Scientific Research Publishing

World Journal of Cardiovascular Diseases, 2019, 9, 149-157
http://www.scirp.org/journal/wjcd
ISSN Online: 2164-5337
ISSN Print: 2164-5329

# Risk Factors for Starr-Edwards Prosthetic Valve Dysfunction: New Insights into an Old Prosthesis

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**How to cite this paper:** Raymundo-Martinez, G.I.M., Gopar-Nieto, R., Araiza-Garaygordobil, D., Martínez-Amezcua, P., Cabello-Lopez, A., Rodríguez-Chavez, L.L. and Espinola-Zavaleta, N. (2019) Risk Factors for Starr-Edwards Prosthetic Valve Dysfunction: New Insights into an Old Prosthesis. *World Journal of Cardiovascular Diseases*, **9**, 149-157.
https://doi.org/10.4236/wjcd.2019.93014

**Received:** February 10, 2019
**Accepted:** March 8, 2019
**Published:** March 11, 2019



## Abstract

**Background:** Starr-Edwards prosthetic valves were used for valve replacement, but due to their high thrombogenic risk, they were withdrawn from market. Nevertheless, there are some cases of Starr-Edwards prosthetic valve carriers that have shown long-term survival reaching up to 50 years. The objective of this study was to determine survival in 12 patients with mechanical Starr-Edwards prosthetic valve and risk factors for predicting valve dysfunction. **Methods:** Cross-sectional study of patients who had valve replacement with a Starr-Edwards prosthetic valve in a single center from 1968 to 1990. Socio-demographic data, valvular dysfunction variables and mortality were recorded. Logistic regression models to determine valvular dysfunction were constructed. Survival was analyzed with Cox regression and Kaplan-Meier survival curves. **Results:** A total of 12 patients were analyzed. The median age was 59 years (48.5 - 64). Eleven patients had normal right and left ventricular function. The most common cause of valve replacement was rheumatic valve disease (75%) and it was more frequently in mitral position (50%). Valvular dysfunction was detected in 3 patients (25%). Atrial fibrillation had the highest association with valvular dysfunction (P = 0.005). Stroke was seen in 25% of the population and the overall mortality was 33.3%. **Conclusions:** The survival of patients with Starr-Edwards prosthetic valve was 66.66% in the 50-year follow-up. Atrial fibrillation had the highest association with prosthetic valvular dysfunction.

**Keywords**

Prosthetic Valve, Starr-Edwards, Survival, Valvular Heart Disease

## 1. Introduction

Rheumatic heart disease (RHD) is one of the leading diseases in low and middle-income countries and accounts for up to 1.4 million deaths per year. Nowadays, RHD has become less prevalent, accounting for 22% of all the etiologies, but in third world countries, rheumatic fever remains the primary cause of valvular heart disease [1] [2]. In developed world, the degenerative etiology has become the most common cause of valvular heart disease [3] [4]. From 1963 until the late 90's, Starr-Edwards prosthetic valves were used for the treatment of valvular heart disease, but these prostheses were replaced by safer and less thrombogenic prostheses. However, there are still many patients with Starr-Edwards prosthetic valves and little is known about their survival and risk of prosthetic valve dysfunction. There are case reports of patients that have lived until 50 years without any fatal events [1] [3]. Only in two cases it was reported a loss of structural integrity in mitral position. Gögjie *et al.* found a duration of 30 years, and recommended that after 20 years of durability, it must not be removed except there is another reason for cardiac surgery other than dysfunction [4]. Hans *et al.* reported 645 patients that were taken valvular surgery with Starr-Edwards prosthesis with a follow-up of 21 years. They reported a lineal rate of complications expressed in percentage of patients per year of 2% ± 0.2 for thromboembolism, 2.1% ± 0.2 for bleeding related to vitamin K antagonists, 0.5% ± 0.1 for infective endocarditis, 0.3% ± 0.1 for other complications, and total of adverse events of 4.8% ± 0.1 [5]. They did not find thrombotic occlusions or valvular dysfunction, during his follow-up [6]. Ikizler *et al.* reported a durability of the prosthetic valve of 34 years, even without anticoagulation and no thrombotic event [4]. It has been informed that the time free of thromboembolism related to prosthetic valve was 59% at 25 years of follow-up. Goedje and colleagues have reported a survival of 16.6% in patients with Starr-Edwards prosthetic valve in aortic position for over 30 years [4]. Orszulak followed 1100 patients with Starr-Edwards aortic prosthetic valve. In-hospital mortality at 30 days was 6.2%, and survival at 5 years was more common in men, and it was 76.9% and at 10, 15 and 20 years, was 59.8%, 44.85% and 31.2%, respectively. The purpose of this study was to determine the survival in a series of patients with Starr-Edwards prosthetic valves and to analyze the risk factors predicting prosthetic valvular dysfunction.

