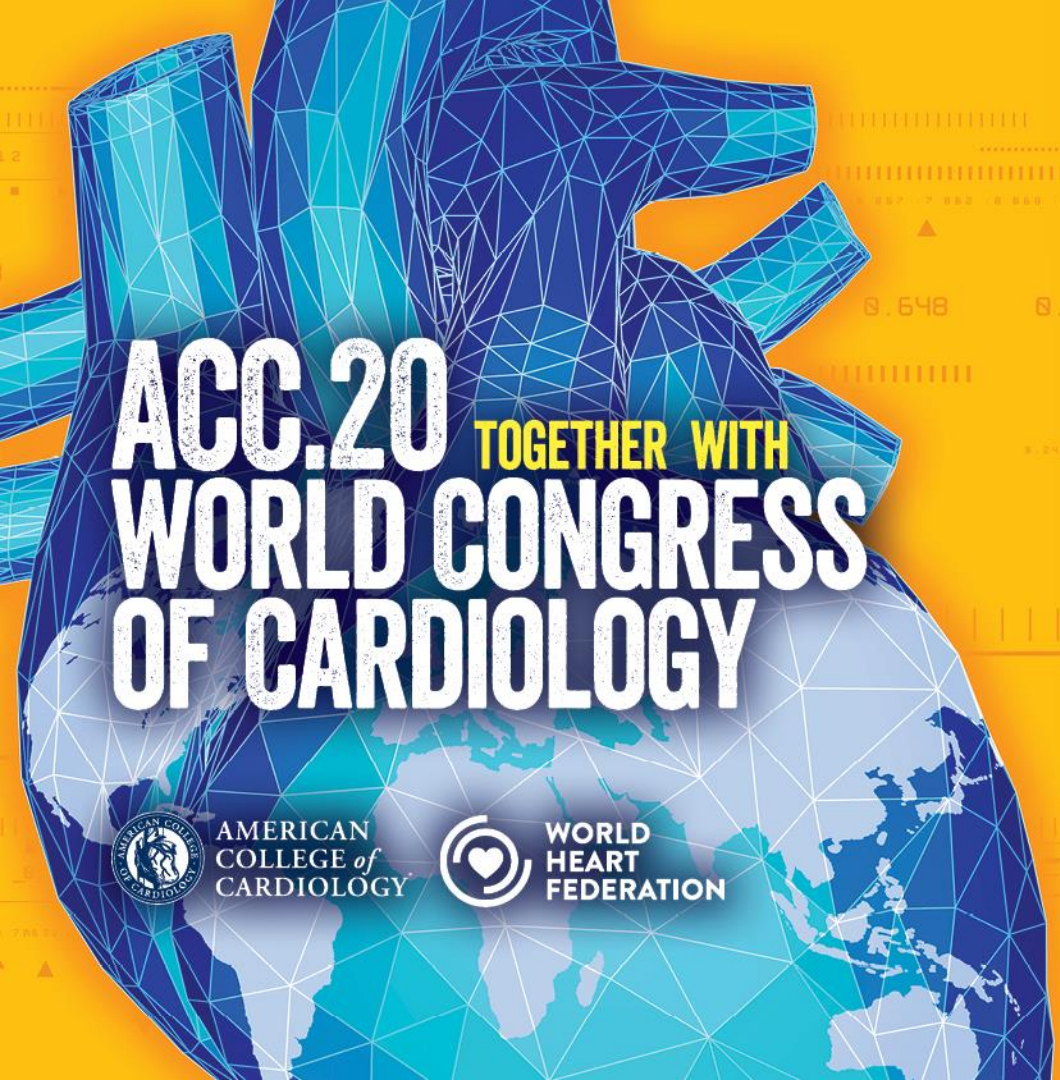


UK TAVI

The United Kingdom Transcatheter Aortic Valve Implantation (UK TAVI) Trial

Professor William D. Toff, MD, FACC
University of Leicester, UK

for the UK TAVI Trial Investigators

UNIVERSITY OF LEICESTER

FUNDED BY
NIHR | National Institute for Health Research

Disclosure Statement of Financial Interests

No relevant financial relationships with any commercial entity

Trial Development and Management Group

William D. Toff (Chair)
Keith R. Abrams
Doug Altman†
Simon P. Conroy
Tim Daniel
Graham Fancourt
Marcus D. Flather
Alastair M. Gray
David Hildick-Smith
Marjan Jahangiri
Jan Kovac
Philip MacCarthy
Neil E. Moat*
Mark J. Monaghan
Michael J. Mullen
Bernard Prendergast
Simon Ray
Tomasz Spyt
Olaf Wendler
Christopher P. Young

† deceased

* to August 2018

Background

- Transcatheter Aortic Valve Implantation (TAVI or TAVR) is a less invasive alternative to conventional surgical Aortic Valve Replacement (AVR)
- When the UK TAVI Trial was initiated:
  - TAVI already shown non-inferior to surgery in high-risk patients
  - Trials in lower risk patients were ongoing
- The previous trials were focused on specific TAVI valves and explanatory rather than pragmatic in their design

Objective

To assess the clinical effectiveness and cost-utility of TAVI, compared with surgical AVR in patients with severe symptomatic aortic stenosis at increased operative risk

