EVOLUT New Trials – New Technology (Optimize PRO, SMART, FLEX etc)

Eberhard Grube, MD, FACC, MSCAI
University Hospital, Dept of Medicine II, Bonn, Germany
University of São Paulo, INCOR Heart Institute, São Paulo, Brazil
Stanford University, Palo Alto, California, USA

Financial Disclosure

I, Eberhard Grube have the following financial interest/arrangement that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation

Speaker Bureau/ SAB: Medtronic, Boston Scientific, HighLife, Jena Valve, Protembis, Anteris, Valve Medical

Equity Interest: Cardiovalve, Claret, Shockwave, Valve medical, CardioMech, Millipede, Imperative Care, Pi-Cardia, Ancora, Laminar, ReNiva Medical

EVOLUT SAFETY/EFFICACY IN SEVERE SYMPTOMATIC AORTIC STENOSIS

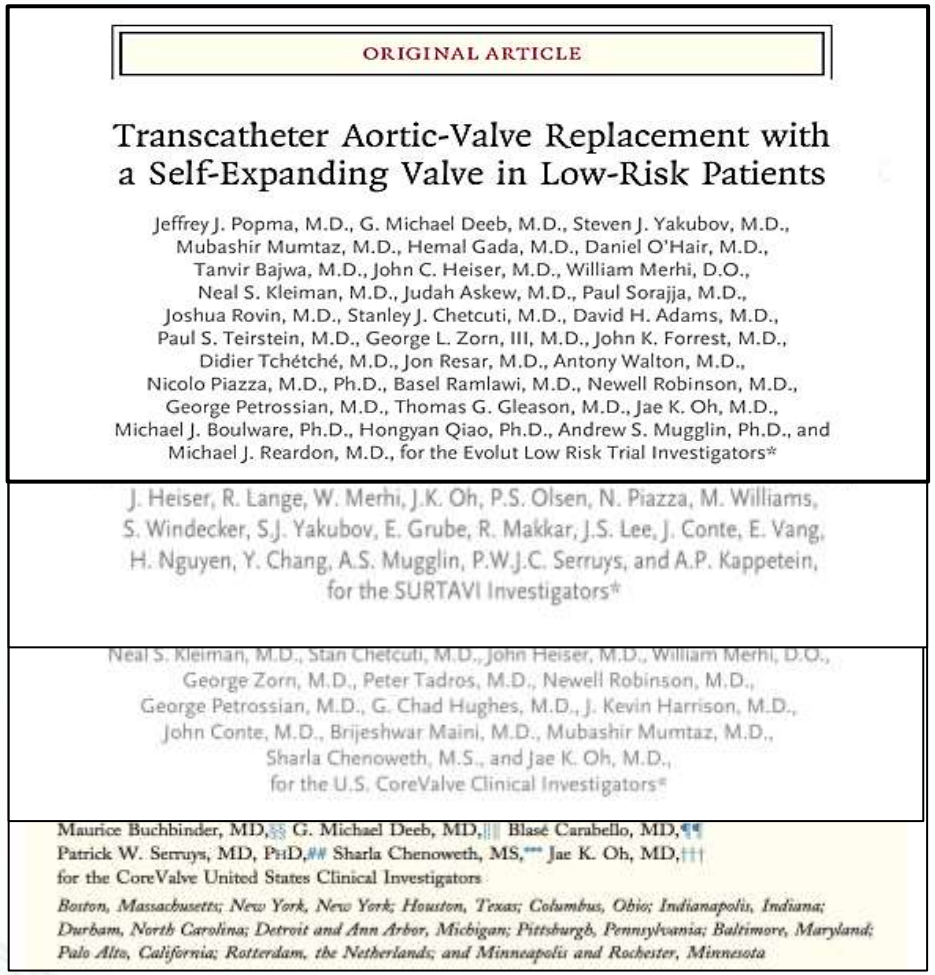
WHAT IS KNOWN

Low Risk

Intermediate Risk

High Risk

Extreme Risk



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*

J. Heiser, R. Lange, W. Merhi, J.K. Oh, P.S. Olsen, N. Piazza, M. Williams, S. Windecker, S.J. Yakubov, E. Grube, R. Makkar, J.S. Lee, J. Conte, E. Vang, H. Nguyen, Y. Chang, A.S. Mugglin, P.W.J.C. Serruys, and A.P. Kappetein, for the SURTAVI Investigators*

Neal S. Kleiman, M.D., Stan Chetcuti, M.D., John Heiser, M.D., William Merhi, D.O., George Zorn, M.D., Peter Tadros, M.D., Newell Robinson, M.D., George Petrossian, M.D., G. Chad Hughes, M.D., J. Kevin Harrison, M.D., John Conte, M.D., Brijeshwar Maini, M.D., Mubashir Mumtaz, M.D., Sharla Chenoweth, M.S., and Jae K. Oh, M.D., for the U.S. CoreValve Clinical Investigators*

Maurice Buchbinder, MD, G. Michael Deeb, MD, Blasé Carabello, MD, Patrick W. Serruys, MD, PhD, Sharla Chenoweth, MS, Jae K. Oh, MD, for the CoreValve United States Clinical Investigators

Boston, Massachusetts; New York, New York; Houston, Texas; Columbus, Ohio; Indianapolis, Indiana; Durham, North Carolina; Detroit and Ann Arbor, Michigan; Pittsburgh, Pennsylvania; Baltimore, Maryland; Palo Alto, California; Rotterdam, the Netherlands; and Minneapolis and Rochester, Minnesota

