Aortic valve diseases and need of re-reading current evidence. The INTEGRITTY initiative

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NO DISCLOSURES

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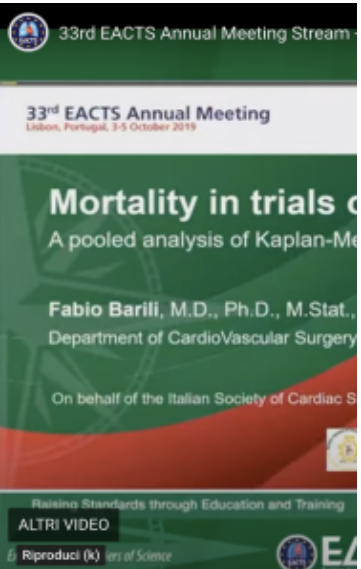
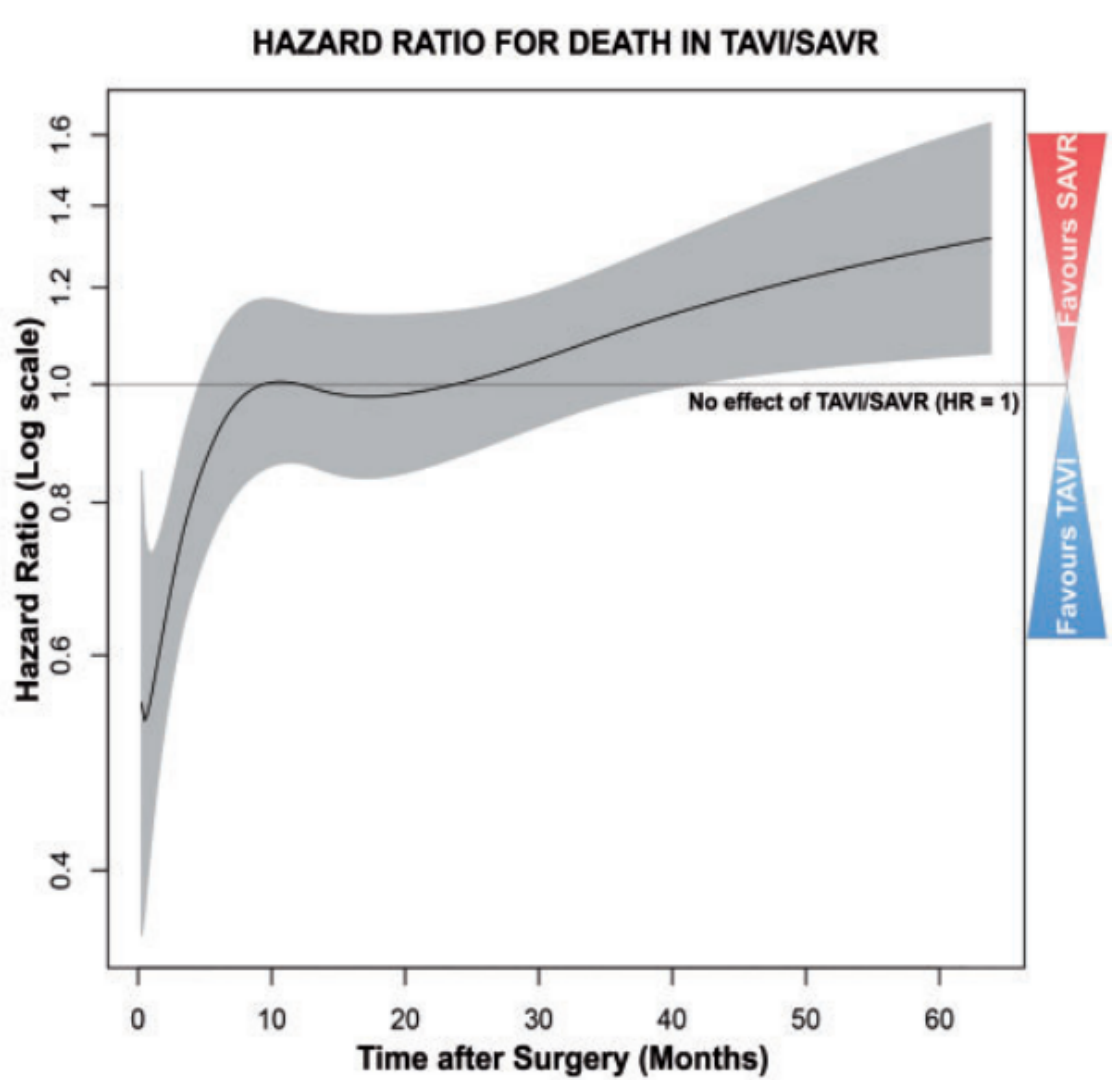
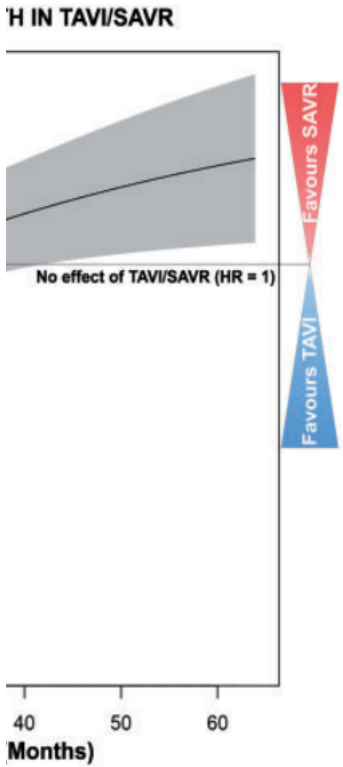
versus surgical aortic valve replacement: a pooled meta-

Mortality in trials o
versus surgical aortic
of Kaplan-Me

Fabio Barili [a,*], Nicholas Freem
Francesco Mus







Background – the early starting

Five-Year Outcomes with Transcatheter Aortic-Valve Replacement

TO THE EDITOR: The key message of the report by Makkar et al.[1] and the editorial by Van Belle[2] (Feb. 27 issue) on the Placement of Aortic Transcatheter Valves (PARTNER) 2 cohort A trial is the effectiveness of transcatheter aortic-valve replacement (TAVR) in terms of death from any cause or disabling stroke at 5 years. Nonetheless, on critical appraisal, other important results are noted. The landmark analysis of events occurring between 2 and 5 years after the procedure (Fig. S4 in the Supplementary Appendix of the article, available at NEJM.org) shows that TAVR was associated with a higher risk of death or disabling stroke after 2 years than was surgical aortic-valve replacement, with a hazard that was 27% higher. Moreover, the intersection of the time-to-event curves (Fig. 1 of the article) and the wide differences between the hazard ratio at 0 to 2 years (0.89; 95% confidence interval [CI], 0.73 to 1.09) and that at 2 to 5 years (1.27; 95% CI, 1.06 to 1.53) suggest that the hazards were not constant over time. Therefore, the reported 5-year hazard ratio is not an accurate reflection of the findings, which require landmark analysis or time-varying modeling.[3,4] The key message of the trial is also overshadowed by the disadvantage of TAVR in terms of reoperations and rehospitalization, which underscores concerns about the durability of TAVR devices. In summary, the 5-year results from the PARTNER 2 cohort A trial are not a swan song for surgery.

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Dr. Barili reports receiving fees from Abbott Medical for serving on an independent clinical event committee for a trial of the Trifecta valve; and Dr. Freemantle, receiving grants from the European Association for Cardio-Thoracic Surgery. No other potential conflict of interest relevant to this letter was reported.

1. Makkar RR, Thourani VH, Mack MJ, et al. Five-year outcomes of transcatheter or surgical aortic-valve replacement. N Engl J Med 2020;382:799-809.
2. Van Belle E. TAVR at 5 years — rematch or swan song for surgery? N Engl J Med 2020;382:867-8.
3. Putter H, van Houwelingen HC. Understanding landmarking and its relation with time-dependent Cox regression. Stat Biosci 2017;9:489-503.
4. Barili F, Freemantle N, Pilozzi Casado A, et al. Mortality in trials on transcatheter aortic valve implantation versus surgical aortic valve replacement: a pooled meta-analysis of Kaplan-Meier-derived individual patient data. Eur J Cardiothorac Surg 2020 April 1 (Epub ahead of print).

DOI: 10.1056/NEJMc2018853

TO THE EDITOR: The report by Makkar et al. from the PARTNER 2 cohort A trial shows that TAVR is similar to surgery in terms of death and disabling stroke at 5 years. However, TAVR resulted in a smaller reduction of both left ventricular end diastolic volume and left ventricular mass index (Table 1). These differences in left ventricular regression occurred within 30 days and persisted up to 5 years after implantation; they have been replicated elsewhere.[1]

Reduced left ventricular regression has previously been associated with increased rehospital-

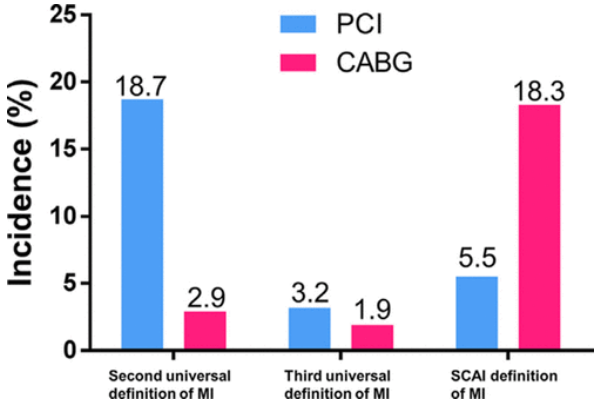
Background – the early starting

CardiovascularNews

BBC Newsnight investigation of EXCEL prompts EACTS to reject 2018 European recommendations on left main disease

9th December 2019 12775

Background : the Early Startings



SCAI definition of MI:
37% higher occurrence of MI in the CABG group
Exaggerates procedural MI after CABG

Universal definition of MI

A fairer comparison?

Hinton et al. Incidence and 1-year outcome of periprocedural myocardial infarction following cardiac surgery: are the Universal Definition and Society for Cardiovascular Angiography and Intervention criteria fit for purpose? EJCTS 2022 Jul 11;62(2):ezac019

NEWS • Conference News

Former EXCEL Investigator Alleges Trial Manipulation, Prompting Vehement Denials

Surgeon David Taggart set the EACTS meeting ablaze when he accused EXCEL researchers of stacking the deck in PCI's favor.

by Michael O'Riordan | OCTOBER 07, 2019

> ***We're not talking about two tablets for a headache. We're talking about people dying.***
>
> *David Taggart*

Dec. 2019

BBC Newsnight investigation of EXCEL prompts EACTS to reject 2018 European recommendations on left main disease

9th December 2019 12775

CENTRAL MESSAGE

Guidelines on the management of cardiovascular disease are constructed on the basis of the best clinical evidence. We believe the recently released AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease 2020 have important sections that fail on this major premise; therefore, our association will not support them.

