Transcatheter aortic valve implantation in patients with high-risk symptomatic native aortic regurgitation (ALIGN-AR): a prospective, multicentre, single-arm study

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Summary

Background Surgery remains the only recommended intervention for patients with native aortic regurgitation. A transcatheter therapy to treat patients at high risk for mortality and complications with surgical aortic valve replacement represents an unmet need. Commercial transcatheter heart valves in pure aortic regurgitation are hampered by unacceptable rates of embolisation and paravalvular regurgitation. The Trilogy transcatheter heart valve (JenaValve Technology, Irvine, CA, USA) provides a treatment option for these patients. We report outcomes with transfemoral transcatheter aortic valve implantation (TAVI) in patients with pure aortic regurgitation using this dedicated transcatheter heart valve.

Methods The ALIGN-AR trial is a prospective, multicentre, single-arm study. We recruited symptomatic patients (aged ≥18 years) with moderate-to-severe or severe aortic regurgitation at high risk for mortality and complications after surgical aortic valve replacement at 20 US sites for treatment with the Trilogy transcatheter heart valve. The 30-day composite primary safety endpoint was compared for non-inferiority with a prespecified performance goal of 40·5%. The primary efficacy endpoint was 1-year all-cause mortality compared for non-inferiority with a performance goal of 25%. This trial is registered with ClinicalTrials.gov, NCT 04415047, and is ongoing.

Findings Between June 8, 2018, and Aug 29, 2022, we screened 346 patients. We excluded 166 (48%) patients and enrolled 180 (52%) patients with symptomatic aortic regurgitation deemed high risk by the heart team and independent screening committee assessments. The mean age of the study population was 75·5 years (SD 10·8), and 85 (47%) were female, 95 (53%) were male, and 131 (73%) were White. Technical success was achieved in 171 (95%) patients. At 30 days, four (2%) deaths, two (1%) disabling strokes, and two (1%) non-disabling strokes occurred. Using standard Valve Academic Research Consortium-2 definitions, the primary safety endpoint was achieved, with events occurring in 48 (27% [97·5% CI 19·2–34·0]) patients ($p_{non\text{-}inferiority}<0·0001$), with new pacemaker implantation in 36 (24%) patients. The primary efficacy endpoint was achieved, with mortality in 14 (7·8% [3·3–12·3]) patients at 1 year ($p_{non\text{-}inferiority}<0·0001$).

Interpretation This study shows the safety and effectiveness of treating native aortic regurgitation using a dedicated transcatheter heart valve to treat patients with symptomatic moderate-to-severe or severe aortic regurgitation who are at high risk for mortality or complications after surgical aortic valve replacement. The observed short-term clinical and haemodynamic outcomes are promising as are signs of left ventricular remodelling, but long-term follow-up is necessary.

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Introduction

Isolated native aortic regurgitation occurs in 8–13% of patients with valvular heart disease.[1,2] The combined pressure and volume overload of aortic regurgitation can cause left-ventricular systolic dysfunction. When symptoms develop, myocardial dysfunction mediated by fibrosis, diastolic dysfunction, and increased myocardial work is often present.[3–5] Surgical aortic-valve replacement remains the standard for treatment of aortic regurgitation,[6] and is associated with substantial survival benefit.[6,7] Nevertheless, only one in five patients with severe aortic regurgitation and left-ventricular ejection fraction (LVEF) of 30–50% are referred for surgical aortic-valve replacement, and only 3% of those with an LVEF below 30% are referred for surgical aortic-valve replacement.[2] Adverse consequences among symptomatic patients with aortic regurgitation are substantial and conservative management is associated with a 1-year mortality rate exceeding 20%.[8] Thus, a less invasive alternative to surgery is needed for patients at high risk of mortality and complications with surgical aortic valve replacement.

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Research in context

Evidence before this study

We searched MEDLINE and online contents of major interventional cardiology meetings (Transcatheter Cardiovascular Therapeutics, EuroPCR, and PCR London Valves) on Oct 7, 2023, with no date restrictions, for articles and presentations published in English, using the search terms "TAVI", "TAVR", and "pure aortic regurgitation". Registries, single-centre studies, and case reports show that existing commercial transcatheter aortic-valve implantation (TAVI) devices in the USA are not approved for patients with native aortic regurgitation and when used off-label are associated with unsatisfactory outcomes.

Added value of this study

The ALIGN-AR trial is the first, prospective pivotal study of transfemoral TAVI in patients with moderate-to-severe or severe aortic regurgitation at high risk for mortality and complications after surgical aortic valve replacement. Transfemoral TAVI with the dedicated transcatheter heart valve used in this study was effective in eliminating aortic regurgitation and showed excellent clinical outcomes with low complication rates. At 1 year, we observed substantial improvements in left-ventricular remodelling and functional status.

Implications of all the available evidence

Transfemoral TAVI is a well-established treatment option for patients with aortic stenosis. However, the use of commercially available transcatheter heart valve devices in patients with aortic regurgitation is difficult, related to challenges with valve anchoring in the native aortic annulus and paravalvular regurgitation. The ALIGN-AR study showed that these anatomical challenges can be largely overcome with a dedicated device with design features that enhance positioning and anchoring in patients with native aortic regurgitation.

