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ORIGINAL ARTICLE

Transapical aortic valve replacement in extreme-risk patients: outcome, risk factors and mid-term results

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Abstract

OBJECTIVES: Transcatheter aortic valve replacement (TAVR) provides good results in selected high-risk patients. However, it is unclear whether this procedure carries advantages in extreme-risk profile patients with logistic EuroSCORE above 35%.

METHODS: From January 2009 to July 2011, of a total number of 92 transcatheter aortic valve procedures performed, 40 'extreme-risk' patients underwent transapical TAVR (TA-TAVR) (EuroSCORE above 35%). Variables were analysed as risk factors for hospital and mid-term mortality, and a 2-year follow-up (FU) was obtained.

RESULTS: The mean age was: 81 ± 10 years. Twelve patients (30%) had chronic pulmonary disease, 32 (80%) severe peripheral vascular disease, 14 (35%) previous cardiac surgery, 19 (48%) chronic renal failure (2 in dialysis), 7 (17%) previous stroke (1 with disabilities), 3 (7%) a porcelain aorta and 12 (30%) were urgent cases. Mean left ventricle ejection fraction (LVEF) was 49 ± 13%, and mean logistic EuroSCORE was 48 ± 11%. Forty stent-valves were successfully implanted with six Grade-1 and one Grade-2 paravalvular leakages (success rate: 100%). Hospital mortality was 20% (8 patients). Causes of death following the valve academic research consortium (VARC) definitions were: life-threatening haemorrhage (1), myocardial infarction (1), sudden death (1), multiorgan failure (2), stroke (1) and severe respiratory dysfunction (2). Major complications (VARC definitions) were: myocardial infarction for left coronary ostium occlusion (1), life-threatening bleeding (2), stroke (2) and acute kidney injury with dialysis (2). Predictors for hospital mortality were: conversion to sternotomy, life-threatening haemorrhage, postoperative dialysis and long intensive care unit (ICU) stay. Variables associated with hospital mortality were: conversion to sternotomy ($P = 0.03$), life-threatening bleeding ($P = 0.02$), acute kidney injury with dialysis ($P = 0.03$) and prolonged ICU stay ($P = 0.02$). Mean FU time was 24 months: actuarial survival estimates for all-cause mortality at 6 months, 1 year, 18 months and 2 years were 68, 57, 54 and 54%, respectively. Patients still alive at FU were in good clinical condition, New York Heart Association (NYHA) class 1–2 and were never rehospitalized for cardiac decompensation.

CONCLUSIONS: TA-TAVR in extreme-risk patients carries a moderate risk of hospital mortality. Severe comorbidities and presence of residual paravalvular leakages affect the mid-term survival, whereas surviving patients have an acceptable quality of life without rehospitalizations for cardiac decompensation.

Keywords: Aortic valve stenosis • Transapical aortic valve replacement • High-risk patients

INTRODUCTION

Degenerative aortic valve stenosis (AS) occurs in the elderly and represents the most frequent acquired heart valve disease in developed countries [1, 2]. Because of the ageing population, the amount of elderly patients with aortic stenosis and severe comorbidities ('high-risk' and 'extreme-risk' profiles) is increasing constantly. Surgery for aortic valve replacement (AVR) with cardiopulmonary bypass (CPB), aortic cross clamping and cardioplegic cardiac arrest remains the treatment of choice in case of symptomatic AS and offers the potential for improved survival with excellent postoperative outcomes [3–5]. However, recently, patients at too high a risk for conventional surgery (logistic EuroSCORE > 20%) have been scheduled for transcatheter AVRs (TAVR) with stented-valves implanted on a beating heart and through minimally invasive accesses [6–8]. Results are good, but it is still unclear if the expected benefits of this technology are present when 'extreme-risk' profile patients with logistic EuroSCORE superior to 35%, are concerned.

We retrospectively selected a group of extreme-risk profile patients operated on for transapical TAVR (TA-TAVR) in our institution using the Sapien™ valve platform (Edwards Lifesciences Inc., Irvine, CA, USA), analysed outcomes and mid-term results (16 months of follow-up (FU)) and identified the risk factors for hospital and mid-term mortalities.

[†] Both authors contributed equally to this work.

MATERIALS AND METHODS

Study design

Using our transcatheter aortic valve registry, we identified patients with extreme-risk profiles who underwent aortic replacements from January 2009 to July 2011 (from 92 consecutive transcatheter aortic valve procedures performed, including 70 transapical and 22 transfemoral). All extreme-risk profile patients were in the transapical group.

The 'extreme-risk' profile was defined as follows: an elderly patient with severe symptomatic AS and predicted surgical mortality equal or superior to 35% (calculated by logistic EuroSCORE), with at least three concomitant EuroSCORE variables collected in the record. As to the choice of the EuroSCORE risk score system (www.euroscore.org), it represents a simple and intuitive tool for simplifying and standardizing the decision-making process for TAVR, and is routinely employed in our institution and in the majority of European hospitals.

