MITRAL (Mitral Implantation of TRAnscatheter vaLves)

30-Day Outcomes of Transcatheter MV Replacement in Patients With Severe Mitral Valve Disease Secondary to Mitral Annular Calcification or Failed Annuloplasty Rings

Mayra Guerrero, MD, FACC, FSCAI
On behalf of the
MITRAL trial investigators

TCT 2017
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NorthShore University HealthSystem
Evanston Hospital

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/ arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Research Grant Support, Proctor	• Edwards Lifesciences
• Consultant	• Tendyne Holdings/Abbott
• Speaker's Bureau	• Abiomed

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MITRAL

Mitral Implantation of TRAnscatheter vaLves

The safety and feasibility of the SAPIEN XT and SAPIEN 3 THVs in patients with symptomatic severe calcific mitral valve disease with severe mitral annular calcification and patients with failing mitral surgical rings or bioprostheses who are not candidates for mitral valve surgery

Background

- There are limited data on outcomes of Transcatheter Mitral Valve Replacement (TMVR) in patients with severe mitral annular calcification (MAC) or failing surgical rings or bioprostheses.

Methods

- Physician-sponsored, prospective, multicenter clinical trial, 13 U.S. sites
- N=90 high surgical risk patients with symptomatic severe MAC (30), failing surgical rings (30) or mitral bioprostheses (30).
- Case review committee prior to approval.
- Independent echo and CT core labs.
- Clinical events adjudicated by clinical events committee.
- Safety monitored by data safety monitoring board.

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Primary and Secondary Endpoints

Primary Safety Endpoints

- Technical Success at Exit from Cath Lab/OR*
- Procedural Success at 30 days*

Primary Effectiveness Endpoint

- Patient Success at 1 year*

Secondary Safety and Effectiveness Endpoints

- Composite of various adverse events at 30 days and 1 year

*Definitions similar to MVARC criteria with minor differences

Primary and Secondary Endpoints

Primary Safety Endpoints

- Technical Success at Exit from Cath Lab/OR:

Successful vascular and/or TA access, delivery and retrieval of the transcatheter valve delivery system, deployment of single valve in correct position, MVA > 1.5 cm2, no residual MR grade ≥2 (+), no additional surgery or reintervention includes drainage of pericardial effusion, patient leave cath lab/OR alive.

- Procedure Success at 30 days:

Device success and no device/procedure related SAE's including: death, stroke, MI or coronary ischemia requiring PCI or CABG, stage 2 or 3 AMI including dialysis, life threatening bleeding, major vascular or access complication requiring additional unplanned surgical or transcatheter intervention, pericardial effusion requiring drainage, severe hypotension, heart failure or respiratory failure requiring IV pressors or IABP or LVAD or prolonged intubation ≥48 hrs, or any valve-related dysfunction, migration, thrombosis or complication requiting surgery or repeat intervention.

Device success: Stroke free survival with original valve in place, no additional surgery or re-intervention related to procedure, access or THV, intended valve function including: no migration, fracture, thrombosis, hemolysis or endocarditis' MVA≥1.5 cm2, MV gradient <10 mmHg, residual MR < 2(+) and without hemolysis, no increase in AI from baseline, and LVOT gradient ≤20 mmHg increase from baseline.

Primary Effectiveness Endpoint

- Patient Success at 1 year:

Device success and all of the following: patient returns to pre-procedural setting, no re-hospitalizations or re-interventions for HF or the underlying MV condition (including HF hospitalization equivalents, drainage pleural effusion, new listing for heart transplant or VAD, NYHA improvement at least 1 class vs baseline, KCCQ improvement >10 vs baseline, 6 MWT improvement >50 meter vs baseline.

Secondary Safety and Effectiveness Endpoints

- Composite of various adverse events at 30 days and 1 year

MITRAL Trial

Physician-sponsored FDA approved IDE Multicenter clinical trial
Prospective evaluation of SAPIEN XT and SAPIEN 3 in patients with severe MAC, ViR and ViV

Sponsor and National PI

Mayra Guerrero, MD, Evanston Hospital, Evanston, IL, USA

Core Laboratories

Cardiac CT	Dee Dee Wang, MD (Director), Henry Ford Hospital, Detroit, MI, USA
Echocardiography	Pamela Douglas, MD (Director), Duke Clinical Research Institute, Durham, NC, USA
Electrocardiography	Jose Nazari, MD (Director), NorthShore University Health System, Evanston, IL, USA
Pathology	Renu Virmani, MD (Director), CV Path Institute, Inc., Gaithersburg, MD, USA

Data Safety Monitoring Board

John Lasala, MD (Chair)	Washington University School of Medicine, St. Louis, MO, USA
Juan Granada, MD	Cardiovascular Research Foundation-Skirball Center for Innovation, New York, NY, USA
Cindy Grines, MD	Hofstra University and Northwell School of Medicine, Manhasset, NY, USA
Alec Vahanian, MD	Bichat Hospital, University of Paris, Paris, France.