LACES

LATIN AMERICAN ASSOCIATION OF CARDIAC AND ENDOVASCULAR SURGERY

ADULT: VALVES: EXPERT OPINION: THE LATIN AMERICAN ASSOCIATION OF CARDIAC & ENDOVASCULAR SURGERY STATEMENT

The Latin American Association of Cardiac and Endovascular Surgery statement regarding the recently released American Heart Association/American College of Cardiology Guideline for the Management of Patients With Valvular Heart Disease 2020

Victor Dayan, MD, PhD,[a] Ovidio A. Garcia-Villarreal, MD,[b] Alejandro Escobar, MD,[c] Javier Ferrari, MD,[d] Eduard Quintana, MD, PhD,[e] Mateo Marin-Cuartas, MD, PhD,[f,g] and Rui Almeida, MD, MSc, PhD[h]

Innovations,Volume 16, Issue 5, September/October 2021

Latin European Alliance of Cardiovascular Surgical Societies (LEACSS)

PORTUGUESE JOURNAL OF CARDIAC THORACIC AND VASCULAR SURGERY

VICE-PRESIDENT'S MESSAGE

Miguel Sousa Uva
Service of Cardiac Surgery, Hospital da Santa Cruz, Carnaxide
Department of Surgery and Physiology, Faculdade de Medicina da Universidade do Porto

Latin European Alliance of Cardiovascular Surgical Societies (LEACSS) – Towards independent evidence-based cardiovascular medicine and shared surgical education

LEACSS

SOCIETA' ITALIANA DI CHIRURGIA CARDIACA
SINCE 1967
ITALIAN SOCIETY FOR CARDIAC SURGERY

SFCTCV
SOCIÉTÉ FRANÇAISE DE CHIRURGIE THORACIQUE ET CARDIO-VASCULAIRE

SPCCTV
SOCIEDADE PORTUGUESA DE CIRURGIA CARDÍACA TORÁCICA E VASCULAR • ORGÃO OFICIAL DA

SECCE
Sociedad Española de Cirugía Cardiovascular y Endovascular

EUROVALVE
CROWNE PLAZA LINATE MILAN
SEPTEMBER 31 & 32, 2023

LACES

LATIN AMERICAN ASSOCIATION
OF CARDIAC AND ENDOVASCULAR
SURGERY

INTEGRITTY

LEACSS

EUROVALVE
CROWNE PLAZA LINATE
MILAN
SEPTEMBER

INTernational Evidence Grading Research Initiative Targeting
Transparency and data qualitY

June 9th, 2021: 1st INTEGRITTY meeting

Mission of INTEGRITTY

- Critical appraisal of evidence to support better and optimized patient management in the cardiovascular field
- Promote integrity and transparency in cardiovascular evidence
- Discuss the role of industry and sponsors in building of evidence
- Discuss and reanalyze scientific evidence and guidelines independently

INTEGRITTY: Areas of Development

- At the moment three major areas of development:
  - **Best treatment in coronary artery disease**

    OMT vs. PCI vs. SURGERY
  - **Best treatment in valve disease**

    OMT vs. TRANSCATHETER vs. SURGERY
  - **COIs in cardiovascular medicine and surgery**

- First of all:
  - **We are not in favor of surgery**
  - **We are in favor of the truth whatever and wherever it is**

Members of INTEGRITTY

USA

- William Boden - Professor of Medicine, Boston University School of Medicine. Lecturer in Medicine, Harvard Medical School, Boston
- Sanjay Kaul - Professor of Medicine, Cedars-Sinai Medical Center, Los Angeles
- John Mandrola - Baptist Health Louisville, Louisville, Kentucky
- Rita Redberg - Professor of Medicine, Araxe Vilensky Endowed Chair in Cardiology, UCSF Division of Cardiology – San Francisco
- Michael Firstenberg, Director of Research and Special Projects at the William Novick Global Cardiac Alliance and Assistant Professor of Surgery, Northeast Ohio Medical University
- David Faxon -Vice Chair of Medicine for Strategic Planning at Brigham and Women's Hospital Boston, Massachusetts
- Marco Zenati, Chief, Division of Cardiac Surgery, VA Boston Healthcare System, Professor of Surgery, Harvard Medical School, Chair, National Surgery Office, Cardiothoracic Surgery Scientific Advisory Board

Australia

- Tristan Yan, Head of Robotic and Minimally Invasive Cardiothoracic Surgery Programs at the Royal Prince Alfred Hospital and the Sydney Adventist Hospital; Clinical Professor of Surgery at the University of Sydney. Editor-in-Chief of the Annals of Cardiothoracic Surgery.

Canada

- James Brophy - Professor of Medicine, Dept. of Medicine, McGill Health University Center, Montreal

Brazil

- Arthur Albuquerque - School of Medicine, Universidade Federal do Rio de Janeiro, Rio de Janeiro
- Rui M. S. Almeida - Dean and Full Professor, University Center Assis Gurgacz Foundation, Cascavel-Pr, Brazil. President elect, The Latin American Association of Cardiac and Endovascular Surgery-LACES
- Walter Gomes - Head, Cardiovascular Surgery, Pirajussara Hospital, Federal University of Sao Paulo, Brasil. Past President, Brazilian Society of Cardiovascular Surgery

Mexico

- Ovidio A. García-Villarreal. Mexican College of Cardiovascular and Thoracic Surgery; Mexico City, México.

Uruguay

- Victor Dayan – Prof. Adj. Cardiac Surgery, Centro Cardiovascular Universitario, Universidad de la Republica del Uruguay. President, The Latin American Association of Cardiac and Endovascular Surgery-LACES

Italy

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- Alessandro Parolari - Full Professor of Cardiac Surgery, University of Milano. Chief, Universitary Cardiac Surgery, Policlinico San Donato. President, Italian Society for Cardiac Surgery.

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- Amedeo Anselmi. Associate Professor - Department of Thoracic and Cardiovascular Surgery, Rennes
- Jacques Tomasi. Division of Thoracic and Cardiovascular Surgery, Pontchaillou University Hospital, Rennes

Spain

- Jorge Rodriguez-Roda Stuart - Chief, Servicio de Cirugía Cardiovascular Hospital Universitario Ramón y Cajal, Madrid. Vice President, Sociedad Española de Cirugía Cardiovascular y Endovascular

Portugal

- Miguel Sousa Uva - Associate Professor at the Porto University Medical School. Vice president (President Elect) of the Portuguese Society of Cardiac Thoracic and Vascular Surgery. Past President of the EACTS

Netherlands

- Milan Milojevic - Chair, Clinical Pracitice Guidelines Task Force, the European Association of Cardio-Thoracic Surgery.

Germany

- Mateo Marin-Cuartas, Chief Resident, Leipzig
- Manuela De LA Cuesta, Resident, Leipzig
- Martin Misfeld Co-Director, University Clinic of Cardiac Surgery, Heart Center Leipzig, Leipzig, Germany and Visiting Professor, University of Sydney, Australia.

Building a team – INTEGRITTY members

USA
- William Boden
- Sanjay Kaul
- John Mandrola
- Rita Redberg
- Michael Firstenberg
- David Faxon
- Marco Zenati

Australia
- Tristan Yan

Canada
- James Brophy

Brazil
- Arthur Albuquerque
- Rui M. S. Almeida
- Walter Gomes

Mexico
- Ovidio A. García-Villarreal

Uruguay
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Italy
- Fabio Barili
- Raffaele De Caterina
- Francesco Musumeci
- Alessandro Parolari

France
- Amedeo Anselmi
- Sylvain Beutheret
- Jacques Tomasi
- Jean-Philippe Verhoye

Spain
- Jorge Rodriguez-Roda

Portugal
- Miguel Sousa Uva -

Netherlands
- Milan Milojevic

…and Board

- Alessandro Parolari *(Chair)*
- Amedeo Anselmi *(Secretary)*
- Rui Almeida
- William Boden
- Raffaele De Caterina
- Sanjay Kaul
- Mateo Marin Cuartas *(Junior member)*

Why we need to re-read current evidence

✓**SAME EVIDENCE, DIFFERENT RECOMMENDATIONS**

✓**ROLE OF SPOSNSORS/INDUSTRY IN TRIALS**

✓**ROLE OF COIs**

✓**CURRENT RCTs of TAVI VS SAVR ARE REALLY COMPARABLE?**

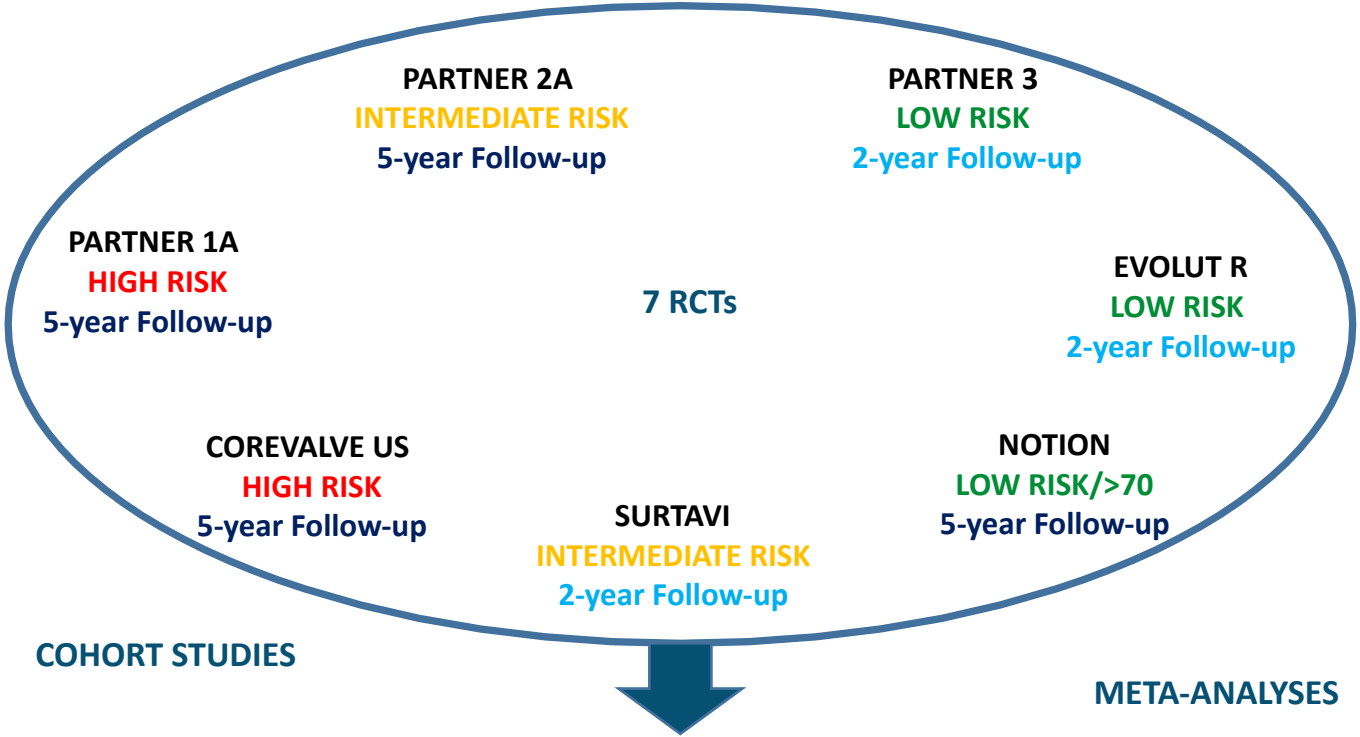
AHA and ESC/EACTS GLs

Same evidence evaluation process

SAME EVIDENCE

DIFFERENT RECOMMENDATIONS BY ESC/ACC

CURRENT EVIDENCE AVAILABLE AT THE TIMES OF GL WRITING – ALL INDUSTRY-SPONSORED TRIALS



ESC/EACTS GLs 2021

TAVI is recommended in older patients (≥75 years), or in those who are high risk (STS-PROM/EuroSCORE II[f] >8%) or unsuitable for surgery.[197–206,245]	I	A
SAVR or TAVI are recommended for remaining patients according to individual clinical, anatomical, and procedural character-istics.[202–205,207,209,210,212 f,g]	I	B
Non-transfemoral TAVI may be considered in patients who are inoperable and unsuitable for transfemoral TAVI.	IIb	C
Balloon aortic valvotomy may be considered as a bridge to SAVR or TAVI in haemodynamically unstable patients and (if feasible) in those with severe aortic stenosis who require urgent high-risk NCS (*Figure 11*).	IIb	C

AHA GLs 2020

Recommendations for Choice of SAVR Versus TAVI for Patients for Whom a Bioprosthetic AVR Is Appropriate

Referenced studies that support the recommendations are summarized in Online Data Supplement 11 to 13.