Trial Methodology

- Potentially eligible patients reviewed by Multi-Disciplinary Heart Team (MDT)
- Eligibility based on clinical equipoise (no risk-score thresholds)
- Randomised to TAVI (any CE-marked valve, any access route) or conventional surgery
- Aim to treat within 6-weeks of randomisation
- Follow-up at 6 weeks (post-intervention) and one year; interim calls; annual calls to 5 years
- Echocardiogram at 6 weeks and one year assessed by Core Laboratory
- Outcomes reviewed by un-blinded End-Points and Events Committee

Trial Management

Funder:

UK National Institute for Health Research Health Technology Assessment Programme (project reference 09/55/63)
Supported by the UK National Institute for Health Research Leicester Biomedical Research Centre

Research Governance Sponsor:

University of Leicester, UK

Trial Management:

Surgical Intervention Trials Unit (SITU)/ Oxford Clinical Trials Research Unit/ Centre for Statistics in Medicine, University of Oxford, Oxford, UK (Statisticians: Anita Mansouri, Ines Rombach, Susan Dutton)

Randomisation and Trial Database:

The Centre for Healthcare Randomised Trials (CHaRT), University of Aberdeen, UK

Echocardiographic Core Laboratory:

Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK
King's College Hospital NHS Foundation Trust, London, UK

Trial Oversight

Trial Steering Committee:

David Crossman (Chair), Nawwar Al-Attar, Martin Bland, Nicholas Boon, Stuart M. Cobbe, Graham Cooper, David Hildick-Smith, Neil E. Moat (to August 2018), Dawn Saunders, William D. Toff, John G.F. Cleland, Ian Wilkinson, Wil Woan

Data Monitoring Committee:

John McMurray (Chair), Peter Crean, Ian Ford, Lars Køber, Tom Treasure

End-Points and Events Committee:

John G.F. Cleland (Chair), Sanjeev Bhattacharyya, Shelley Rahman Haley, Marc Randall, Olaf Wendler

Clinical Events Safety Review:

John Dean, James Yeh, Abtehale Al-Hussaini, William D. Toff

Participating Sites

34 UK sites:

- England 30
- Wales 2
- Scotland 1
- N. Ireland 1

Liverpool	80 pts
Royal Papworth	80 pts
Oxford	59 pts
Manchester Royal	59 pts
Brighton	57 pts
Royal Brompton	51 pts
Southampton	50 pts
Leeds	42 pts
Middlesbrough	41 pts
Edinburgh	40 pts
Barts Health†	37 pts
King's College	34 pts

Wolverhampton	28 pts
Newcastle	25 pts
Harefield	25 pts
Leicester	24 pts
Plymouth	23 pts
St Thomas'	22 pts
Royal Stoke	21 pts
Nottingham	17 pts
Bristol	14 pts
Swansea	13 pts
Blackpool	11 pts

Cardiff	11 pts
Glasgow*	10 pts
QEH Birmingham	10 pts
Wythenshawe	8 pts
St George's	6 pts
Imperial/Hammersmith	5 pts
Coventry	4 pts
Sheffield	3 pts
Belfast	2 pts
Basildon*	1 pts
Hull*	0 pts

† London Chest Hospital and UCLH merged as Barts Health (April 2015)

* Surgery-only site

Inclusion Criteria

- Severe symptomatic aortic stenosis referred for intervention;
- Age ≥80 years;
  or
  Age ≥70 years with intermediate or high operative risk from conventional AVR, as determined by the MDT;
- Both conventional AVR and TAVI deemed to be acceptable treatment options;
- Participant able and willing to give written informed consent;
- Participant able and willing to comply with all trial requirements.

Exclusion Criteria

- Intervention deemed inappropriate due to co-morbidity or frailty;
- Life expectancy less than one year due to co-morbidity;
- Previous AVR or TAVI;
- Technically unsuitable for either AVR or TAVI;
- Concomitant coronary artery disease (CAD) requiring revascularisation for which only surgery is considered appropriate;
- Predominant aortic regurgitation (AR);
- Severe mitral regurgitation (MR) or need for concomitant surgery other than planned coronary revascularisation

Primary End-Point

All-cause mortality at one year

Primary Hypothesis:

TAVI is not inferior to surgery in respect of death from any cause at one year

Key Secondary Outcomes

- All-cause mortality (2, 3, 4 & 5 years)
- Stroke
- Death from any cause or stroke
- Conduction disturbance requiring pacing
- Infective endocarditis
- Myocardial infarction
- Re-intervention
- Vascular complications
- Major bleeding
- Renal replacement therapy
- Quality of life (MLWHF & EQ-5D-5L)
- Functional capacity (NYHA, 6-MWT)
- Echocardiographic measures
- Costs and cost-utility

Clinical outcomes assessed at 30 days and one year (definitions based on VARC 2)

Sample-size Calculation

Initial calculation:

Assumption:	One-year mortality of 15% for surgery
Non-inferiority margin:	7.5% (absolute difference favouring surgery)
Sample size:	808 patients allowing for 2% dropout

Pre-specified interim analysis of pooled data after one-third of participants reached one-year time-point

Revised calculation:

