RHEIA

Randomized researc**H** in wom**E**n all comers w**I**th **A**ortic stenosis

Transcatheter versus surgical aortic valve replacement in women

Hélène Eltchaninoff & Didier Tchétché, on behalf of the RHEIA investigators

August 31, 2024

Declaration of interest

Speaker fees Edwards LifeSciences

Background

- Recent data suggest that the risk of mortality after aortic valve replacement is higher following Surgery but lower following Transcatheter Aortic Valve Implantation (TAVI) in women vs. men

- However, women are under-represented in low-risk TAVI vs. Surgery trials

- **A randomized clinical trial is needed to confirm the benefit of TAVI over Surgery in women**

Purpose

Compare the outcomes of **TAVI** with a balloon-expandable valve vs. conventional **surgery** in **women all comers** with severe symptomatic aortic stenosis

RHEIA Trial Design

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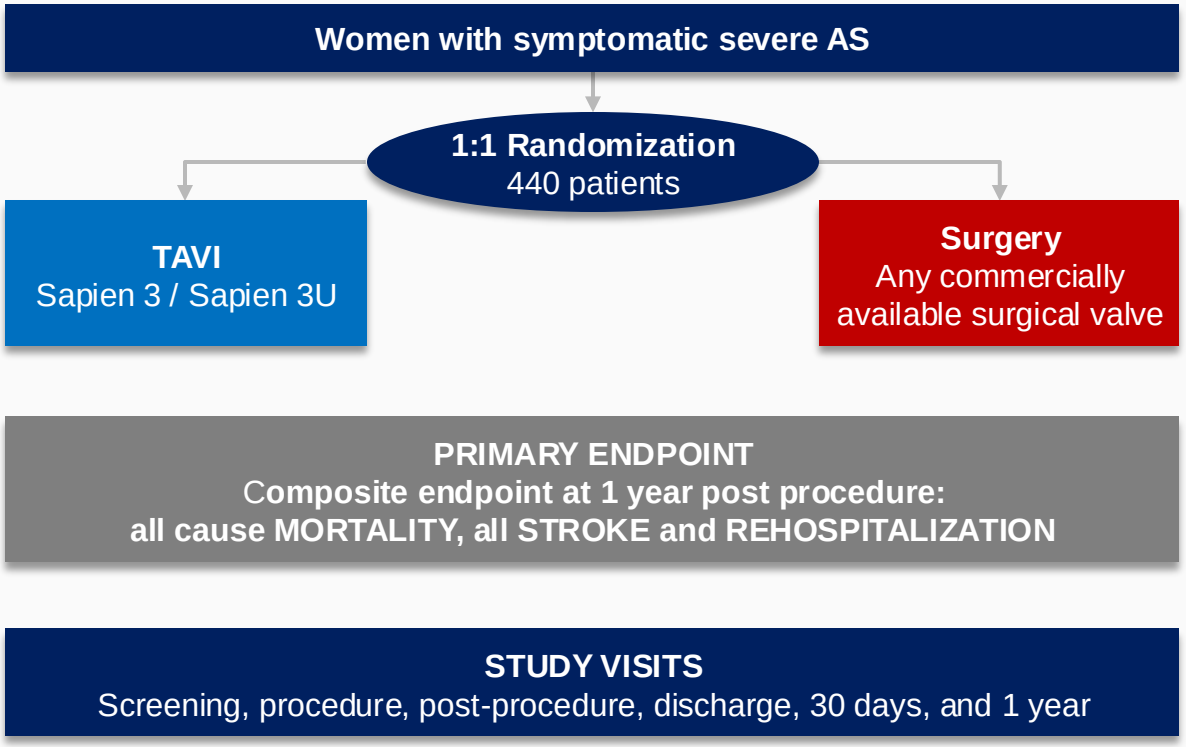
Investigator initiated, multicenter, international RCT to evaluate safety and efficacy of TAVI vs. Surgery in women with symptomatic severe AS



48 Clinical Sites - 443 Patients - 12 Countries

Top 10 enrolling sites

1. **Clinique Pasteur**, Toulouse, France (Tchétché Didier, Berthoumieu Pierre, 31 pts.)
2. **St Antonius Ziekenhuis Nieuwegein**, Nieuwegein, The Netherlands (Swaans Martin, Timmers Leo, 29 pts.)
3. **Universitätsklinik der Ruhr-Universität Bochum Herz- und Diabeteszentrum Nordrhein-Westfalen**, Bad Oeynhausen, Germany (Rudolph Tanja, Bleiziffer Sabine, 27 pts.)
4. **Hôpital Cardiologique du Haut-Lévêque**, Bordeaux, France (Leroux Lionel, Modine Thomas, 25 pts.)
5. **Leids University Medical Center**, Leiden, The Netherlands (Bax Jeroen, Frank van der Kley, 22 pts.)
6. **CHU Rouen - Hopital Charles Nicolle**, Rouen, France (Eltchaninoff Hélène, 18 pts.)
7. **CHU Rennes - Hopital de Pontchaillou**, Rennes, France (Auffret Vincent, Tomasi Jacques, 18 pts.)
8. **Universitätskliniken Innsbruck**, Innsbruck, Austria (Bonaros Nikolaos, Stastny Lukas, 17 pts.)
9. **Allgemeines Krankenhaus der Stadt Wien**, Vienna, Austria (Hengstenberg Christian, Andreas Martin, 17 pts.)
10. **CHU Montpellier - Hopital Arnaud de Villeneuve**, Montpellier, France (Leclercq Florence, Gandet Thomas, 16 pts.)