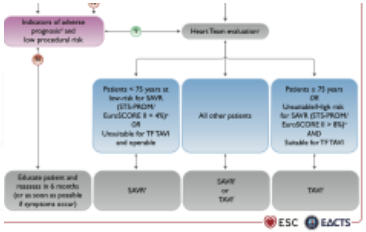
COR	LOE	Recommendations
1	A	1. For symptomatic and asymptomatic patients with severe AS and any indication for AVR who are <65 years of age or have a life expectancy >20 years, SAVR is recommended.[1–3]
1	A	2. For symptomatic patients with severe AS who are 65 to 80 years of age and have no anatomic contraindication to transfemoral TAVI, either SAVR or transfemoral TAVI is recommended after shared decision-making about the balance between expected patient longevity and valve durability.[1,4–8]
1	A	3. For symptomatic patients with severe AS who are >80 years of age or for younger patients with a life expectancy <10 years and no anatomic contraindication to transfemoral TAVI, transfemoral TAVI is recommended in preference to SAVR.[1,4–10]

SAME EVIDENCE….DIFFERENT GLs

EUROPE

C) Mode of intervention		
Aortic valve interventions must be performed in Heart Valve Centres that declare their local expertise and outcomes data, have active interventional cardiology and cardiac surgical programmes on site, and a structured collaborative Heart Team approach.	I	C
The choice between surgical and transcatheter intervention must be based upon careful evaluation of clinical, anatomical, and procedural factors by the Heart Team, weighing the risks and benefits of each approach for an individual patient. The Heart Team recommendation should be discussed with the patient who can then make an informed treatment choice.	I	C
SAVR is recommended in younger patients who are low risk for surgery (<75 years[a] and STS-PROM/EuroSCORE II <4%)[b], or in patients who are operable and unsuitable for transfemoral TAVI.[244]	I	B
TAVI is recommended in older patients (≥75 years), or in those who are high risk (STS-PROM/EuroSCORE II[b] >8%) or unsuitable for surgery.[247–266,345]	I	A
SAVR or TAVI are recommended for remaining patients according to individual clinical, anatomical, and procedural characteristics.[203–205,207,209,210,213 §§]	I	B
Non-transfemoral TAVI may be considered in patients who are inoperable and unsuitable for transfemoral TAVI.	IIb	C
Balloon aortic valvotomy may be considered as a bridge to SAVR or TAVI in haemodynamically unstable patients and (if feasible) in those with severe aortic stenosis who require urgent high-risk NCS (Figure 11).	IIb	C

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



1. AGE **(OVER 75)**
2. **RISK PROFILE IS IMPORTANT!**
3. CLASS 1A FOR TAVI

U.S.A.

COR	LOE	Recommendations
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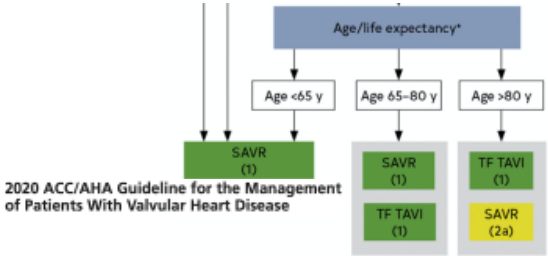


2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease

1. AGE **(OVER 65 or 10-years E.o.L)**
2. **RISK PROFILE???**
3. CLASS 1A FOR TAVI

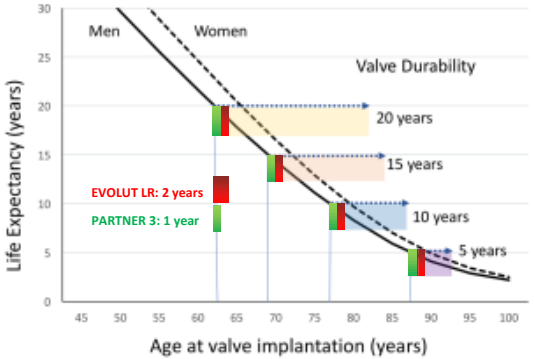
GLs COMMON POINT: AGE TO DECIDE INDICATION TO TAVI OR SAVR

Expansion of TAVR into Low-Risk Patients and Who to Consider for SAVR

Cardiol Ther (2020) 9:377–394

	PARTNER 3			Evolut Low Risk		
	TAVR	SAVR		TAVR	SAVR	
Age (years)	73.3	73.6		74	73.8	
% Female	32.5%	28.9%		36.2%	33.5%	
STS-PROM %	1.9	1.9		1.9	1.9	
Concomitant PCI/CABG	6.5%	12.8%		6.9%	13.6%	
Primary outcome	Death, stroke, rehospitalization at 1 year[1]			Death or disabling stroke at 2 years[2]		
	8.5%	15.1%	p<0.05	5.3%	6.7%	p<0.05
Death 1 year	1%	2.5%	NS	2.4%	2.9%	NS
Stroke 1 year	1.2%	3.1%	NS	0.8%	2.1%	p<0.05
Rehospitalization	7.3%	11%	p<0.05	3.6%	6.7%	p<0.05
New pacemaker	7.3%	5.4%	NS	19.4%	6.7%	p<0.05
Mean Gradient (1 year)	13.7mmHg	11.3mmHg		8.6mmHg	11.2mmHg	
≥Moderate PVL at 1 year	0.6%	0.5%		3.6%	0.6%	
New LBBB	23.7%	8%		NR	NR	

Bagur R, *et al. Heart* November 2017 Vol 103 No 22



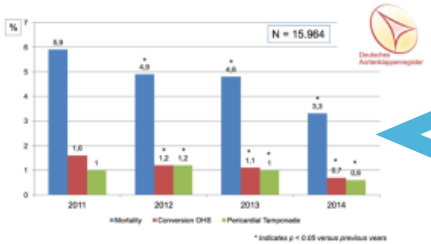
TRIALS IN LOW RISK PTS: ENDPOINT AT 1-2 YRS

PROSTHESIS-RELATED EVENTS NOT ASSESSABLE

DESIGN BIAS IN CASE OF INCREASED FOLLOW-UP TIMES

EVIDENCE THAT IS NEEDED vs. EVIDENCE THAT IS AVAILABLE

AVAILABLE



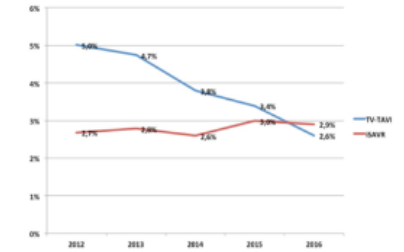


Fig. 2 In-hospital mortality of transvascular TAVI vs. isolated surgical aortic valve replacement. *TV-TAVI* transvascular TAVI, *iSAVR*

SAFETY

EFFICACY

SHORT-TERM

EFFICACY

COMPLICATIONS

LONG-TERM

New perspectives: transcatheter aortic valve implantation in the year 2020

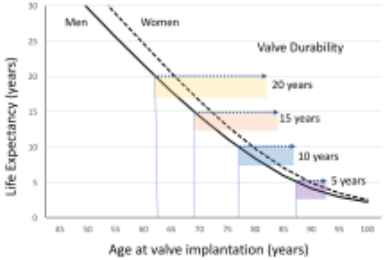
In 2020 transcatheter aortic valve implantation (TAVI) will be the default treatment in patients with aortic stenosis

European Heart Journal (2015) **36**, 1200–1206

Why is this the case? Because more than half a million patients will have been treated by this technique worldwide, allowing its efficacy, safety, and durability to be assessed.

WHEN AVAILABLE?

10-YRS STUDIES?



1A RECOMMENDATION: >65 o >75 YRS?

CLASS 1 (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

2020 ACC/AHA

65 YRS? MEAN AGE OF RTCs >73 YRS

E.o.L. 10 YRS? MAX 5 YRS F-UP

2020 ACC/AHA & 2021 ESC/EACTS

5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial

5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients

Five-Year Clinical and Echocardiographic Outcomes from the Nordic Aortic Valve Intervention (NOTION) Randomized Clinical Trial in Lower Surgical Risk Patients

Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients

Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients

Two-year Clinical and Echocardiographic Outcomes from the PARTNER 3 Low-risk Randomized Trial

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

RCTs BUILT ON RISK, NOT ON AGE

CLASS 1A NEEDS TO BE RECONSIDERED

Why we need to re-read current evidence

✓SAME EVIDENCE, DIFFERENT RECOMMENDATIONS

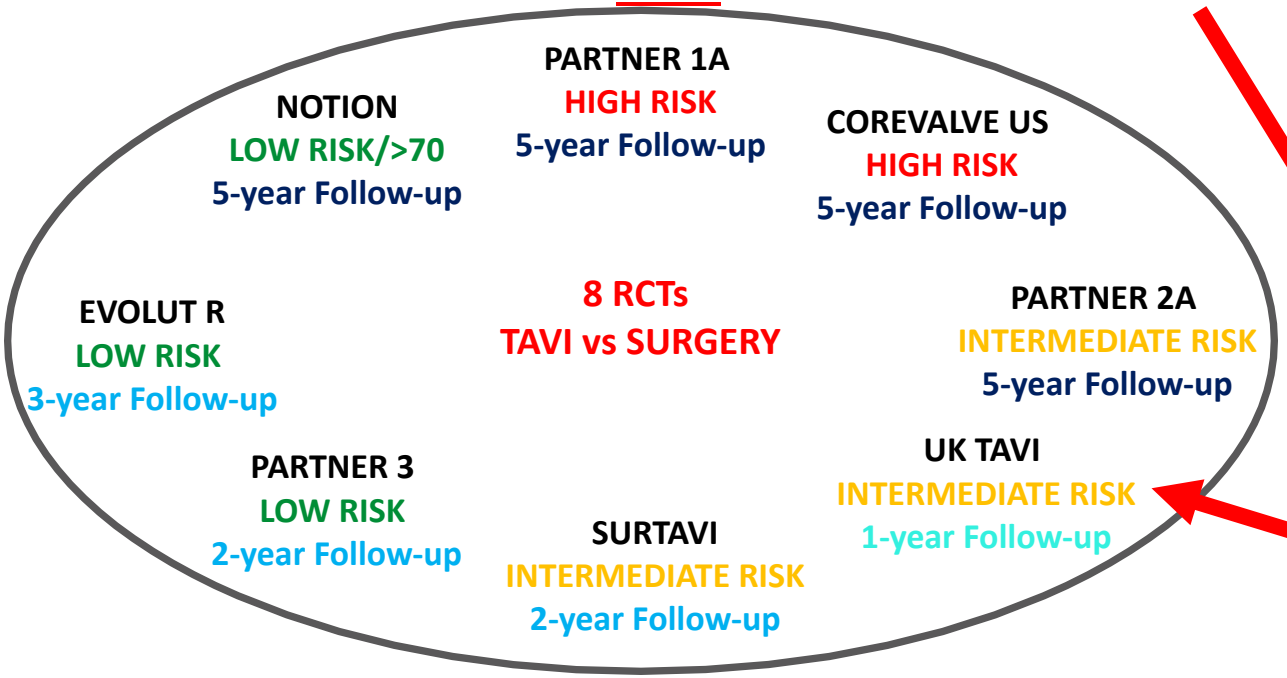
✓ROLE OF SPOSNSORS/INDUSTRY IN TRIALS

✓ROLE OF COIs

✓CURRENT RCTs of TAVI VS SAVR ARE REALLY COMPARABLE?

