

# Age-stratified outcomes of bioprosthetic and mechanical aortic valve replacements in an Australian cohort of 13 377 patients

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## ABSTRACT

**Objectives** To quantify age-stratified outcomes of bioprosthetic valve (BV) and mechanical valve (MV) surgical aortic valve replacement (AVR) in Australian patients.

**Design** Retrospective cohort study using population-based linked hospital morbidity and mortality data.

**Setting** Public and private hospitals.

**Participants** Patients aged 18 years and over undergoing AVR from 2001 to 2013, stratified by age (18–64 years; 65+ years).

**Main outcome measures** Age-standardized index AVR rates; rates and multivariable-adjusted (age, sex, Charlson Comorbidity Index) incidence rate ratios (IRRs) for reoperation, incident cardiovascular events (hospitalization or death for acute myocardial infarction (AMI), stroke, major hemorrhage or thromboembolism) and mortality (cardiovascular and all-cause).

**Results** Our cohort comprised 13 377 patients, of whom 3464 (26%) were aged 18–64 years. Annual age-standardized AVR rates increased by 2.7% with BV implants increasing in both age groups. After 5 years of follow-up, patients implanted with BV had lower rates of stroke (IRR: 0.40, 95% CI 0.27 to 0.60) and hemorrhage (IRR: 0.36, 95% CI 0.26 to 0.50). Among patients 65+ years, those implanted with BV had lower rates of AMI, hemorrhage, and cardiovascular and all-cause mortality than those implanted with MV (IRR: 0.71, 95% CI 0.53 to 0.96; IRR: 0.77, 95% CI 0.62 to 0.95; IRR: 0.80, 95% CI 0.69 to 0.92 and IRR: 0.85, 95% CI 0.74 to 0.97, respectively). After 6–10 years of follow-up, reoperation rates among patients 18–64 years were markedly higher in those implanted with BV compared with MV (IRR: 5.48, 95% CI 2.38 to 12.62) and rates of AMI were lower among patients implanted with BV compared with MV (IRR: 0.49, 95% CI 0.26 to 0.94). Among patients 65+ years rates of cardiovascular and all-cause mortality remained significantly lower for patients implanted with BV compared with MV.

**Conclusions** This study provides real-world evidence of AVR use and outcomes. Use of BV implants is increasing irrespective of age. Valve choice in younger patients requires thorough evaluation of patient factors influencing both short-term outcomes and longer-term risks of reoperation, stroke and hemorrhage.

## Key messages

### What is already known about this subject?

► Use of bioprosthetic valve implants in patients aged less than 65 years is controversial, but there is a worldwide trend towards increased implantation of bioprosthetic valves particularly with the advent of transcatheter aortic valves.

### What are the new findings?

► Patients aged 18–64 years receiving bioprosthetic compared with mechanical valves had an increased risk of reoperation after 5 years, but lower risk of stroke and hemorrhage within 5 years. Older patients (65+) receiving bioprosthetic valves had lower rates of acute myocardial infarction, hemorrhage and mortality within 5 years, and lower rates of mortality after 5 years.

### How might these results affect future research or surgical practice?

► Choice of valve implant in patients requires thorough evaluation of patient factors influencing both short-term outcomes and the longer-term risks of reoperation, stroke, hemorrhage and mortality. The introduction of transcatheter aortic valve replacement requires more research as outcomes might be different from surgically implanted bioprosthetic valves.

## INTRODUCTION

Valvular heart diseases are increasing worldwide, with aortic stenosis (AS) being the most prevalent.<sup>1–3</sup> Surgical aortic valve replacement (AVR) is the standard treatment for severe AS<sup>1 2</sup> and is performed with bioprosthetic (BV) or mechanical (MV) valves.<sup>4</sup> Historically, international guidelines recommended BV for patients aged 65 years and over due to their shorter life expectancy and reduced likelihood of valve degeneration requiring reoperation;<sup>5</sup> MV was recommended for patients under 65 years due to increased longevity of the valve, although it

requires lifelong anticoagulant use and therefore poses the risk of major hemorrhage.<sup>4-6</sup> Current guidelines have moved away from age-specific recommendations, and now stipulate the use of BV for patients with lower life expectancy and those unlikely to adhere to, or with major contraindications to, anticoagulant therapy.<sup>4-7</sup> Early versions of bioprosthetic valves failed in as little as 5 years, particularly among young patients,<sup>8,9</sup> and lasted for up to 10 years, while current valves last for up to 15 years.<sup>10-11</sup> In the last decade, there has been increased use of BV worldwide,<sup>12</sup> coinciding with a substantial reduction in MV implantation.<sup>13-18</sup>

Outcomes of AVR are typically measured by short-term (30–90 days) or longer-term ( $\geq 12$  months) morbidity, mortality and reoperation rates. Most studies report on single-center,<sup>11-19</sup> restricted<sup>10-20-23</sup> or small cohorts<sup>23</sup> and most have less than 10 years of follow-up postimplantation.<sup>20-21-23</sup> Previous studies examining age-specific outcomes have shown patients receiving BV have fewer long-term anticoagulant-related events such as hemorrhage (a major driver of mortality), but significantly higher major adverse prosthesis-related events and reoperation.<sup>10-14-22-23</sup> Among studies examining outcomes across all age groups, the same findings were observed.<sup>11-19-24</sup> Recent systematic reviews examining outcomes in patients aged 50–70 years have conflicting conclusions around patient survival.<sup>25-26</sup> A review of observational studies found no significant differences in long-term patient survival based on valve type<sup>25</sup> but a more recent analysis of randomized controlled trials (RCTs) and propensity score matched observational studies showed increased survival in patients receiving MV.<sup>26</sup>

Valve choice in younger patients is of particular interest because of the potential trade-offs between reoperation risk with BV and the risk of major complications with MV.<sup>27</sup> Given the increasing prevalence of valvular heart disease,<sup>28</sup> it is important to assess the real-world impact of valve choice in relation to age.<sup>1-29</sup> Furthermore, as transcatheter AVR (TAVR) is being adopted increasingly as a minimally invasive approach for bioprosthetic valves, it is important to establish a benchmark for outcomes of surgical AVR.<sup>13-30</sup> Therefore, we sought to use linked, administrative health data from the state of New South Wales (NSW), Australia, to provide real-world evidence on age-stratified outcomes of patients receiving BV and MV from surgical AVR.