Trial Leadership

Principal investigators
Hélène Eltchaninoff, Didier Tchétché

Data Safety Monitoring Board
Marco Barbanti, Torsten Doenst
Katja Bohmann

Clinical Endpoint Committee
Richard Steeds, Anna Franzone
Francesco Saia

Case Review Board
Didier Tchétché, Philippe Pibarot
Nicolas Dumonteil, other SC members

Steering committee
Nicolas Dumonteil, Fabian Nietlispach, Nikolaos Bonaros, Bernard Prendergast, Mariuca Vasa-Nicotera, Stephan Windecker, Philippe Pibarot, Jeroen Bax, Alaide Chieffo

Core Labs
CT: David Messika-Zeitoun
Echo: Philippe Pibarot

Sponsor Independent CRO

Funder Edwards Lifesciences

Key Inclusion and Exclusion Criteria

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Inclusion:

Women with severe symptomatic AS meeting the following criteria:

- High gradient severe AS

  or

- Low gradient severe AS

per ESC guidelines

Exclusion:

- Bicuspid aortic valve
- Unicuspid aortic valve
- Non-calcified aortic valve
- Complex coronary artery disease
- Other anatomical features increasing the risk of complications with TAVI or surgery

Study methodology

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- Eligibility for study participation of each patient was assessed by multi-disciplinary Heart Team and Case Review Board
- Primary endpoint events were adjudicated by the CEC (VARC-2 definitions when applicable) that was blinded to treatment assignment
- 30 day and 1 year clinical and echocardiography follow-up were collected and analyzed by core labs

Primary Endpoint

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Composite of **all-cause mortality**, **stroke**, and **rehospitalization** for valve or procedure-related symptoms or worsening heart failure within one year of randomization

Sample size calculation

- Assumed **event rates** for the primary endpoint: 16% for Surgery vs. 8% for TAVI

- Sample size of **132** patients provides 80% power to demonstrate **non-inferiority** with a margin of 6.0% and a one-sided alpha of 0.05

- Sample size of **402** patients provides 70% power to demonstrate **superiority** with a two-sided alpha 0.05 (increased to 440 patients for loss to follow-up, withdrawals and other contingencies)

Statistical analysis

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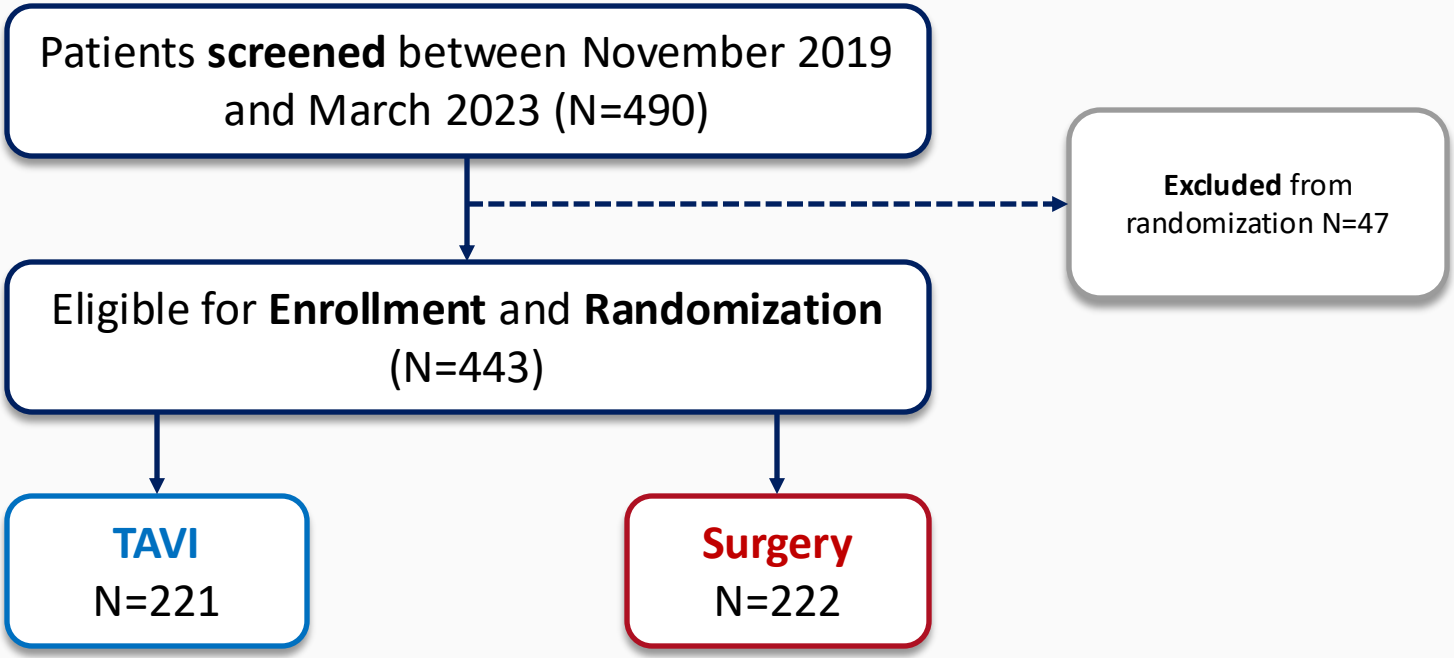
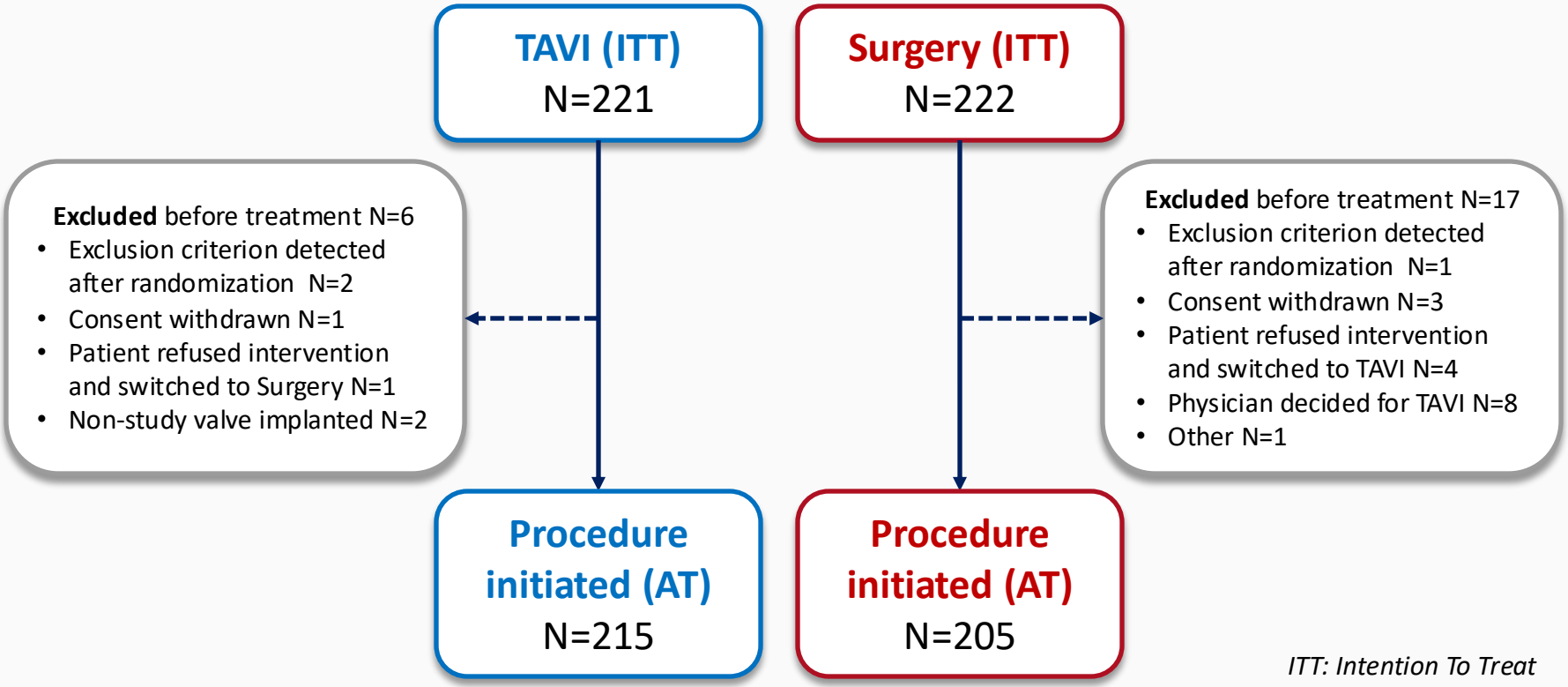
- **Non-inferiority Testing for Primary Endpoint**
  - Upper bound of the 95% CI for the risk difference (TAVR-surgery) less than the pre-specified non-inferiority margin of 6%