CURRENT EVIDENCE AVAILABLE

ALL INDUSTRY-SPONSORED RANDOMIZED TRIALS BUT ONE



COHORT STUDIES

META-ANALYSES

AHA 2020

ESC/EACTS 2021

Cochrane Library

Cochrane Database of Systematic Reviews

Industry sponsorship and research outcome (Review)

Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L

Sponsorship of drug and device studies by the manufacturing company leads to more favorable results and conclusions than sponsorship by other sources.

Comparison 1. Results: Industry sponsored versus non-industry sponsored studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable efficacy results	14	1588	Risk Ratio (IV, Fixed, 95% CI)	1.24 [1.14, 1.35]
2 Number of studies with favorable harms results	3	561	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.54, 2.27]

Why we need to re-read current evidence

✓SAME EVIDENCE, DIFFERENT RECOMMENDATIONS

✓ROLE OF SPOSNSORS/INDUSTRY IN TRIALS

✓ROLE OF COIs

✓CURRENT RCTs of TAVI VS SAVR ARE REALLY COMPARABLE?

Analysis of conflicts of interest among authors and researchers of European clinical guidelines in cardiovascular medicine

Clinical Medicine 2021 Vol 21, No 2: e166–70

Authors: Jonathan Hinton,[A] Thomas Reeves[B] and Benoy N Shah[C]

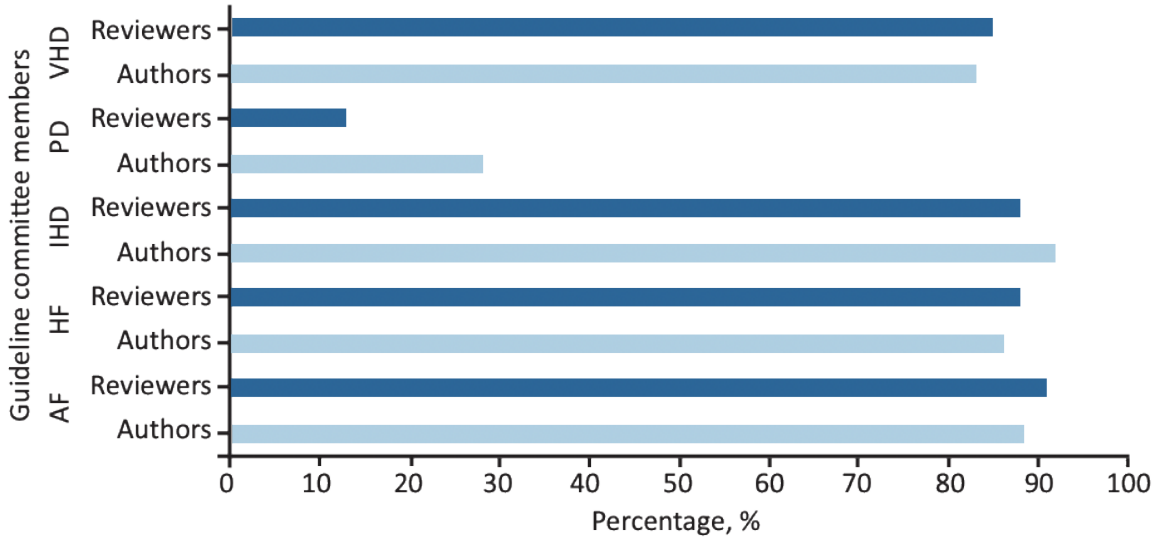


Fig 1. Frequency of any financial conflict of interest among guideline committee members. AF = atrial fibrillation; HF = heart failure; IHD = myocardial revascularisation; PD = pericardial diseases; VHD = valvular heart disease.

The New York Times

Doctor Is Pressed Again on Ties to Device Makers

Two leading senators have charged that a well-known heart doctor affiliated with Columbia University may have failed to tell the university about millions of dollars in payments and other income he received from medical device makers.

In a letter sent Friday, the lawmakers, Herb Kohl, Democrat of Wisconsin, and Charles E. Grassley, Republican of Iowa, said that their review of financial data subpoenaed last year from device makers and physicians indicated that the cardiologist, Dr. Martin B. Leon, might have failed to tell Columbia about significant amounts in consulting fees, speaking fees and other payments.

"Dr. Leon appears to have failed to report millions of dollars that he has received in outside income," their letter stated.

Dr. Leon, who was in San Francisco on Monday attending the opening sessions of a conference sponsored by a Columbia University-affiliated group he helped found, did not respond to two e-mail messages and an interview request made through a university spokeswoman. In a statement, Columbia University Medical Center said that it was reviewing the information in the lawmakers' letter and Dr. Leon's disclosure statements to determine "if all appropriate disclosures" were made.

Influence and management of conflicts of interest in randomised clinical trials: qualitative interview study

Lasse Østengaard,[1,2,3,4] Andreas Lundh,[1,2,3,5] Tine Tjørnhøj-Thomsen,[6] Suhayb Abdi,[1] Mustafe H A Gelle,[1] Lesley A Stewart,[7] Isabelle Boutron,[8] Asbjørn Hróbjartsson[1,2,3]

- Considerable variability was found between trial researchers of what they considered to be conflicts of interest and when they should be reported.

- Financial conflicts of interest related to non-commercial funders (eg, governmental health agencies with a political agenda) were considered equally or more important than commercial financial conflicts of interest (eg, drug and device companies), but more challenging to report and manage

the bmj | *BMJ* 2020;371:m3764 | doi: 10.1136/bmj.m3764

Why we need to re-read current evidence

✓SAME EVIDENCE, DIFFERENT RECOMMENDATIONS

✓ROLE OF SPOSNSORS/INDUSTRY IN TRIALS

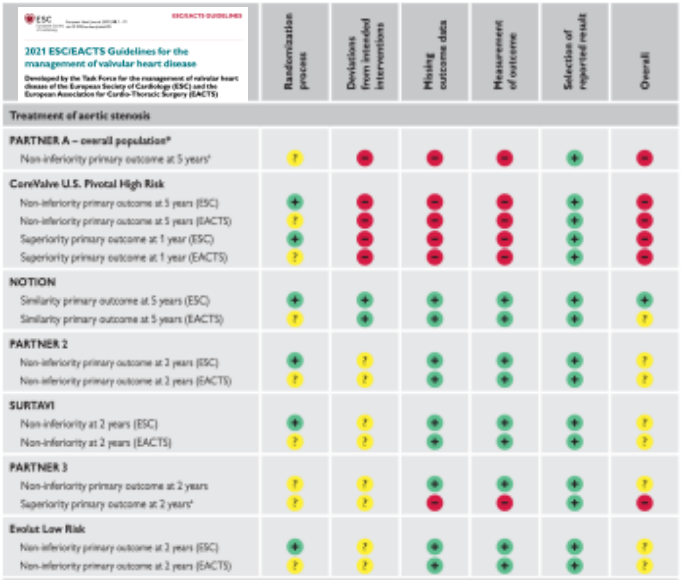
✓ROLE OF COIs

✓CURRENT RCTs of TAVI VS SAVR ARE REALLY COMPARABLE?

CAN RCTs BE BIASED?

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

Supplementary data



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

	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of outcome	Selection of reported result	Overall
Treatment of aortic stenosis						
PARTNER A – overall population*						
Non-inferiority primary outcome at 5 years†	?	−	−	−	+	−
CoreValve U.S. Pivotal High Risk						
Non-inferiority primary outcome at 5 years (ESC)	+	−	−	−	+	−
Non-inferiority primary outcome at 5 years (EACTS)	?	−	−	−	+	−
Superiority primary outcome at 1 year (ESC)	+	−	−	−	+	−
Superiority primary outcome at 1 year (EACTS)	?	−	−	−	+	−
NOTION						
Similarity primary outcome at 5 years (ESC)	+	+	+	+	+	+
Similarity primary outcome at 5 years (EACTS)	?	+	+	+	+	?
PARTNER 2						
Non-inferiority primary outcome at 2 years (ESC)	+	?	+	+	+	?
Non-inferiority primary outcome at 2 years (EACTS)	?	?	+	+	+	?
SURTAVI						
Non-inferiority at 2 years (ESC)	+	?	+	+	+	?
Non-inferiority at 2 years (EACTS)	?	?	+	+	+	?
PARTNER 3						
Non-inferiority primary outcome at 2 years	?	?	+	+	+	?
Superiority primary outcome at 2 years†	?	?	−	−	+	−
Evolut Low Risk						
Non-inferiority primary outcome at 2 years (ESC)	+	?	+	+	+	?
Non-inferiority primary outcome at 2 years (EACTS)	?	?	+	+	+	?

RoB 2: a revised tool for assessing risk of bias in randomised trials

the bmj | BMJ 2019;366:l4898 | doi: 10.1136/bmj.l4898

SUMMARY POINTS

- Assessment of risk of bias is regarded as an essential component of a systematic review on the effects of an intervention; the most commonly used tool for assessing risk of bias in randomised trials is the Cochrane risk-of-bias tool, which was introduced in 2008
- Potential improvements to the Cochrane risk-of-bias tool were identified on the basis of reviews of the literature, user experience and feedback, approaches used in other risk-of-bias tools, and recent developments in estimation of intervention effects from randomised trials
- We developed and piloted a revised tool for assessing risk of bias in randomised trials (RoB 2)
- Bias is assessed in five distinct domains. Within each domain, users of RoB 2 answer one or more signalling questions. These answers lead to judgments of "low risk of bias," "some concerns," or "high risk of bias"
- The judgments within each domain lead to an overall risk-of-bias judgment for the result being assessed, which should enable users of RoB 2 to stratify meta-analyses according to risk of bias

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

Random allocation **does NOT protect RCTs against OTHER types of BIAS**.

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

Supplementary data

	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of outcome	Selection of reported result	Overall
Treatment of aortic stenosis						
PARTNER A – overall population*						
Non-inferiority primary outcome at 5 years[a]	?	−	−	−	+	−
CoreValve U.S. Pivotal High Risk						
Non-inferiority primary outcome at 5 years (ESC)	+	−	−	−	+	−
Non-inferiority primary outcome at 5 years (EACTS)	?	−	−	−	+	−
Superiority primary outcome at 1 year (ESC)	+	−	−	−	+	−
Superiority primary outcome at 1 year (EACTS)	?	−	−	−	+	−
NOTION						
Similarity primary outcome at 5 years (ESC)	+	+	+	+	+	+
Similarity primary outcome at 5 years (EACTS)	?	+	+	+	+	?
PARTNER 2						
Non-inferiority primary outcome at 2 years (ESC)	+	?	+	+	+	?
Non-inferiority primary outcome at 2 years (EACTS)	?	?	+	+	+	?
SURTAVI						
Non-inferiority at 2 years (ESC)	+	?	+	+	+	?
Non-inferiority at 2 years (EACTS)	?	?	+	+	+	?
PARTNER 3						
Non-inferiority primary outcome at 2 years	?	?	+	+	+	?
Superiority primary outcome at 2 years[a]	?	?	−	−	+	−
Evolut Low Risk						
Non-inferiority primary outcome at 2 years (ESC)	+	?	+	+	+	?
Non-inferiority primary outcome at 2 years (EACTS)	?	?	+	+	+	?

