Supplementary Appendix

Supplement to: Gammie JS, Chu MWA, Falk V, et al. Concomitant tricuspid repair in patients with degenerative mitral regurgitation. N Engl J Med. DOI: 10.1056/NEJMoa2115961

This appendix has been provided by the authors to give readers additional information about the work.

Table of Contents

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Grading of Tricuspid Regurgitation Severity

The degree of tricuspid valve regurgitation was categorized according to American Society of Echocardiography guidelines (Table 8, Zoghbi et al., 2003) as:

1. None/Trace
2. Mild
3. Moderate
4. Severe

Methods for Measuring Tricuspid Annular Dilatation

The tricuspid annulus diameter was measured in a right ventricle focused view apical 4 chamber per American Society of Echocardiography guidelines (Lang RM et al., 2015). The tricuspid annulus was identified as the point where leaflets were attached and the distance from the lateral and septal points of the tricuspid was measured at end-diastole.

Specifications for the Tricuspid Valve Repair

General Surgical Considerations

Patients will be randomized to either (a) tricuspid valve (TV) repair using a legally marketed annuloplasty ring in addition to mitral valve surgery (MVS), or (b) MVS alone.

After induction of anesthesia, all patients will undergo a transesophageal echocardiogram (TEE). The TEE will be performed under loading conditions as close as possible to the patient's baseline. Intra-operative TEEs will be performed according to a standardized acquisition protocol developed by the Echo Core Lab. A laminated copy of this acquisition protocol will be provided to the site and affixed to the operating room echo machine.

All procedures will be performed using cardiopulmonary bypass support and cardioplegic arrest. The management of cardiopulmonary bypass and myocardial protection will be at the discretion of the surgeon, using standard techniques. MV repair or replacement will be performed using standard techniques.

Tricuspid Valve Repair

It is recognized that surgical techniques for TV surgery may need to be adjusted at the discretion of the surgeon based on intra-operative findings that may not be previously recognized in the preoperative evaluation. The common elements for tricuspid annuloplasty planned as part of this trial are listed below:

- All procedures will be performed with cardiopulmonary bypass and with bicaval cannulation
- Both trans-septal and bi-atriatomies are acceptable as the approach to the TV
- Performance of TV repair on the arrested or the beating heart will be at the discretion of the surgeon
- TV repair will be performed with a rigid, incomplete, nonplanar, undersized annuloplasty ring
- Nominal annuloplasty ring sizes 26, 28, or 30 mm will be used. It is anticipated that normal tricuspid annular dimensions will be restored in most cases with a size 26 or 28 mm annuloplasty ring. The rationale for an approved rigid, incomplete, nonplanar and undersized (26, 28 or 30 mm) annuloplasty ring was based upon principles learned in functional MR trials, where inadequate mitral annular downsizing without a remodeling ring annuloplasty was associated with more recurrent MR (Bolling, Bax). Whereas some observational studies suggested higher recurrent TR rates following TV repair (McCarthy, Fukuda, Navia), more recent studies demonstrated less recurrent TR when an undersized, remodeling nonplanar annuloplasty ring was used (Filsoufi, Min, Ghoreishi).
- Commercially available rigid incomplete nonplanar tricuspid annuloplasty rings include:
  - Edwards MC3 tricuspid annuloplasty ring (model 4900)
  - Medtronic Contour 3D tricuspid annuloplasty ring (model 690R)
  - Medtronic Tri-Ad tricuspid annuloplasty ring (model 900SFC)
  - ATS TriAd Tricuspid Annuloplasty Ring
  - Carpentier-Edwards Classic tricuspid annuloplasty ring (model 4500)[1]
  - Carpentier-Edwards Physio Tricuspid ring (model 6200)
- Interrupted non-pledgeted mattress sutures will be placed from 9:00 o'clock to 6:00 o'clock (the mid-point of the septal leaflet) around the tricuspid annulus. In general, 10 to 12 sutures will be required to assure reliable seating of the tricuspid annuloplasty ring.

[1]Needs to be manually bent into nonplanar shape similar to other commercially available annuloplasty rings

Imputation of Missing Primary Endpoint Data

Patients missing the primary endpoint had their 24 month treatment status (success/failure) imputed via multiple imputation assuming the data were missing at random. The main feature of this imputation approach is the creation of a set of clinically reasonable imputations for treatment failure for each patient with missing data. This was accomplished using a set of repeated imputations created by predictive models based on the majority of participants with complete data. These imputation models reflect uncertainty in the modeling process and inherent variability in patient outcomes, as reflected in the complete data.

The pre-specified imputation model was stratified by randomization assignment and included age, sex, randomization strata for moderate or less TR at baseline, degree of TR at 6 months, and degree of TR at 12 months. Since this model included a mixture of variables types (i.e. continuous, ordinal, and binary), a fully conditional specification method was used (Berglund, Heeringa, & SAS Institute., 2014). Thirty datasets were imputed and combined using Rubin's method of multiple imputation to estimate treatment effect (Rubin & Schenker, 1986).

Missing Secondary Endpoint Data at 2 Years

The Statistical Analytical Plan pre-specified a missing data plan for baseline, primary outcome and secondary outcome data (see section 6.2 of the SAP). Multiple imputation was pre-specified for the primary endpoint, but for secondary endpoints, in general (with the exception of cost analyses), we pre-specified that missing endpoints would not be imputed and instead would be based on all available data.

In post-hoc analyses of secondary endpoints at 2- years, we assessed the reasons for missingness of echocardiographic, quality of life, and functional status endpoints (tabled below). Overall, completion of the two-year echo was high. The rate of missingness for the degree of TR was only ~7%. Among patients with a missed echo, the reasons for missingness included either the patient missing the visit, or technical issues where the patient underwent the echo but the images were not readable by the core lab (saved in the wrong format, correct view not taken, etc.). These reasons for missingness imply the echo data are likely missing completely at random, or at worst, missing at random. Completion of quality of life and functional status assessments was also high. Among survivors, KCCQ, SF-12, Euro-QOL and diuretic use had ~95% completion rates (NYHA was ~93%). Although the rate of missingness is low, estimates of treatment effects based on all available data may still be biased if data are not missing completely at random. Although we can review reasons for missingness, the mechanism of missing data is not truly testable. Therefore, as a supplemental analysis, we have assumed that 2-year cross-sectional endpoints are not missing completely at random in survivors, and instead assumed that data are missing at random conditional on patients' age, sex, randomization strata (moderate or less TR as baseline), and measures of the outcome of interest at prior visits (baseline, 6 months, and 1 year). The mixed model approach pre-specified for Quality of life analyses already assumed data were missing at random and therefore these supplemental analyses only include cross-sectional 2-year echocardiographic and functional status endpoints.