- **Superiority Testing for Primary Endpoint**
  - If non-inferiority hypothesis met, superiority testing performed using a 2-sided alpha 0.05

Patient Enrollment



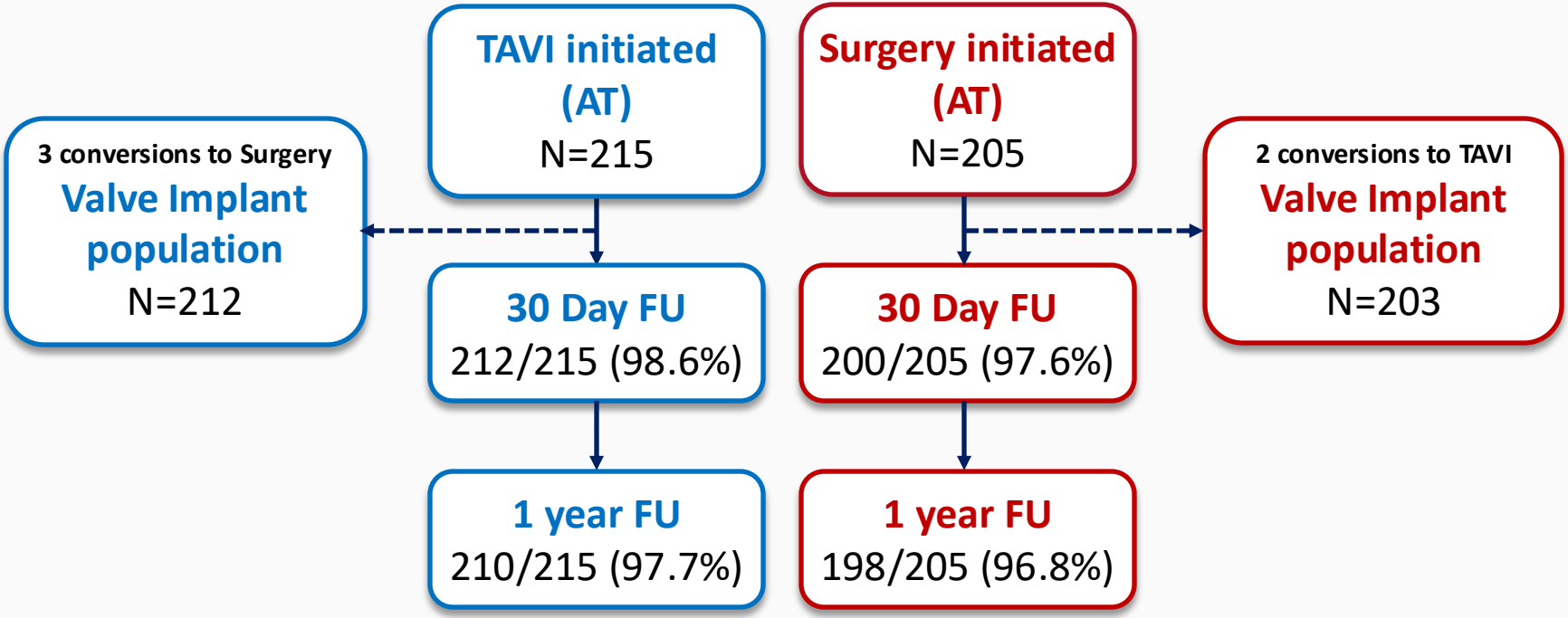
Patient Allocation



ITT: Intention To Treat

AT: As Treated

Patient Follow up



Baseline Patient Characteristics

	TAVI (N=215)	Surgery (N=205)
Age — years	73.1 ± 4.5	73.3 ± 5.2
Race/ethnicity (non-white) — %	0%	0%
Body Mass Index	29.2 ± 5.8	29.8 ± 5.8
Society of Thoracic Surgeons risk score — %	2.1 ± 1.1	2.2 ± 1.3
EuroSCORE II risk score — %	1.7 ± 0.8	1.7 ± 1.1
New York Heart Association class III or IV — %	34.0%	39.0%
Coronary artery disease — %	19.1%	19.0%
Previous stroke — %	3.7%	3.4%
Carotid artery stenosis >50% — %	1.9%	3.9%
Peripheral arterial disease — %	2.3%	5.4%
Creatinine >2 mg/dl (177 µmol/L) — %	0%	0%
Diabetes — %	26.0%	27.3%