## 2. Methods

This is a retrospective study conducted from January to December 2017 in patients with Starr-Edwards prosthetic valves of the National Institute of

Cardiology Ignacio Chávez in Mexico City, implanted from 1968 to 1990. These cases were identified using the electronic health record of the study hospital.

Gender, age, weight and height, background of cigarette smoking, hypertension, diabetes mellitus, atrial fibrillation, atrial flutter, stroke, pacemaker, coronary artery disease, New York Heart Association (NYHA) functional class were recorded as demographic and clinical history data. Among laboratory studies collected were glycosylated hemoglobin, hemoglobin, internalized normalized ratio (INR), lipid profile and NT pro BNP. Among the studied variables of valve dysfunction were the presence of atrial fibrillation, mitral position, coronary artery disease, INR, age above 65 years, atrial flutter, diabetes mellitus, left ventricular ejection fraction below 40% and systemic arterial hypertension.

### Statistical Analysis

Categorical variables were reported as frequencies and proportions. For continuous variables, Shapiro-Wilk normality test was performed to describe them as parametric (mean, standard deviation, minimum-maximum) or nonparametric (median, interquartile range, minimum and maximum). We constructed a logistic regression model to determine the risk factors that predict prosthetic valvular dysfunction.

Furthermore, we analyzed survival with a Cox regression model and Kaplan-Meier survival curves.

## 3. Results

A total of twelve patients were included (n = 12), 83% were female and the median age was 59 years (48.5 - 64). The most common comorbidity was atrial fibrillation, which appeared in 41.6%, followed by systemic hypertension, atrial flutter and stroke (Table 1).

Eleven patients (92%) had normal right and left ventricular function and the median ejection fraction was 58% (55 - 62), while the tricuspid annulus systolic plane excursion had a borderline median values of 16 mm (14 - 20).

The median INR was also below normal values: 2.4 (2.2 - 3.4) (Table 1).

The most common cause of valvular replacement was RHD (75%), followed by congenital heart disease, valvular infective endocarditis and degenerative valvular heart disease. The mitral valve replacement was the most common position (50%, Figure 1 with x-ray showing cardiomegaly, echocardiography with Starr-Edwards mitral prosthetic valve and cardiac catheterization with normal coronary arteries and Starr-Edwards mitral prosthetic valve), followed by aortic in (41.6%. Valvular dysfunction was seen in 3 patients (25%). Overall mortality was 33.3%, corresponding to 4 of the 12 subjects, (Table 2), Figure 2.

In the logistic regression model, atrial fibrillation had the highest association with valvular dysfunction (OR = 3.49, 95%CI 3.31 - 12.43), but we also found other factors associated with valvular dysfunction including mitral position