Clinical Events Committee

Carl Tommaso, MD (Chair) (Interventional Cardiologist) Highland, Park Hospital, Highland Park, IL, USA
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Ronald Berger, MD (Clinical Cardiologist), Skokie Hospital, Skokie, IL, USA
Steven Meyers, MD (Neurologist) Evanston Hospital, Evanston, IL, USA

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MITRAL Trial

90 patients enrolled between February 2015 and October 2017 at 13 centers
ViMAC (n=30), ViR (n=30) and ViV (n=30)

Participating/enrolling Sites	Principal Investigator	Patients
Evanston Hospital, Evanston, IL	Ted Feldman	20
Henry Ford Hospital, Detroit, MI	William O'Neill	13
Columbia University Medical Center, New York, NY	Martin Leon	12
Mayo Clinic, Rochester, MN	Mackram Eleid	9
Cedars Sinai Medical Center, Los Angeles, CA	Raj Makkar, Saibal Kar	7
Piedmont Heart Institute, Atlanta, GA	Christopher Medurii	7
Massachusetts General Hospital, Boston, MA	Igor Palacios	6
Medstar Washington Hospital Medical Center, Washington, DC	Lowell Satler	5
University of Washington Medical Center, Seattle, WA	Mark Reisman	4
Mount Sinai Hospital, New York, NY	George Dangas, David Adams	3
Banner University Medical Center, Phoenix, AZ, USA	Ashish Pershad, Kenith Fang	2
Intermountain Medical Center, Murray, UT	Brian Whisenant	1
Memorial Hermann Texas Medical Center, Houston, TX	Richard Smalling, Pranav Loyalka	1

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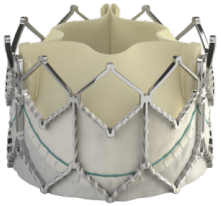
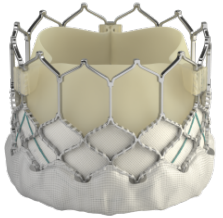
MITRAL Trial



SAPIEN XT

90 patients extremely high surgical risk (STS PROM >15% or M&M >50%)



SAPIEN 3

Inclusion Criteria

NYHA II or greater

Native MV (MAC)
n=30

Severe MS (MVA ≤1.5 cm2)
Severe MR + Moderate MS

Valve-in-Ring
n=30

Severe MS (MVA ≤1.5 cm2)
At least Moderate-Severe MR

Valve-in-Valve
n=30

Severe MS (MVA ≤1.5 cm2)
At least Moderate-Severe MR

Results of MViV at AHA
Nov 13, 2017

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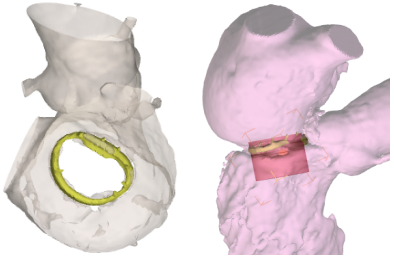
Cardiac CT & Procedural Planning

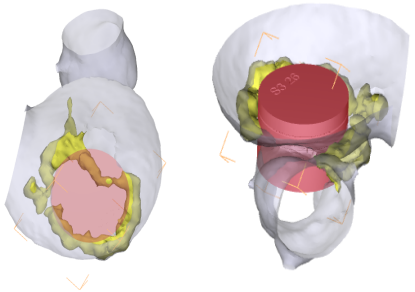
- THV size selection based on mitral annular area
- Risks of LVOT obstruction and embolization were evaluated
- Access route (transeptal preferred if adequate anatomy)
- Deployment angle for procedural planning

Valve in Ring



Compared with ViV app recommendation:
Sizing agreement in 80%
Difference size chosen in **20%** (smaller=2, larger=4)

Valve in MAC



If high risk of LVOTO:
Pre-emptive alcohol ablation in selected cases, or
Transatrial TMVR with surgical resection of anterior leaflet