Baseline Patient Characteristics

	TAVI (N=215)	Surgery (N=205)
Atrial fibrillation — %	5.1%	3.0%
Permanent pacemaker — %	2.3%	4.0%
Left bundle-branch block — %	7.5%	5.5%
Right bundle-branch block — %	5.2%	7.5%
Overall frailty — %	1.4%	0%
Pulmonary hypertension — %	2.8%	3.9%
Aortic-valve area — cm^2	0.8 ± 0.2	0.8 ± 0.2
Aortic-valve gradient (mean) — mm Hg	47.8 ± 13.7	47.5 ± 13.8
Left ventricular ejection fraction — %	66.9 ± 9.7	68.5 ± 8.0
Moderate or severe valve regurgitation — %		
Aortic	4.7%	3.4%
Mitral	1.4%	0%
Systolic annular area on CT — mm^2	403.7 ± 63.1	392.8 ± 55.3
Small annulus: annular area < 430 mm^2 — %	70.4 %	75.5%

Procedural Findings

TAVI

	%
Valve type:	
SAPIEN 3 / SAPIEN 3 ULTRA	43% / 57%

Concomitant procedures	%
Percutaneous Coronary Intervention	0%
Pacemaker implantation	0.5%
Other	0%

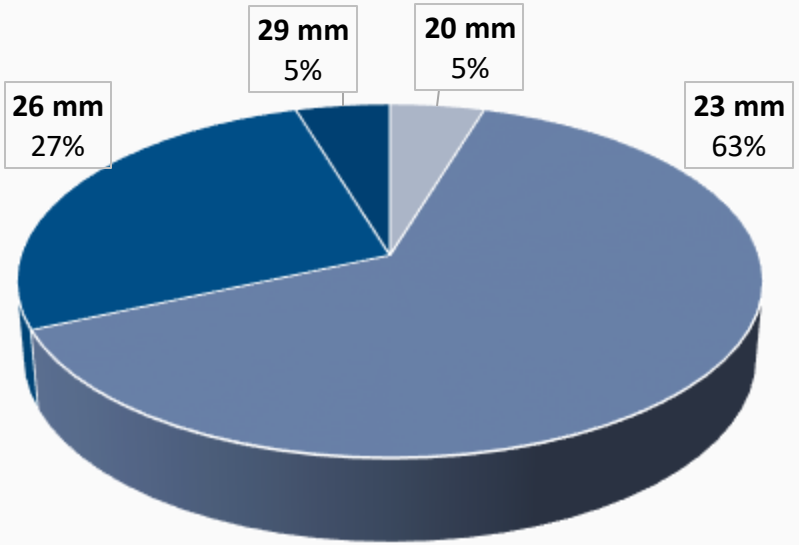
Surgery

	%
Valve type:	
Edwards Magna Ease / Intuity	59.7% / 12.2%
Livanova Perceval	15.5%
Surgery approach:	
Full / Mini sternotomy	66.3% / 27.3%

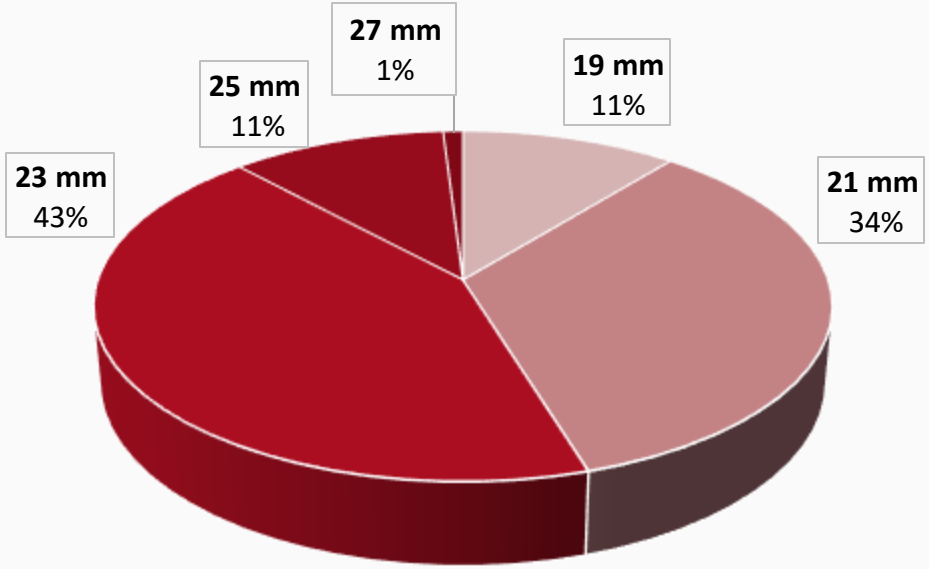
Concomitant procedures	%
CABG	6.8%
Aortic annulus enlargement	0%
Surgery for AF	2.9%
Ascending Aorta replacement	1.5%
Mitral valve intervention	0.5%
Tricuspid valve intervention	1.0%
Other	0.5%

