

# Developments In TAVR

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Healthcare for what's  next.

# NO DISCLOSURES

Healthcare for what's  next.

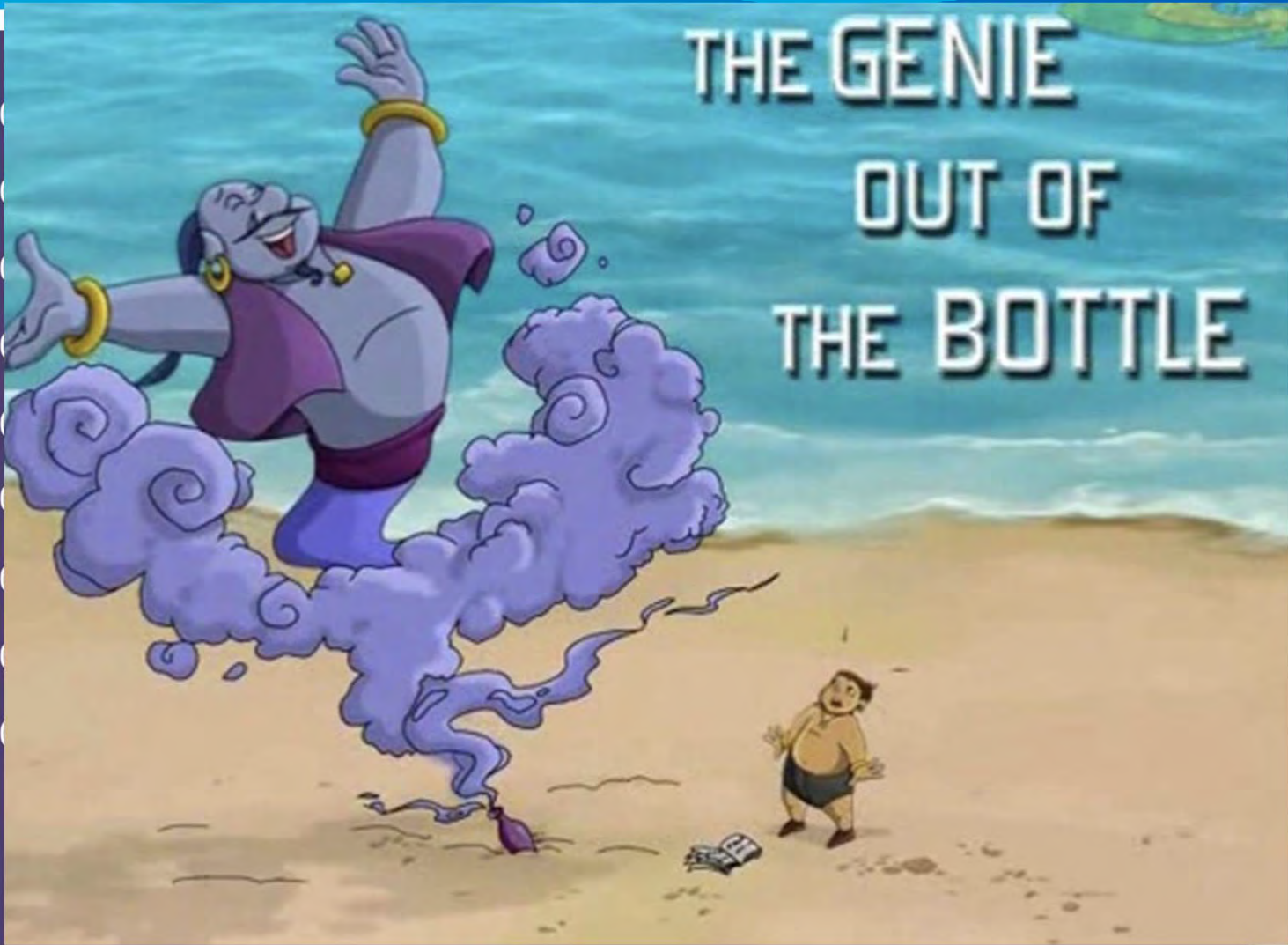


# Introduction

- Transcatheter aortic valve replacement (TAVR) first performed in 2002 by Cribier. First prototype designed by Cribier and his start up Percutaneous Valve Technologies.
- Evolution of TAVR technology for the last 15 years has been unprecedented.
- Randomized trials have demonstrated that TAVR versus SAVR
  - Lower Stroke
  - Lower Mortality
  - Lower rates of Atrial Fibrillation
  - Quicker recovery, no scars
  - Better hemodynamics

# Aortic Valve Replacement

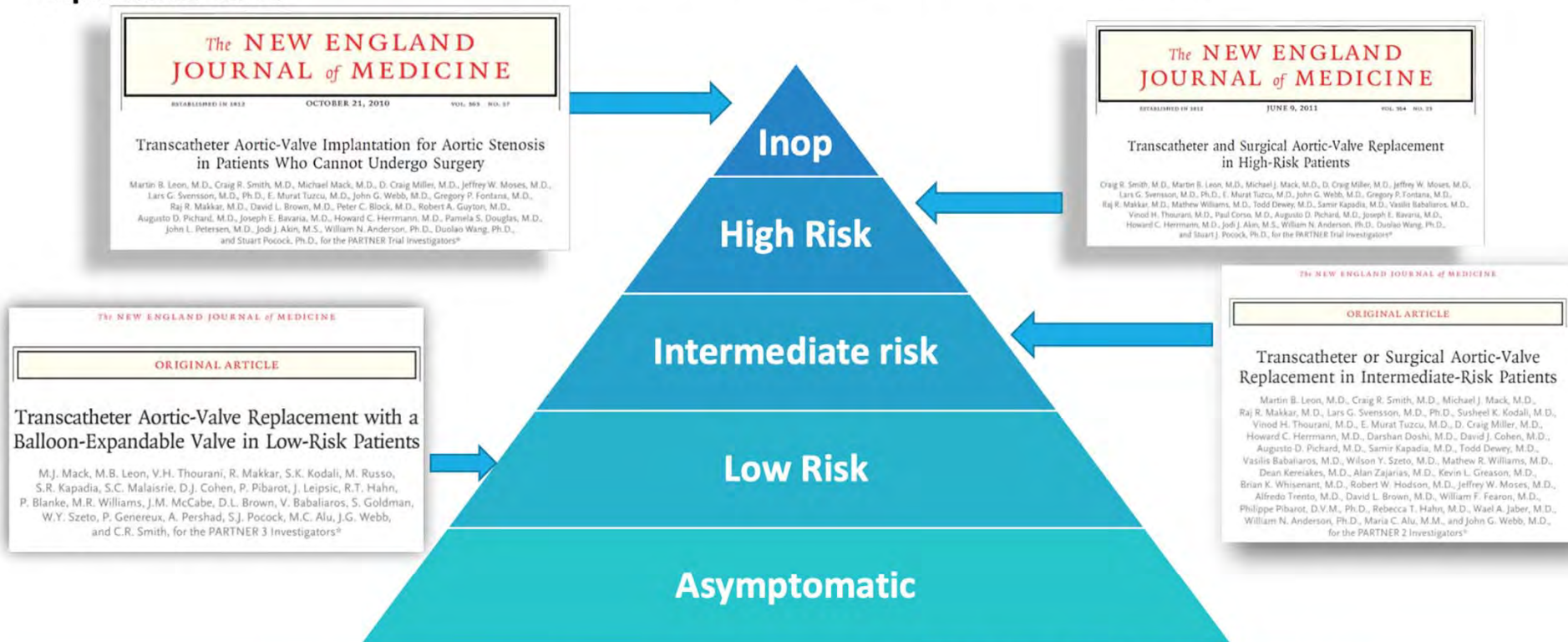
45,000  
40,000  
35,000  
30,000  
25,000  
20,000  
15,000  
10,000  
5,000





**Balloon-expandable Valve**

# Risk Trends in Transcatheter Aortic Valve Therapy



N Engl J Med. 2010;363(17):1597-607.

