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Dafodil™

Pericardial Bioprosthesis

Dafodil-1: First-in-Human Study

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Dafodil-1 First-in-Human Trial Presented at the 69th Annual conference of the Indian Association of Cardio Thoracic Surgery 2023, Coimbatore (February 2023)

INTRODUCTION

Artificial heart valves have been used in routine clinical practice to replace diseased or deteriorated native valves. Surgical aortic valve replacement (AVR) and mitral valve replacement (MVR) are considered the standard-of-care, particularly when the patient does not have advanced age. This is a sternotomy-based procedure that requires temporary cardiopulmonary bypass support and cardioplegia. Since the published evidence on the long-term outcomes of surgical AVR have beenfavorable over the last few decades and the prevalence of valvular heart disease has been rising, the number of surgical AVR and MVR has been increasing as well.

Moreover, the prevalence of valvular heart disease has increased dramatically including the incidences of bioprosthetic valve degeneration because of changing societal demographics and the increasing ageing population. Meanwhile, rheumatic valve disease remains endemic in low- and middle-income countries [1].

Newer bioprosthetic valve designs have become available that aim to reduce the deployment failure rates, facilitate easier valve seating, reduce residual paravalvular regurgitation, and limit the chances of valve deterioration. One such newer generation bioprosthetic valve is the Dafodil™ Pericardial Bioprosthesis, which is composed of glutaraldehyde-fixed bovine pericardial tissues made into three semicircular-shaped leaflets that are treated with a proprietary anti-calcification technology (AntiCa+).The tri-leaflet composite bovine tissues are mounted on a firm frame, which contains a polymeric support ring, a commissural ring made up of polyethylene terephthalate (PET) film structures, and an Elgiloy alloy wire-form that provides a sturdy structure. The device consists of a PET-backed sewingring with suture markers that ensure an equal distribution of sutures and aid in the proper orientationof the implanted valve. The structure has fatigue-resistant characteristics and a superior spring efficiency. The triple composite design of this tissue valve aids in optimal leaflet co-aptation and provide a larger effective blood-flow area, thereby ensuring a higher capability of minimizing intravalvular regurgitation.

The Dafodil™ Pericardial Bioprosthesis (Meril Life Sciences Pvt Ltd, India) has been designed for both aortic and mitral valve replacements with appropriate enhancements to enable more accurateplacement and valve orientation in both the positions. Because of the Elgiloy alloy wire-form, the valve provides good radio-opacity that aids in precise positioning, attachment, and orientation. This trileaflet tissue valve has an optimal magnetic resonance capability, confirmed by testing in a magnetic field of 1.5 and 3.0 Tesla. Like warranted for any medical device, it is important to conduct long-term clinical studies with this surgical valve for evaluating the clinical safety and effectiveness in patients requiring AVR and MVR. Hence, this report highlights the data obtained from the Dafodil-1, the firstin-human trial, which aims to evaluate the clinical safety and performance of Dafodil™ Pericardial Bioprosthesis.

DAFODIL™-1 TRIAL METHODOLOGY & FOLLOW-UP

The Dafodil-1 study is a prospective, non-randomized, multi-center clinical study with 136 patients enrolled (aortic=67 and mitral=69) across 19 centers in the country.

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Currently, the Dafodil-1 trial has advanced to the 5-year follow-up stage and Dr Anil Jain from the Epic Hospital, Ahmedabad presented the clinical outcomes data. The safety and efficacy endpoints of the trial included the assessment of MACE, defined as a composite of all-cause mortality, myocardial infarction, and all stroke, and the hemodynamic performance based on the mean/peak pressure gradient and the effective orifice area after implantation of Dafodil™ Pericardial Bioprosthesis in the aortic and mitral positions. In addition, the device success, quality of life assessment with the Short Form-12 version 1 (SF-12 v. 1), improvement in the New York Heart Association functional classes, and the rates of valve implantation-related thrombosis or reoperation, explant, conduction disturbances,repeat hospitalizations, hemolysis, prosthetic valve endocarditis, major valvular leakage, and occurrence of stroke/transient ischemic attack were assessed in addition to MACE to establish the safety outcomes of this trial. The patients are being followed up for 5 years through clinical visits and telephonic interviews. All patients are required to appear for mandatory echocardiographic follow-up at 1 month, 6 months, 1 year, and once every year up till the 5-year follow-up visit. The NYHA classes of the patients is monitored over the same period. Valve sizes starting from 19 mm to 27 mm were implanted in patients requiring AVR and valves sized 23 mm to 31 mm were implanted in those who underwent MVR.

