**Effect of Transcatheter Aortic Valve Implantation vs Surgical Aortic Valve Replacement on All-Cause Mortality in Patients with Aortic Stenosis: A Randomized Clinical Trial**

**The UK TAVI Trial Investigators**a

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# KEY POINTS

## Question:

Is transcatheter aortic valve implantation (TAVI) noninferior to surgical aortic valve replacement in patients aged 70 years or older with severe symptomatic aortic stenosis at moderately increased operative risk?

## Findings:

In this randomized clinical trial that included 913 patients at moderately increased operative risk due to age or co-morbidity, all-cause mortality at one year was 4.4% with TAVI *vs* 6.6% with surgery, a difference that met the prespecified noninferiority margin of 5%.

## Meaning:

Among patients aged 70 years or older with severe symptomatic aortic stenosis at moderately increased operative risk, treatment with TAVI was noninferior to surgery in respect of all-cause mortality at one year.

# ABSTRACT

## Importance:

Transcatheter aortic valve implantation (TAVI) is a less invasive alternative to surgical aortic valve replacement and the treatment of choice for patients at high operative risk. Its role in patients at lower risk is unclear.

## Objective:

To determine whether TAVI is noninferior to surgery in patients at moderately increased operative risk.

## Design, Setting and Participants:

In this randomized clinical trial conducted in 34 UK centers, 913 patients aged ≥70 years with severe symptomatic aortic stenosis at moderately increased operative risk due to age or co-morbidity were enrolled between April 2014 and April 2018, and followed to April 2019.

## Interventions:

TAVI using any valve with a CE mark (indicating conformity of the valve with all legal and safety requirements for sale throughout the European Economic Area) and any access route (n=458) or surgical aortic valve replacement (n=455).

## Main Outcomes and Measures:

The primary end-point was all-cause mortality at one year. The primary hypothesis was that TAVI was noninferior to surgery, with a noninferiority margin for the upper limit of the one-sided 97.5% confidence interval for the absolute difference in mortality between the groups of 5%. There were 36 secondary outcomes (30 reported herein), including duration of hospital stay, major bleeding, vascular complications, conduction disturbance requiring pacemaker implantation and aortic regurgitation.

## Results:

Among 913 patients randomized (median (IQR) age, 81 (78, 84) years; 424 (46%) female; median (IQR) Society of Thoracic Surgeons risk score, 2.6 (2.0, 3.4)), 912 (99.9%) completed follow-up and were included in the non-inferiority analysis. At one year, there were 21 deaths (4.6%) in the TAVI group and 30 (6.6%) in the surgery group, with an adjusted absolute risk difference of -2.0% [one-sided 97.5% CI, -∞ to 1.2%], *P* <0.001 for noninferiority. Of 30 prespecified secondary outcomes reported herein, 24 showed no significant difference at one year. TAVI was associated with significantly shorter post-procedural hospitalisation (median (IQR), 3 (2-5) vs 8 (6-13) days). At one year, there was significantly less major bleeding after TAVI (7.2% vs 20.2%; HR, 0.33 [95% CI, 0.24 to 0.45]) but significantly more vascular complications (10.3% vs 2.4%; HR, 4.42 [95% CI, 2.54 to 7.71]), conduction disturbance requiring pacemaker implantation (14.2% vs 7.3%; HR, 2.05 [95% CI, 1.43 to 2.94]), and mild (38.3% vs 11.7%) or moderate (2.3% vs 0.6%) aortic regurgitation (OR for mild, moderate or severe (no instance of severe reported) aortic regurgitation combined vs none, 4.89 [95% CI, 3.08 to 7.75]).

## Conclusions and Relevance:

Among patients aged 70 years or older with severe symptomatic aortic stenosis at moderately increased operative risk, TAVI was noninferior to surgery in respect of all-cause mortality at one year.

## Trial Registration:

ISRCTN.com Identifier ISRCTN57819173

**INTRODUCTION**

Transcatheter aortic valve implantation (TAVI) is a less invasive alternative to surgical aortic valve replacement for patients with severe symptomatic aortic stenosis requiring intervention. The first clinical use of TAVI was in 20021 and evidence from randomized trials has supported its adoption as the treatment of choice for patients who are unfit for conventional surgery2 or at high operative risk.3-6 Early trials used first-generation TAVI devices, which were associated with a high rate of procedural complications.7,8 Technological developments, procedural refinements and increased operator experience have subsequently resulted in improved outcomes, and there is increasing interest in the use of TAVI in patients at lower operative risk. The United Kingdom Transcatheter Aortic Valve Implantation (UK TAVI) trial was conducted to compare TAVI with surgery in patients at only moderately increased operative risk due to age or co-morbidity.

# METHODS

## Trial Design and Oversight

This was an investigator-initiated, pragmatic, multicenter trial involving all National Health Service (NHS) hospitals performing TAVI in the United Kingdom. Details of the participating sites and investigators are provided in the eAppendix in Supplement 3. The Trial was designed by the investigators and overseen by an independent Trial Steering Committee and an independent Data Monitoring Committee (eMethods 1 in Supplement 3). TAVI and surgical valves were procured through standard NHS commissioning. The protocol received a favourable opinion from the London Stanmore Research Ethics Committee. All participants gave written informed consent. The protocol and the statistical analysis plan are available in Supplements 1 and 2 respectively. One-year outcomes are presented herein. Follow-up to a minimum of five years is ongoing and longer-term outcomes will be reported at a later date.

## Participants

Eligible patients were aged 70 years or older, with severe symptomatic aortic stenosis, and at increased operative risk due to co-morbidity or age. Age alone was a sufficient criterion for inclusion in patients aged 80 years or older. Eligibility was determined by a multidisciplinary team at each site, based on clinical equipoise regarding the choice of intervention. Society of Thoracic Surgeons Predicted Risk of Mortality (STS)9,10 and EuroSCORE II11,12 risk scores were calculated but used in a discretionary manner, with no prespecified thresholds for inclusion. Patients requiring coronary revascularization were included unless only surgical revascularization was considered appropriate. Inclusion and exclusion criteria are listed in eMethods2, with further details of the patient identification process in eMethods3. Ethnicity data were recorded to assess the diversity of the study population, which may have implications for the external validity of the trial. Ethnicity was determined by the site staff based on discussion with the participant or review of hospital records, using a list of prespecified options corresponding to those used by the UK Office for National Statistics.