Valve size distribution

TAVI



Surgery

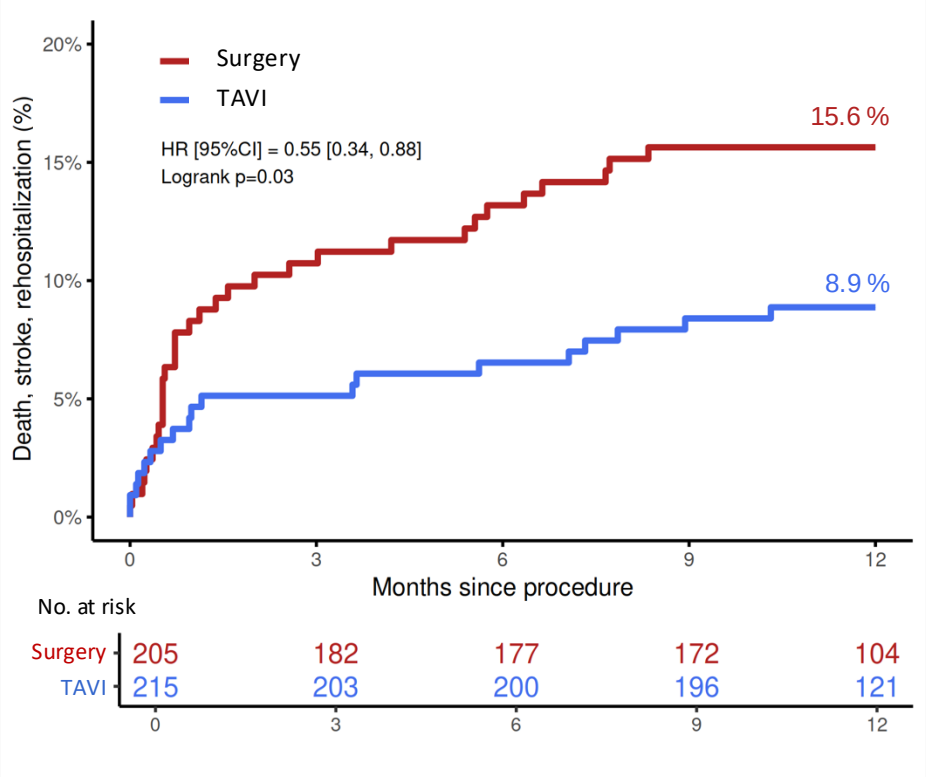


No 29 mm

Procedural Complications and Outcomes

Complication / Outcome	TAVI (N=215)	Surgery (N=205)	P-Value
In-hospital death – %	0.5%	0.5%	1.00
Valve embolization - %	0%	NA	NA
Annulus rupture	0%	NA	NA
Aortic dissection	0.5%	0%	1.00
Coronary obstruction	0.5%	0%	1.00

Primary Endpoint Kaplan–Meier Estimates



Primary Endpoint at 1 year

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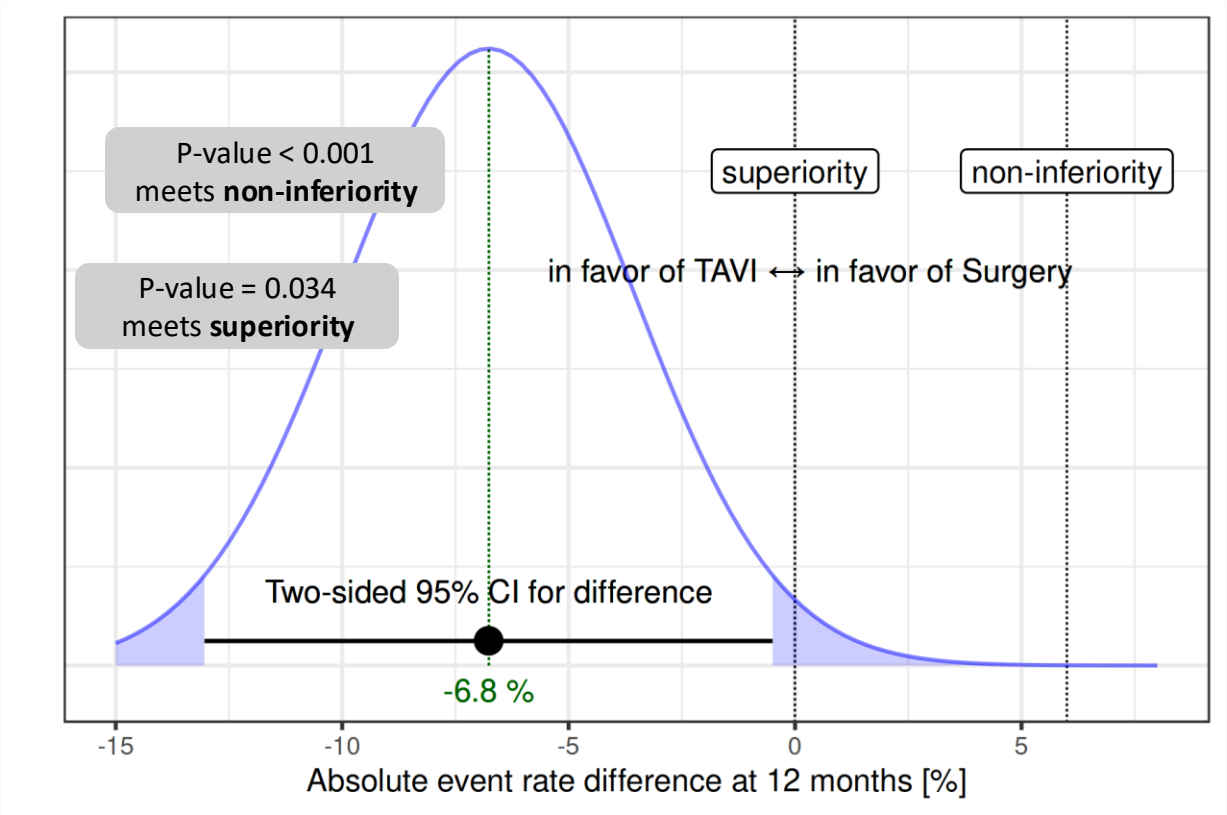
NON-INFERIORITY ✓