N Engl J Med. 2011;364(23):2187-98.

N Engl J Med 2016; 374:1609-1620

## Presented at the American College of Cardiology, Sunday, March 17, 2019

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

### Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients

M.J. Mack, M.B. Leon, V.H. Thourani, R. Makkar, S.K. Kodali, M. Russo, S.R. Kapadia, S.C. Malaisrie, D.J. Cohen, P. Pibarot, J. Leipsic, R.T. Hahn, P. Blanke, M.R. Williams, J.M. McCabe, D.L. Brown, V. Babaliaros, S. Goldman, W.Y. Szeto, P. Genereux, A. Pershad, S.J. Pocock, M.C. Alu, J.G. Webb, and C.R. Smith, for the PARTNER 3 Investigators\*

Mack MJ, Leon MB, Thourani VH, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. March 16, 2019, DOI: 10.1056/NEJMoa1814052

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

### Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients

Jeffrey J. Popma, M.D., G. Michael Deeb, M.D., Steven J. Yakubov, M.D., Mubashir Mumtaz, M.D., Hemal Gada, M.D., Daniel O'Hair, M.D., Tanvir Bajwa, M.D., John C. Heiser, M.D., William Merhi, D.O., Neal S. Kleiman, M.D., Judah Askew, M.D., Paul Sorajja, M.D., Joshua Rovin, M.D., Stanley J. Chetcuti, M.D., David H. Adams, M.D., Paul S. Teirstein, M.D., George L. Zorn III, M.D., John K. Forrest, M.D., Didier Tchétché, M.D., Jon Resar, M.D., Antony Walton, M.D., Nicolo Piazza, M.D., Ph.D., Basel Ramlawi, M.D., Newell Robinson, M.D., George Petrossian, M.D., Thomas G. Gleason, M.D., Jae K. Oh, M.D., Michael J. Boulware, Ph.D., Hongyan Qiao, Ph.D., Andrew S. Mugglin, Ph.D., and Michael J. Reardon, M.D., for the Evolut Low Risk Trial Investigators\*

Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. March 16, 2019 DOI: 10.1056/NEJMoa1816885



# PARTNER 3 Clinical Sites



1 site

St. Paul's Hospital  
Vancouver, BC  
University of Washington Seattle  
Seattle, WA

Providence Heart & Vascular  
Institute Portland  
Portland, OR



3 sites

JAPAN

Osaka University  
Hospital  
Osaka

Keio University Hospital  
Tokyo  
Teikyo University Hospital  
Tokyo



1 site

AUSTRALIA

Auckland City  
Hospital  
Grafton, Auckland  
NEW ZEALAND



1 site



65 sites

The Queen's  
Medical Center  
Honolulu, HI

HAWAII

Kaiser San Francisco  
Medical Center  
San Francisco, CA  
Sutter Medical Center, Sacramento  
Walnut Creek, CA  
Mills-Peninsula Health Services  
Burlingame, CA  
Stanford University Medical Center  
Stanford, CA

Cedars-Sinai Medical Center  
Los Angeles, CA  
UCLA  
Los Angeles, CA  
Hoag Memorial  
Hospital  
Newport Beach, CA  
Banner University  
Medical Center  
Phoenix, AZ

Intermountain  
Medical Center  
Murray, UT  
Medical Center of the Rockies  
Loveland, CO

Nebraska Heart  
Institute  
Lincoln, NE  
Rush University  
Medical Center  
Chicago, IL

St. Luke's Hospital  
Kansas City, MO  
Cardiovascular Research  
Institute of Kansas  
Wichita, KS  
Oklahoma  
Cardiovascular  
Research Group  
Oklahoma City, OK

Medical City Dallas  
Dallas, TX  
The Heart Hospital  
Baylor Plano  
Plano, TX  
Austin Heart  
Austin, TX

NorthShore University  
Health System Research  
Institute Evanston  
Evanston, IL  
Northwestern  
University  
Chicago, IL  
Mayo Clinic  
Rochester, MN  
University of Wisconsin  
Madison, WI  
University of Iowa  
Hospitals and Clinics  
Iowa City, IA

Henry Ford  
Hospital  
Detroit, MI  
Mount Carmel  
Health System  
Columbus, OH  
Allegheny-Singer  
Research  
Institute  
Pittsburgh, PA  
The Christ Hospital  
Cincinnati, OH  
University of Virginia  
Charlottesville  
Charlottesville, VA

St. Thomas  
Health  
Nashville, TN  
Baptist  
Memorial Hospital  
Memphis, TN  
University of Alabama  
Birmingham, AL  
Emory University  
Atlanta  
Atlanta, GA  
Ochsner Clinic  
Foundation  
New Orleans, LA  
University of Florida  
Gainesville, FL  
Florida  
Hospital  
Orlando, FL  
JFK Medical  
Center  
Atlanta, FL  
Mount Sinai  
Medical Center  
Miami Beach, FL

University of Buffalo -  
Kaleida Health  
Buffalo, NY  
The Cleveland  
Clinic Foundation  
Cleveland, OH  
Newark  
Beth Israel  
Medical Center  
Newark, NJ  
Dartmouth-Hitchcock  
Medical Center  
Lebanon, NH  
Central Maine  
Medical Center  
Lewistown, ME  
Albany Medical College  
Albany, NY  
Brigham and Women's Hospital  
Boston, MA  
Hartford Hospital  
Hartford, CT  
Winthrop-University  
Hospital Mineola  
Mineola, NY  
Columbia University  
Medical Center  
New York, NY  
Cornell (New York Hospital)  
New York, NY  
New York  
Presbyterian Hospital  
New York, NY  
NYU Langone Medical Center  
New York, NY  
Morristown  
Morristown, NJ  
Lankenau Medical Center  
Wynnewood, PA  
University of Pennsylvania  
Philadelphia  
Philadelphia, PA  
Inova Heart and  
Vascular Institute  
Falls Church, VA  
Sentara Cardiovascular  
Research Institute, Norfolk  
Norfolk, VA  
NC Heart and Vascular  
Raleigh, NC  
Carolina's Health System  
Charlotte, NC

# Endpoints



## Primary Endpoint

- **Non-hierarchical composite of all-cause mortality, all strokes, or CV re-hospitalization at 1 year**
  - Primary analysis was non-inferiority, followed by superiority
  - Analysis cohort was the 'as-treated' (AT) population, defined as all randomized patients in whom the procedure was initiated.
  - Multiple sensitivity analyses performed

## Study Endpoints

Evolut™  
Low Risk  
Trial

**Primary Safety and Effectiveness Endpoint**  
All-cause mortality or disabling stroke at 2 years

### Hierarchical Powered Secondary Endpoints

#### Noninferiority

- Mean gradient at 1 year
- EOA at 1 year
- Change in NYHA class from baseline to 1 year
- Change in KCCQ score from baseline to 1 year