## Randomization

Participants were randomly assigned, in a 1:1 ratio, to receive TAVI or surgery. Randomization was performed using an electronic web-based system developed and hosted by the Centre for Healthcare Randomised Trials at the University of Aberdeen. The randomization used minimization, including an 80% probabilistic element, with stratification for randomizing site, age (70-79 years versus 80 years or over) and the presence of coronary artery disease considered by the multidisciplinary team to require revascularization if the patient was assigned to receive surgery. Participants and site staff were unblinded to the treatment assigned.

## Interventions

Participants assigned to TAVI were treated using any valve with a CE mark (indicating conformity of the valve with all legal and safety requirements for sale throughout the European Economic Area). All aspects of the TAVI procedure, including the choice of local or general anaesthesia, access route and prior or concurrent revascularization were determined by the local clinical team. For participants assigned to surgery, the use of any commercially available valve was permitted apart from sutureless valves. All aspects of the surgical procedure and peri-operative care were determined by the local clinical team. The use and choice of anticoagulant and antithrombotic therapy were at the discretion of the responsible physician.

Participants underwent clinical assessment at baseline, six weeks post-intervention and one year post-randomization. Interim telephone follow-up was performed three months post-intervention and six months post-randomization. Frailty at baseline was assessed using the Fried criteria13 and the Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale.14

## Outcomes

The primary endpoint was all-cause mortality, defined as death from any cause within one year from randomization. Secondary outcomes included cardiovascular death, stroke, re-intervention, a composite of death or stroke, a composite of death or disabling stroke, a composite of death, disabling stroke or reintervention, vascular complications, major bleeding, conduction disturbance requiring permanent pacing, myocardial infarction, kidney replacement therapy and infective endocarditis. A list of all prespecified outcomes and the outcome definitions, based on VARC-2 criteria,15 are provided in eMethods 4 and 5 respectively in Supplement 3. Only 30-day and one-year outcomes are reported herein; longer-term follow-up is ongoing. Six of the 36 secondary outcomes (identified in eMethods 4 in Supplement 3), are not included and will be reported separately. Disability after stroke was assessed using the modified Rankin scale at 90 days.16 Outcome events were adjudicated by an End-Points and Events Committee, aware of the assigned treatment. The data presented are based on adjudicated outcomes.

Symptoms and functional capacity were assessed using the Canadian Cardiovascular Society (CCS) angina grading system,17 the New York Heart Association (NYHA) classification,18 the Nottingham Extended Activities of Daily Living (NEADL) scale19 and the 6-minute walk test.20 Cognitive function was assessed using the Mini-Mental State Examination.21 Quality of life was assessed using the EuroQol EQ-5D-5L22 and the Minnesota Living with Heart Failure Questionnaire (MLHFQ).23 Details of these instruments, including their ranges, directionality and minimal clinically important differences are provided in eMethods 5 in Supplement 3. Participants underwent echocardiography at baseline, six-weeks and one year. Images were analyzed by an independent core laboratory. Assessors were not informed of the scan timepoint or the treatment allocation but the presence of a prosthetic valve will usually have been evident and the type will often have been identifiable, so blinding was incomplete.

## Sample Size

The initial sample size was 808 patients, based on assumed one-year mortality of 15% after surgery (based on age-specific data for 2004-2008 from the UK National Adult Cardiac Surgery database24), with a noninferiority margin of 7.5% absolute difference in the evaluation of whether TAVI is noninferior to surgery. However, a prespecified interim analysis of pooled data showed lower one-year mortality than expected and the sample size was increased on the recommendation of the Trial Steering Committee. The revised sample size was based on assumed one-year mortality of 7.5% after surgery and a noninferiority margin of 5%. It was estimated that at least 890 participants would provide 80% power to show that the upper limit of the one-sided 97.5% confidence interval of the treatment difference would not be above the noninferiority margin, allowing for 2% dropout. The chosen noninferiority margin was based on the principle of balancing clinical preference for the lowest possible margin with feasibility of recruitment in an acceptable timeframe. Five percent was considered to be an acceptable margin in the collective opinion of the Trial Steering Committee, which included clinical and lay members, noting that the margin relates to the upper limit of the one-sided 97.5% confidence interval for the difference in mortality that would be accepted for TAVI to be considered non-inferior to surgery.

## Statistical Analysis

## For the primary statistical analysis, participants were included in the groups as randomly assigned.

The analysis data set included all randomized participants, except those with unknown vital status at one year due to withdrawal from the trial. For the primary outcome, the absolute risk difference was derived from a logistic regression model using delta-method estimated standard errors.25 The model was adjusted for randomisation minimization factors and used robust standard errors to account for clustering of outcomes by randomizing site. Noninferiority was met if the upper limit of the one-sided 97.5% confidence interval for the adjusted absolute difference in mortality between TAVI and surgery was less than 5%. The robustness of the conclusions was assessed by a per-protocol analysis, which included the subset of participants who were treated as randomly assigned (i.e. went to the catheter laboratory or operating theatre for their randomly assigned intervention within one year of randomization, even if the procedure was subsequently abandoned or converted to an alternative intervention). A sensitivity analysis was also performed, in which participants with unknown vital status at one year were assumed to have died if assigned to TAVI and survived if assigned to surgery.

Event-related outcomes at 30 days post-procedure and one year post-randomization were analyzed using Cox proportional hazard models adjusted for randomization minimization factors and using robust standard errors to account for clustering of outcomes by randomizing site. Participants were censored at their date of withdrawal or death, if applicable. Log-log survival plots and Schoenfeld residuals were used to check the assumption of proportionality. Kaplan-Meier plots were constructed for time-to-event analyses. Risk differences with 95% confidence intervals were also calculated. Descriptive statistics are based on all available data. Exploratory subgroup analyses for the primary endpoint were performed using logistic regression models including covariates for the treatment, the relevant subgroup, and an interaction term for both, and presented graphically. Unless otherwise specified, statistical analyses were carried out using Stata software, version 15.1 (StataCorp).