## METHODS

### Setting

NSW is the largest state in Australia, with a population of 7.8 million people in 2016. Australia's healthcare system comprises both a universal publicly financed health sector and a private health sector. All residents are provided with free care in public hospitals but they can also take out private medical insurance giving them subsidized care for specific services, choice of provider and generally shorter wait times for elective services.<sup>31</sup>

### Study design and data sources

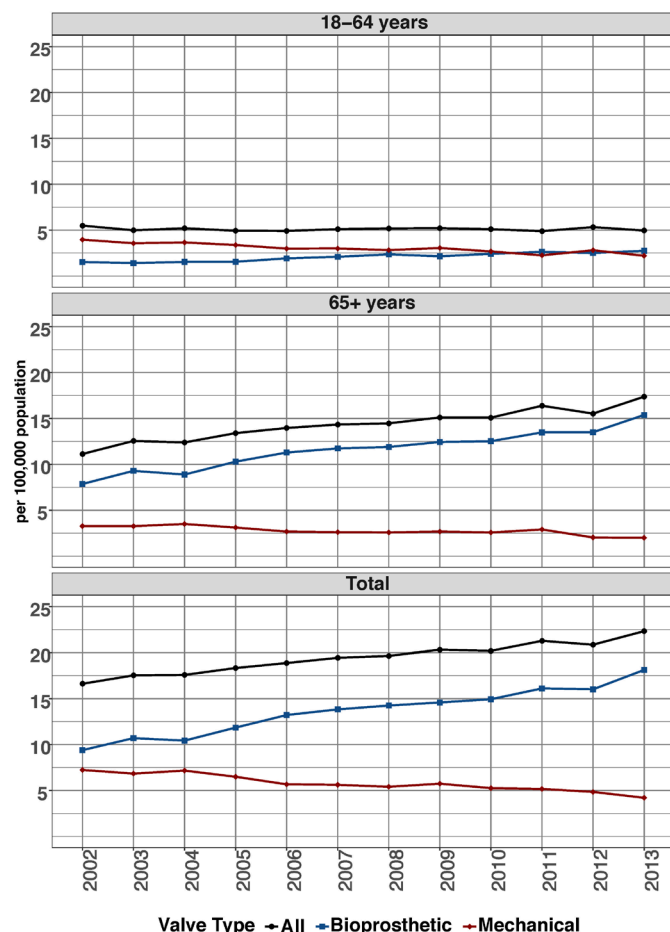
We conducted a retrospective observational cohort study using whole-of-population linked administrative hospital and mortality data. We used the New South Wales (NSW) Admitted Patient Data Collection (APDC); regardless of patient insurance or hospital type, all services performed in NSW hospitals are captured in this collection. APDC data comprise records for all separations (discharges, transfers and deaths) from public and private hospitals, and day procedure centers in NSW. The APDC records up to 50 procedure codes, using the Australian Classification of Health Interventions (ACHI)<sup>32</sup> and up to 51 diagnosis codes, using the International Classification of Diseases (ICD), 10th Revision, Australian Modification.<sup>32</sup> These data were linked with the fact of death from the Registry of Births Deaths and Marriages (RBDM) mortality data file and cause of death from the Australian Bureau of Statistics (ABS) mortality data file. Data linkage was performed by the Centre for Health Record Linkage (CHeReL).<sup>33</sup> The CHeReL uses probabilistic linkage procedures, and has a false-positive and false-negative rate of 0.5%.<sup>34</sup>

### Study cohort

We identified all patients who underwent isolated and concomitant surgical AVR with bioprosthetic (ACHI code 38488-01) or mechanical (38488-00) valves in any NSW hospital from July 2001 to June 2013. We defined each patient's 'index' AVR procedure as the first recorded within the study period. Where AVR procedure dates were missing (n=1621), we used the principal procedure or episode start date. We excluded patients if they were aged under 18 years at the time of index procedure; if there was a secondary procedure code indicating the index procedure was a reoperation (38640-00); if there was a second AVR procedure recorded within the same hospital stay; or if the index AVR date occurred after a patient's recorded date of death (figure 1). Changes to the type of care within a hospital (eg, from acute to subacute care) and transfers between facilities were considered a continuation of the same hospital stay.

### Patient and hospital characteristics

We characterized patients at their index admission according to demographic, hospital and episode characteristics. Patient Aboriginal and Torres Strait Islander status was initially examined, however was not included for further analysis due to low numbers. Patient comorbidities were identified using the Charlson Comorbidity Index (CCI)<sup>35</sup> based on all diagnoses in the index hospitalization and any other hospital stays in a 1-year lookback period. Patients' socioeconomic status was classified using the ABS Socio-Economic Index for Areas Index of Relative Social Disadvantage, based on their Statistical Local Area (SLA) of residence, and grouped into quintiles.<sup>36</sup> Remoteness of residence was derived from the Accessibility/Remoteness Index of Australia, based on SLA of residence, and grouped into four categories (major city, inner regional, outer regional and remote/very



**Figure 1** Age-standardized rates of bioprosthetic and mechanical aortic valve implantations between financial years ending in 2002 and 2013, among all patients and stratified by age group.

remote).<sup>37</sup> Hospital volume was calculated as the median annual number of AVR procedures performed across the study period and classified as high ( $\geq 100$  per year) and low ( $< 100$  per year).