Surviving patients' missing outcomes were imputed via multiple imputation. For each outcome, the imputation model was stratified by randomization assignment and included age, sex, randomization strata for moderate or less TR at baseline, and corresponding values (if collected) of the outcome at baseline, 6 months, and 1 year. A fully conditional specification method was used and thirty datasets were imputed per outcome and combined using Rubin's method of multiple imputation to estimate treatment effect (Rubin & Schenker, 1986). Results using all available data and results in the post-hoc analyses that incorporated multiple imputation were consistent and are described in the table below.

Completion of the 2-Year Echo (N=401):

Echo Status	Readability if Complete/ Reason if Not Completed	N	%
Echo Completed	All Outcomes Readable[a]	303	75.6
	Some Outcomes Not Readable[b]	56	14.0
	Images Not Received	2	0.5
	Total	361	90.0
Echo Not Completed	Refusal	6	1.5
	Missed Visit/Assessment[c]	8	2.0
	Withdrawal	9	2.2
	Loss to Follow-up	2	0.5
	Death	15	3.7
	Total	40	10.0

a - Outcomes considered are degree of TR, degree of MR, LVEF, RV function, and trans-tricuspid diastolic peak gradient.

b – The missing data pattern for the outcomes of interest within the 56 echos where some outcomes were not readable is table below

c – Reasons for missed echo included COVID restrictions (n=3), unable to reach patient (n=1), and missed echo – reason not specified (n=4)

Missing Data Pattern in 2-Year Echos where Some Outcomes Not Readable (N=56)

Degree of TR	Degree of MR	Trans TR Peak Gradient	RV Function	LVEF	N	%
Complete	Complete	Complete	Complete	Not Readable	8	14.3
Complete	Complete	Complete	Not Readable	Not Readable	1	1.8
Complete	Complete	Not Readable	Complete	Complete	36	64.3
Complete	Complete	Not Readable	Complete	Not Readable	7	12.5
Complete	Complete	Not Readable	Not Readable	Not Readable	1	1.8
Complete	Not Readable	Complete	Complete	Not Readable	1	1.8
Complete	Not Readable	Not Readable	Complete	Not Readable	1	1.8
Not Readable	Complete	Not Readable	Not Readable	Not Readable	1	1.8

Completion of Quality of Life and Functional Status Assessments at 2-Years (N=401)

	KCCQ		SF-12		EuroQOL		NYHA		Diuretic Use	
	N	%	N	%	N	%	N	%	N	%
Survey Complete	369	92.0	364	90.8	369	92.0	358	89.3	367	91.5
Survey Started but not Completed	0	0	5	1.2	0	0	0	0	0	0
Refusal	2	0.5	2	0.5	2	0.5	3	0.7	1	0.2
Missed Visit/Assessment	4	1.0	4	1.0	4	1.0	14	3.5	7	1.7
Withdrawal	9	2.2	9	2.2	9	2.2	9	2.2	9	2.2
Loss to Follow-up	2	0.5	2	0.5	2	0.5	2	0.5	2	0.5
Death	15	3.7	15	3.7	15	3.7	15	3.7	15	3.7

Cross-sectional 2-Year Echocardiographic and Functional Status Outcomes as Observed (using all available data) and in a Post-hoc Supplemental Analysis using Multiple Imputation in Survivors:

	Observed							Imputed		
	MVS Alone (N=194)			MVS+TA (N=192)				MVS Alone (N=194)	MVS+TA (N=192)	
	No. Observed	No. Missing	Point Estimate [a] (SE)	No. Observed	No. Missing	Point Estimate [a] (SE)	Treatment Effect [a] (95% CI)	Point Estimate [a] (SE)	Point Estimate [a] (SE)	Treatment Effect [a] (95% CI)
Echocardiographic Endpoints										
Moderate/Severe TR	179	15	25.1 (3.2)	179	13	3.4 (1.3)	0.13 (0.06, 0.30)	24.9 (3.2)	3.2 (1.3)	0.13 (0.06, 0.29)
Recurrent Moderate/Severe MR	178	16	10.1 (2.3)	179	13	8.4 (2.1)	0.83 (0.43, 1.59)	10.1 (2.2)	7.9 (2.0)	0.79 (0.41, 1.51)
Trans-tricuspid diastolic peak gradient	145	49	1.8 (0.1)	168	24	3.1 (0.1)	1.32 (0.94, 1.70)	1.9 (0.1)	3.2 (0.1)	1.24 (0.88, 1.60)
Normal RV Function	178	16	91.6 (2.1)	178	14	91.0 (2.1)	0.99 (0.93, 1.06)	91.1 (2.1)	91.0 (2.1)	1.00 (0.94, 1.06)
LVEF	166	28	59.5 (0.6)	173	19	59.6 (0.6)	0.06 (-1.73, 1.85)	59.4 (0.6)	59.5 (0.6)	0.13 (-1.61, 1.87)
Functional Status										
NYHA Class III/IV	179	15	2.8 (1.2)	179	13	1.1 (0.8)	0.40 (0.08, 2.03)	2.6 (1.1)	1.1 (0.8)	0.43 (0.08, 2.24)
Diuretic Use	185	9	29.7 (3.4)	182	10	22.5 (3.1)	0.76 (0.53, 1.07)	29.9 (3.3)	22.7 (3.0)	0.76 (0.54, 1.06)