For the statistical analysis of the secondary outcomes that were not event-related, continuous outcome variables were summarized as mean and standard deviation or median and interquartile range (IQR). Treatment effects were estimated using a multilevel mixed-effects model including repeated measures of the secondary outcome variables at the relevant time-points post-randomization nested within participants. The model was adjusted for the randomization factors in line with the primary analysis model, as well as baseline values of the outcomes, if appropriate. Time was added to the model as a categorical variable, and interactions between treatment and time were included. Robust standard errors were used to account for clustering of outcomes by randomizing site. Categorical outcomes were analyzed similarly, using multilevel mixed-effects logistic regression models. Analyses used the available cases subset, with participants included in the groups as randomly-assigned, regardless of treatment received.

A post hoc sensitivity analysis was also performed using a fully Bayesian hierarchical joint model, which simultaneously adjusted for intermittent missing data and dropout due to death, as well as randomization minimization factors. Details are provided in eMethods 6 in Supplement 3.

Secondary outcomes were tested at a 5% two-sided significance level. Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary outcomes should be interpreted as exploratory.

# RESULTS

## Participants

Between April 9, 2014 and April 30, 2018, 913 participants were randomly assigned to undergo either TAVI (458) or surgery (455). In the TAVI group, 450 participants underwent TAVI, five crossed over to surgery, and three received no treatment. In the surgery group, 419 participants underwent surgery, 17 participants crossed over to TAVI, and 19 participants received no treatment. Patient flow is summarised in the CONSORT Diagram (Figure 1).

Baseline characteristics were well balanced between the groups (Table 1 and eTable 1 in Supplement 3). The median (IQR) age was 81 (78, 84) years and 46.4% of the participants were women. The median (IQR) STS risk score was 2.6 (2.0, 3.4). Coronary artery disease that was considered to require revascularization if the patient was assigned to receive surgery was present in 19.8% of the participants.

## Interventions

The median (IQR) time from randomization to treatment was 40 (22, 69) days in the TAVI group and 37 (21, 63) days in the surgery group.

In the TAVI group, a valve was deployed in 443 of the 450 participants who were treated as randomly assigned (98.4%). More than one valve was used in five participants. Details of the valves and access routes are provided in eTable 2 in Supplement 3. Conscious sedation or local/regional anaesthesia was used in 313 participants (69.6%) and general anaesthesia in 137 (30.4%). The median (IQR) procedure duration was 82 (63, 113) minutes. Coronary revascularization was performed as a staged procedure or during the same admission in 33 participants (7.3%).

In the surgery group, a valve was implanted in 416 of the 419 participants (99.3%) who were treated as randomly assigned. Midline sternotomy was performed in 375 participants (89.5%) and minimally invasive surgery in 44 (10.5%). Details of the valves are provided in eTable 3 in Supplement 3. The median (IQR) procedure duration, cardiopulmonary bypass time and cross-clamp time were 182 (150, 230) minutes, 85 (66, 106) minutes and 63 (50, 80) minutes respectively. Concurrent coronary revascularization was performed in 90 participants (21.5%).

The median (IQR) number of days in intensive care and high-dependency units respectively was 0 (0, 0) and 0 (0, 1) after TAVI, and 1 (1, 3) and 1 (0, 3) after surgery. Further details are provided in eTable 4 in Supplement 3. The percentage of participants discharged to home was 94.2% in the TAVI group and 82.6% in the surgery group.

Details of anticoagulant and antithrombotic medication at discharge and during follow-up are provided in eTables 5 and 6 in Supplement 3.

## Primary Outcome

For the primary outcome, data were unavailable for one patient, who withdrew from follow-up. At one year, 21 participants (4.6%) in the TAVI group had died, compared with 30 participants (6.6%) in the surgery group, with an absolute adjusted risk difference between the groups of -2.0 percentage points (one-sided 97.5% confidence interval, -∞ to 1.2%). The upper limit of the one-sided 97.5% confidence interval (1.2%) was less than the prespecified noninferiority margin (5%), consistent with noninferiority of TAVI in respect of death from any cause at one year (P-value <0.001 for noninferiority). The findings were also consistent with noninferiority in the per-protocol population and in the sensitivity analysis allowing for missing data (Table 2). The hazard ratio for death from any cause was 0.69; 95% confidence interval, 0.38 to 1.26 (Table 3). The Kaplan Meier plot is shown in Figure 2A. The treatment effect was consistent across prespecified sub-groups (eFigure 1 in Supplement 3). Details of deaths are provided in eTables 7, 8 and 9 in Supplement 3.

## Secondary Outcomes

The median (IQR) duration of the post-procedural hospital stay following TAVI or surgery was 3 (2, 5) days and 8 (6, 13) days respectively. Event-related secondary clinical outcomes are reported in Table 3. At 30 days post-procedure and one year post-randomization, major bleeding was significantly less frequent in the TAVI group (5.5% vs 19.5%; HR, 0.27 [95% CI, 0.19 to 0.37]; *P*<0.001, and 7.2% vs 20.2%; HR, 0.33 [95% CI, 0.24 to 0.45]; *P*<0.001 respectively) but there was a significantly higher incidence of vascular complications (10.1% vs 2.3%; HR, 4.43 [95% CI, 2.53 to 7.78]; *P*<0.001, and 10.3% vs 2.4%; HR, 4.42 [95% CI, 2.54 to 7.71]; *P*<0.001) and conduction disturbance requiring permanent pacing (11.0% vs 6.7%; HR, 1.72 [95% CI, 1.13 to 2.61]; *P*=0.01, and 14.2% vs 7.3%; HR, 2.05 [95% CI, 1.43 to 2.94]; *P*<0.001). There was no significant difference in the rate of stroke at 30 days (2.4% vs 2.3%; HR, 1.05 [95% CI, 0.35 to 3.17]; *P*=0.94) or at one year (5.2% vs 2.6%; HR, 1.98 [95% CI, 0.95 to 4.11]; *P*=0.07). There was no significant difference in the rate of cardiovascular death, the composite of death from any cause or non-fatal stroke, and other clinical outcomes at 30 days post-procedure or one year post-randomization (Figure 2B, C and D; Table 3).