WHAT WE NEED TO LEARN

Cusp Overlap Technique

Optimize PRO

Moderate Aortic Stenosis

SE TAVR vs Medical Therapy

Evolut Expand TAVR Study

SMALL ANNULI

SMART Trial

TAV in TAV

Revalving Registry

Design Improvements

Fx Registry

EVOLUT NEW TECHNOLOGY, NEW TRIALS

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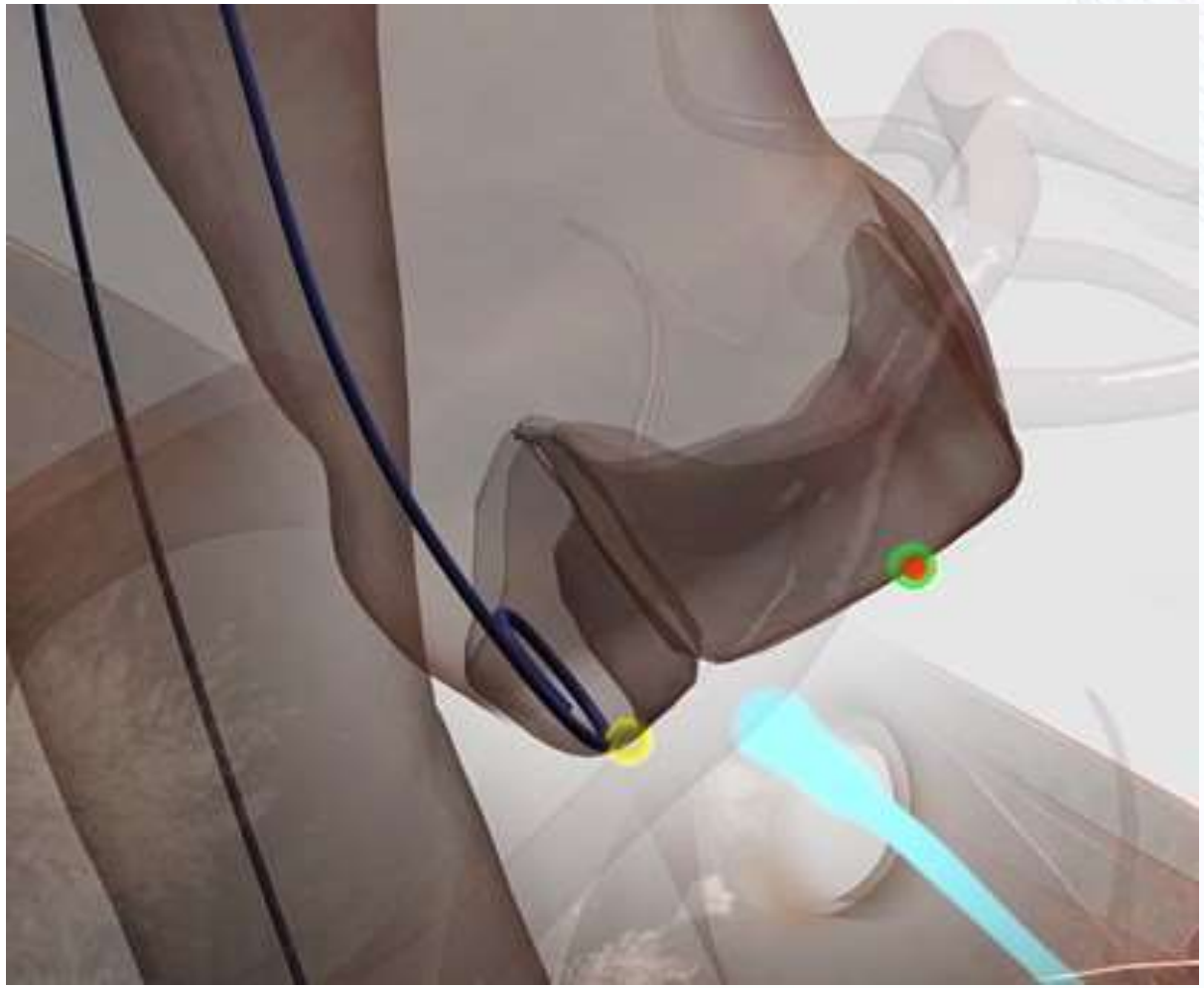
Improving Deployment Accuracy with Cusp Overlap Technique



OPTIMIZE PRO

REDUCTION IN PPI RATE WITH COT ADHERENCE

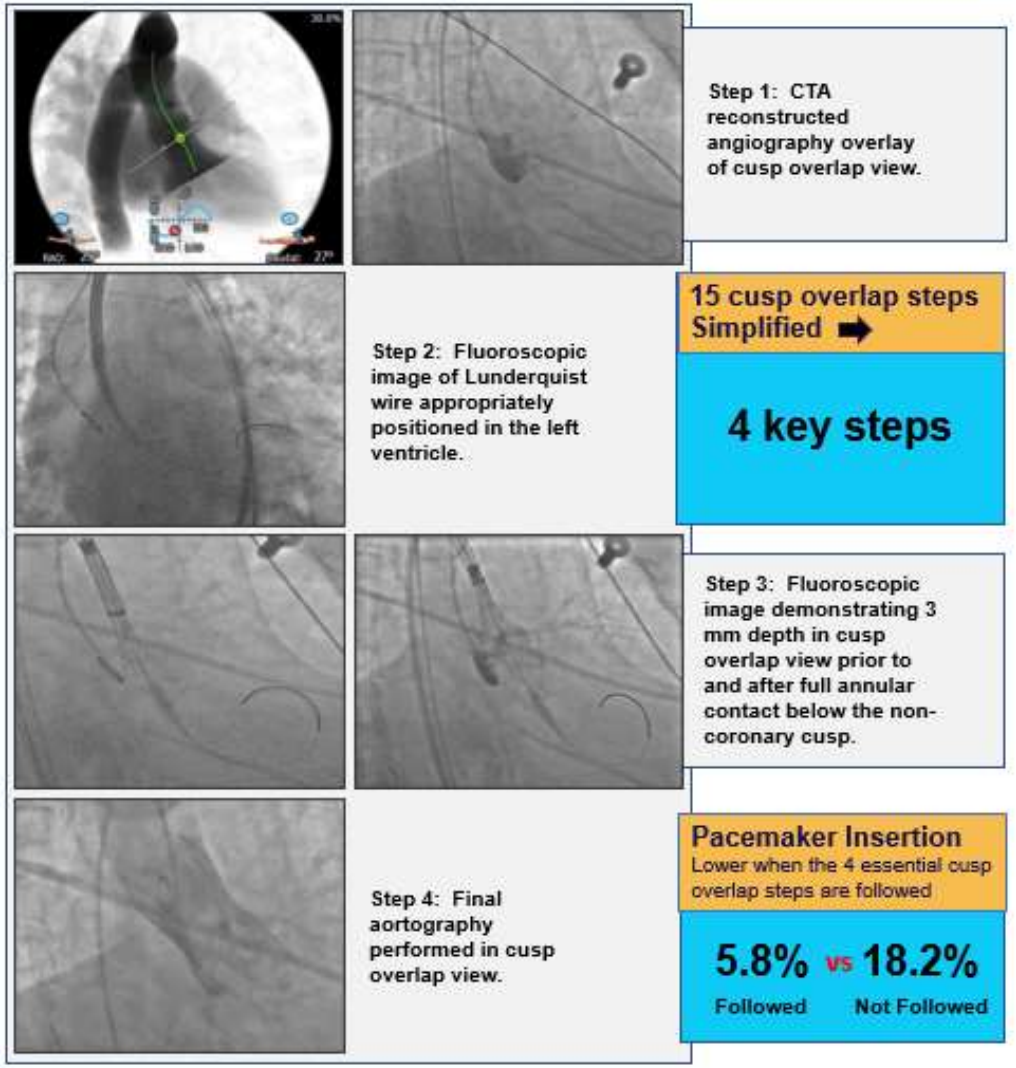
- 400 patients enrolled in the Optimize PRO

Demographics	(N=400)
Age, years	78.7 ± 6.6
BMI, kg/m^2	30.4 ± 6.2
Male	54.0
STS-PROM score,	3.0 ± 2.4
Pre-existing RBBB	6.5
Lunderquist extra-stiff guide wire	86.7
Pre-BAV	59.5
Post-dilatation	12.3
Embolic protection device used	33.8
Length of stay (median days)	1.0 (1.0,2.0)
Discharged with Holter monitor	21.1

Four key steps in the Cusp Overlap Technique was evaluated:

- **Step 1:** CTA reconstructed angiography overlay of cusp overlap view.
- **Step 2:** Double Curve Lunderquist wire appropriately positioned in the left ventricle.
- **Step 3:** No greater than 3 mm depth in cusp overlap view prior to and after full annular contact below the non-coronary cusp.
- **Step 4:** Final aortography performed in cusp overlap view.