#### Superiority

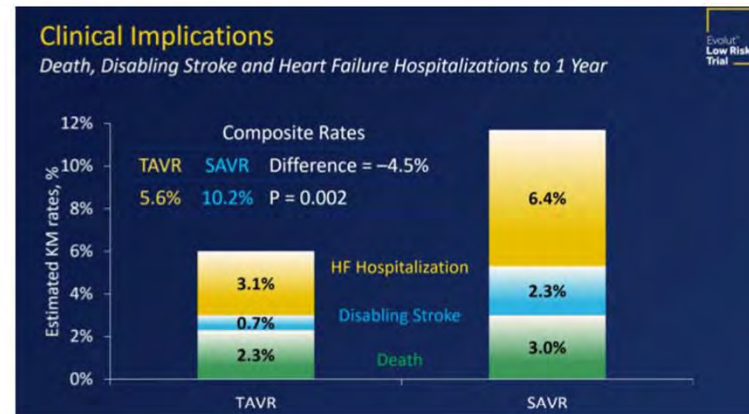
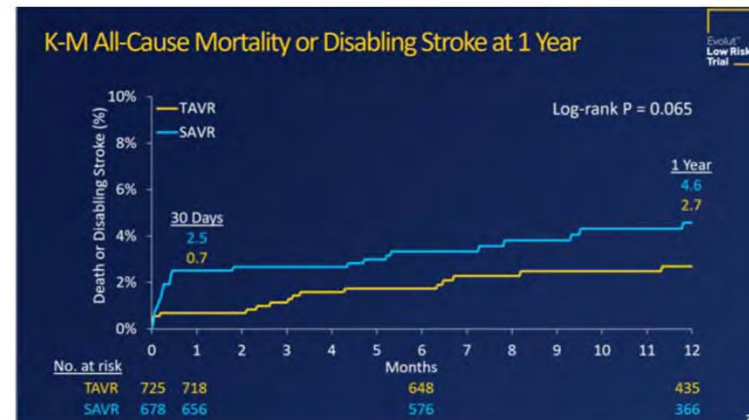
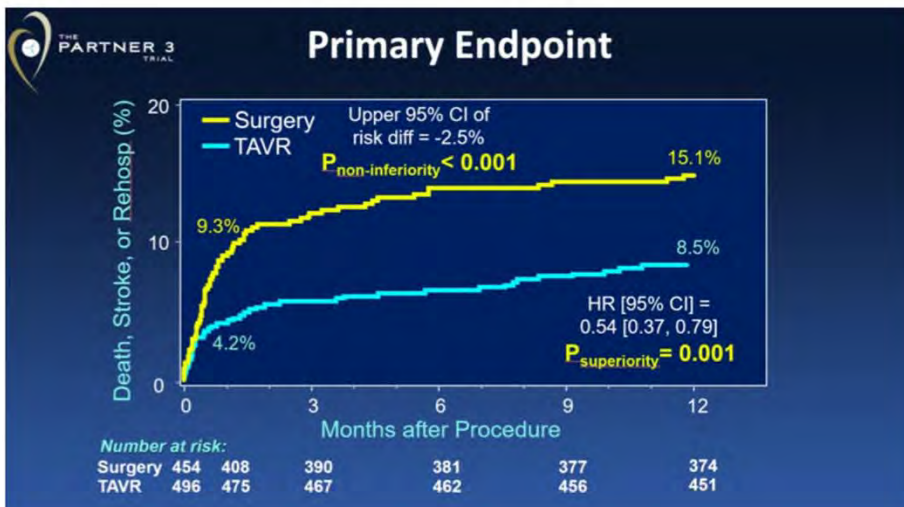
- Mean gradient at 1 year
- EOA at 1 year
- Change in KCCQ score from baseline to 30 days

### Other Secondary Endpoints

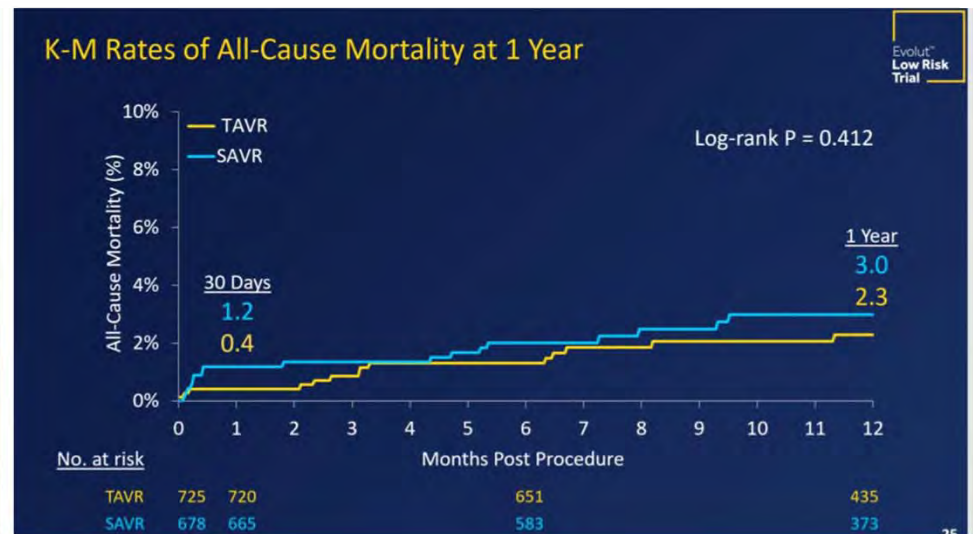
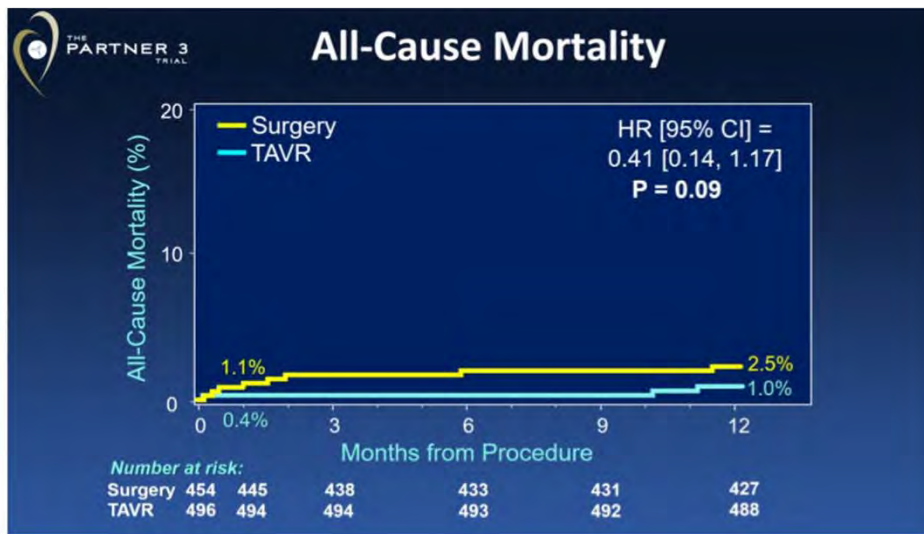
- 30-day safety composite of
  - All-cause mortality
  - Disabling stroke
  - Life-threatening bleeding
  - Major vascular complications
  - Stage 2 or 3 acute kidney injury
- New pacemaker implantation at 30 days
- Heart failure rehospitalizations at 1 year
- Aortic-valve reintervention at 1 year
- Moderate/severe AR at 1 year
- All stroke at 1 year
- Life-threatening bleeding at 1 year