Echocardiographic findings are reported in eTables 10 and 11 in Supplement 3. At 6 weeks, the mean aortic valve mean gradient was 10.36 mmHg in the TAVI group vs 10.01 mmHg in the surgery group (adjusted difference, 0.31 [95% CI -0.53 to 1.15]; *P*=0.47), and the mean aortic valve effective orifice area was 1.53 cm2 vs 1.51 cm2 (adjusted difference, 0.04 [95% CI, -0.02 to 0.09] *P*=0.22). These haemodynamic improvements were sustained and not significantly different between the groups at one year (eTable 10 in Supplement 3). Mild and moderate aortic regurgitation were significantly more prevalent in the TAVI group than in the surgery group at 6 weeks (43.7% and 2.4%, vs. 12.3% and 0.9%, respectively; adjusted odds ratio for mild, moderate or severe (no instance of severe reported) aortic regurgitation combined vs none, 5.37 [95% CI, 3.86 to 7.46]; *P*<0.001). The findings were similar at one year (38.3% and 2.3%, vs. 11.7% and 0.6%, respectively; adjusted odds ratio, 4.89 [95% CI, 3.08 to 7.75] *P*<0.001).

There was a reduction in the prevalence of angina in both groups at six weeks and one year with no statistically significant difference between them (eTable 12 in Supplement 3). There was a significantly greater improvement in NYHA class, Minnesota Living with Heart Failure scores and six-minute walk distance in the TAVI group at six weeks but at one year there was no significant difference between the groups (eTables 13, 14 and 15 in Supplement 3). There was significantly greater independence in activities of daily living after TAVI at six weeks but no significant difference at one year (eTable 16 in Supplement 3). There were no significant differences in cognitive function (eTable 17 in Supplement 3). EuroQol EQ-5D-5L utility and EQ visual analogue scale (VAS) scores improved within two weeks after TAVI and the benefits were sustained out to one year. In the surgery group, quality of life was diminished at two weeks. It improved after six weeks but utility and VAS scores were significantly higher in the TAVI group and the utility score remained so at one year (eTable 18 in Supplement 3).

## Adverse Events

There were a total of 483 serious adverse events in the TAVI group and 545 in the surgery group, and the number of participants with at least one serious adverse event was 252 (55%) and 255 (56%) respectively (eTable 19 in Supplement 3). Details of relatedness to the interventions and the type of events (classified using the Medical Dictionary for Regulatory Activities - MedDRA) are reported in eTables 20 and 21 in Supplement 3.

# DISCUSSION

In this trial that enrolled patients aged 70 years or older with severe symptomatic aortic stenosis at moderately increased operative risk, TAVI was noninferior to surgery in respect of all-cause mortality at one year. These findings are concordant with those from other trials in intermediate-risk29,30 and low-risk31-33 patients and recent meta-analyses.34,35

In contrast to previous trials, this trial was publicly-funded, pragmatic and designed to compare a TAVI strategy, using any valve type and access route, with a conventional surgical strategy in a broad range of patients. Inclusion was based on clinical equipoise regarding the treatment options and not bound by prespecified risk scores. Entry to the trial thus reflected a site-specific assessment of risk, encompassing factors not reflected in the risk scores, such as frailty. This approach also allowed for the temporal evolution of clinicians’ individual perspectives on the risk threshold for considering TAVI as an alternative to surgery, with increasing local and global experience of the procedure as recruitment progressed. The inclusion of every center performing TAVI in the United Kingdom and having few exclusion criteria, further increased the likelihood that the trial outcomes reflected effectiveness in routine clinical practice in the UK, rather than efficacy under optimal conditions.

When the trial was conceived in 2009, it was envisaged that it would recruit patients at intermediate or high operative risk but by the time enrolment commenced in 2014 clinical practice had evolved. With a median STS risk score of 2.6, the trial population would conventionally be classified as ‘low-risk’. This was reflected in the procedural outcomes, with 30-day mortality in the surgery group of 0.9%, which is similar to that in the low-risk PARTNER 3 (1.1%) and Evolut Low-Risk (1.3%) trials.32,33 However, the one-year surgical mortality in this trial (6.6%) was higher than in PARTNER 3 (2.5%) and Evolut Low-Risk (3.0%) most likely reflecting the older age, increased co-morbidity and increased prevalence of frailty in this study. The treatment effect was consistent in a sub-group analysis assessing the interaction with these factors and in those with and without the need for coronary revascularization.

Improvements in aortic valve area and gradient were similar between the groups but mild and moderate aortic regurgitation were more prevalent after TAVI. This was predominantly mild and may partly reflect the use of earlier generation TAVI valves in the initial recruitment phase and the inclusion of patients with bicuspid valves. The prognostic significance of mild aortic regurgitation is uncertain and long-term follow-up is required to determine its clinical effect. Concerns have been raised about the increased frequency of sub-clinical valve leaflet thrombosis after TAVI compared with surgery.36,37 This was not examined, nor was any specific antithrombotic or anticoagulant regimen mandated to prevent it but the early improvements in valve areas and gradients were sustained in both groups at one year. There was some late divergence of the event curves for stroke with a higher frequency in the TAVI group at one year but the number of events was small and the difference was not statistically significant, so this may reflect the play of chance.

## Limitations

This study has several limitations. First, the lack of site-specific screening data makes it difficult to determine what proportion of the total referrals for aortic valve replacement the trial population represents and how selected was the group that was reviewed by the multidisciplinary team in each site. Background data on all patients treated with TAVI or surgery are available from the relevant national registries26-28 and a comprehensive analysis is planned, which will address this issue. Second, the data presented in this report only address one-year outcomes. Further follow-up is required and ongoing to monitor clinical outcomes and the need for re-intervention in the longer term. There is some uncertainty about the long-term durability of TAVI valves. Data from the UK TAVI registry found the incidence of moderate and severe structural valve deterioration to be 8.7% and 0.4% respectively after median follow-up of 5.8 years but the data predominantly relate to early-generation devices and their reliability is limited by high background mortality and possible survival bias.38 Five-year follow-up from the intermediate-risk PARTNER 2 trial showed more frequent aortic valve re-intervention after TAVI (3.2%) compared with surgery (0.8%).39 Pending longer-term follow-up, treatment selection should be individualised and take account of these uncertainties, particularly in younger patients with longer life expectancy.