Assumption:	One-year mortality of 7.5% for surgery
Non-inferiority margin:	5.0% (absolute difference favouring surgery)
	80% power to show upper limit of 97.5% one-sided CI of treatment difference not above 5%
Sample size:	872 patients - increased to at least 890 patients to allow for 2% dropout

Randomisation

- Electronic, web-based system
- Randomised 1:1 TAVI or Surgery
- Minimisation, with stratification for:
  - Age 70-79 vs. 80 years or over
  - Enrolling site
  - Presence of CAD considered to require revascularisation if assigned to receive surgery

Statistical Methods

Primary End-Point - Criteria for Non-Inferiority:

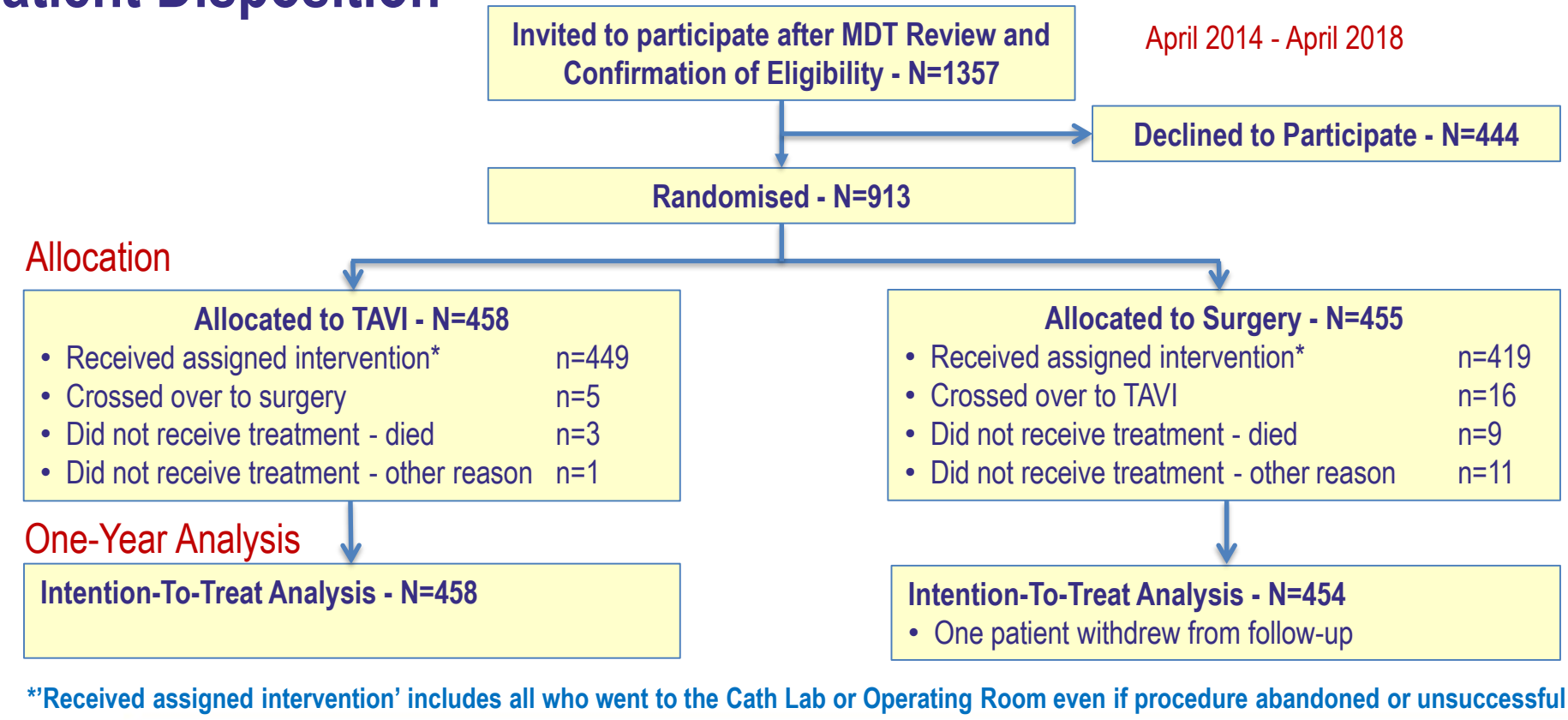
- Upper limit of 2-sided 95% CI for the absolute difference in mortality (TAVI - AVR) is less than 5%
- Data adjusted for randomisation stratification variables (age, CAD requiring revascularisation and site)
- Sensitivity analyses for missing data (worst-case) and based on per-protocol population

Secondary Outcomes:

Categorical outcomes:	Logistic regression models adjusted for covariates
Event-related outcomes:	Cox proportional hazard models adjusted for co-variates; Kaplan-Meier plots
Continuous outcomes:	Multi-level mixed-effects model including repeated measures, adjusted for randomisation stratification factors and baseline values

Primary analyses based on intention-to-treat

Patient Disposition



*'Received assigned intervention' includes all who went to the Cath Lab or Operating Room even if procedure abandoned or unsuccessful

