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Final 5-year clinical and echocardiographic results for treatment of severe aortic stenosis with a self-expanding bioprosthesis from the ADVANCE Study

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Aims The ADVANCE study was designed to evaluate the safety and effectiveness of transcatheter aortic valve implantation (TAVI) with a self-expanding bioprosthesis in real-world patients with symptomatic, severe aortic stenosis at high surgical risk for valve replacement.

Methods and results Study participants were enrolled from 44 experienced centres in 12 countries. Patient eligibility, treatment approach, and choice of anaesthesia were determined by the local Heart Team. The study was 100% monitored, and adverse events were adjudicated by an independent clinical events committee using Valve Academic Research Consortium (VARC-1) criteria. There were 1015 patients enrolled with 996 attempted TAVI procedures. Mean age was 81 years, and mean logistic EuroSCORE was 19.3 ± 12.3%. Five-year follow-up was available on 465 (46.7%) patients. At 5 years, the rate of all-cause mortality was 50.7% (95% confidence interval: 46.7%, 54.5%), and the rate of major stroke was 5.4%. Haemodynamic measures remained consistent for paired patients with a mean aortic valve gradient of 8.8 ± 4.4 mmHg ($n = 198$) and an effective orifice area of 1.7 ± 0.4 cm^2 ($n = 123$). Aortic regurgitation (AR) decreased over time and among paired patients dropped from 12.8% to 8.0% moderate AR at 5 years ($n = 125$). Of the 860 patients with echocardiographic data or a reintervention after 30 days, there were 22 (2.6%) patients meeting the VARC-2 criteria for valve dysfunction and 10 (1.2%) patients with a reintervention >30 days.

Conclusion Five-year results in real-world, elderly, high-risk patients undergoing TAVI with a self-expanding bioprosthesis provided evidence for continued valve durability with low rates of reinterventions and haemodynamic valve dysfunction.

Trial registration ClinicalTrials.gov, NCT01074658.

Keywords Transcatheter aortic valve implantation • Aortic valve durability • CoreValve • Aortic stenosis

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Introduction

Short-term safety and efficacy of transcatheter aortic valve implantation (TAVI) in symptomatic severe aortic stenosis patients at high and extreme risk for surgery has been established in several prospective clinical trials.[1–4] More recently, TAVI has been shown to be non-inferior to surgical valve replacement in symptomatic patients, deemed intermediate risk for surgical intervention,[5,6] and data from one randomized, clinical trial have demonstrated similar safety and efficacy to surgery in low-risk patients with symptomatic severe aortic stenosis.[7] As adoption of TAVI expands into younger and lower risk patients, longer term clinical outcomes and bioprosthetic valve durability are of increasing importance. Although clinical outcomes through 3 to 5 years from multiple randomized clinical trials[8–10] provide evidence for the safety of TAVI in higher risk patients, questions regarding bioprosthetic valve durability remain a concern.[11–13]

The CoreValve ADVANCE study is a prospective, global multicentre observational clinical study that evaluated the self-expanding CoreValve bioprosthesis for TAVI in a real-world population. Unlike other large registries that may have under-reported adverse events, the ADVANCE study was fully monitored, and all events were independently adjudicated. Complete 5-year clinical and echocardiographic data are now available. Additional *post hoc* analyses were conducted to evaluate bioprosthetic valve durability through 5 years and factors impacting mortality.

Methods

Patients and study design

Patient selection and design of the ADVANCE study have been previously described.[14] Briefly, ADVANCE is a global, prospective, non-randomized, multicentre clinical study that enrolled real-world patients with symptomatic, severe aortic valve stenosis suitable for TAVI. Participants were enrolled at 44 centres from 12 countries; all centres were required to have TAVI experience of at least 40 cases. Each centre was also required to have a Heart Team comprised of at least one TAVI-experienced interventional cardiologist and one cardiothoracic surgeon to evaluate patient suitability for TAVI. The ADVANCE study complied with the Declaration of Helsinki, with approval of the research protocol from all locally appointed ethics committees, and informed consent was obtained from all patients or their legally authorized representative. Description of the CoreValve bioprosthesis and corresponding implant details have been presented previously.[15,16] CoreValve sizes of 26 and 29 mm were available during the ADVANCE study to treat aortic valve annulus sizes from 20 mm to 27 mm. Each centre's Heart Team determined the access route (iliofemoral, direct aortic, or subclavian) and type of anaesthesia (general or conscious sedation) for each patient. Follow-up visits were scheduled at 30 days and then annually up to 5 years.

The primary endpoint of the ADVANCE study was major adverse cardiac and cerebrovascular events at 30 days post-procedure, defined as a composite of all-cause mortality, myocardial infarction, stroke, or reintervention. Additional clinical endpoints included cardiovascular mortality, vascular complications, major and minor stroke, and new pacemaker implantation. The study was fully monitored, and adverse events were adjudicated by an independent clinical events committee comprised of interventional cardiologists and cardiac surgeons using definitions from Valve Academic Research Consortium (VARC-1).[17] The committee reviewed patient source data as well as assessments from an independent neurologist to adjudicate all events.