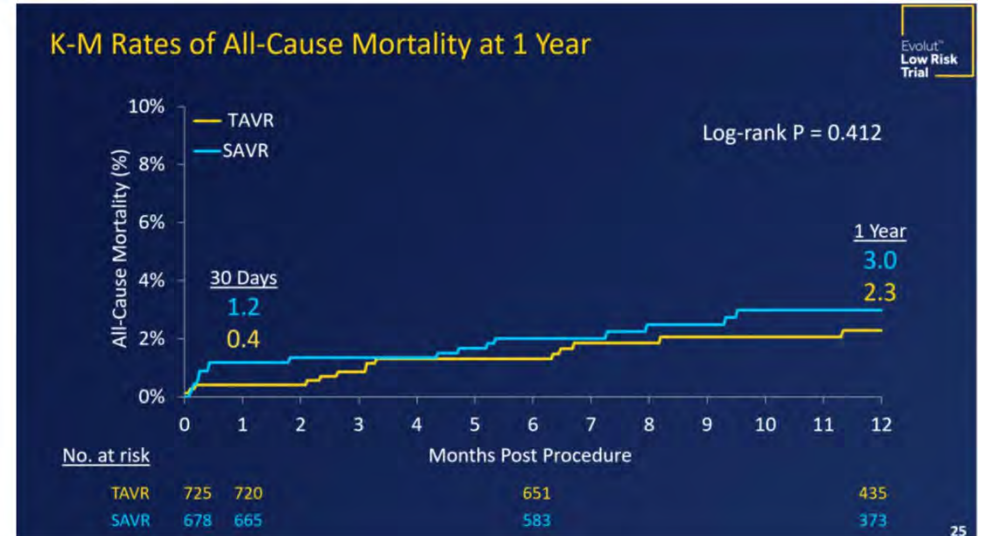
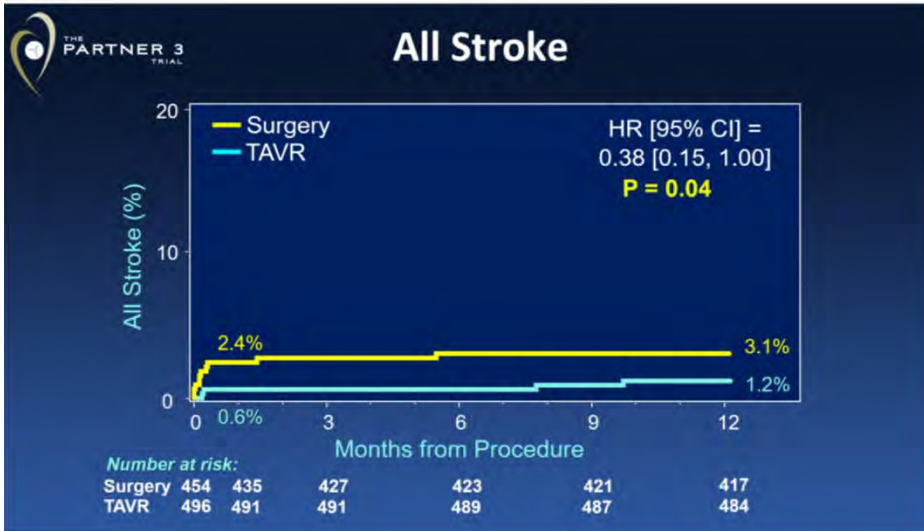
# Primary Endpoint



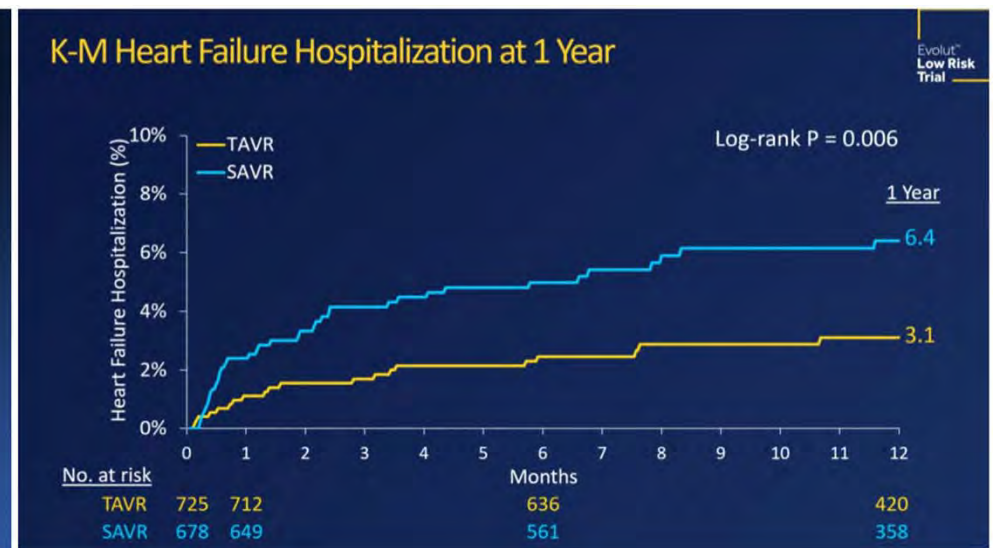
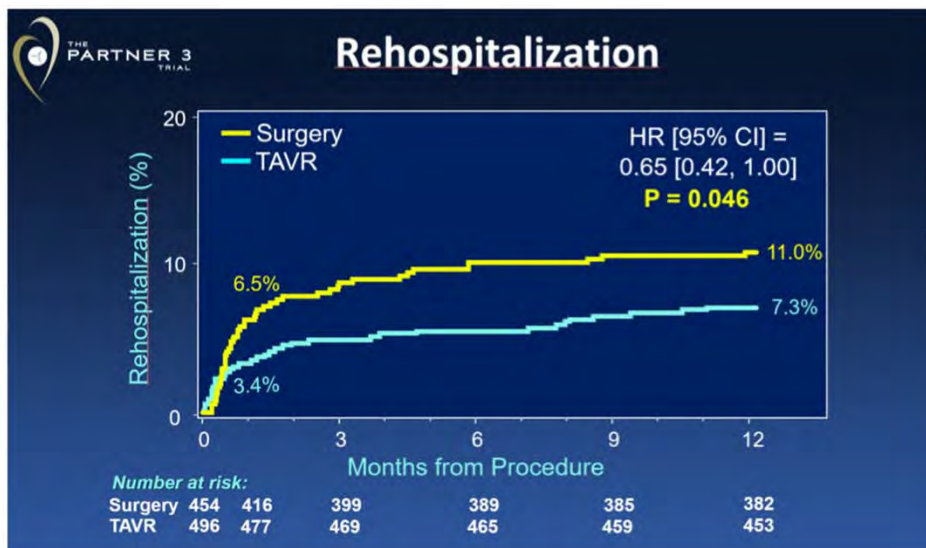
# All-Cause Mortality



