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Carpentier-Edwards Magna Ease bioprosthesis: a multicentre clinical experience and 12-year durability

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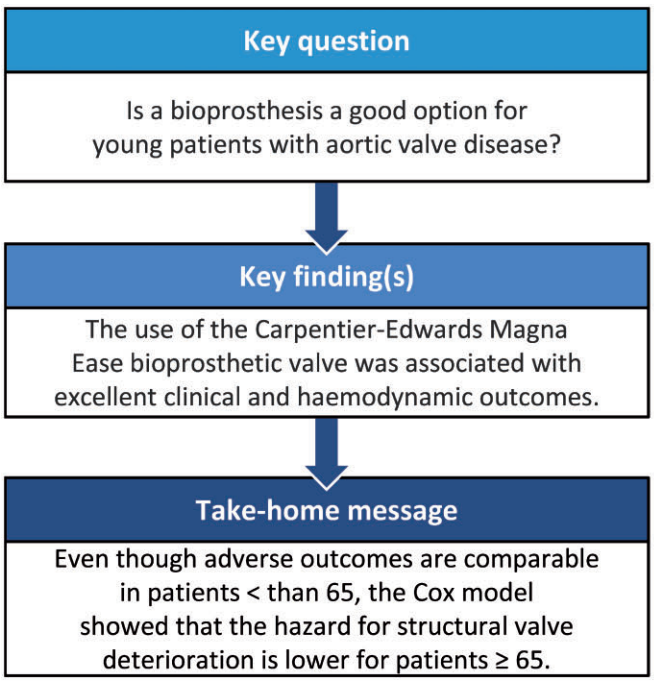

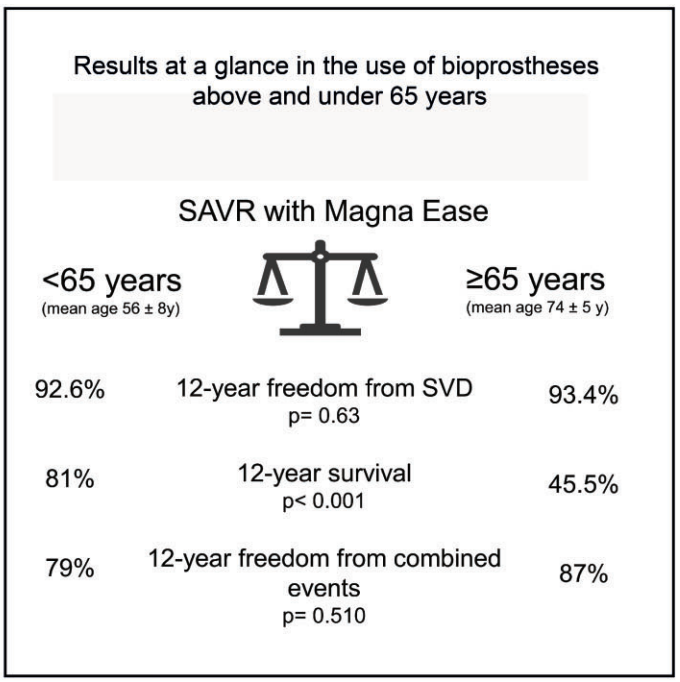

Abstract

OBJECTIVES: The goal of this multicentre retrospective study was to compare long-term clinical and haemodynamic outcomes of the Carpentier-Edwards Magna Ease (CEME) bioprosthesis by patient age.

†The first two authors contributed equally to this study.

METHODS: We included consecutive patients who underwent isolated and combined surgical aortic valve replacement (AVR) with CEME valve between January 2008 and March 2020 at 4 cardiac surgery centres in Italy. Survival distribution was evaluated at follow-up according to age and surgery type (combined or isolated AVR), together with freedom from structural valve deterioration (SVD), reoperation and combined events, i.e. SVD, reoperation, endocarditis and thromboembolic events.

RESULTS: A total of 1027 isolated and 1121 combined AVR were included; 776 patients were younger than 65 years whereas 1372 were 65 years or older. The 30-day Valve-Academic-Research-Consortium mortality was 2% (<65 years) and 6% (≥ 65 years) ($P < 0.001$), whereas it was 3% for isolated AVR and 7% for combined AVR ($P < 0.001$). The 12-year survival was 81% for those younger than 65 years vs 45% for those equal to or older than 65 years ($P < 0.001$), whereas they were 61% vs 49% for isolated and combined AVR ($P = 0.10$). The 12-year freedom from combined events, excluding death, was 79% for those younger than 65 years vs 87% for those equal to or older than ($P = 0.51$), whereas they were 83% for isolated and 86% for combined AVR ($P = 0.10$). The 12-year freedom from SVD was 93% and 93% in patients younger than 65 and those equal to or older than 65 years ($P = 0.63$), and the results were comparable even in cases with isolated and combined AVR (92% vs 94%, $P = 0.21$). A multivariable Cox analysis including gender, presence of patient–prosthesis mismatch, isolated AVR and age showed that only the age was an independent risk factor for the incidence of SVD ($P = 0.029$).

CONCLUSIONS: Outcomes from this large multicentre analysis demonstrated that a CEME bioprosthesis provides good clinical results and long-term durability even in patients younger than 65 years. Furthermore, the hazard for SVD has been shown to be lower for older age.

Clinical trial registration number: 105n/AO/21.

