Midterm results from COMMENCE Mitral: freedom from death and structural valve deterioration at 5 years

Methods: Prospective, single arm trial at 17 sites in the United States and Canada, enrolling 83 patients requiring mitral valve replacement.

Results: Eighty-two patients successfully underwent mitral valve replacement with the study valve. Five year event-free probabilities for all-cause mortality, structural valve deterioration, and reoperation were 79.9%, 98.7%, and 97.1%, respectively. Hemodynamic valve function measurements were stable through the 5-year follow-up period.

Implications: Results of this study support the use of RESILIA tissue in the mitral position with excellent hemodynamics and durability out to 5 years. This is important as younger patients are requesting tissue bioprostheses and are in need of improved durability.
Mid-term Outcomes of the COMMENCE Trial Investigating Mitral Valve Replacement Using a Bioprosthesis with a Novel Tissue

*4 year COMMENCE Mitral outcomes were presented at the 101st Annual AATS Meeting (May 2021)

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Disclosure Statement

DAH: None

CB: None

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HT: Consultant, Edwards Lifesciences

FD: Consultant Cook Medical, honoraria Edwards Lifesciences and Medtronic

DST: None

MAM: Consultant, honoraria, and research with Medtronic, Edwards Lifesciences, ZMedica, Atricure, JOMDD, and Abbott Laboratories.

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Clinical Trial Registry Number NCT01757665
Institutional Review Board approvals in Supplementary Materials

Informed Consent Statement

Written informed consent, in accordance with applicable international standards and trial center regulations, was obtained from each study participant, prior to enrollment and any trial procedures.

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Word Count: 2866
Glossary of Abbreviations

AC = anti-coagulant
CABG = coronary artery bypass graft
DVI = Doppler velocity index
EOA = effective orifice area
IQR = interquartile range
MR = mitral regurgitation
MS = mitral stenosis
MVR = mitral valve replacement
NSVD = non-structural valve dysfunction
NYHA = New York Heart Association
PVL = paravalvular leak
STS = Society of Thoracic Surgeons
SVD = structural valve deterioration

Central Picture legend:
Freedom from death and structural valve deterioration at 5 years in COMMENCE Mitral patients.

Central Message: Through 5 years of patient follow-up, mitral valve replacement patients implanted with a RESILIA tissue bioprosthesis had a good safety profile and clinically stable hemodynamic performance.

Perspective Statement:
Patient preferences in mitral valve replacement are evolving, as the use of anticoagulation falls out of favor; meanwhile, reoperations have become safer with catheter based valve-in-valve replacements a reality. Improved durability is the focus of new tissue valve designs. This study reports outcomes of a new pericardial tissue designed to reduce leaflet calcification and improve long term durability.

Structured Abstract – Word count: 163

Objective: Novel tissue leaflets (RESILIA tissue) may improve durability of bioprosthetic heart valves. The COMMENCE trial is an ongoing prospective study to evaluate valve replacement using RESILIA tissue. This report describes mid-term outcomes in the mitral cohort of COMMENCE.

Methods: Adult patients requiring mitral valve replacement were enrolled in a prospective, single arm trial at 17 sites in the United States and Canada. An independent clinical events committee adjudicated safety events using definitions from established guidelines, and hemodynamic performance was evaluated by an independent echocardiographic core laboratory.

Results: Eighty-two patients (mean age 69 years) successfully underwent mitral valve replacement with the study valve. Five-year event-free probabilities for all-cause mortality, structural valve deterioration, and reoperation were 79.9%, 98.7%, and 97.1%, respectively. Hemodynamic valve function measurements were stable through the 5-year follow-up period; valvular leaks were infrequently observed and primarily clinically insignificant / mild.

