EUROVALVE
& STRUCTURAL CARDIOMYOPATHIES
NH PALERMO

SAVE
THE DATE
OCTOBER
24&25,2024

RCTS AND REAL WORD REGISTRIES: OPPOSITE OR COMPLIMENTARY?

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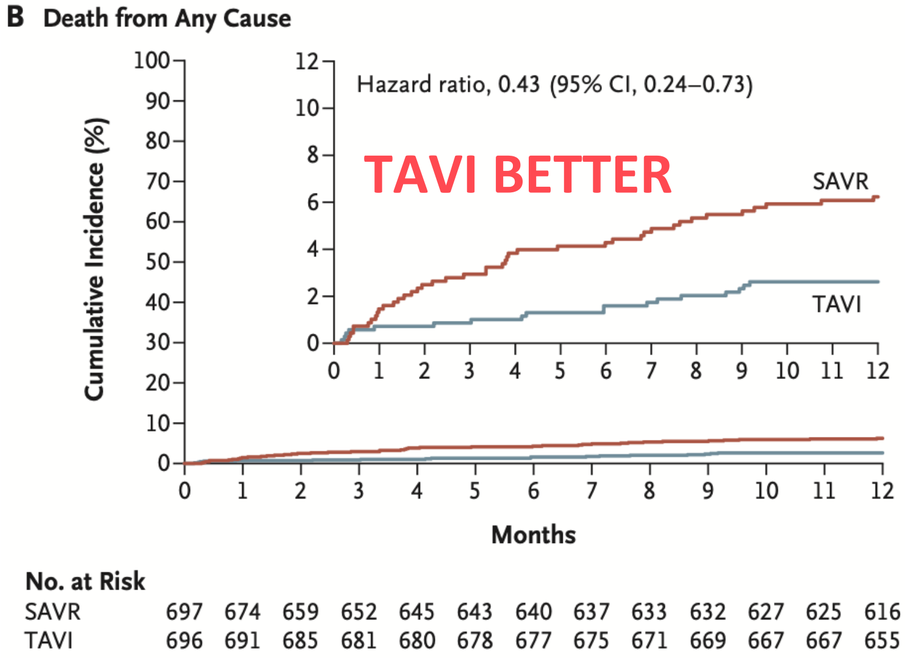
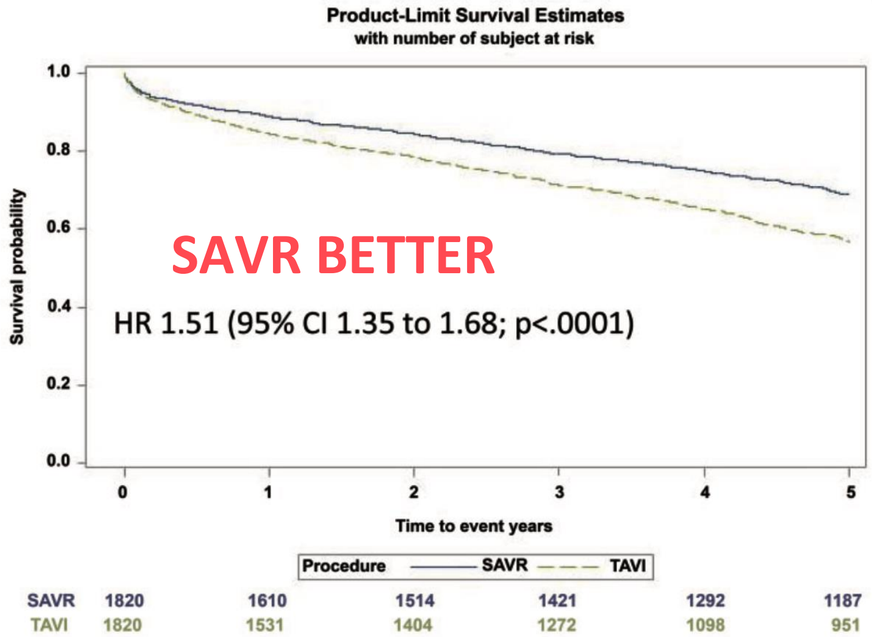
A PARADOX?... Or maybe not!



RCT (DEDICATE Trial)



REGISTRY (GARY)

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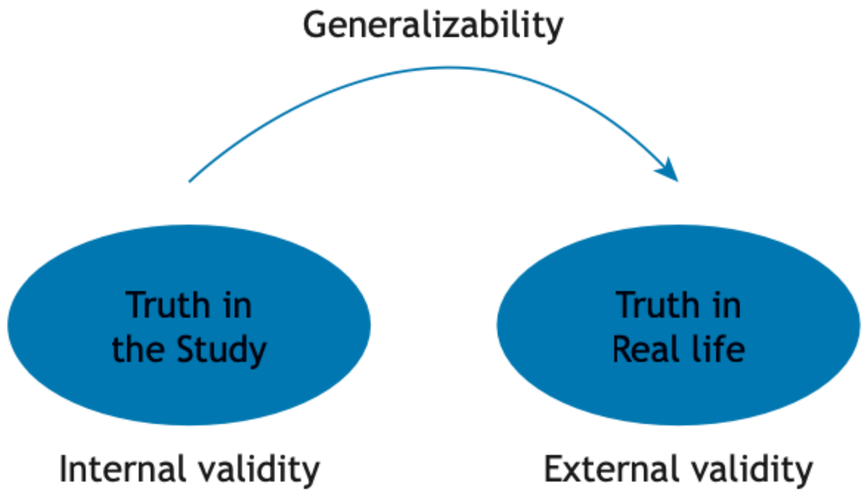
CAN WE APPLY STUDY RESULTS TO OUR PATIENTS?