Utilization of 4 Essential Cusp Overlap Technique Steps Lowers Pacemaker Implantation Rates to 5.8%



Grubbet al

EVOLUT NEW TECHNOLOGY, NEW TRIALS

MODERATE AORTIC STENOSIS: TREAT OR NOT TO TREAT WITH TAVR

Cusp Overlap Technique

Optimize PRO

Moderate Aortic Stenosis

SE TAVR v. Medical Therapy

Evolut EXPAND TAVR Study

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ASE Echocardiographic Criteria

Table 3 Recommendations for grading of AS severity

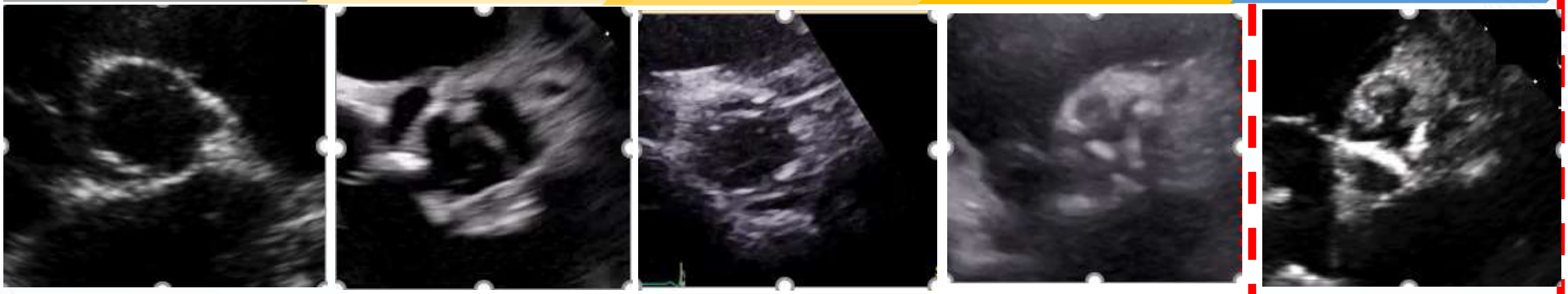
	Aortic sclerosis	Mild	Moderate	Severe
Peak velocity (m/s)	≤2.5 m/s	2.6–2.9	3.0–4.0	≥4.0
Mean gradient (mmHg)	–	<20	20–40	≥40
AVA (cm^2)	–	> 1.5	1.0–1.5	<1.0
Indexed AVA (cm^2/m^2)	–	>0.85	0.60–0.85	<0.6
Velocity ratio	–	> 0.50	0.25–0.50	<0.25

Otto et al JACC 2021; 77 (4) e25–e197

AORTIC STENOSIS IS A PROGRESSIVE DISEASE

Current treatment paradigm for Aortic Stenosis is to wait for stenosis to be severe before intervention[1-3]

Healthy → **Aortic sclerosis** → **Mild aortic stenosis** → **Moderate aortic stenosis** → **Severe aortic stenosis**



	Sclerosis	Mild	Moderate	Severe
Max velocity (m/s)	≤ 2.5	2.6–2.9	3.0–4.0	≥ 4.0 (m/sec(
Mean gradient (mm Hg)	-	< 20	20–40	≥ 40 (mmHg)
AVA (cm^2)	-	> 1.5	1.0–1.5	< 1.0 (cm^2)

AVR
Class I recommendation

[1] Vahanian A, et al. Eur Heart J. 2022
[2] Otto CM, et al. Circulation. 2021
[3] Izumi C, et al. Circ J. 2021

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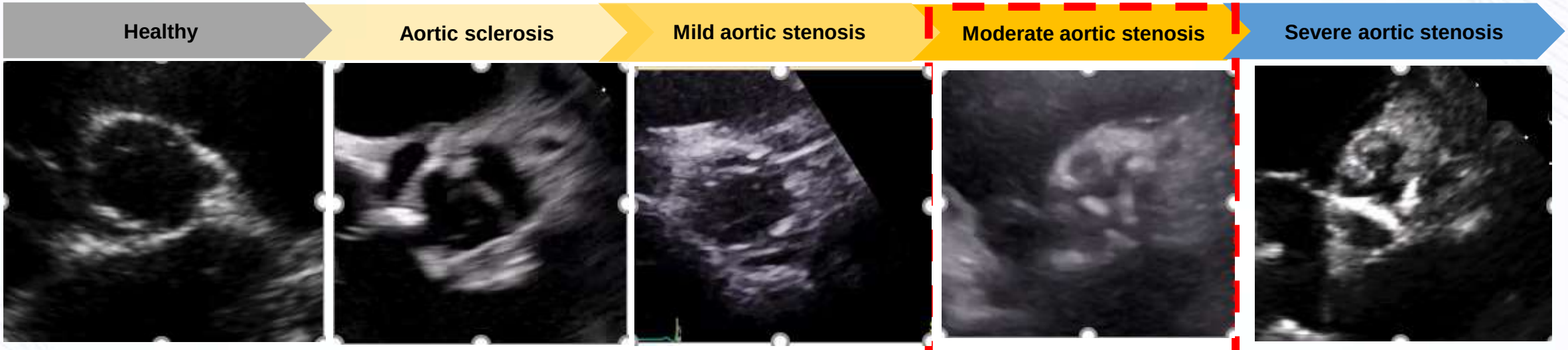

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Watchful Waiting?

[1] Vahanian A, et al. Eur Heart J. 2022
[2] Otto CM, et al. Circulation. 2021
[3] Izumi C, et al. Circ J. 2021

MODERATE AORTIC STENOSIS | GUIDELINES I TIMING AND F/U

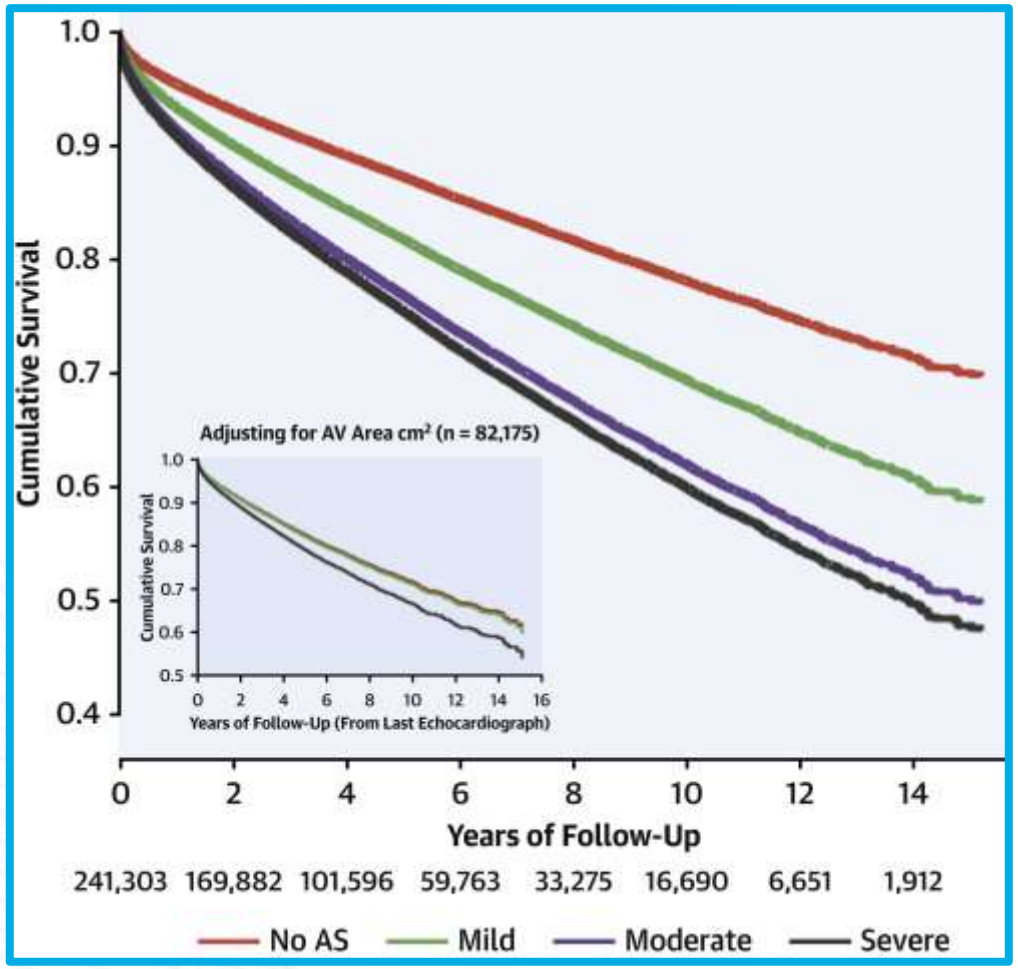
Timing of Intervention Recommendations (Expert Consensus only)