Clinical data were collected, analysed and studied as risk factors for hospital mortality, all-cause mid-term mortality and cardiovascular mortality. A mid-term FU was obtained (mean time: 24 months; full term: 100%).

Transapical TAVR

All procedures were performed with balloon-expandable Sapien™ and Sapien-XT™ stent-valves (Edwards Lifesciences, Irvine, CA, USA) following standard guidelines [9]. In patients with impaired kidney function, we did not use contrast [10]. In one case, a redo patient with impaired left ventricular function (LVEF: 30%) and patent coronary bypasses, a femoro-femoral CPB was instituted before the procedure in order to decrease the risk of haemodynamic instability following the rapid pacing (preoperative strategic plan). All procedures were performed under general anaesthesia, in the operating room, by a team of dedicated cardiac surgeons, cardiologists and anaesthesiologists and using a high-quality C-arm fluoroscopic machine and a transoesophageal echocardiographic imaging system. All cases were discussed by a multidisciplinary team and all patients signed an informed consent. After the procedure, patients were placed on anticoagulation treatment for 3 months (following the protocol in use for standard bioprosthesis) plus aspirin (100 mg/day).

Statistical analysis

The statistical analysis was performed using the STATA 12.0 Data Analysis and Statistical Software package for Windows (StataCorp LP, College Station, TX, USA). Continuous variables are presented as mean ± one standard deviation (SD) where normally distributed, and as median and inter-quartile range if not normally distributed. Categorical variables are given as frequencies and percentages (%). Selected preoperative, intraoperative and postoperative variables were analysed as risk factors for hospital mortality (any death occurring within 30 days of the operation or death during the same hospital admission) using the Fisher's exact test. To identify predictors for hospital mortality (all death confounded and only cardiovascular death) and for mortality during the FU time (all-cause mortality and cardiovascular mortality), survival curves were computed using the Kaplan–Meier method [log-rank tests or Wilcoxon (Breslow) test for equality of survivor functions depending on the number of events]. For the

Table 1: Baseline characteristics

Characteristics	TA-TAVR ($n = 40$)	P for hospital mortality
Age (years)	81 ± 10 (range: 54–95)	
Sex, female	27 (67)	
Logistic EuroSCORE (%)	48 ± 11 (range: 35–77)	
Risk factors and comorbidities		
Coronary disease (any)	25 (62)	1.00
Peripheral vascular disease (severe)	32 (80)	1.00
Hypertension	21 (52)	1.00
Diabetes (type 1)	9 (22)	1.00
BMI < 20	6 (15)	0.35
COPD (any)	12 (30)	0.67
Previous stroke	7 (17)	0.61
Porcelain aorta (at CT-scan)	3 (7)	1.00
Chronic kidney failure	19 (48)	0.69
Chronic haemodialysis	2 (5)	1.00
Previous thoracic radiotherapy	4 (10)	1.00
Critical state (hospitalization in intermediate or ICU with drug infusions)	12 (30)	1.00
Cardiac history		
Previous cardiac surgery	14 (35)	1.00
Previous CABG	10 (25)	1.00
Previous aortic bioprosthesis	5 (13)	1.00
Previous PCI/stenting	7 (17)	0.13
Previous pacemaker implantation	3 (7)	1.00

TA-TAVR: transapical transcatheter aortic valve replacement; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention.
Data are presented as mean ± SD or number (%).

all death confounded, a Cox regression model was also run with the best predictors defined through the Kaplan–Meier analysis. A *P*-value <0.05 was considered significant. Authors had full access to, and take full responsibility for the integrity of the data.

RESULTS

Of the 92 consecutive transcatheter aortic valve procedures performed, we identified 40 elderly patients with logistic EuroSCORE superior or equal to 35% plus, at least 3 concomitant EuroSCORE variables collected in the record. Preoperative characteristics are listed in Table 1.