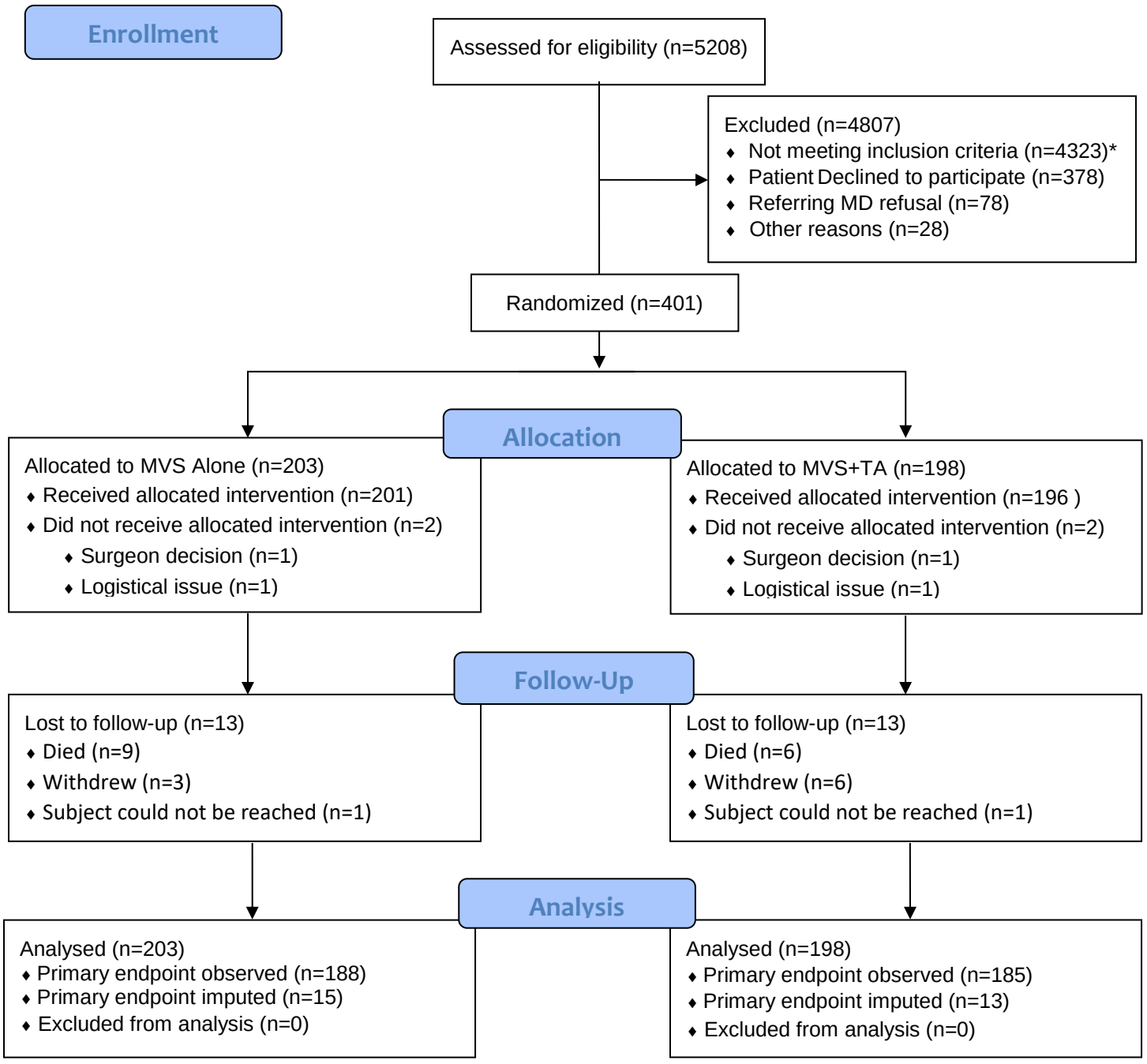
a- For categorical measures the point estimate is the percentage of patients and the treatment effect is the relative risk. For continuous measures the point estimate is the mean and the treatment effect is the difference of means. For both, MVS alone is the reference group.

b- Abbreviation: SE = standard error, CI = confidence interval, TR= tricuspid regurgitation, MR= mitral regurgitation, RV = right ventricular, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association

Sample Size Estimates

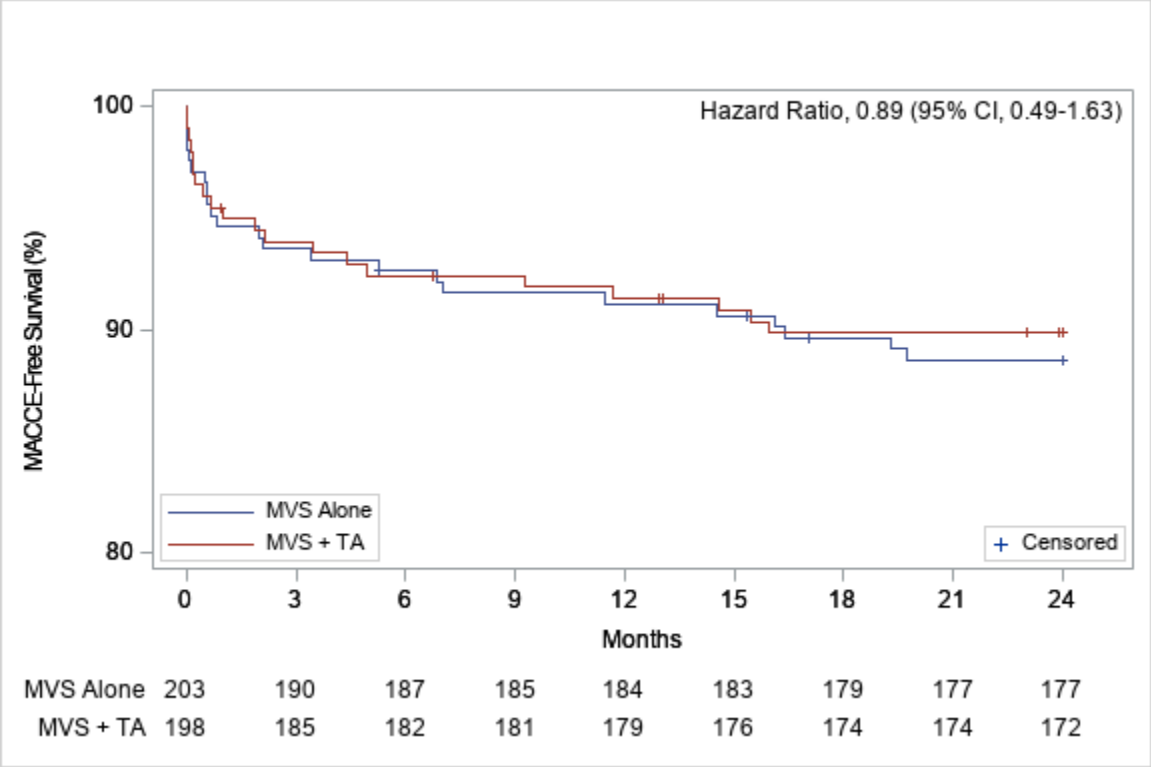
In our sample size calculations, we assumed based on the literature that 25% of patients treated with MVS only at 2 years would experience the primary composite endpoint (Nath et al., 2004; Kwak et al., 2008). We believe a meaningful effect worth detecting is at least a 50% relative reduction to 12% for patients undergoing TA in addition to MVS.