Keywords: Age • PPM • Durability • Bioprosthesis • Carpentier-Edwards Magna Ease

ABBREVIATIONS

AVR	Aortic valve replacement
CEME	Carpentier-Edwards Magna Ease
CI	Confidence interval
EOA	Effective orifice area
HR	Hazard ratio
PPM	Patient–prosthesis mismatch
SAVR	Surgical aortic valve replacement
SVD	Structural valve deterioration
VARC-2	Valve Academic Research Consortium-2

INTRODUCTION

Surgical aortic valve replacement (SAVR) is an excellent option for patients with severe aortic valve disease. Current guidelines recommend the use of mechanical valves in patients younger than 60 and of tissue bioprostheses in patients 65 or older [1, 2].

The use of bioprostheses has increased significantly in recent years, including patients <65 years old [3–5]. Available on the market since 2007, the modern Carpentier-Edwards Magna Ease (CEME) aortic valve (Edwards Lifesciences, Irvine, CA, USA) (model 3300TFX) is the third generation of pericardial bioprosthesis [6–11].

The goal of this retrospective study was to compare long-term clinical and haemodynamic outcomes of patients undergoing aortic valve replacement (AVR) with the CEME bioprosthesis. In particular, the primary outcomes were long-term survival and freedom from structural valve deterioration (SVD) at follow-up; secondary outcomes were freedom from reoperation and combined events, i.e. SVD, reoperation, endocarditis and thromboembolic events at follow-up. Both primary and secondary outcomes were evaluated according to patient age and type of surgery (isolated and combined AVR). A multivariable Cox model including age, gender, patient–prosthesis mismatch (PPM) and type of surgery (isolated AVR) completed the analysis.

PATIENTS AND METHODS

Ethics statement: Every reasonable effort was made to obtain written informed consent from patients to participate in this study. The use of data for scientific and research purposes is already included in the written informed consent agreements used at the participating centres. The local ethics committee (Azienda Ospedaliera Universitaria, Padova, Veneto Region, Italy) approved of the study design, consent process and review and analysis of the data (IRB n. 8954/AO/18-02-2021).

We also guarantee the respect of anonymity and professional secrecy and use the collected data and the statistical analyses solely for the scientific purposes granted in accordance with the law in effect (General Data Protection Regulation).

Study population

We included consecutive patients who underwent isolated and combined SAVR with the CEME valve between January 2008 and March 2020 at 4 cardiac surgery centres in Italy. The choice to implant a bioprosthesis regardless of the patient's age instead of a mechanical valve was based on contraindications to mechanical valves and patients' willingness but was ultimately left to the discretion of each surgeon.

Indications for surgery were aortic valve stenosis, aortic valve regurgitation and aortic root aneurysm established according to the current clinical and echocardiographic recommendations [12]. We included endocarditis, aortic dissection, reoperations and concomitant procedures. The exclusion criterion was SAVR using a prosthesis other than the CEME. All the analyses were conducted considering the patients as isolated and combined AVR. PPM was calculated by dividing the effective orifice area (EOA) by the body surface area. The PPM was classified as not clinically significant (indexed EOA: >1 cm^2/m^2), mild (indexed EOA: <1 and >0.85 cm^2/m^2), moderate (0.65–0.85 cm^2/m^2) and severe (<0.65 cm^2/m^2) [13]. The SVD was defined as the presence of a mean transvalvular gradient ≥30 mmHg, associated with an EOA ≤1 cm^2 or intraprosthetic aortic

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regurgitation grade ≥3 [14]. A supra-annular technique using interrupted U-shaped stitches was used in all patients to implant the prostheses. The proper functioning of the prosthesis and the evidence of any paravalvular leak were evaluated with an intraoperative transoesophageal echocardiogram after the patient was weaned from cardiopulmonary bypass.

Preoperative variables were outlined according to the European system for cardiac operative risk evaluation definitions [15], and postoperative outcomes were outlined according to the updated Valve Academic Research Consortium-2 (VARC-2) definitions [16]. Events were classified as occurring early (within 30 days of implantation) or late (>31 days after implantation). We decided to use the VARC-2 definitions to allow easy comparison between these data and those of transcatheter AVR. Patients underwent clinical and echocardiographic assessment at the study site before the operation, at hospital discharge, at the first outpatient visit and during the follow-up examination. PPM was calculated at the first outpatient visit, 1 month after the AVR. In-hospital data were obtained and analysed retrospectively from an electronic database. For those patients without access to the centre's outpatient follow-up system, follow-up data including clinical and echocardiographic evaluations were collected via a telephone survey from January 2020 to March 2021. For those patients, the echocardiographic data were backdated more than 12 months, and a new echocardiographic examination was requested from each and obtained via email or fax.

Statistical analyses

Descriptive statistics were reported as I quartile/median/III quartile for continuous variables and percentages (absolute numbers) for categorical variables. The distribution of the variables among subjects <65 and ≥65 and undergoing isolated and combined AVR was compared using the Wilcoxon and the χ^2 tests for continuous and categorical variables, respectively. *P*-values of the postoperative outcomes underwent the Benjamini–Hochberg correction to control for a false discovery rate resulting from the multiplicity of testing [17].

Survival distribution was evaluated using the Kaplan–Meier approach. Differences in survival between subjects <65 and ≥65 and those undergoing isolated and combined AVR were examined using the log-rank test. Freedom from SVD, reoperation and the composite end point, including death, SVD, reoperation, endocarditis and a thromboembolic event, were evaluated in a competing risk framework using the cumulative incidence functions. Finally, to assess the effect of age on SVD, a multivariable Cox proportional hazard model was estimated, accounting for potential confounders. The results were reported as the hazard ratio (HR) and 95% confidence interval (CI).