### Outcome measures

We identified reoperation as any subsequent AVR procedure over the study period, irrespective of valve type. We identified incident cardiovascular events based on literature<sup>21 22 38-42</sup> as any emergency admission, or death, with a principal diagnosis/cause of death of acute myocardial infarction (AMI), stroke (infarction or hemorrhage), hemorrhage or thromboembolism (online supplemental table 1). We also classified mortality as cardiovascular (ICD codes I00-99) and all-cause mortality.<sup>43</sup> Where patients had inconsistent death dates in the RBDM and ABS data sets, we used the RBDM date of death.

### Statistical analyses

#### Clinical and hospital characteristics

We stratified patients by valve type and age group (18–64 years and 65 years and over). We chose the age cut-off of 65 years based on recommendations by the American Heart Association, American College of Cardiology

and European Society of Cardiology.<sup>47 9 44</sup> We presented continuous data as median and IQR and expressed categorical data as proportions. All analyses were performed in R V.3.5.2.

#### Procedure rates

We calculated annual rates of index AVR implantation per 100 000 population aged 18 years and over by Australian financial year from July 2001/2002 to June 2012/2013. We calculated overall rates and age-stratified rates (18–64 years; 65+ years) using NSW population estimates from the ABS<sup>45</sup> and directly age standardized to single years of age in the 2001 Australian population.<sup>46</sup>

#### Reoperation, incident cardiovascular events and mortality

We calculated incident event rates for each outcome as the total number of first events (hospital admission or death for a specific cause) observed divided by total person-years of follow-up for each group. We calculated total person-years for each patient from their index AVR date, and ending at death or end of follow-up (30 June 2013), depending on which occurred first. For each outcome, we right censored patient follow-up time at the first event, death or end of follow-up. To compare incidence rates between patients receiving BV and MV, we calculated incidence rate ratios (IRRs) using Poisson models, on the count of incident events (in 5-year age brackets) with the sum of the follow-up time as an offset. Due to inconsistencies in rates over time, we partitioned the models into two time periods ( $\leq 5$  years and 6–10 years) of follow-up. We adjusted for age, sex and CCI and unless otherwise stated, IRR results presented are fully adjusted. We used cumulative incidence function curves to examine the risk of reoperation and cardiovascular mortality, accounting for the competing risk of all-cause mortality and non-cardiovascular mortality, respectively. We used Kaplan-Meier curves to examine all-cause mortality.

#### Sensitivity analysis

We conducted a sensitivity analysis to assess the impact of early mortality on the time-partitioned incident event rates, by excluding patients who died within 30 days of the index AVR procedure.

## RESULTS

### Patient and hospital characteristics

Our eligible study cohort comprised 13 377 patients with index AVR procedures between 1 July 2001 and 30 June 2013, of whom 9500 (71.0%) received BV implants and 3877 (29.0%) received MV implants (online supplemental figure 1). The median age of patients undergoing AVR with BV implants was 76 years (IQR 69–81) compared with 65 years (IQR 55–74) for MV (table 1). A small proportion (15.5%) of patients implanted with BV were aged 18–64 years; 51.5% of patients 18–64 years were implanted with MV. The proportion of patients with a CCI Score of 1 or more was similar across valve types

**Table 1** Patient and hospital characteristics at index aortic valve replacement (AVR) procedure

Characteristic	18–64 years		65+ years		Total	
	BV	MV	BV	MV	BV	MV
	N (% of N)	N (% of N)	N (% of N)	N (% of N)	N (% of N)	N (% of N)
<b>Number of patients (N)</b>	1468	1996	8032	1881	9500	3877
<b>Patient characteristics</b>						
Age, median (Q1–Q3)	59 (53–63)	55 (47–61)	77 (73–82)	74 (69–80)	76 (69–81)	65 (55–74)
Sex						
Female	404 (27.5)	606 (30.4)	2946 (36.7)	751 (39.9)	3350 (35.3)	1357 (35.0)
Male	1064 (72.5)	1390 (69.6)	5086 (63.3)	1130 (60.1)	6150 (64.7)	2520 (65.0)
Charlson Score*						
0	791 (53.9)	1119 (56.1)	3389 (42.2)	750 (39.9)	4180 (44.0)	1869 (48.2)
1–2	484 (33.0)	682 (34.2)	3028 (37.7)	716 (38.1)	3512 (37.0)	1398 (36.1)
3+	193 (13.1)	195 (9.8)	1615 (20.1)	415 (22.1)	1808 (19.0)	610 (15.7)
Remoteness†						
Major city	965 (65.7)	1344 (67.3)	5446 (67.8)	1209 (64.3)	6411 (67.5)	2553 (65.8)
Inner regional	331 (22.5)	341 (17.1)	1758 (21.9)	449 (23.9)	2089 (22.0)	790 (20.4)
Outer regional‡	96 (6.5)	133 (6.7)	590 (7.4)	150 (8.0)	686 (7.2)	283 (7.3)
IRSD (quintile) §						
1 (most disadvantaged)	323 (22.0)	431 (21.6)	1691 (21.1)	447 (23.8)	2014 (21.2)	878 (22.7)
2	169 (11.5)	217 (10.9)	985 (12.3)	255 (13.6)	1154 (12.1)	472 (12.2)
3	152 (10.4)	221 (11.1)	951 (11.8)	212 (11.3)	1103 (11.6)	433 (11.2)
4	299 (20.4)	404 (20.2)	1663 (20.7)	344 (18.3)	1962 (20.7)	748 (19.3)
5 (least disadvantaged)	445 (30.3)	538 (27.0)	2475 (30.8)	544 (28.9)	2920 (30.7)	1082 (27.9)
<b>Hospital and episode characteristics</b>						
Concomitant procedures						
Other valve replacement	83 (5.7)	341 (17.1)	268 (3.3)	190 (10.1)	351 (3.7)	531 (13.7)
CABG¶	397 (27.0)	419 (21.0)	3899 (48.5)	825 (43.9)	4296 (45.2)	1244 (32.1)
Admission status						
Elective	1122 (76.4)	1498 (75.1)	6036 (75.1)	1419 (75.4)	7158 (75.3)	2917 (75.2)
Emergency	328 (22.3)	462 (23.1)	1852 (23.1)	425 (22.6)	2180 (22.9)	887 (22.9)
Not assigned	18 (1.2)	36 (1.8)	144 (1.8)	37 (2.0)	162 (1.7)	73 (1.9)
Payment status**						
Private	703 (47.9)	772 (38.7)	3606 (44.9)	709 (37.7)	4309 (45.4)	1481 (38.2)
Public	664 (45.2)	1034 (51.8)	3431 (42.7)	949 (50.5)	4095 (43.1)	1983 (51.1)
Other	100 (6.8)	187 (9.4)	993 (12.4)	219 (11.6)	1093 (11.5)	406 (10.5)
Hospital AVR volume††						
High (≥90)	529 (36.0)	755 (37.8)	3451 (43.0)	937 (49.8)	3980 (41.9)	1692 (43.6)
Low (<90)	939 (64.0)	1240 (62.1)	4581 (57.0)	944 (50.2)	5520 (58.1)	2184 (56.3)
<b>Person-years of follow-up</b>						
Total	6765.6	11795.7	32993.0	9244.2	39758.6	21039.9
Median (Q1–Q3)	4.1 (1.7–7.0)	5.9 (2.9–9.0)	3.6 (1.4–6.3)	4.4 (2.0–7.7)	3.6 (1.5–6.4)	5.1 (2.3–8.4)