Figure S1. CONSORT Diagram



*The most common reasons for not meeting inclusion/exclusion criteria included not undergoing MVS for degenerative MR with a. Moderate TR as determined by transthoracic 2D echocardiography or b. tricuspid annular dimension ≥ 40 mm (index ≥ 21 mm/M2 BSA) and none/trace or mild TR determined by echocardiography (N=3127) and concomitant cardiac surgery other than atrial fibrillation correction surgery (PVI, Maze, LAA closure), closure of PFO or ASD, or coronary artery bypass grafting (CABG) (N=472)

Figure S2. MACCE-free Survival by Randomization Group*



*MACCE (major cerebrovascular or cardiac event) was defined as the composite event of death, stroke, and serious heart failure events.

Figure S3. Index Length of Stay after Surgery by Region. For each region, the Hodges-Lehmann estimate of location shift between the randomization groups is shown in the top right corner.

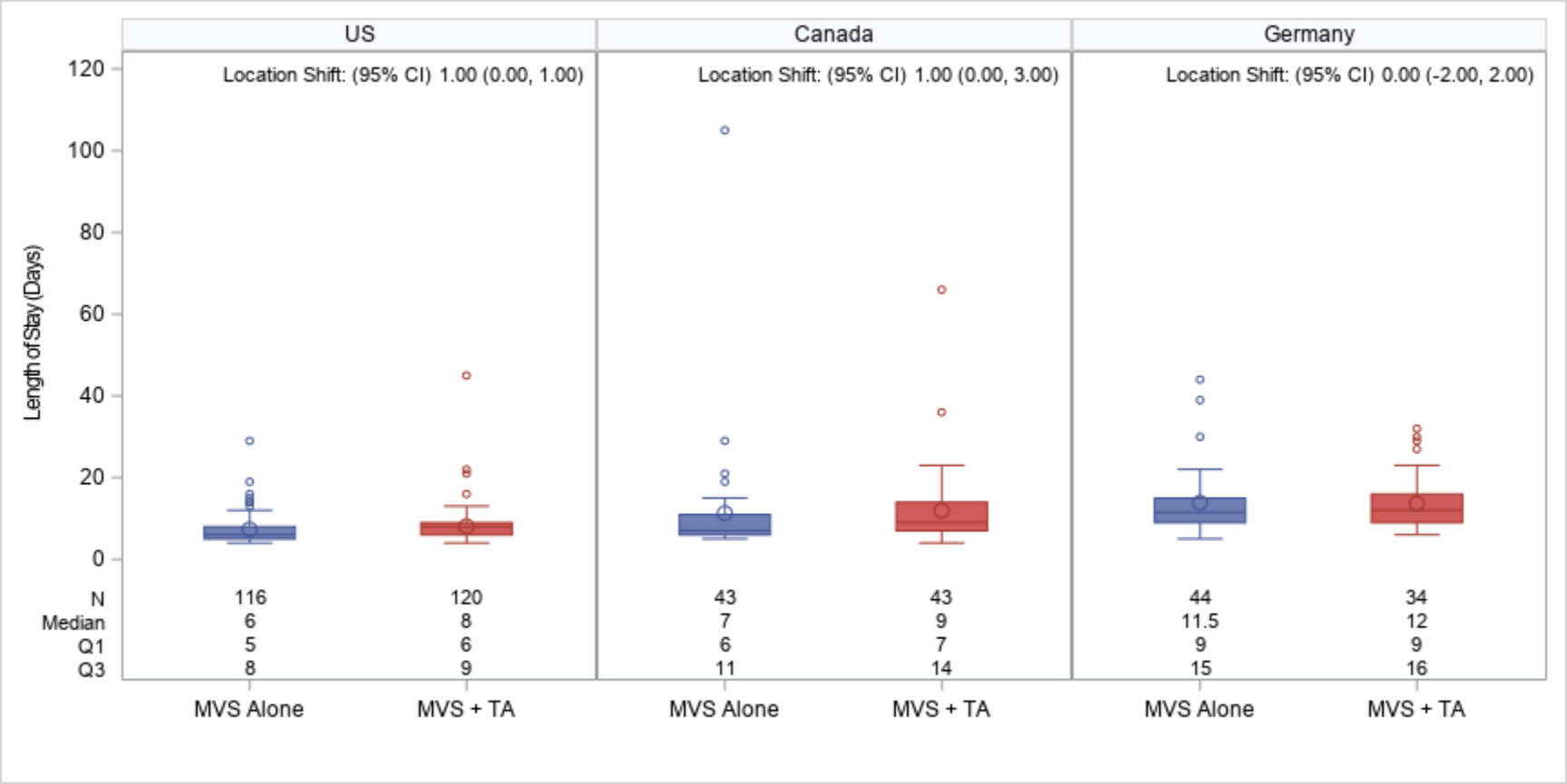
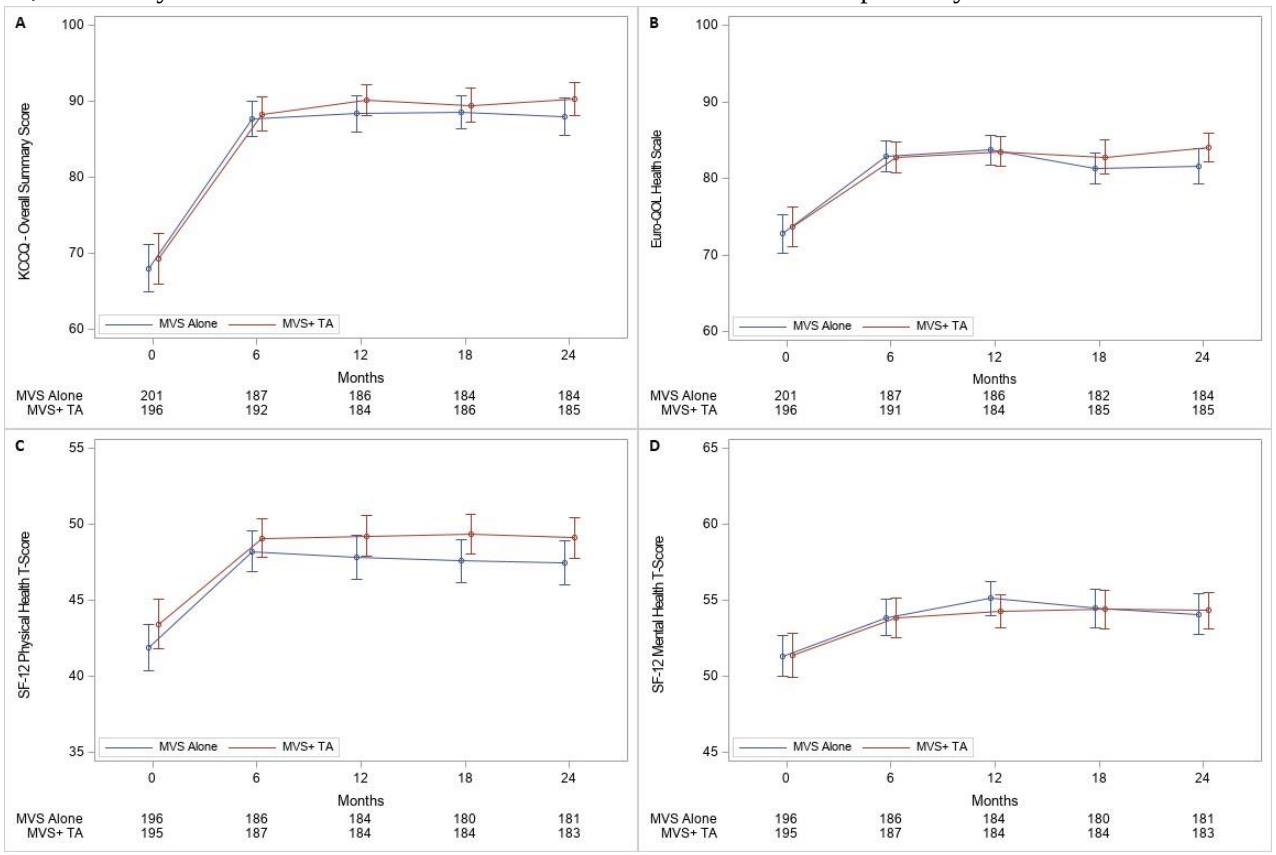


