Propensity Score Matched Analysis of Mechanical vs. Bioprosthetic Valve Replacement in Patients With Previous Stroke

Shao-Wei Chen, MD; Victor Chien-Chia Wu, MD; Yu-Sheng Lin, MD; Ching-Chang Chen, MD; Dong-Yi Chen, MD; Chih-Hsiang Chang, MD; Pao-Hsien Chu, MD; Pei-Chi Ting, MD; An-Hsun Chou, MD, PhD; Tien-Hsing Chen, MD

Background: This study compared the long-term outcomes of prosthetic heart valve replacement with mechanical or bioprosthetic valves in patients with prior stroke.

Methods and Results: In total, 1,984 patients with previous stroke who had received valve replacement between 2000 and 2011 were identified using the Taiwan National Health Insurance Research Database. Propensity score matching analysis was used. Ultimately, 547 patients were extracted from each group and were eligible for analysis. On survival analysis, the risks of all-cause mortality and recurrence of stroke were similar. The incidence of major bleeding was greater in the mechanical valve group than in the bioprosthetic valve group (P=0.040), whereas no difference was observed in re-do valve surgery. On subgroup analysis, the bioprosthetic valve was favored for older age (≥60 years) and previous gastrointestinal (GI) bleeding patients. The mechanical valve, however, was favored for younger patients (<60 years).

Conclusions: In patients with previous stroke, bioprosthetic valves had a lower incidence of complications connected to major bleeding than did the mechanical valves. Survival and stroke recurrence rates, however, did not differ between the 2 groups. We recommend bioprosthetic valves for patients >60 years or who have a history of GI bleeding.

Key Words: Long-term prognosis; Old stroke; Valve replacement

Bioprosthetic valves have been increasingly used in valve replacement surgery in the recent 20 years. In a recent paper, however, titled “Mechanical or biologic prostheses for aortic-valve and mitral-valve replacement” in New England Journal of Medicine, Goldstone et al, using data from an administration database in California, reported that mechanical prosthetic valve replacement was associated with significantly better survival than bioprosthetic valve replacement.¹ This landmark study raised the concern that there is in fact limited evidence supporting the implantation of bioprosthetic valves in diseased or elderly patients. The choice of prosthetic heart valve during valve replacement surgery is between the bioprosthetic valve and the mechanical valve for the majority of patients. Determining which to use is primarily dependent on the age of the patient at the time of the valve replacement.²³ The Veterans Affairs randomized trial, however, determined that 50% of deaths were not related to prosthetic valve complications and emphasized that comorbidity was key in determining patient outcomes.⁴ Furthermore, the indications for valves in patients with a specific comorbidity are still controversial, similar to the previous debate concerning dialysis patients.⁵

Patients who have previously had a stroke when undergoing valve surgery are not uncommon. Cardiac surgery in patients with previous stroke is associated with increased mortality and an increased risk of postoperative stroke.⁶⁹ A history of stroke may affect long-term outcome after valve replacement, and influences the decision making for the type of valve selection. Few studies, however, have
reported the long-term outcomes of cardiac surgery according to valve replacement type in patients with previous stroke. Furthermore, valve selection in this high-risk patient group has not been previously addressed. Evaluating the balance of risk and benefits between bleeding because of anticoagulant therapy and prosthetic valve structure deterioration is complex and multifactorial in this specific population. Therefore, the aim of this nationwide population-based cohort study was to compare mortality, recurrence of stroke, major bleeding, and re-do valve surgery between bioprosthetic and mechanical valves using propensity score matching analysis.

**Methods**

**Data Source**

The data were obtained from the Taiwan National Health Insurance Research Database (NHIRD). Taiwan has a mandatory government-operated universal health insurance program, the National Health Insurance (NHI) program, which was launched in 1995 and covers almost all (99%) of the approximately 23 million residents of Taiwan as of December 2015, providing comprehensive medical care coverage and reimbursing the medical expenditure of all medical services for all Taiwanese people. The NHIRD is derived from the NHI program; thus, NHI claims data accurately represent the Taiwan population, with only minimal data omitted and a small participation bias present. The claim data for each patient can be linked using a consistent data encryption process, which allows for continual tracking of all of the claims of any individual within the NHI program. All personal information in the NHIRD is anonymized and de-identified to protect privacy; thus, this study was exempt from a full review by the Ethics Institutional Review Board of Chang Gung Memorial Hospital.