2b	11. In patients with moderate AS (Stage B) who are undergoing cardiac surgery for other i tions, AVR	
	Severe Asymptomatic (Vmax ≥4 m/s)	Every 6-12 months

Both the ACC/AHA and ESC new VHD guidelines have upgraded some AVR recommendations, but in general, still reflect more traditional late-stage clinical practices and intervention!

NATURAL HISTORY OF UNTREATED MODERATE AS

NATIONAL ECHO DATABASE (241,303 PTS; MEDIAN 1208 DYS FU)



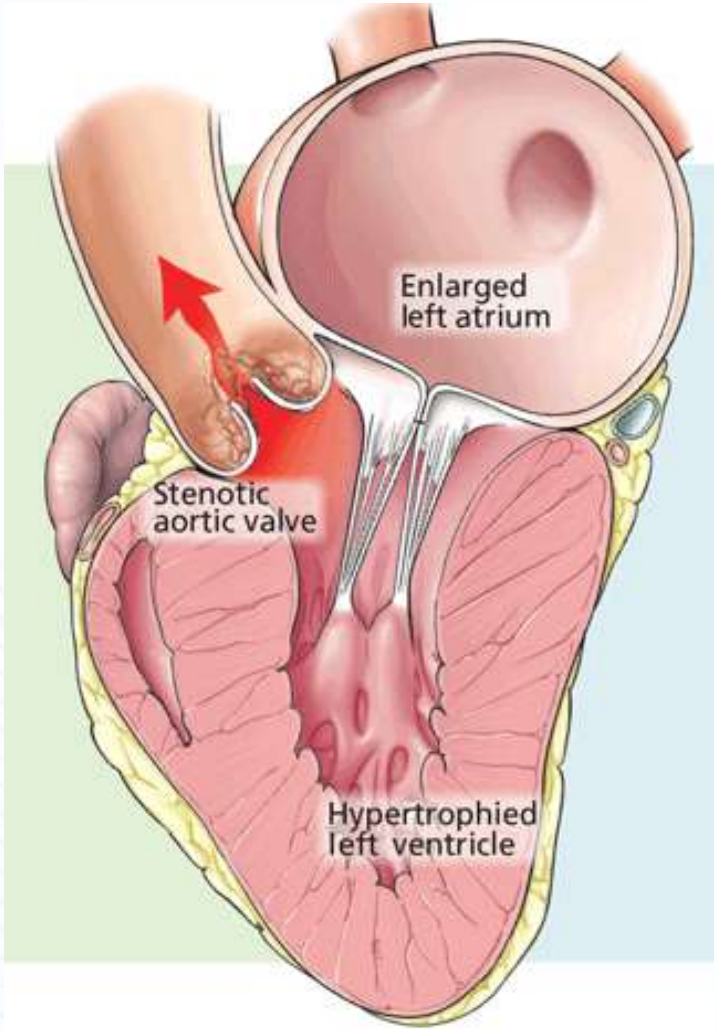
Poor Long-Term Survival in Patients With Moderate Aortic Stenosis

Geoff Strange, PhD,[a] Simon Stewart, PhD,[b] David Celermajer, MD, PhD,[c] David Prior, MBBS, PhD,[d] Gregory M. Scalia, MBBS (Hons), MMedSc,[e] Thomas Marwick, MBBS, PhD,[f] Marcus Ilton, MD,[g] Majo Joseph, MBBS,[h] Jim Codde, PhD,[i] David Playford, MBBS, PhD,[a] on behalf of the National Echocardiography Database of Australia contributing sites

Moderate AS is NOT a Benign Disease!

WHY IS MODERATE AS NOT BENIGN?

Cardiac **Consequences** of AS



- Misclassification of severity
- Echo diagnosis can be challenging
- Progression can be rapid and undetected
- Sub-clinical myocardial damage can occur
- Patients may present late

Intervention too late?

CURRENT TREATMENT PARADIGM FOR MODERATE AORTIC STENOSIS

Watchful waiting is ingrained in clinical practice

Current Guidelines

- Clinical and echo follow-up every 1-2 years for progression of AS, and medical therapy for hypertension and other cardiovascular conditions[1-3]
- AVR may be considered for patients undergoing cardiac surgery for another reason (IIb)

Issues with watchful waiting for moderate AS

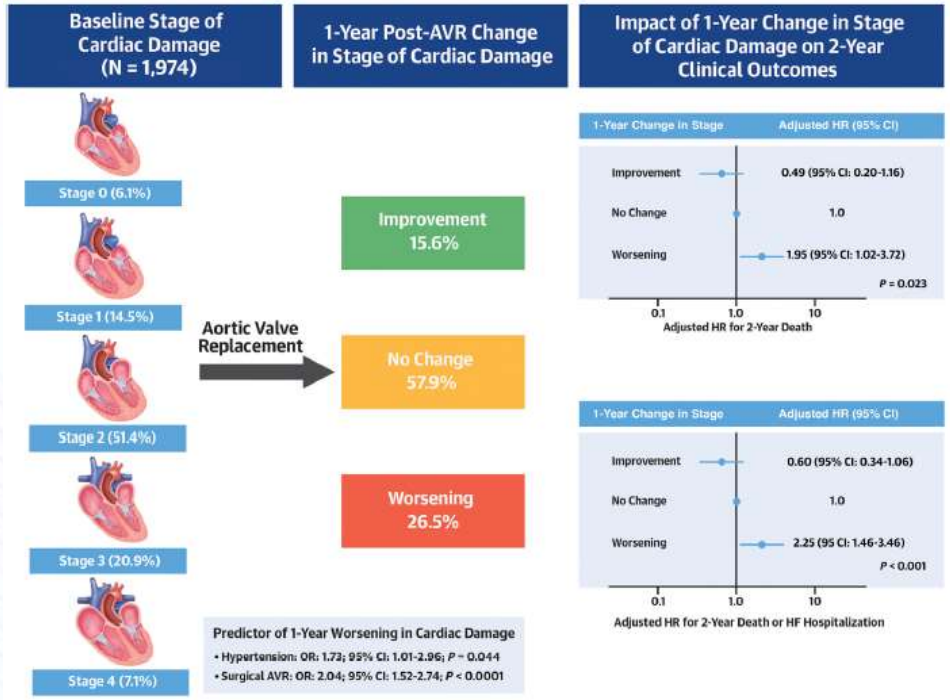
- Rate of stenosis progression is highly variable[1,2]
- Moderate AS has been associated with significant cardiovascular events and mortality in observational studies.[4,5]
- Waiting for AS to progress to severe before intervening may result in irreversible cardiac damage and worse prognosis even with AVR[6]

- [1] Nishimura RA, et al. J Am Coll Cardiol. 2017
- [2] Vahanian A, et al. Eur Heart J. 2022
- [3] Izumi C, et al. Circ J. 2020
- [4] Strange, G, et al. J Am Coll Cardiol. 2019
- [5] Coisne A et al. J Am Coll Cardiol 2022
- [6] Généreux P el al. J AM Cardiol. 2022

WHAT IS THE IMPACT OF AVR ON CARDIAC DAMAGE IN PATIENTS WITH SEVERE AS?