INTERNAL VALIDITY. **The extent to which the observed results represent the truth in the population we are studying and are not due to methodological errors.**

EXTERNAL VALIDITY. **Whether the study results apply to similar patients in a different setting.**

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WHAT ARE WE DEALING WITH? THE LEVELS OF EVIDENCE

RCT

Better Internal Validity

External Validity?

REAL WORD REGISTRIES

Worse Internal Validity

Better Ext Validity?

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RANDOMIZED CLINICAL TRIALS: **STRONGEST AND MOST RELIABLE EVIDENCE**

The main appeal of the randomized controlled trial in health care comes from its potential to **reduce selection bias**.

Does random allocation **protect RCTs against OTHER types of BIAS?**

Does RCTs guarantee **external validity?**

RANDOMIZED CLINICAL TRIALS: **STRONGEST AND MOST RELIABLE EVIDENCE BUT..**

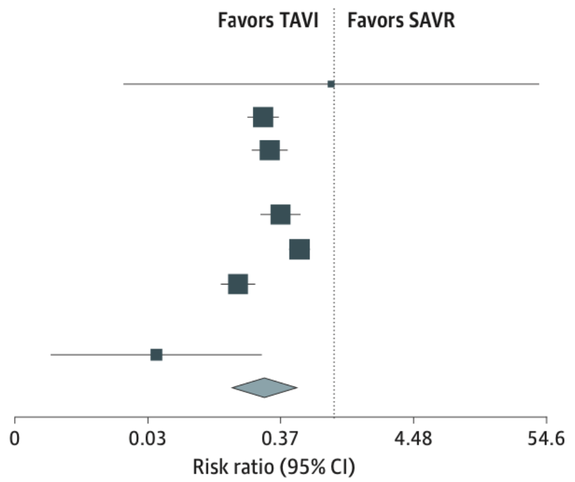
Original Investigation | Statistics and Research Methods

Risk of Bias in Randomized Clinical Trials Comparing Transcatheter and Surgical Aortic Valve Replacement
A Systematic Review and Meta-analysis

Fabio Barili, MD, PhD; James M. Brophy, MD, PhD; Daniele Ronco, MD; Patrick O. Myers, MD; Miguel Sousa Uva, MD; Rui M. S. Almeida, MD; Mateo Marin-Cuartas, MD; Amedeo Anselmi, MD, PhD; Jacques Tomasi, MD, PhD; Jean-Philippe Verhoye, MD, PhD; Francesco Musumeci, MD; John Mandrola, MD; Sanjay Kaul, MD; Stefania Papatheodorou, MD, PhD; Alessandro Parolari, MD, PhD; for the International Evidence Grading Research Initiative Targeting Transparency and Quality (INTEGRITTY)

Figure 5. Forest Plot Presenting the Risk Ratio of Patients Who Received Additional Treatments in Transcatheter Aortic Valve Implantation (TAVI) vs Surgical Aortic Valve Replacement (SAVR)

Randomized clinical trial	Risk ratio (95% CI)
Low risk	
NOTION Trial	0.94 (0.02-47.24)
Evolut Low-Risk Trial	0.26 (0.20-0.35)
PARTNER 3 Trial	0.30 (0.21-0.42)
Intermediate risk	
UK TAVI Trial	0.36 (0.25-0.53)
SURTAVI Trial	0.52 (0.43-0.63)
PARTNER 2A Trial	0.16 (0.12-0.23)
High risk	
CoreValve US Pivotal Trial	0.04 (0.00-0.26)
RE model ($Q = 46.24$; $df = 6$; $P < .01$; $I^2 = 93.8\%$; $\tau^2 = 0.51$)	0.27 (0.15-0.50)



Key Points

Question Does randomization protect randomized clinical trials (RCTs) comparing transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR) from biases other than nonrandom allocation?

Findings This systematic review and meta-analysis of 8 RCTs including 8849 participants and comparing TAVI vs SAVR found substantial overall proportions of deviation from assigned treatment, loss to follow-up, additional procedures, and additional myocardial revascularization together with a systematic selective imbalance in the same direction characterized by significantly lower proportions among participants undergoing TAVI.

Meaning This study suggests that RCTs comparing TAVI and SAVR show serious methodological imbalances with a common selective pattern, and should be considered at high risk of performance and attrition bias that may affect internal validity.