The analyses were performed using R software (version 4.0.3) (R Foundation for Statistical Computing, Institute for Statistics and Mathematics, Vienna, Austria) [18] loaded with the packages survival, cmprsk [19] and rms [20].

RESULTS

Study population

Baseline and preoperative characteristics of the overall population are reported in Table 1. We included 2148 consecutive patients who underwent isolated (1027) or combined (1121) SAVR. A total of 776 patients were younger than 65 years, and 1372 patients were ≥65 years. Sixty-seven (3.12%) patients were <45 years with an age distribution as follows: 32.50/39.50/43.00. Each cohort of patients had many preoperative differences that ultimately led to a higher physiological risk profile in the older and combined AVR cohort**s**.

Operative variables and postoperative clinical and echocardiographic outcomes are reported in Tables 2 and 3. Thirty-day Valve Academic Research Consortium mortality occurred in 19 (2%) and 88 (6%) patients in the younger and older cohorts ($P < 0.001$), and it occurred in 30 (3%) and 77 (7%) who had isolated and combined AVR ($P < 0.001$), respectively. VARC-2 cardiovascular-related mortality occurred in 11 (1%) and 49 (4%) patients in the younger and older cohorts ($P = 0.009$), and it occurred in 12 (1%) and 48 (4%) patients who had isolated and combined AVR ($P = 0.003$). We did not observe intraoperative moderate/severe aortic regurgitation requiring prosthesis reimplantation or replacement. A total of 98 cases of paravalvular leaks were reported at discharge (4.6%), of which 83 were mild and 15 were moderate.

Long-term outcomes

Follow-up was 100% complete. The median follow-up time was 4.5 years (interquartile range: 1.96–6.91). There were 404 deaths at follow-up, 52 of which were cardiovascular-related. The 12-year overall survival was 54% (95% CI 47.8–62%). The 12-year survival was significantly higher in patients younger than 65 compared to those ≥65 (81% vs 45%; $P < 0.001$), but it was comparable for those with isolated and combined AVR (61% vs 49%; $P = 0.10$) (Fig. 1). Overall combined event-free survival at 12 years (death, SVD, reoperation, endocarditis, cerebral and vascular systemic embolic events) was 44% (95% CI 38–52%). The 12-year combined event-free survival was 65% (95% CI 54–78%) vs 37% (95% CI 30–47%) for those <65 years and those ≥65 years (7 patients at risk: $P < 0.001$). It was higher for isolated AVR (48%; 95% CI 39–57%) versus combined AVR (42%; 33–55%) (7 patients at risk: $P = 0.05$). The 12-year freedom from combined events, excluding death, was 85% (95% CI 80–89%), and it was comparable (79% vs 87% for those < and ≥ 65 years, respectively; $P = 0.51$) as well as for isolated AVR and combined AVR (84% vs 86%) ($P = 0.10$) (Fig. 2). Cumulative 12-year freedom from SVD was 93% (95% CI 88–97%), whereas it was 93% and 93% in patients <65 years and in those ≥65 years, respectively ($P = 0.63$) (Fig. 3 and Table 4). Freedom from SVD was comparable even when the isolated AVR group was compared to the combined AVR group (92% vs 94%; $P = 0.21$) (Table 4). Overall, 25 SVD events were registered at a median time of 6 years after implantation (interquartile range 2.5–10.5 years). SVD occurred in 14 patients <65 years, whereas it occurred in 11 patients ≥65 years. The majority of SVD events occurred in patients with a prosthesis smaller than 23 mm (24/25). PPM was evident in 4 SVD cases (2 patients older than 70 years, and 2 older than 65 years). Seven patients with SVD underwent reoperations (3 SAVR and 4 transcatheter aortic valve implantation); 14 cases of SVD with stable/moderate dysfunction and limited clinical impact were medically managed. Four patients died of SVD. The overall 12-year freedom from reoperation was 90% (95% CI 85–95%) (Fig. 4). Freedom from reoperation at 12 years was significantly lower in younger versus older patients (85% vs 92%, respectively;