## Conclusions

Among patients aged 70 years or older with severe symptomatic aortic stenosis at moderately increased operative risk, TAVI was noninferior to surgery in respect of all-cause mortality at one year.

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Miss Mansouri and Dr Rombach had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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## Conflict of Interest Disclosures:

All authors received grant funding from the National Institute for Health Research to their institution for the conduct of the submitted study. Dr Hildick-Smith reported receiving personal fees from Edwards Lifesciences, Boston Scientific, Medtronic and Abbott outside the submitted work. Dr Kovac reported proctoring and receiving personal fees from Boston Scientific, Medtronic and Edwards Lifesciences outside the submitted work. Dr Mullen reported receiving grants from Edwards Lifesciences and Abbott Vascular; and personal fees from Edwards Lifesciences and Abbott Vascular during the conduct of the study. Dr Abrams reported receiving personal fees from Visible Analytics Limited, NICE/ABPI, Pfizer Oncology, Vifor Pharma, Amaris Limited, EUSA Pharma, NovoNordisk, and NICE/DHSC; grants from Duchenne UK, and Swiss Precision Diagnostics outside the submitted work; and membership of the National Institute for health & Care Excellence (NICE) Diagnostics Advisory Committee. Dr MacCarthy reported proctoring and receiving personal fees from Edwards Lifesciences; lecture/speaker fees from Edwards Lifesciences; and an Educational grant from Edwards Lifesciences during the conduct of the study. Dr Prendergast reported receiving unrestricted educational and research grants to his institution; speaker fees from Edwards Lifesciences; speaker fees from Medtronic; consultancy fees from Anteris; and consultancy fees from Microport outside the submitted work. Dr Cleland reported personal fees from Abbott for serving on an advisory board and providing support for a health economic analysis of the MitraClip device; non-financial support from Boston Scientific - access to data from a clinical trial; personal fees from Medtronic for serving on a data monitoring committee; and grants to his institution from Medtronic for a trial of a subcutaneous monitoring device. Dr Sayeed reported serving as a Company Director and receiving dividends from Oxford Heart Surgery Ltd outside the submitted work. Dr Fraser reported proctoring and receiving personal fees and speaker fees from Medtronic; and receiving speaker fees from Edwards Lifesciences outside the submitted work. Dr Curzen reported receiving grants from Boston Scientific, Haemonetics, Heartflow, and Beckmann Coulter; and non-financial support from Edwards Lifesciences, Biosensors, and Boston Scientific outside the submitted work. Dr Malkin reported receiving personal fees from Medtronic, Abbott, and Boston Scientific during the conduct of the study. Dr Muir reported receiving personal fees from Edwards Lifesciences, and Abbott Vascular outside the submitted work. Dr Pessotto reported proctoring and receiving personal fees from Edwards Lifesciences outside the submitted work. Dr Khogali reported serving as a consultant and proctor, and receiving personal fees from Boston Scientific, and Medtronic outside the submitted work. Dr Dalby reported proctoring and consultancy, and receiving personal fees from Medtronic; and consultancy and receiving personal fees from Edwards Lifesciences, and Boston Scientific outside the submitted work. Dr Redwood reported proctoring and receiving personal fees and speaker fees from Edwards Lifesciences during the conduct of the study. No other disclosures were reported.

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## Group Information:

A complete list of the UK TAVI Trial Investigators, with details of their contributions, appears in Supplement 3. Study center staff and other individuals who participated in the conduct of the trial are listed in Supplement 4.

## Data Sharing Statement:

See Supplement 5.

## Meeting Presentation:

Presented at the American College of Cardiology Scientific Session/ World Congress of Cardiology virtual meeting; March 29, 2020. The data have been amended since the presentation.

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# TABLES

## Table 1. Characteristics of the Participants at Baseline

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **TAVIa**  **(N=458)** | **Surgerya**  **(N=455)** |
| Age, median (IQR), y | 81 (79 to 84) | 81 (78 to 84) |
| Age group, No. (%) |  |  |
| 70-79 | 143 (31.2) | 143 (31.4) |
| ≥80 | 315 (68.8) | 312 (68.6) |
| Sex, No. (%) |  |  |
| Male | 247 (53.9) | 242 (53.2) |
| Female | 211 (46.1) | 213 (46.8) |
| Ethnicity, No. (%)a |  |  |
| Asian/Asian British | 5 (1.1) | 6 (1.3) |
| Black/African/Caribbean/Black British | 0 (0) | 6 (1.3) |
| Mixed/Multiple Ethnic Groups | 1 (0.2) | 1 (0.2) |
| White | 447 (97.6) | 434 (95.4) |
| Other | 5 (1.1) | 8 (1.8) |
| Body-mass index, median (IQR), kg/m2,b | 27.1 (24.0 to 30.5) [n=458] | 27.7 (24.7 to 31.2) [n=452] |
| STS risk score, median (IQR)c | [n=458] | [n=454] |
| Overall | 2.6 (2.0, 3.5) | 2.7 (2.0, 3.4) |
| Age 70-79 y | 2.1 (1.6, 2.8) | 2.0 (1.6, 2.8) |
| Age ≥80 y | 2.9 (2.2, 3.7) | 2.9 (2.3, 3.8) |
| EuroSCORE II risk score, median (IQR)d | [n=458] | [n=454] |
| Overall | 2.0 (1.4, 3.0) | 2.0 (1.5, 3.3) |
| Age 70-79 y | 1.7 (1.3, 2.6) | 1.8 (1.3, 2.8) |
| Age ≥80 y | 2.2 (1.5, 3.2) | 2.3 (1.6, 3.4) |
| NYHA Class III or IV, No./total no. (%)e | 184/457 (40.3) | 204/451 (45.2) |
| Frailty: CSHA CFS ≥5, No./total no. (%)f | 58/454 (12.8) | 60/449 (13.4) |
| Frailty: Fried classification, No./total no. (%)g |  |  |
| Pre-Frail | 221/433 (51.0) | 204/417 (48.9) |
| Frail | 122/433 (28.2) | 124/417 (29.7) |
| Coronary artery disease, No./total no. (%)h | 133/444 (30.0) | 145/435 (33.3) |
| Aortic valve area, median (IQR), cm2,i | 0.7 (0.6 to 0.9) [n=442] | 0.7 (0.6 to 0.8) [n=434] |
| Aortic valve peak gradient, median (IQR), mm Hgi | 73 (59 to 89) [n=453] | 74 (60 to 88) [n=445] |
| Left ventricular ejection fraction, median (IQR), %i | 57 (55 to 64) [n=438] | 57 (55 to 64) [n=437] |
| Moderate or severe AR, No./total no. (%)i | 47/441 (10.7) | 58/436 (13.3) |