BETTER INTERNAL VALIDITY BUT NOT OPTIMAL

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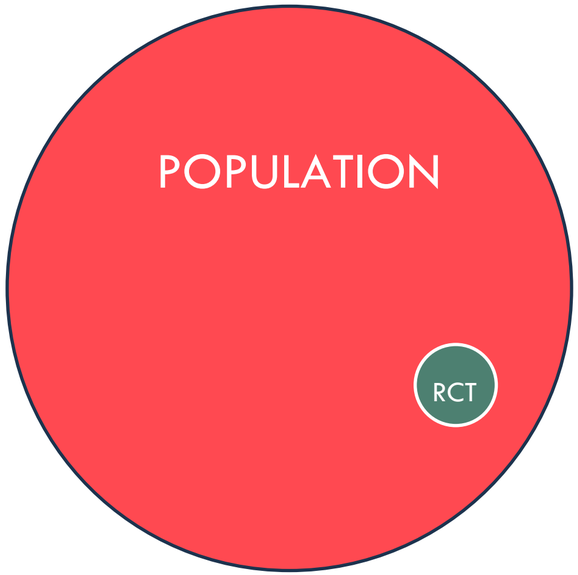
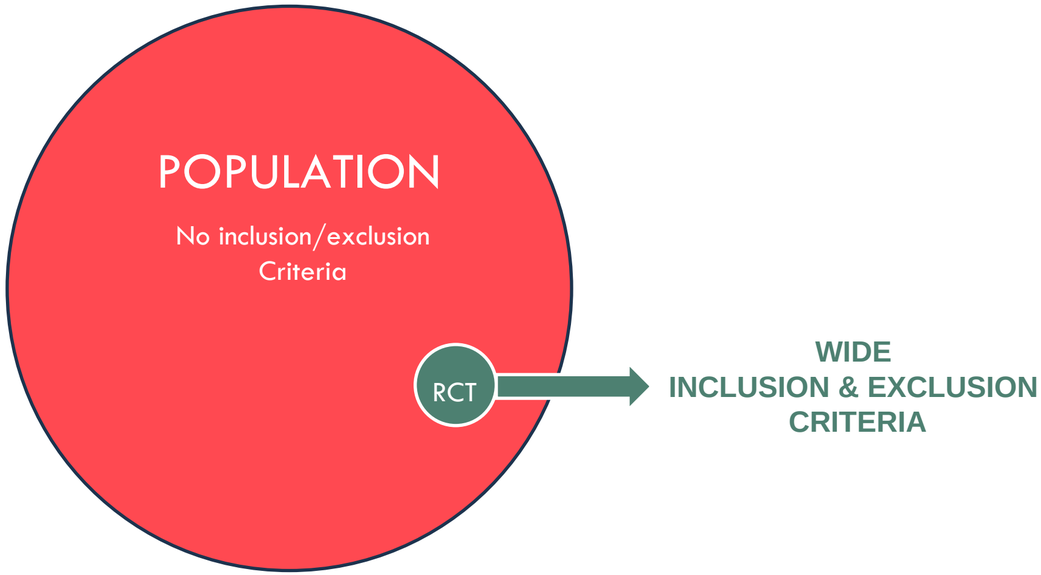
RCT AND EXTERNAL VALIDITY



Does the RCT results apply to similar patients in a different setting?

RCT AND EXTERNAL VALIDITY



Does the RCT results apply to similar patients in a different setting?

RCT AND EXTERNAL VALIDITY

COAPT TRIAL

Transcatheter Mitral-Valve Repair in Patients with Heart Failure

6.3.2 Eligibility Criteria

Assessment of eligibility criteria is based on the subject's medical records. Clinical and laboratory tests of eligibility assessments shall be per site standard. If a specific test required to determine subject's eligibility is not included in site's standard tests, the test must be performed after written informed consent has been obtained from subject.

6.3.2.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to participate in the trial:

1. Symptomatic (NYHA Functional Class II, III or ambulatory IV) functional MR (≥3+) determined by assessment of a TTE obtained within the prior 6 months of enrollment, and MR severity is confirmed by the Echocardiography Core Lab.
2. Subject must have co-morbidities such that a CT surgeon investigator at the site determines that medical factors preclude surgery, based on a conclusion that the probability of death or serious morbidity, exceeds the probability of meaningful improvement, and this conclusion is confirmed by the Eligibility Committee.
3. In the judgment of an experienced cardiologist investigator at the site, the subject is likely to benefit from MR reduction, and this conclusion is confirmed by the Eligibility Committee.
4. The subject has been adequately treated per applicable standards, such as for coronary artery disease, left ventricular dysfunction, mitral regurgitation or heart failure (e.g., cardiac resynchronization therapy, revascularization, optimal medical therapy; see **APPENDIX A: Definitions** for definitions).
5. Left ventricular ejection fraction (LVEF) > 30% and left ventricular end-systolic dimension (LVESD) ≤ 60 mm based on an echocardiogram obtained within the prior 6 months.
6. The primary regurgitant jet originates from malcoaptation of the A2 and P2 scallops of the mitral valve. If a secondary jet exists, it must be considered clinically insignificant.
7. Transseptal catheterization and femoral vein access is determined to be feasible.
8. Age 18 years or older.
9. The subject or the subject's legal representative has been informed of the nature of the trial and agrees to its provisions, including the possibility of randomization to the Control group and returning for all required post-procedure follow-up visits, and has provided written informed consent.