Table 1: Population baseline characteristics

Variable	<65 (776)	≥65 (1372)	*P*-value	Isolated (1027)	Combined (1121)	*P*-value
Age (years)	59 (53–62)	74 (70–78)	<0.001	69 (61–76)	69.7 (62–76)	0.364
Gender, male	75% (582)	62% (849)	<0.001	62% (640)	71% (791)	<0.001
Arterial hypertension	64% (495)	76% (1037)	<0.001	70% (717)	73% (815)	0.149
Obesity	9% (73)	13% (180)	0.01	13% (134)	11% (119	0.082
Diabetes	13% (100)	20% (270)	<0.001	18% (184)	17% (186)	0.369
Smokers	25% (195)	20% (270)	0.003	20% (206)	23% (259)	0.083
Peripheral vascular disease	4% (34)	13% (176)	<0.001	9% (91)	11% (119)	0.174
COPD	7% (55)	14% (189)	<0.001	12% (128)	10% (116)	0.121
Previous neurological deficit	5% (37)	5% (68)	0.851	4% (45)	5% (60)	0.297
NYHA functional class III/IV	32% (245)	40% (548)	<0.001	38% (393)	36% (400)	0.504
Preoperative LVEF (%)	59 (51–62)	59 (52–63)	0.26	60 (54–64)	57 (50–62)	<0.001
LVE[a]	36% (273)	24% (328)	<0.001	25% (257)	31% (344)	0.003
Endocarditis	8% (60)	4% (51)	<0.001	5% (56)	5% (55)	0.563
Acute aortic dissection	2% (17)	1% (17)	0.089	0% (0)	3% (34)	<0.001
Preoperative IABP	0% (2)	0% (2)	0.564	0% (1)	0% (3)	0.361
Preoperative ECMO	0% (2)	0% (3)	0.856	0% (3)	0% (2)	0.583
Preoperative AMI	5% (41)	8% (110)	0.017	5% (47)	9% (104)	<0.001
Redo	6% (49)	3% (45)	<0.001	4% (42)	5% (52)	0.535
CKF	4% (33)	11% (145)	<0.001	7% (71)	10% (107)	0.028
Aortic valve disease			<0.001			<0.001
Stenosis	49% (378)	68% (921)		68% (689)	55% (610)	
Regurgitation	28% (217)	16% (209)		14% (145)	25% (281)	
Mixed (stenosis/regurgitation)	12% (90)	15% (200)		13% (131)	14% (159)	
Bicuspid aortic valve	28% (199)	11% (147)	<0.001	15% (143)	19% (203)	0.006
Heart rhythm			<0.001			0.004
Sinus rhythm	90% (654)	83% (1025)		89% (843)	83% (836)	
Atrial fibrillation	8% (60)	15% (190)		10% (98)	15% (152)	
Pacing	1% (9)	1% (17)		1% (11)	1% (15)	
Pulmonary hypertension	6% (47)	12% (169)	<0.001	9% (95)	11% (121)	0.23
EuroSCORE I	2.2 (1.2–3.8)	5.4 (3.3–10.1)	<0.001	2.94 (1.7–5.0)	6.3 (3.4–11.1)	<0.001
EuroSCORE II	1.4 (0.8–2.3)	1.9 (1.2–3.2)	<0.001	1.2 (0.8–1.8)	2.4 (1.6–4.0)	<0.001

Table reports median (I quartile–III quartile) for continuous variables and percentages (absolute numbers) for categorical variables.

[a]>74 ml/mq for males; >61 ml/mq for females.

AMI: acute myocardial infarction; CKF: chronic kidney failure; COPD: chronic obstructive pulmonary disease; ECMO: extracorporeal membrane oxygenation; EuroSCORE: European system for cardiac operative risk evaluation; IABP: intra-aortic balloon pump; LVE: left ventricle enlargement; LVEF: left ventricle ejection fraction; NYHA: New York Heart Association functional class.

P = 0.013). Freedom from reoperation was comparable in younger and older patients for the isolated AVR cohort (86% vs 94%, respectively; *P* = 0.13). To account for potential confounding factors, a multivariable proportional hazards model was estimated, including gender, presence of PPM, isolated AVR and age that was entered in the model as a continuous variable. The model showed that only the age is an independent risk factor for SVD, showing that the hazard for SVD is lower for older age (HR: 0.957, 95% CI 0.921–0.996; *P* = 0.029). Gender (HR: 0.462, 95% CI 0.180–1.186; *P* = 0.1085), PPM (HR: 1.157, 95% CI 0.453–5.425; *P* = 0.478) and isolated AVR (HR: 2.264, 95% CI 0.809–6.341; *P* = 0.120) were not independent risk factors. At the end of the follow-up period, 1423 patients are still in New York Heart Association functional class I–II (93%).

DISCUSSION

According to the 2020 American College of Cardiology/American Heart Association guidelines for the management of aortic valve disease, in patients below the age of 65 who do not have contraindications for anticoagulation, it is reasonable to individualize the choice of either a mechanical or bioprosthetic AVR. The purpose of our multicentre study was to answer the question of whether or not we should use a CEME bioprosthesis in patients below the age of 65.

The main findings of our study were as follows:

1. At 12 years of follow-up, the CEME bioprosthesis demonstrated a similar incidence of adverse outcomes regardless of patient age.
2. Freedom from all combined events (death excluded) was similar regardless of patient age.
3. The 12-year freedom from reoperation was comparable in patients <65 and ≥65 in the isolated-AVR group.
4. The hazard for SVD was lower for older age.

The ongoing dilemma regarding the choice of the best aortic prosthetic device for young patients has always been centred on the premise that bioprosthetic devices suffer from structural deterioration over time and require 1 or more subsequent surgical procedures [3–5]. The cut-off age was 65 years, the point at which the risks of SVD occurrence and subsequent bioprosthesis replacement become lower than the risks of implanting a mechanical device [21].

Surgeons revised the cut-off age down and were comfortable conducting surgery on this younger cohort because a new generation of bioprostheses promises better outcomes [22, 23], especially in the presence of novel technologies (e.g.