If high risk of embolization:
Transatrial TMVR with sutures

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Patient Flow

Valve-in-Ring Arm

Ring Type	n
Edwards Physio	9
Edwards Classic	4
St. Jude Seguin	3
Medtronic CG Future Ring	3
Medtronic CG Future Band	2
Edwards Physio 2	2
Edwards ET Logix	1
St. Jude Tailor Band	1
Medtronic Simulus SemiRigid	1
Duran AnCore	1
Sorin Memo 3D	1
Sorin Annuloflex	1
Cosgrove Band	1

36 patients presented in case review call*

→ 6 patients excluded:
3= Risk of Embolization
(2 Cosgrove bands, 1 Perigard band)
2= Risk of LVOTO
1= Dehiscense with para-ring leak

↓

30 patients enrolled

↓

30 patients treated

Failure mode	n(%)
Regurgitation	17 (56.7%)
Stenosis	10 (33.3%)
Both	3 (10%)

Last implant 10-3-17
Not all data monitored yet
(this is a preliminary analysis)

*All patients presented at case review call
All CT scans reviewed by Core Lab prior to presentation

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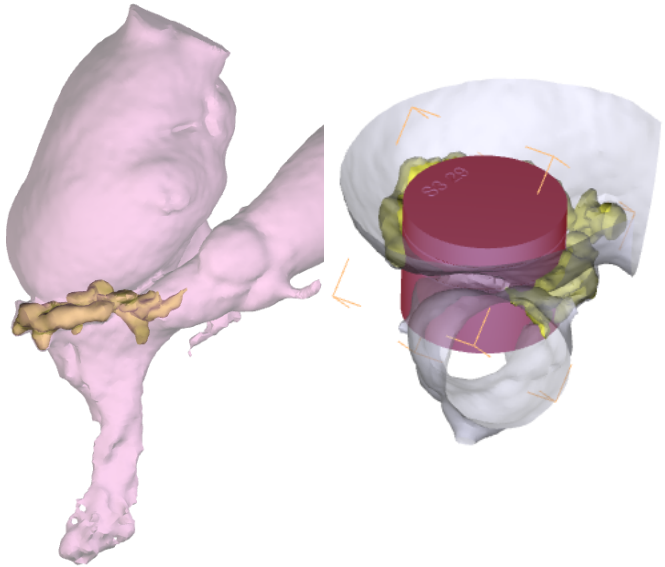
Patient Flow

Valve-in-MAC Arm



92 patients presented in case review call* → 61 patients excluded:
29= Risk of LVOTO
16= Risk of Embolization
16= Both

↓

30 patients enrolled

↓

30 patients treated → 1 patient withdrew consent at discharge post TMVR
1 patient approved awaiting enrollment and procedure

Last implant 10-19-17
Not all data monitored yet
(this is a preliminary analysis)

*All patients presented at case review call
All CT scans reviewed by Core Lab prior to presentation

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Patient Characteristics

Characteristics	Valve-in-Ring n (%), or mean (±SD)	MAC n (%), or mean (±SD)
Age	72 (±9.0)	74.5 (±7.7)
Female	**10 (33.33%)**	**21 (70%)***
NYHA		
II	7 (23.33%)	5 (16.67%)
III	20 (66.67%)	21 (70%)
IV	3 (10%)	4 (13.33%)
Diabetes	8 (26.67%)	10 (33.33%)
COPD	4 (13.33%)	13 (43.33%)*
Home Oxygen	3 (10%)	5 (16.67%)
Atrial Fibrillation	19 (63.33%)	12 (40%)*
Renal Failure	10 (33.33%)	8 (26.67%)
Prior CABG	18 (60%)	12 (40%)
Prior AVR	**4 (13.33%)**	**16 (53.33%)***
STS score	**9.1 (±6.6)**	**8.8 (±8.3)**

ViR Failure mode	n(%)
Regurgitation	17 (56.7%)
Stenosis	10 (33.3%)
Both	3 (10%)

MAC Failure mode	n(%)
Regurgitation	3 (10%)
Stenosis	22 (73.3%)
Both	5 (16.7%)

* $p < 0.05$

Data monitoring not yet complete, may be subject to change.