Note: missing data where % values do not add to 100%.

\*Charlson Comorbidity Index calculated with a 1-year lookback, including index AVR admission and any admissions in the year prior

†Accessibility/Remoteness Index of Australia

‡Includes outer regional, remote and very remote

§IRSD: ABS Socio-Economic Index for Areas Index of Relative Social Disadvantage (SEIFA IRSD)

¶CABG: coronary artery bypass graft

\*\*Other payment status on separation includes compensation (workers, NSW motor vehicle accident and other), Department of Veterans Affairs and Medicare ineligible

††Median annual number of AVR procedures performed classified as high (≥90 per year) and low (<90 per year)

ABS, Australian Bureau of Statistics; BV, bioprosthetic valve; MV, mechanical valve.



(56.0% for BV, 51.8% for MV). Overall, 41.4% of AVR patients had coronary artery bypass graft (CABG) procedures in the same hospital episode, with this being more prevalent in patients aged 65 years and over (47.7%) than in younger patients (23.6%). A greater proportion of patients receiving BV (45.4%) than MV (38.2%) were treated as private rather than public patients. The clinical profiles of patients undergoing AVR were consistent over the study period (online supplemental table 2). Patients had a median of 4.0 years IQR (1.7–7.0) follow-up from their index AVR procedure (median 3.6; IQR 1.5–6.4; maximum 12 for BV; median 5.1; IQR 2.3–8.4; maximum 12 for MV), for a total of 60 798.5 years of follow-up.

### AVR procedure rates

Age standardized AVR rates increased from 17 per 100 000 persons in 2001/2002 to 22 per 100 000 persons in 2012/2013, an average 2.7% annual increase (figure 1). Rates of BV implantation doubled over the same period, from 9 to 18 per 100 000 persons (an average increase of 6.1% per year) and MV implantation rates decreased from 7 to 4 per 100 000 persons over the same period (4.7% annual decrease). Among patients aged 18–64 years, rates of MV implantation (4 per 100 000 persons) were more than twice those for BV implantation (2 per 100 000 persons) in 2001/2002 but these rates were similar by 2009/2010 (2 and 3 per 100 000 persons for BV and MV, respectively) (online supplemental table 3).

### Reoperation rates

In the first 5 years of follow-up, reoperation rates were lower for patients receiving BV compared with MV, across all ages (IRR: 0.65, 95% CI 0.51 to 0.83) and among patients aged 18–64 years (IRR: 0.77, 95% CI 0.52 to 1.14) and 65 years and over (IRR: 0.61, 95% CI 0.37 to 1.01) (table 2). However, the age-stratified findings were not statistically significant.

After 6–10 years of follow-up, the rate of reoperation among patients aged 18–64 years was significantly higher for patients implanted with BV compared with MV (IRR: 5.48, 95% CI 2.38 to 12.62), but this finding was not observed among patients aged 65 years and over (IRR: 0.86, 95% CI 0.45 to 1.65).

The cumulative incidence functions for reoperation showed a low, and similar, probability of reoperation for both valve types and age groups in the first 5 years after surgery (figure 2).

However, after approximately 5 years, there was a rapid increase in reoperation rates for patients aged 18–64 years receiving BV, such that by the 10-year mark, they had a threefold greater rate of reoperation than patients receiving MV (12% vs 4%). Among older patients, the rate of reoperation was consistently low. These findings were similar for both sexes (online supplemental figure 2).

### Incident cardiovascular event rates

Rates of incident cardiovascular events (hospital admission or death) were low across age groups and valve types (table 2). In the first 5 years of follow-up, across all ages, there were significant differences favoring BV for AMI, stroke and hemorrhage: (IRR: 0.77, 95% CI 0.60 to 0.98); (IRR: 0.75, 95% CI 0.63 to 0.89); (IRR: 0.66, 95% CI 0.54 to 0.82), respectively. Age-stratified analyses show that patients aged 18–64 years implanted with BV had lower rates of stroke (IRR: 0.40, 95% CI 0.27 to 0.60) and hemorrhage (IRR: 0.36, 95% CI 0.26 to 0.50) compared with those implanted with MV. Among older patients, those implanted with BV had lower rates of AMI and hemorrhage: (IRR: 0.71, 95% CI 0.53 to 0.96) and (IRR: 0.77, 95% CI 0.62 to 0.95), respectively.