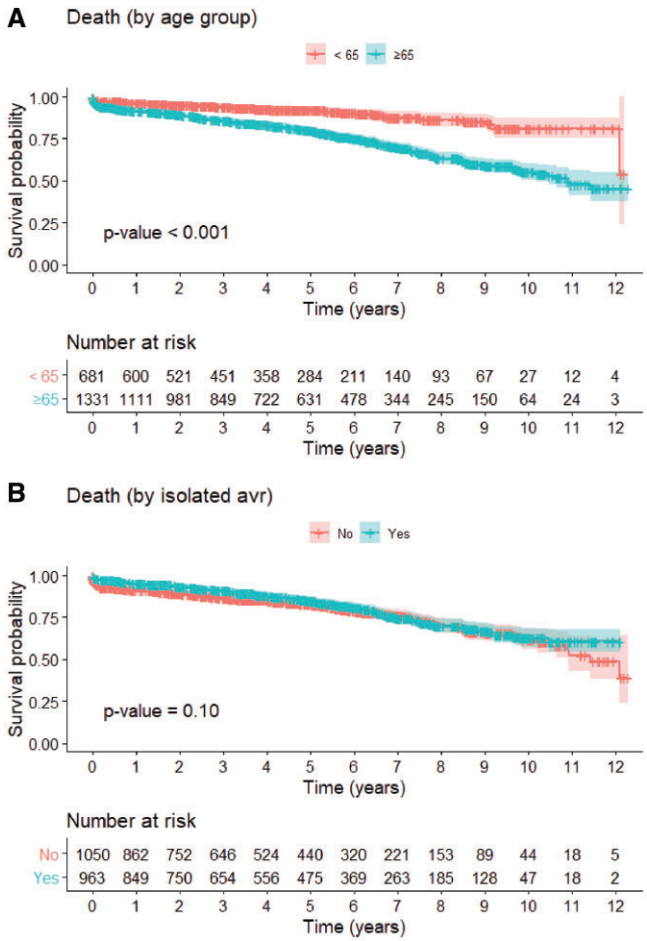


Figure 1: Kaplan–Meier survival curve stratified for patient's age and type of aortic valve replacement. avr: aortic valve replacement.

transcatheter aortic valve implantation). We observed significantly higher long-term survival in patients younger than 65, which is an expected outcome, because inherently more older patients die than younger patients [22–24]. We then compared the incidence of SVD based on the age of the patients. In theory, a higher incidence of SVD in younger patients should be fairly predictable, considering that the degeneration of a bioprosthesis is correlated to young patient age [25]. Surprisingly, in our study, the long-term freedom from SVD was comparable through 12 years of follow-up. This finding is certainly limited by the fact that there are few SVD events, both in the young and in the older population. Even when the isolated-AVR cohort was analysed, the 12-year freedom from SVD was comparable in younger and older patients ($P = 0.63$) as was the freedom from reoperation ($P = 0.13$). An SVD event occurred at a median average of 6 years after the prosthesis was implanted and mostly in patients with bioprostheses smaller than 23 mm; 50% of the patients with SVD were younger than 65 years. Seven confirmed cases of SVD required re-replacement. Although longer-term verification is required, we observed that a CEME bioprosthesis performs the same at 12 years, independently of the age of the patient, and that SVD only affects small prostheses [6, 9, 10, 15, 20–23, 26].

Furthermore, we analysed both freedom of survival from combined events (including death) and freedom from combined events by censoring the death event. We observed that, excluding the death event, which penalizes in particular the oldest cohort of patients, the incidence of all combined adverse events is similar in both age groups ($P = 0.281$), regardless of whether the surgery was isolated or combined AVR ($P = 0.10$). Although these results may justify the choice of lowering the age limit for implanting a bioprosthesis, the Cox analysis restituted a different conclusion that attenuated our inference. In fact, the hazard for SVD is lower for older age.

Table 2: Operative variables

Variable	<65 (776)	≥65 (1372)	*P*-value	Isolated (1027)	Combined (1121)	*P*-value
Surgical approach						
Full sternotomy	96% (745)	97% (1335)	<0.001	94% (964)	100% (1116)	<0.001
Ministernotomy J + T	4% (29)	3% (37)		6% (63)	0% (3)	
Minithoracotomy	0% (2)	0% (0)		0% (0)	0% (2)	
Cardiopulmonary bypass time (min)	126 (93–166)	137 (111–177)	<0.001	113 (94–135)	160 (129–199)	<0.001
Aortic cross-clamp time (min)	98 (72–135)	106 (85–134)	<0.001	87 (71–105)	126 (100–153)	<0.001
Size of the prosthesis (cm)			<0.001			<0.001
19	6% (47)	16% (219)		16% (162)	9% (104)	
21	22% (171)	28% (387)		29% (300)	23% (259)	
23	33% (255)	34% (466)		33% (341)	34% (380)	
25	31% (241)	18% (245)		18% (189)	27% (297)	
27	8% (60)	4% (52)		3% (34)	7% (78)	
	0% (1)	0% (1)		0% (0)	0% (2)	
Isolated AVR	37% (384)	63% (643)	0.232	–	–	–
Concomitant procedures	35% (392)	65% (729)	0.232	–	–	–
CABG	14% (113)	31% (421)	<0.001	0% (0)	48% (534)	<0.001
Mitral valve repair	5% (36)	4% (49)	0.223	0% (0)	8% (85)	<0.001
Mitral valve replacement	8% (59)	7% (92)	0.426	0% (0)	14% (151)	<0.001
Tricuspid valve repair	2% (19)	4% (50)	0.132	0% (0)	6% (69)	<0.001
Tricuspid valve replacement	0% (0)	0% (2)	0.288	0% (0)	0% (2)	0.175
Ascending aortic surgery	22% (174)	14% (192)	<0.001	0% (0)	33% (366)	<0.001
Bentall procedure	10% (76)	4% (57)	<0.001	0% (0)	12% (133)	<0.001
VARC-2 device success	100% (776)	100% (1372)	1	100% (1027)	100% (1121)	1
Intraoperative death	0% (0)	0% (0)	1	0% (0)	0% (0)	1

Table reports median (I quartile–III quartile) for continuous variables and percentages (absolute numbers) for categorical variables.
AVR: aortic valve replacement; CABG: coronary artery bypass grafting surgery; VARC-2: Valve Academic Research Consortium-2.