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Baseline Echocardiogram

	Valve in Ring n (%), or mean (±SD)	MAC n (%), or mean (±SD)
Ejection fraction (%)	**45.6 (±13.7)**	**63.4 (±10.5)***
Mean MVG (mmHg)	**7.4 (±4.8)**	**12.3 (±4.2)***
MVA (cm2)	**2.7 (±0.7)**	**1.2 (±0.36)***
Systolic PAP (mmHg)	48.9 (±14.1)	57.1 (±23.3)
Peak LVOT gradient (mmHg)	3.7 (±2.0)	5.6 (±3.0)
MV Pathology		
Regurgitation	**17 (56.7%)**	3 (10%)
Stenosis	10 (33.3)	**22 (73.3%)**
Both MR and MS	3 (10%)	5 (16.7%)

* $p < 0.05$

Data not yet finalized by echo core lab, may be subject to change.

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ViR Procedural Outcomes

100% Transseptal Access

Outcomes	In-Hospital n=30	30 Days n=29*
All-Cause Mortality	2 (6.6%)	2 (6.8%)
Cardiovascular death	1 (3.3%)	1 (3.4%)
Non-Cardiac death	1 (3.3%)	1 (3.4%)

* Last implant 10-3-17 (POD # 28 at time of this presentation)
Data not yet adjudicated, may be subject to change.

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ViR Primary Safety Endpoints

	n (%)
Technical success at exit from Cath Lab (n=30)	**21 (70%)**
Need for second valve* (position too atrial causing MR=5, leaflet infolding at ventricular edge of THV causing MR=1) * In early experience: Operator's first ViR in MITRAL trial=3, second implant=3)	6 (20%)
2 (+) Mitral Regurgitation (1 treated with paravalvular leak closure)	3 (10%)
Procedural Success at 30 days (n=29, last implant 10-3-17)	**18/29 (62%)**
Death at 30 days	2 (6.8%)
Reintervention (1 PVL closure attempt followed by surgical MVR)	1 (3.4%)
Mean MVG >10 mmHg (2 were on HD)	4 (13.8%)
MVA < 1.5 cm2	3 (10.3%)
Intracranial hemorrhage (spontaneous bleed in undiagnosed preexisting brain tumor)	1 (3.4%)

Data not yet adjudicated, may be subject to change.

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Outcomes of 2nd Valve Requirement

	Alive at 30 Days	Procedural Success Criteria Met	NYHA Class at 30 days
1	Yes	Yes	1
2	Yes	Yes	3
3	Yes	Yes	2
4	Yes	Yes	2
5	Yes	Yes	2
6	Yes	Yes	3

MAC Procedural Outcomes

50% Transseptal or TA
(TS=14, TA=1)
Difficult anatomy for TS=1

50% Transatrial (n=15)
Risk of LVOTO=3
Risk of embolization=6
Both=6

Outcomes	In-Hospital n=30	30 Days n=26*
All-Cause Mortality	5 (16.7%) Transeptal=1 Transapical=1 Transatrial=3	5 (19.2%)
Cardiovascular death	1 (3.3%)	1 (3.8%)
Non-Cardiac death	4 (13.3%) MOF=4	4 (15.3%)

* 3 patients treated in October 2017 (POD # 13, 21 and 27 at time of this presentation)
1 patient withdrew consent while being discharged after successful transatrial TMVR

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MAC Primary Safety Endpoints

	n (%)
Technical success at exit from Cath Lab (n=30)	**22 (73.3%)**
LVOT Obstruction (Transseptal=1, Transpical=1, Transatrial=1)	3 (10%)
Need for second valve	1 (3.3%)
≥ 2 (+) Mitral Regurgitation on procedural TEE confirmed by core lab	2 (6.6%)
Left ventricular perforation (transatrial TMVR)	1 (3.3%)
Ventricular septal defect (transatrial TMVR)	1 (3.3%)
Procedural Success at 30 days (n=26, 1 withdrew consent, 3 not due for 30 day endpoint)	**12/26 (46%)**
Death at 30 days	5 (19.2%)
Hemolysis (1 required ViV, 2 conservative with spontaneous resolution)	3 (11.5%)
Bleed (GI bleed with shock=1, hemothorax=1)	2 (3.8%)
Heart failure requiring ASD closure	1 (3.8%)
Acute Kidney Injury	1 (3.8%)
Left ventricular perforation during transatrial TMVR	1 (3.8%)
3 (+) Mitral regurgitation	1 (3.8%)

Data not yet adjudicated, may be subject to change.