Specifically, the mean EuroSCORE was 48 ± 11%, with 32 patients (80%) suffering from severe peripheral vascular disease contra-indicating transfemoral transcatheter procedures (all patients showed severe advanced aortic atherosclerosis at computed tomography (CT)-scan and transoesophageal echocardiogram). The vascular assessment was performed under angio CT-scan and Doppler for the aorta and carotid arteries, and the subclavian access was never used in our hospital ('off-label' use with the Edwards Sapien™ platform at that time). Seven patients had a history of stroke and one carried impaired left arm motility as residual disability. With regard to cardiac diseases, 14 patients (35%) had previous cardiac surgery and 5 a concomitant implantation of an aortic bioprosthesis (3 Sorin Mitroflow™ (21, 23 and 25 mm) and 2 Edwards Perimount® (23 and 25 mm)) [11]. Severe coronary disease was previously diagnosed and treated in 15 patients (37%), with surgery for coronary revascularization in 10, and percutaneous procedure in 7. Nineteen patients (48%) suffered from chronic kidney insufficiency (chronic increase of blood creatinine level of at least double the standard limits, following the RIFLE classification), and 2 were already under intermittent haemodialysis: in the whole group of extreme-risk patients, the mean blood preoperative creatinine and urea levels were 108 ± 54 µmol/l and 12 ± 7 mmol/l, respectively (ranges in our hospital: creatinine 62–106 µmol/l; urea 3–7 mmol/l).

Concerning their preoperative clinical state, 12 patients (30%) were critical, with signs of cardiac failure requiring surveillance in the mid-care or intensive-care unit and drug infusions or, in one case, intubation (low cardiac output due to late stage AS). From an echocardiographic point of view (Table 2), the mean LVEF was 49 ± 13%, the mean trans-valvular peak gradient was 63 ± 25 mmHg, the calculated orifice area was 0.6 ± 0.2 cm^2 (indexed: 0.4 ± 0.1 cm^2/m^2) and 23 patients (57%) suffered from chronic pulmonary hypertension (pulmonary artery systolic pressure above 50 mmHg). All patients showed severe AS except one, a 'valve-in-valve' patient, where the degenerated aortic bioprosthesis was severely incompetent.

Intraoperatively, 40 Sapien™ stent-valves were placed correctly [procedural success rate according to the valve academic research consortium (VARC) definition: 100%] with a mean stent-valve diameter of 24 ± 2 mm; (22 valves: 23 mm; 17 valves: 26 mm; and 1 valve: 29 mm) corresponding to a measured mean aortic annulus of 23 ± 2 and 22 ± 2 mm at CT-scan and transoesophageal echocardiogram imaging, respectively (Tables 2 and 3). CPB support was required three times: in a coronary redo case with low LVEF, the CPB was established before the procedure to sustain the haemodynamic status during the rapid pacing phases (femoro-femoral cannulation in a patient with tortuous femoral arteries and previous peripheral vascular surgery); in two more cases CPB was urgently instituted to treat life-threatening haemorrhages (from the apex and from the left ventricle). With respect to CPB use, although patients are at extreme-risk or inoperable, we maintain the machine on stand-by, and its usage is justified when severe bleedings occur: once the patient is haemodynamically stable and the left ventricle is unloaded, the apical haemostasis becomes easier and, in the mean time, the lost blood is rapidly reinfused. Nevertheless, CPB strongly depends on the availability of cannulation sites, this being determined prior to surgery, and requires a prompt reaction from the entire team.

Table 2: Preoperative echocardiographic and CT-scan assessment

Variables	TA-TAVR (*n* = 40)
Mean LVEF (%)	49 ± 13
LVEF 0–30%	4 (10)
LVEF 30–50%	17 (45)
LVEF > 50%	17 (45)
Mean EOA (cm^2)	0.6 ± 0.2
Mean trans-valvular peak gradient (mmHg)	65 ± 25
Pulmonary hypertension (>50 mmHg)	23 (57)
Mean aortic annulus diameter at TEE (mm)	22 ± 2
Mean aortic annulus diameter at CT-scan (mm)	23 ± 2
Mean aortic annulus-LCA distance (mm)	11 ± 2
Mean aortic annulus-RCA distance (mm)	12 ± 3
Pure degenerative AS	39 (97)
Pure valve regurgitation (in a degenerated bioprosthesis)	1 (3)

TA-TAVR: transapical aortic valve replacement; LVEF: left ventricle ejection fraction; EOA: effective orifice area; TTE: transthoracic echocardiogram; TEE: transeosophageal echocardiogram; CT: computed tomography; LCA: left coronary artery; RCA: right coronary artery; AS: aortic valve stenosis.
Data are presented as mean ± SD or number (%).

The mean procedural time was 95 ± 29 min and 13 patients were extubated in the operating room. Two patients died on the operating table: the first, an 84-year-old female, died from a life-threatening haemorrhage originating from a tear in the left ventricle (after surgical repair we were unable to wean the CPB support), whereas the second patient, also a frail 88-year-old female with a 19-mm aortic annulus, died from an irreversible occlusion of the left coronary ostium with consequent intraprocedural myocardial infarction and cardiac arrest: the stent-valve displaced the severely calcified left coronary leaflet against the aortic wall and, despite the sternotomy and the attempt to institute a CPB support, the haemodynamic status deteriorated rapidly and irreversibly.