Echocardiographic analysis

Echocardiographic data are reported by each investigative centre. Mean gradient; effective orifice area (EOA); and total and paravalvular aortic regurgitation (AR) data at baseline, discharge, 1 month, and annually to 5 years were analysed.

Prosthetic valve durability analysis

Prosthetic valve durability was assessed *post hoc* using echocardiographic data and VARC-2 definitions.[18] This analysis used the last available echo post 30 days after implantation or the last echo before a reintervention greater than 30 days post-procedure; only patients who had an echo in at least one of these categories were included in the analysis. Surgical criteria for aortic valve stenosis was defined as a greater than 50% increase of mean gradient from 1 month to 5 years.[19] VARC-2 criteria for aortic valve stenosis was defined as: [(aortic valve mean gradient ≥20 mmHg or peak velocity ≥3 m/s) and (EOA ≤0.9 cm^2 if body surface area is <1.6 or ≤1.1 cm^2 if body surface area is ≥1.6)] or moderate to severe total AR.[18] Structural aortic valve deterioration, defined as valve dysfunction or deterioration, exclusive of infection or thrombosis, as determined by reoperation, autopsy, or clinical investigation was also collected during the study. Specifically, this included changes intrinsic to the valve, such as wear, fracture, calcification, leaflet tear, stent creep, or suture line disruption of components of a trial valve as site reported.

Statistical analysis

Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as the number and percentage. Clinical outcomes were calculated using Kaplan–Meier survival analysis, and freedom from mortality curves were also generated using Kaplan–Meier methods. The log-rank test was used to test for differences across and between groups. For subjects without an event, the date of censoring was the latest date of all follow-up visits (including study exit) and events (including death). Predictors of mortality at 5 years were evaluated using univariable and stepwise multivariable Cox regression models with an entry *P*-value of 0.1 and a stay *P*-value of 0.05. Hazard ratios with two-sided 95% confidence interval (CIs) were calculated. All tests were two sided. All analyses were performed using SAS software (Cary, NC, USA), version 9.2 or above.

Results

Patient and procedural characteristics

Baseline characteristics and procedural data for patients enrolled in ADVANCE have been described previously.[14] In brief, from March 2010 to July 2011, 1015 patients were enrolled and TAVI procedures were attempted in 996 patients; 49.3% of patients were male, mean age was 81 years, 80.0% were in NYHA Class III or IV, the mean STS score was 6.4 ± 4.4%, and the mean logistic EuroSCORE was 19.3 ± 12.3%. Additional baseline characteristics can be found in Supplementary material online, *Table S1*. For TAVI procedures, iliofemoral access was used in 88.4% of patients, subclavian access in 9.5% and 2.1% had direct aortic access.[14] Balloon valvuloplasty was performed pre-procedure in 91.0% of patients and post-procedure in 23.6%.[14] Five-year follow-up is available for 465 of 506 (91.9%) patients with attempted implant. There were 25 patient withdrawals,

Table 1 Clinical outcomes at 1 and 5 years ($n = 996$)

	1 Year		5 Years	
	% (*n*)	95% CI	% (*n*)	95% CI
All-cause mortality[a]	17.6 (174)	[15.3, 20.1]	50.7 (489)	[46.7%, 54.5%]
Cardiovascular mortality	11.6 (112)	[9.7, 13.8]	33.5 (289)	[29.3%, 37.8%]
All-cause mortality or major stroke	18.1 (179)	[15.8, 20.6]	51.8 (501)	[47.9%, 55.6%]
Stroke[a]	4.4 (42)	[3.2, 6.0]	10.2 (78)	[7.2%, 13.7%]
Major stroke	2.1 (20)	[1.3, 3.3]	5.4 (41)	[3.3%, 8.2%]
Minor stroke	2.3 (22)	[1.4, 3.5]	5.3 (40)	[3.2%, 8.1%]
Transient ischaemic attack	1.7 (15)	[0.9, 2.7]	2.6 (21)	[1.2%, 4.8%]
Myocardial infarction[a]	0.9 (8)	[0.4, 1.8]	3.7 (27)	[2.0, 6.1]
New pacemaker implantation	29.1 (284)	[26.0, 32.3]	33.7 (312)	[28.4, 39.0]
Emergent cardiac surgery or percutaneous reintervention[a]	1.6 (15)	[0.9, 2.6]	2.8 (23)	[1.4, 5.0]
Acute kidney injury (all 3 stages)	6.6 (64)	[5.0, 8.4]	10.1 (87)	[7.1, 13.6]
Life-threatening or disabling bleeding	4.9 (48)	[3.6, 6.5]	6.2 (57)	[3.9, 9.2]
Structural valve deterioration[b]	0.2 (2)	[0.0, 0.8]	0.9 (6)	[0.2, 2.5]
Major adverse cardiac and cerebrovascular events	21.0 (208)	[18.5, 23.6]	55.8 (541)	[51.9, 59.5]

Data presented as Kaplan–Meier estimates of outcomes in the attempted implant study cohort.
[a]Components which comprise major adverse cardiac and cerebrovascular events.
[b]Structural valve deterioration includes trial valve dysfunction or deterioration, exclusive of infection or thrombosis, as determined by reoperation, autopsy, or clinical investigation. The term refers to changes intrinsic to the valve, such as wear, fracture, calcification, leaflet tear, stent creep, or suture line disruption of components of a trial valve.