Intraprocedural Complications

	ViR n (%)	MAC n (%)
Valve embolization	0	0
LVOT Obstruction with hemodynamic compromise	0	3 (10%)
Left ventricular perforation	0	1 (3.3%)
Pericardial effusion requiring pericardiocentesis	0	1 (3.3%)
Conversion to open heart surgery during index procedure	0	0
Paravalvular leak closure	1 (3.3%)	0
Myocardial infarction requiring intervention	0	0
New pacemaker (TS=1, transatrial=3)	0	**4 (13.3%)**
Vascular complications (RP bleed post-TMVR=2, hematoma=1)	3 (10%)	0

4 of 30 TS ViR (13.3%) had percutaneous closure of septostomy during index procedure
2 of 14 TS MAC patients (14%) had percutaneous closure of septostomy during index procedure

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Adverse Events at 30 days

	ViR n=29* n (%)	MAC n=26 ** n (%)
Valve embolization	**0**	**0**
Valve thrombosis	**0**	**0**
Reintervention (ViR: surgical MVR=1, ViMAC: MViV=1)	**1 (3.4%)**	**1 (3.8%)**
Myocardial infarction	0	0
Ischemic stroke	0	1 (3.8%)
Intracranial hemorrhage (spontaneous bleed in undiagnosed preexisting brain tumor)	1 (3.4%)	0
Hemolytic anemia	**1 (3.3%)**	**3 (11.5%)**
Acute renal failure requiring new hemodialysis	3 (10.3%)	1 (3.8%)
Blood transfusion	6 (20.6%)	9 (34%)

* 1 Patient on PDO # 28 at time of this presentation
** 3 patients treated in October 2017 (POD # 13, 21 and 27 at time of this presentation)
1 patient withdrew consent while being discharged after successful transatrial TMVR

Data not yet adjudicated, may be subject to change.

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Role of Alcohol Septal Ablation

15 non-transatrial TMVRprocedures
Transseptal=14, Transapical=1

↓

1st TMVR in the trial (TS) was complicated with LVOTO
Treated with bail-out alcohol ablation (Dr. O'Neill)

→ Bail out
Proof of concept

↓

2st TMVR in the trial (TA) was complicated with LVOTO
Treated with bail-out alcohol ablation at Evanston Hospital
LVOT gradient recurred the following day

→ Generated concept of Preemptive ablation weeks prior to TMVR

↓

13 additional transseptal TMVR procedures
(7 pretreated with alcohol septal ablation weeks prior to TMVR)

↓

100% discharged from the hospital
12 of 13 alive at 30 days
1 at home alive on POD #13 at time of this presentation

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Echocardiogram at 30 days

	ViR N=24	ViMAC N=20
Ejection Fraction (%)	45.4 (±9.9)	61.1 (±10.2)*
Mean MVG (mmHg)	8.4 (±3.4)	6.6 (±1.4)*
MVA (cm2)	2.1 (±0.5)	3.2 (±1.2)*
Peak LVOT gradient (mmHg)	47.5 (±11.9)	51.4 (±15.5)
Systolic PAP (mmHg)	4.9 (±2.8)	8.2 (±5.4)
Mitral Regurgitation		
None or Trace	18/24 (75%)	16/20 (80%)
1 (+)	6/24 (25%)	2/20 (10%)
2(+)	0	1/20 (5%)
≥3 (+)	0	1/20 (5%)

* $p < 0.05$

Data not yet finalized by echo core lab, may be subject to change.