SUPERIORITY ✓



Primary Endpoint Components at 1 year

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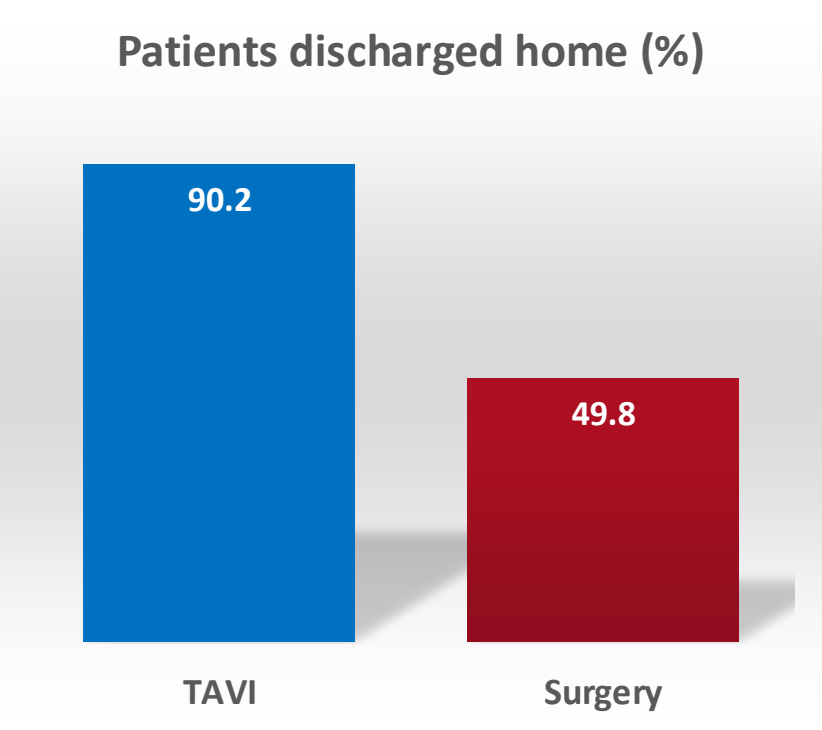
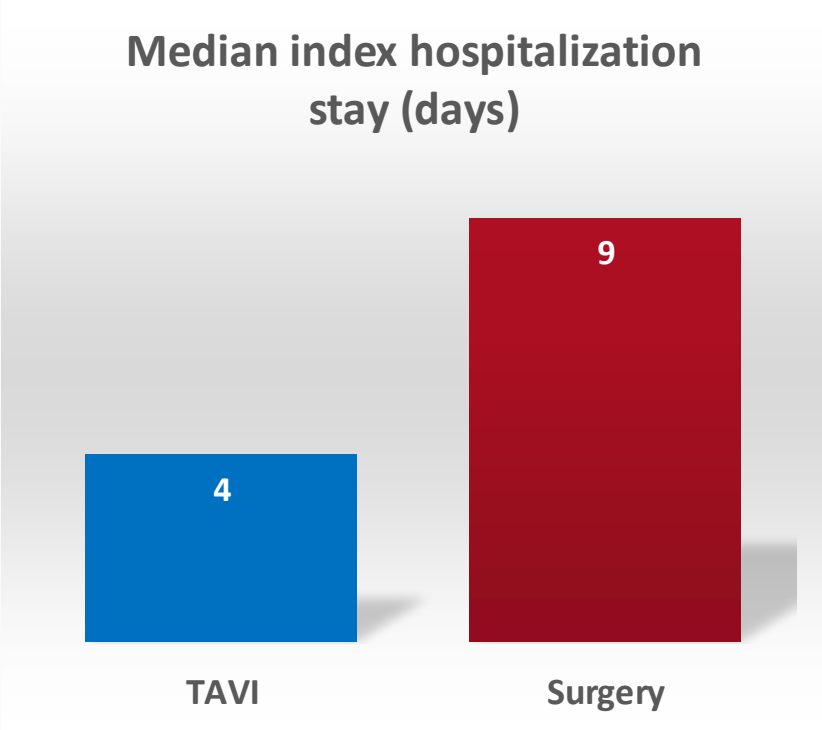
	TAVI (N=215)	Surgery (N=205)	TAVI- Surgery	P-Value
Death	**2 (0.9%)**	**4 (2.0%)**	**-1.0% [-3.3%, 1.3%]**	0.44
Cardiac death	1 (0.5%)	1 (0.5%)	0.0% [-1.3%, 1.3%]	1.00
Non-cardiac death	1 (0.5%)	3 (1.5 %)	-1.0% [-2.9%, 0.9%]	0.36
Stroke	**7 (3.3%)**	**6 (3.0%)**	**0.3% [-3.0%, 3.7%]**	1.00
Disabling stroke	2 (0.9%)	3 (1.5%)	-0.6% [-2.7%, 1.6%]	0.68
Non-disabling stroke	5 (2.4%)	3 (1.5%)	0.9% [-1.7%, 3.5%]	0.72
Rehospitalization valve-related or procedure-related or worsening congestive heart failure	**10 (4.8%)**	**23 (11.4%)**	**-6.6% [-11.9%, -1.4%]**	**0.02**