Baseline Characteristics

Characteristic	TAVI (N=458)	Surgery (N=455)
Age (years) - mean ±SD (range)	81.1±4.4 (70-91)	81.0±4.5 (70-91)
Age group - %		
70-79 years	31.2	31.4
≥80 years	68.8	68.6
Male sex - no. (%)	53.9	53.2
Body-mass index (kg/m^2) - mean ±SD	27.7±5.1	28.3±5.1
STS Score - median (IQR)	2.6 (2.0, 3.5)	2.7 (2.0, 3.4)
NYHA Class III or IV (%)	40.3	45.2
Aortic Valve Area (cm^2) - mean ±SD	0.7±0.2	0.7±0.2
Peak AV Gradient (mmHg) - mean ±SD	75.2±24.8	76.5±26.2
LV Ejection Fraction (%)	57.4±9.0	57.3±10.0

Characteristic	TAVI (N=458)	Surgery (N=455)
Coronary disease (%)	29.6	31.7
Previous Cardiac Surgery (%)	2.2	1.8
Previous PCI (%)	12.2	9.0
Previous Stroke (%)	5.7	5.1
Extracardiac arteriopathy (%)	8.9	7.8
History of Atrial Fibrillation (%)	24.0	24.3
Hypertension (%)	72.1	72.3
Diabetes (%)	23.4	24.5
History of Pulmonary Disease (%)	20.7	23.3
Pacemaker, CRT or ICD (%)	6.8	6.4

TAVI Procedure

TAVI Access Route	Number (N=449) (%)
Transfemoral	412 (91.8)
Transapical	19 (4.2)
Subclavian	10 (2.2)
Direct Aortic	8 (1.8)

Valve deployed in 441 patients (98.2%)

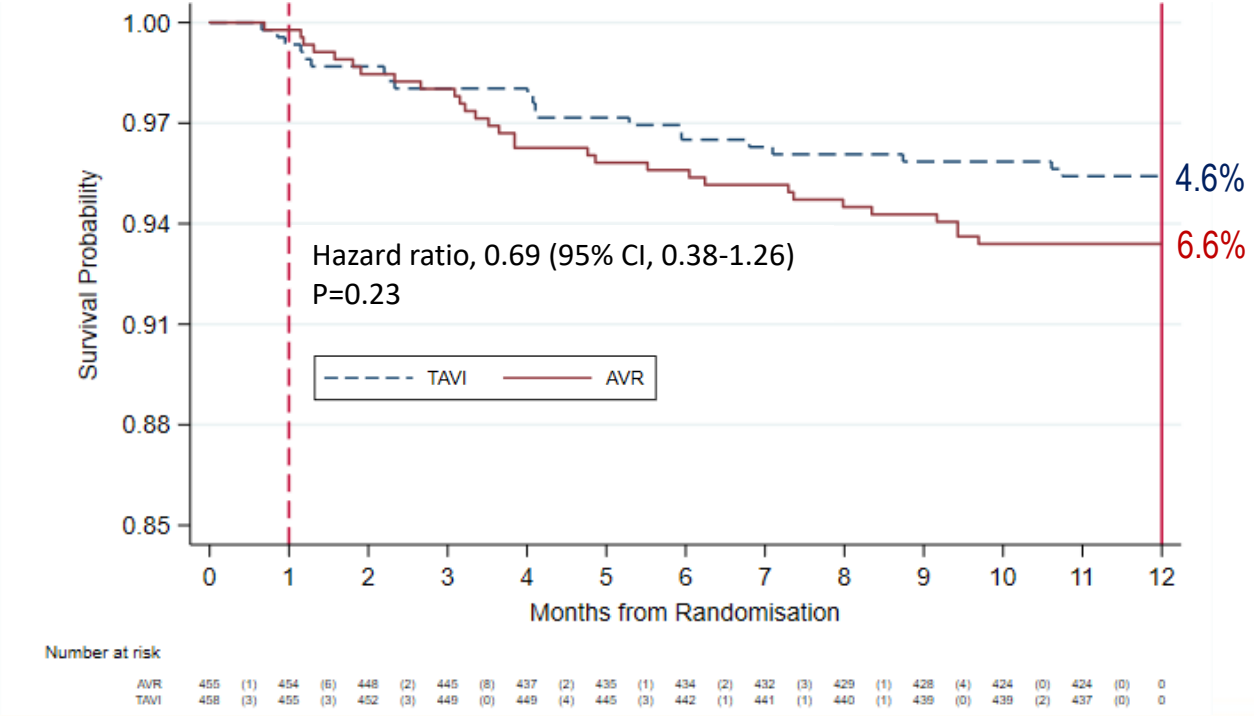
Procedural success with single valve in 434 (96.7%)

TAVI Valve Model (Manufacturer)	Number (N=449) (%)
SAPIEN (Edwards Lifesciences)	36 (8.0)
SAPIEN XT (Edwards Lifesciences)	19 (4.2)
SAPIEN 3 (Edwards Lifesciences)	203 (45.2)
CoreValve (Medtronic)	37 (8.3)
Evolut/ Evolut R (Medtronic)	63 (14.0)
Evolut Pro (Medtronic)	10 (2.2)
Lotus (Boston Scientific)	44 (9.8)
Symetis Acurate/ Neo (Boston Scientific)	22 (4.9)
Other - Portico, Direct Flow Medical	7 (1.6)
No valve deployed	8 (1.8)