### FOOTNOTES TO TABLE 1:

#### Table 1 reports key demographic, clinical and echocardiographic characteristics at baseline. Additional clinical details and past medical history are reported in eTable 1 in Supplement 3.

#### Abbreviations: STS, Society of Thoracic Surgeons Predicted Risk of Mortality; EuroSCORE, European System for Cardiac Operative Risk Evaluation; NYHA, New York Heart Association; CSHA, Canadian Study of Health and Aging; CFS, Clinical Frailty Scale.

#### a Ethnicity data were recorded in order to assess the diversity of the study population, which may have implications for the external validity of the trial in different ethnic groups. Ethnicity was determined by the site staff based on discussion with the participant or review of hospital records, using a list of prespecified options corresponding to those used by the UK Office for National Statistics. Ethnicity reported as ‘other’ in the TAVI group was specified as Italian (2), Maltese (1) and Polish (1). Ethnicity reported as ‘other’ in the surgery group was specified as Arab (1), French (1), German (1), Greek Armenian (1), Greek Cypriot (1), Polish (1) and White Italian (1); no further details were reported for one participant.

#### b Body-mass index is the weight in kilograms divided by the square of the height in meters.

#### c The Society of Thoracic Surgeons Predicted Risk of Mortality (STS) score provides an estimate of the predicted 30-day mortality, expressed as a percentage, among patients undergoing surgical aortic valve replacement on the basis of a number of demographic and procedural variables.9,10

#### d EuroSCORE II is a risk model for estimating the predicted in-hospital mortality after cardiac surgery, expressed as a percentage. The score is based on a combination of patient-related factors, cardiac-related factors and operation-related factors. A higher score denotes a higher operative risk.11,12

#### e The New York Heart Association (NYHA) class18 was determined by site staff during the baseline clinical assessment. It is a functional classification based on the extent to which the patient is limited by their symptoms (Class I, no limitation of physical activity; Class II, slight limitation of ordinary physical activity; Class III, marked limitation of ordinary physical activity; Class IV, symptoms at rest or with minimal activity).

f The Canadian Study of Health and Aging Clinical Frailty Scale (CSHA CFS) evaluates function to generate a frailty score, determined by the interviewer during clinical assessment. Scores range from 1 (very fit) to 7 (severely frail), with a higher score indicating greater frailty and an increased risk of death and other adverse outcomes.14

g The Fried classification identifies a frailty phenotype based on five criteria: unintentional weight loss, self-reported exhaustion, weakness (based on grip strength), slow walking speed and low physical activity level. Patients are classified as non-frail (no frailty criteria), pre-frail (one or two criteria) or frail (three or more criteria). The frailty phenotype is independently predictive of incident falls, worsening mobility or disability, hospitalization, and death.13

h “Coronary artery disease” denotes the presence of greater than 50% diameter stenosis in one or more coronary arteries on angiography.

#### i Echocardiographic parameters in this table are as reported by the site.

## Table 2. Noninferiority Analysis of Death From Any Cause at One Year (Primary Endpoint)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Analysis Population** | **TAVI**  **No./total (%)a** | **Surgery**  **No./total (%)a** | **Absolute Risk Difference in Death**  **From Any Cause at One Year** | |
| **Unadjusted (97.5% CI)** | **Adjusted (97.5% CI)** |
| Primary analysis of population based on randomly assigned groupb | 21/458 (4.6) | 30/454 (6.6) | -2.0% (-∞, 1.0%) | -2.0% (-∞, 1.2%) |
| Sensitivity analysis of population based on randomly assigned group with allowance for missing data | 21/458 (4.6) | 30/455 (6.6) | -2.0% (-∞, 1.0%) | -2.0% (-∞, 1.2%) |
| Per-protocol population | 19/450 (4.2) | 21/416 (5.0) | -0.8% (-∞, 2.0%) | -0.9% (-∞, 2.0%) |

### FOOTNOTES TO TABLE 2:

Table 2 reports the absolute risk difference in the primary endpoint of death from any cause between TAVI and surgery, with a one-sided 97.5% confidence interval, for each of three analysis populations. These comprised the population based on randomly assigned group (the primary analysis), the population based on randomly assigned group with allowance for missing data (a sensitivity analysis), and the per-protocol population, comprising all participants who received their randomly assigned intervention, including those in whom the procedure was commenced but subsequently abandoned or converted to an alternative procedure.

For the sensitivity analysis, there was only one participant with missing data for the primary endpoint; the participant was in the surgery group and was assumed to be alive at one year. Data are shown both unadjusted and with adjustment for randomization minimization factors (age as a continuous variable, presence of coronary artery disease which was considered to require revascularization if the patient was assigned to receive surgery, and clustering within sites).

a Number of participants with an event/number in the relevant analysis population (percentage).

b One participant in the surgery group who withdrew was excluded from the noninferiority analysis of the primary outcome.