Currently, there is no US Food and Drug Administration (FDA)-approved device for transcatheter treatment of native aortic regurgitation. Outcomes with off-label use of existing commercial transcatheter aortic valve implantation (TAVI) systems in this population remain suboptimal. The absence of leaflet calcification in pure aortic regurgitation can result in device malpositioning and inadequate annular sealing leading to valve embolisation rates exceeding 12% and moderate or greater paravalvular regurgitation rates of over 9%.[9,10]

The JenaValve Trilogy transcatheter heart valve (JenaValve Technology, Irvine, CA, USA) is designed specifically to address the challenges of TAVI for aortic regurgitation (figure 1). Three radiopaque locators are centred in the native aortic cusps and limit implant depth. Each of these locators clip onto the native leaflets, providing an anchoring mechanism, and also enhance the seal around the transcatheter heart valve (figure 1). The valve is tri-leaflet and uses porcine pericardial tissue sutured within a self-expanding, nitinol frame. The frame has three large open cells, 27–31 French (8·9–10·2 mm) in diameter, enabling coronary artery access after implantation (figure 1). This is the first report of the primary and secondary outcomes of patients enrolled in the ALIGN-AR trial with 1-year follow-up.

Methods

Study design and participants

The ALIGN-AR trial is an ongoing, single-arm, prospective, multicentre, US study enrolling patients with symptomatic and greater-than-moderate native valve aortic regurgitation deemed high risk for surgery by the enrolling site heart team, which included an interventional cardiologist and a cardiac surgeon. We enrolled patients at 20 US sites (appendix pp 1–2) with a planned 5-year follow-up. The design of the ALIGN-AR investigational device exemption trial and a complete list of inclusion and exclusion criteria are given in the appendix (pp 3–4), as well as the study protocol (pp 9–98).

Eligible patients were aged 18 years or older with New York Heart Association (NYHA) functional class II or higher symptoms and moderate-to-severe or severe native aortic regurgitation using the multiparametric approach defined by the American Society of Echocardiography (ASE).[11] An independent case review board (CRB), which included a cardiac surgeon, assessed all patients for eligibility. Sites reported adverse events and a clinical events committee or data safety and monitoring board adjudicated these according to Valve Academic Research Consortium-2 (VARC-2) criteria described in the clinical events committee charter (appendix pp 140–145).[12] The institutional review board of all participating sites approved the trial and all patients provided written informed consent.

Procedures

Pre-procedural evaluation

Patient assessment consisted of physical examination, medical history assessment, Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) and quality of life (Kansas City Cardiomyopathy Questionnaire [KCCQ]) scoring, echocardiographic and cardiac CT angiography assessments, NYHA functional classification, cardiac medications documentation, and standard blood testing.

Baseline cardiac CT angiography scans were assessed by an independent core laboratory (Cardiovascular Research Foundation, New York, NY, USA). Aortic regurgitation severity was assessed by both the site cardiologists and an independent echocardiographic core laboratory (Cardiovascular Research Foundation)

See Online for appendix

according to the ASE criteria.[11] Transthoracic echocardiogram was the primary imaging modality for aortic regurgitation assessment for most patients, but either transoesophageal echocardiography or cardiac MRI were permitted if necessary. Key anatomical exclusion criteria were congenital unicuspid or bicuspid valve morphology, previous prosthetic aortic valve implant, straight ascending aorta length less than 55 mm, aortic annulus angulation less than 70°, and severely reduced LVEF (<25%). CT angiography was used to assess iliofemoral arterial access.

Patients were considered high risk for surgical aortic valve replacement if the STS-PROM score was 8% or higher. If the STS-PROM score was lower than 8%, the Heart Team agreed that significant comorbidities were present and not captured by the STS-PROM risk model. Frailty assessments were ultimately at the discretion of the local Heart Team to support surgical risk identification as assessed by four standard parameters: grip strength, serum albumin, 5-m or 6-min walk test, and Katz activities of daily living score.[13,14]

Study device and implantation

The Trilogy transcatheter heart valve is available in three sizes (23 mm, 25 mm, and 27 mm) to treat annular aortic perimeters between 66 mm and 85 mm. During the study, less oversizing was recommended by the principal investigators, steering committee, and sponsor, and treatment of aortic annulus perimeters up to 90 mm was allowed to reduce oversizing (figure 1). The implantation technique has been detailed previously.[15] Briefly, the transcatheter heart valve is delivered through an 85-cm sheath with an outer diameter equivalent to standard 18 French sheaths. The sheath is placed at the sinotubular junction and the delivery system is advanced to the aortic root. After accurate placement of the locators is confirmed in all three native aortic cusps and the appropriate depth position is reached, the valve is deployed with rapid pacing at the operator's discretion. Clinical follow-up visits were scheduled at 30 days, 6 months, and 12 months, and annually up to 5 years.