**Subjects**

We examined the NHIRD inpatient records of all patients admitted for valve replacement between January 2000 and December 2011. Both Taiwan NHI procedure codes (68016, 68017, and 68018), which are used for claims for reimbursement, and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure codes (35.21, 35.22, 35.23, 35.24), were used to extract data for patients who received a valve replacement (Figure 1A). In total, 21,547 patients who underwent valve replacement in any position during the study period in...
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During the study period (Figure 1B). To minimize potential selection bias, we calculated a propensity score from selected variables (Table 1) and matched each patient in the bioprosthetic valve group with each patient in the mechanical valve group. Finally, 547 patients from each group were identified and were eligible for analysis.

### Comorbidity and Outcome

Preoperative comorbidity and surgery details were identified using ICD-9-CM and NHI procedure codes for the index hospitalization and prior hospitalizations (Table S1). We obtained inpatient records for ≥3 years before the index admission for all patients to track the history of comorbidity. For example, we enrolled patients in 2000 and identified comorbidities from their medical records.

### Table 1. Clinical and Surgical Subject Characteristics vs. PSM Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before PSM</th>
<th>After PSM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Bioprosthetic valve</td>
</tr>
<tr>
<td>n</td>
<td>1,984</td>
<td>606</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.7±13.2</td>
<td>67.4±11.6</td>
</tr>
<tr>
<td>Male gender</td>
<td>1,120 (56.5)</td>
<td>349 (56.7)</td>
</tr>
<tr>
<td>Stroke type</td>
<td>1.729 (87.1)</td>
<td>534 (88.1)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>185 (9.3)</td>
<td>51 (8.4)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>70 (3.5)</td>
<td>21 (3.5)</td>
</tr>
<tr>
<td>Both</td>
<td>2.7±3.0</td>
<td>3.3±3.4</td>
</tr>
<tr>
<td>Time from last stroke (years)</td>
<td>0.12</td>
<td>0.743</td>
</tr>
<tr>
<td>Valve disease etiology</td>
<td>667 (33.6)</td>
<td>180 (29.7)</td>
</tr>
<tr>
<td>Rheumatic heart</td>
<td>335 (16.9)</td>
<td>96 (15.8)</td>
</tr>
<tr>
<td>Degeneration and others</td>
<td>982 (49.5)</td>
<td>330 (54.5)</td>
</tr>
</tbody>
</table>

Data given as mean±SD or n (%). AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; MVR, mitral valve replacement; PAD, peripheral artery disease; PSM, propensity score matching; TV, tricuspid valve.

Taiwan were identified. Of these, 2,016 patients (9.36%) with a history of stroke were identified from ICD-9-CM procedure codes 430.xx–437.xx. Patients were excluded if they were aged <18 years, had missing demographic or surgical information, or it was not their first admission for valve replacement. In total, 1,984 adult patients with a history of stroke were identified for first-time valve replacement.

Valve type was further identified using ICD-9-CM procedure codes (bioprosthetic valve codes 35.21 and 35.23 and mechanical valve codes 35.22 and 35.24). Patients were more likely to undergo valve replacement with a mechanical valve (1,378 patients; 69.5%) than with a bioprosthetic valve (606 patients; 30.5%). The bioprosthetic valves, however, were increasingly used in valve replacement surgery during the study period (Figure 1B). To minimize potential selection bias, we calculated a propensity score from selected variables (Table 1) and matched each patient in the bioprosthetic valve group with each patient in the mechanical valve group. Finally, 547 patients from each group were identified and were eligible for analysis.