Key Secondary Endpoints at 1 year

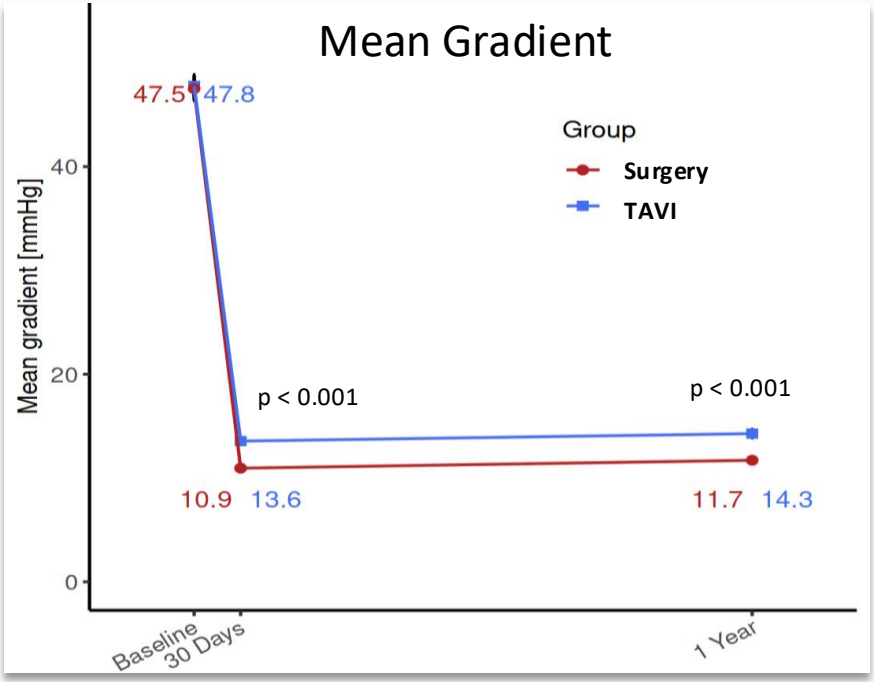
	TAVI (N=215)	Surgery (N=205)	TAVI - Surgery	P-Value
Major vascular complications	7 (3.3%)	1 (0.5%)	2.8% [0.2%, 5.3%]	0.07
Life-threatening / disabling bleeding	9 (4.2%)	9 (4.4%)	-0.2% [-4.1, 3.7]	1.00
Life-threatening / disabling, or major bleeding	13 (6.0%)	22 (10.7%)	-4.7% [-10.0, 0.6]	0.11
Myocardial infarction	0 (0.0%)	2 (1.0%)	-1.0% [-2.3%, 0.4%]	0.24
Acute kidney injury Stage II or III	2 (0.9%)	6 (2.9%)	-2.0% [-4.6%, 0.6%]	0.17
New permanent pacemaker	19 (8.8%)	6 (2.9%)	5.9% [1.5%, 10.4%]	**0.01**
New onset atrial fibrillation	7 (3.3%)	59 (28.8%)	-25.5% [-32.2%, -18.9%]	**<0.001**
NYHA Class II/III/IV	83 (38.6%)	92 (44.9%)	-6.3% [-15.7%, 3.1%]	0.20
5m walk test (sec) change from baseline	-1.1 ± 4.5	-0.9 ± 4.6	-0.17 [-1.16, 0.82]	0.38
KCCQ-OS score change from baseline	20.7 ± 1.1	18.2 ± 1.2	2.5 [-0.7, 5.7]	0.13
Valve Reintervention	2 (0.9%)	0	0.9% [-0.4, 1.4%]	0.50
Valve thrombosis	1 (0.5%)	0	0.5% [-0.4%, 1.4%]	1.00
Valve dysfunction	1 (0.5%)	0	0.5% [-0.4%, 1.4%]	1.00

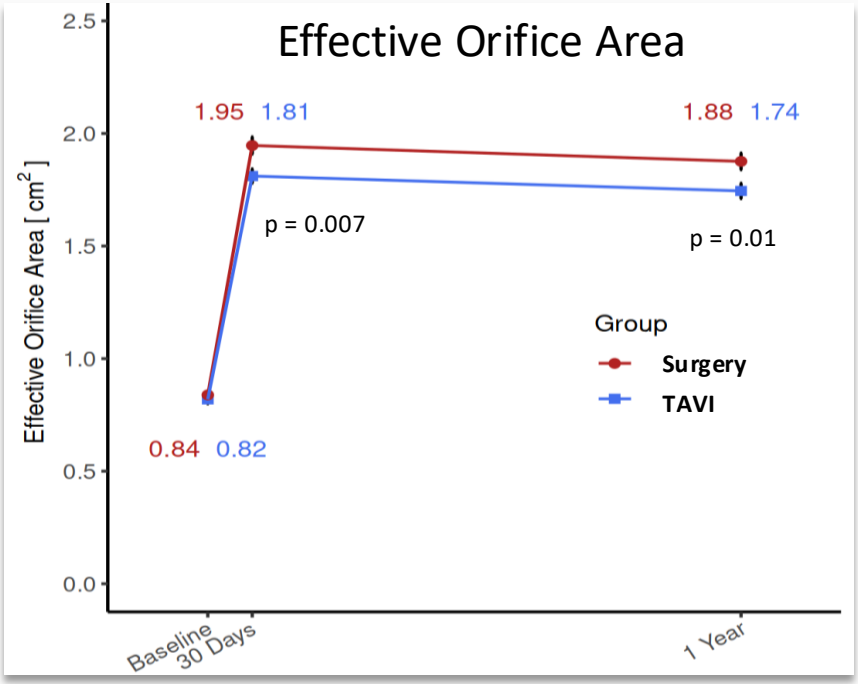
Other Secondary Endpoints





Echocardiography findings





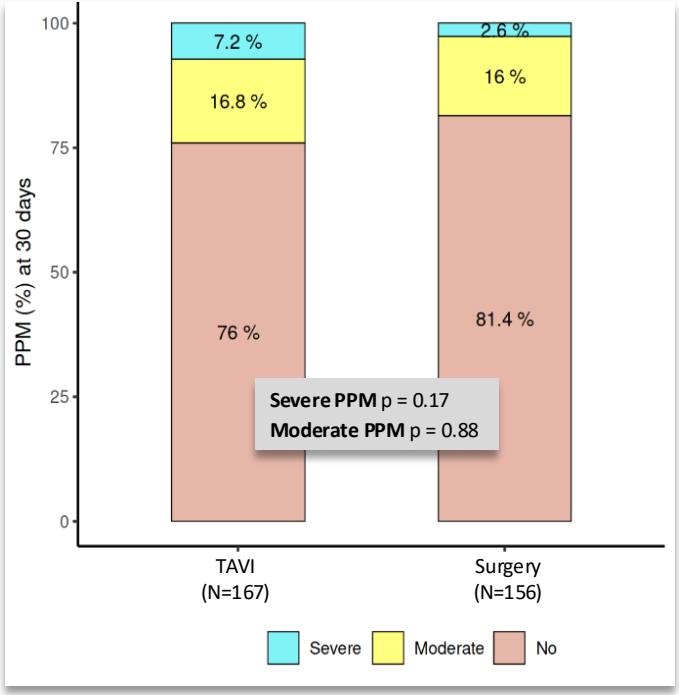
No. of echos			
Surgery	142	171	174
TAVI	157	185	192