**Table 3. Primary Outcome and Secondary Clinical Outcomes One-Year Post-Randomization and 30 Days Post-Procedure**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **TAVIa** | **Surgerya** | **Risk Difference Unadjusted (95% CI)** | **Risk Differenced**  **Adjusted (95% CI)** | **Hazard Ratioe**  **Unadjusted (95% CI)** | **Hazard Ratiod,e**  **Adjusted (95% CI)** | ***P* Value** |
| **Primary Outcome: One Year Post-Randomizationb** | **(n=458)** | **(n=455)** |  |  |  |  |  |
| Death from any cause [Primary outcome] | 21 (4.6%) | 30 (6.6%) | -2.0% (-5.0%, 1.0%) | -2.0% (-5.2%, 1.2%) | 0.69 (0.39, 1.20) | 0.69 (0.38, 1.26) | 0.23 |
| **Secondary Outcomes: One Year Post-Randomizationb** | **(n=458)** | **(n=455)** |  |  |  |  |  |
| Cardiovascular death | 13 (2.8%) | 15 (3.3%) | -0.5% (-2.7%, 1.8%) | -0.5% (-2.8%, 1.9%) | 0.85 (0.41, 1.80) | 0.86 (0.40, 1.83) | 0.69 |
| Stroke (fatal or non-fatal) | 24 (5.2%) | 12 (2.6%) | 2.6% (0.1%, 5.1%) | 2.6% (0.0%, 5.2%) | 1.98 (0.99, 3.95) | 1.98 (0.95, 4.11) | 0.07 |
| Death from any cause or non-fatal stroke | 39 (8.5%) | 40 (8.8%) | -0.3% (-3.9%, 3.4%) | -0.3% (-4.4%, 3.9%) | 0.96 (0.62, 1.50) | 0.96 (0.58, 1.59) | 0.88 |
| Death from any cause or non-fatal disabling stroke | 30 (6.6%) | 35 (7.7%) | -1.1% (-4.5%, 2.2%) | -1.1% (-5.4%, 3.1%) | 0.84 (0.52, 1.38) | 0.84 (0.45, 1.58) | 0.59 |
| Death from any cause, non-fatal stroke or re-intervention | 65 (14.2%) | 74 (16.3%) | -2.1% (-6.7%, 2.6%) | -2.1% (-7.1%, 3.0%) | 0.86 (0.62, 1.20) | 0.86 (0.60, 1.24) | 0.41 |
| Major bleeding | 33 (7.2%) | 92 (20.2%) | -13.0% (-17.4%, -8.6%) | -13.0% (-18.3%, -7.7%) | 0.33 (0.22, 0.49) | 0.33 (0.24, 0.45) | <0.001 |
| Conduction disturbance requiring permanent pacing | 65 (14.2%) | 33 (7.3%) | 6.9% (3.0%, 10.9%) | 6.9% (2.9%, 11.0%) | 2.04 (1.34, 3.11) | 2.05 (1.43, 2.94) | <0.001 |
| Infective endocarditis | 5 (1.1%) | 2 (0.4%) | 0.7% (-0.5%, 1.8%) | 0.7% (-0.5%, 1.8%) | 2.44 (0.47, 12.60) | 2.46 (0.54, 11.17) | 0.24 |
| Kidney replacement therapy | 3 (0.7%) | 8 (1.8%) | -1.1% (-2.5%, 0.3%) | -1.1% (-2.4%, 0.2%) | 0.37 (0.10, 1.39) | 0.37 (0.11, 1.23) | 0.11 |
| Vascular complications | 47 (10.3%) | 11 (2.4%) | 7.8% (4.7%, 11.0%) | 7.8% (4.2%, 11.4%) | 4.43 (2.30, 8.55) | 4.42 (2.54, 7.71) | <0.001 |
| Myocardial infarction | 6 (1.3%) | 5 (1.1%) | 0.2% (-1.2%, 1.6%) | 0.2% (-1.3%, 1.7%) | 1.18 (0.36, 3.88) | 1.17 (0.33, 4.20) | 0.81 |
| Re-intervention - any | 30 (6.6%) | 37 (8.1%) | -1.6% (-5.0%, 1.8%) | -1.6% (-4.5%, 1.3%) | 0.80 (0.49, 1.29) | 0.80 (0.51, 1.23) | 0.31 |
| Re-intervention on aortic valve complex | 10 (2.2%) | 5 (1.1%) | 1.1% (-0.6%, 2.7%) | 1.1% (-0.5%, 2.6%) | 1.98 (0.68, 5.80) | 1.98 (0.72, 5.42) | 0.19 |
| Re-intervention - otherf | 21 (4.6%) | 32 (7.0%) | -2.4% (-5.5%, 0.6%) | -2.5% (-5.2%, 0.3%) | 0.64 (0.37, 1.12) | 0.64 (0.37, 1.11) | 0.11 |
| **Secondary Outcomes: 30 Days Post-Procedurec** | **(n=455)** | **(n=431)** |  |  |  |  |  |
| Death from any cause | 8 (1.8%) | 4 (0.9%) | 0.8% (-0.7%, 2.3%) | 0.8% (-0.9%, 2.5%) | 1.90 (0.57, 6.33) | 1.91 (0.52, 7.03) | 0.33 |
| Cardiovascular death | 7 (1.5%) | 3 (0.7%) | 0.8% (-0.5%, 2.2%) | 1.1% (-0.8%, 2.9%) | 2.22 (0.57, 8.59) | 2.22 (0.54, 9.14) | 0.27 |
| Stroke (fatal or non-fatal) | 11 (2.4%) | 10 (2.3%) | 0.1% (-1.9%, 2.1%) | 0.1% (-2.5%, 2.7%) | 1.05 (0.44, 2.46) | 1.05 (0.35, 3.17) | 0.94 |
| Death from any cause or non-fatal stroke | 17 (3.7%) | 14 (3.2%) | 0.5% (-1.9%, 2.9%) | 0.5% (-2.9%, 3.8%) | 1.16 (0.57, 2.35) | 1.16 (0.43, 3.09) | 0.77 |
| Death from any cause or disabling non-fatal stroke | 14 (3.1%) | 11 (2.6%) | 0.5% (-1.7%, 2.7%) | 0.5% (-2.9%, 3.9%) | 1.21 (0.55, 2.67) | 1.21 (0.35, 4.16) | 0.76 |
| Death from any cause, non-fatal stroke or re-intervention | 33 (7.3%) | 40 (9.3%) | -2.0% (-5.7%, 1.6%) | -2.0% (-6.1%, 2.1%) | 0.78 (0.49, 1.24) | 0.78 (0.46, 1.31) | 0.35 |
| Major bleeding | 25 (5.5%) | 84 (19.5%) | -14.0% (-18.3%, -9.7%) | -14.0% (-19.4%, -8.6%) | 0.27 (0.17, 0.42) | 0.27 (0.19, 0.37) | <0.001 |
| Conduction disturbance requiring permanent pacing | 50 (11.0%) | 29 (6.7%) | 4.3% (0.5%, 8.0%) | 4.3% (0.2%, 8.3%) | 1.72 (1.09, 2.71) | 1.72 (1.13, 2.61) | 0.01 |
| Infective endocarditisg | 0 (0%) | 0 (0%) | - | - | - | - | - |
| Kidney replacement therapy | 1 (0.2%) | 7 (1.6%) | -1.4% (-2.7%, -0.1%) | -1.4% (-2.8%, 0.0%) | 0.13 (0.02, 1.10) | 0.14 (0.01, 1.24) | 0.08 |
| Vascular complications | 46 (10.1%) | 10 (2.3%) | 7.8% (4.7%, 10.9%) | 7.8% (4.2%, 11.4%) | 4.44 (2.24, 8.79) | 4.43 (2.53, 7.78) | <0.001 |
| Myocardial infarctiong | 3 (0.7%) | 0 (0%) | - | - | - | - | - |
| Re-intervention - any | 18 (4.0%) | 27 (6.3%) | -2.3% (-5.2%, 0.6%) | -2.3% (-5.1%, 0.5%) | 0.63 (0.35, 1.15) | 0.63 (0.34, 1.17) | 0.15 |
| Re-intervention on aortic valve complex | 4 (0.9%) | 1 (0.2%) | 0.6% (-0.3%, 1.6%) | 0.6% (-0.3%, 1.6%) | 3.82 (0.43, 34.21) | 3.80 (0.42, 34.20) | 0.23 |
| Re-intervention - otherf | 15 (3.3%) | 26 (6.0%) | -2.7% (-5.5%, 0.0%) | -2.7% (-5.4%, -0.1%) | 0.55 (0.29, 1.03) | 0.55 (0.28, 1.08) | 0.08 |