# Stroke



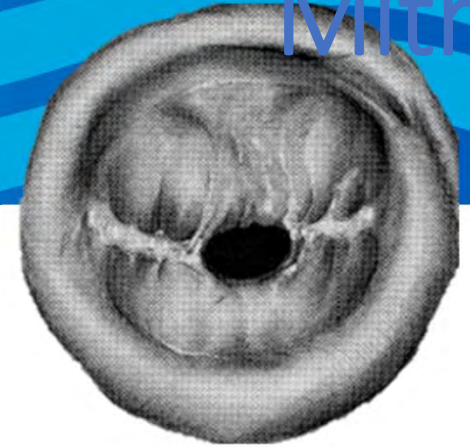
# Rehospitalization



# Conclusions

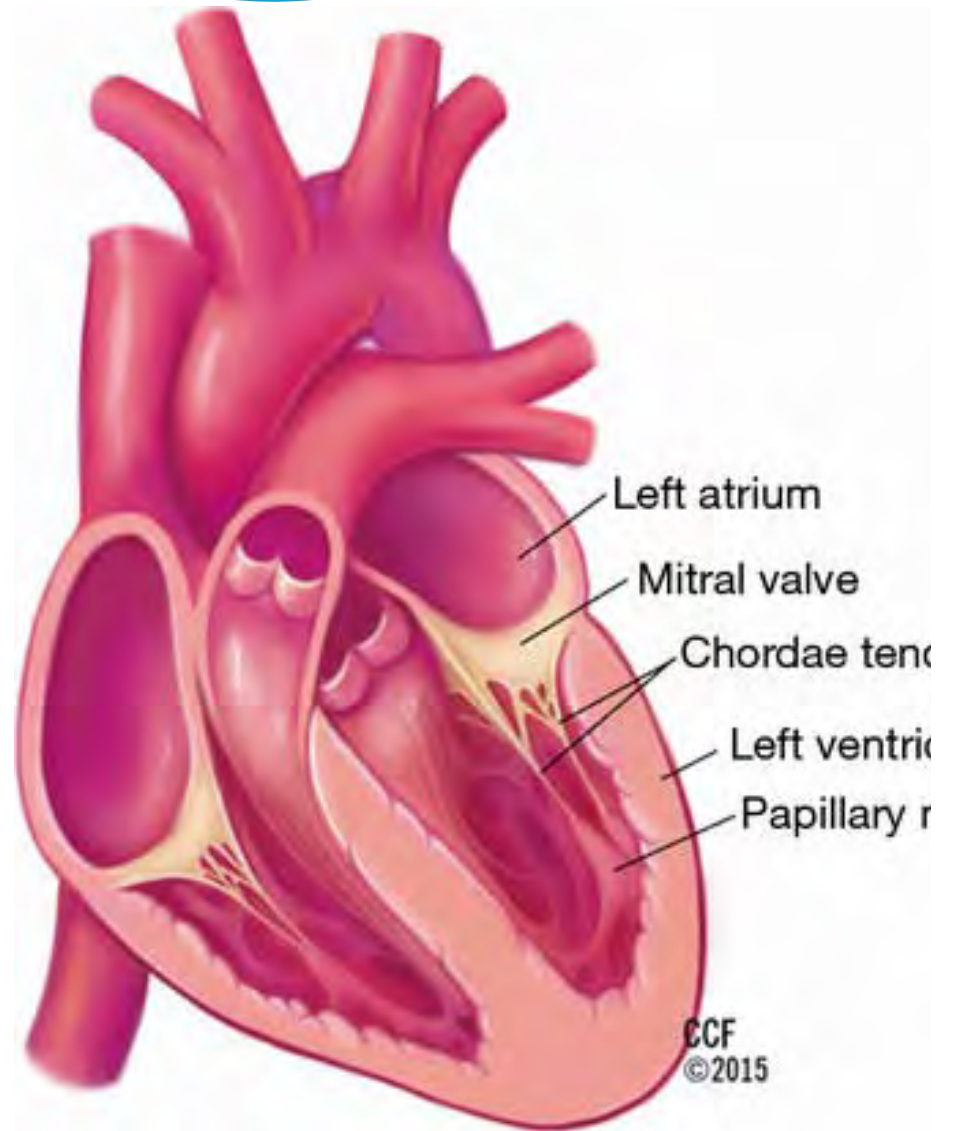
- TAVR in low surgical risk using the Sapien 3 Valve:
  - Significantly reduces the rate of death, stroke, or re-hospitalization at 1 year by 46%
  - Secondary endpoints (adjusted) showed that TAVR reduced new-onset atrial fibrillation, index hospitalization days, and measure of poor treatment outcome (death or low KCCQ score at 30 days)
  - Other secondary endpoint analysis showed reduced bleeding after TAVR and no difference in the need for new permanent pacemaker placement, major vascular complications, coronary obstruction, and moderate to severe perivalvular leak
  - Some secondary endpoints favored surgery, including reduced LBBB, reduced mild PVR, and lower aortic gradients

- 1902
  - Concept of mitral commissurotomy proposed
  - Brunton
- 1920
  - 1st successful Surgical Mitral Commissurotomy
- 1950-60
  - Transatrial and Transventricular Closed MV commissurotomy
- 1982
  - Inoue
  - Percutaneous Transvenous MV Commissurotomy (PTMC)
- 1994
  - PMBV Clinically approved in US
- 2014
  - FDA approval for Mitral Clip in High Risk Degenerative MR
- 2019
  - FDA approval for Mitral Clip in Functional MR



## 6 Anatomical Parts of the Mitral Valve

- Leaflets
- Annulus
- Chordae
- Papillary Muscles
- Left Ventricle
- Left Atrium

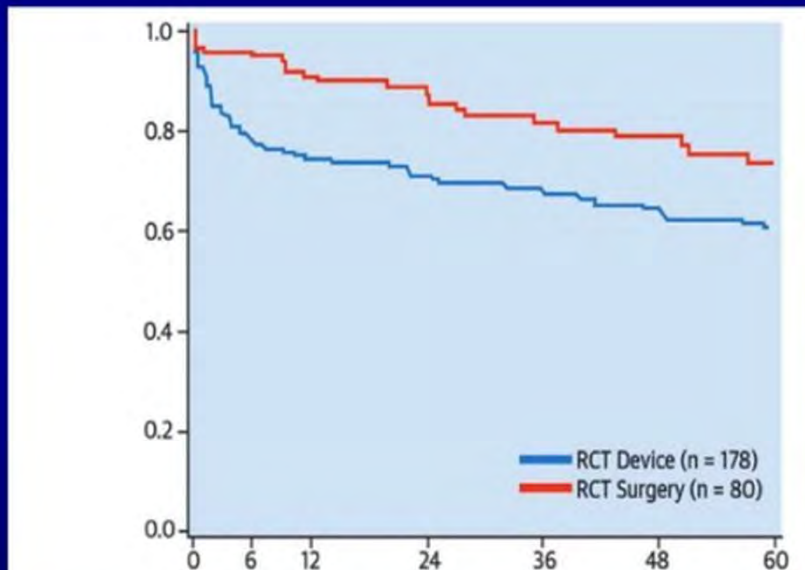


| Intervention Mechanism |                       | Abandoned       | In Development and/or Approved        |
|------------------------|-----------------------|-----------------|---------------------------------------|
| Mitral Repair          | Leaflet Repair        | Mobius Edwards  | MitraClip (Degenerative & Functional) |
|                        | Indirect Annuloplasty | Monarch Edwards | PASCAL                                |
|                        |                       | PMTA Viacor     | MitraFlex                             |
|                        | Direct Annuloplasty   | ReCor (US)      | Arto-MVRx                             |
|                        |                       |                 | Cardioband                            |
|                        |                       |                 | Millipede                             |
|                        |                       |                 | MitraSpan TASRA                       |
|                        |                       |                 | Micardia Encor                        |
|                        |                       |                 | Mitral Bridge                         |
|                        | Chordal Repair        |                 | QuantumCor (RF)                       |
|                        |                       |                 | Harpoon                               |
|                        |                       |                 | Valtech Vchordal                      |
|                        |                       |                 | MISTRAL                               |
|                        | Enhanced Coaptation   | Myocor Coapsys  | Mitralis                              |
| MitraSpacer            |                       |                 |                                       |
| Middle Peak            |                       |                 |                                       |
| LV Remodeling          | Acorn                 | MitrAssist      |                                       |
|                        | Myocor                | Accucinch       |                                       |
| Mitral Replacement     | Replacement           |                 | BACE Mardil                           |
|                        |                       |                 | Sapien 3                              |
|                        |                       |                 | Cephea                                |
|                        |                       | Tiara           |                                       |



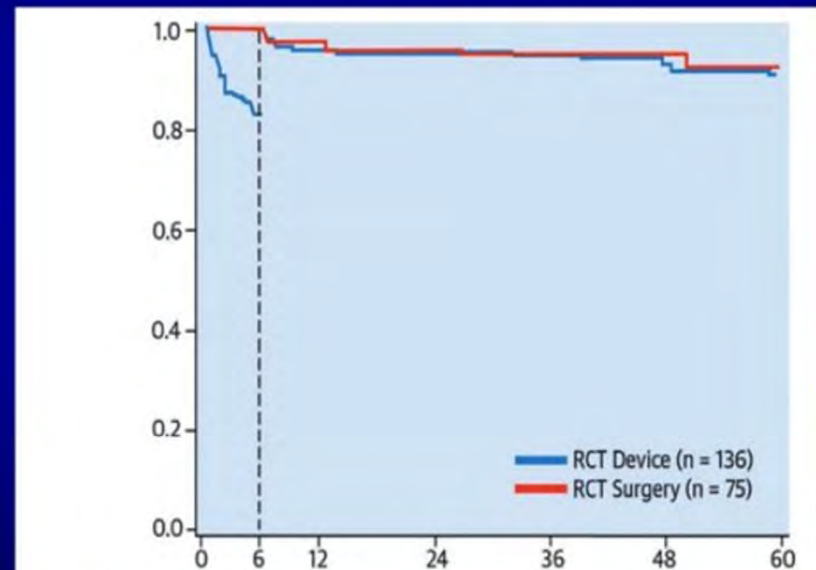
# EVEREST II TRIAL: 5 year Clinical Outcomes Clip vs. Surgery

## Freedom from Death, MV Surgery or Reoperation



|               | Patients At Risk |     |     |     |     |    |    |
|---------------|------------------|-----|-----|-----|-----|----|----|
|               | Months           |     |     |     |     |    |    |
|               | 0                | 6   | 12  | 24  | 36  | 48 | 60 |
| Device Group  | 178              | 136 | 128 | 117 | 109 | 98 | 45 |
| Control Group | 80               | 75  | 69  | 63  | 54  | 49 | 21 |