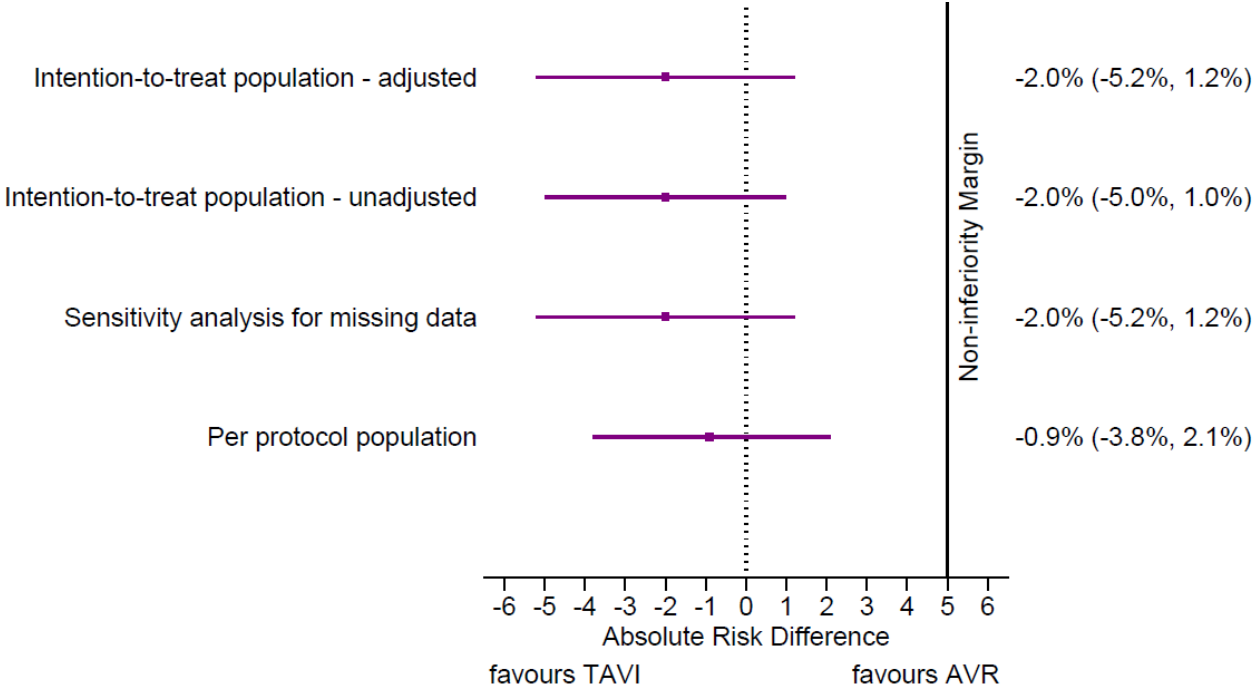
Details of Procedure and Hospitalisation

Variable	TAVI (N=449)	Surgery (N=419)
Procedure Duration (min) - median (IQR)	82 (63, 112)	182 (150, 230)
Local Anaesthetic/ Conscious Sedation	69.5	N/A
Minimally Invasive Incision (%)	N/A	10.5
Aortic Cross-Clamp Time (min) - median (IQR)	N/A	63 (50, 80)
Cardiopulmonary Bypass Time (min) - median (IQR)	N/A	85 (66, 106)
Revascularisation (staged or hybrid) (%)	7.3	21.5
ICU Stay (days) - median (IQR)	0 (0, 0)	1 (1, 3)
Hospital Stay Post-Procedure (days) - median (IQR)	3 (2, 5)	8 (6, 13)
Discharge to Home (± Support) (%)	94.2	82.5
Antithrombotic Medication at Discharge (%)	80.1	75.6
Anticoagulant Medication at Discharge (%)	26.1	36.1