6.3.2.2 Exclusion Criteria

Subjects must NOT meet any of the following exclusion criteria to participate in the trial:

1. Mitral regurgitation is primarily due to degenerative disease of the mitral valve apparatus (Degenerative MR).
2. Evidence of an acute myocardial infarction in the prior 90 days (defined as: Q wave or non-Q wave infarction having CK enzymes ≥ 2X the upper laboratory normal limit with the presence of a CK-MB elevated above the institution's upper limit of normal).
3. Untreated clinically significant coronary artery disease requiring revascularization.
4. Cerebrovascular accident within 6 months prior to randomization or severe carotid stenosis (> 70% by ultrasound).
5. ACC/AHA Stage D heart failure
6. Presence of any of the following:
   - Severe TR or AR or moderate to severe AS (< 1.0 cm^2)
   - Estimated pulmonary artery systolic pressure (PASP) > 60 mm Hg assessed by echocardiography
   - Hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non ischemic etiology
   - Infiltrative cardiomyopathies (e.g., amyloidosis, hemochromatosis, sarcoidosis)
   - Hemodynamic instability requiring inotropic support or mechanical heart assistance
7. Any percutaneous cardiac intervention or carotid surgery within the 30 days prior to randomization, or any cardiac surgery within the 6 months prior to randomization.
8. Implant of any rhythm management device (i.e., pacemaker, Cardiac Resynchronization Therapy (CRT), Cardiac Resynchronization Therapy with cardioverter-defibrillator (CRT-D), or Implantable Cardioverter Defibrillator (ICD)) within the last 90 days, or revision of any implanted rhythm management device within the last 90 days.
9. Mitral valve orifice area < 4.0 cm^2.
10. If leaflet tethering is present, vertical coaptation length is less than 2 mm.
11. Leaflet anatomy which may preclude MitraClip implantation, proper MitraClip positioning on the leaflets or sufficient reduction in MR. This may include:
    - Evidence of calcification in the grasping area of the A2 and/or P2 scallops
    - Presence of a significant cleft of A2 or P2 scallops
    - Lack of both primary and secondary chordal support
12. Hemodynamic instability defined as systolic pressure < 90 mmHg without afterload reduction, cardiogenic shock or the need for inotropic support or intra-aortic balloon pump.
13. Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months.
14. Life expectancy < 12 months due to non-cardiac conditions.
15. Modified Rankin Scale ≥ 4.
16. Status 1 heart transplant or prior orthotopic heart transplantation.
17. Prior mitral valve leaflet surgery or any currently implanted prosthetic mitral valve.
18. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
19. Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic diseased (i.e., noncompliant, perforated).
20. Active infections requiring current antibiotic therapy.
21. Subjects in whom transesophageal echocardiography (TEE) is contraindicated.
22. A known hypersensitivity or contraindication to procedure medications which cannot be adequately managed medically.
23. Pregnant or planning pregnancy within next 12 months.
24. In the judgment of the Investigator, subjects in whom the presence of a permanent pacemaker or pacing leads would interfere with placement of the MitraClip device or the placement of the MitraClip device would disrupt the leads.
25. Currently participating in an investigational drug or another device study. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.

6.3.3 Justification for Inclusion and Exclusion Criteria

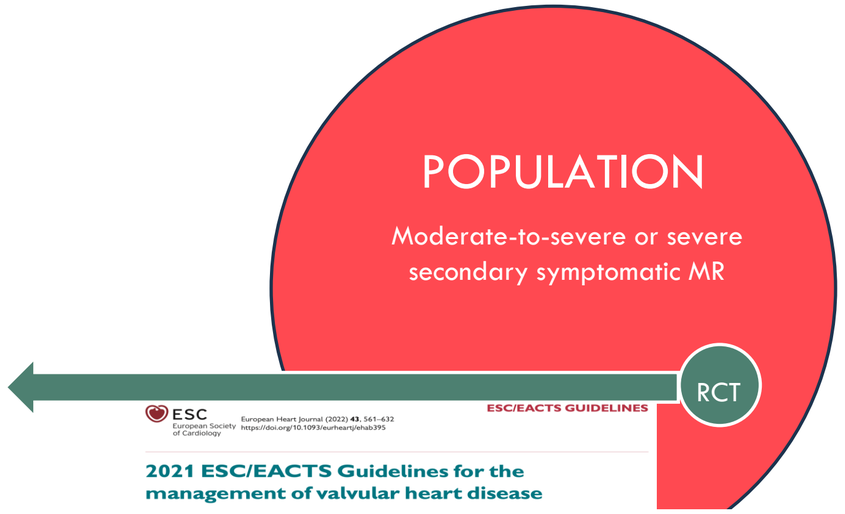
The COAPT Trial is designed to ensure randomization of subjects with moderate-to-severe (3+) or severe (4+), symptomatic functional mitral regurgitation that 1) will likely benefit from MR reduction and 2) are too high risk for mitral valve surgery. These are patients with mild to moderate left ventricular dysfunction would typically be referred for mitral valve surgery, but have advanced age and/or multiple co-morbidities making them extremely high risk for surgical mortality and serious morbidity.

Several eligibility criteria are defined to include subjects who are at high surgical risk and who are likely to benefit from MR reduction. To ensure there is high likelihood the subject will benefit from MR reduction, outside limits are set on LV ejection fraction (> 30%) and LV end systolic dimension (≤ 60mm). To ensure high surgical risk status, all subjects must be examined by an experienced CT surgeon at the site. The surgeon must determine that subject's medical history precludes mitral valve surgery. Additionally, a cardiologist at the investigational site is required to examine the subject to ensure the subject is likely to benefit from MR reduction. Finally, to ensure consistency of criteria applied to determine high surgical risk status of the subject, an Eligibility Committee, consisting of at least one CT surgeon and one cardiologist, will review pertinent medical history to make the final determination regarding eligibility of prospective subjects (see **Section 10.2 Central Eligibility Committee** for more details).