After 6–10 years of follow-up, rates of AMI among patients aged 18–64 years were lower in those implanted with BV compared with MV (IRR: 0.49, 95% CI 0.26 to 0.94). There were no other significant differences in incident cardiovascular events among older patients.

### Cardiovascular and all-cause mortality rates

In the first 5 years of follow-up, rates of cardiovascular and all-cause mortality were lower in patients implanted with BV compared with MV, in the overall cohort (IRR: 0.90, 95% CI 0.82 to 0.98 and IRR: 0.90, 95% CI 0.84 to 0.97, respectively) and 65 years and over (IRR: 0.80, 95% CI 0.69 to 0.92 and IRR: 0.85, 95% CI 0.74 to 0.97). The age-stratified findings for younger patients were not statistically significant.

Between 6–10 years of follow-up, rates of cardiovascular and all-cause mortality across all ages and in patients aged 18–64 years did not differ significantly according to valve type. However, patients aged 65 years and over and implanted with BV had significantly lower rates of both all-cause and cardiovascular mortality (IRR: 0.69, 95% CI 0.59 to 0.81 and IRR: 0.85, 95% CI 0.75 to 0.95, respectively). The cumulative incidence curves for cardiovascular mortality were similar for both valve types for younger patients until approximately 6 years follow-up, where we saw a higher rate among patients implanted with BV (figure 3). Between 6–10 years of follow-up among older patients, those implanted with MV had slightly higher rates. Kaplan-Meier survival curves for all-cause mortality showed higher rates among young patients with BV and very similar rates for older patients (figure 4). Mortality findings were similar by sex (online supplemental figure 3 and online supplemental figure 4). The top causes of cardiovascular mortality are presented in online supplemental figure 5 and online supplemental figure 6 and crude incident event rates are reported in online supplemental table 4.

### Sensitivity analysis

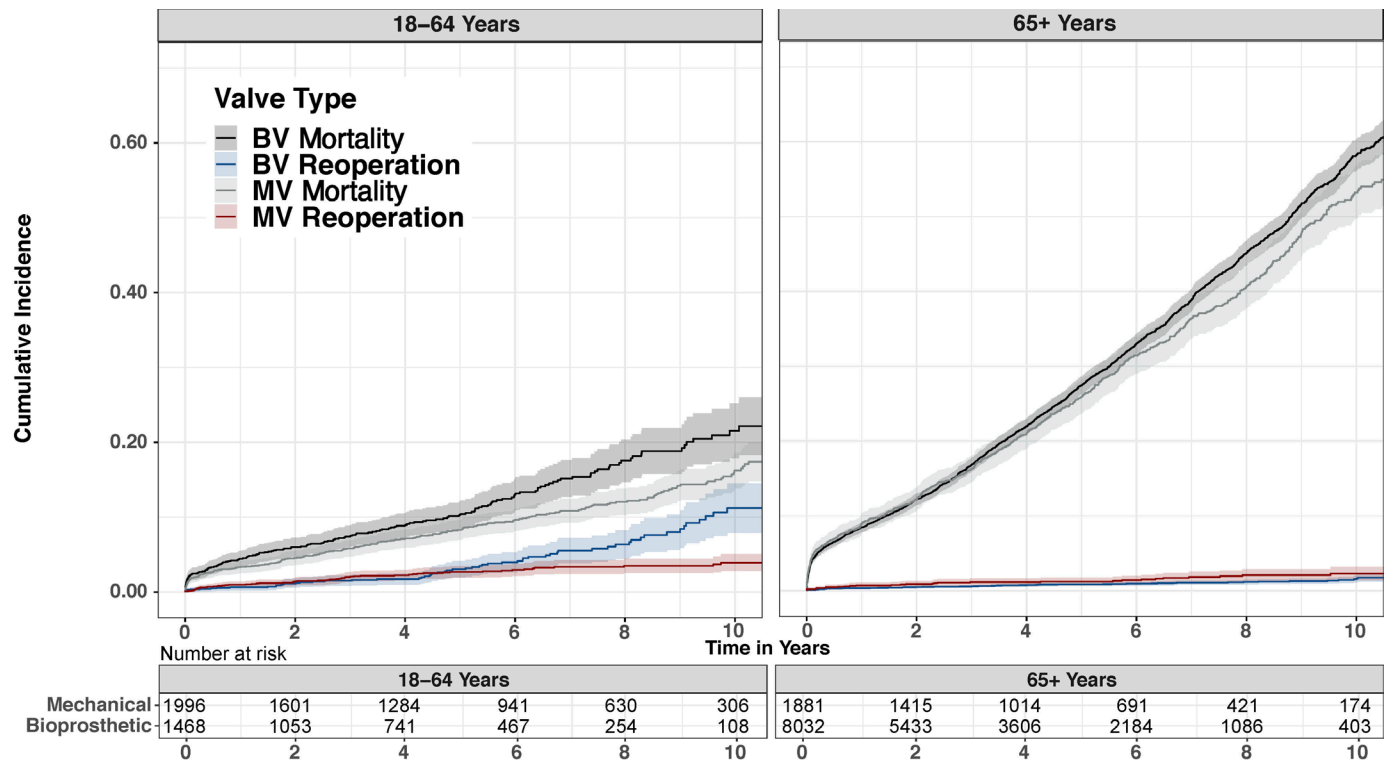
Mortality rates within 30 days of the index AVR procedure did not differ significantly between patients implanted with BV and MV, overall (3.5% vs 2.9%), for patients aged 18–64 years (2.1% vs 1.7%, respectively) or for older patients

**Table 2** Incident rate ratios (IRR) of outcomes following index aortic valve replacement (AVR) procedure between patients implanted with BV or MV, overall and stratified by follow-up time, and adjusted for age, sex and Charlson Comorbidity Index Score group