Extent of Cardiac Damage @ Baseline and its change @ 1yr have prognostic Implications after AVR

Evolution and Prognostic Impact of Cardiac Damage After AVR



- Généreux P. et al. J AM Coll Card (2022)

- 1,974 patients with severe AS who underwent AVR in PARTNER 2 and 3 trials

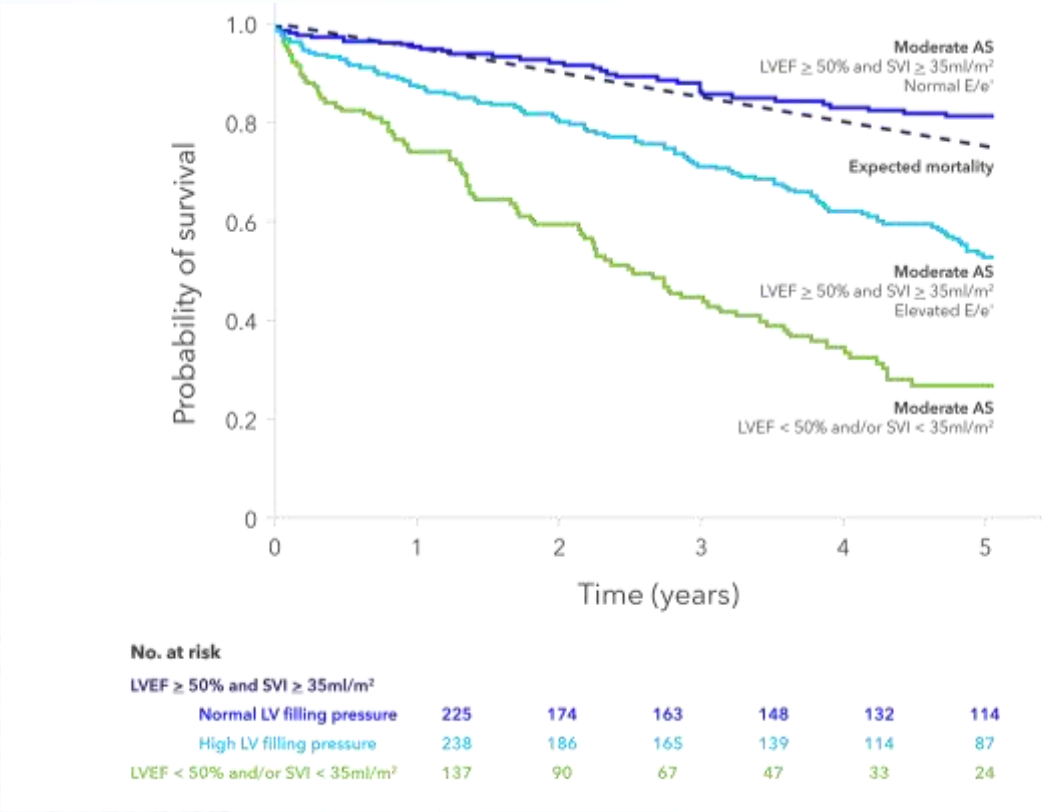
Stage 0 (no cardiac damage):	6.1%
Stage 1 (LV damage):	14.5%
Stage 2 (LA or MV damage):	51.4%
Stage 3 (Pulmonary vascular damage):	20.9%
Stage 4 (RV damage):	7.1%

- One year post–AVR , 57.9% remained unchanged, and 26.5% worsened by at least one stage. T
- **One year change in cardiac damage stage is significantly associated with death and composite of death or HF hospitalization two years post–AVR**
- ***"Findings suggest earlier detection and intervention before development of irreversible cardiac damage may improve cardiac function and prognosis of patients with AS." (Pre-emptive AVR)***

Moderate Aortic Stenosis: Predicting Myocardial Damage

Higher BNP, Lower GLS, Higher E/E', Low SVI

Mayo Clinic Echo Database



Ito S, et al JASE Mayo Clinical Database 2021;34:248-256.

2020 ACC Guidelines for Moderate

2b	C-EO

11. In patients with moderate AS (Stage B) who are undergoing cardiac surgery for other indications, AVR may be considered.

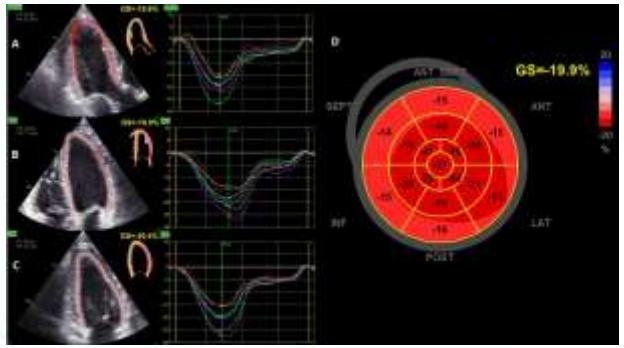
Why Perform TAVR Preemptively?

- Pre-Emptive definition:…"as a measure taken against something anticipated or feared; preventively…"
  - To prevent **death**
  - To prevent irreversible **symptoms**
  - To prevent irreversible **lost of quality of life**
  - To prevent irreversible **cardiac damage**

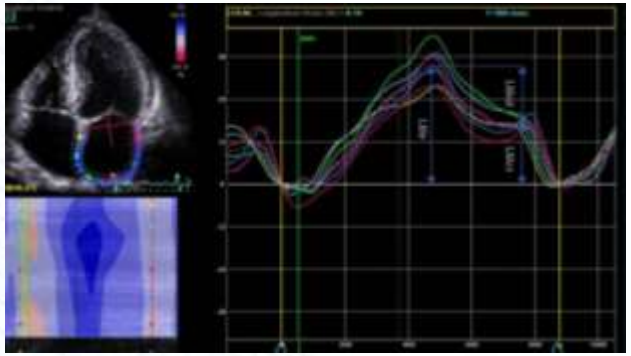
EARLIER INTERVENTION| CHALLENGES IN EVALUATING CARDIAC FUNCTION

Multi-modalities to evaluate impact of intervention and enhance prognostic risk stratification

Echocardiography
(Baseline and follow-up)

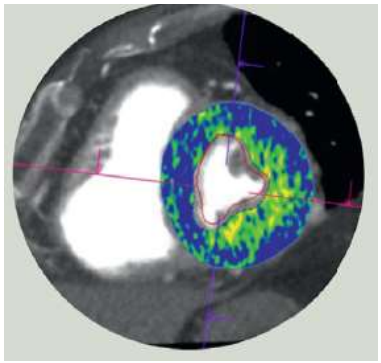


Left Ventricular Global Longitudinal Strain

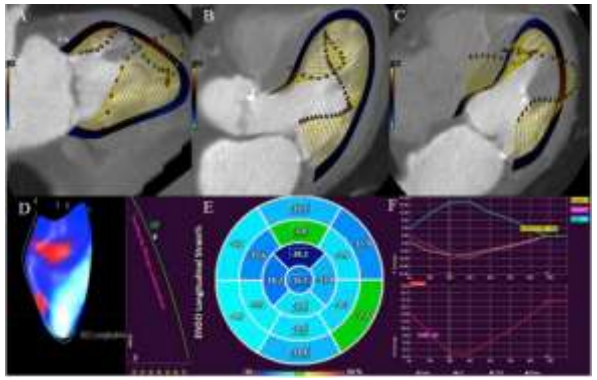


Left Atrial Strain

MDCT
(Baseline)