To isolate the effect of the MitraClip device, eligible subjects must have been adequately treated per applicable standards, such as for coronary artery disease, left ventricular dysfunction, mitral regurgitation or heart failure prior to enrollment. Subjects must also have received appropriate revascularization therapy for their coronary artery disease, and cardiac resynchronization therapy, if eligible, at least 90 days prior to randomization.

Subjects who are unlikely to benefit from the MitraClip intervention, have a life expectancy of less than 12 months due to non-cardiac conditions, or who have refractory heart failure requiring specialized interventions, such as implantation of a LVAD or listing for heart transplant, are excluded from the trial. As such, ACC/AHA Stage D heart failure subjects, non-ambulatory NYHA Functional Class IV subjects, subjects dependent on inotropic support, subjects with baseline modified Rankin Scale grade ≥ 4 and subjects with concomitant right heart failure are specifically excluded from the trial. Finally, subjects presenting with hypertrophic and restricted cardiomyopathies are also excluded on the grounds that their left ventricle is less likely to reverse remodel.

Additionally, appropriate mitral valve anatomical criteria ensure subjects are candidates for the MitraClip procedure.



ESC European Society of Cardiology
European Heart Journal (2022) **43**, 561–632
https://doi.org/10.1093/eurheartj/ehab395
ESC/EACTS GUIDELINES

2021 ESC/EACTS Guidelines for the management of valvular heart disease

Therefore, TEER should be considered in selected patients with severe SMR fulfilling the COAPT inclusion criteria,[346–348] who receive optimal medical therapy supervised by a heart failure specialist and are as close as possible to the patients actually enrolled in the study. Optimization of the procedural result should also be pursued. In addition, TEER may be considered only in selected cases when the COAPT criteria are not fulfilled with the aim of improving symptoms

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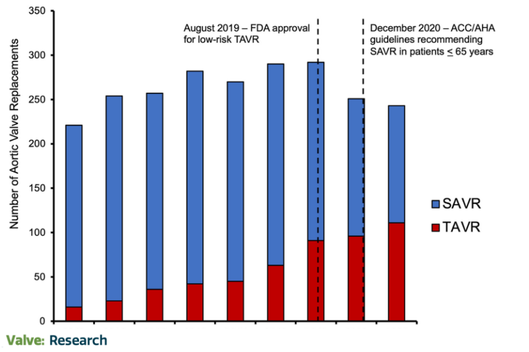
RCT AND EXTERNAL VALIDITY

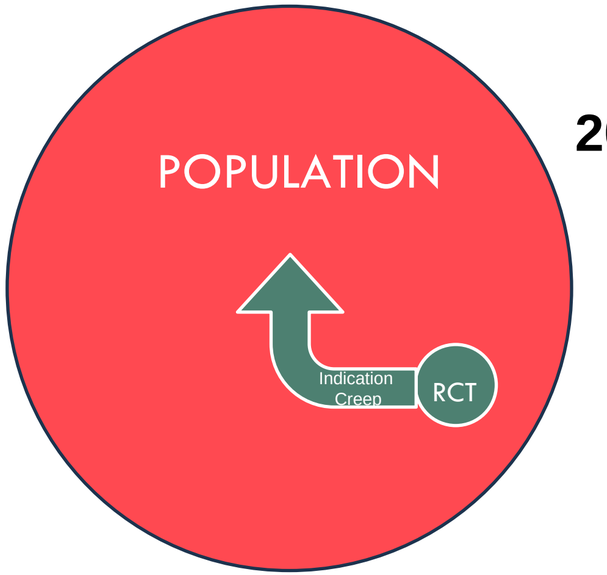
California <60yrs: 22.2%TAVI



Valve: Research

Cardiac Surgery After Transcatheter Aortic Valve Replacement: Trends and Outcomes

Michael E. Bowdish, MD, MS,[1] Robert H. Habib, PhD,[2] Tsuyoshi Kaneko, MD,[3] Vinod H. Thourani, MD,[4] and Vinay Badhwar, MD[5]



2019: 7618 TAVI/SAVR

531 (7%) TAVI IN LOW-RISK

Transcatheter Aortic Valve Implantation Compared With Surgical Aortic Valve Replacement in Low-Risk Patients

Stefano Rosato, MSc; Francesco Santini, MD, PhD; Marco Barbanti, MD, PhD; Fausto Biancari, MD, PhD; Paola D'Errigo, MSc; Francesco Onorati, MD, PhD; Corrado Tamburino, MD, PhD; Marco Ranucci, MD, PhD; Remo Daniel Covello, MD; Gennaro Santoro, MD; Claudio Grossi, MD; Martina Ventura, MSc; Danilo Fusco, MSc; Fulvia Seccareccia, MSc; on behalf of the OBSERVANT Research Group

WHAT IS KNOWN

- TAVI is widely recognized as an effective treatment method in high-risk patients with severe aortic valve stenosis.
- The excellent results of TAVI are leading to the expansion of its indications toward lower-risk patients, without evidence of any benefit over surgical aortic valve replacement.