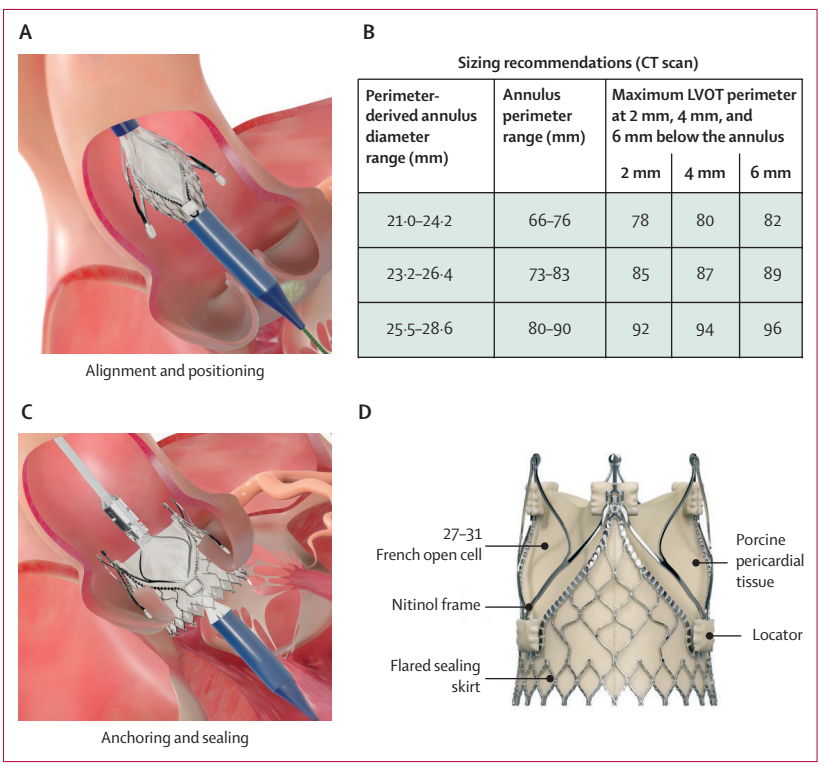
Post-procedural imaging

Haemodynamic assessments of the transcatheter heart valve were mean gradient, peak gradient, peak velocity, effective orifice area, and indexed effective orifice area. Chamber measurements including left-ventricular end-systolic diameter and volume, left-ventricular end-diastolic diameter and volume, LVEF, and left-ventricular mass were obtained at each follow-up. We analysed transvalvular and paravalvular regurgitation after implantation and at each follow-up.

Outcomes

The primary safety endpoint was a non-hierarchical composite consisting of all-cause mortality, any stroke, life-threatening or major bleeding, acute kidney injury stage 2–3 or dialysis (7-day endpoint), major vascular complications, surgery or intervention related to the device (including coronary intervention), new permanent pacemaker implantation, and moderate or severe total aortic regurgitation at 30-days after the procedure according to VARC-2 definitions. The clinical events committee adjudicated all site-reported adverse events for VARC-2 categorisation. The performance goal for the primary safety composite endpoint was 40·5%. There was no predicate clinical study investigating TAVI in aortic regurgitation. As such, we derived the safety endpoint from literature that was based on VARC-2 composites, rates of new permanent pacemakers, and transcatheter heart valve aortic regurgitation of moderate or greater as reported with TAVI for aortic stenosis. The literature-based VARC-2 composite was calculated from the weighted mean rates reported in the PORTICO IDE,[16] SOLVE-TAVR,[17] and REPRISE-III TAVI[18] trials, which included patients with high surgical risk and aortic stenosis (appendix p 7). We defined the non-inferiority margin as 1·35, as used in previous heart-valve clinical studies.

The performance goal for the primary efficacy endpoint of all-cause mortality at 1 year was 25%. The endpoint was developed and predicated on the assumption that the proportion of patients with NYHA III–IV disease was between 60% and 80%. A weighted average for the



Perimeter-derived annulus diameter range (mm)	Annulus perimeter range (mm)	Maximum LVOT perimeter at 2 mm, 4 mm, and 6 mm below the annulus		
		2 mm	4 mm	6 mm
21·0–24·2	66–76	78	80	82
23·2–26·4	73–83	85	87	89
25·5–28·6	80–90	92	94	96

Figure 1: **The JenaValve Trilogy transfemoral transcatheter heart valve**
(A) Alignment and positioning of the locators. (B) Sizing recommendations. (C) Anchoring and sealing of the valve with the native leaflets. (D) Attributes of the Trilogy valve. LVOT=left-ventricular outflow tract.