Table 3: Postoperative clinical and echocardiographic outcomes

Variable	<65 (776)	≥65 (1372)	*P*-value	Isolated (1027)	Combined (1121)	*P*-value
ICU stay	2 (1–3)	1 (1–3)	0.119	1 (1–2)	2 (1–3)	<0.001
Hospital stays	10 (8–13)	11 (8–15)	0.004	10 (8–13)	11 (8–15)	0.003
VARC-2 AMI	2% (16)	2% (32)	0.677	1% (12)	3% (36)	0.005
VARC-2 stroke			0.072			0.132
TIA	1% (9)	2% (30)		1% (13)	2% (26)	
Not disabling	1% (5)	1% (16)		1% (6)	1% (15)	
Disabling	0% (1)	1% (11)		1% (6)	1% (6)	
VARC-2 bleeding	5% (41)	7% (89)	0.487	4% (45)	7% (85)	0.007
VARC-2 vascular complication			0.377			0.819
Minor	0% (3)	0% (6)		0% (4)	0% (5)	
Major	1% (7)	2% (34)		2% (19)	2% (22)	
VARC-2 all-cause mortality	2% (19)	6% (88)	<0.001	3% (30)	7% (77)	<0.001
VARC-2 cardiovascular mortality	1% (11)	4% (49)	0.009	1% (12)	4% (48)	0.003
Pacemaker implant	6% (44)	4% (60)	0.261	5% (49)	5% (55)	0.892
New-onset atrial fibrillation	26% (201)	42% (579)	0.004	33% (341)	39% (439)	0.008
LVEF (%)	57 (50–60)	57 (51–62)	0.113	59 (53–62)	56 (49–60)	0.003
Peak aortic gradient (mmHg)	24 (19–32)	23 (17–30)	0.004	25 (20–33)	22 (16–28)	0.003
Mean aortic gradient (mmHg)	14 (11–18)	13 (10–17)	0.004	14 (11–18)	12 (9–16)	0.003
EOA (cm^2)	1.9 (1.6–2.3)	1.8 (1.6–2.3)	0.568	1.8 (1.6–2.2)	1.9 (1.6–2.4)	0.003
PVL	3% (25)	5% (73)	0.051	4% (42)	5% (56)	0.367
Grade of PVL			0.072			0.779
Mild	2% (19)	5% (64)		4% (36)	4% (47)	
Moderate	0.8% (6)	0.6% (9)		0.6% (6)	0.8% (9)	
Severe	0% (0)	0% (0)		0% (0)	0% (0)	
PPM	7% (48)	10% (117)	0.072	11% (96)	7% (69)	0.009

Table reports median (I quartile–III quartile) for continuous variables and percentages (absolute numbers) for categorical variables. *P*-values underwent Benjamini–Hochberg correction to account for the multiplicity of testing.

AMI: acute myocardial infarction; EOA: effective orifice area; ICU: intensive care unit; LVEF: left ventricle ejection fraction; PPM: patient–prosthesis mismatch; PVL: paravalvular leaks; TIA: transient ischaemic attack; VARC-2: Valve Academic Research Consortium-2.

Table 4: Freedom from structure valve deterioration together with 95% confidence interval (lower 95% confidence interval and upper 95% confidence interval) by age class and isolated/combined aortic valve replacement status

Time (years)	<65 group			≥65 group			Isolated AVR			Combined AVR		
	Freedom from (%)	Lower 95% CI	Upper 95% CI	Freedom from (%)	Lower 95% CI	Upper 95% CI	Freedom from (%)	Lower 95% CI	Upper 95% CI	Freedom from (%)	Lower 95% CI	Upper 95% CI
1	99.5	98.9	100	100	1	100	99.8	99.4	100	99.9	99.7	100
3	98.6	97.6	99.6	99.9	99.7	100	99.5	99	100	99.5	99	100
5	98	96.6	99.3	99.8	99.5	100	99.2	98.5	99.8	99.3	98.7	99.9
7	97.1	95.2	98.9	99.5	99	100	98.5	97.5	99.5	99.1	98.3	99.8
10	92.6	87	98.1	98.1	96	100	95.7	92.5	98.8	97.9	95.6	100
12	92.6	87	98.1	93.4	87.8	99	91.6	85.4	97.9	94.2	86.7	100

P-value for the difference between the age classes (<65 vs ≥65): 0.63. *P*-value for the difference between isolated and combined AVR: 0.21.

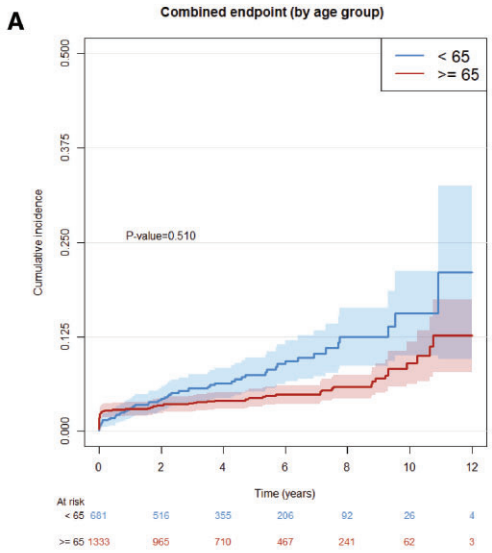
AVR: aortic valve replacement; CI: confidence interval.