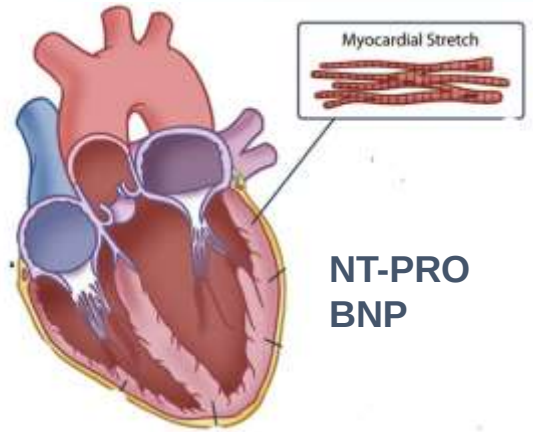


Extra-Cellular Volume



Left Ventricular Global Longitudinal Strain

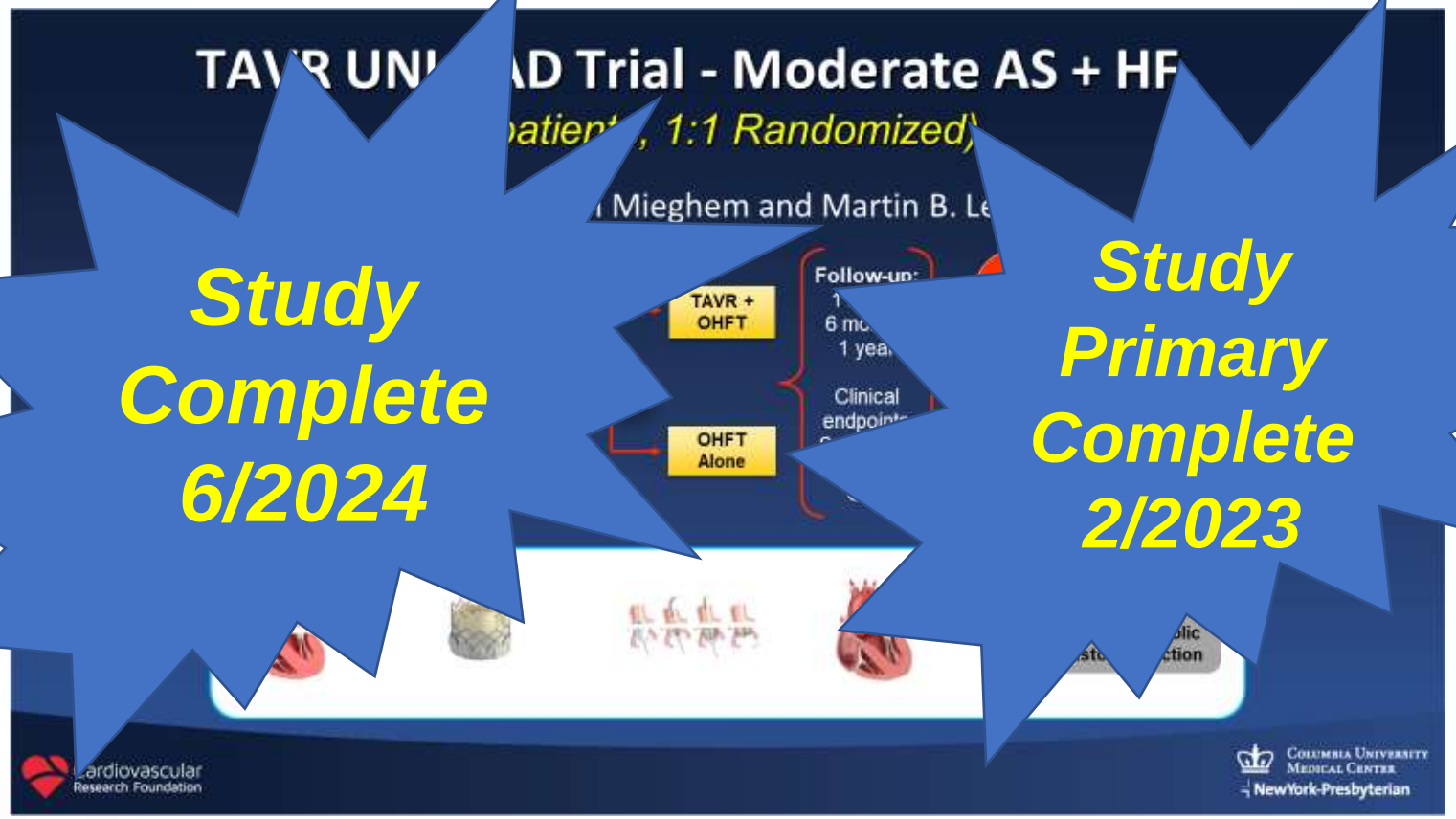
Bio-markers
(Baseline and follow-up)



NT-PRO BNP

Earlier TAVR Trial I TAVR UNLOAD Trial

TAVR vs GDMT and TAVR vs Afterload Reduction and GDMT



Study Complete 6/2024

Study Primary Complete 2/2023

MODERATE AORTIC STENOSIS

TAVR STUDIES

The PROGRESS Trial

Randomized, prospective trial
450 to 750 patients

1:1 Randomization
TAVR (Sapien3 Ultra) vs Clinical Surveillance

Interim Analysis (180 pts finish 2 yr f/u)

Primary Endpoint
All cause Mortality, Stroke and unplanned CV Hospitalisation at 2 years

The EXPAND II Trial

Randomized, prospective trial
550 patients

1:1 Randomization
TAVR (Evolut + GDMT) vs GDMT (delayed AVR allowed)

Primary Endpoint
All cause Mortality, HF events or Medical Instability leading to AVR at 2 years