INTENTION TO TREAT vs PER-PROTOCOL

Cochrane Training

An ITT analysis maintains the benefit of randomization: that, on average, the intervention groups do not differ at baseline with respect to measured or unmeasured prognostic factors.

However, two approaches to estimation of per-protocol effects that are commonly used in randomized trials may be seriously biased. These are:

- 'as-treated' analyses in which participants are analysed according to the intervention they actually received, even if their randomized allocation was to a different treatment group; and
- naïve 'per-protocol' analyses restricted to individuals who adhered to their assigned interventions.

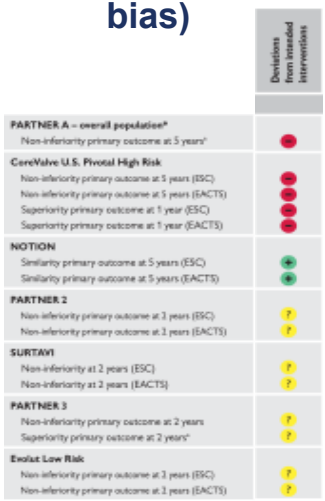
. When authors wish to assess the risk of bias in the estimated effect of adhering to intervention, use of results based on modern statistical methods may be at lower risk of bias than results based on 'as-treated' or naïve per-protocol analyses.

ITT DATA: PARTNER 1A
PARTNER 2A
SURTAVI

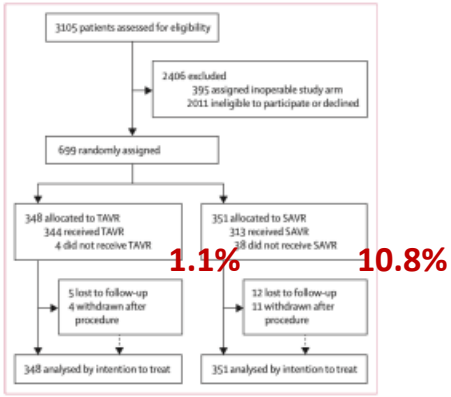
AS TREATED: COREVALVE US PIVOTAL
NOTION
EVOLUT LOW RISK
PARTNER 3

INTENTION TO TREAT vs PER-PROTOCOL

Bias due to deviations from intended interventions (Performance bias)



5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial



U.S. CoreValve High Risk Study

N Engl J Med 2014;370:1790-8.

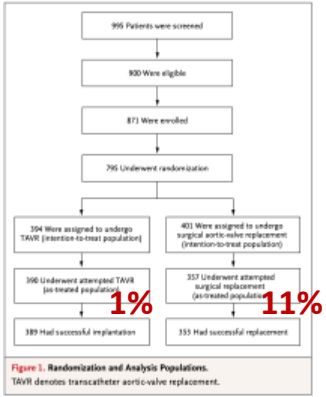


Figure 1. Randomization and Analysis Populations.
TAVR denotes transcatheter aortic-valve replacement.

Table 1: Baseline characteristics of the 7 trials

Cite this article as: Barili F, Freemantle N, Musumeci F, Martin B, Anselmi A, Rinaldi M et al. Five-year outcomes in trials comparing transcatheter aortic valve implantation versus surgical aortic valve replacement: a pooled meta-analysis of reconstructed time-to-event data. Eur J Cardiothorac Surg 2021; doi:10.1093/ejcts/ezab516

Risk profile	High				Low		Intermediate				Low		Low	
Trial name	PARTNER 1A, 5 years		COREVALVE US, 5 years		NOTION		PARTNER 2A, 5 years		SURTAVI, 2 years		PARTNER 3, 2 years		EVOLUT LOW RISK, 2 years	
Treatment group	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
ITT patients	348	351	395	402	145	135	1011	1021	864	796	503	497	734	734
As-treated patients, *n*	344	313	391	359	142	134	994	944	863	764	496	454	725	678
	1.1%	10.8%	1%	11%	2%	1%	1.7%	7.5%	0.01%	4%	1.4%	8.7%	1.2%	7.6%

ASSOCIATED PROCEDURES

Bias due to deviations from intended interventions (Performance bias)

ASSOCIATED PROCEDURES | TREATMENT GROUPS

PARTNER 2 Trial		SURTAVI Trial		EVOLUT R Trial		PARTNER 3 Trial	
Surgery	9.1% concomitant 14.5% CABG	Surgery	27.8%	Surgery	26.2%	Surgery	26.4%
TAVR	3.9% PCI	TAVR	14.5%	TAVR	6.9%	TAVR	7.9%
P-value < 0.0001		**P-value < 0.0001**		**P-value < 0.0001**		**P-value < 0.0001**	

ASSOCIATED PCI/CABG | TREATMENT GROUPS

PARTNER 2 Trial		SURTAVI Trial		EVOLUT R Trial		PARTNER 3 Trial	
Surgery	14.5%	Surgery	22.1%	Surgery	13.6%	Surgery	12.8%
TAVR	3.9%	TAVR	14.5%	TAVR	6.9%	TAVR	6.5%
P-value < 0.0001		**P-value < 0.0001**		**P-value < 0.0001**		**P-value 0.0012**	

BIAS FOR MISSING OUTCOME DATA

Cochrane Training

8.5 Bias due to missing outcome data #section-8-5

Missing measurements of the outcome may lead to bias in the intervention effect estimate. Possible reasons for missing outcome data include (National Research Council 2010):

1. participants withdraw from the study or cannot be located ('loss to follow-up' or 'dropout');
2. participants do not attend a study visit at which outcomes should have been measured;
3. participants attend a study visit but do not provide relevant data;
4. data or records are lost or are unavailable for other reasons; and
5. participants can no longer experience the outcome, for example because they have died.

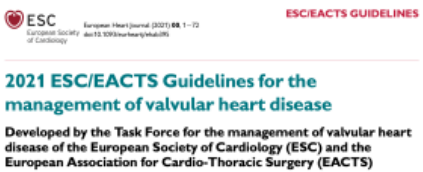
No sensible threshold for 'small enough' in relation to the proportion of missing outcome data

What is an acceptable rate of loss to follow-up? Only one answer, 0%, ensures the benefits of randomisation. Obviously, this is unrealistic at times. Some researchers suggest a simple five-and-20 rule of thumb, with fewer than 5% loss probably leading to little bias, greater than 20% loss potentially posing serious threats to validity, and in-between levels leading to intermediate levels of problems.[22] Indeed, in their experience with sensitivity analyses, use of the worst case scenario, they opine, and we agree, that a trial would be unlikely to successfully withstand challenges to its validity with losses of more than 20%.[6] Indeed, some journals refuse to publish trials with losses greater than 20%.[6]

SMALL: 5% missing outcome data
LARGE: >20% missing outcome data

BIAS FOR MISSING OUTCOME DATA

Attrition bias happens when participants drop out from a study; The drop-outs have unique study-related characteristics, resulting in a difference between initial and ending samples.
Selective attrition bias happens when the differences are between control and treatment

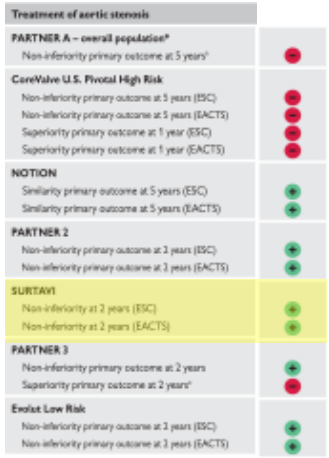


	TAVI		SAVR
PARTNER 1A 5 YEARS:	2.5%	vs	6.6%
COREVALVE US 5 YEARS:	7.3%	vs	12.0%
PARTNER 2A 5 YEARS:	9.1%	vs	18.6%
SURTAVI 5YEARS:	9%	vs	24.4%
PARTNER 3:	1.4%	vs	8.6%
EVOLUT LOW-RISK:	1.6%	vs	7.2%

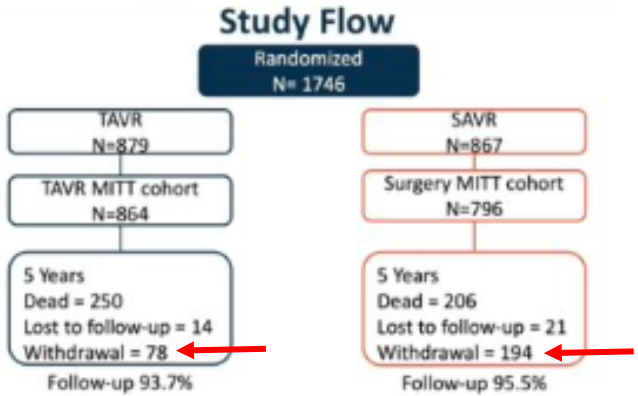
BIAS FOR MISSING OUTCOME DATA

Attrition bias happens when participants drop out from a study; The drop-outs have unique study-related characteristics, resulting in a difference between initial and ending samples. ***Selective attrition bias*** happens when the differences are between control and treatment

If the study-related characteristics are completely random with no systematic pattern, then attrition bias does not happen.



SURTAVI 5 YEARS, Presented at TCT 2021



Withdrawal
78/864=9.0%

Withdrawal
194/796=24.4%

BIAS IN MEASUREMENT OF THE OUTCOME

PARTNER A – overall population*	
Non-inferiority primary outcome at 5 years[a]	−
CoreValve U.S. Pivotal High Risk	
Non-inferiority primary outcome at 5 years (ESC)	−
Non-inferiority primary outcome at 5 years (EACTS)	−
Superiority primary outcome at 1 year (ESC)	−
Superiority primary outcome at 1 year (EACTS)	−
NOTION	
Similarity primary outcome at 5 years (ESC)	+
Similarity primary outcome at 5 years (EACTS)	+
PARTNER 2	
Non-inferiority primary outcome at 2 years (ESC)	+
Non-inferiority primary outcome at 2 years (EACTS)	+
SURTAVI	
Non-inferiority at 2 years (ESC)	+
Non-inferiority at 2 years (EACTS)	+
PARTNER 3	
Non-inferiority primary outcome at 2 years	+
Superiority primary outcome at 2 years[a]	−
Evolut Low Risk	
Non-inferiority primary outcome at 2 years (ESC)	+
Non-inferiority primary outcome at 2 years (EACTS)	+

Errors in measurement of outcomes can bias intervention effect estimates.

Depends on the following five considerations:

1. Whether **the method of measuring the outcome** is appropriate.
2. Whether measurement or **ascertainment of the outcome differs**, or could differ, **between intervention groups.**
3. Who is the **outcome assessor**.
4. Whether the **outcome assessor is blinded** to intervention assignment.
5. Whether the **assessment of outcome** is likely to be **influenced by knowledge of intervention received**.