Conclusions: Mitral valve replacement patients implanted with a RESILIA tissue bioprosthesis had a good safety profile and clinically stable hemodynamic performance.
Keywords: Mitral valve replacement, Mitral valve diseases, bioprosthetic valve, RESILIA tissue

Introduction

Mitral valve disease is one of the most common valvular heart diseases, with functional classifications of mitral regurgitation together affecting an estimated 5% of the US population, and resulting in approximately 29,000 hospitalizations in the US in 2018.1 Further, prevalence is increasing in developed nations as the population ages.2 Current valvular heart disease guidelines establish that mitral valve replacement (MVR) may be considered in mitral regurgitation (MR) and mitral stenosis (MS) patients when durable repair is not feasible.3 The optimal prosthetic valve in MVR remains a matter of debate, particularly for patients under 65 years of age.3-5 Patients can be implanted with either a bioprosthetic valve or a mechanical valve. Mechanical valves may offer longer durability but require lifelong anticoagulation with a potential risk of bleeding or pannus formation with leaflet restriction depending on the adequacy of anticoagulation.6 In contrast, bioprosthetic valves have been associated with higher risk of structural valve deterioration (SVD), especially in younger patients, and with reduced overall survival in patients under 50 years.7-8 The potential of valve-in-valve therapies may reduce the need for redo MVR thereby impacting the likelihood of younger patients receiving a bioprosthetic valve. Taken together, balancing patient quality of life and the competing risks of reoperation and potential bleeding events requires long-term data to inform decision-making on appropriate valve selection.9

RESILIA tissue designed for use in heart valve replacement is a promising option that may improve durability of bioprosthetic valves. The tissue incorporates a novel integrity
preservation technology, which prevents calcium binding through stable capping of residual aldehyde groups and allows dry tissue storage via glycerolization. RESILIA tissue has exhibited reduced tissue calcification in preclinical studies compared with both prior bovine tissue preparations and porcine tissues treated with amino oleic acid.\textsuperscript{10} When evaluated in a juvenile sheep model, RESILIA tissue valves implanted in the mitral position exhibited reduced transvalvular pressure gradients and approximately 72% less calcium relative to the PERIMOUNT control group after 8 months.\textsuperscript{11}

Clinically, the European Aortic Feasibility Study investigated RESILIA tissue in aortic valve replacement with a good hemodynamics profile and no SVD observed through 5-years of follow up.\textsuperscript{12} The COMMENCE Investigational Device Exemption trial was planned to evaluate performance of RESILIA tissue in both aortic and mitral valve replacement. Promising outcomes have been observed through 5 years of follow up in the aortic position with clinically stable hemodynamics and no evidence of SVD reported.\textsuperscript{13} Herein, we report mid-term outcomes of the mitral cohort of the COMMENCE trial. The objective of this study was to evaluate safety and effectiveness of mitral valve replacement with RESILIA tissue.

\textbf{Methods}

The COMMENCE trial was designed as a prospective, single arm Food and Drug Administration Investigational Device Exemption trial with enrollment of the mitral cohort at 17 sites in the US and Canada. Patients underwent MVR with Model 11000M (Edwards Lifesciences LLC), a pericardial mitral bioprosthesis with RESILIA tissue. This tri-leaflet bioprosthesis is the same as the Carpentier-Edwards PERIMOUNT Magna Mitral Ease valve (Model 7300TFX, Edwards Lifesciences), except including RESILIA tissue leaflets.
Patients over 18 years old with mitral valve disease requiring replacement based on a preoperative evaluation and scheduled to undergo MVR with or without coronary artery bypass graft (CABG), were eligible. Concomitant tricuspid valve repair and Maze procedure were allowed; no other valve replacements were allowed as part of the procedure. Patients with acute myocardial infarction within 30 days prior to surgery, cerebrovascular accident within 6 months, ejection fraction less than 20%, or renal failure, or who required emergency surgery, were not eligible for inclusion in the study. The decision for antiplatelet or anti-coagulation (AC) therapy was not dictated per protocol, but rather left to the physician’s discretion per existing American College of Cardiology/American Heart Association guidelines for the management of patients with valvular heart disease. The Institutional Review Board (IRB) of each participating site approved the study protocol and publication of data. Institutional Review Board approval details for each center are listed in Supplementary Materials. Written informed consent, in accordance with applicable international standards and trial center regulations, was obtained from each study participant, prior to enrollment and any trial procedures. The patient(s) provided informed consent for the publication of the study data.