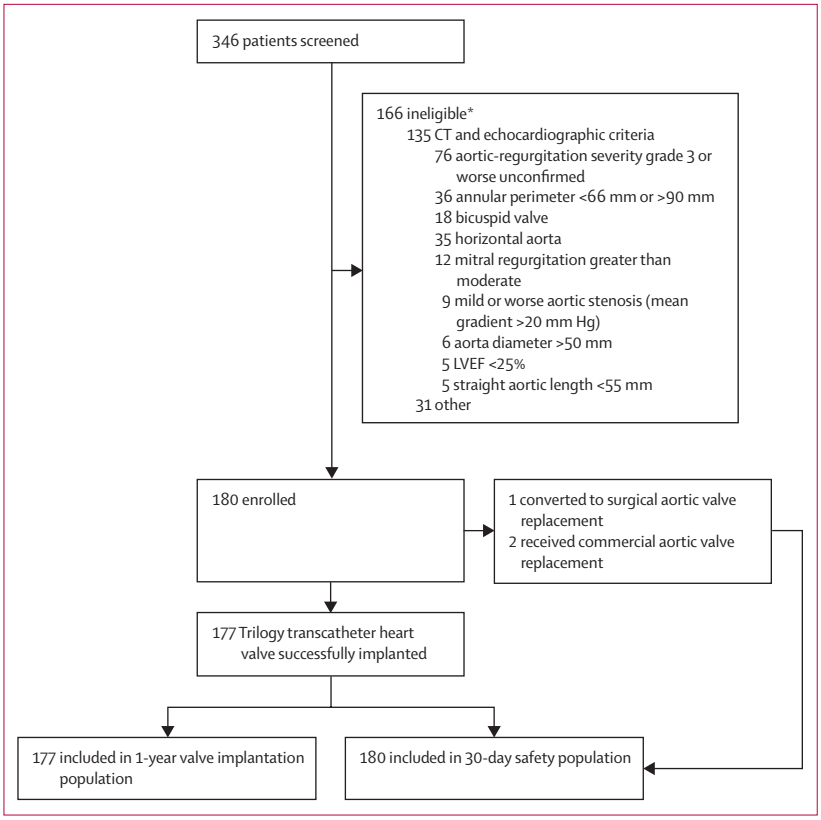


Figure 2: **Trial profile**
LVEF=left-ventricular ejection fraction. *Patients could have met multiple exclusion criteria.

all-cause mortality rate for patients with congestive heart failure or NYHA class III–IV was based on the studies in the appendix (p 8). More detailed data regarding the derivation of the performance goals for safety and efficacy are found in the appendix (pp 7–8). Hypothesis testing for non-inferiority compared the observed outcome with the performance goals for safety and efficacy using the binomial proportion test.

Secondary endpoints included technical success at time of exit from the OR, hybrid room or catheterisation laboratory defined as meeting all the following criteria: absence of procedural mortality, successful access, delivery, and retrieval of transcatheter delivery system, deployment and correct positioning of a single intended transcatheter heart valve, freedom from reintervention related to the device or access procedure. Other pre-specified secondary endpoints were moderate or greater aortic regurgitation at any timepoint after transcatheter heart valve implantation, KCCQ overall summary score, evidence of left-ventricular remodelling by echocardiography, NYHA class, and 6-min walk test at 1 year compared with baseline. All statistical analyses were done using SAS software (version 9.4). The trial is registered with ClinicalTrials.gov, NCT 04415047. The complete statistical analysis plan is available in the appendix (pp 99–126).

Statistical analysis

The primary hypothesis of this study was that TAVI is non-inferior compared with pre-specified performance goals. To achieve 80% power assuming a one-sided α of 0·025, we calculated that 171 evaluable participants would be needed. With an anticipated, combined loss-to-follow-up and unsuccessful deployment rate of 5%, the target enrolment was 180 patients. As stated in the statistical analysis plan (appendix p 117), an interim data assessment occurred when 139 (81%) participants completed 1-year follow-up and, as a result, the cutoff for statistical significance was p=0·0213. We summarised categorical variables by counts and percentages. All continuous variables values are reported as the mean (SD). We tested nominal variables with the Fisher–Freeman–Halton test and continuous variables with ANOVA.

Role of the funding source

The funder designed the trial in collaboration with the study executive committee and the FDA and was responsible for the selection of investigational sites, monitoring of the data, management of all source data, and statistical analyses.

Results

Between June 8, 2018, and Aug 29, 2022, we screened 346 patients. We excluded 166 patients and enrolled 180 patients (figure 2). The mean age of the study population was 75·5 (SD 10·8) years (median 78 years [IQR 69–73]), and 85 (47%) were female, 95 (53%) were male, and 131 (73%) were White (table 1). The mean STS-PROM score was 4·1% (SD 3·4; table 1). 161 (89%) patients were deemed to be at high risk by the heart team on the basis of comorbidities that are not captured by the existing STS-PROM risk-score model. Frailty parameters were not systematically collected in the screening process; however, 61 (34%) patients were deemed to have frailty by the local Heart Team, which established their high surgical-risk profile. Furthermore, we calculated the reported STS-PROM score for isolated aortic valve replacement for the ten (5·6%) patients requiring combined surgical procedures with increased surgical risk, such as coronary bypass grafting or mitral valve surgery.[10] These patients underwent staged percutaneous procedures instead.

All patients were symptomatic, with 122 (68%) patients having NYHA functional class III–IV disease (table 1). A pre-existing pacemaker was present in 30 (16%) patients. 78 (43·3%) patients had pre-existing conduction disease: right bundle branch block (19 [11%]), left bundle branch block (13 [7%]), prolonged PR interval (18 [10%]), and atrial fibrillation (72 [41%]; table 1). The mean aortic annulus perimeter was 79·1 mm (SD 6·1) and the mean area was 484·6 mm² (81·8). Aortic regurgitation severity was classified by the core laboratory as moderate to severe in 57 (32%) patients and severe in 116 (64%) patients.