	≤5 years follow-up				6–10 years follow-up				0–10 years follow-up			
	Number of events		IRR (95% CIs)		Number of events		IRR (95% CIs)		Number of events		IRR (95% CIs)	
	BV	MV	BV	MV	BV	MV	BV	MV	BV	MV	BV	MV
<b>18–64 years</b>												
Reoperation	31	46		0.77 (0.52 to 1.14)	30	11		5.48 (2.38 to 12.62)	61	57		1.88 (1.29 to 2.74)
Readmissions												
AMI	18	36		0.75 (0.41 to 1.38)	10	28		0.49 (0.26 to 0.94)	28	64		0.68 (0.43 to 1.09)
Stroke	22	59		0.40 (0.27 to 0.60)	16	29		1.00 (0.50 to 2.04)	38	88		0.70 (0.50 to 0.98)
hemorrhage	33	102		0.36 (0.26 to 0.50)	18	59		0.58 (0.32 to 1.05)	51	158		0.53 (0.41 to 0.69)
Thromboembolism	21	37		0.68 (0.41 to 1.12)	14	23		1.14 (0.66 to 1.96)	35	60		1.01 (0.67 to 1.52)
Mortality (cardiovascular)	70	84		0.94 (0.72 to 1.23)	23	26		1.50 (0.99 to 2.27)	93	110		1.33 (1.12 to 1.59)
Mortality (all-cause)	125	144		0.89 (0.70 to 1.11)	55	80		1.25 (0.93 to 1.69)	180	224		1.29 (1.12 to 1.49)
<b>65+ years</b>												
Reoperation	55	21		0.61 (0.37 to 1.01)	17	9		0.86 (0.45 to 1.65)	72	30		0.78 (0.53 to 1.17)
Readmissions												
AMI	249	70		0.71 (0.53 to 0.96)	113	37		0.95 (0.66 to 1.36)	362	107		0.86 (0.67 to 1.10)
Stroke	347	90		0.82 (0.64 to 1.06)	132	43		0.85 (0.60 to 1.21)	479	133		0.90 (0.74 to 1.09)
hemorrhage	471	133		0.77 (0.62 to 0.95)	163	46		1.00 (0.69 to 1.44)	634	179		0.92 (0.76 to 1.12)
Thromboembolism	249	60		0.87 (0.65 to 1.17)	82	18		1.34 (0.84 to 2.14)	331	78		1.10 (0.91 to 1.33)
Mortality (cardiovascular)	919	239		0.80 (0.69 to 0.92)	280	105		0.69 (0.59 to 0.81)	1199	344		0.82 (0.72 to 0.95)
Mortality (all-cause)	1670	415		0.85 (0.74 to 0.97)	798	252		0.85 (0.75 to 0.95)	2468	667		0.89 (0.82 to 0.97)
<b>Total</b>												
Reoperation	86	67		0.65 (0.51 to 0.83)	47	20		2.75 (1.00 to 7.55)	133	87		1.25 (0.78 to 2.01)
Readmissions												
AMI	267	106		0.77 (0.60 to 0.98)	123	65		0.93 (0.71 to 1.23)	390	171		0.92 (0.74 to 1.14)
Stroke	369	149		0.75 (0.63 to 0.89)	148	72		0.98 (0.78 to 1.23)	517	221		0.95 (0.83 to 1.08)
hemorrhage	504	235		0.66 (0.54 to 0.82)	181	102		0.94 (0.73 to 1.20)	685	337		0.86 (0.70 to 1.06)
Thromboembolism	270	97		0.84 (0.69 to 1.01)	96	41		1.35 (1.05 to 1.72)	366	138		1.15 (1.01 to 1.30)
Mortality (cardiovascular)	989	323		0.90 (0.82 to 0.98)	303	131		0.92 (0.73 to 1.16)	1292	454		1.04 (0.92 to 1.18)
Mortality (all-cause)	1795	559		0.90 (0.84 to 0.97)	853	332		1.05 (0.94 to 1.18)	2648	891		1.10 (1.01 to 1.21)

NB: total follow-up time, patients were right censored at either death or end of follow-up, depending on which occurred first. Each cardiovascular event had separate follow-up times to include if the event, death or end of follow-up period occurred first.