BMJ

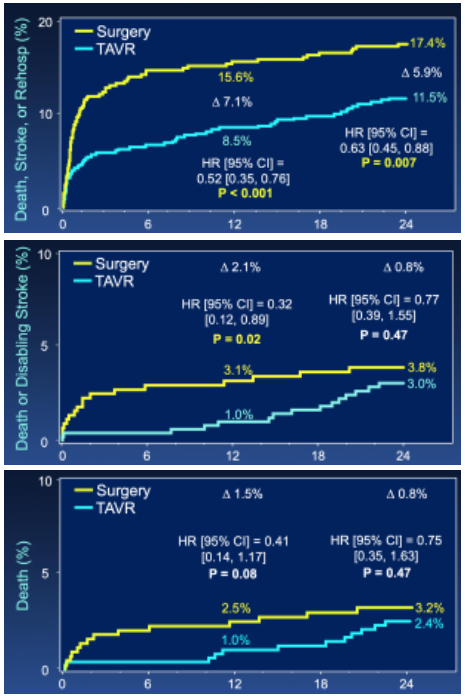
RESEARCH

Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials

Ignacio Ferreira-González, research fellow,[1] Jason W Busse, research associate,[3] Diane Heels-Ansdell, statistician,[3] Victor M Montori, associate professor,[5] Elie A Akl, assistant professor,[6] Dianne M Bryant, clinical epidemiologist,[8] Pablo Alonso-Coello, general practitioner,[9] Jordi Alonso, general practitioner,[10] Andrew Worster, associate professor,[3] Suneel Upadhye, associate member,[3] Roman Jaeschke, clinical professor,[4] Holger J Schünemann, associate professor,[7] Gaietà Permanyer-Miralda, senior consultant,[2] Valeria Pacheco-Huergo, research fellow,[1] Antònia Domingo-Salvany, senior scientist,[10] Ping Wu, senior scientist,[11] Edward J Mills, assistant professor,[12] Gordon H Guyatt, professor[3]

Conclusion The use of composite end points in cardiovascular trials is frequently complicated by large gradients in importance to patients and in magnitude of the effect of treatment across component end points. Higher event rates and larger treatment effects associated with less important components may result in misleading impressions of the impact of treatment.

CHOICE OF COMPOSITE ENDPOINTS



PARTNER 3 2-yrs FU-UP

Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials
Cite this article as: BMJ, doi:10.1136/bmj.39136.682083.AE

WHAT IS ALREADY KNOWN ON THIS TOPIC

Clinical trialists use composite end points, outcomes that capture the number of patients who have one or more of several events, to increase event rates and statistical power

When the gradient of importance to patients is large, and the more important events are uncommon and show negligible treatment effects, use of composite end points can be misleading

WHAT THIS STUDY ADDS

Almost half of a sample of recent prominently published cardiovascular trials used composite end points, which were often inadequately reported and showed large gradients in importance to patients

End points of least importance to patients typically contributed most events

Composite end points, as currently used in cardiovascular trials, may often be misleading

Less important outcomes provide larger contributions to the composite end point event rate and show larger treatment effects. In particular, mortality outcomes, present in almost all cardiovascular composite end points, provide the lowest event rate and show the smallest treatment effects.

Thus, an important and plausible risk of misleading conclusions associated with the use of composite end points is to attribute reductions in mortality to interventions that do not, in fact, reduce death rates.

BIAS IN DESIGN: LONG-TERM OUTCOMES

Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research

Table 1 Valve Academic Research Consortium proposed clinical endpoints

Mortality
Neurologic events
Hospitalization (or re-hospitalization)
Bleeding and transfusions
Vascular and access-related complications
Cardiac structural complications
Other procedural or valve-related complications
New conduction disturbances and arrhythmias
Acute kidney injury
Myocardial infarction
Bioprosthetic valve dysfunction
Leaflet thickening and reduced motion
Clinically significant valve thrombosis
Patient-reported outcomes and health status
Composite endpoints

SAFETY

EFFICACY

LONG-TERM SAFETY

LONG-TERM EFFICACY

ETHICS/SOCIAL ISSUES

ECONOMICAL ISSUES

Systematic review of the methodological instruments used in Health Technology Assessment

agenas

DURABILITY

EXPECTANCY of LIFE

BIAS IN DESIGN: LONG-TERM OUTCOMES

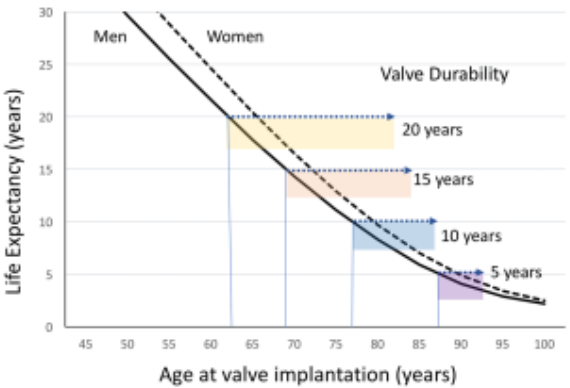
2017 ESC/EACTS Guidelines for the management of valvular heart disease

LOW RISK (STS < 4% - EuroSCORE II <4% - Log EuroSCORE <10%)
AGE 65-75 YRS

YOUNG
No comorbidity

CRITICAL ROLE
LIFE EXPECTANCY

Bagur R, *et al*. *Heart* November 2017 Vol 103 No 22



WE NEED LONG TERM FOLLOW-UP FOR PATIENTS WITH LONG LIFE EXPECTANCY (AT LEAST 10 YRS)

LONG TERM EFFICACY/SAFETY
- DURABILITY
- VALVE-RELATED EVENTS

LONG TERM FOLLOW-UP

BIAS IN DESIGN: LONG-TERM OUTCOMES

Expansion of TAVR into Low-Risk Patients and Who to Consider for SAVR

Cardiol Ther (2020) 9:377–394

	PARTNER 3			Evolut Low Risk		
	TAVR	SAVR		TAVR	SAVR	
Age (years)	73.3	73.6		74	73.8	
% Female	32.5%	28.9%		36.2%	33.5%	
STS-PROM %	1.9	1.9		1.9	1.9	
Concomitant PCI/CABG	6.5%	12.8%		6.9%	13.6%	
Primary outcome	Death, stroke, rehospitalization at 1 year[1]			Death or disabling stroke at 2 years[2]		
	8.5%	15.1%	p<0.05	5.3%	6.7%	p<0.05
Death 1 year	1%	2.5%	NS	2.4%	2.9%	NS
Stroke 1 year	1.2%	3.1%	NS	0.8%	2.1%	p<0.05
Rehospitalization	7.3%	11%	p<0.05	3.6%	6.7%	p<0.05
New pacemaker	7.3%	5.4%	NS	19.4%	6.7%	p<0.05
Mean Gradient (1 year)	13.7mmHg	11.3mmHg		8.6mmHg	11.2mmHg	
≥Moderate PVL at 1 year	0.6%	0.5%		3.6%	0.6%	
New LBBB	23.7%	8%		NR	NR	

Bagur R, *et al. Heart* November 2017 Vol 103 No 22

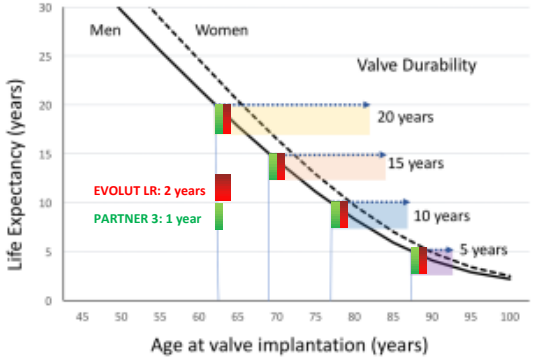


TABLE 1 | Results of major prospective randomized trials on TAVI vs. SAVR in high and intermediate to low risk patients.

	PARTNER 1A (6)	CoreValve HR (7)	PARTNER 2A (10)	NOTION (9)	SURTAVI (8)
Time of recruitment	May 2007–August 2009	February 2011–December 2012	December 2011 –November 2013	December 2009–April 2013	June 2012 –June 2016
THV	SAPIEN	CoreValve	SAPIEN XT	CoreValve	CoreValve
Primary endpoint	All-cause death at 1 year	All-cause death at 1 year	All-cause death or disabling stroke at 2 years	All-cause death, disabling stroke or myocardial infarction at 1 year	All-cause death or disabling stroke at 2 years

Front. Cardiovasc. Med. 5:92. doi: 10.3389/fcvm.2018.00092

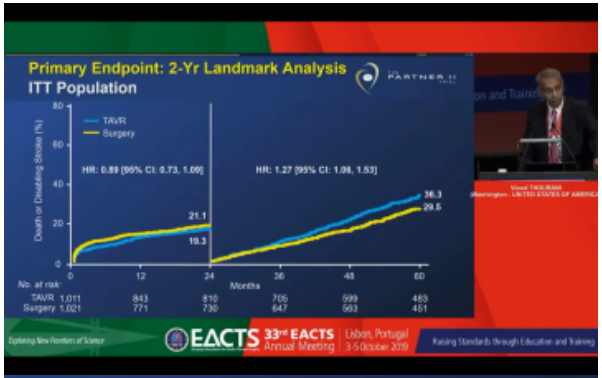
STUDY DESIGN CANNOT PERMIT TO EVALUATE LONG-TERM OUTCOMES

CHANGING ENDPOINTS AND STUDY POWER

Two-year Clinical and Echocardiographic Outcomes from the PARTNER 3 Low-risk Randomized Trial

Michael J. Mack, MD & Martin B. Leon, MD
on behalf of the PARTNER 3 Trial Investigators

- Less follow-up data available in the surgical group due to greater patient withdrawal
- Reduced primary endpoint events (37% reduction in death, stroke or CV rehospitalization); BUT…
  - More death and stroke events in TAVR patients from 1 to 2 years; no significant differences @ 2 years
  - Reduced CV rehospitalizations favoring TAVR
- Results reflect only 2-year outcomes; long-term assessment of structural valve deterioration is required
  - 10-year clinical and echocardiographic FU planned in all patients



- The current findings at 5 years mandate re-examination at later timepoints; follow-up has been extended in PARTNER 2A to 10 years

Changing follow-up time should lead to design again the study

JAMA Network Open

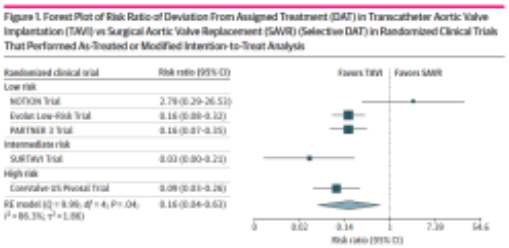
Original Investigation | Statistics and Research Methods

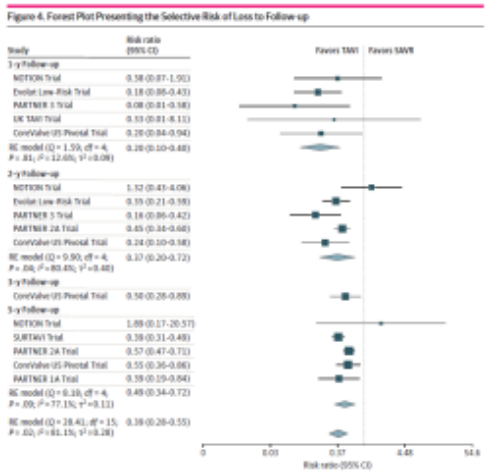
Risk of Bias in Randomized Clinical Trials Comparing Transcatheter and Surgical Aortic Valve Replacement

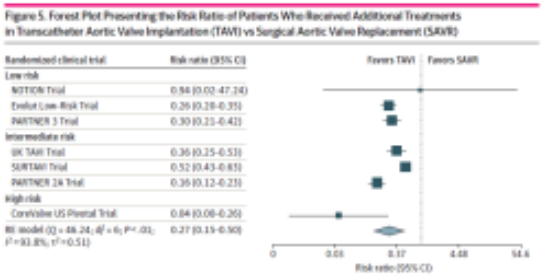
A Systematic Review and Meta-analysis

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 (INTEGRITY)

JAMA Network Open. 2023;6(1):e2249321. doi:10.1001/jamanetworkopen.2022.49321







Across 8 RCTs comparing TAVR vs. SAVR (8,849 pts):

- Imbalances in loss to FU favoring TAVR (p<0.001)
- Imbalances in deviation from assigned treatment favoring TAVR (p<0.001)
- Imbalances in associated procedures favoring TAVR (p<0.001)
- Overall, concerns over internal validity

Risk of Bias in Randomized Clinical Trials Comparing Transcatheter and Surgical Aortic Valve Replacement

Overview of attention for article published in JAMA Network Open, January 2023

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Title	Risk of Bias in Randomized Clinical Trials Comparing Transcatheter and Surgical Aortic Valve Replacement
Published in	JAMA Network Open, January 2023
DOI	10.1001/jamanetworkopen.2022.49321
Pubmed ID	36595294
Authors	Fabio Barili, James M. Brophy, Daniele Ronco, Patrick O. Myers, Miguel Sousa Uva, Rui M. S. Almeida... [show]
Abstract	Recent European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS)... [show]

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Letters

TO THE EDITOR

Concerns Regarding the Report of 3-Year Outcomes of the Evolut Low Risk Trial

The 3-year outcomes of the Evolut Low Risk trial show durable benefit of the self-expandable transcatheter aortic valve replacement (TAVR) with respect to all-cause mortality or disabling stroke.[1] However, this data should be interpreted with caution. The updated results confirm the high risk of bias previously underscored for 1-year and 2-year follow-up,[2] because there is no correction of the selective loss to follow-up (26 of 730 = 3.6% for TAVR; 60 of 684 = 8.8% for surgical aortic valve intervention; RR: 0.41), which might both undermine the advantages of randomization, and thereby challenge the comparability of the treatment groups. Most of the loss to follow-up was caused by voluntary patient withdrawal from the study (23 of 730 = 3.2% for TAVR vs 51 of 684 = 7.5% for surgical aortic valve intervention).