WHAT THE STUDY ADDS

- This prospective study showed that surgical aortic valve replacement and TAVI can be performed in patients with EuroSCORE <4% with similar 30-day mortality rates.
- Surgical aortic valve replacement had significantly better 3-year outcomes than TAVI.
- These data suggest that expanding the use of TAVI in low-risk patients may not be justified.

Indication creep occurs when an intervention program to benefit patients with a specific health condition is either expanded to a broader patient population or expanded to a different health condition.

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VIEWPOINT

Indication Creep in Transcatheter Aortic Valve Implantation—Data or Desire?

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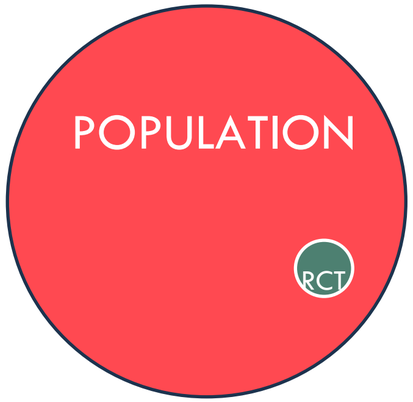
Department of Cardiology, Houston Methodist Hospital, Houston, Texas.

Michael J. Reardon, MD
Department of Cardiovascular Surgery, Houston Methodist Hospital, Houston, Texas.

JAMA Cardiology Published online April 19, 2023



We should ask, however, if this indication creep for TAVI in younger, low-risk patients is based on the data or just the desire (of both patients and physicians) for TAVI. To answer this question, we must remember that RCT results apply only to the populations tested and examine how we apply these findings to other populations.

We are advocates for TAVI in appropriate cases. We urge our colleagues to consider and hopefully fill existing knowledge gaps to allow the continued rational expansion of indications for TAVI based on data that can support desire.

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EXTERNAL VALIDITY? THE RISK OF INDICATION CREEP

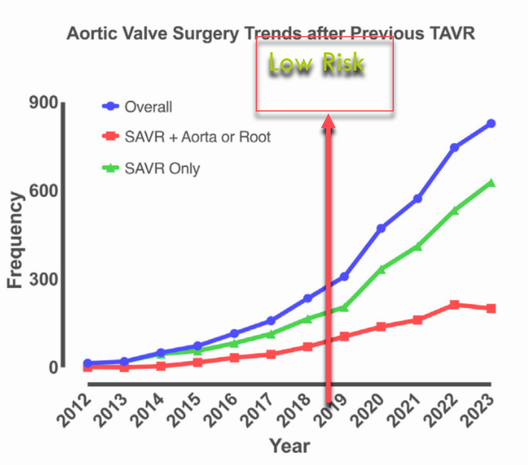

FIGURE 2 Trends in surgical aortic valve replacement (SAVR) after previous transcatheter aortic valve replacement (TAVR). Note: 2023 values are projections. All trends are significantly nonlinear by the Cochrane–Armitage test ($P < .05$).

TABLE 4 Postoperative Outcomes (Unadjusted)

Outcome	Any Cardiac Surgery After TAVR (n = 5457)	Non-AVR Cardiac Surgery After TAVR (n = 2485)	SAVR After TAVR (n = 2972)
Operative mortality	863 (15.8)	444 (17.9)	419 (14.1)
Morbidity and mortality	2114 (38.7)	967 (38.9)	1147 (38.6)
Permanent stroke	246 (4.5)	109 (4.4)	137 (4.6)
Prolonged ventilator	1594 (29.2)	703 (28.3)	891 (30.0)
Renal failure	608 (11.1)	280 (11.3)	328 (11.0)
Return to operating room	481 (8.8)	195 (7.8)	286 (9.6)
Vascular complication	94 (1.7)	41 (1.6)	53 (1.8)
Postoperative atrial fibrillation	1554 (28.5)	666 (26.8)	888 (29.9)
Permanent pacemaker	566 (10.4)	131 (5.3)	435 (14.6)
Postoperative length of stay, d	9.0 (6–14)	8.0 (5–14)	9.0 (7–15)

Data are presented as n (%) or median (interquartile range). AVR, aortic valve replacement; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

MORTALITY

SAVR AFTER TAVI: 14.1%

NON AVR SURGERY AFTER TAVI: 17.9%

CONCLUSIONS The need for cardiac surgery, including redo SAVR after TAVR, is increasing rapidly. Risks are higher, and outcomes are worse than predicted. These data should closely inform heart team decisions if TAVR is considered at lowering age and risk profiles in the absence of longitudinal evidence.