	Patients (n=180)
Age, years	75·5 (10·8)
Sex	
Male	95 (53%)
Female	85 (47%)
Race or ethnicity	
White	131 (73%)
Black	19 (11%)
Asian	13 (7%)
Native American or Alaskan	1 (0.6%)
Unknown	16 (9%)
BMI, kg/m²	25·3 (6·1)
<20 kg/m²	25 (14%)
>40 kg/m²	6 (3%)
STS-PROM score	4·1% (3·4)
Assessed as frail by heart team	64 (34%)
Albumin <3·5 g/dL	18 (10%)
5-m walk test >6 s or 6-min walk test <250 m	103 (57%)
Grip strength below threshold	38 (21%)
NYHA class III–IV	122 (68%)
Hypertension	149 (83%)
Diabetes (any type)	26 (14%)
Vascular and other comorbidities	
History of atrial fibrillation	72 (40%)
COPD (any)	32 (18%)
Previous endocarditis	21 (12%)
Renal insufficiency	58 (33%)
Permanent pacemaker	30 (16%)
Left bundle branch block	13 (7%)
Right bundle branch block	19 (11%)
Previous percutaneous coronary intervention	37 (23%)
Previous coronary artery bypass graft surgery	20 (12%)
Previous stroke	19 (11%)
Peripheral vascular disease	21 (12%)

(Table 1 continues in next column)

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	Patients (n=180)
Echocardiographic and CT angiographic characteristics	
Core laboratory aortic regurgitation severity	
Severe	116 (64%)
Moderate to severe	57 (32%)
Moderate	5 (3%)
Not evaluable	2 (1%)
Vena contracta width, cm	0·6 (0·6–0·7)
Regurgitant fraction >50%	75 (42%)
Prominent holodiastolic flow reversal	84 (47%)
Effective regurgitant orifice area ≥0·30 cm²	68 (38%)
Pressure half-time, ms	417 (138)
Mean aortic valve gradient, mm Hg	8·7 (6·6)
Aortic valve regurgitant fraction by proximal isovelocity surface area	55·3% (12·9)
Aortic valve regurgitant volume by proximal isovelocity surface area, mL	55·5 (17·2)
Left-ventricular end systolic diameter, mm	39·6 (10·2)
Left-ventricular end systolic volume, mL	70·6 (38·9)
Left-ventricular ejection fraction, %	53·8% (11·4)
Left-ventricular mass Index, g/m²	172·7 (61·8)
CT annulus perimeter, mm	79·1 (6·1)
CT annulus area, mm²	484·6 (81·8)
CT maximum ascending aorta diameter, mm	37·3 (5·0)
CT sinus of Valsalva diameter, mm	
Right	33·5 (4·2)
Left	35·4 (4·1)
Non-coronary	35·1 (4·6)

Data are n (%), mean (SD), or median (IQR). NYHA=New York Heart Association. STS-PROM=Society of Thoracic Surgeons Predicted Risk of Mortality.

Table 1: **Baseline characteristics**

We used general anaesthesia in 164 (91%) patients and the remaining 16 (9%) patients were treated with monitored anaesthesia care. Technical success using a single Trilogy transcatheter heart valve implanted in the appropriate position via transfemoral access without access site intervention was achieved in 171 (95%) patients. A Trilogy transcatheter heart valve was not implanted in three patients; two patients had valve embolisation and one had a catheter-induced aortic dissection before transcatheter heart valve insertion that was treated with an aortic endograft followed by a commercial transcatheter heart valve, without an attempt at implantation of the Trilogy transcatheter heart valve. Four valve embolisations occurred in total. In two of these patients, the embolised valves were placed in the descending aorta followed by successful implantation of a second Trilogy transcatheter heart valve. In the other two patients, one was treated with a commercial transcatheter heart valve and one with a surgical aortic valve replacement. The delivery system was successfully retrieved in all cases. The sizes of the implanted Trilogy transcatheter heart valve were 23 mm (40 [23%] patients), 25 mm (35 [20%]), and 27 mm (102 [58%]). Overall mean oversizing was 14·3% (SD 5·4). After changes in the sizing algorithm after approximately two-thirds of enrolment was completed, mean oversizing decreased from 15·1% (5·6) for the first 120 (67%) patients to 12·7% (4·9) for the final 60 (33%) patients (p=0·0053). Stratifying by valve size, mean oversizing was 12·6% (SD 4·9%) for the 27-mm valve, 15·4% (SD 4·9%) for the 25-mm valve, and 17·7% (SD 5·5%) for the 23-mm valve. Post-dilatation was performed in seven (4%) patients. We found no cases of coronary occlusion or annular rupture. The mean time from sheath insertion to transcatheter heart valve deployment was 20·7 min (SD 15·2) and the mean total procedure time was 71·8 min (SD 24·9).

For the primary safety endpoint, four (2%) deaths occurred at 30 days (table 2). Two (1%) disabling and two (1%) non-disabling strokes occurred (table 2). Permanent pacemaker implantation was required in 36 (24%) of 150 patients without a previous pacemaker

(table 2). Of these, new biventricular resynchronisation devices were implanted in eight patients and one upgrade of a pre-existing pacemaker was performed. Comparing the approximately two-thirds of patients enrolled before the sizing algorithm changed with the final third of patients enrolled afterwards, the permanent pacemaker implantation rate for patients without a previous permanent pacemaker was 29·0% (29/100) for the initial two-thirds and 14·0% (7/50) for the final third (p=0·043). A component of the safety endpoint occurred in 48 (27%) patients, achieving non-inferiority when compared with the pre-specified safety performance goal of 40·5% (97·5% CI 19·2–34·0; $p_{non\text{-}inferiority}$<0·0001). At 1 year, the primary efficacy endpoint, all-cause mortality, occurred in 11 (6·2% [97·5% CI 2·2–10·3]; $p_{non\text{-}inferiority}$<0·0001) of 177 patients among the pre-specified group who received successful valve implantation and in 14 (7·8% [3·3–12·3]; $p_{non\text{-}inferiority}$<0·0001) of all 180 patients, achieving the pre-specified efficacy performance goal of 25%.