### FOOTNOTES TO TABLE 3:

Table 3 reports the primary outcome and all event-related secondary clinical outcomes. Additional secondary outcomes, including duration of hospital stay, echocardiographic outcomes, functional capacity and quality of life, are reported in eTable 4 and eTables 10-18 in Supplement 3. Cause of death (see eTable 7 in Supplement 3 for further details) and all events were adjudicated by the End-Points and Events Committee, with reference to outcome definitions based on the VARC-2 criteria15 (eMethods 5 in Supplement 3). Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary outcomes should be interpreted as exploratory.

a Number of participants with an event (percentage of those in the relevant analysis population). The data were analyzed with participants included in the groups to which they were randomly assigned, irrespective of the treatment received.

b At one year, the analysis population included all randomized participants and applied censoring at the time of loss to follow-up, in line with the Cox proportional hazards model. One participant in the surgery group who withdrew and was excluded from the noninferiority analysis of the primary outcome presented in Table 2 was included in this analysis of the primary and secondary outcomes, with censoring at the time of withdrawal. The participant was assumed not to have had an event if no relevant event was reported prior to withdrawal.

c At 30 days, the analysis population included all randomized participants who received an intervention, whether as randomly assigned or otherwise, in time for the 30-day post-intervention follow-up to be completed within one year from randomization. In the TAVI group, 3 of the randomized participants were excluded, as they received no intervention. In the surgery group, 24 of the randomized participants were excluded, comprising 19 who received no intervention, 3 who received their intervention more than one year after randomization (one of these participants received TAVI and is thus shown as a crossover in the CONSORT diagram), and 1 who crossed over and received TAVI, for whom the procedure date was not known.

d Adjusted for randomization minimization factors (age as a continuous variable, presence of coronary artery disease which was considered to require revascularization if the patient was assigned to receive surgery, and clustering within sites using robust standard errors). Risk differences and delta-method estimated standard errors were obtained from logistic regression models.

e A visual analysis of log-log survival plots and Schoenfeld residuals was consistent with the assumption of proportional hazards.

f ’Re-intervention - other’ excludes permanent pacemaker implantation for conduction disturbance, which is reported separately, but includes pacemaker implantation for other indications.

g For outcomes with no events in one of the groups, the risk difference and hazard ratio could not be calculated.

# FIGURES

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## Figure 1. Patient Selection, Allocation, and Flow in a Trial of Transcatheter Aortic Valve Implantation for Aortic Stenosis

### FOOTNOTES TO FIGURE 1:

a Participating sites maintained monthly screening logs of all patients recommended for consideration of enrolment by the multidisciplinary team. Some logs were missing, with an estimated overall shortfall of 22% (based on the number of patients randomized but not included on the screening logs). This would imply that the actual number of patients reviewed by the multidisciplinary team and invited to participate was in the region of 1,740 rather than the stated figure of 1,357, which was derived directly from the screening logs. Data regarding overall national TAVI and surgery activity in the relevant period are available from the relevant national audits.26-28

b Randomization used minimization, including an 80% probabilistic element, with stratification for randomizing site, age (70-79 years vs 80 years or over) and the presence of coronary artery disease considered by the multidisciplinary team to require revascularization if the patient was assigned to receive surgery.

## Figure 2. Time-to-Event Curves for the Primary Endpoint and Major Secondary Outcomes

### LEGEND TO FIGURE 2:

Kaplan-Meier survival analysis at one year post-randomization for death from any cause (Panel A), cardiovascular mortality (Panel B), stroke - fatal or non-fatal (Panel C), and the composite of death from any cause or non-fatal stroke (Panel D). All patients were followed to time of event, withdrawal from the study, or one year post-randomisation. The hazard ratios are specific to the one-year outcomes. P values were derived from a Cox proportional hazards model, which was adjusted for randomization minimization factors and used robust standard errors to account for clustering of outcomes by randomizing site. Cause of death (cardiovascular vs non-cardiovascular) and stroke events were adjudicated by the End-Points and Events Committee, with reference to outcome definitions based on the VARC-2 criteria15 (eMethods 5 in Supplement 3).

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## Figure 2