Valve: Research

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EXTERNAL VALIDITY? THE RISK OF INDICATION CREEP

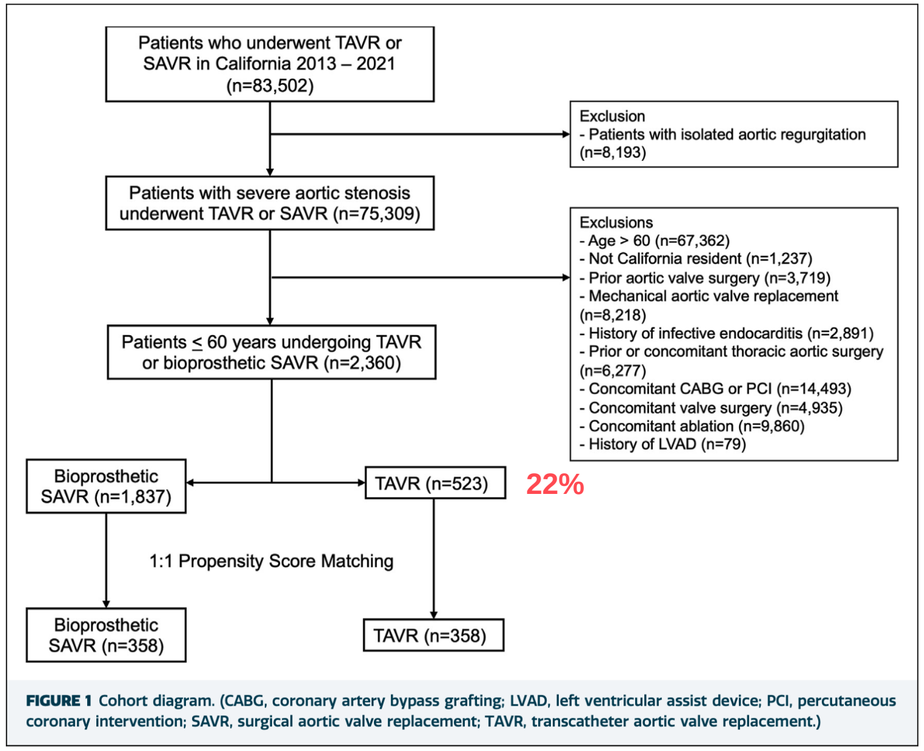

FIGURE 1 Cohort diagram. (CABG, coronary artery bypass grafting; LVAD, left ventricular assist device; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.)

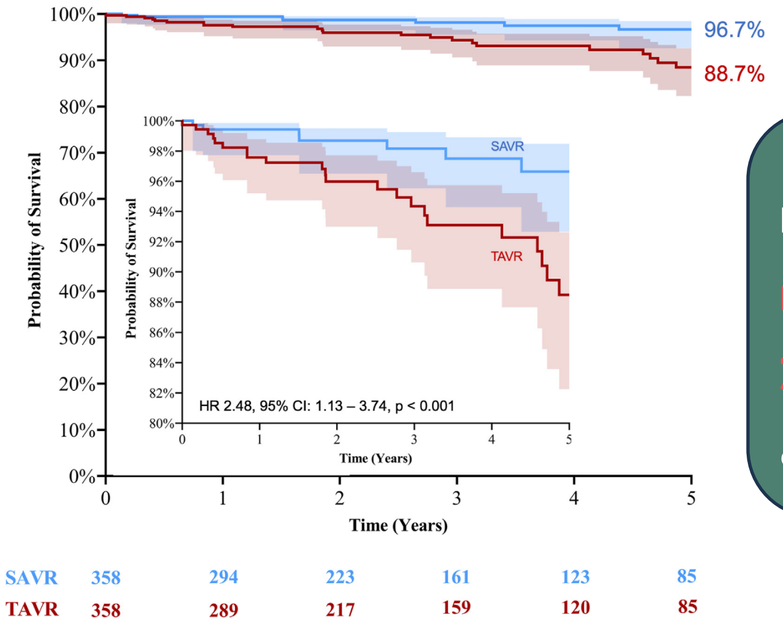

FIGURE 5 Survival at 5 years of patients who underwent transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) in California after propensity score matching. The shaded areas indicate the 95% CI. (HR, hazard ratio.)

RESULTS

Between 2013 and 2021 TAVR rates in patients aged <60 years increased from 7.2% to 45.7% (annual increase of 4.7%, P < .001).

Guidelines vs Practice: Surgical Versus Transcatheter Aortic Valve Replacement in Adults ≤60 Years
https://doi.org/10.1016/j.athoracsur.2024.07.036