**Comorbidity and Outcome**

Preoperative comorbidity and surgery details were identified using ICD-9-CM and NHI procedure codes for the index hospitalization and prior hospitalizations (Table S1). We obtained inpatient records for ≥3 years before the index admission for all patients to track the history of comorbidity. For example, we enrolled patients in 2000 and identified comorbidities from their medical records.
The outcomes of interest in this study were all-cause mortality, recurrence of stroke, re-do valve surgery, and major bleeding. Death records and records of withdrawal from the NHI program were used to identify mortality, as validated in previous studies. Major bleeding was defined as any admission after the index admission with an ICD-9-CM diagnosis code 430*–432*, 578*, 719.1*, 423.0, 599.7, 626.2, 626.6, 626.8, 627.0, 627.1, 786.3, 784.7, and 459.0 as the principal diagnosis. The date of admission for valve replacement was defined as the index hospitalization. The patients were followed from the index admission, however, was longer in the bioprosthetic valve group (3.3 vs. 2.4 years). Regarding disease etiology by valve, the bioprosthetic valve group had a lower incidence of rheumatic heart disease and infective endocarditis but a higher incidence of degeneration pathology than did those in the mechanical valve group. The time between last stroke and index admission, however, was longer in the bioprosthetic valve group (3.3 vs. 2.4 years). Regarding disease etiology by valve, the bioprosthetic valve group had a lower incidence of rheumatic heart disease and infective endocarditis but a higher incidence of degeneration pathology than did those in the mechanical valve group. No differences, however, in demographic and surgery details were observed between the 2 groups (Table 1).

### Statistical Analysis

We compared clinical and surgical characteristics between the 2 groups (bioprosthetic valve vs. mechanical valve) using chi-squared test for categorical variables or t-test for continuous variables. Rates (categorical parameter) or levels (continuous parameter) of postoperative complications between the 2 groups were compared on logistic regression analysis and linear regression analysis, respectively. Cumulative incidence of primary outcomes (i.e., all-cause mortality) was compared between the groups, and log-rank test used to compare group differences. The risk factors of in-hospital mortality after valve replacement in patients with previous stroke before matching were investigated using multivariable logistic regression analysis. Finally, the causes of major bleeding were compared between the 2 groups using chi-squared test. Statistical analysis was carried out using SPSS 22 (IBM SPSS, Armonk, NY, USA).

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**Subject Characteristics**

Before matching, patients with bioprosthetic valve replacement were older and had a higher prevalence of comorbidity (e.g., hypertension, heart failure, coronary artery disease, atrial fibrillation, gastrointestinal (GI) bleeding history, and higher Charlson score) than did those in the mechanical valve group. The time between last stroke and index admission, however, was longer in the bioprosthetic valve group (3.3 vs. 2.4 years). Regarding disease etiology by valve, the bioprosthetic valve group had a lower incidence of rheumatic heart disease and infective endocarditis but a higher incidence of degeneration pathology than did the mechanical valve group. No differences, however, in demographic and surgery details were observed between the 2 groups after propensity score matching (Table 1).

**In-Hospital Mortality and Postoperative Complications**

Table 2 lists the early results of valve replacement in patients with previous stroke according to valve type before and after matching. The in-hospital mortality rate of valve replacement surgery was 10.2%, and the incidence rate for postoperative stroke was 13.4%. Before propensity score matching, a higher incidence of postoperative sepsis, more prolonged in-hospital stay, longer intensive care unit stay, and higher in-hospital medical expenditure was observed in the bioprosthetic valve group, but the incidence of postoperative short-term outcomes was similar between the 2 groups after propensity score matching.

**Primary Outcomes During Follow-up**

Figure 2 illustrates the cumulative incidence of primary outcomes. The mortality rate was 40.6% and 40.0% (P=0.912, Figure 2A) and the incidence of recurrent stroke...
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In terms of the proportion of intracerebral hemorrhage and genitourinary bleeding (Figure 3).

Risk of In-Hospital Mortality Before Matching

The risk factors for in-hospital mortality in patients with previous stroke before matching were advanced age; infective endocarditis, degeneration, or other as valve disease etiology (compared with rheumatic heart); heart failure; dialysis; GI bleeding history; valve type of mitral valve replacement alone (compared with aortic valve replacement alone), additional coronary artery bypass grafting (CABG) or aortic surgery (Table S2).
We further identified the age at valve replacement and that at which a history of previous GI bleeding might influence the selection of valve type.