There are inconsistencies in assessing the as-treated population among different papers. The 3-year follow-up of the trial reported outcomes from 1,414 patients with attempted implantation (730 TAVR, 684 surgery), which contrasts with the as-treated population of 1-year outcomes (1,403 patients: 725 TAVR, 680 surgery), although the total ITT sample did not change.[3] The as-treated population should be identical among the reports and deviation from assigned treatment should be justified, as well as the inclusion of further patients.

The authors also applied landmark analysis selectively at 30 days to permanent pacemaker implantation. The same methodology might be employed to evaluate the early and midterm impact of procedures on primary outcome. The visual analysis of Figure 1 of Forrest et al[1] suggests that HR changes over time and that the overall 3-year TAVR benefit is related to intergroup differences occurring during the first 30 days. Long-term follow-up is critical to clarify long-term efficacy and will provide much-needed evidence for a realistic trend over time that is not based on prediction alone, to allow rational decision-making in patients whose life expectancy exceeds 3 years.

*Fabio Barili, MD, PhD, MStat
Amedeo Anselmi, MD, PhD
William E. Boden, MD
Miguel Sousa Uva, MD
Alessandro Parolari, MD, PhD
on behalf of the International Evidence Grading Research Initiative Targeting Transparency and Quality (INTEGRITTY)

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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1. Forrest JK, Deeb GM, Yakubov SJ, et al, for the Low Risk Trial Investigators. 3-year outcomes after transcatheter or surgical aortic valve replacement in low-risk patients with aortic stenosis. *J Am Coll Cardiol*. 2023;81(17):1663-1674.

2. Barili F, Brophy JM, Ronco D, et al, for the International Evidence Grading Research Initiative Targeting Transparency and Quality (INTEGRITTY). Risk of bias in randomized clinical trials comparing transcatheter and surgical aortic valve replacement: a systematic review and meta-analysis. *JAMA Netw Open*. 2023;6(1):e2249321.

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3-Year Outcomes After Transcatheter or Surgical Aortic Valve Replacement in Low-Risk Patients With Aortic Stenosis

John K. Forrest, MD,[a] G. Michael Deeb, MD,[b] Steven J. Yakubov, MD,[c] Hemal Gada, MD,[d] Mubashir A. Mumtaz, MD,[d] Basel Ramlawi, MD,[e] Tanvir Bajwa, MD,[f] Paul S. Teirstein, MD,[g] Michael DeFrain, MD,[h] Murali Muppala, MD,[h] Bruce J. Rutkin, MD,[i] Atul Chawla, MD,[j] Bart Jenson, MD,[j] Stanley J. Chetcuti, MD,[b] Robert C. Stoler, MD,[k] Marie-France Poulin, MD,[l] Kamal Khabbaz, MD,[l] Melissa Levack, MD,[m] Kashish Goel, MD,[m] Didier Tchétché, MD,[n] Ka Yan Lam, MD,[o] Pim A.L. Tonino, MD,[o] Saki Ito, MD,[p] Jae K. Oh, MD,[p] Jian Huang, MD, MSc,[q] Jeffrey J. Popma, MD,[q] Neal Kleiman, MD,[r] Michael J. Reardon, MD,[r] on behalf of the Low Risk Trial Investigators*

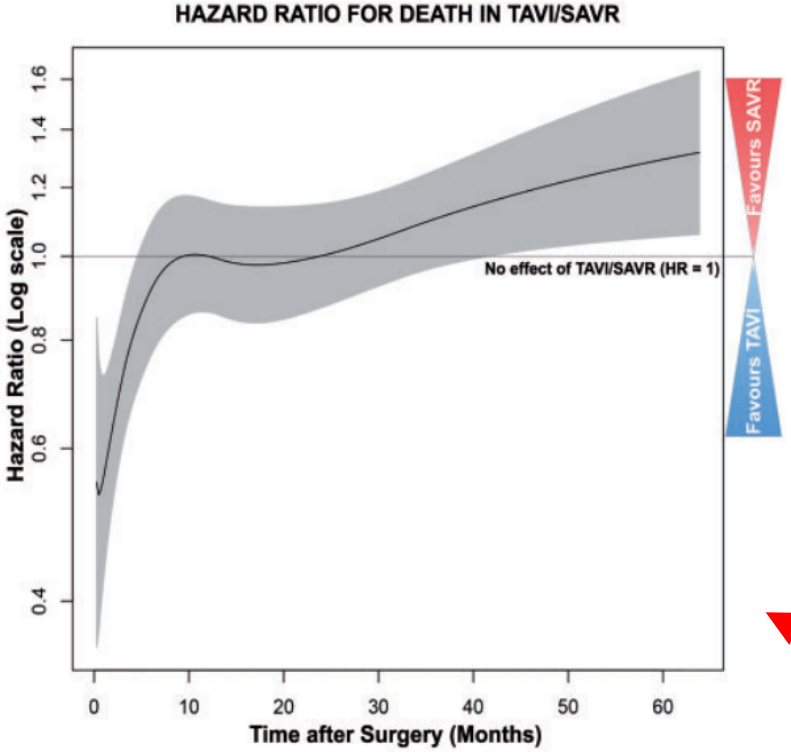
1) high risk of bias previously underscored for 1- and 2-year follow-up, as there is not attenuation of the selective loss to follow-up (26/730=3.6% for TAVI; 60/684=8.8% for SAVR, RR 0.41), which might both undermine the advantages of randomization, and thereby challenge the comparability of the treatment groups.

2) There is also inconsistency in assessing the as-treated population among different papers.

More to come….
Next steps of INTEGRITTY Research on valves

Different behavior of hazard ratios over time

Restricted mean survival time (RMST) is suggested as a novel alternative measure in survival analyses and may be useful when proportional hazards assumption cannot be made or when event rate is low.



META-ANALYSIS

European Journal of Cardio-Thoracic Surgery 61 (2022) 977–987
https://doi.org/10.1093/ejcts/ezab516 Advance Access publication 16 December 2021

Cite this article as: Barili F, Freemantle N, Musumeci F, Martin B, Anselmi A, Rinaldi M *et al.* Five-year outcomes in trials comparing transcatheter aortic valve implantation versus surgical aortic valve replacement: a pooled meta-analysis of reconstructed time-to-event data. Eur J Cardiothorac Surg 2022;61:977–87.

Five-year outcomes in trials comparing transcatheter aortic valve implantation versus surgical aortic valve replacement: a pooled meta-analysis of reconstructed time-to-event data

Fabio Barili [a,b,*], Nicholas Freemantle [c], Francesco Musumeci [d], Barbara Martin [e], Amedeo Anselmi [f], Mauro Rinaldi [g], Sanjay Kaul [h], Jorge Rodriguez-Roda [i], Michele Di Mauro [j], Thierry Folliguet [k], Jean-Philippe Verhoye [f], Miguel Sousa-Uva [l] and Alessandro Parolari [m,n]; on behalf of the Latin European Alliance of CardioVascular Surgical Societies (LEACSS) and with the endorsement of the Latin American Association of Cardiac and Endovascular Surgery (LACES), LEACSS members are the Italian Society of Cardiac Surgery (FB FM MR MdM AP), the Portuguese Society of Cardiac Surgery (MSU), the French Society of Cardiac Surgery (JFV, AA) and the Spanish Society of Cardiac Surgery (JRR) Institutions

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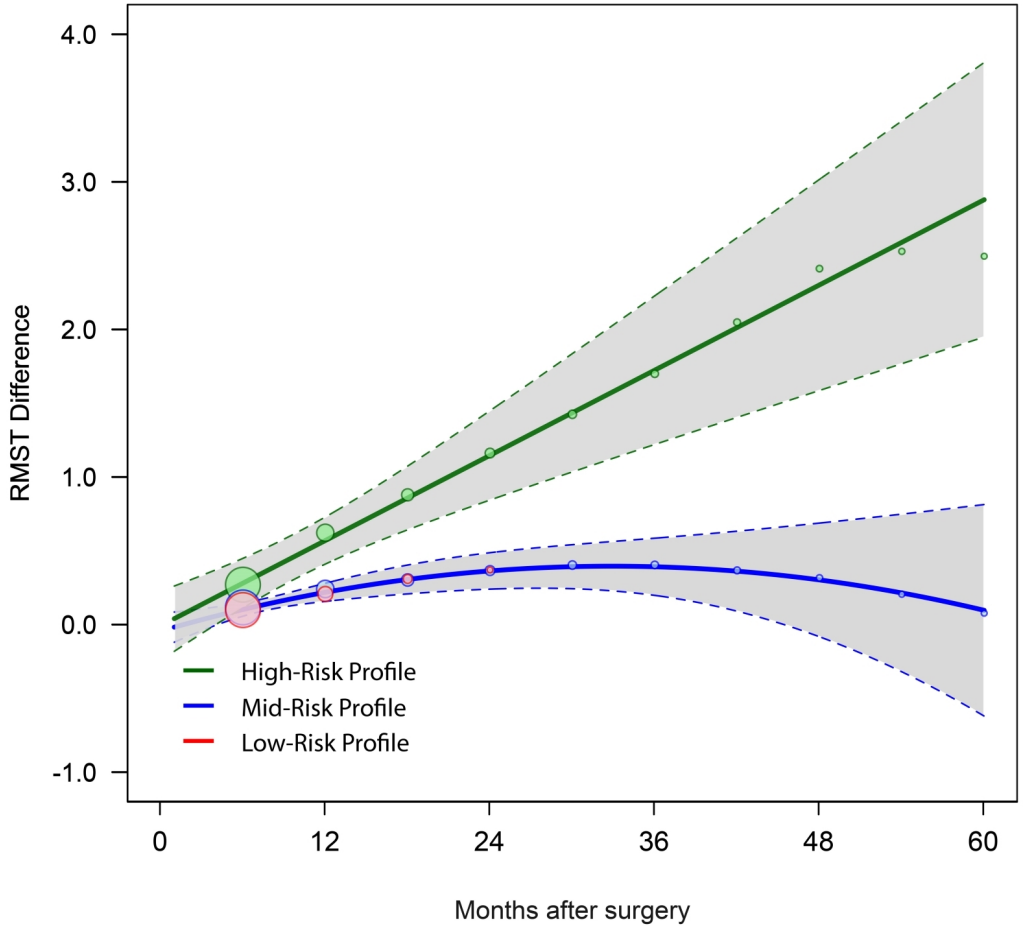
Landmark analysis