EVOLUT NEW TECHNOLOGY, NEW TRIALS

PROCEDURAL IMPROVEMENTS

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SMALL ANNULI

SMART Trial – Valve Performance

TAV in TAV

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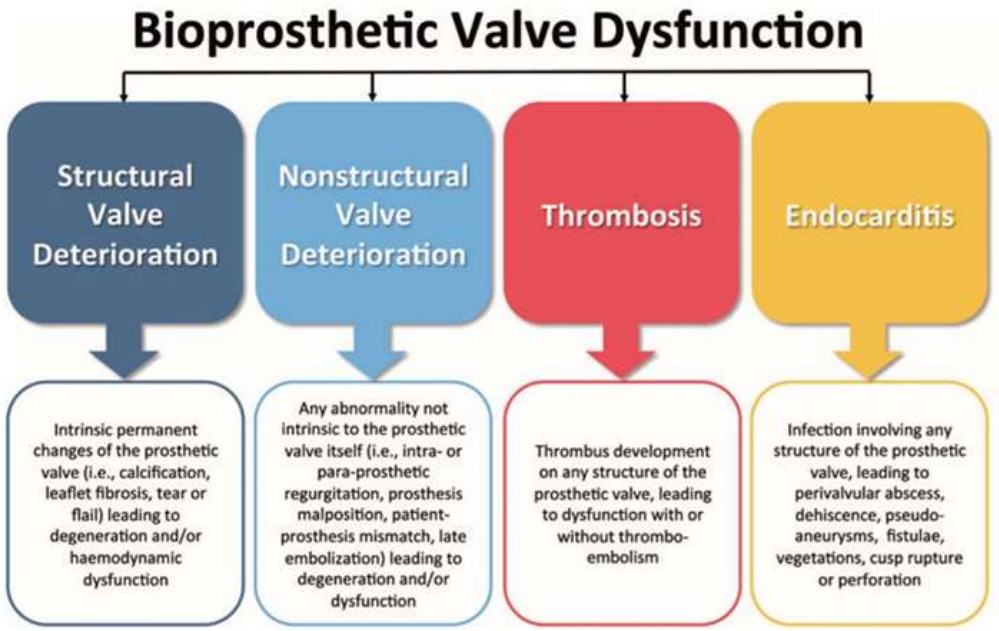


Bioprosthetic Valve Dysfunction Definition:

HSVD: hemodynamic SVD: mean gradient ≥20mmHg

NSVD: severe PPM, ≥ moderate AR

Thrombosis (VARC-3): clinically apparent leaflet thrombosis (leaflet thrombus formation associated with clinically relevant hemodynamic changes, symptoms, or sequela compatible with valve thrombosis or thromboembolism)

Endocarditis (VARC-3): Duke endocarditis criteria or abscess/pus/vegetation confirmed at reop or autopsy

Aortic valve re-operation or re-intervention

Capodanno D et al EHJ 2017; 0, 1–10

CLINICAL EVIDENCE ADDRESSING UNMET NEEDS

FOCUS ON SMALL ANNULI: THE SMART TRIAL

TRIAL UPDATES: SMART (SMall Annuli Randomized To evolut or sapien)

Severe native aortic valve stenosis with a small annulus
(≤ 430 mm² by MDCT)

Randomization
1:1 Stratified by Sex
(~700 patients)

Prospective, multi-center, international, randomized controlled, post-market study at 90 sites in Canada, EMEA and the United States

Medtronic Evolut PRO/PRO+/FX

Edwards SAPIEN 3/ SAPIEN 3 Ultra

Co-primary endpoints at 12 mos:
1. Death, disabling stroke, HF re-hosp
2. Bioprosthetic valve dysfunction

30-Day and annual 5-Year follow-ups for all patients

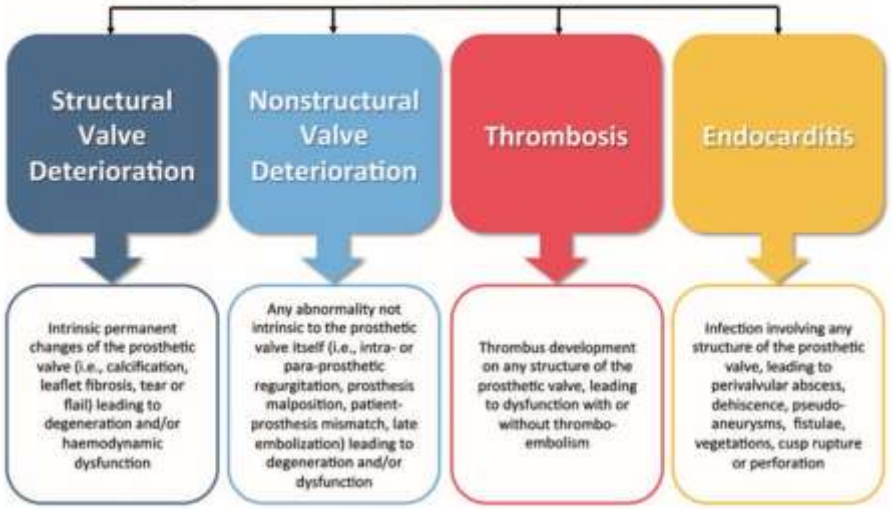
Enrollment Completed

CRF TCT

ClinicalTrials.gov Identifier: NCT04722250
Am Heart J 2022;243:92-102

Powered Secondary Endpoints	1. Mean grad/EOA (continuous) at 12 mos 2. Hemo SVD at 12 mos 3. BVD in the female subjects at 12 months 4. Mod/severe PPM at 30 days

Bioprosthetic Valve Dysfunction



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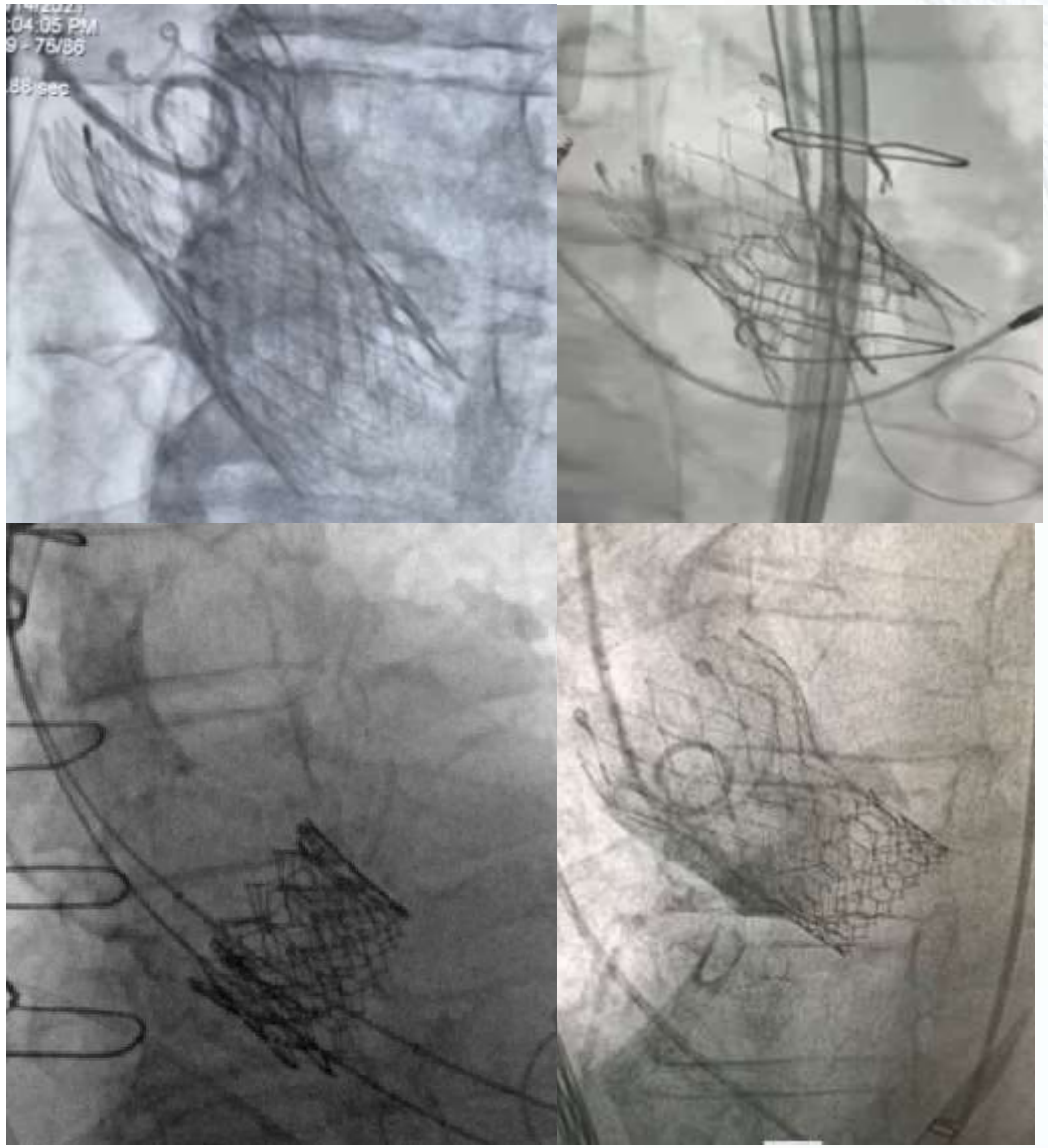