16 lost to follow-up and 490 patient deaths over 5 years (see Supplementary material online, *Figure S1*).

Clinical outcomes and predictors of mortality

Clinical outcomes at 1 and 5 years are shown in *Table 1*. At 5 years, the rate of all-cause mortality was 50.7%, all-cause mortality or major stroke was 51.8%, and cardiovascular mortality was 33.5% (*Figure 1A*). The rate of stroke at 5 years was 10.2% with approximately half ajudicated as major stroke (5.4%) (*Figure 1B*).

The rate of new pacemaker implantation within 30 days post-TAVI was 33.7% at 5 years but was not associated with an increase in mortality (*Figure 2A*). When rates of freedom from all-cause mortality were stratified by EuroSCORE the highest baseline EuroSCORE was associated with the worst survival through 5 years (*Figure 2B*). The impact of discharge AR is shown in *Figure 2C*. Moderate or severe AR was associated with the lowest survival (45.2% at 5 years). There also appears to be an impact of mild AR on mortality demonstrated only after 2 years with a rate of 50.7% at 5 years. NYHA classification for 320 patients who were assessed at all time points of baseline, 1 month, and annually to 5 years indicated a gradual increase in Class III symptoms during Years 3 through 5, but the majority of patients remained Class I or II (80.9%) (see Supplementary material online, *Figure S2*).

Multivariable predictors of mortality through 5 years are shown in *Figure 3*; complete univariable and multivariable predictors are found in Supplementary material online, *Table S2*. Multivariable predictors of mortality were age, presence of peripheral vascular disease, chronic obstructive lung disease, elevated serum creatinine, baseline left ventricular ejection fraction ≤50%, major bleeding and Stage 3 acute kidney injury. Higher baseline mean aortic valve gradient was associated with lower mortality.

Echocardiographic measures

Echo compliance decreased over time with a follow-up rate of 67% at Years 3 and 4 and 56% at 5 years. There were 125 patients with AR measurements at baseline and all follow-up time points (discharge, 1 month, and annually to 5 years). At 5 years, 40.8% of these paired patients had no AR, compared with 21.6% at discharge. Degree of moderate AR went from 12.8% at discharge to 8.0% at 5 years, and no patients had severe AR from discharge to 5 years, inclusively (*Figure 4A*). Similarly, *Figure 4B* shows AR for all patients, including a category for patients who were deceased or had a missed visit. Mean aortic valve effective orifice area and mean gradient from baseline to 5 years are shown in *Figure 5*. In patients with data at baseline and 5 years mean gradient dropped from 45.3 ± 15.9 at baseline to 9.8 ± 4.4 mmHg at discharge and 8.8 ± 4.4 mm Hg at 5 years ($n = 198$). Mean gradient measurements for all available patients vs. patients with echocardiographic follow-up at all time points are shown in Supplementary material online, *Table S3*. Mean EOA for paired patients was 0.8 ± 0.5 at baseline and 1.7 ± 0.4 cm^2 at 5 years ($n = 123$).

Prosthetic valve durability

The incidence of structural valve deterioration was site reported as 0.9% at 5 years. Additional *post hoc* analysis on durability of the CoreValve bioprosthesis was analysed in 860 patients (*Table 2*). Mean follow-up time was 36.0 ± 21.1 months, and 267 patients had follow-up through 5 years. There was a >50% increase in baseline mean gradient in 9.3% of patients and the rate of valve dysfunction per VARC-2 criteria was 2.6% ($n = 22$) at 5 years of follow-up. Two of the 22 patients meeting criteria for aortic valve stenosis also had a reintervention, 10 patients had a high mean gradient or peak velocity, 11 patients had moderate or severe AR, and 1 patient had a high mean gradient and peak velocity plus moderate AR (*Figure 6*).