Stroke is a manifestation of cardiovascular disease and has a negative impact on outcome in surgical patients, potentially leading to long-term subsequent complications and mortality. Preoperative stroke or neurological dysfunction is a known risk factor for cardiac surgery and has been included in all current risk assessment models. Recently, Bottle et al demonstrated that preoperative stroke was associated with perioperative mortality doubling, increasing the risk of postoperative stroke and prolonged hospital stay in 62,104 patients with CABG. Limited information is available, however, on the long-term outcomes of valve replacement surgery in patients with previous stroke. Furthermore, no previous studies have focused on the impact of medical history of stroke on outcomes by comparing bioprosthetic and mechanical valves. We next examined the history of valve disease guidelines for patients with specific comorbidities. The American Heart Association/American College of Cardiology (AHA/ACC) valvular heart disease guidelines of 1998 previously featured a specific indication for valve selection in specific populations, with class IIa recommended for mechanical complications associated with major bleeding compared with the mechanical valve, but survival, stroke recurrence, and re-do valve surgery did not differ between the 2 groups. We further identified the age at valve replacement and that at which a history of previous GI bleeding might influence the selection of valve type.

**All-Cause Mortality During Follow-up**

On subgroup analysis, the effect of valve type (bioprosthetic vs. mechanical) was neutral on all-cause mortality in terms of gender, stroke type, years to prior stroke, valve disease etiology, atrial fibrillation, valve type, and 3 additional surgeries. This suggests that younger patients might benefit more from mechanical valve surgery than would older patients (P for interaction=0.037). In contrast, patients with a history of GI bleeding might benefit more from bioprosthetic valve surgery than would those without (P for interaction=0.047; Figure 4).

**Discussion**

In this study, we compared the outcomes of mechanical valve vs. bioprosthetic valve replacement in patients with previous stroke during a 12-year period using a national database that covers nearly the entire population of Taiwan. Finally, data on 547 patients from each group were extracted and analyzed using propensity score matching to ensure that the baseline patient characteristics were similar. The in-hospital mortality rate was relatively high at 10.2%, and the incidence of postoperative stroke was 13.4%. To our knowledge, this is the first study to compare the long-term outcomes of valve replacement in this specific patient group. We found that the bioprosthetic valve resulted in superior outcome with regard to reducing the complications associated with major bleeding compared with the mechanical valve, but survival, stroke recurrence, and re-do valve surgery did not differ between the 2 groups. We further identified the age at valve replacement and that at which a history of previous GI bleeding might influence the selection of valve type.

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**Figure 4.** Hazard ratios for all-cause mortality vs. replacement valve type. AVR, aortic valve replacement; CABG, coronary artery bypass grafting; GI, gastrointestinal; MVR, mitral valve replacement.
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The choice of valve prosthesis type is based on the consideration of several factors, including the age at valve implantation, the potential need for long-term anticoagulation or reoperation, and, most vitally, patient preference. The balance between the risk of reoperation for structural valve degeneration in bioprosthetic valves and the risk associated with long-term anticoagulant therapy should be discussed with the patient. The ACC/AHA 2014 guidelines for valvular heart disease recommend using mechanical valves for patients aged <60 years, and bioprosthetic valves for patients >70 years. Using either bioprosthetic or mechanical valves is reasonable in patients between 60 and 70 years of age. In the basis of the present study, we recommend a bioprosthetic valve for patients with previous stroke and age >60 years. This corresponds to the current trend for bioprosthetic valves in patients aged >60 years. Further investigation in the form of prospective randomized multicenter studies, however, is warranted.

According to the present study, bioprosthetic valves are associated with superior outcomes in reducing major bleeding compared with mechanical valves. This corresponds to other studies that have directly compared bioprosthetic valve and mechanical valve use in the general population. No differences, however, in all-cause mortality or recurrent stroke in patients with a history of stroke were evident. The causes of major bleeding in patients with a history of stroke are complex and include poor general health, comorbidity and stress ulcer. We further identified that, of the major bleeding events, GI bleeding and respiratory bleeding occur more often in the mechanical valve group than in the tissue valve replacement group. Furthermore, on subgroup analysis, a history of GI bleeding was associated with superior long-term outcome in the bioprosthetic valve group relative to the mechanical valve group.