	Patients (n=180)
Death	4 (2%)
Any stroke	4 (2%)
Disabling stroke	2 (1%)
Non-disabling stroke	2 (1%)
Major or life-threatening bleeding	8 (4%)
Major vascular complication	7 (4%)
Acute kidney injury stage 2 or 3 or dialysis (7 days)	2 (1%)
Surgery or intervention related to the device	5 (3%)
Aortic Endograft and Commercial THV for aortic dissection	1 (<1%)
Surgical aortic valve replacement for Trilogy transcatheter heart valve embolisation	1 (<1%)
Commercial transcatheter heart valve for Trilogy transcatheter heart valve embolisation	1 (<1%)
Trilogy transcatheter heart valve for Trilogy transcatheter heart valve embolisation	2 (1%)
New pacemaker implantation	36/150 (24%)*
Moderate or greater aortic regurgitation	1 (<1%)
Total	48 (27%)

Data are n (%) or n/N (%). *30 patients had a previous pacemaker.

Table 2: **Primary safety endpoint at 30 days**

Key echocardiographic parameters at screening and follow-up are listed in table 3. Paravalvular regurgitation at 1 year was none or trace in 130 (92%) patients. Mild or mild-to-moderate paravalvular regurgitation declined from 31 (19%) patients at 30 days to 11 (8%) at 1 year. Moderate paravalvular regurgitation was present in one patient at 30 days that was mild at 1 year. Paired analyses showed evidence of left-ventricular remodelling (table 3). Mean left-ventricular mass declined from 323·7 g (SD 123·4) at baseline to 219·5 g (SD 101·4; p<0·0001) at 1 year and mean left-ventricular end-systolic dimension decreased from 39·6 cm (SD 10·2) at baseline to 34·2 cm (SD 9·0; p<0·0001) at 1 year (table 3).

At 30 days, NYHA functional class status was class I in 91 (51%) of 180 patients, class II in 62 (34%) patients, and class III in 17 (9%) patients (figure 3). At 1 year, 90 (50%) patients were class I and 48 (27%) patients were class II (figure 3). NYHA functional class improved by at least one category in 125 (83%) patients. From baseline to 1-year follow-up, the mean KCCQ overall score increased by 20·6 points (SD 24·3) from a mean of 55·3 (27·1) to 77·6 (22·7; p<0·0001; figure 3). Of 151 respondents, the number of patients alive at 1 year (KCCQ overall score ≥60 without a decrease of 10) was 109 (71%), and the proportion who felt worse (≥5 point decline from baseline) was 16 (11%; table 4). The number of patients with a KCCQ overall score of at least 75 was 88 (63%). We found an increase in 6-min walk test distance and 62 (48%) patients had an improvement of at least 15 m from screening to 1 year (figure 3).

Discussion

The key findings of the ALIGN-AR trial are that TAVI using a dedicated transfemoral system in patients with symptomatic severe aortic regurgitation at high risk for surgical mortality and complications is associated with (1) low rates of 30-day and 1-year mortality; (2) a composite safety event rate that was non-inferior to rates in TAVI performed for aortic stenosis; (3) significant and sustained improvement in functional status and patient-reported outcomes; (4) improvements in left-ventricular

	Baseline (n=180)	30 days (n=172)	6 months (n=154)	1 year (n=141)
Left-ventricular end systolic dimension, mm	39·6 (10·2)	37·4 (10·2)	34·7 (9·4)	34·2 (9·0)
Left-ventricular end systolic dimension index, mm/m²	22·8 (6·5)	21·3 (6·0)	19·0 (5·6)	19·3 (5·2)
Left-ventricular end systolic volume, mL	70·6 (38·9)	67·3 (41·0)	59·0 (39·2)	52·1 (39·8)
Left-ventricular end diastolic volume, mL	144·8 (56·6)	132·6 (83·1)	115·9 (50·3)	109·9 (50·1)
Left-ventricular mass, g	323·7 (123·4)	254·3 (109·0)	235·1 (95·4)	219·5 (101·4)
Left-ventricular mass index, g/m²	172·7 (61·8)	133·8 (48·1)	126·8 (46·9)	117·5 (47·1)
Mean gradient, mm Hg	8·7 (6·6)	3·9 (1·6)	4·3 (2·0)	4·3 (1·8)
Effective orifice area, cm²	..	2·9 (0·6)	2·7 (0·6)	2·8 (0·6)
Effective orifice area index, cm²/m²	..	1·7 (0·4)	1·5 (0·4)	1·6 (0·3)
Left ventricular ejection fraction, %	53·8 (11·4)	49·7(12·6)	51·9 (12·0)	55·0 (11·6)

Data are mean (SD).

Table 3: **Left-ventricular dimensions and valve haemodynamic outcomes**

remodelling; (5) excellent valve haemodynamics with a large effective orifice area, low mean gradients, and minimal paravalvular regurgitation; and (6) high permanent pacemaker rates that declined during the course of the trial.