Figure S4. Quality of Life Overtime by Randomization Group*. Panel A shows the observed mean KCCQ Overall Summary Score in each group. The lines above and below the means denote the 95% confidence interval around the mean. Panels B, C and D depict the same for EuroQOL health state, SF-12 Physical Health T-Score and SF-12 Mental Health T-Score respectively.



*The trajectory of each QOL measure overtime was compared between randomization groups using linear mixed-effects models. No differences between the groups were detected for any measure. In addition, because mixed models assume that patient dropout is ignorable and the probability of dropping out at any time is related only to previously observed data (i.e. the data are missing at random), the statistical analysis plan pre-specified an alternative approach not subject to this assumption as a sensitivity analysis. We used pattern mixture models in which the data were stratified by missing data pattern (missing the two-year assessment versus not) following the approach outlined by Hedeker and Gibbons (1997). Across all four QOL measures, the interaction effect between pattern, time, and treatment effect was non-significant, indicating that the effect of treatment on quality of life overtime does not depend on the patient's completion status of their quality of life assessments.

Figure S5. Six Minute Walk Distance Overtime

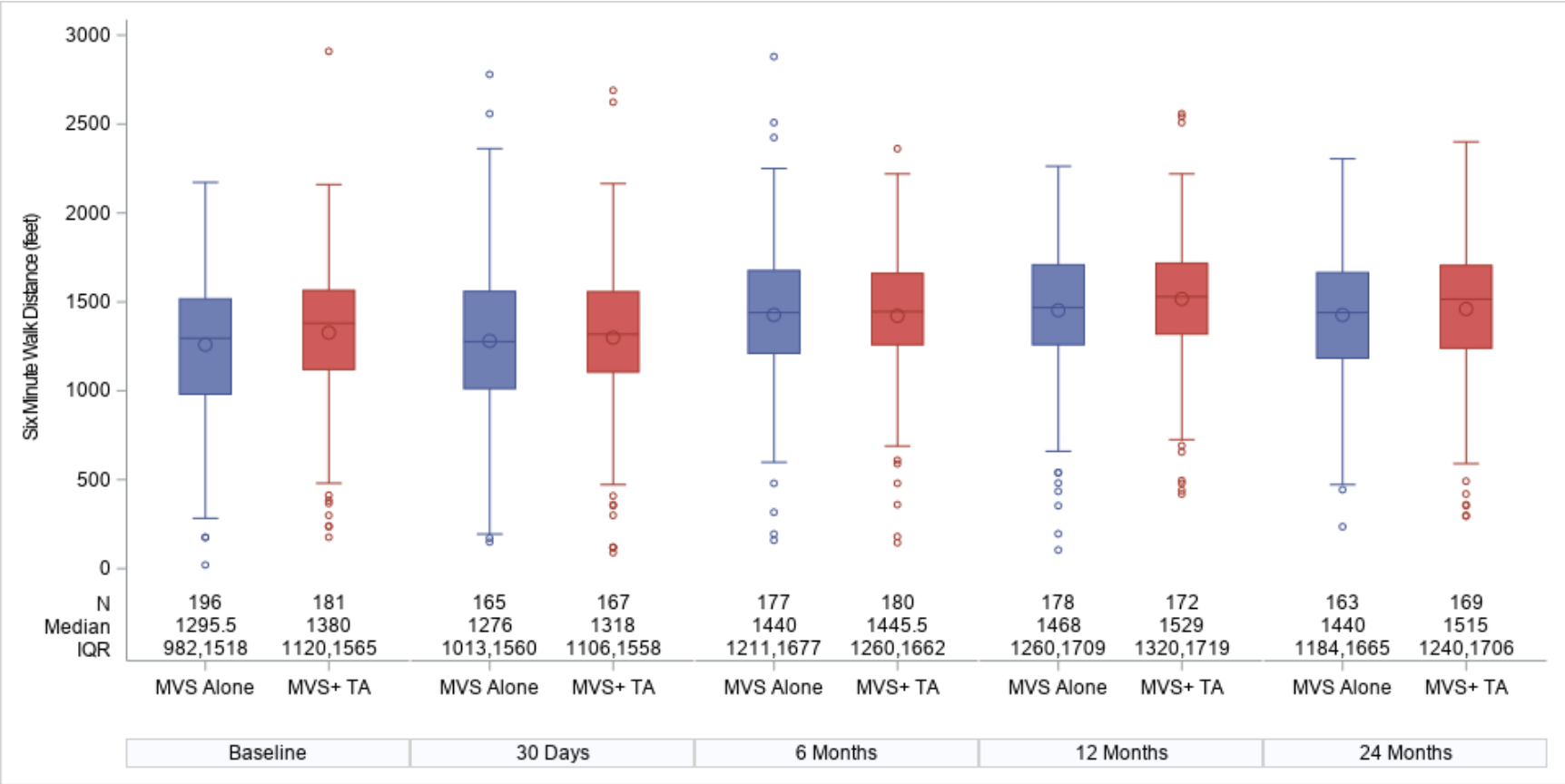


Figure S6. Gait Speed Test Overtime

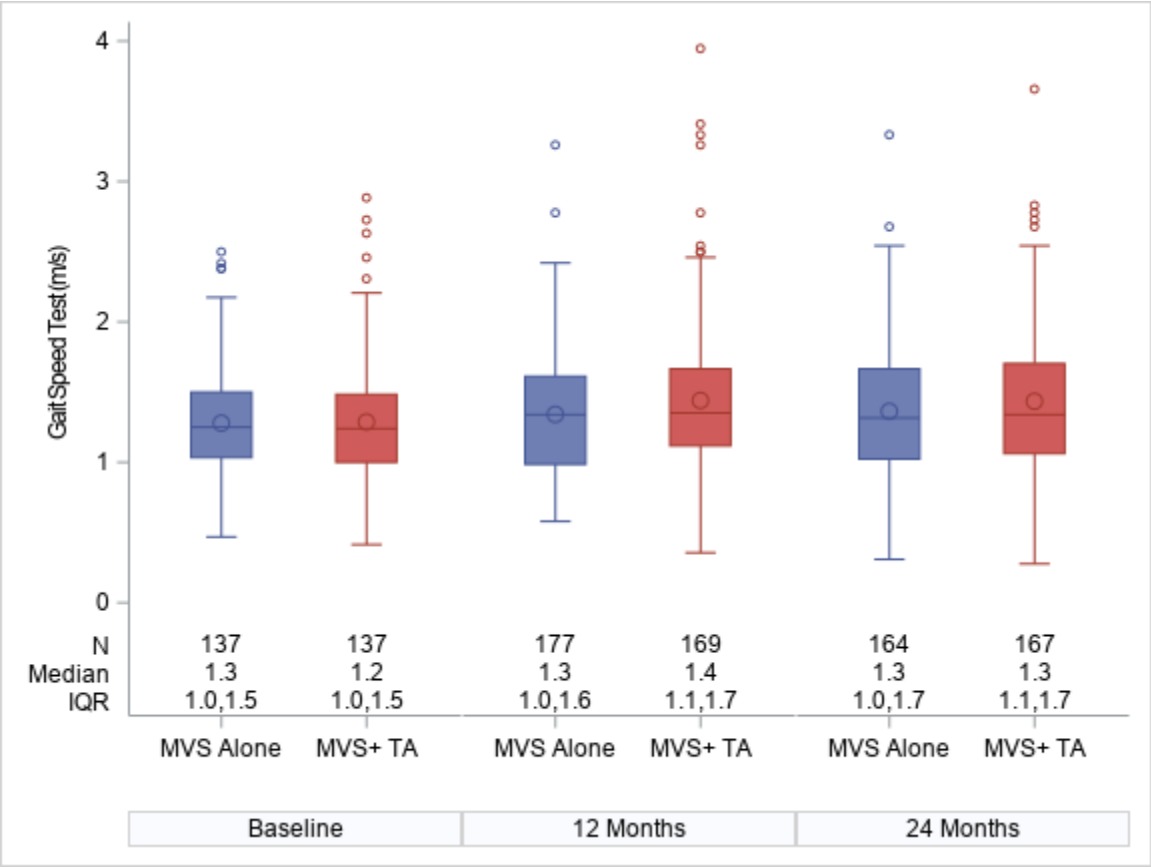
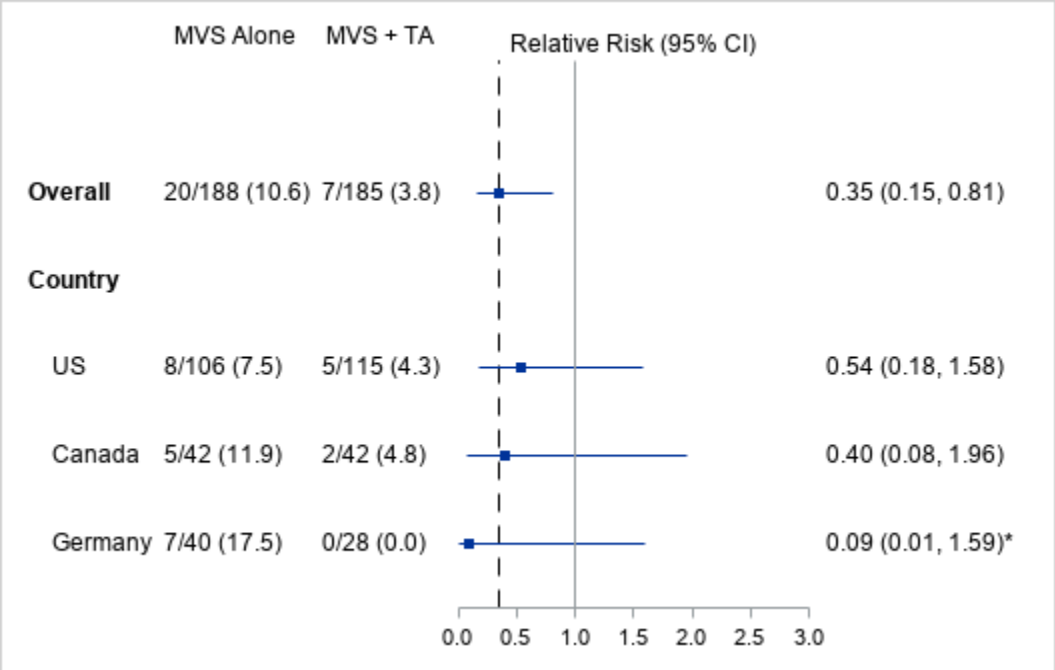


