesting missing data or additional information. We received three initial replies, but none to subsequent e-mails and deemed the data unavailable. Table 1 presents patient characteristics of included studies and Appendix C a table of study characteristics.

Five studies were at moderate RoB due to selection of reported results; they lacked a pre-registered protocol or statistical analysis plan[27,39,50]. Twenty two studies were at serious RoB due to confounding; statistical adjustment was inexistent or insufficient. One study was at critical RoB as the authors did not report baseline variables, making controlling confounding infeasible[47]. We could not conduct sensitivity or subgroup analyses due to overall serious RoB of included studies. Appendix D presents a RoB table for each study.

Mortality :

Fifteen studies (n=3664) reported 30-day mortality. Mortality was 8.9%(148/1661) in the mechanical group and 12.7%(255/2003) in the bioprosthetic group (RR0.79, 95%CI[0.65,0.97], P=0.02, I^2=0%, very-low quality)(Fig. 2). We rated down the quality of evidence for very serious RoB and imprecision. On visual

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inspection, we suspected publication bias but the arcsine test did not confirm publication bias (p=0.06).

Twenty studies (n=8274) reported one-year mortality. Mortality in mechanical group was 42.8%(2508/5856) and 35.9%(868/2418) in the bioprosthetic group (RR0.97, 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 RoB and imprecision. The arcsine test did not detect publication bias (p=0.97).

Nineteen studies (n=8187) reported three-year mortality, suggesting no significant difference (RR0.97, 95%CI[0.90,1.06], P=0.52, I^2=17%, very-low quality). We rated down the quality of evidence due to RoB, and imprecision. The arcsine test did not detect publication bias (p=0.60).

Twenty studies (n=8254) reported five-year mortality; it was 80.1%(4669/5826) with mechanical and 72.1%(1751/2428) with bioprosthetic valves (RR0.88, 95%CI[0.79,0.97], P=0.01, I^2=67%, very-low quality)(Fig. 3). We rated down the quality of evidence for RoB, inconsistency, and imprecision. We did not detect publication bias using the arcsine test (p=0.20).

Ten studies (n=6369) reported mortality at [?]6 years (mean 9.7 years); mortality was 92.7%(4972/5361) with mechanical valves and 85.3%(1214/1423) with bioprostheses (RR0.83, 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 RoB 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 (β=-.0001, P=0.98). Appendix E presents the plot of the meta-regression.

Bleeding at latest follow-up (post-operative, non gastrointestinal)

Sixteen studies (n=3548) reported on bleeding with a median follow-up of 2.8 years, occurring in 8.7%(144/1650) in the mechanical group and 6.2%(118/1898) in the bioprosthetic group (RR2.04, 95%CI[1.29,3.24], P<0.01, I^2=49%, very-low quality). Small studies favouring mechanical valves were missing in the funnel plot, creating asymmetry. Arcsine test confirmed publication bias (p=0.001). We rated down the quality of evidence for serious RoB and publication bias.

Given the very-low certainty in evidence among dialysis-dependent ESKD patients, we pooled bleeding reported from five RCTs (n=2786) comparing warfarin to placebo in the general population (RR2.46, 95%CI[1.35,4.48], P<0.01, I^2=69%, low quality)[54–58]. We rated down the quality of evidence for serious inconsistency and indirectness. Appendix D details how we assessed the RoB for the five RCTs.

Gastrointestinal bleeding at latest follow-up

We pooled 11 studies (n=2475) reporting gastrointestinal bleeding at a median follow-up of 3.2 years. Gastrointestinal bleeding occurred in 6.4%(84/1314) with mechanical and 6.3%(73/1161) with bioprosthetic valves (RR1.04, 95%CI[0.68,1.58], P=0.87, I^2=13%, very-low quality). We rated down the quality of evidence due to RoB and imprecision. Arcsine test confirmed publication bias (p=0.03).

Stroke

Seventeen studies (n=2870) reported stroke at a median of 2.6 years; it occurred more frequently with mechanical valves (6.0%, 103/1718) than with bioprosthetic valves (3.9%, 81/2060) for a RR1.53 (95%CI[1.13,2.07], P<0.01, I^2=0%, very-low quality). We rated down the quality of evidence for serious RoB and publication bias (p=0.01).

Reoperation

Sixteen studies (n=3602) 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 4.8%(95/1975) with bioprosthetic valves (RR0.94, 95%CI[0.71,1.25], P=0.69, 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 RoB and imprecision.

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Valve-related complications

Table 2 summarizes the study results for valve-related complications. We found no significant difference, and very-low quality evidence for each of the following: endocarditis, myocardial infarction, valve thrombosis, systemic thromboembolism, valve deterioration, and a composite of valve-related complications (valve thrombosis, systemic thromboembolism, and valve deterioration). Appendix B includes the forest plots and funnel plots for each outcome. Appendix F contains the GRADE summary of findings table for all outcomes in this review.