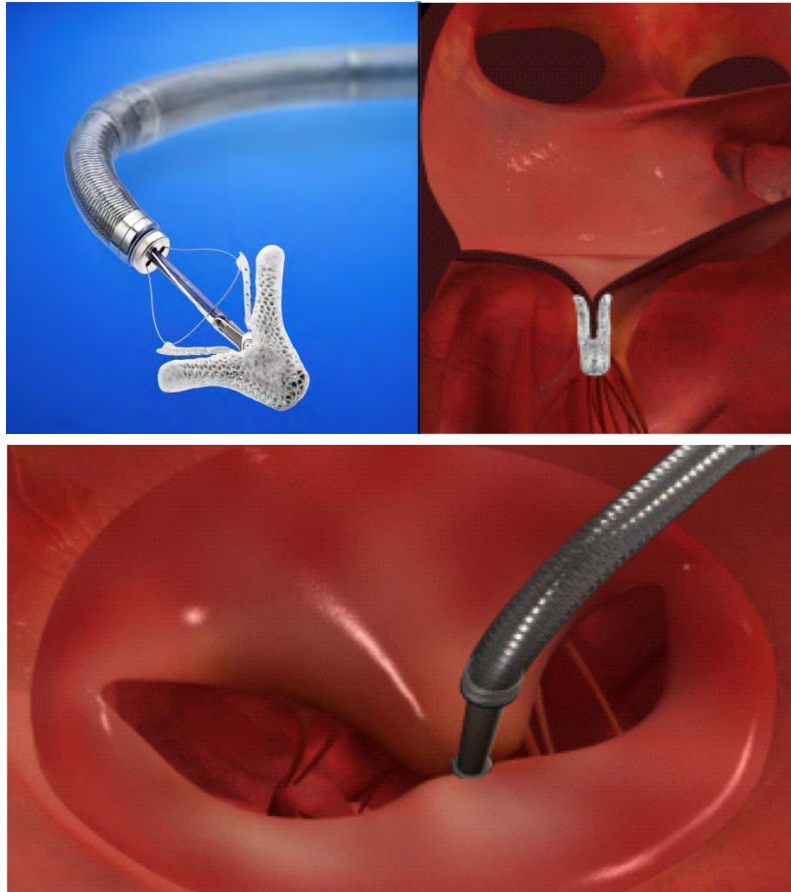
## Landmark Analysis of Freedom from Death, MV Surgery or Reoperation Beyond 6 Months



|               | Patients At Risk |     |     |     |     |    |    |
|---------------|------------------|-----|-----|-----|-----|----|----|
|               | Months           |     |     |     |     |    |    |
|               | 0                | 6   | 12  | 24  | 36  | 48 | 60 |
| Device Group  | 178              | 136 | 128 | 117 | 109 | 98 | 45 |
| Control Group | 80               | 75  | 69  | 63  | 54  | 49 | 21 |

# COAPT

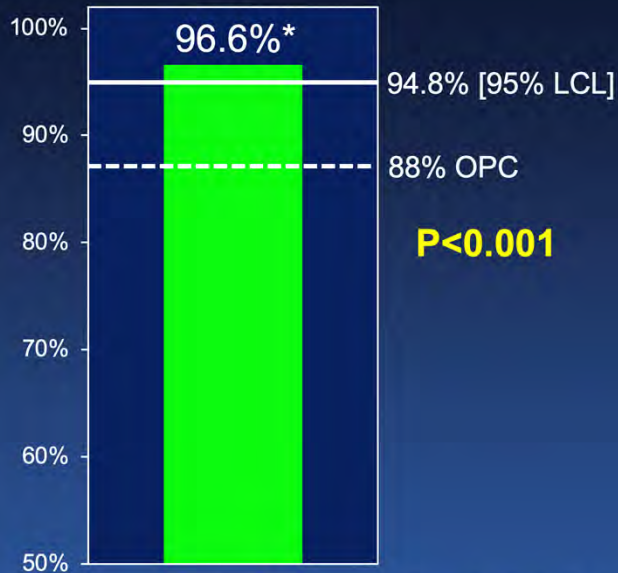
A Randomized Trial of Transcatheter Mitral Valve Leaflet Approximation in Patients with Heart Failure and Secondary Mitral Regurgitation





# Primary Safety Endpoint

## Freedom from Device-related Complications within 12 months



### MitraClip procedure attempted

N=293

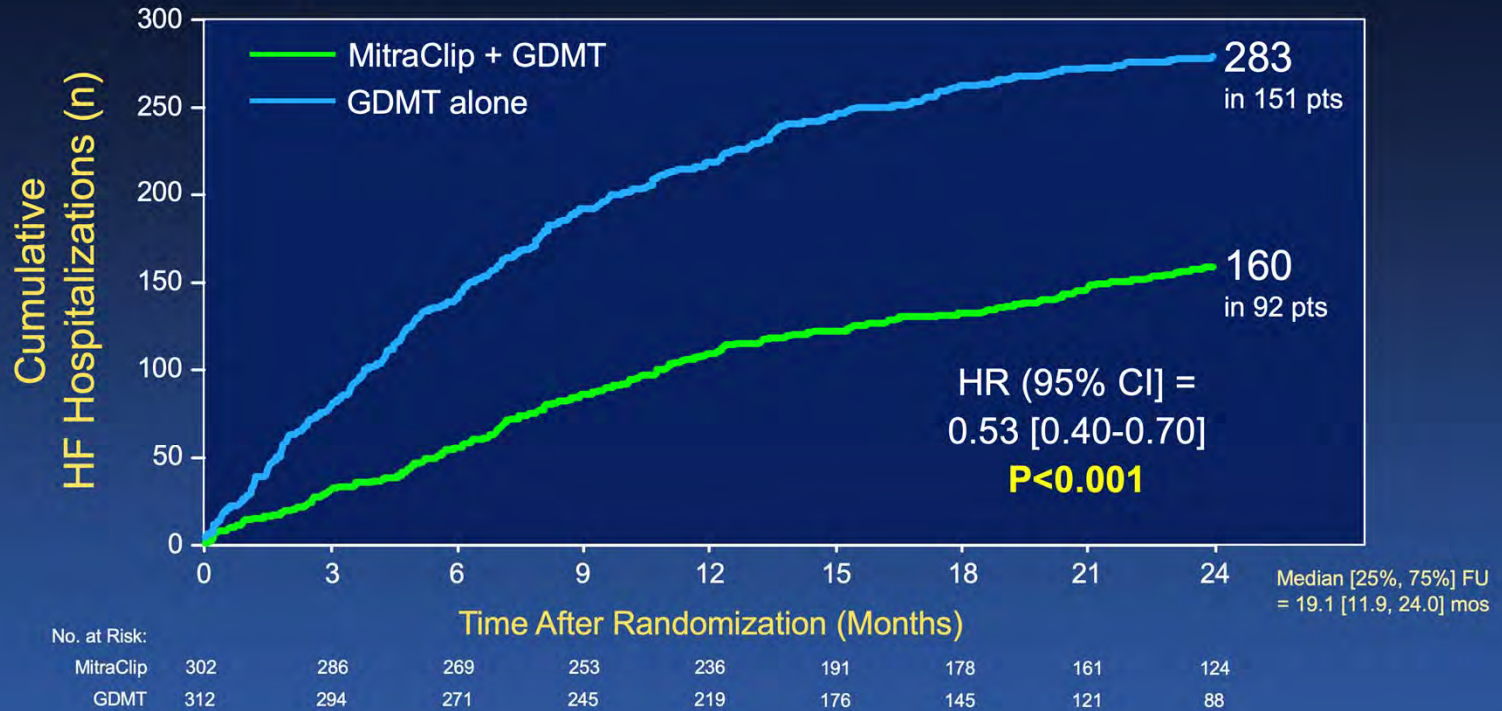
|   |          |
|---|----------|
| Device-related complications  | 9 (3.4%) |
| - Single leaflet device attachment                                  | 2 (0.7%) |
| - Device embolization   | 1 (0.3%) |
| - Endocarditis requiring surgery                                    | 0 (0.0%) |
| - Mitral stenosis requiring surgery                                 | 0 (0.0%) |
| - Left ventricular assist device implant                            | 3 (1.2%) |
| - Heart transplant  | 2 (0.8%) |
| - Any device-related complication requiring non-elective CV surgery | 1 (0.3%) |