BREAKING NEWS

Different behavior of risk profiles over time

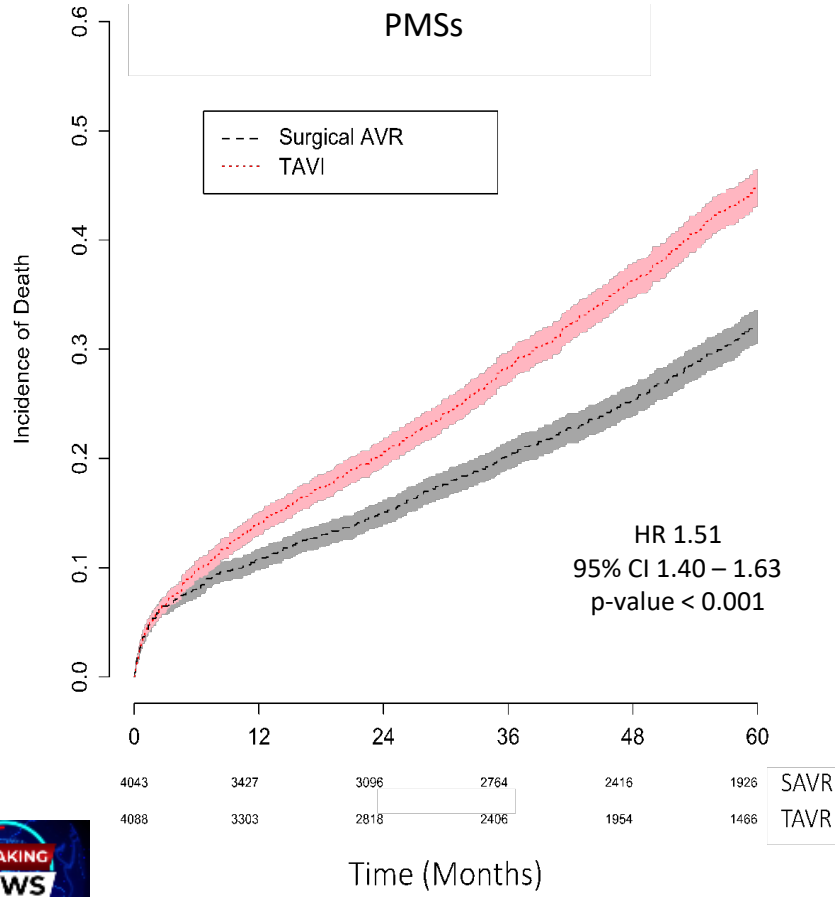
Restricted mean survival time (RMST) is suggested as a novel alternative measure in survival analyses and may be useful when proportional hazards assumption cannot be made or when event rate is low.

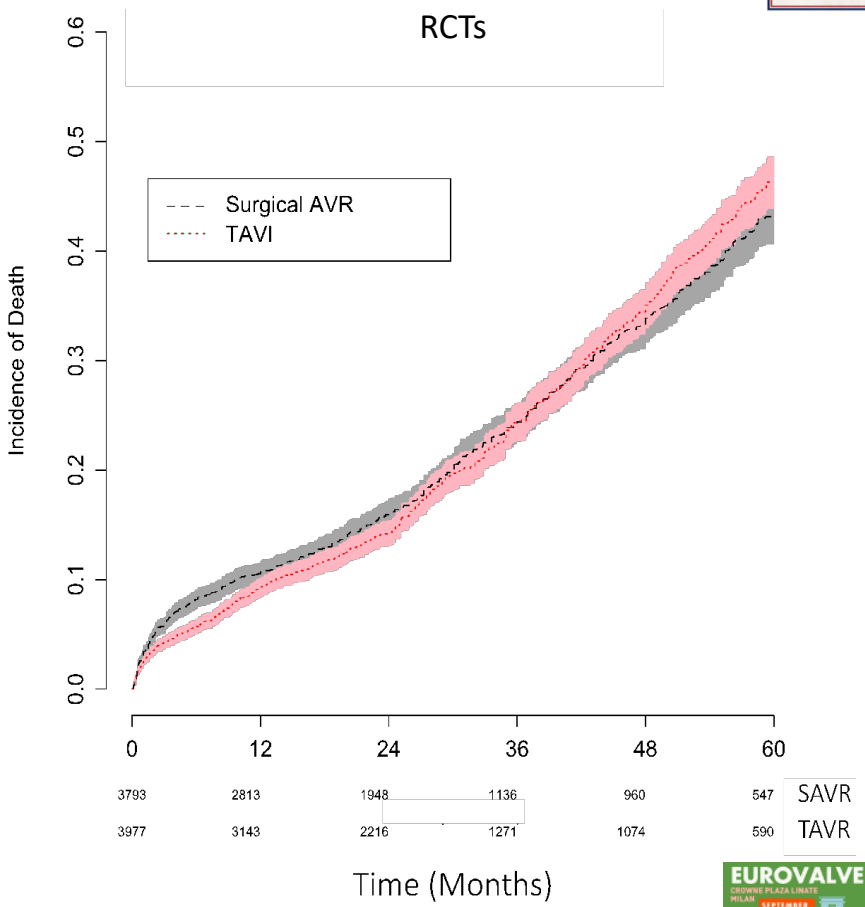


Favors TAVI

Favors SAVR

Moving to propensity-matched studies vs. RCTs
Incidence of death in SAVR vs. TAVI





INTEGRITTY: Public Communications

- Website
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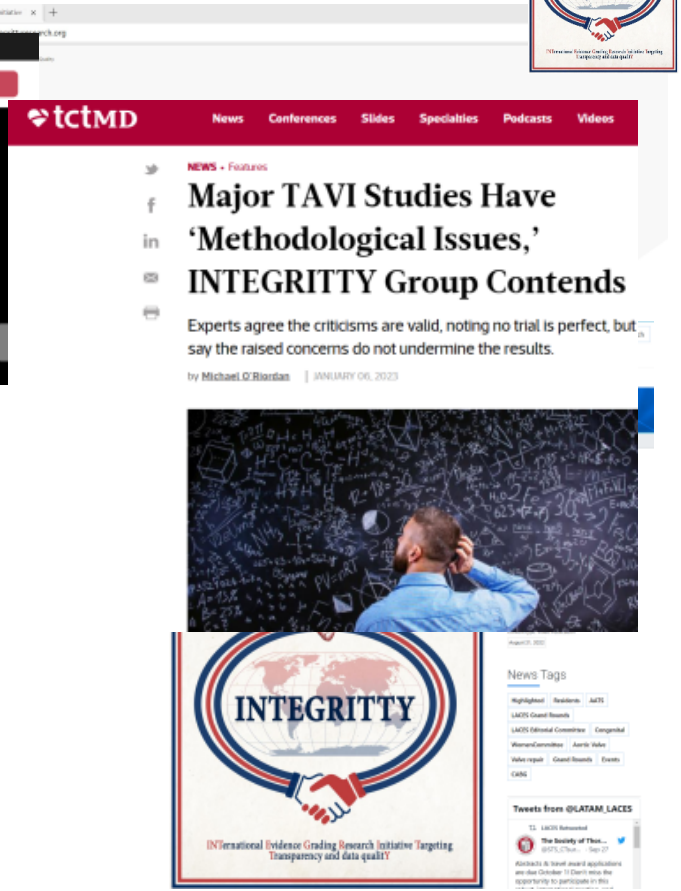
- Specialized news websites
- Scientific societies support



Conclusions

"My mama always said, life is like a box of chocolates. You never know what you're gonna get." (Forrest Gump).

Forrest: [running] I had run for 3 years, 2 months, 14 days, and 16 hours.
[he stops and turns around]
Young Man Running: Quiet, quiet! He's gonna say something!
Forrest: I'm pretty tired... I think I'll go home now.

WE ARE NOT TIRED RUNNING YET!

Thank you for your attention!!!

alessandro.parolari@unimi.it

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“SCHRODINGER’s PARADOX” OF GLs

Schrödinger's Cat

TAVI

SURGERY

AGE: BUT….. AMERICA'S GLs……..

advantages. TAVI valves are durable to at least 5 years, and the limited data on TAVI durability are of less concern to most patients >80 years of age because the valve durability is likely to be longer than the patient's life expectancy.[22] If significant

Circulation

ACC/AHA CLINICAL PRACTICE GUIDELINE

2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

COR	LOE	Recommendations
1	A	2. For symptomatic patients with severe AS who are 65 to 80 years of age and have no anatomic contraindication to transfemoral TAVI, either SAVR or transfemoral TAVI is recommended after shared decision-making about the balance between expected patient longevity and valve durability.[1,4–8]

Recommendations for Choice of SAVR Versus TAVI for Patients for Whom a Bioprosthetic AVR Is Appropriate

Referenced studies that support the recommendations are summarized in Online Data Supplement 11 to 13.

COR	LOE	Recommendations
1	A	3. For symptomatic patients with severe AS who are >80 years of age or for younger patients with a life expectancy <10 years and no anatomic contraindication to transfemoral TAVI, transfemoral TAVI is recommended in preference to SAVR.[1,4–10]

RCTs HAVE A MAX FOLLOW-UP OF 5 YRS

…BUT…

CLASS 1A FOR E.o.L. < 10 YRS

CLASS 1A FOR 65 TO 80 YRS

AHA GLs 2020

Recommendations for Choice of SAVR Versus TAVI for Patients for Whom a Bioprosthetic AVR Is Appropriate

Referenced studies that support the recommendations are summarized in Online Data Supplement 11 to 13.

COR	LOE	Recommendations
1	A	1. For symptomatic and asymptomatic patients with severe AS and any indication for AVR who are <65 years of age or have life expectancy >20 years, SAVR is recommended.
1	A	2. For symptomatic patients with severe AS who are 65 to 80 years of age and have no anatomic contraindication to transfemoral TAVI, either SAVR or transfemoral TAVI is recommended after shared decision-making about the balance between expected patient longevity and valve durability.[1,4–8]
1	A	3. For symptomatic patients with severe AS who are >80 years of age or for younger patients with a life expectancy <10 years and no anatomic contraindication to transfemoral TAVI, transfemoral TAVI is recommended in preference to SAVR.[1,4–10]

Comparison 1. Results: Industry sponsored versus non-industry sponsored studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable efficacy results	14	1588	Risk Ratio (IV, Fixed, 95% CI)	1.24 [1.14, 1.35]
2 Number of studies with favorable harms results	3	561	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.54, 2.27]

Newest treatment Oldest treatment

Comparison 2. Results: Industry sponsorship by test treatment company versus sponsorship by comparator treatment company

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable test treatment efficacy results	2	131	Risk Ratio (M-H, Fixed, 95% CI)	4.64 [2.08, 10.32]

Comparison 3. Conclusions: industry sponsored versus non-industry sponsored studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable conclusions	21	3941	Risk Ratio (IV, Random, 95% CI)	1.31 [1.20, 1.44]

Newest treatment

Oldest treatment

Comparison 4. Conclusions: Industry sponsorship by test treatment company versus sponsorship by comparator treatment company

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable test treatment conclusions	3	154	Risk Ratio (M-H, Fixed, 95% CI)	5.90 [2.79, 12.49]