We further analysed whether the presence of PPM could affect survival, freedom from SVD and in general freedom from adverse events. Ochi *et al.* [27] identified 4 factors that influenced bioprosthetic long-term performance: younger age, PPM, body surface area and smoking. Similar conclusions were published by Pibarot *et al.* [13]. Our multicentre study, with 2148 CEME implants, showed that the incidence of SVD is independent of gender, PPM presence and type of surgery.

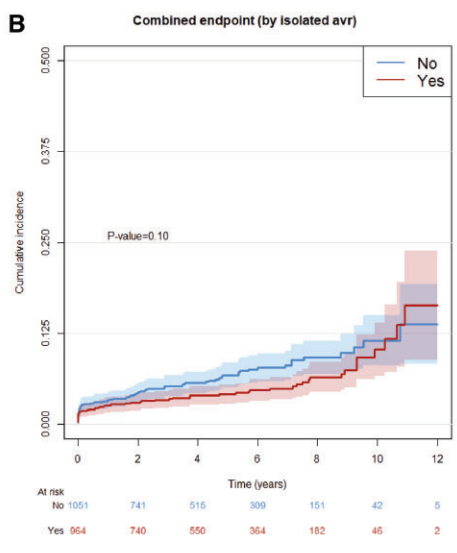
We performed a retrospective observational, multicentre study with a 12-year follow-up. We analysed the results on a relatively small sample of patients under 65 years, and the data concerning SVD incidence were extremely limited. A further limiting factor was the inclusion of findings from patients with associated procedures that may have increased the number of deaths within 30 days. To overcome this limitation, we performed an individual analysis for each group of patients (<65 and ≥65 years, isolated AVR versus combined AVR). Although the number of patients younger than 65 is almost 50% of those ≥65 years, the total number is huge (776 patients) and the mean age of these patients is significantly lower.

CONCLUSIONS

According to our data, the CEME valve provides good and similar long-term outcomes in younger and older patients. In isolated

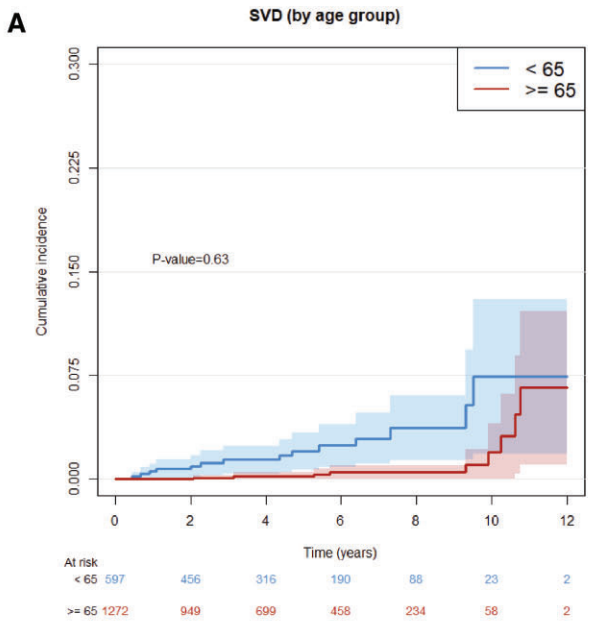


	Time (years)	Cumulative Incidence	Lower 95% CI	Upper 95% CI
<65	1	0.03	0.017	0.043
	5	0.075	0.052	0.097
	10	0.156	0.1	0.212
	12	0.21	0.096	0.325
>=65	1	0.029	0.02	0.038
	5	0.044	0.033	0.056
	10	0.09	0.062	0.118
	12	0.127	0.078	0.175

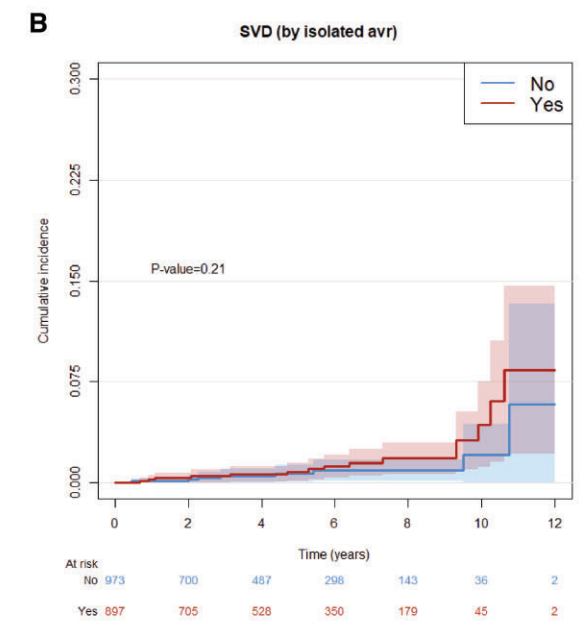


	Time (years)	Cumulative Incidence	Lower 95% CI	Upper 95% CI
No	1	0.033	0.022	0.044
	5	0.067	0.05	0.084
	10	0.115	0.081	0.149
	12	0.138	0.083	0.193
Yes	1	0.026	0.016	0.036
	5	0.041	0.028	0.054
	10	0.103	0.066	0.14
	12	0.164	0.088	0.239

Figure 2: Cumulative incidence curve for combined events, stratified for patient's age and type of aortic valve replacement. avr: aortic valve replacement.