The rates of mortality and major periprocedural complications in the ALIGN-AR trial are promising and provide the foundation for a percutaneous treatment option for patients with aortic regurgitation at high surgical risk. The 30-day mortality of 2·2% observed in this population compares favourably with the predicted mortality of 4·1% based on the STS-PROM score. In a contemporary study,[10] the in-hospital mortality rate with off-label TAVI was 5·0%, and 30-day mortality is reported to range from 7% to 14%.[9,19–21] In the ALIGN-AR trial, TAVI resulted in substantial improvement of heart failure symptoms, with 50% of patients with NYHA class-I disease at 1 year. Comparatively, off-label TAVI studies report less than 20% of patients with NYHA functional class-I disease at 30 days.[21]

The technical success rate observed in this study was 95%, which compares favourably with off-label TAVI for pure aortic regurgitation. The technical success rate of off-label TAVI for aortic regurgitation is estimated to be 74–86%, and failure is mainly due to device migration and embolisation.[10,19,20] Mortality is reportedly 25% when valve embolisation occurs.[10] The design features of the transcatheter heart valve used in this study provide a solution to the procedural and anatomical challenges that have been observed with off-label TAVI for aortic regurgitation. Insufficient anchoring not only leads to device embolisation but also predisposes to incomplete seal, leading to substantial paravalvular regurgitation. The locators on this transcatheter heart-valve frame allow fixation of the native leaflets to the prosthesis, incorporating them into the sealing mechanism, thereby reducing paravalvular regurgitation. Only one patient in follow-up had moderate paravalvular leak, comparing favourably with the 9·5% observed with off-label TAVI in patients with aortic regurgitation.[10]

The rate of new permanent pacemaker implantation was 24·0%, and is similar to rates reported for off-label TAVI in aortic regurgitation (22·3%)[10,19] and higher than reported in patients undergoing surgical aortic-valve replacement for pure aortic regurgitation (160 [11·5%] of 1390).[22] The prevalence of atrial fibrillation, a risk factor of permanent pacemaker implantation in TAVI, was high (40·0%) in this study, signifying the cardiac damage engendered by regurgitant disease.[23] The prevalence of conduction disorders, specifically right bundle branch block, was not higher than in TAVI for aortic stenosis;[24] however, 58% of patients with right bundle branch block required a permanent pacemaker compared with approximately 38% in aortic stenosis.[24]

The reduction in the rate of patients requiring a new pacemaker during the trial can be attributed to two hypotheses that require further validation. First, the initial sizing algorithm was adapted from studies of TAVI in patients with aortic stenosis and used associated oversizing thresholds. Although aggressive oversizing was thought to improve anchoring and seal, this method also probably resulted in increased interaction with the conduction system, particularly in anatomy unconstrained by calcification. Transcatheter heart-valve sizing was empirically reduced and average oversizing decreased over the course of the trial. Second, the implantation technique was modified to limit implant depth. Initially, the delivery system was advanced until all

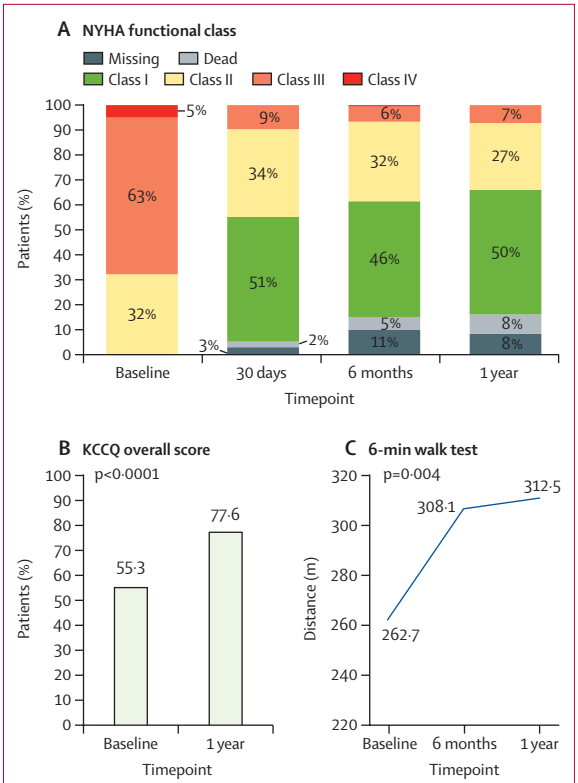

Figure 3: **Functional outcomes**
(A) NYHA functional class. (B) KCCQ overall score. (C) 6-min walk test. KCCQ=Kansas City Cardomyopathy Questionnaire. NYHA=New York Heart Association.

	Patients (n=152)
Large improvement (≥20-point increase)	63 (41%)
Moderate improvement (increase between 10 and <20 points)	24 (16%)
Small improvement (increase between 5 and <10 points)	11 (7%)
No change (change between –5 and <5 points)	27 (18%)
Worse (>5-point decrease from baseline)	16 (11%)
Dead	11 (7%)

Data are n (%).

Table 4: **Kansas City Cardiomyopathy Questionnaire quality-of-life outcomes comparing baseline with 1 year**

three locators reached the nadir of the coronary cusps. Later in the trial the implant depth was reduced by aligning the sealing ring approximately 5 mm below the aortic annulus. Temporally related to these changes, rates of new pacemaker implantation were noted to decline in the final third of enrolled patients in the trial.