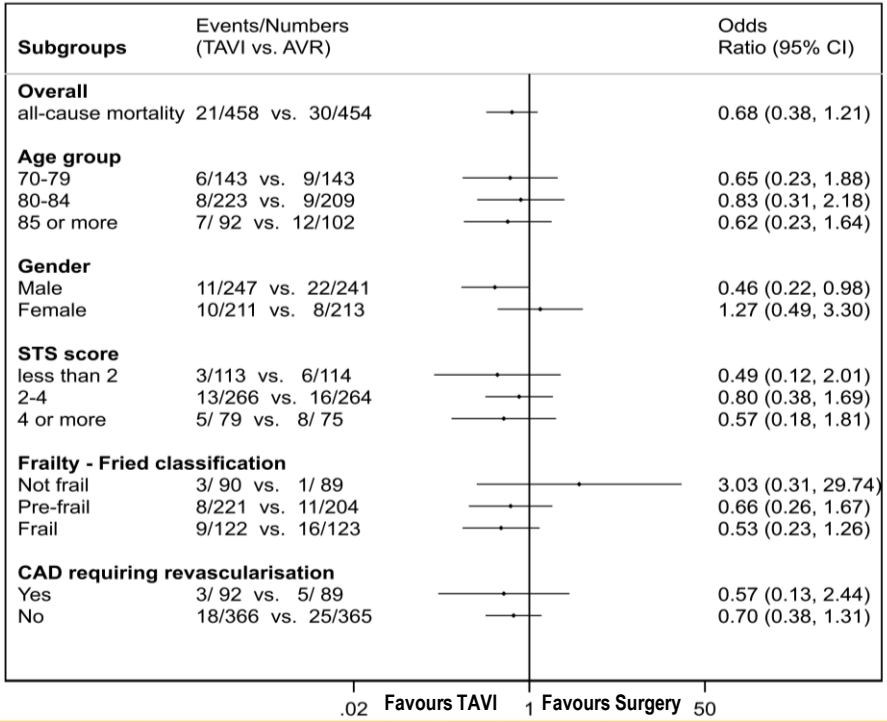
Time to Death From Any Cause



Non-Inferiority Assessment



Primary End-Point – Sub-Group Analysis



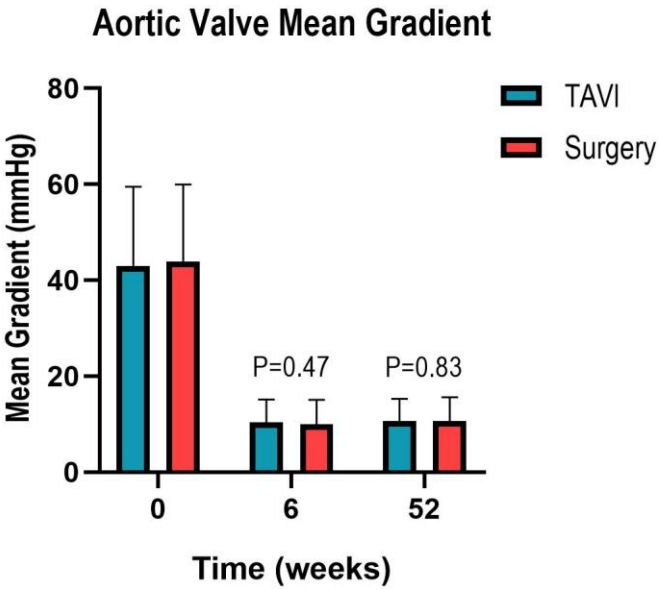
Pre-Specified Outcomes at 30 Days - post-procedure (ITT)

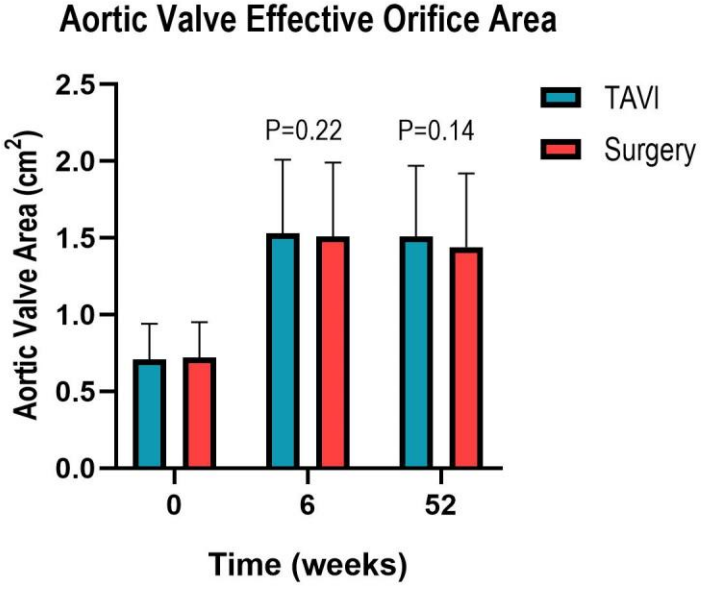
Characteristic	TAVI (N=454) n (%)	Surgery (N=431) n (%)	Hazard Ratio (95% CI)	P-value
Death from any cause	8 (1.8)	4 (0.9)	1.91 (0.52, 7.03)	0.33
Cardiovascular death	7 (1.5)	3 (0.7)	2.22 (0.54, 9.14)	0.27
Stroke	11 (2.4)	11 (2.6)	0.95 (0.31, 2.96)	0.93
Death from any cause or stroke	17 (3.7)	15 (3.5)	1.08 (0.39, 2.97)	0.88
Major bleeding	21 (4.6)	71 (16.5)	0.27 (0.19, 0.38)	<0.001
Conduction disturbance requiring permanent pacing	42 (9.3)	26 (6.0)	1.60 (1.08, 2.35)	0.02
Infective endocarditis	1 (0.2)	1 (0.2)	0.95 (0.06, 15.92)	0.97
Myocardial Infarction	3 (0.7)	0 (0)	-	-
Renal replacement therapy	0 (0)	7 (1.6)	-	-
Vascular complications	20 (4.4)	5 (1.2)	3.84 (1.76, 8.38)	<0.001
Re-intervention	5 (1.1)	7 (1.6)	0.14 (0.02, 1.18)	0.07