No. of echos			
Surgery	132	163	159
TAVI	153	172	176

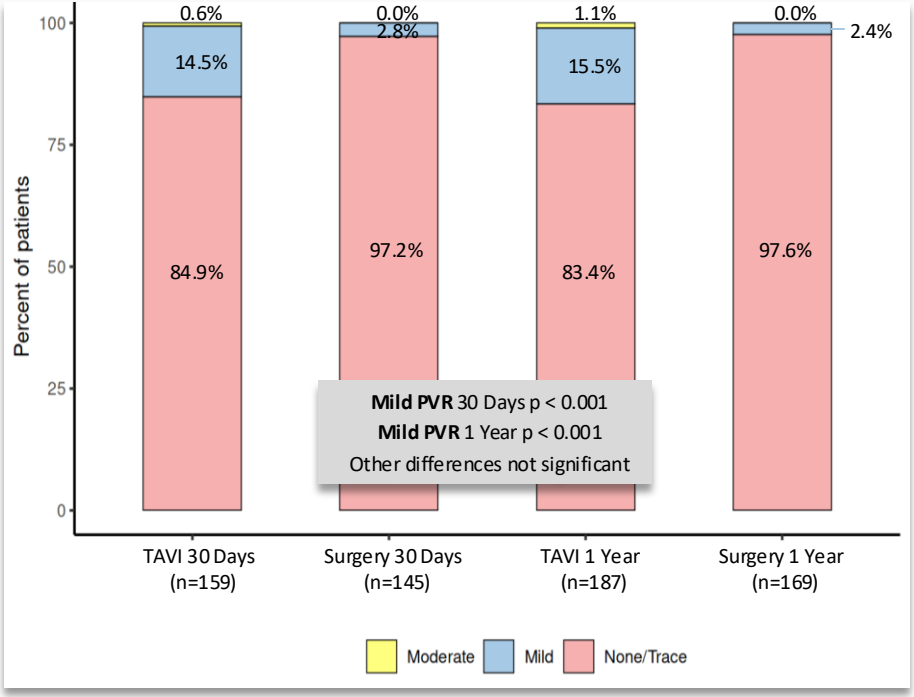
P-values for TAVI vs Surgery

Echocardiography findings

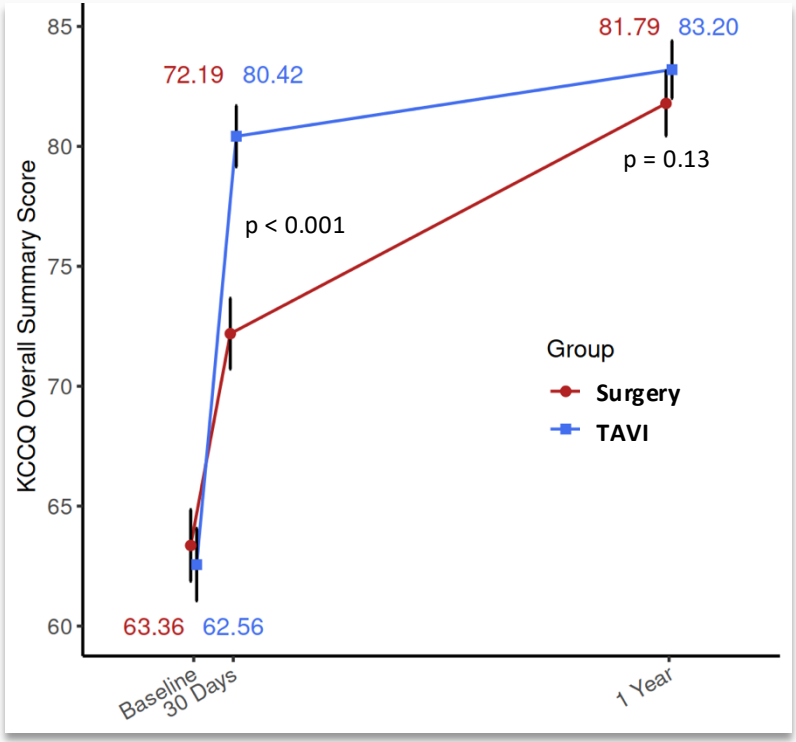
Patient-Prosthesis Mismatch 30 Days



Paravalvular Aortic Regurgitation



Quality of Life KCCQ evaluation



No. of patients			
Surgery	198	191	186
TAVI	209	204	203

Conclusions

- In **women all comers** with severe aortic stenosis, **TAVI** using SAPIEN 3 or SAPIEN 3 Ultra was **superior to surgery** for the **primary composite end point** of death, stroke, or rehospitalization at one year. This superiority was essentially driven by the lower rate or rehospitalizations

- **TAVI** had a **lower incidence** of new onset atrial fibrillation, a quicker recovery and shorter length of index hospital stay, but **higher rates** of mild paravalvular aortic regurgitation and new permanent pacemaker implantation

Conclusions (cont.)

- Excellent **hemodynamics** were achieved with both procedures in a population where around 75% of women had a small annulus

- Besides the patient benefit, the less invasive TAVI treatment also provides **benefits** in terms of **health care resources**:
  - Less rehospitalization
  - Shorter index hospital stay
  - More patients discharged home

Clinical Implications

In **women** with **symptomatic severe aortic stenosis**, **TAVI** using balloon-expandable devices could be considered the **preferred therapy**

Study Limitations

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- RHEIA trial was of **limited size** so there is inevitable uncertainty reflected by wide confidence intervals for treatment difference
- Women with unicuspid, biscuspid, or non-calcified valves were **excluded**
- The **recruitment period was long** (~3·5 years) and this was related to the fact that this phase of the trial occurred during the COVID pandemic
- **Concomitant** procedures were performed in 13.2 % of the surgical patients
- The findings relate to a third-generation balloon-expandable valve system and **cannot be extrapolated** to other valve types