The haemodynamic outcomes of the transcatheter heart valve were excellent, with a 30-day mean effective orifice area of 2·9 cm² and mean gradient of 3·9 mm Hg, comparing favourably with TAVI devices for aortic stenosis, where mean effective orifice area was 1·66 cm² and mean gradient was 11·2 mm Hg with Sapien 3 (Edwards Life Sciences; Irvine, CA, USA) and mean effective orifice area was 2·01 cm² and mean gradient was 7·5 mm Hg with Evolut R (Medtronic; Minneapolis, MN, USA).[25] The absence of calcification of the aortic annulus, leaflets, and left-ventricular outflow tract in aortic regurgitation might minimise transcatheter heart-valve constraint, resulting in improved haemodynamic performance. Future studies comparing valve haemodynamics with aortic stenosis and aortic regurgitation are needed to address this question. Patients with aortic regurgitation often have dilated aortic roots and annuli and, in this study, the largest valve was implanted in 58% of patients. However, mean gradients were similar across all valve sizes suggesting that the excellent haemodynamics are largely a function of prothesis design and not simply the distribution of valve sizing.

In our cohort, the mean STS-PROM score was 4·1%. This score is lower than that reported in the very first high-risk TAVI studies in patients with aortic stenosis, but similar to contemporary high-risk aortic stenosis studies and registries assessing off-label TAVI for patients with aortic regurgitation and compassionate-use assessments for TAVI in aortic regurgitation.[26] The STS-PROM risk-score model is widely used to predict operative risk and to aid medical decision making and patient counselling; however, the score does have limitations. First, the STS-PROM risk model is periodically updated to reflect the contemporary population and surgical outcomes. The current STS-PROM risk model's mean PROM and cutoff value for high risk are both lower than those of the 2008 model (mean PROM difference –1·0% [SD 1·8] and cutoff for high risk 6·3%).[27] Second, the average age of this cohort is approximately 10 years younger than those enrolled in the studies of high-risk TAVI in aortic stenosis. Although age plays an important role in the risk adjudication of the existing STS-PROM calculator, the patients enrolled in this study were still determined to be at high risk by their heart teams on the basis of several clinical factors unaccounted for in the current STS-PROM risk-score model. Third, the STS-PROM score was based on isolated aortic-valve replacement, regardless of whether or not patients had multi-valvular or associated coronary artery disease that was frequently treated percutaneously before study enrolment. These factors include conditions such as pulmonary hypertension, frailty, hostile chest, home oxygen requirement, and cirrhosis. Importantly, despite substantial comorbidities, the procedure-related mortality and morbidity observed in this study compared favourably with the predicted outcomes based on STS-PROM score.

Limitations of this study should be noted. First, this was a single-arm, non-blinded, and non-randomised study. As such, the findings were not compared with a control group but with a pre-specified performance goal. Second, since this study represents the first use of this transfemoral TAVI system in aortic regurgitation, the early experiences resulted in several changes, including anatomical exclusions, sizing algorithm, and implantation technique during the course of the study. Third, our analysis focuses on early outcomes and longer-term follow-up is needed. Extended studies will be required to better understand longer-term clinical outcomes and transcatheter heart-valve function over time, as well as predictors of left-ventricular remodelling.

In conclusion, in this study examining transfemoral TAVI for pure aortic regurgitation in patients at high surgical risk in the USA, the Trilogy transcatheter heart valve showed a high technical success rate and promising safety profile as well as low morbidity and mortality at 1-year follow-up. Additionally, this transcatheter heart valve provided favourable haemodynamics, with low mean gradients and paravalvular leak rates and significant clinical improvement. We also found substantial improvements in patient-reported outcomes and left-ventricular remodelling. Further investigations are needed to reduce rates of permanent pacemakers and to assess the outcomes and the role of this therapeutic option in a broader population of patients.

Contributors

The principal investigators (VHT, TPV, and MBL) had unrestricted access to the data and had final responsibility for the decision to submit for publication. TPV, VHT, and MBL contributed to the conceptualisation, methodology, design, supervision, and implementation of the trial. TPV, VHT, LSR, MBL, and DSP wrote the first draft of the manuscript. TPV, VHT, MBL, and DSP participated in data curation and data verification. All coauthors provided substantial contributions to the investigation, acquisition of data, critically reviewed the manuscript for important intellectual content, provided final approval of the version to be published, and agree to be accountable for the all aspects of the work presented.

Declaration of interests

TPV reports institutional funding to Columbia University Irving Medical Center from JenaValve Technology, Abbott Vascular, Boston Scientific, Edwards Lifesciences, and Medtronic; and he personally received consulting fees from 4C Medical and Philips. OKK reports that he is part of a core laboratory contracting with JenaValve Technology but he has not received any direct compensation; he further reports consulting fees from Edwards Lifesciences, VDyne, Siemens, Philips, Laralab, and Restore Medical. NH reports that she is part of a core laboratory contracting with JenaValve Technology but she has not received any direct compensation. JMM reports consulting fees and honoraria from Edwards Lifesciences, Medtronic, Abbott, Shockwave, and Equity in Excision Medical, and Conkay Medical. IG reports consulting fees from Edwards Lifesciences, Medtronic, Boston Scientific, Abbott SJM, and Atricure. SKK reports consultant fees (honoraria) from Admedus, Meril Lifesciences, JenaValve Technology, and Abbott Vascular; scientific advisory board participation (equity) with Dura Biotech,

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Data sharing

The data collected for this study will not be made available to others without approval from the sponsor and study chairman. Access can be requested through JenaValve Technology.

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