Figure S7. Primary Endpoint by Country The incidence of the primary outcome stratified by country of enrollment is shown below. The number with the primary endpoint over the number observed (percent) in each strata are given in the MVS Alone and MVS + TA columns.



*Since there were zero events in the MVS +TA group in Germany, the relative risk and confidence interval were calculated using a Wald modified approach in which 0.5 was added to each cell (SAS Institute Inc., 2017)

Table S1. Screening and Randomization by Clinical Center

	Screened (n)	Eligible (n)	Randomized (n)
London Health Sciences Centre	196	53	43
University of Maryland	126	72	39
Duke University	93	51	37
Baylor Research Institute	212	40	32
University of Virginia Health System	171	41	29
Hôpital Laval	652	61	27
German Heart Center Munich	27	25	24
Cleveland Clinic Foundation	163	63	23
University of Southern California	445	35	15
University Heart Center Hamburg	24	17	14
Dartmouth-Hitchcock Medical Center	201	35	11
Heart Center, University of Freiburg	150	27	11
Heart Center Leipzig	121	14	9
Yale New Haven	15	11	9
University of Alberta Hospital	168	8	8
Mission Hospital	77	8	7
University of Pennsylvania	154	14	7
German Heart Center Berlin	132	11	6
HDZ-NRW Bad Oeynhausen	260	6	6
Stanford University	33	14	6
University Medical Center Jena	20	7	6
University of Michigan	457	15	6
Emory University	94	6	5
Montreal Heart Institute	447	17	5
Baylor College of Medicine	14	7	3
Mayo Clinic	251	141	2
Toronto General Hospital	250	33	2
University Medical Center Göttingen	7	4	2
University of Wisconsin	69	29	2
Hôpital du Sacré-Cœur de Montréal	48	2	1
MedStar Heart & Vascular Institute	35	1	1
Montefiore - Einstein	45	1	1
University of Ottawa Heart Institute	2	1	1
WakeMed	6	1	1
Columbia University Medical Center	14	9	0
NIH Heart Center at Suburban Hospital	6	1	0
Ohio State University Medical Center	17	0	0
Stony Brook University Medical Center	5	4	0
University Medical Center Frankfurt	1	0	0
All	5208	885	401

Table S2. Reasons Screened Patients Ineligible for Randomization (N = 4,323)

	N	%
Not undergoing MVS for degenerative MR with a. Moderate TR as determined by transthoracic 2D echocardiography or b. tricuspid annular dimension ≥ 40 mm (index ≥ 21 mm/M2 BSA) and trace/mild TR determined by echocardiography	3127	72.3
Age <18	5	0.1
Unable to sign Informed Consent and Release of Medical Information Forms	25	0.6
Functional MR	303	7.0
Evidence of sub-optimal fluid management (e.g. lack of diuretics, weight in excess of dry weight) in the opinion of the cardiology investigator)	18	0.4
Structural/organic TV disease	81	1.9
Severe TV regurgitation as determined by preoperative transthoracic echocardiography (TTE)	219	5.1
Implanted pacemaker or defibrillator, where the leads cross the tricuspid valve from the right atrium into the right ventricle	204	4.7
Concomitant cardiac surgery other than atrial fibrillation correction surgery (PVI, Maze, LAA closure), closure of PFO or ASD, or coronary artery bypass grafting (CABG)	472	10.9
Cardiogenic shock at the time of randomization	3	0.1
STEMI requiring intervention within 7 days prior to randomization	2	0.0
Evidence of cirrhosis or hepatic synthetic failure	35	0.8
Severe, irreversible pulmonary hypertension in the judgment of the investigator	46	1.1
Pregnancy at the time of randomization	1	0.0
Therapy with an investigational intervention at the time of screening, or plan to enroll patient in additional investigational intervention study during participation in this trial	18	0.4
Any concurrent disease with life expectancy < 2 years	11	0.3
Unable or unwilling to provide informed consent	86	2.0
Unable or unwilling to comply with study follow up in the opinion of the investigator	136	3.1

Table S3. Pre-specified Analysis of the Primary Endpoint by Randomization Group Stratified by Concomitant CABG

No CABG	**MVS Alone (N=181)**	**MVS + TA (N=177)**	**Relative Risk (95% CI)**
Primary Endpoint (Observed)	16/166 (9.6)	5/165 (3.0)	0.31 (0.12, 0.82)
Died within 2 Years	8/177 (4.5)	4/170 (2.4)	0.50 (0.16, 1.63)
TV Operation within 2 Years	0/169 (0.0)	0/166 (0.0)	-
Progression of TR at 2 Years	8/158 (5.1)	1/161 (0.6)	0.12 (0.02, 0.96)
CABG	**MVS Alone (N=22)**	**MVS + TA (N=21)**	**Relative Risk (95% CI)**
Primary Endpoint (Observed)	4/22 (18.2)	2/20 (10.0)	0.58 (0.12, 2.81)
Died within 2 Years	1/22 (4.5)	2/20 (10.0)	-
TV Operation within 2 Years	0/21 (0.0)	0/18 (0.0)	-
Progression of TR at 2 Years	3/21 (14.3)	0/18 (0.0)	-

Table S4. Post-hoc Analysis of the Primary Endpoint by Randomization Group Stratified by Moderate or less TR at Baseline