\*KM estimate; \*\*Calculated from Z test with Greenwood's method of estimated variance against a pre-specified objective performance goal of 88%

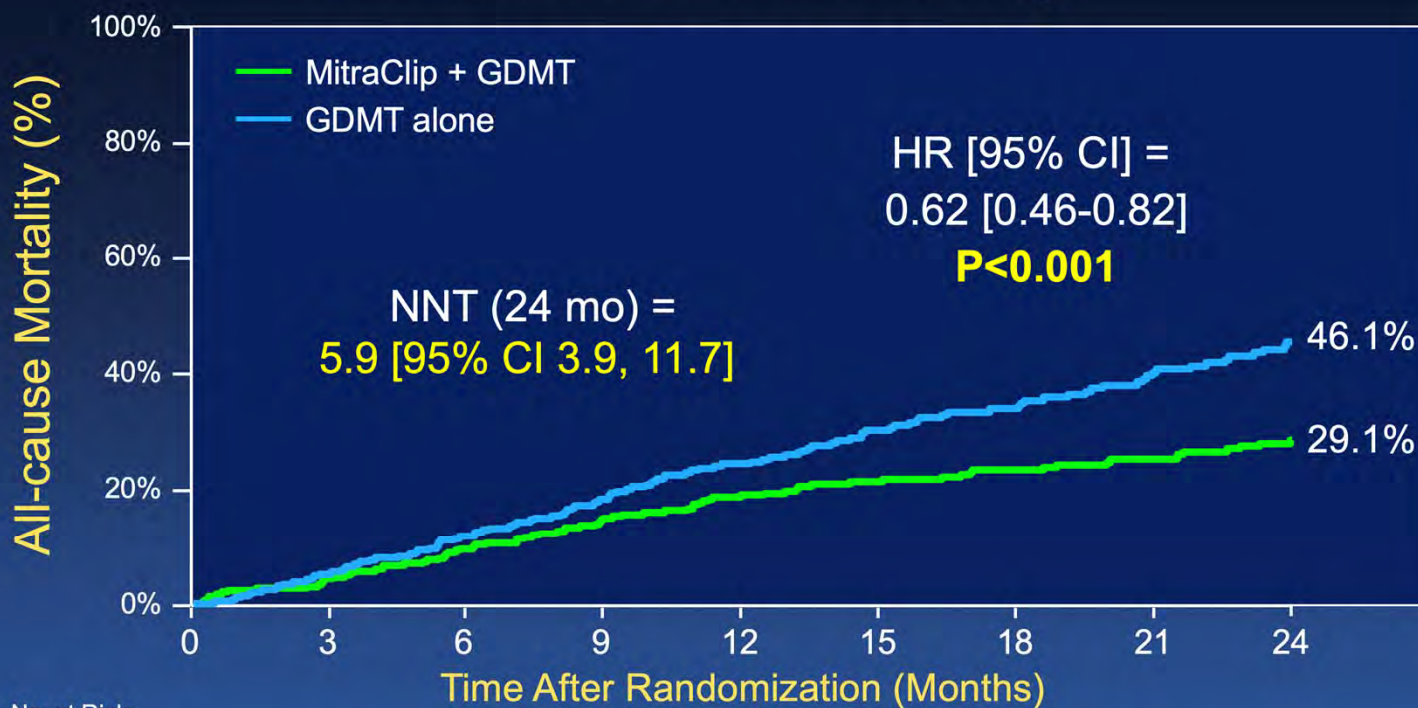


# Primary Effectiveness Endpoint

## All Hospitalizations for HF within 24 months



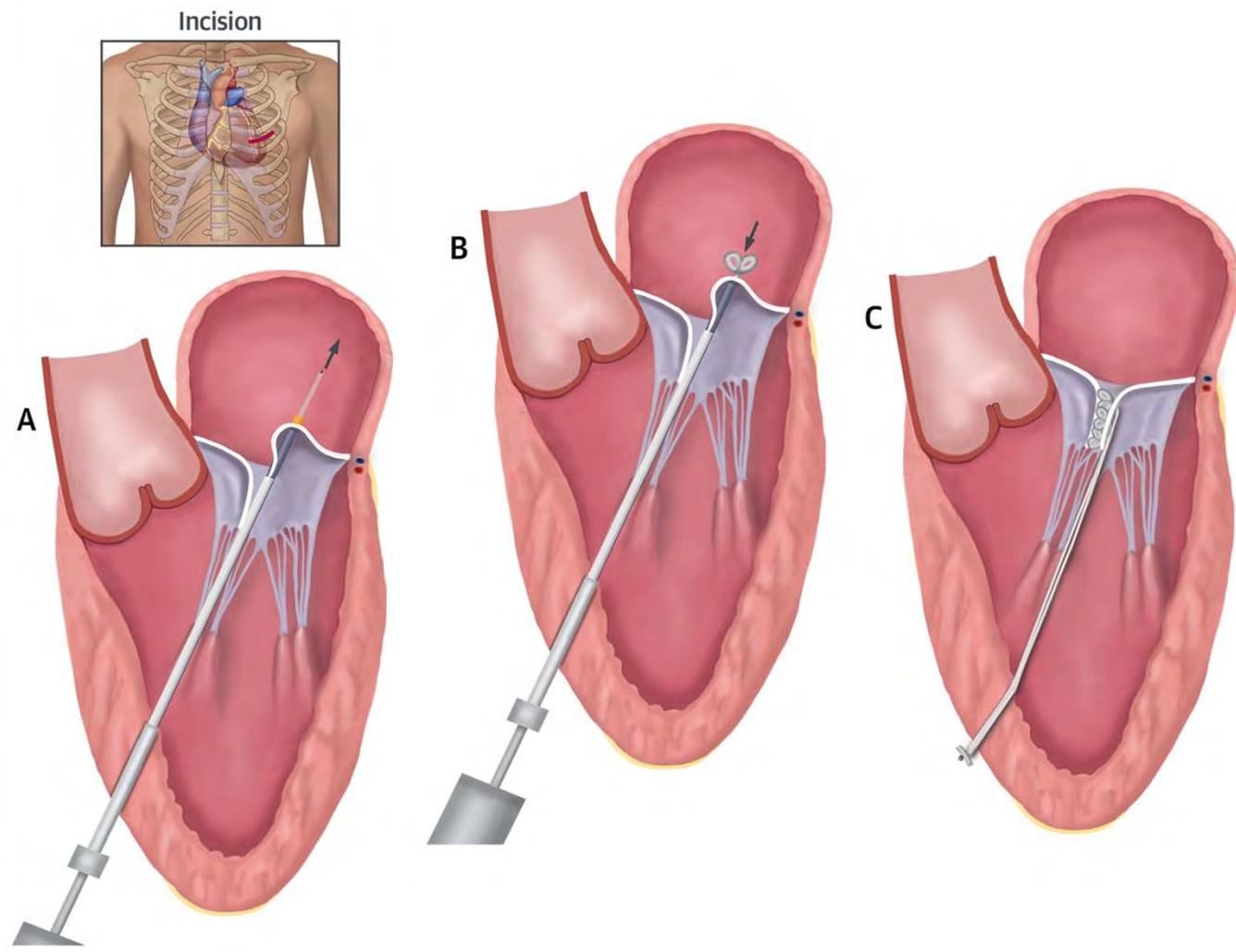
# All-cause Mortality



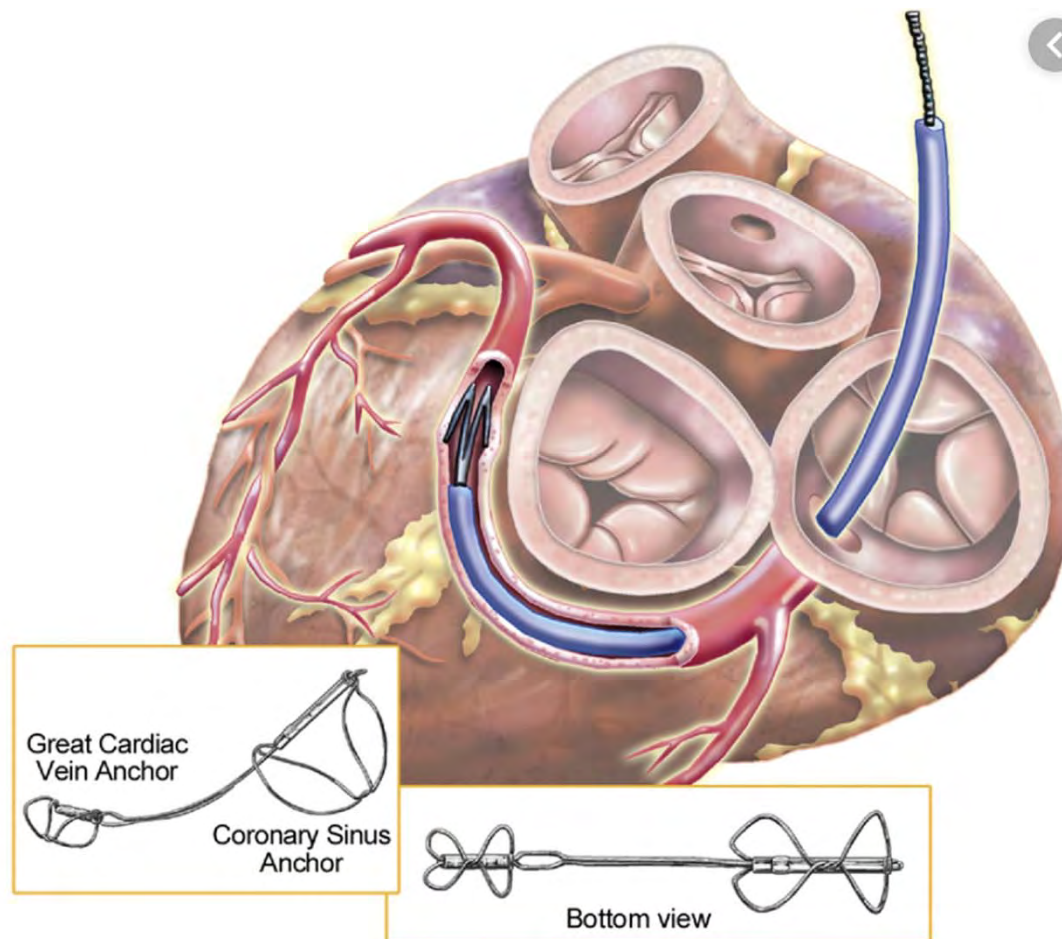
| No. at Risk:     |     | 0   | 3   | 6   | 9   | 12  | 15  | 18  | 21  | 24 |
|------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| MitraClip + GDMT | 302 | 286 | 269 | 253 | 236 | 191 | 178 | 161 | 124 |    |
| GDMT alone       | 312 | 294 | 271 | 245 | 219 | 176 | 145 | 121 | 88  |    |