**Table 1.** Demographic description of 12 patients with Starr-Edwards prosthetic valve.

| Variables | n = 12 | % |
|---|---|---|
| **Male** | 2 | 16.6 |
| **Female** | 10 | 83.3 |
| **Age (years)** | 12 | 59 (48.5 - 64) |
| **Height (cm)** | 12 | 160 (152 - 168) |
| **Weight (kg)** | 12 | 64.5 (59.5 - 74.5) |
| **HBA1C (%)** | 5 | 5.7 (5.6 - 5.7) |
| **RDW (%)** | 12 | 15.7 (13.9 - 16.9) |
| **Hemoglobin (g/dl)** | 12 | 13.65 (12.9 - 15.5) |
| **INR** | 12 | 2.4 (2.2 - 3.4) |
| **LDL** | 12 | 87.5 (73.5 - 102.5) |
| **HDL** | 12 | 49.6 (40.1 - 56.6) |
| **TSH** | 9 | 1.9 (1 - 4.8) |
| **CRP** | 9 | 2.5 (1.6 - 6.1) |
| **NT-proBNP** | 5 | 673 (613 - 1296) |
| **Smoking** | 1 | 8.3 |
| **Hypertension** | 4 | 33.3 |
| **Diabetes mellitus** | 1 | 8.3 |
| **Atrial fibrillation** | 5 | 41.6 |
| **Atrial flutter** | 2 | 16.6 |
| **Stroke** | 3 | 25 |
| **Pacemaker** | 1 | 8.3 |
| **Coronary artery disease** | 1 | 8.3 |
| **NYHA functional class > 2** | 4 | 33.3 |
| **Indication for valve replacement** | **n = 12** | **100** |
| **Rheumatic valve disease** | 9 | 75 |
| **Congenital** | 1 | 8.3 |
| **Degenerative** | 1 | 8.3 |
| **Infective endocarditis** | 1 | 8.3 |
| **Left ventricular ejection fraction (%)** | 11 | 58 (55 - 62) |
| **TAPSE (mm)** | 11 | 16 (14 - 20) |
| **RV 2D FAC (%)** | 7 | 36 (30 - 50) |
| **PSAP (mmHg)** | 10 | 34 (32 - 38) |

TAPSE: tricuspid annulus plane systolic excursion; RV 2D FAC: right ventricular two-dimensional fractional area change; PSAP: pulmonary artery systolic pressure; HBA1C: glycosylated hemoglobin; RDW: red-blood cell distribution width; INR: international normalized ratio; LDL: low density lipoproteins; HDL: high-density lipoproteins; TSH: thyroid stimulating hormone; CRP: C-reactive protein; NT-proBNP: n-terminal pro brain natriuretic peptide.

**Table 2.** Valve characteristics in patients with Starr-Edwards prosthetic valve.

| | N = 12 | % |
|---|---|---|
| **Mitral position** | 6 | 50 |
| **Aortic position** | 5 | 41.6 |
| **>1 prosthetic valve** | 2 | 16.6 |
| **Mitral and aortic position** | 1 | 8.3 |
| **Valve dysfunction** | 3 | 25 |
| **Mortality** | 4 | 33.3 |

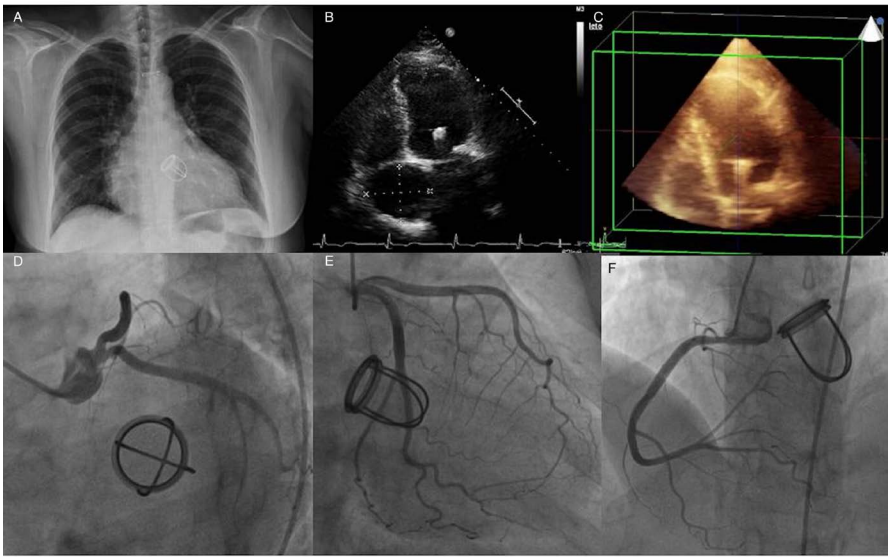


**Figure 1.** A- X-ray showing cardiomegaly and mitral Starr-Edwards prosthetic valve. B-2D and C-3D transthoracic echocardiogram in four chamber view with Starr-Edwards mitral prosthetic valve and bi-atrial enlargement. E, F, G- cardiac catheterization showing epicardial coronary arteries without obstructions and Starr-Edwards mitral prosthetic valve.