RESULTS OF DAFODIL-1 TRIAL

A total of 136 patients were enrolled in the Dafodil-1 trial. The patients who underwent AVR (n=67)had a higher age (60.18±8.28 years) and those who underwent MVR (n=69) were younger (mean age= 49.78±14.40 years). Slight proportions of previous major cardiovascular events were observed among the patients, as some of them had previous stroke, prior valve repair surgery, and congestive heart failure.

The aortic group had 65.67% men and 28.4% patients who underwent AVR had concomitant CABG while selected few patients underwent concomitant mitral valve repair (14.9%), ascending aorta replacement (1.5%), and aortic root enlargement (2.9%) surgeries. Overall, 43.3% AVR and 34.8% MVR procedures have been conducted in patients who required concomitant surgery.

In the MVR group, the patients underwent concomitant tricuspid valve repair (26.1%) and CABG (7.3%), while two of the 136 patients underwent double valve replacement. As of now, the 3-year follow-up of 134 patients is complete (98.53%) and 89 patients have completed the 4-year follow-up.

As regards the hemodynamic improvements, in AVR patients who received the 19-mm and 21-mm valves, a marked reduction in the mean pressure gradients was observed post SAVR, which was maintained at 12.25 mmHg and 11.26 mmHg over the 3 years follow-up, and at 12.18 mmHg and 9.3 mmHg at the 4-years follow-up. In particular, the mean pressure gradients for the 19 mm - 25 mm sizes in the AVR cohort were (a) 19 mm (12.25 ± 6.06 mmHg at 36 months, (b) 21 mm (11.26 ± 6.71 mmHg at 36 months), (c) 23 mm (8.09 ± 2.79 mmHg at 36 months), (d) 25 mm (4 ± 1.41 mmHg at 36 months). The effective orifice areas in the subgroup of sizes of the AVR group were (a) 19 mm (1.81 ±0.67 cm2 at 36 months), (b) 21 mm (1.76 ± 0.27 cm2 at 36 months), (c) 23 mm (2.53 ± 0.60 cm2 at 36 months), (d) 25 mm (1.95 cm2 at 36 months). All the patients exhibited an overall hemodynamic improvement, which was maintained over the 3-years follow-up (mean gradient: 10.59 mmHg;effective orifice area: 1.91 ± 0.53 cm2).

In the MVR patients, the overall hemodynamic improvement was satisfactory, as the mean pressure gradient and effective orifice areas stabilized to 4.32 ± 2.23 mmHg and 2.57 ± 0.97 cm2 post procedure,

respectively. At the end of 12-months, the mean pressure gradient was maintained at 4.34 ± 2.24 mmHg, peak gradient was 9.76 ± 4.79 mmHg, and the effective orifice area index was 1.59 ± 0.62 cm2 /m2

The improvements observed in the NYHA functional classes were remarkable, as the majority of AVR patients (96.5%) and MVR patients (90.74%) were having NYHA class I at the end of 3 years. Even the SF-12 scores showed significant improvement in the quality of life from the baseline scores over 3 years following the implantation of Dafodil™ in both the AVR and MVR subsets. The trial has shown exceptional clinical results regarding efficacy of the device over long-term follow-up. In terms of safety, it is commendable that no cases of valve deterioration have been reported while the rate of explant and valve-related reoperation have been negligible (1.47%). We report a MACE rate of 9.09% in AVR cohort and 22.05% in the MVR cohort at 3-year follow-up. One patient who underwent AVR experienced conduction disturbances including arrhythmia (1.51%). The safety outcomes are satisfactory as no patient experienced peri-procedural or post-procedural myocardial infarction. Repeat hospitalizations were reported in both the AVR and MVR cohorts (15.15% and 16.17%, respectively).

Overall, the Dafodil-1 trial reports satisfactory clinical outcomes and continues to report low frequencies of MACE and other serious adverse events in both subsets. At the completion of 4-year follow-up of 43 patients in the MVR cohort, 2 new cases of all-cause mortality and 1 case of valverelated reoperation have been reported; similarly, of 46 patients in the AVR cohort who completed 4-year follow-up, 1 new case of all-cause mortality has been reported. Of 28 patients (12 in AVR cohort and 16 in MVR cohort) who have completed 5-year follow-up, no new endpoint-related events were reported.