Pre-Specified Outcomes at One Year - post-randomisation

Characteristic	TAVI (N=458) n (%)	Surgery (N=455) n (%)	Hazard Ratio (95% CI)	P-value
Death from any cause	21 (4.6)	30 (6.6)	0.69 (0.38, 1.26)	0.23
Cardiovascular death	13 (2.8)	15 (3.3)	0.86 (0.40, 1.83)	0.69
Stroke	23 (5.0)	13 (2.9)	1.75 (0.84, 3.61)	0.13
Death from any cause or stroke	39 (8.5)	41 (9.0)	0.94 (0.56, 1.56)	0.8
Major bleeding	29 (6.3)	78 (17.1)	0.34 (0.25, 0.46)	<0.001
Conduction disturbance requiring permanent pacing	56 (12.2)	30 (6.6)	1.92 (1.33, 2.76)	<0.001
Infective endocarditis	6 (1.3)	2 (0.4)	2.96 (0.68, 12.9)	0.15
Myocardial Infarction	7 (1.5)	4 (0.9)	1.69 (0.39, 7.30)	0.48
Renal replacement therapy	2 (0.4)	8 (1.8)	0.25 (0.06, 1.10)	0.07
Vascular complications	22 (4.8)	6 (1.3)	3.69 (1.79, 7.60)	<0.001
Re-intervention	10 (2.2)	13 (2.9)	0.76 (0.36, 1.60)	0.46

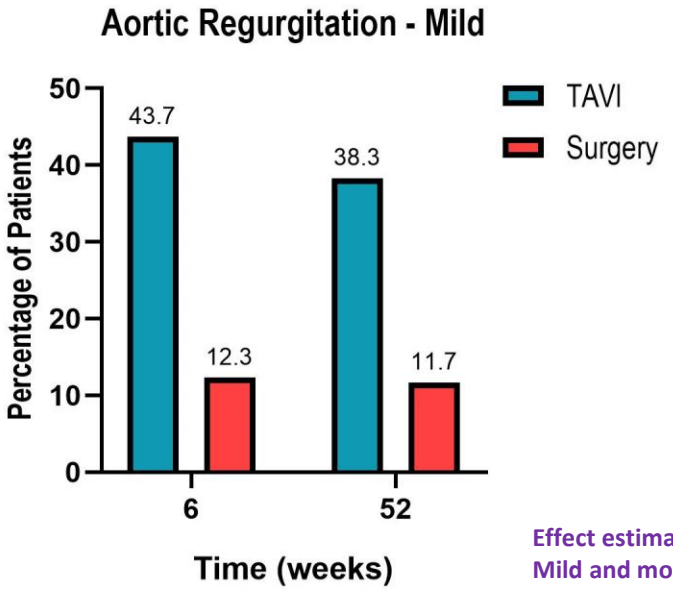
Echocardiographic Outcomes

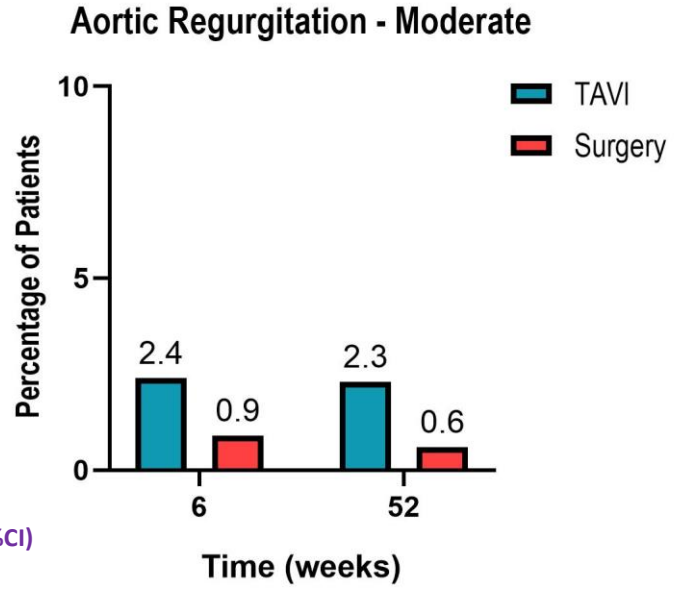




(Data shown are mean ± Standard Deviation)