Endpoints were defined in consultation with the US Food and Drug Administration. An independent Clinical Events Committee adjudicated endpoint related adverse events, using definitions from the established guidelines at the time of study development. Safety endpoints included all-cause mortality, reoperation, valve explant, thromboembolism, valve thrombosis, endocarditis, all bleeding, major paravalvular leak, hemolysis, SVD, and nonstructural valve dysfunction (NSVD). As detailed by Akins, et. al, SVD was defined as dysfunction or deterioration involving the operated valve (exclusive of infection or thrombosis), as determined by reoperation, autopsy, or clinical investigation. Conversely, NSVD was defined as any
abnormality not intrinsic to the valve itself that results in stenosis or regurgitation of the operated valve or hemolysis.\textsuperscript{14} Hemodynamic performance was evaluated by an independent echocardiography core laboratory (BioTelemetry Research, Rockville, MD). Hemodynamic assessments for this analysis included peak mitral valve velocity, peak and mean mitral pressure gradients, effective orifice area (EOA), doppler velocity index (DVI), and severity of valve regurgitation. Paravalvular or transvalvular regurgitation were graded as none, trace, mild, moderate, and severe. Statistical analysis was performed by the study sponsor, Edwards Lifesciences LLC, per the protocol and statistical analysis plan. Descriptive summary statistics for categorical variables are the percentage of subjects with a recorded value for variables of interest. Median (interquartile range) are presented for continuous measures after assessing for normality. Kaplan-Meier analyses were undertaken on safety endpoints of all patients successfully implanted with the study valve. SAS version 9.3 (SAS Institute Inc, Cary, NC) was used for all statistical analyses. Midterm results through a data extraction date of July 21, 2022 are reported herein.

**Results**

Between January 2013 and February 2016, 83 patients were enrolled at 17 centers in North America with 82 patients successfully implanted with the study valve. One patient had major perivalvular leak (4+) after the heart was restarted prior to leaving the OR and was deemed a technical failure; this patient was reintervened with a 27 mm Magna Mitral Ease valve. The median follow-up for the study cohort was 5.1 (1.4) years (total 374.2 patient-years in aggregate). There were 15 deaths (2 valve-related), 1 explant (due to NSVD), 1 re-intervention (due to SVD), 6 that withdrew consent, 3 that were exited due to being lost to follow-up, and 3
that missed the 5-year visit, leaving 54 patients with available data at 5-year follow up (Figure 1).

Patients were predominantly elderly and had concomitant cardiovascular conditions. Mean patient age at the time of the procedure was 69 years, with 52.4% of patients 70 years old and above (Table 1). The median Society of Thoracic Surgeons predicted risk of operative mortality was 3.4 (2.7)%. Of the 82 patients implanted with the trial valve, the following diagnoses were present in the cohort: 48.8% pure insufficiency (n=40/82), 30.5% stenosis with insufficiency (n=25/82), 11.0% stenosis (n=9/82), 7.3% prosthetic valve dysfunction (n=6/82), and 2.4% other diagnosis (n=2/82). A majority of patients were on anti-platelet therapy (51.2%) and 46.3% of patients were on anticoagulant therapy at baseline. Fewer than half of the patients (42.7%) underwent an isolated MVR. A similar number underwent MVR with concomitant procedures including atrial ablation or left atrial appendage ligation. Of note, nearly 15% of the cohort underwent CABG along with the valve procedure.

Adverse events in the post-operative period are summarized in Table 2. All-cause mortality within 30 days of MVR was 1.2%. There were 2 early ischemic strokes related to the procedure (2.4%) and 1 early bleeding event (1.2%) due to an esophageal tear, also deemed procedure-related. No study valve explants, valve thrombosis, endocarditis, hemolysis, or reoperations were observed in the 30 days following the procedure. In addition, 68% of patients were on AC therapy at 3 months post-op, while 57.4% of patients were on AC therapy at 5 yrs.