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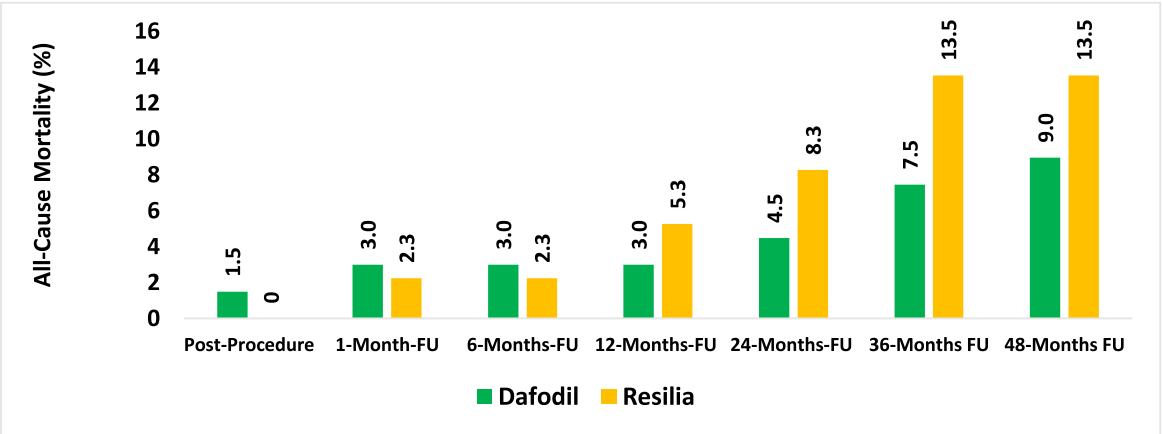
On comparing the all-cause mortality through 48-month follow-up in patients implanted with Dafodil™aortic valve and its contemporary Resilia™ (2), the rate of all-cause mortality waslower for the patients treated with Dafodil™ (Figure 1). Even the comparisons of the effective orifice area and mean gradient of Dafodil™ versus Resilia™ for AVR have encouraging observations, as the Dafodil-1 AVR cohort has maintained an improving trend over 48 months (Dafodil™ vs Resilia™ at 24-months: 1.6 cm2 for both; Dafodil™ vs Resilia™ at 36-months: 1.8 cm2 vs 1.4 cm2) (2,3).

Figure 1: Comparison of one-year and two-year safety outcomes between Dafodil™ and Resilia™



The outcomes with the sizes of Dafodil™ and Resilia™ used for treating patients with small annulus (that required 19 mm or 21 mm of bioprosthesis), aortic valve performance of Dafodil™ (19 mm and

21 mm) is comparatively better than Resilia™ (19 mm and 21 mm) as shown by the better control of EOA and mean pressure gradient by Dafodil™ (Figures 2 and 3) (2,3).

Figure 2: Comparison of Hemodynamic data between Dafodil™ and Resilia™ valves (19-mm size)