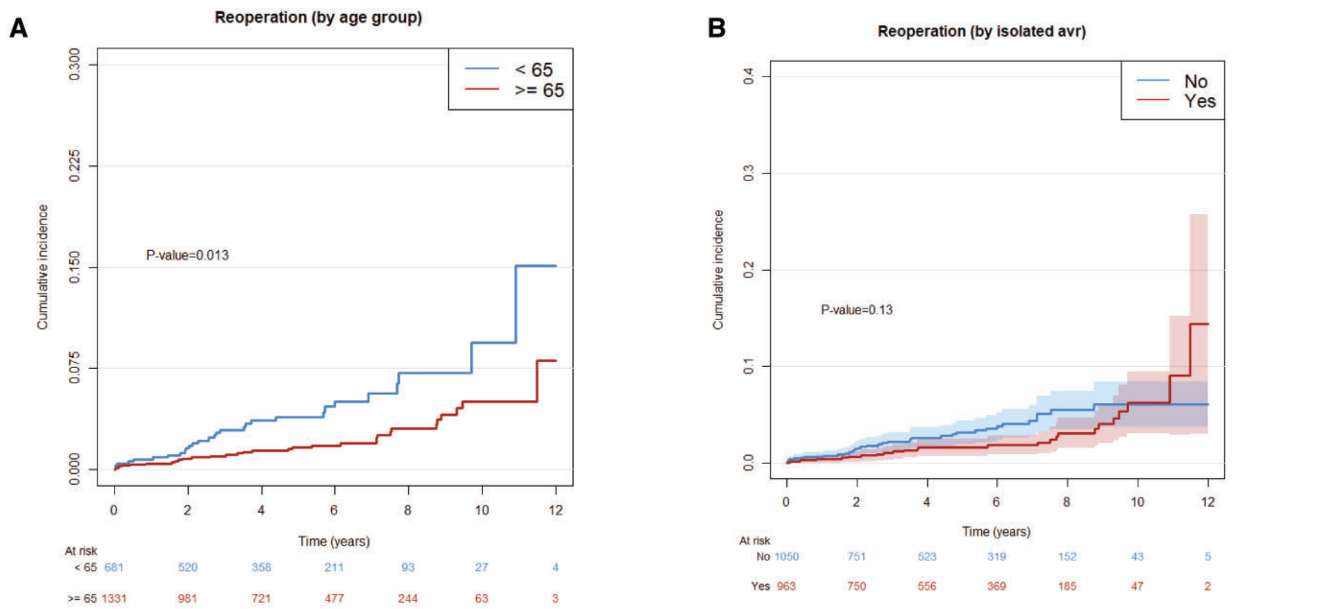


	Time (years)	Cumulative Incidence	Lower 95% CI	Upper 95% CI
<65	1	0.005	0	0.011
	5	0.02	0.007	0.034
	10	0.074	0.019	0.13
	12	0.074	0.019	0.13
>=65	1	0	0	0
	5	0.002	0	0.005
	10	0.019	0	0.04
	12	0.066	0.01	0.122



	Time (years)	Cumulative Incidence	Lower 95% CI	Upper 95% CI
No	1	0.001	0	0.003
	5	0.007	0.001	0.013
	10	0.021	0	0.044
	12	0.058	0	0.133
Yes	1	0.002	0	0.006
	5	0.008	0.002	0.015
	10	0.043	0.012	0.075
	12	0.084	0.021	0.146

Figure 3: Cumulative incidence curve for structural valve deterioration stratified by patient's age and type of aortic valve replacement. avr: aortic valve replacement; CI: confidence interval; SVD: structural valve deterioration.



	Time (years)	Cumulative Incidence	Lower 95% CI	Upper 95% CI
<65	1	0.007	0.001	0.014
	5	0.039	0.022	0.056
	10	0.094	0.041	0.147
	12	0.151	0.033	0.269
>=65	1	0.005	0.001	0.008
	5	0.017	0.009	0.024
	10	0.05	0.029	0.072
	12	0.081	0.02	0.142

	Time (years)	Cumulative Incidence	Lower 95% CI	Upper 95% CI
No	1	0.007	0.002	0.012
	5	0.032	0.019	0.044
	10	0.061	0.038	0.084
	12	0.061	0.038	0.084
Yes	1	0.004	0	0.008
	5	0.016	0.007	0.025
	10	0.063	0.031	0.095
	12	0.144	0.03	0.257

Figure 4: Cumulative incidence curve for reoperation stratified by patient's age and type of aortic valve replacement. avr: aortic valve replacement; CI: confidence interval.

AVR patients, the 12-year freedom from reoperation is similar regardless of the age at implant. The weak point is that the hazard for SVD is lower for older patients.

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Conflict of interest: none declared.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author (Tomaso Bottio) on request The data are not publicly available due to restrictions because the information could compromise the privacy of research participants.

Author contributions

Antonio Piperata: Conceptualization; Data curation. **Alessandro Fiocco:** Data curation. **Andrea Cavicchiolo:** Data curation. **Matteo Ponzoni:** Data curation. **Rita Pesce:** Conceptualization; Data curation. **Marco Gemelli:** Data curation. **Giuseppe Evangelista:** Data curation. **Elisa Gastino:** Data curation. **Sara Michelotti:** Data curation. **Enzo Mazzaro:** Data curation. **Luigi Garufi:** Data curation. **Ruggero DePaulis:** Data curation. **Luca Zanella:** Data curation. **Matteo Nadali:** Data curation. **Domenico Mangino:** Data curation. **Giulia Lorenzoni:** Formal analysis. **Dario Gregori:** Formal analysis. **Vjola Jorgji:** Writing—review & editing. **Gino Gerosa:** Writing—review & editing. **Tomaso Bottio:** Conceptualization; Formal analysis; Writing—original draft.

Reviewer information

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