Five year event-free probabilities for all-cause mortality, SVD, and reoperation were 79.9%, 98.7%, and 97.1%, respectively (Table 2). The risk of death exceeded that of SVD throughout the follow-up period, as shown in the Kaplan-Meier curve (Figure 2). Two patients underwent reoperations: 1 for NSVD and 1 for SVD. Approximately 1 year post-implant, the
NSVD patient presented with severe MR. The posterior leaflet was thickened and stuck in intermediate position resulting in a severe, eccentric leak. The patient was reintervened with a 29 mm Magna Mitral Ease valve shortly thereafter. Upon post-explant investigation, the valve had signs of pannus overgrowth on both leaflets with no evidence of SVD. The observed SVD occurred in a 75-year old patient implanted with the trial valve. The patient presented with end-stage renal disease on hemodialysis and underwent valve-in-valve with a 29 mm Sapien-3 transcatheter heart valve on post-operative day 638 for severe central regurgitation. The second NSVD was observed in a patient that was hospitalized for chronic heart failure in the setting of severe RV dysfunction. Clinically, the patient presented with mild-moderate stenosis seen functionally as elevated mitral valve pressure gradients, which the clinical events committee deemed as NSVD due to study valve stenosis. The patient did not require reintervention as of the 5 yr. follow-up visit.

A variety of valve function measurements were evaluated by echocardiography (Figure 3). Stable mean pressure gradients were observed from discharge to 5 years (4.1 (2.0) and 3.7 (2.2) mmHg, respectively). Peak mitral velocity was also stable during the following up period (1.6 (0.4) m/s, discharge; 1.6 (4.0) m/s, 5 years). Effective orifice areas (EOAs) were lower than expected during the follow-up period (1.2 (0.6) cm², discharge; 1.4 (0.6) cm², 5 years). Given that literature suggests the continuity equation may underestimate EOAs due to variability in left ventricular outflow tract diameter measurements, DVI is presented to supplement the EOA data. From discharge to 5 years follow-up, DVI was stable (2.4 (1.3) and 2.0 (0.8), respectively) and largely within expected range. New York Heart Association (NYHA) class improved universally after MVR, and 94% of patients were maintained in NYHA class I or II.
through 5 years of follow-up. In addition, clinically insignificant trivial to mild paravalvular or transvalvular leak was predominantly observed. (Figure 4).

Discussion

Through 5 years of follow-up, the COMMENCE Mitral trial reported a good safety profile and clinically stable hemodynamic performance of a bioprosthetic valve with RESILIA tissue. These findings are consistent with the midterm safety and efficacy outcomes observed with the RESILIA tissue in the aortic position. Durability results are promising with 2 observed reoperations (1 NSVD, 1 SVD) and a reported freedom from SVD at 5 years of 98.7%. Mitral valve pressure gradients are the most common measure of valve function, while EOAs are more difficult to measure and may be less predictive of valve dysfunction. As such, DVI was also included as an additional measure to document any significant change or deterioration in valve function. Hemodynamics were clinically stable, as measured by mean valve gradients, peak velocities, DVI, and EOAs.

In surgical literature, several studies have reported mid-term MVR outcomes for bioprosthetic valves. A comparative analysis of 940 MVR patients implanted with either Medtronic Mosaic or PERIMOUNT mitral valves reported 5 year rates of echocardiographic freedom from SVD of 91.0% and 90.3%, respectively. Further, publications for the PERIMOUNT Magna Ease, Medtronic Mosaic, and Abbott Epic bioprosthetic valves reported 5 year rates of freedom from SVD of 90%, 94%, and 93% respectively. It is important to note that all of these studies represent single center retrospective studies without clinical events committee adjudicated safety endpoints or core-lab adjudicated echo data. In addition, study
cohort characteristics need to be carefully considered when comparing these results (e.g. demographics, study location). Lastly, the interpretation of the Akins definition varies greatly from study to study.

There have been very few clinical trials in the MVR space over the last 25 years\textsuperscript{22-24}. As such, COMMENCE Mitral is unique in that it reports the first clinical data of RESILIA tissue in the mitral position and is a prospectively collected MVR clinical trial. Given the level of scientific rigor in this trial, the observed 98.7\% freedom from SVD rate compares favorably relative to other published mid-term MVR studies. The patients in COMMENCE Mitral are demographically similar when compared to MVR populations in published literature.\textsuperscript{8,18} Surgical outcomes were excellent compared to risk scores, allowing more focus on actual valve function. The trial data set followed more standardized definitions for safety events than a retrospective single-center analysis and were adjudicated by a clinical events committee. In addition, all echocardiography results were adjudicated rigorously by an independent echo-core laboratory, and high compliance with follow-up visits was achieved (95\%). Overall, the study is encouraging for durability of RESILIA tissue in the mitral position.