GI bleeding after cardiac surgery is a common complication and is associated with high mortality and morbidity. Predictive factors must be identified early and preventive measures must be applied to ensure the best possible outcomes. Mori et al noted an ethnicity effect in bleeding after valve surgery and recommended lower international normalized ratio (INR) of prothrombin time after prothetic heart valve replacement surgery to prevent hemorrhagic complications in Asian patients. Krawiec et al reported that instances of GI bleeding after cardiac surgery are increasing and the most common cause is peptic ulcer, which is related to Helicobacter pylori (H. pylori) infection. They recommended identification of this risk factor during preoperative evaluation alongside a test for H. pylori to decrease the risk of GI bleeding. Based on the present findings, preoperative GI bleeding history critically affected in-hospital mortality after valve replacement surgery in patients with previous stroke. Additionally, preoperative GI bleeding may have influenced valve type selection. Routine preoperative risk evaluation of GI bleeding including tests for occult blood in stool and H. pylori infection should be performed. Additionally, use of a GI tract endoscope in high-risk patients is reasonable and potentially beneficial because it may provide information relevant to valve type selection. Careful monitoring of INR after valve surgery and use of aggressive preventive agents such as a proton pump inhibitors in patients who have received mechanical valves are justified.

Study Limitations
Some limitations should be noted. First, the NHIRD does not include data on ventricular ejection fraction, neurological status, or Society of Thoracic Surgeon (STS) score. The lack of these data may have influenced the analysis and the reported outcomes. Furthermore, the NHIRD held no data regarding other prosthetic valve-related parameters such as valve size and brand. We, however, adopted alternative variables as proxies for unavailable information, such as congestive heart failure, which is associated with left ventricular ejection fraction. Moreover, the accuracy of the NHIRD NHI procedure codes and ICD-9-CM has been validated in patients with major cardiovascular disease and cardiac surgery; the diagnosis code of stroke in NHIRD was also validated; the database appears to be a valid resource for population research in cardiovascular research and is highly accurate in patients with intervention. Second, the duration of follow-up might not have been long enough to demonstrate the difference in re-do valve surgery because structural valve deterioration usually occurs >10 years after bioprosthetic valve implantation. Third, no data on anticoagulant or antiplatelet medication type or dosage during follow-up were available for use in this study; the influence of this lack of data on the identified outcomes of major bleeding should be acknowledged and evaluated.

Finally, this study was conducted in patients based in south Asia. The incidence of rheumatic heart disease in developing countries and industrialized countries is higher than in western countries and thus the results may not be directly extrapolated to other countries. Despite these limitations, we believe that the present study provides a valuable contribution to the outcome analysis of valve replacement in patients with previous stroke.

Conclusions
Compared with the mechanical valve replacement group, the bioprosthetic valve replacement group had a lower incidence of complications related to major bleeding. Survival and recurrence of stroke during follow-up, however, did not differ between these 2 groups.

In conclusion, for patients with previous stroke, we recommend the bioprosthetic valve for patients >60 years old or who have a history of previous GI bleeding. The present data provide further information on valve selection in patients with specific comorbidity. The final decision-making process, however, should still take into account patient values and preferences in a detailed discussion.

Acknowledgments
The study was based on data from the NHIRD provided by the National Health Insurance Administration of the Ministry of Health and Welfare, Taiwan, and managed by the National Health Research Institutes of Taiwan. The interpretation and conclusions contained, however, do not represent those of the National Health Insurance Administration, Ministry of Health and Welfare, or the National Health Research Institutes of Taiwan. S.-W.C. and T.-H.C. had full access to all the data used in the study and take responsibility for the integrity of the data and the accuracy of analysis. The authors thank Alfred Hsing-Fen Lin for his assistance with statistical analysis.
Disclosures
The authors declare no conflicts of interest.

References

Supplementary Files

Supplementary File 1
Figure S1. Sensitivity test: Kaplan-Meier survival curves for stroke without transient ischemic stroke.

Table S1. ICD-9-CM codes

Table S2. Risk of in-hospital mortality after valve replacement in patients with previous stroke before PSM (n=1,984)