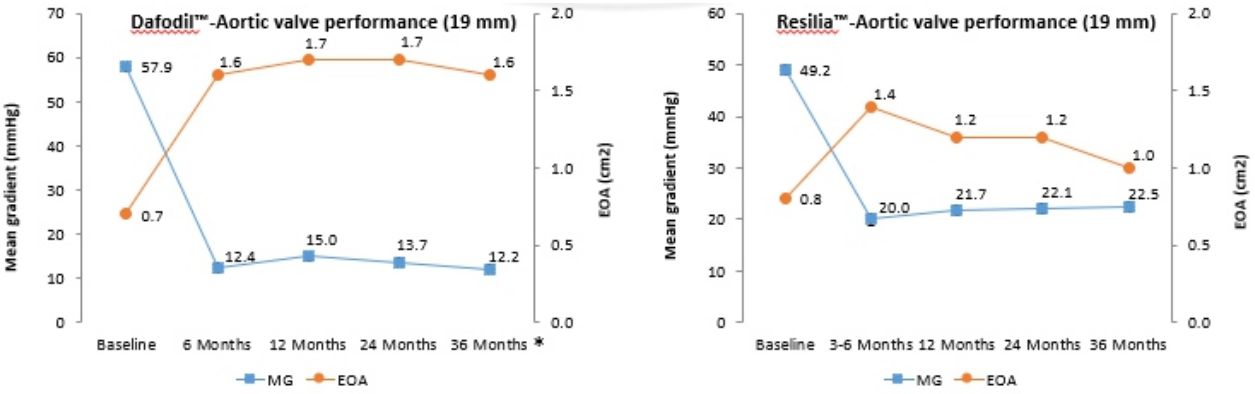
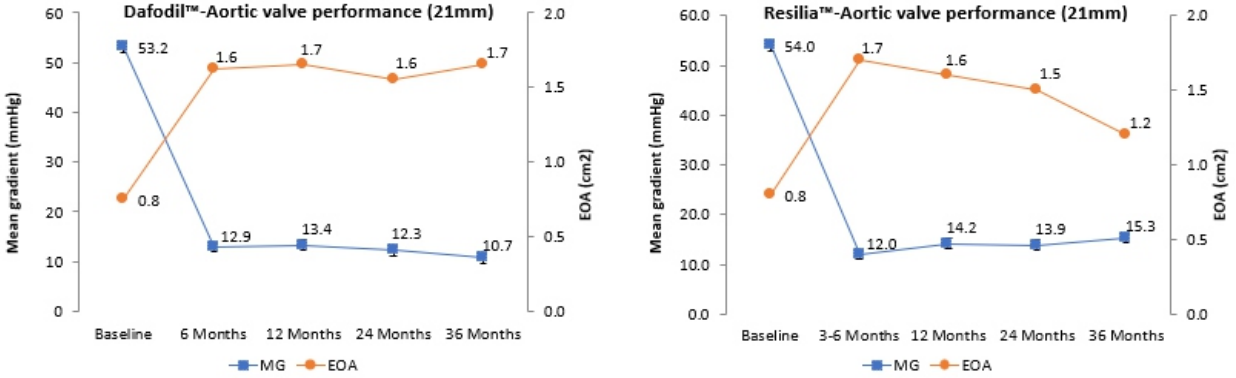


Figure 3: Comparison of hemodynamic performance between Dafodil™ vs. Resilia™ (21-mm size)



On comparing the two-year safety outcomes of the Dafodil-1 trial with that of a contemporary stented bovine AV bioprosthesis (Avalus, Medtronic Inc., Minneapolis, Minnesota, USA) from the PERIGON pivotal trial (4), it was found that the all-cause mortality was comparable between Dafodil™ and Avalus™ (Figure 4). Moreover, the cumulative frequencies of reoperation and explants are found comparable (Dafodil™ vs. Avalus™: 0% vs 1.3% and 0% vs. 1.1%), respectively. Hemodynamically, performance of Dafodil™ and Avalus™ were comparable as seen in the Figure 5.

Figure 4: Comparison of one-year and two-year safety outcomes between Dafodil™ and Avalus™