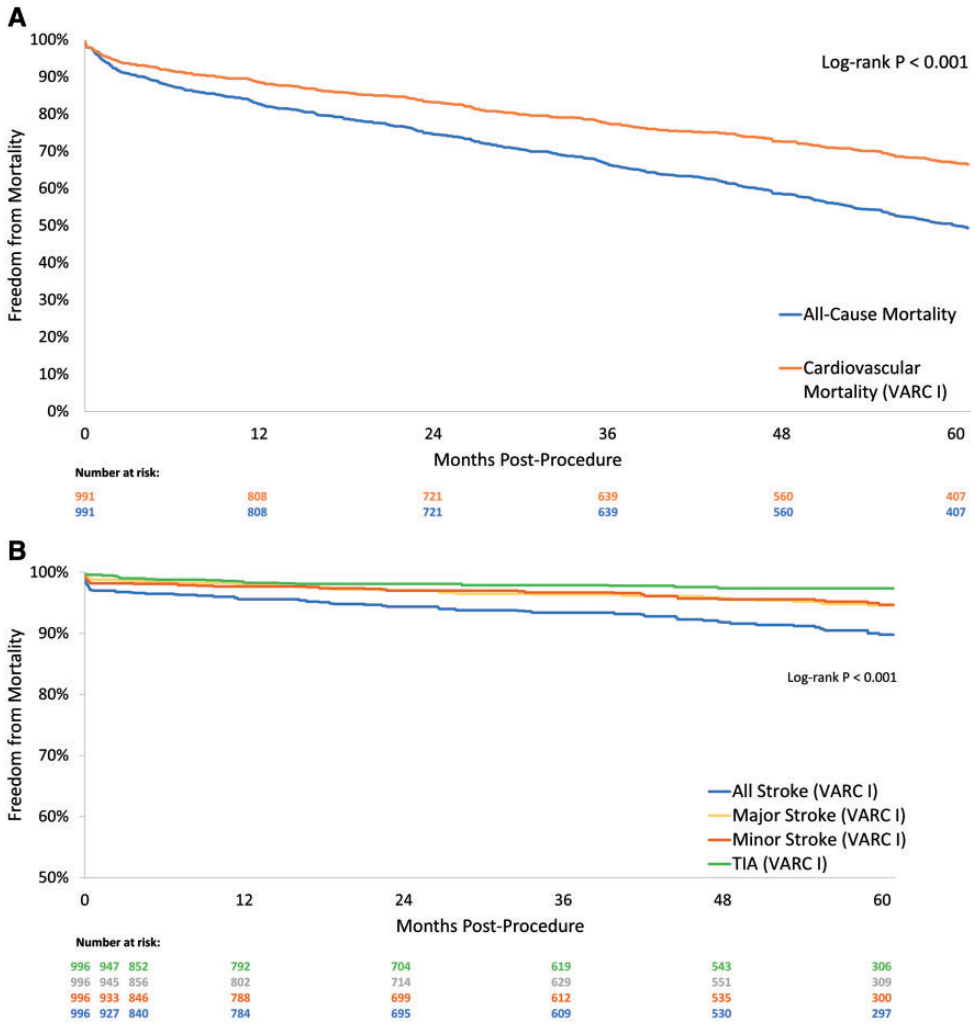

Figure 1 Kaplan–Meier time to event analyses for select clinical endpoints. (*A*) Freedom from all-cause mortality through 5 years; (*B*) Freedom from all stroke, major stroke, minor stroke, and transient ischaemic attacks per VARC-1 definitions.[16]

Ten (1.2%) patients had reinterventions after 30 days post-procedure, where 4 procedures were surgical reinterventions and 6 were percutaneous. For these 10 reinterventions, 2 were caused by prosthetic degeneration and subsequent aortic stenosis. Additional details on the patients and their reintervention procedures are found in Supplementary material online, *Table S4*.

Of the 996 patients, 1.8% (18 patients) were diagnosed with endocarditis, where 2 patients had 2 occurrences each of endocarditis. Thirty-five per cent of cases were related to the prosthetic valve and 4 cases occurred within 6 months of the procedure. Three patients died due to endocarditis.

Discussion

The CoreValve ADVANCE clinical study provides longer term data on a large, real-world international population of TAVI patients.[14,20,21] The 5-year results from ADVANCE continue to demonstrate the strong haemodynamic performance of the CoreValve bioprosthesis, as well as low rates of stroke, AR, and a 5-year mortality rate within the expected range for this elderly TAVI population.

As the first TAVI procedure was performed just 15 years ago, to date, there are only a few multicentre clinical studies with reported results from 5 years of follow-up.[9,13,22] All-cause mortality for patients in the CoreValve ADVANCE study was 50.7% (95% CI: 46.7%, 54.5%) at 5 years, similar to results described by Barbanti [55% (95% CI: 49–60%)][13] and Duncan (54.5%).[22] PARTNER 1, a randomized controlled trial of TAVI vs. surgical implantation, reported all-cause mortality of 67.8% at 5 years,[9] higher than ADVANCE, potentially due to differences in study design and baseline risk of enrolled patients (STS score of 10.7 ± 3.5% for PARTNER 1 vs. 6.4 ± 4.4% for ADVANCE). Likewise, cardiovascular mortality was 33.5% at 5 years in ADVANCE and 53.1% for PARTNER 1.[9] Barbanti *et al.*[13] reported