Although this trial presents highly relevant outcomes, it is not without limitations. This study is limited by small cohort size. Further, the study reports midterm MVR outcomes, which is notable since several studies show a significant increase in valve deterioration beginning after 5 years.\textsuperscript{18-22,25} As a result, long-term follow-up is needed to understand if these findings are maintained beyond 5 years. This limitation will be addressed in part when outcomes from the 10 year COMMENCE trial extended follow-up cohort are evaluated. Further, real world data on acute and long-term safety and performance of the MITRIS RESILIA Mitral valve will be
collected in the prospective, global MOMENTIS trial with outcomes reported through 10 years post-implant ([https://clinicaltrials.gov/ct2/show/NCT05526560](https://clinicaltrials.gov/ct2/show/NCT05526560)).

The clinical implications of this study support the use of RESILIA tissue in the mitral position with excellent hemodynamics and durability out to 5 years. This is important as younger patients are requesting tissue bioprostheses and are in need of improved durability. The MITRIS RESILIA mitral valve is now available for clinical use in the United States and Japan, and will contribute to further information on durability.

**Conclusions**

Through 5 years of follow-up, the COMMENCE Mitral trial reported a good safety profile and clinically stable hemodynamic performance of a bioprosthetic valve with RESILIA tissue. Longer-term follow up is needed to fully assess durability of this novel option for mitral valve replacement.

**ACKNOWLEDGEMENTS**

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**References**


Table 1. Baseline Patient and Procedure Characteristics

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<thead>
<tr>
<th>Variable</th>
<th>Median (IQR) or % patients</th>
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<tr>
<td>Number of patients successfully implanted</td>
<td>82</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70 (13)</td>
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<td>STS risk score (%)</td>
<td>3.4 (2.7)</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
<td>58.5%</td>
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<tr>
<td>Male</td>
<td>41.5%</td>
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<td>Age (years)</td>
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<td>Age 80+</td>
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<td>Age 70-79</td>
<td>37.8%</td>
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<td>Age 60-69</td>
<td>26.8%</td>
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<td>Age 50-59</td>
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<tr>
<td>I</td>
<td>6%</td>
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<tr>
<td>II</td>
<td>35%</td>
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<tr>
<td>III</td>
<td>42%</td>
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<tr>
<td>IV</td>
<td>17%</td>
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<td>Concomitant procedures*</td>
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<tr>
<td>Coronary artery bypass grafting</td>
<td>14.6%</td>
</tr>
<tr>
<td>Other^</td>
<td>42.7%</td>
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None (isolated MVR) 42.7%

Valve size

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<th>Size</th>
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<td>27 mm</td>
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<td>19.5%</td>
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<td>33 mm</td>
<td>7.3%</td>
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* Patients may have undergone more than one concomitant procedure, therefore percentages may sum to more than 100%

^ Other procedures included atrial ablation, left atrial appendage closure, Maze procedure, and tricuspid valve repair.

IQR = interquartile range
STS = Society of Thoracic Surgeons
NYHA = New York Heart Association
MVR = mitral valve replacement
mm = millimeters
<table>
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<tr>
<th>Event</th>
<th>Early (≤ 30 days)</th>
<th>Cumulative at 5 years</th>
<th>Probability event-free at 5 yrs % (95% CI)</th>
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<tbody>
<tr>
<td>All cause mortality</td>
<td>1 (1.2%)</td>
<td>15</td>
<td>79.9% (70.8-89.1%)</td>
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<tr>
<td>Reoperation</td>
<td>0 (0%)</td>
<td>2</td>
<td>97.1% (93.1-100%)</td>
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<tr>
<td>Thromboembolism</td>
<td>2 (2.4%)</td>
<td>9</td>
<td>87.0% (78.9-95.0%)</td>
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<td>All bleeding</td>
<td>1 (1.2%)</td>
<td>18</td>
<td>74.6% (64.4-84.9%)</td>
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<tr>
<td>Endocarditis</td>
<td>0 (0%)</td>
<td>2</td>
<td>96.9% (92.7-100%)</td>
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<td>Hemolysis</td>
<td>0 (0%)</td>
<td>0</td>
<td>100% (100-100%)</td>
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<td>Valve dysfunction</td>
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<tr>
<td>SVD</td>
<td>0 (0%)</td>
<td>1</td>
<td>98.7% (96.1-100%)</td>
</tr>
<tr>
<td>NSVD</td>
<td>0 (0%)</td>
<td>2</td>
<td>97.0% (92.8-100%)</td>
</tr>
<tr>
<td>Major PVL*</td>
<td>0 (0%)</td>
<td>0</td>
<td>100% (100-100%)</td>
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<tr>
<td>Study valve explant</td>
<td>0 (0%)</td>
<td>1</td>
<td>98.6% (95.8-100%)</td>
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<tr>
<td>Valve thrombosis</td>
<td>0 (0%)</td>
<td>1</td>
<td>98.5% (95.5-100%)</td>
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</tbody>
</table>