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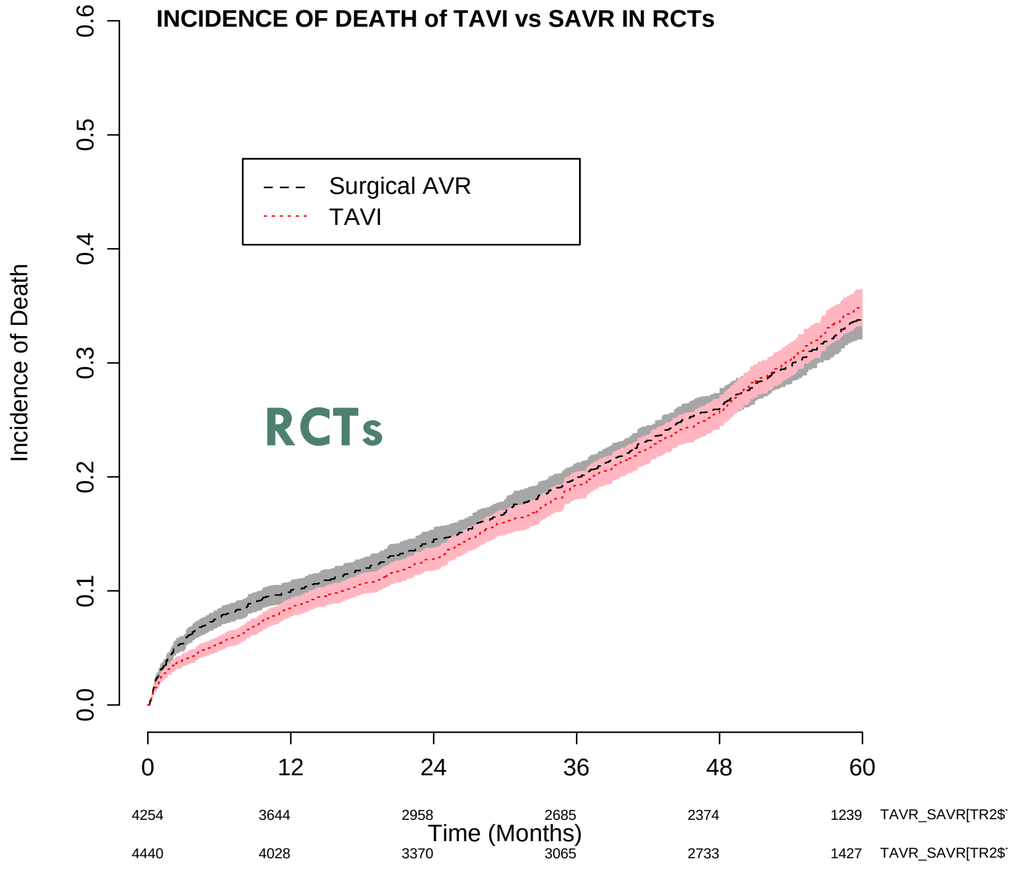
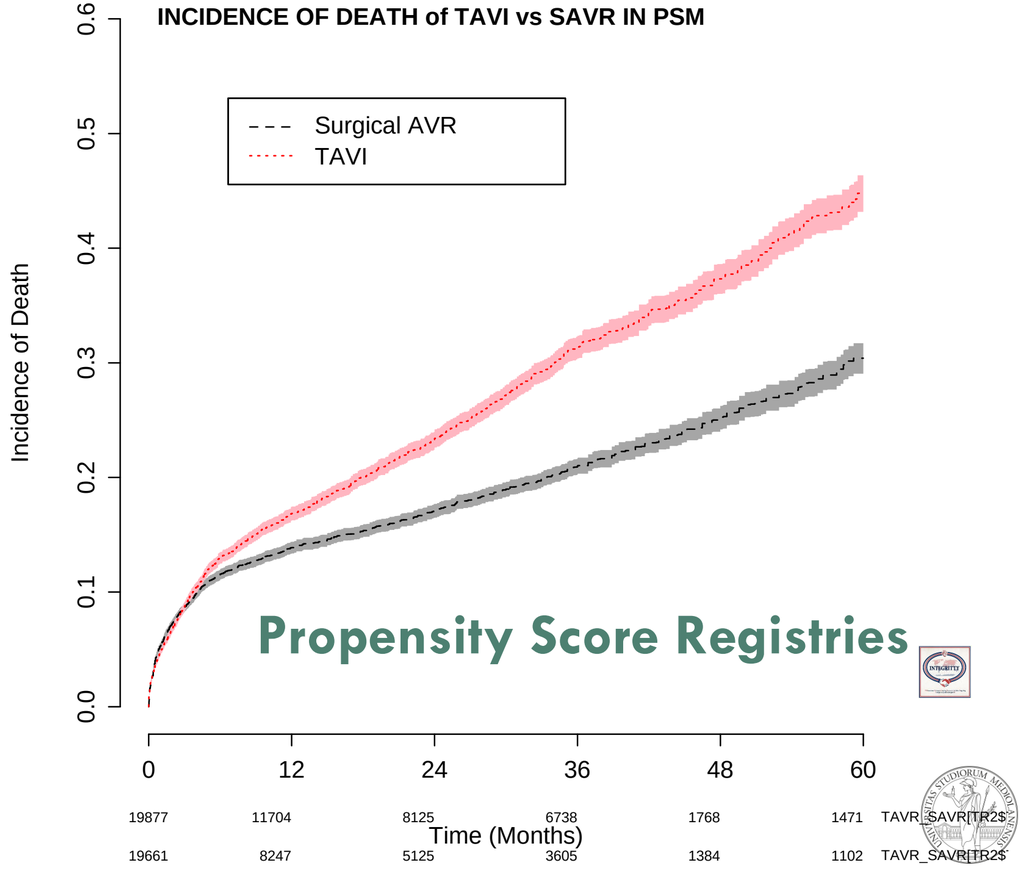
•OPPOSITE OR COMPLIMENTARY?





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•OPPOSITE OR COMPLIMENTARY?

Replication of randomized clinical trial results using real-world data: paving the way for effectiveness decisions

Kristin M Sheffield*[1], Nancy A Dreyer[2], James F Murray[1], Douglas E Faries[3] & Megan N Klopchin[1]

Journal of Comparative Effectiveness Research

RCTs and RWE are complementary and each contribute valuable information about patient outcomes.

The FDA is preparing guidance about using real-world evidence (RWE) to support decisions about product effectiveness. Several ongoing efforts aim to replicate randomized clinical trial (RCT) results using RWE with the intent of identifying circumstances and methods that provide valid evidence of drug effects. Lack

THANK YOU!