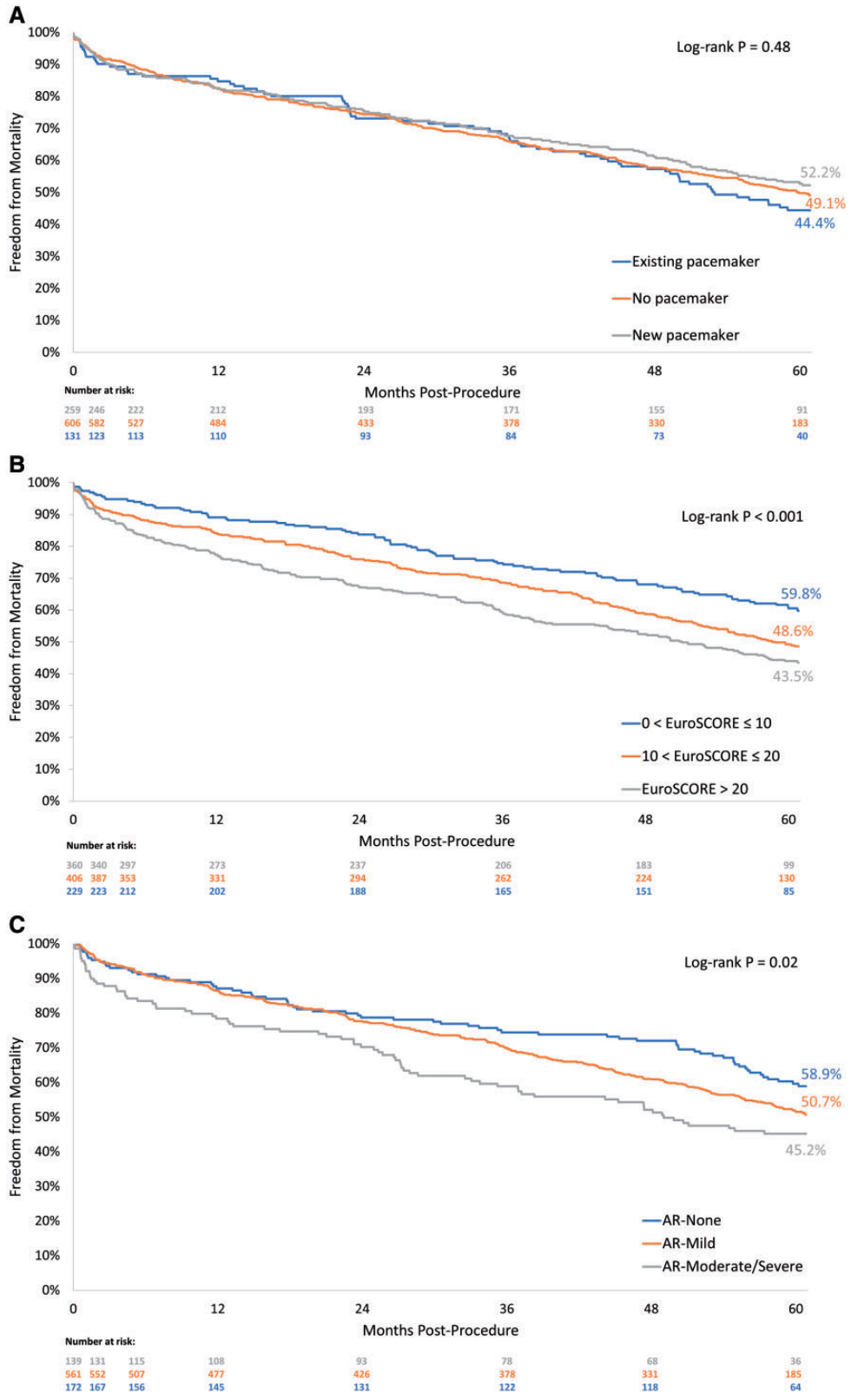

Figure 2 Kaplan–Meier time-to-event analyses for all-cause mortality stratified by: (*A*) the presence of an existing pacemaker prior to TAVI, the need for a new pacemaker, and no pacemaker; (*B*) logistic EuroSCORE (≤10%, >10–20%, and >20%); (*C*) aortic regurgitation (none, mild, and moderate or severe).

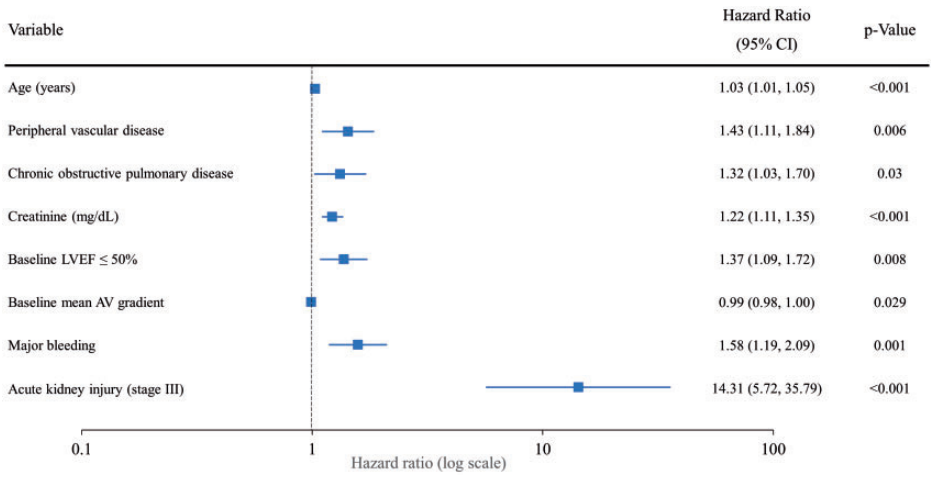

Figure 3 Forest plot for multivariable analysis of predictors of all-cause mortality through 5 years.