*Major PVL = perivalvular leak of any grade requiring surgical intervention or considered a serious adverse event

N = number of events

CI = confidence interval

SVD = structural valve deterioration

NSVD = non-structural valve dysfunction
All events as defined by Akins, et al.\textsuperscript{14} and as adjudicated by Clinical Events Committee. All percentages computed as \% of the total number of successfully implanted patients (N=82). One patient was omitted from further analysis due to major PVL (4+) after the heart was restarted prior to leaving the OR and was deemed a technical failure; this patient was reintervened with a 27 mm Magna Mitral Ease valve.
Figure Legends

Central Picture

Freedom from death and structural valve deterioration at 5 yrs in COMMENCE Mitral patients

Figure 1. CONSORT Diagram

N = Number of patients

Figure 2. Kaplan-Meier: Overall Survival and Freedom from SVD (Graphical Abstract)

CI = confidence interval

SVD = structural valve deterioration

Figure 3. Echocardiography-derived valve hemodynamic outcomes over the follow-up period:

A) Mean mitral pressure gradients, B) Effective orifice area, C) Doppler velocity index (DVI), and D) Peak velocity.

Figure 4. Paravalvular A and B) transvalvular leak during the study period.

N = number of patients
Enrolled
N=83

Study valve implanted
N=82

1 yr follow up
N = 73

2 yr follow up
N = 66

3 yr follow up
N = 63

4 yr follow up
N = 57

5 yr follow up
N = 54

98.8% Technical Success:
N = 1 did not receive study valve
• N = 1 anatomical/procedural complications

N = 28 did not undergo 5 yr follow up:
N = 25 exited study prior to 5 yr visit:
• N = 15 deaths
• N = 1 expellant
• N = 6 withdrew consent
• N = 3 lost to follow up
N = 3 missed 5 yr visit
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Implications: Results of this study support the use of RESILIA tissue in the mitral position with excellent hemodynamics and durability out to 5 years. This is important as younger patients are requesting tissue bioprostheses and are in need of improved durability.
A New Biologic Mitral Valve Replacement

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Mid-term Outcomes of the COMMENCE Trial Investigating Mitral Valve Replacement Using a Bioprosthesis with a Novel Tissue

Institutional Review Board approvals

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<td>601 E. Rollins Street, MB #99 Orlando, FL 32803</td>
<td>Kevin Accola, MD</td>
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<td>David Adams, MD</td>
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<td>2725 Chemin Ste-Foy Québec (Québec) G1V4G5</td>
<td>François Dagenais, MD</td>
<td>Centre De Recherche Instutit Universitaire de Cardiologie et de Pneumologie de Québec</td>
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<td>Bartley Griffith, MD</td>
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<td>St. Vincent’s Hospital</td>
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<td>Princeton Baptist Med Ctr</td>
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<td>New York Presbyterian Hospital – Columbia University Medical Center 177 Fort Washington Ave., Suite 7-435 New York, NY 10032</td>
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<td>Columbia University Institutional Review Board 154 Haven Avenue, 1 Floor New York, NY 10032</td>
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<td>North Mississippi Medical Center, Inc. 830 South Gloster Street Fourth Floor East Tower Tupelo, MS 38801 Research Office Address: Cardiology Associates Research LLC 830 South Gloster Street Third Floor East Tower Tupelo, MS 38801</td>
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2021 AATS Annual Meeting
Mid-term Outcomes of the COMMENCE Trial Investigating Mitral Valve Replacement Using a Bioprosthesis with a Novel Tissue