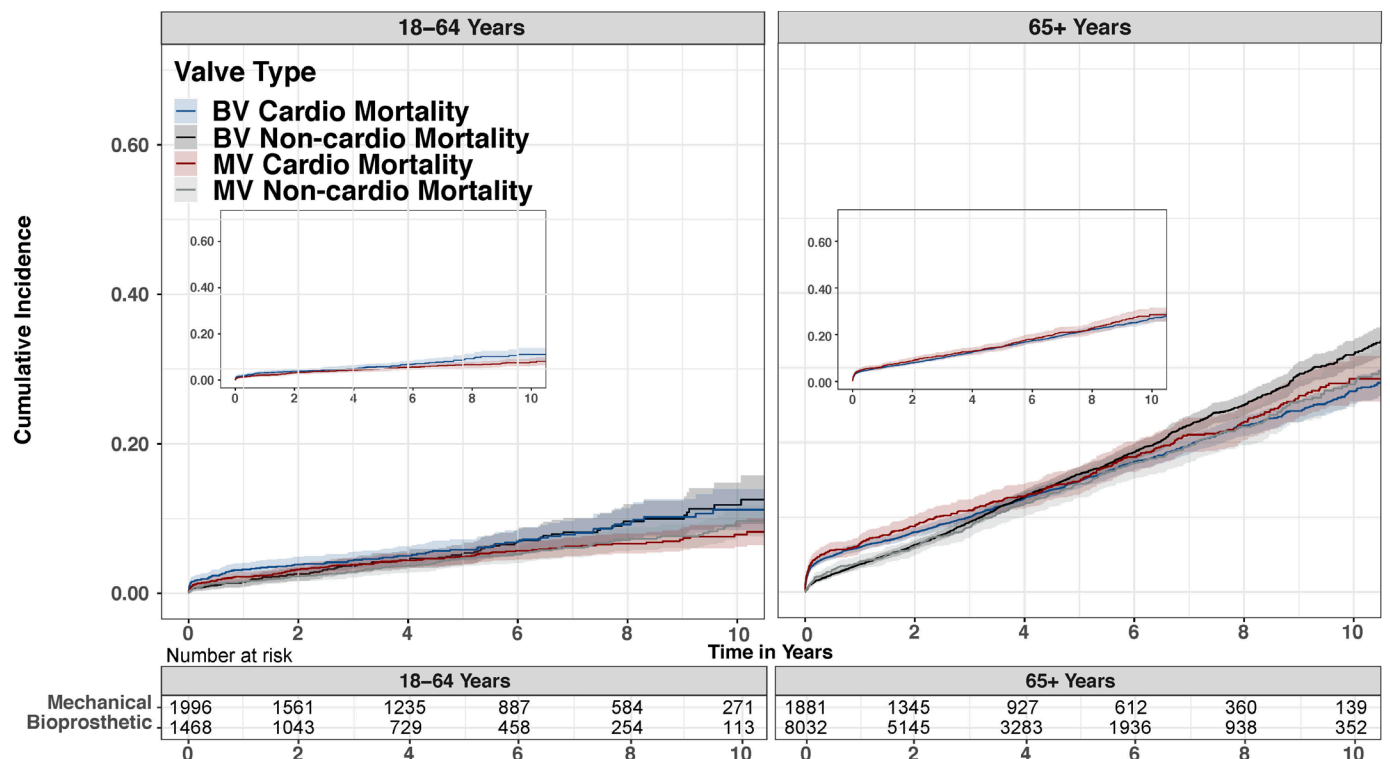
AMI, acute myocardial infarction; BV, bioprosthetic valve; MV, mechanical valve.



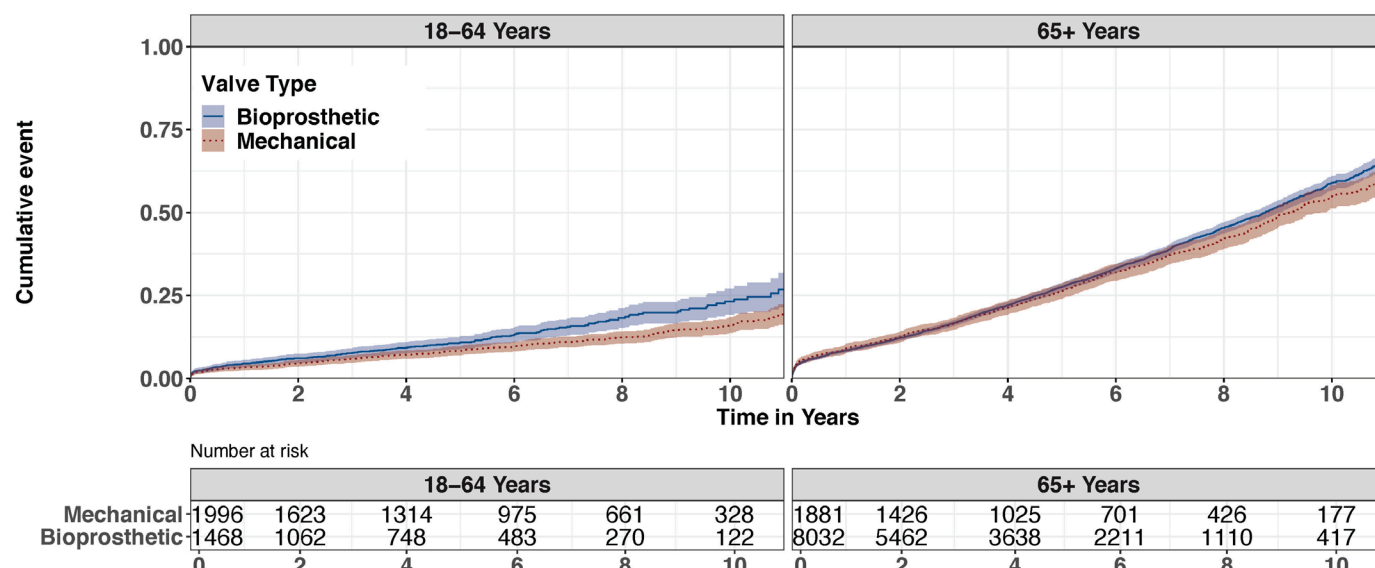
**Figure 2** Cumulative incidence curves for reoperation following index aortic valve replacement (AVR) procedure, by valve type and age group. BV, bioprosthetic valve; MV, mechanical valve.

(3.8% vs 4.2%, respectively). After excluding patients who died within 30 days of their index procedure ( $n=9167$  for BV and  $n=3764$  for MV), IRRs for cardiovascular mortality remained similar to the main analysis (online supplemental

table 5). We did not observe any notable differences in the results for reoperation and other cardiovascular events between the main and sensitivity analyses. Crude incident event rates are reported in online supplemental table 6.



**Figure 3** Cumulative incidence curves for cardiovascular mortality following index aortic valve replacement (AVR) procedure, by valve type and age group (inset represents cardiovascular mortality only by valve type).



**Figure 4** Time to all-cause mortality following index aortic valve replacement (AVR) procedure, by valve type and age group. BV, bioprosthetic valve; MV, mechanical valve.