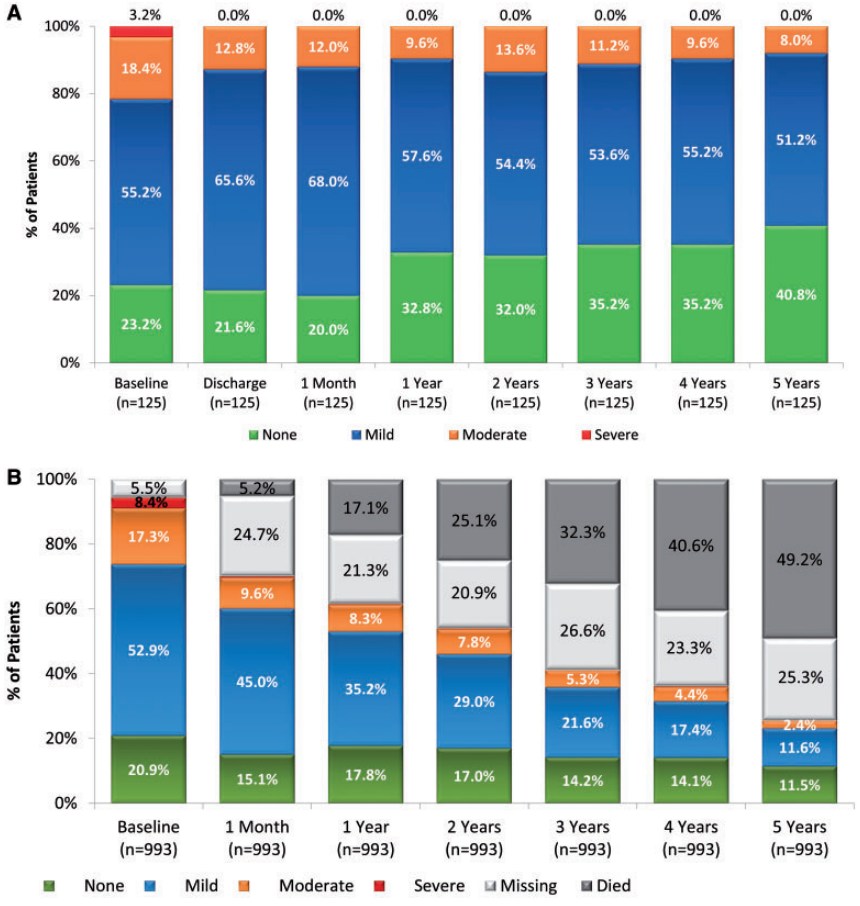

Figure 4 Aortic regurgitation through 5 years: (*A*) for patients with available data at all follow-up time points and (*B*) for all patients accounting for those missing or dead.