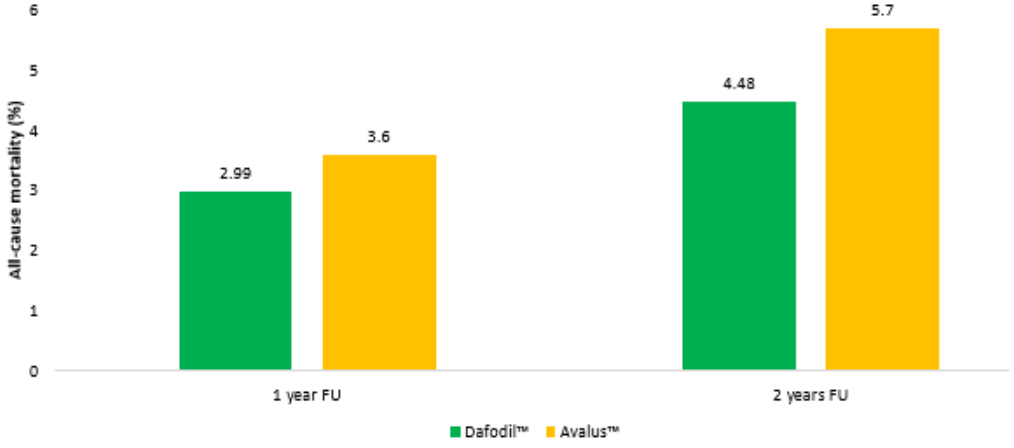


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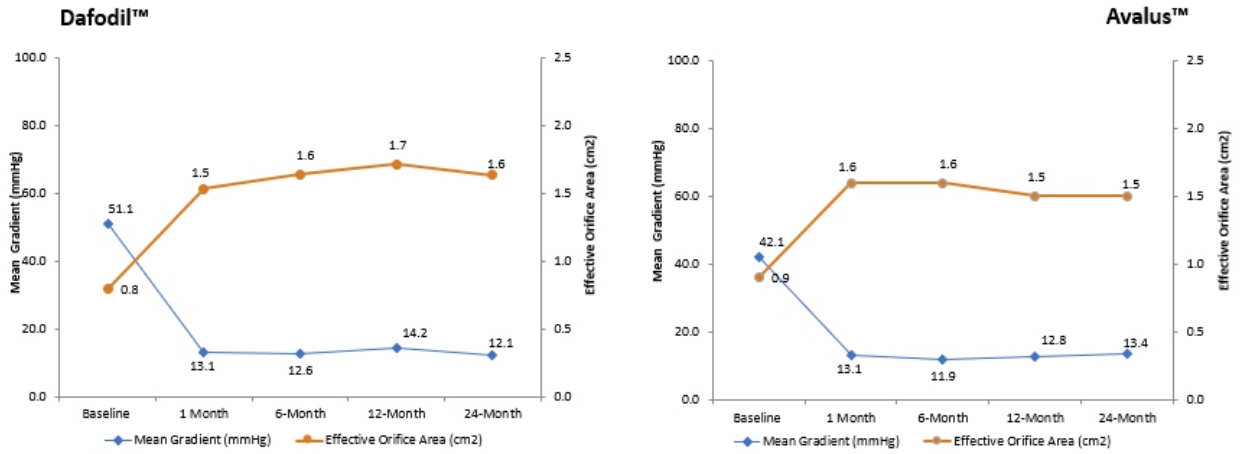
Figure 5: Hemodynamic outcomes compared between Dafodil™ and Avalus™ valves (all sizes)



The only other valve that has been evaluated on Indian patients is Trifecta (St Jude's Medical, MN,USA) for similar time-periods (5). Comparison of the 12-month data revealed that the mean gradient across all sizes was higher with Dafodil™ (Dafodil™ vs Trifecta™: 14.2 mmHg vs 10.4 mmHg, respectively) and the EOA across all sizes was comparable between the two devices (Dafodil™ vs Trifecta™: 1.7 cm2 vs 1.6 cm2, respectively).

COMMENT

As of now, the Dafodil™ Pericardial Bioprosthesis shows considerable safety with minimal rates of valve related major adverse cardiac events up to 5 years in valve replacement at aortic and mitral position. This assessment was performed as a non-cumulative clinical evaluation at 4 years and 5 years from implant.

Dr. Anil Jain also presented his own experience of implanting 70 Dafodil™ Pericardial Bioprosthesis valves (66.70% and 33.30% in AVR and MVR cohorts, respectively) in the last two years, from which he stated that the acute clinical outcomes (including in-hospital, post-discharge, and early [30-day] outcomes) have been satisfactory so far.

On comparing the clinical outcomes of Dafodil™ from this ongoing trial with the other contemporary devices, it was found that the 36-month follow up outcomes data were satisfactory for Dafodil™.

The Dafodil™ pericardial bioprosthesis, a newer generation valve, has shown considerably positive data in terms of early clinical safety as well as long-term safety. In patients who require concomitant surgery with MVR, obtaining technical and device success is a critical challenge that requires not only the acumen of most experienced surgeons but also an efficient bioprosthetic valve having a high clinical feasibility. In addition, the Dafodil-1 trial reported no events of valve degeneration or deaths due to valve thrombosis over 4 years follow-up, which is a significant finding for the current practice of surgical valve replacement. With the encouraging data of this first-in-human trial, we believe that this bioprosthetic valve can help in reducing the high health economic burden of valvular heart disease in the Asian populations particularly because it offers patients the freedom from long-term anticoagulation and repeated hospital visits for coagulation monitoring, and offers a marked improvement in the quality of life.

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