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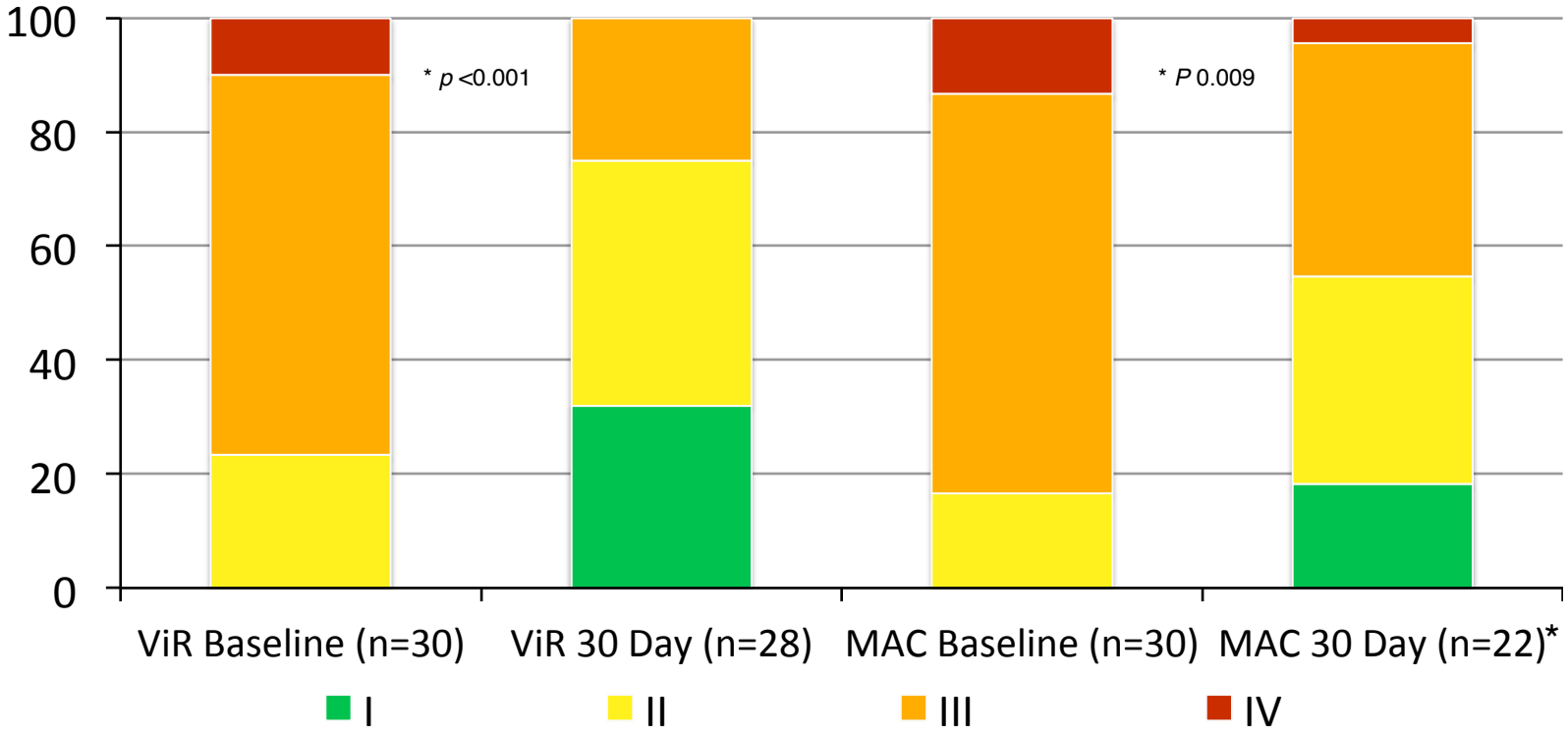
NYHA Class at 30 days



* 2 MAC patients treated in October 2017 (POD # 13 and 21 at time of this presentation)
1 patient withdrew consent while being discharged after successful transatrial TMVR
5 deaths

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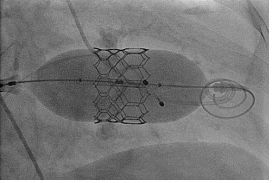
ViR Conclusions

- Transseptal access for ViR can be achieved in most patients (100% in this cohort)
- TS ViR is associated with low 30 day mortality and low complication rate
- Technical success limited by need for second valve improved with experience
- Need for second valve was not associated with poor outcomes
- THV design changes (longer inner skirt) may further improve technical success
- Patients treated with TS ViR experienced significant improvement of symptoms
- These results suggest that TS ViR is a reasonable alternative for high risk patients



ViMAC Conclusions

- TMVR in MAC is a challenging procedure associated with complications
- Outcomes have improved with better patient selection and techniques
- Most patients have high risk of LVOTO and require risk reduction strategies
- Pre-emptive alcohol septal ablation facilitates successful TS TMVR in selected patients
- Cardiac CT analysis is key to improve patient selection and outcomes
- Transatrial approach allows resection of anterior leaflet to decrease LVOTO risk and sutures to decrease embolization risk, but is more invasive and associated with M&M
- ViMAC may become a reasonable alternative for high surgical risk patients with favorable anatomy, but techniques require further refinement

Summary

- Compared with data from registries, outcomes of ViR and ViMAC procedures have improved with better patient selection and techniques
- Transseptal access should be preferred for all ViR procedures and selected ViMAC patients when anatomy is favorable
- TS ViR is a reasonable alternative for high surgical risk patients
- ViMAC remains challenging but with improved techniques may become a reasonable alternative for high surgical risk patients