## DISCUSSION

In this whole-of-population observational cohort study, we showed that increasing rates of surgical AVR are driven predominantly by large increases in BV implants in older patients and marginal increases in younger patients. Importantly, we found that the outcomes of AVR according to valve type vary markedly with patient age. Among patients aged 18–64 years, those implanted with BV rather than MV had a lower risk of stroke and hemorrhage in the first 5 years, and a lower risk of AMI and dramatically increased risk of reoperation after 5 years. Older patients implanted with BV had lower risk of AMI and hemorrhage in the first 5 years, and a significantly lower risk of cardiovascular and all-cause mortality both up to and after 5 years.

Our reoperation rates are consistent with recent systematic reviews.<sup>6,25</sup> The Veterans Affairs RCT comparing long-term survival and valve-related complications by valve type<sup>10</sup> reported that 15-year reoperation was significantly higher for patients receiving BV. More recent trials have reported similar results for 20-year<sup>47</sup> and 17-year reoperations.<sup>24</sup> This highlights the concern around using BV in younger patients, given the increasing risk of morbidity and mortality with each subsequent AVR procedure.<sup>7</sup> However, our findings suggest that the gains of valve durability with MV may be achieved at the cost of increased incidence of hemorrhage and stroke in the first 5 years postprocedure.

We found that patients aged 18–64 years implanted with BV had significantly higher cardiovascular and all-cause mortality for 0–10 years of follow-up. This was consistent with a recent systematic review of studies in patients aged 50–70 years.<sup>26</sup> A previous RCT<sup>24</sup> also reported significantly higher all-cause mortality associated with use of BV in patients aged 45–54 years, but not in patients aged 55–64 years. The higher mortality

rate in younger patients implanted with BV in our study may be linked to valve selection being based on the perceived likelihood of survival, with newer guidelines recommending use of BV for frail patients. Patients in our study 18–64 years of age who received BV rather than MV had a slightly higher number of comorbidities, but were less likely to have a concomitant CABG procedure. It is possible the higher mortality rate observed in patients implanted with BV may be explained by greater clinical complexity. However, our sensitivity analysis excluding patients who died within 30 days of the procedure—presumably those with highest baseline risk of mortality—also confirmed a higher rate of mortality for younger patients implanted with BV. While we did not observe a significant difference in mortality for patients aged 18–64 years within follow-up time (0–5 years, or 6–10 years), the significant effect over 0–10 years of follow-up period is likely due to increased statistical power.

Among older patients, we found that use of BV rather than MV was associated with a significantly lower rate of cardiovascular and all-cause mortality. As patients implanted with BV had a lower number of Charlson comorbidities, this mortality difference may also reflect differences in patient clinical complexity, as well as the associated risk of anti-coagulants. Some of the differences may also be due to postoperative mortality following reoperation. The existing evidence regarding mortality by valve type for older patients—who make up the vast majority of patients in most previous studies—is inconsistent. The Veterans Affairs Trial,<sup>10</sup> in which 47.2% of patients were aged over 60 years, reported better overall survival for patients receiving MV. In another RCT<sup>23</sup> among middle-aged to older patients



(aged 55–70 years), the two valve groups had similar survival rates. Observational studies using propensity score matching methods have variously found that overall survival is better for patients receiving MV or that there is no difference in mortality between valve types,<sup>22 48–50</sup> which was also the conclusion of a systematic review.<sup>25</sup> The inconsistencies in findings may reflect variation in age inclusion criteria and patient selection between studies.

Our findings on hemorrhage are also consistent with previous studies<sup>10 11 19 23 27 47 51–56</sup> and guidelines on the expected risk of placing patients receiving MV on anticoagulation therapy.<sup>4 7</sup> Hemorrhage is considered the main driver of mortality, suggesting the risk of reoperation is favored when compared with the known risk of anticoagulant use.<sup>25</sup> However, our results for younger patients do not support this, although patients aged 18–64 years implanted with MV had a higher incidence of hemorrhage.

Uniquely, we observed a higher incidence of AMI among younger patients receiving MV only after 5 years of follow-up. This effect remained significant in our sensitivity analysis excluding patients who died within 30 days. The median follow-up time to AMI was 3.4 years (IQR 1.4–5.4), and we hypothesize that as a result of increased use of BV in more recent years, younger patients implanted with BV in our cohort had a shorter median follow-up time (4.1 years, IQR 1.7–7.0) than those implanted with MV (5.9 years, IQR 2.9–9.0), and so BV patients had less follow-up time in which to experience AMI. Conversely, among older BV patients, we observed a lower risk of AMI within the first 5 years of follow-up.

## LIMITATIONS

The linked administrative health data used in this study are valuable for investigating outcomes following surgery because they provide full population coverage. However, they include only limited information on patient risk factors and clinical complexity, limiting our ability to explore how patient selection, as well as valve choice, influenced the observed differences in outcomes between patients who received BV and MV. A further limitation of the use of administrative data was that it was not possible to know whether the identified index procedure was in fact the first AVR surgery for each patient. Given the average interval between AVR procedures ranges from 5 years to 10 years, it was not feasible to use a ‘wash-out’ period to exclude patients who may have had an AVR procedure prior to the study period. We attempted to mitigate this limitation by using the ACHI reoperation for cardiac procedures code (38 640–00) to identify and exclude reoperations. Further, because we used hospital data for one Australian state only, out-of-state hospitalizations, reoperations or death may have been missed.

## CONCLUSIONS

Our study provides real-world evidence to examine the impact of AVR valves on patient reoperation, cardiovascular events and mortality. It adds to the consensus that use of BV in younger patients increases risk of reoperation, while MV presents risks associated with use of anticoagulation therapy. Our findings urge caution and indicate that choice of valve implant in patients requires thorough evaluation of patient factors influencing both short-term outcomes and the longer-term risks of reoperation, stroke, hemorrhage and mortality. These results from Australia are important considering widespread worldwide adoption of TAVRs in lower-risk groups, and the lack of information about their outcomes, especially in younger patients. Ongoing studies using real-world data as it accumulates are required to provide this evidence.

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