# Chordal repair

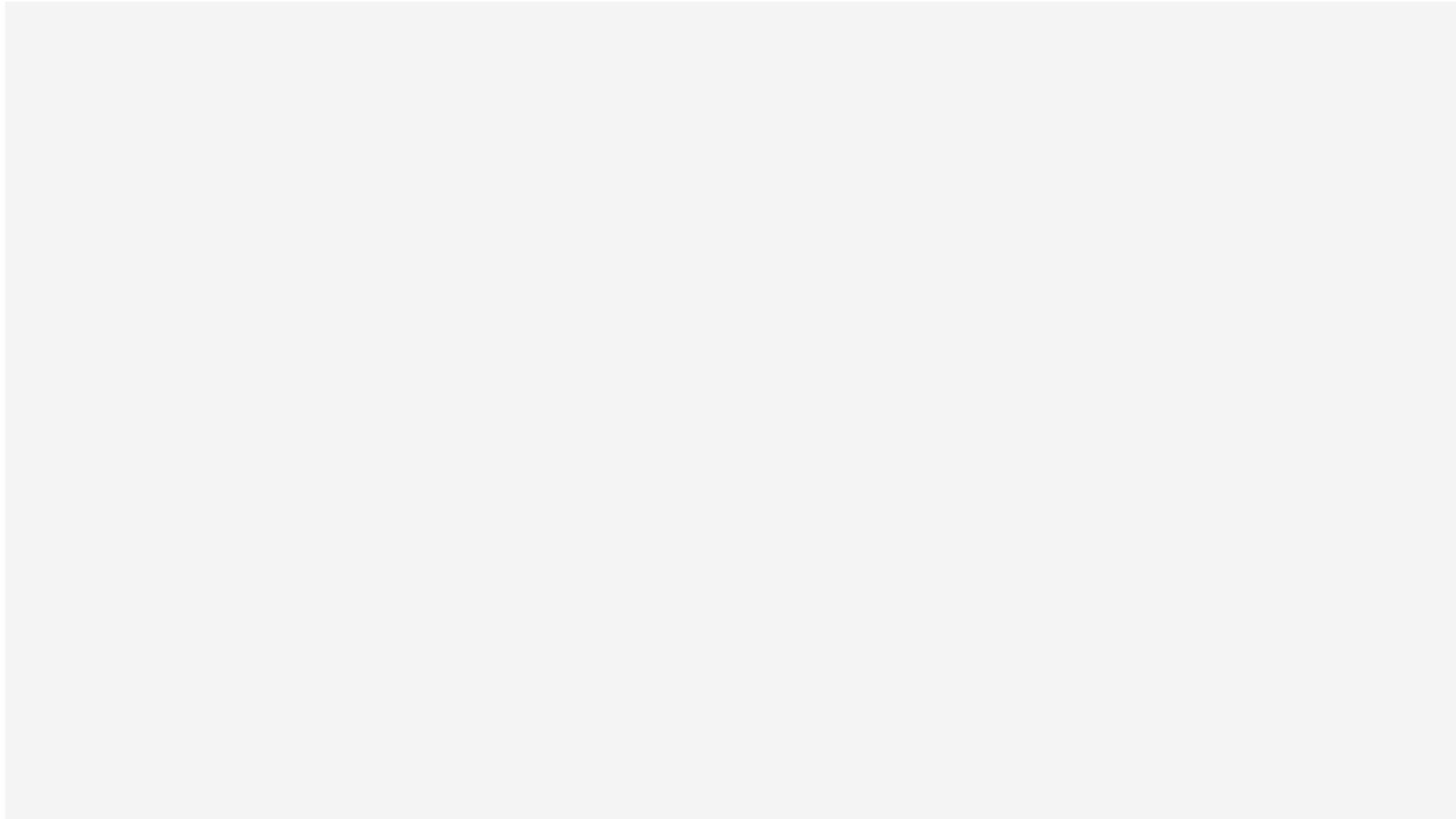
## Harpoon



# Indirect Annuloplasty



# Direct Annuloplasty





# Mitral Valve Replacement



Braile Biomedica



Braile Biomedica



CardiaQ 1<sup>st</sup> G



CardiaQ Edwards



Cephea



Direct Flow Medical



Twelve Medtronic



M-Valve



Edwards Fortis



HighLife



Navigate



Neovasc Tiara



PermaValve MID



Sinomed



Tendyne Abbott



SATURN TMVR



Valtech CardioValve



Caisson

**Others:** MitraHeal, Mitrasist, Mitraltech, Mehr Medical, Mitracath, Mitralix MAESTRO, Nakostech, St. George ATLAS, Transcatheter Technologies Tresillo

# Sapien M-3