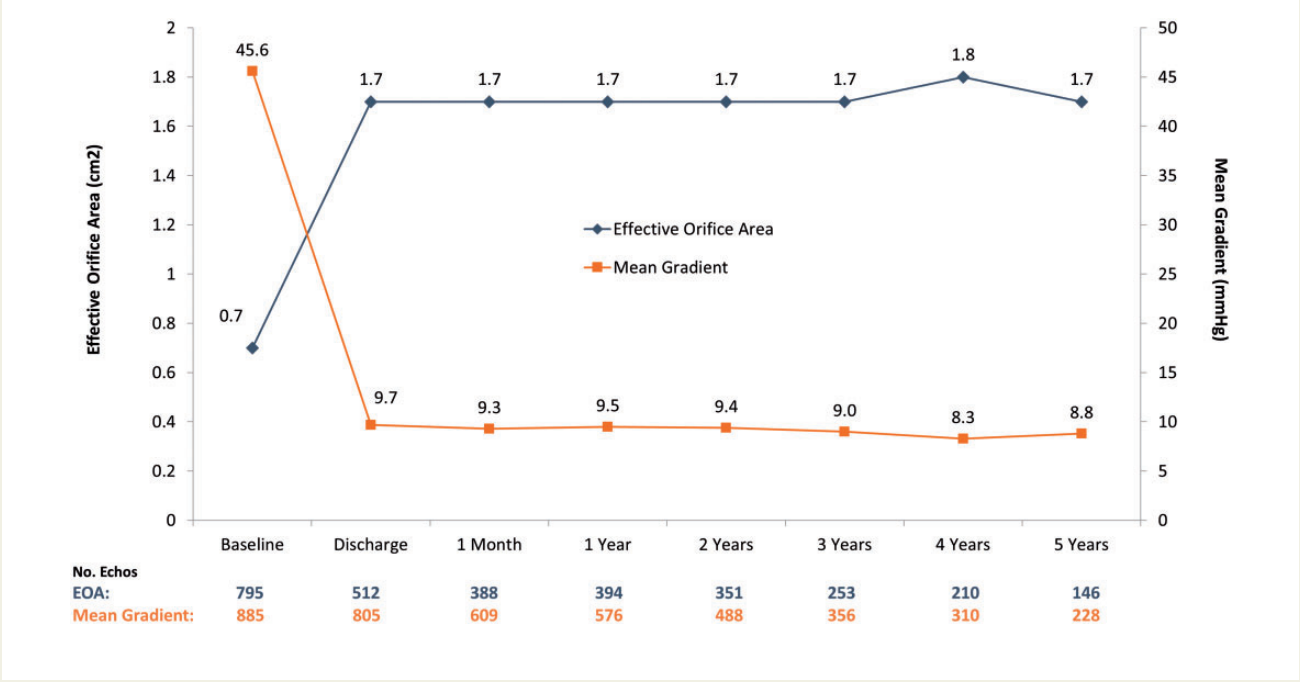

Figure 5 Haemodynamic measures from baseline through 5 years. Effective orifice area is shown in blue and mean gradient is shown in orange.

Table 2 Prosthetic valve durability

Characteristic	*n* = 860
Mean follow-up (months)	36.0 ± 21.1
First and third quartile of follow-up time (months)	[13.5, 59.3]
Reintervention after 30 days	10 (1.2%)
Surgical criteria for aortic valve stenosis[a]	80 (9.3%)
VARC-2[b] criteria for aortic valve stenosis[c]	22 (2.6%)
Reintervention after 30 days or VARC-2 criteria	30 (3.5%)

VARC, Valve Academic Research Consortium; AV, aortic valve; EOA, effective orifice area; BSA, body surface area.
[a]>50% increase of mean gradient from 1 month to 5 years.
[b]The analysis set included subjects with at least 1 echo post 30 day or reintervention >30 days; 267 patients had follow-up at 5 years.
[c]VARC-2 definition: (AV mean gradient ≥20 mmHg or peak velocity ≥3 m/s) and (EOA ≤0.9 cm^2 if BSA <1.6 or ≤ 1.1 cm^2 if BSA ≥1.6) or (≥moderate/severe total aortic regurgitation).

cardiovascular mortality of 28% at 5 years in a large Italian registry, similar to ADVANCE.

There are limited data on rate of stroke at 5 years post-TAVI. The rate of stroke at 5 years in ADVANCE was 10.2%, similar to the rate of 10.4% in PARTNER 1.[9] The Italian registry reported a 5-year stroke rate of 7.5%.[13] A number of clinical studies have described an early incidence of strokes post-TAVI, followed by lower rates of stroke over time.[13,23] Similarly, in ADVANCE, the stroke rate at 30 days post-TAVI was 3.0%, and increased at a much slower rate after that to 5 years.

The observed continued improvement in AR over time for paired patients followed through 5 years are confirming of the findings from the US CoreValve Pivotal Trial[8] and may be related to continued valve frame expansion or tissue ingrowth over time.

An evaluation of surgical bioprosthetic valve explants suggests that an increase in mean gradient of >50% over discharge may correlate with valve thrombosis.[19] A recent presentation further showed an association between subclinical leaflet thrombosis and a higher rate of transient ischemic attacks.[24] There was no measure of valve thrombosis in ADVANCE; however, 9.3% of patients had a 50% or more increase in mean gradient. Additional clinical studies are ongoing to further assess the relationship between leaflet immobility, subclinical thrombosis, and clinical outcomes.

In ADVANCE, we identify a low rate of reinterventions after 30 days that is consistent with reports from other studies. There were 2 cases (0.6%) with aortic valve reintervensions with the CoreValve bioprosthesis in the Italian registry; both were valve-in-valve TAVI procedures occurring between 4 and 5 years.[13] Moreover, there were 3 patients with prosthetic dysfunction who did not undergo reintervention: 1 case of endocarditis, 1 case of asymptomatic valve degeneration with severe AR and 1 case of worsening (moderate-to-severe) paravalvular regurgitation. Three-year follow-up of the CoreValve High-Risk US pivotal trial reported a reintervention rate of 2.5% in patients receiving TAVI but noted that the majority of these events occurred before 30 days.[8] Although 22 patients in ADVANCE met VARC-2 criteria for aortic stenosis, only 2 had reinterventions. The low rate of reintervention and aortic valve stenosis assessed after 30 days provides reassuring data regarding the durability of the self-expanding CoreValve through 5 years.