<Moderate TR at Baseline[a]	**MVS Alone (N=126)**	**MVS + TA (N=124)**	**Relative Risk (95% CI)**
Primary Endpoint (Observed)	7/115 (6.1)	4/117 (3.4)	0.56 (0.17, 1.87)
Died within 2 Years	6/123 (4.9)	3/119 (2.5)	0.52 (0.13, 2.02)
TV Operation within 2 Years	0/117 (0.0)	0/116 (0.0)	-
Progression of TR at 2 Years	1/109 (0.9)	1/114 (0.9)	0.96 (0.06, 15.10)
Moderate TR at Baseline[a]	**MVS Alone (N=76)**	**MVS + TA (N=73)**	**Relative Risk (95% CI)**
Primary Endpoint (Observed)	13/72 (18.1)	3/67 (4.5)	0.25 (0.07, 0.83)
Died within 2 Years	3/75 (4.0)	3/70 (4.3)	1.07 (0.22, 5.13)
TV Operation within 2 Years	0/72 (0.0)	0/67 (0.0)	-
Progression of TR at 2 Years	10/69 (14.5)	0/64 (0.0)	-

a - Two patients are excluded from stratified analyses because the echo core lab was unable to read/confirm the degree of TR at baseline

Table S5. Readmissions through 2 Years

	MVS Alone (N=201; patient months=4608.0)		MVS+TA (N=194; patient months=4489.0)			
	No. Patients (%)	**No. Events (Rate per 24 Pt Months)[a]**	**No. Patients (%)**	**No. Events (Rate per 24 Pt Months)[a]**	**Hazard Ratio (95% CI)[b]**	**Relative Rate (95% CI)[c]**
All-cause Readmissions	66 (32.8)	124 (0.646)	69 (35.6)	104 (0.556)	1.09 (0.78, 1.53)	0.86 (0.58,1.27)
Cardiovascular Readmissions	38 (18.9)	70 (0.365)	42 (21.6)	59 (0.315)	1.16 (0.75, 1.79)	0.87 (0.52,1.43)
Heart Failure Readmissions	7 (3.5)	16 (0.083)	5 (2.6)	11 (0.059)	0.74 (0.23, 2.31)	0.71 (0.18,2.71)

a- Patient months at risk for readmission were calculated using the patients days alive and free of hospitalization through 2 years post-randomization. Readmission was defined as any emergency department admission or hospitalization >24 hours. 2 patients in the MVS alone and 3 patients in the MVS+TA group died during the index hospitalization, 1 patient in the MVS+TA group withdrew prior to discharge from the index hospitalization – these patients are excluded from analyses of readmission by 2 years post-randomization

b- In a post-hoc analysis, we compared time to first readmission treating death as a competing risk using the methods of Fine and Gray (1999)

c- In a pre-specified analysis, we compared rates of readmission within two years of randomization using Poisson regression with robust variance estimation.

Table S6. Representativeness of Study Participants

Category	Example
Disease, problem, or condition under investigation	Patients with moderate tricuspid regurgitation or less than moderate tricuspid valve regurgitation with a dilated tricuspid valve annulus undergoing mitral valve surgery for severe degenerative mitral regurgitation
Special consideration related to	
Sex, gender, and age	A study based on the Society of Thoracic (STS) Surgeons Adult Cardiac Surgery Database, the most comprehensive prospectively collected registry of cardiac surgery procedures, demonstrated that of 165,405 patients undergoing mitral valve surgery between 2014 and 2018, mean (IQR) age was 66.0 (57-74) and women represented 45.2% of the cohort (Vermulapalli et al., 2019). In a 2018 STS study of degenerative MR and TR, 36.1% of patients undergoing surgery were women (Gammie et al, 2018). In the study by Vermulapalli and colleagues, race/ethnic distributions were reported as follows: White (77.2%), Black (9.9%), Hispanic (5.9%), Asian (3.0%), Native American (0.4%), and other (1.8%). As this registry represents >95% of all cardiac surgery in the United States, these demographic characteristics are the best non-biased representation of surgical mitral valve disease available. Data on race and ethnicity specific to tricuspid valve repair in the setting of mitral valve repair is lacking.
Geography	In Germany's Heart Surgery Report 2020 (Beckmann et al., 2021), mitral valve procedures are not listed separately, but included as "Heart Valve Procedures". Of the 15,302 procedures, 43% were in women. Race and ethnicity are not reported. The demographics of race and ethnicity of patients undergoing MVS varies among the US, Germany and Canada.
Other considerations	The prevalence of TR in the setting of moderate or greater MR is not reported (Singh et al., 1999).
Overall representativeness of this trial	The participants in the present study were of similar age to that reported in the registry (68.2 ± 9.7 and 66.6 ± 10.7 years in control vs. treatment group). Biologic sex was reported by participants; during screening patients were asked whether they were female or male. While women appear to represent approximately 40% of those undergoing mitral valve surgery in registry, our study enrolled less women than expected (25%). Patients in North America were asked about their race and ethnicity, according to NIH categories. Our study was also less representative regarding race and ethnicity, with 2.5% Black and 1.5% Hispanics, in contrast to the 9.9% Blacks and 5.9% Hispanics in the STS registry. The lack of diversity in this study is a limitation to the interpretation of this trial.

Table S7. Race, Ethnicity and Sex by Country of Enrollment

	US (N=236)	Canada (N=87)	Germany (N=78)	Overall (N=401)
Race - No. (%)				
American Indian or Alaska Native	1 (0.4)	0 (0)	0 (0)	1 (0.2)
Asian	2 (0.8)	6 (6.9)	0 (0)	8 (2.0)
Black or African American	10 (4.2)	0 (0)	0 (0)	10 (2.5)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0 (0)	0 (0)	1 (0.2)
White	215 (91.1)	76 (87.4)	75 (96.2)	366 (91.3)
More than one Race	0 (0)	0 (0)	0 (0)	0 (0)
Unknown or Not Reported	7 (3.0)	5 (5.7)	3 (3.8)	15 (3.7)
Ethnicity - No. (%)				
Hispanic or Latino	6 (2.5)	0 (0)	0 (0)	6 (1.5)
Not Hispanic or Latino	225 (95.3)	82 (94.3)	72 (92.3)	379 (94.5)
Unknown or Not Reported	5 (2.1)	5 (5.7)	6 (7.7)	16 (4.0)
Sex - No. (%)				
Male	180 (76.3)	58 (66.7)	62 (79.5)	300 (74.8)
Female	56 (23.7)	29 (33.3)	16 (20.5)	101 (25.2)

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