(OR = 2.01, 95%CI 1.95 - 11.43), coronary artery disease (OR = 2.01, 95%CI 1.89 - 7.89), INR < 2.5 (OR = 1.44, 95%CI 1.35 - 7.44), age > 65 years (OR = 1.34, 95%CI 1.25 - 10.34), atrial flutter (OR = 1.32, 95%CI 1.19 - 5.43), diabetes mellitus (OR = 1.28, 95%CI 1.17 - 6.34), left ventricular dysfunction with ejection fraction < 40% (OR = 1.04, 95%CI 1.02 - 3.45) and systemic hypertension (OR = 1.03, 95%CI 1.01 - 10.19) (Table 3).

## 4. Discussion

Valvulotomy was one of the first efforts for treating valvular heart disease, nevertheless, it was until 1954, when Charles Hufnagel placed the first mechanical prosthetic valve in a patient with aortic regurgitation [5] [6] Along with the implementation of cardiopulmonary bypass, valvulotomy became the hallmark event in the treatment of valvular heart disease. In 1960, Nina Braunwald placed the first caged-ball prosthetic valve in mitral position, and later, Lowell Edwards

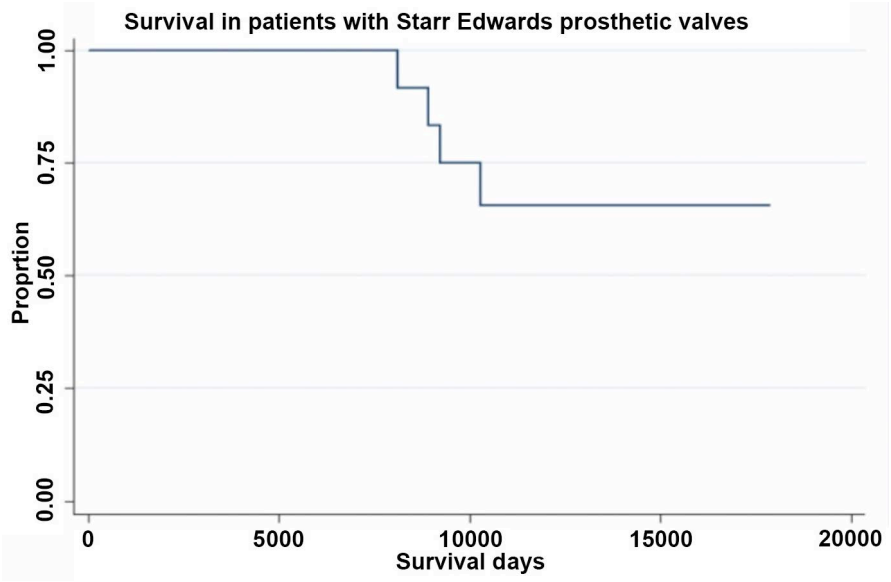


**Figure 2.** Survival in patients with Starr-Edwards prosthetic valves.

**Table 3.** Logistic regression model for valve dysfunction in patients with Starr-Edwards prosthetic valve.

| Variables | OR | 95%CI | P |
|---|---|---|---|
| **Atrial fibrillation** | 3.49 | 3.31 - 12.43 | 0.001 |
| **Mitral position** | 2.01 | 1.95 - 11.43 | 0.001 |
| **Coronary artery disease** | 2.01 | 1.89 - 7.89 | 0.003 |
| **INR < 2.5** | 1.44 | 1.35 - 7.84 | 0.001 |
| **Age > 65 years** | 1.34 | 1.25 - 10.34 | 0.001 |
| **Atrial flutter** | 1.32 | 1.19 - 5.43 | 0.005 |
| **Diabetes mellitus** | 1.28 | 1.17 - 6.34 | 0.007 |
| **Left ventricular ejection fraction < 40%** | 1.04 | 1.02 - 3.45 | 0.002 |
| **Hypertension** | 1.03 | 1.01 - 10.19 | 0.03 |

OR: odds ratio; CI: confidence interval; INR: international normalized ratio. $R^2 = 1$.

and Albert Starr settled the path for to the era of vascular surgery [5] [6]. By 1968 more than 2000 caged-ball prosthetic valves were placed in the world, but given the high thrombogenic risk and hemorrhagic complications, many physicians decided to have a safer prosthetic valve. However, there are still many Starr-Edwards prosthetic valves and in our experience the survival of these patients in the 50 year follow-up was of 66.6%.