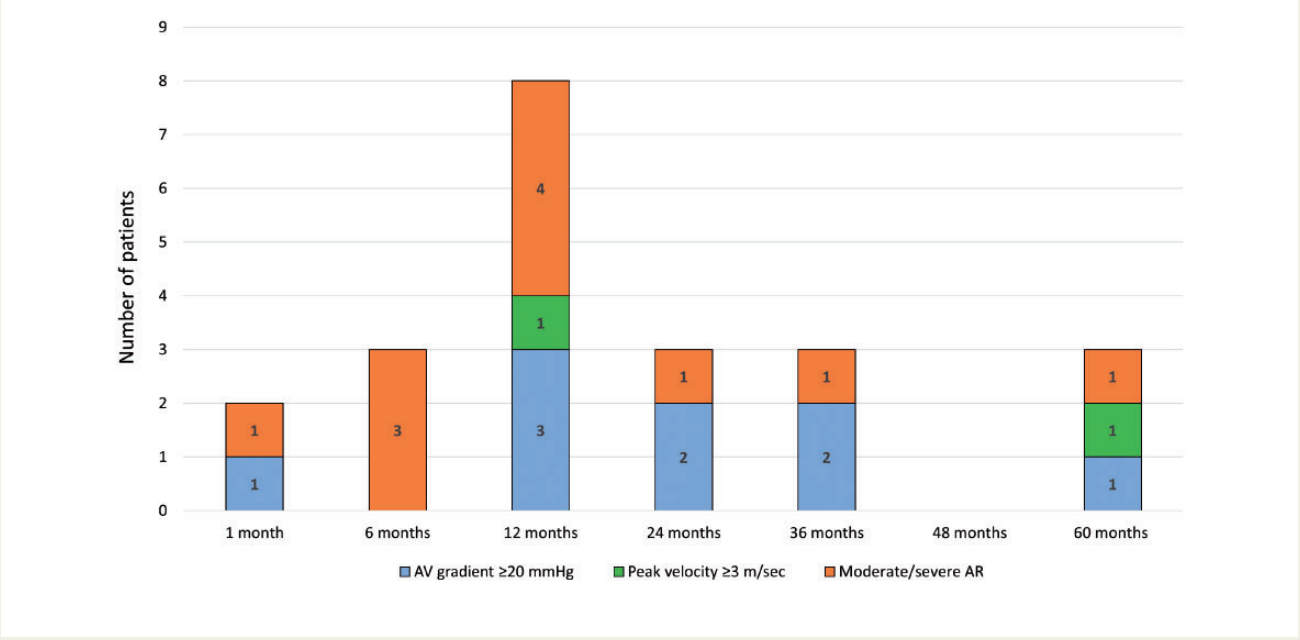

Figure 6 The number of patients meeting criteria for valve dysfunction per VARC-2 criteria classified by criteria met: patients with an aortic valve gradient ≥20 mmHg are shown in blue, patients with a mean gradient <20 mmHg but with a peak velocity ≥3 m/s are shown in green and patients with moderate or severe aortic regurgitation are shown in orange.

Predictors of mortality through 5 years were consistent with those identified at 1 year.[14] Peripheral vascular disease, elevated serum creatinine, low ejection fraction, and acute kidney injury remained as predictors and as expected, greater age is associated with a higher risk for mortality through 5 years. When freedom from mortality was stratified by degree of AR, we noted lower rates of survival for patients with moderate/severe and mild AR (detectable after 2 years) at discharge, suggesting that AR may contribute to higher mortality over time. The FRANCE-2 Registry, which enrolled over 3000 patients, found that moderate-to-severe post-procedural AR was the strongest independent predictor of 1-year mortality.[25] Patients who received a new pacemaker within 30 days post-procedure had similar 5-year survival to patients with an existing pacemaker or no pacemaker (log-rank $P = 0.48$). This is consistent with previous CoreValve clinical studies that did not find any increase in mortality between patients with and without a new pacemaker.[7,26]

There are several limitations in our analysis. Echo visit compliance at 5 years was only 56% and assessment of haemodynamic valve function overtime may underestimate the rate of valve dysfunction at 5 years. It is possible that patients who died during the study duration without a recent echo may have had undiagnosed valve deterioration, but the available echo data argue against a premature valve deterioration. It is likely that some patients with AR died earlier in the study, which affects the proportion of patients with mild or greater AR at 5 years. Nevertheless, the paired echo data indicates that AR is improving over time. In addition, echo measurements were site reported, as there was no echo core lab adjudication for this study.

The 5-year results from the ADVANCE clinical study demonstrated consistent low mean aortic valve gradients associated with the self-expanding CoreValve and provide insights into longer term clinical outcomes for 'real-world' TAVI patients. Analysis of bioprosthetic valve durability through 5 years further demonstrated low rates of reinterventions and haemodynamic valve dysfunction. As the use of TAVI moves into lower risk, younger patients continued follow-up will be essential to reassure physicians and patients of the long-term safety of TAVI.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: U.G. has received consulting and lecture fees and study-related travel expenses from Medtronic and Edwards Lifesciences and serves as a proctor for Medtronic and Boston Scientific. S.B. has served as a consultant and proctor for Medtronic, a proctor for JenaValve, a proctor for Boston Scientific, and has received travel expenses from Medtronic. J.B. serves as a proctor for Medtronic. S.B. has received consultant fees from Medtronic and Boston Scientific. P.W. has received consulting fees from Medtronic

and Edwards Lifesciences and has received remuneration from Medtronic for study-related travel and for development of educational materials. C.T. has no relevant relationships to disclose. A.L. has received speaker honoraria or served as a consultant for the following companies: Medtronic, St. Jude Medical, Claret Medical Inc., Boston Scientific, Edwards Lifesciences, Symetis, and Bard and holds stock options from Claret Medical Inc. In addition, he received grant support from Medtronic and Claret Medical Inc.

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