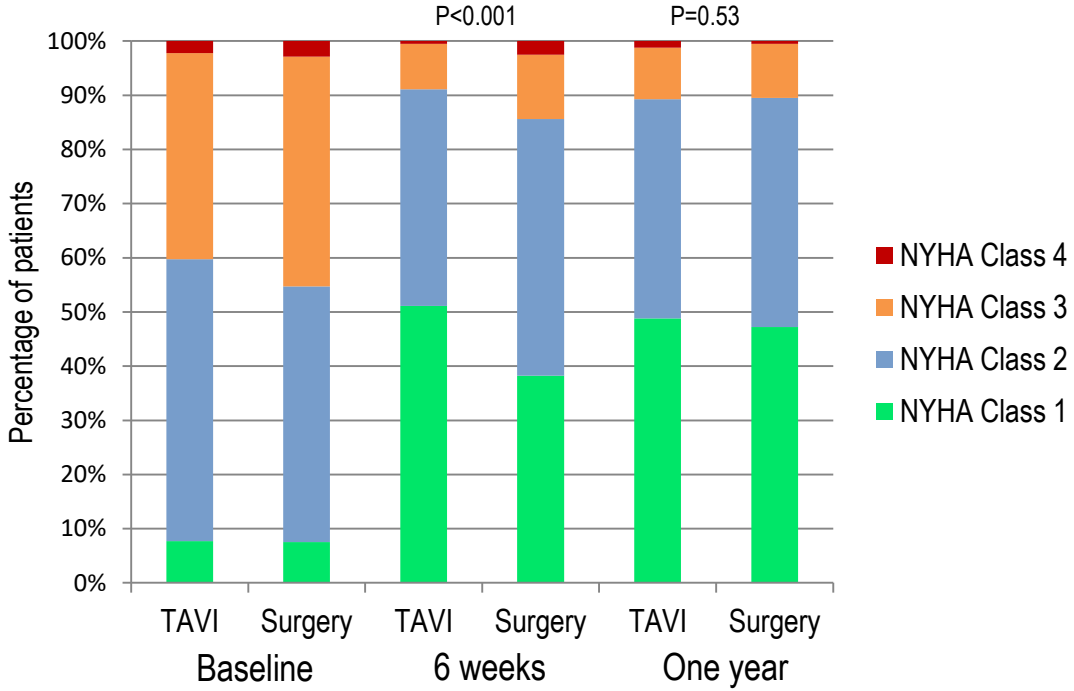
Echocardiographic Outcomes



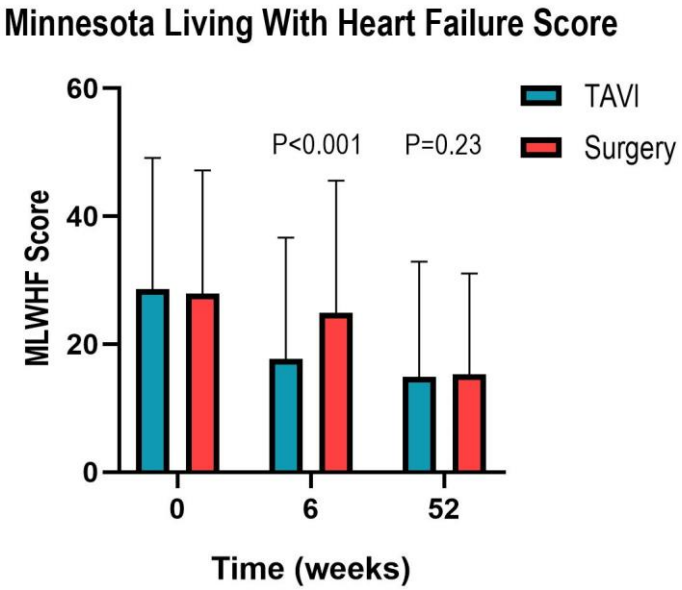


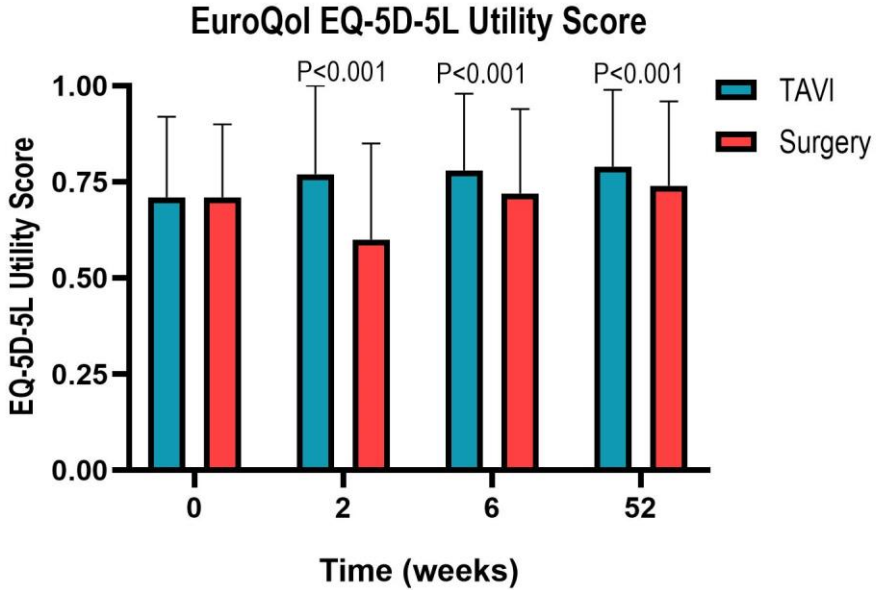
Effect estimate (Odds Ratio and 95%CI)
Mild and moderate AR combined:
Six weeks: 5.37 (3.86, 7.46) P<0.001
One year: 4.89 (3.08, 7.75) P<0.001

Functional Outcomes - NYHA Class



Quality of Life





(Data shown are mean ± Standard Deviation)

Conclusions

- In patients aged 70 years or older with severe symptomatic aortic stenosis at increased operative risk due to age or co-morbidity, TAVI is not inferior to conventional surgery in respect of death from any cause at one year.
- TAVI is associated with less major bleeding than surgery but an increased rate of vascular complications, pacemaker implantation and mild or moderate aortic regurgitation.
- TAVI is associated with a shorter hospital stay and more rapid improvement in functional capacity and quality of life.
- Longer follow-up is required and ongoing to confirm sustained clinical benefit and valve durability to inform clinical practice, particularly in younger patients.

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (project reference 09/55/63). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.