Presenter: David Heimansohn
Invited Discussant: Gabriel Aldea

Dr. Gabriel Aldea (Seattle, WA):

Thank you. I wanted to again congratulate Dr. Heimansohn and his colleagues for presenting these data, for allowing me to review the presentation ahead of time, and we all fully agree with efforts to enhance durability of bioprosthetic valves studied here with a resilient platform. The authors demonstrated safety with excellent early mortality - it's actually four times better than predicted, - low gradience, excellent [inaudible] association class with a follow-up of four years. So, I'd like to make several comments and ask several questions of the authors because the study highlights the difficulty and challenges of such studies. To begin with, if we compare it with the aortic [inaudible] trial, the enrollment here was one-eighth of that, which I think has to do with the selection of patients. Most of us will repair most mitral valves for particularly and specifically this reason. The second is that the study is mostly a study of elderly patients, 80% greater than 60 and over 50% greater than 70. So presumably, the etiology for mitral valve replacement is significant mitral calcium and stenosis, perhaps with some element of regurgitation that cannot be repaired, and we know that those patients do not do as well long term. In addition, only two-thirds of the patients had follow-up data. 13.4% died in four years, again highlighting the complexity of these patients, and therefore only two-thirds of the patients had echocardiographic data.

Finally, the definitions used here, which are the common, standard definitions of an [inaudible], published in 2008, really underestimate the incidence of valve degeneration. And again, a publication by Dr. Devere, my colleague, in 2018 in circulation, with several of the panelists here being co-authors, demonstrated that there are morphological valve changes that precede physiological changes, including regurgitation of gradient before we get to the point of structural valve degeneration. So, the questions I had to the authors are-- one is patient selection, one is were tricuspid valve repairs excluded, just to make a more pure patient selection? The other is anticoagulation strategy for the patients. The third in their own practice now, given this data - and it's very young data, intermediate data, which we know the majority of degeneration occurs at eight or greater years - would they choose porcine pericardial or mechanical valves in their patients? What is the follow-up that is required for all bioprosthetic valve,
particularly in these patients—trans thoracic echo, CT, because again as the failure that they reviewed noted were talking and focusing on valve calcification— but perhaps we should equally focus on valve thrombosis? And finally, given the very small denominator which is expected to decrease with attrition of some of these patient population, at the end of 10 years, would we have to extrapolate data from aortic valve implantation at [inaudible] trial to mitral and tricuspid valves? I really thank the association for the opportunity to comment on this important work.

Dr. David Heimansohn (Indianapolis, IN):

Thank you, Dr. Aldea for taking your time to review this presentation and you asked spot-on questions, some of which have answers and some of which don't. This study absolutely was limited because of the strict patient selection. They did not allow tricuspid valve repair. And there was a lot of discussion at the time of the study design and the ongoing study, and near the end, I believe they changed it and allowed it, but that severely limited patient enrollment. The anticoagulation was standard, three-month anticoagulation after mitral valve repair, and then per the site's choice, depending on AFib and other reasons to undergo anticoagulation. Your valve choice is something we all face every day, and being a busy mitral valve surgeon, as we all are on this presentation, nobody wants mechanical valves. Nobody wants to deal with Warfarin. It's striking to me, even when you push patients and recommend it, they don't want it.

So, I think that's where the value of these kind of research studies are and even if you can make an incremental improvement in a valve's success and durability, I think you've gone a long way to helping this population. The other key question, follow-up— in fact, there's been a lot of discussions with this as well, and I'm involved in other valve studies where I think the science is evolving to 4D CT scans, certainly in the aortic position—whether it ends up being in the mitral position as well, time will tell. But that's certainly something that gives us more and different information than the echos do because the echos are more physiologic and flow, and the CT gives you much more anatomic details and can certainly quantitate calcification. And finally, this is going to be carried out to 10 years. Obviously - who knows - it may be single digits by the time we get to 10 years because the mean age is 69 years of age. And it probably will have to be correlated with the aortic study, which they've recently decided to follow those patients under age 65 as a 10-year sub-study, so that may help answer some of the questions, at least for the tissue processes in this complex tissue valve world.