Starr-Edwards' prosthetic valve cage was made of titanium and the ball of silastic, with a moderate thrombogenic risk, given by a rate of thrombogenic events of 4% - 6% per year [7], and thus having an INR therapeutic goal of 2.5 - 3.5. Previous studies found that prosthetic mitral valves posed greater risk of thrombogenic events, which might be explained by an elevated risk of left ventricular outflow tract obstruction by pinching the ventricular wall after implantation [5] [6] [7].

Worldwide, there are case reports of patients that have lived up to 45 years without any fatal events. In the literature, there are reported only two cases with loss of structural integrity of prosthetic mitral valve [8] [9] [10], while in our series, one patient has lived 51 years without losing structural integrity of the prosthetic valve [7]. The following complications per year have been reported: thromboembolism (2%), bleeding related to vitamin K antagonists (2.1%) and infective endocarditis (0.5%), with a total of adverse events of 4.8% [6]. In the current series, the most common complication was stroke, which appeared in 25% of the studied population. It is important to mention that the proportion of patients free of thromboembolism related to prosthetic valve is 59% at 25 years of follow-up [6]. Another important issue is anticoagulation, for which high INR goals have been set, in our patients the median INR was below goals, making our population more prone to thrombotic events, such as stroke.

In the current study, we were unable to record in-hospital mortality; nevertheless, other studies have reported an in-hospital mortality of 6.2%. Regarding valvular dysfunction, Misawa et al. reported a case of a 69 year-old patient that had a mitral and aortic Starr-Edwards prosthetic valve for 39 years, which had dysfunction due to pannus [9]. Additionally, there are two cases of mitral Starr-Edwards prosthetic valve with a survival of 41 and 45 years, respectively, which were replaced because of paravalvular leakage [11]. Tarzia *et al.* published a case of mitral prosthetic valve with a 31 year survival that was taken to prophylactic replacement [12]. Yamada *et al.* had a case with a 40 year survival replaced because of mismatch patient-prosthesis [13]. Ata *et al.* reported a case of dysfunction due to thrombus [11]. We found that the main predictors for prosthetic valvular dysfunction of any type were: atrial fibrillation, mitral position, coronary artery disease, INR < 2.5, age > 65 years, atrial flutter, diabetes mellitus, left ventricular systolic dysfunction with ejection fraction of <40% and systemic hypertension.

In the context of Latin-American population, Storino *et al.*, reported 103 patients with Starr-Edwards prosthesis with a survival at 10 years of 87% [14]. Unfortunately, we have to mention that there is no registry in Mexico that characterizes the patients still living with this type of prosthetic valve, nor their survival.

Even though nowadays we have safer prosthetic valves, we must not forget that in our daily practice we can still find patients with Starr-Edwards prosthetic valves. This fact expands our boundaries to have medical evidence-based facts on this particular subject. Furthermore, we must recognize that Starr-Edwards prosthetic valve carriers that have survived for more than 25 years can have a good prognosis if we make adequate surveillance to prevent potential complications. Finally, we have to make clear that with a longer survival there is an increased risk of embolism and a longer time of anticoagulation with high INR goals.

## 5. Limitations

There is no a general registry of valve replacements made with Starr-Edwards

prosthetic valves in our country and the obtained information is of a single center, which explains why the sample is small. Patients were located individually in ambulatory clinic or emergency room.

In our study, the survival was of 66.66%, even though we have to state that we were not able to collect data from all the patients that once had a Starr-Edwards prosthetic valve.

## 6. Conclusion

The overall survival in Starr-Edwards prosthetic valve carriers was 66.66% and mitral valve replacement was the most common. The risk factors that predict valve dysfunction were atrial fibrillation, mitral position, coronary artery disease, INR < 2.5, age > 65 years, atrial flutter, diabetes mellitus, left ventricular ejection fraction < 40% and systemic hypertension.

## Authors' Contributions

GIMRM: Research idea, study design, data acquisition, data analysis, manuscript drafting. RGN: Research idea, study design, data acquisition, data analysis, statistical analysis, manuscript drafting. DAG: Research idea, study design, data analysis, manuscript drafting. PMA: Data analysis, statistical analysis, manuscript drafting. ACL: Study design, data acquisition, data analysis, statistical analysis, manuscript drafting. LLRC: Study design, data analysis, manuscript drafting, and mentorship. NEZ: Research idea, study design, data analysis, statistical analysis, manuscript drafting, supervision and mentorship.

## Conflicts of Interest

The authors declare that they have no conflict of interests.

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