Zajarias et al Abstract TCT 2021

PROSPECTIVE REDO TAVI REGISTRY

PRESERVING LIFETIME TREATMENT OPTIONS

The REVALVE Study

REVALVE: RE-do Transcatheter Aortic VALVE Implantation for the management of Transcatheter Aortic Valve Failure:

Re-TAV Trial: Structure

Collaborative Clinical Research Project

Medtronic as sole funder, with input into study design & conduct throughout the study

Steering Committee with ultimate control over study design, conduct, and dissemination of results

Sponsor Leeds Teaching Hospitals

Clinical Research Organisation for trial conduct

Core Labs for CT / Echo / Angiography

DSMB and CEC

The Leeds Teaching Hospitals NHS

The REVALVE Study

Re-TAV Trial: Study Design

Re-do TAVI for Bio-prosthetic Valve Failure*
Any type of failing valve; Any type of treatment valve

500 patients from 50-100 centres in Europe & Israel
Recruitment over 3 years; 5 years follow-up

Parallel registries:	Surgical explantation + SAVR Conservative treatment
Proposed Sub-studies:	Post Re-do TAVI CT Pre Re-do TAVI FEOPS modelling Post Re-do TAVI Coronary catheterisation

The REVALVE Study Leadership

Chief Investigator:	Dan Blackman, Leeds, UK	
Steering Committee:	Mohamed Abdel-Wahab	Leipzig, Germany
	Marco Barbanti	Catania, Italy
	Ole de Backer	Copenhagen, Denmark
	Dave Hildick-Smith	Brighton, UK
	Uri Landes	Petich, Israel
	Hendrik Treede	Mainz, Germany
	Nicolas van Mieghem	Rotterdam, Netherlands
Funder:	Medtronic	

The Leeds Teaching Hospitals NHS

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Design Improvements

Fx Registry

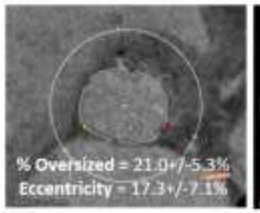
Evolut FX Design Features

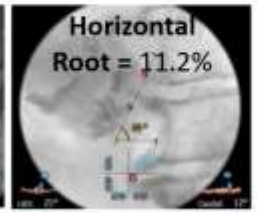
- Nosecone redesign
- More flexible capsule
- Single spine shaft
- Optimized stability layer
- Three inflow markers

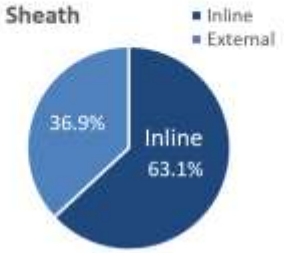
EVOLUT FX

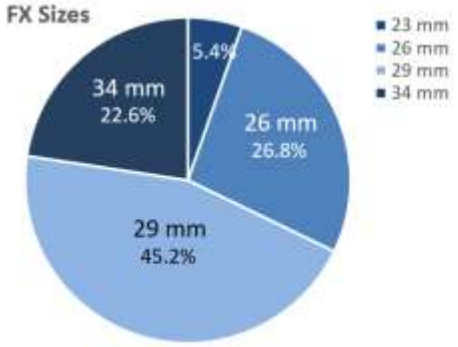
INITIAL MULTICENTER RESULTS

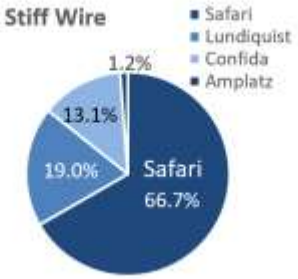
EVOLUT FX
INITIAL MULTICENTER RESULTS







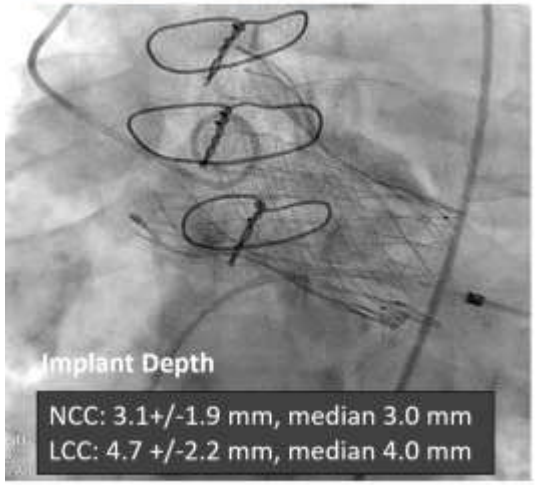




Tang et al London Valves 2022 Abstract

Procedural Characteristics	N=168
Valve-in-Valve - TAV-in-SAV - TAV-in-TAV (failed BEV)	18 (10.7%) 16 (9.5%) 2 (1.2%)
Transfemoral: Right	144 (85.7%)
Conscious Sedation	157 (93.5%)
Pre Dilatation	88 (52.4%)
Post Dilatation	25 (14.9%)
Sentinel Use	39 (23.2%)
Device Recapture / Reposition	48 (28.6%)
IV Contrast Use	83+/-42 mL
2nd Valve Required	1 (0.6%)

EVOLUT FX
INITIAL MULTICENTER RESULTS



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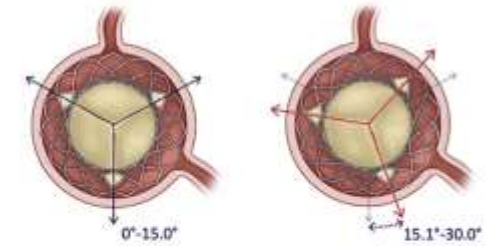

95.8%
Commissures aligned

EVOLUT FX
INITIAL MULTICENTER RESULTS

- 'Hat' marker position at center front at cusp overlap view in >93% of cases
- Commissural alignment achieved in 95.8% of cases
- Improved trackability, more symmetric final deployment
- Low LBBB / reasonable pacemaker rates with early experience
- No moderate/severe and only 13.1% mild paravalvular leak at 30 days
- Excellent hemodynamics similar to prior Evolut systems

30-Day Outcomes	Evolut FX, N=168
Death	2 (1.2%)
Stroke	3 (1.8%)
Major Vascular Complication	2 (1.2%)
New LBBB	29 (19.0%)
Permanent Pacemaker* - 34 mm FX - Excluding prior RBBB (N=9) - Excluding prior RBBB + 34mm FX (N=14)	23 (15.0%) 7 (18.4%) **14 (9.7%)** **9 (6.5%)**

*prior pacemaker excluded, no association with learning curve or no Lundiquist wire use

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