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

Outcome	Number of studies	Number of Participants	Effect Estimate RR (9
Endocarditis	12	1318	1.55 (0.90, 2.69)
Myocardial Infarction	4	848	2.50 (0.99, 6.26)
Valve Thrombosis	3	408	2.87 (0.34, 24.52)
Systemic Thromboembolism	8	1067	1.98, (0.96, 4.07)
Valve Deterioration	13	1385	0.60 (0.23, 1.54)
Composite of Valve-related Complications	13	1385	1.60 (0.99, 2.56)

Legend: RR = relative risk; CI = confidence interval

Discussion/Conclusion

Key Results

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

The Results in the Context of Previous Literature

We found four previously published systematic review and meta-analyses on the topic. The most recent systematic review found long-term survival benefit for patients who received mechanical valves, similar to findings in this review[17]. Despite this similarity, there are several strengths in our review. First, we include four additional studies than the most recent review. We attribute this to our comprehensive search strategy allowing the inclusion of two studies in Japanese and conference abstracts[39,47–49]. Second, we report mortality at specific timepoints while other reviews have only reported early and/or late mortality[14–17]. Specific timepoints are critical for two reasons: 1) prognosis in dialysis-dependent ESKD patients can vary widely dependent on variables not measured (e.g. kidney transplantation) and 2) length of follow-up between studies varied greatly (30 days to 12 years). We also report pooled-analysis of stroke and gastrointestinal bleeding which no past review reports. Both outcomes are important in all patients starting VKA therapy, but especially important in ESKD patients who are at an increased baseline risk of bleeding. Fourth, we provide the most comprehensive estimate of valve deterioration. Past reviews have qualitatively described valve deterioration and the most recent review pooled two studies[14–17]. We pooled a total of 13 studies using the continuity correction that allows including studies with zero-outcomes in both groups[26]. Finally, this is the only systematic review and meta-analysis to apply the GRADE framework providing clinical practice recommendations for choosing a prosthetic valve for dialysis-dependent ESKD patients. With the GRADE framework, we used indirect evidence to inform risk of bleeding with greater certainty. We identified five

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RCTs from a systematic review comparing warfarin to placebo in the general population[59]. We believed that the pooled effect estimate underestimates the true bleeding risk in patients with dialysis-dependent ESKD who are at an increased risk of bleeding compared to the general population. Therefore, we downgraded for serious indirectness.

Interpretation of the Results

This systematic review reveals the paucity of evidence to guide clinicians when choosing a prosthetic valve for dialysis-dependent ESKD patients. These patients were excluded in past RCTs comparing outcomes of prosthetic valves[60–62]. Most included studies are underpowered and present unadjusted results.

Although we found a significantly lower mortality on short and long-term follow-up with mechanical valves, no RCT informs the question and included studies did not address confounding or appropriately adjust for known confounding variables. This prevents causal inferences; differences in outcomes may be due to differences in baseline characteristics and residual confounding. For example, bioprosthetic valves are likely selected for frail patients with lower life expectancies while mechanical prostheses may more likely be selected for patients with better overall health and/or awaiting renal transplant which significantly improves life expectancy[63]. Despite this, age and comorobidities did not differ substantially between bioprosthetic and mechanical valve recipients in this review.

Lower mortality with mechanical valves may also be attributed to survivor bias. Traditionally, structural valve deterioration is defined as requirement for reoperation[64,65]. Dialysis patients may not be offered reoperation due to their comorbidities. Amongst the bioprosthetic valve group this may result in: increased mortality, 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 when inspecting funnel plots of 30-day mortality, one-year mortality, three-year mortality, five-year mortality, gastrointestinal bleeding, stroke, post-operative bleeding, and endocarditis. We demonstrated publication bias with arcsine test for gastrointestinal bleeding, stroke, post-operative 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.

Strengths and Weaknesses

Our study has several strengths. We used PlotDigitizer software[66] to extract mortality at specific time points from survival curves. We calculated proportion deceased from the difference of those who survived at a specific time point and the total sample assuming that dialysis patients were unlikely to be lost to follow-up after surgery. We also included studies with zero events in both groups in the meta-analysis of all outcomes providing conservative and generalizable estimate[26] of infrequent outcomes. We used the ROBINS-I tool for transparent and detailed RoB assessment[20] and GRADE to assess the quality of evidence[21]. This study also has several weaknesses. First, we only identified observational studies with significant confounding, resulting in very-low/low quality of evidence. We were also unable to conduct sensitivity or subgroup analyses due to high RoB 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. Lastly, 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].

Conclusion

Based on very-low quality evidence, mortality 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 mortality. To further inform clinical practice, future studies should be large

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enough to allow for adjusted analyses and to generate narrow confidence intervals. Until higher quality evidence is generated, patient values and preferences should guide decisions.

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