At echocardiography, we had one Grade 2 (severe annular calcifications) and six Grade 1 paravalvular leakages with a mean trans-valvular mean gradient of 11 ± 5 mmHg. In the subgroup of five patients with 'valve-in-valve' treatments, the mean trans-valvular mean gradient was 20 ± 6 mmHg and the patient carrying the smallest bioprosthesis (the 21 mm Sorin Mitroflow™) had peak and mean gradients of 28 and 17 mmHg, respectively [11, 12].

Hospital mortality was 20% (in total eight patients died; six within 30 days) and cardiovascular causes of death, according to the VARC definition, were four: one intraprocedural life-threatening ventricular haemorrhage requiring CPB and surgical repair of the tear, ending up with severe irreversible ventricular

Table 3: Clinical operative results

Variables	TA-TAVR ($n = 40$)	P for hospital mortality
Successful procedure (one correctly implanted stent-valve and system retrieval)	40 (100%)	
Valve-in-valve procedure (VinV)	5 (13)	1.00
Redo surgery	14 (35)	1.00
Conversion to sternotomy	2 (5)	0.03
IABP support	0	
CPB use	3 (7)	0.09
Mean procedural time (min)	95 ± 29	
Mean stent-valve diameter (mm) 22× a 23 mm; 17× a 26 mm; 1× a 29 mm)	24 ± 2	
Surgical outcome and complications		
Valve embolization	0	
Valve malfunctioning	0	
Paravalvular leak (Grade 1 = 6; Grade 2 = 1)	7 (17)	0.13
Trans-valvular mean gradient (mmHg)	11 ± 5	
Myocardial infarction (left coronary ostium obstruction)	1 (2)	0.26
Life-threatening bleeding (one apical and one ventricular)	2 (5)	0.02
Rethoracotomy for minor haemostasis	1 (2)	1.00
Early extubation (up to 5 h postoperatively)	33 (82)	0.02
On-table extubation	13 (32)	1.00
Long ICU stay, long intubation, tracheotomy	2 (5)	0.02
Acute kidney injury (RIFLE stage 3)	2 (5)	0.03
Pacemaker implantation for BAV3	2 (5)	1.00
Pneumonia	3 (7)	0.56
Stroke	2 (5)	0.46
ICU stay (days)	3 ± 7 (median = 1; IQR = 1)	
Hospital stay (days)	16 ± 11(median = 12; IQR = 6)	
Mortality		
Intraprocedural death	2 (5)	
Thirty-day mortality	6 (15)	
In-hospital mortality	8 (20)	

TA-TAVR: transapical aortic valve replacement; IABP: intra-aortic balloon pump; CPB: cardiopulmonary bypass; ICU: intensive care unit; IQR: inter-quartile range.
Data are presented as mean ± SD or number (%).

dysfunction; one intraprocedural myocardial infarction for left coronary ostium obstruction; one sudden death at postoperative day 12 (probably a pulmonary oedema due to a peak of blood pressure in systemic hypertension) and one severe stroke following intraoperative hypotension in a coronary redo case who required reanimation manoeuvres after the rapid cardiac pacing. Two more patients died of multiorgan failure (MOF) during the intensive care unit (ICU) stay and two frail old female patients (cachexia) died of severe respiratory dysfunction in pneumonia.

Following the VARC definitions for postoperative complications during TAVR procedures, we also had one patient who had an apical life-threatening bleeding successfully treated under CPB, two (5%) who suffered from acute kidney injury requiring continuous haemofiltration (RIFLE classification stage 3), one with a stroke with haemiplegia at postoperative day 9 despite the anticoagulation treatment and aspirin, and patients requiring definitive pacemakers for Grade 3 atrio-ventricular-block (Tables 3 and 4, Fig. 1).

Concerning the predictors for hospital mortality, we did not find preoperative variables that predicted hospital mortality (limited number of patients in this cohort). However, some intra- and postoperative complications were statistically significant to predict hospital mortality ($P < 0.05$): conversion to sternotomy ($P = 0.03$), intraoperative life-threatening bleeding ($P = 0.02$), postoperative acute kidney injury with dialysis ($P = 0.03$) and prolonged ICU stay ($P = 0.02$). The rapid extubation within 5 h of surgery was a positive predictor for lower risk of hospital mortality ($P = 0.02$).

FU was performed in May 2012 and the mean FU time was 24 months (Table 5). Among the 32 patients who were discharged, 20 were still alive and 12 deceased. The cause of death was cardiovascular in 10 patients (cardiovascular mortality: 31%): 7 documented cardiac failures, 1 cardiac arrest and 2 cerebral haemorrhages. The actuarial survival estimates from cardiovascular mortality at 6 months, 1 year, 18 months and 2 years were 90, 77, 73 and 73%, respectively (Fig. 2A). MOF and pneumonia were causes of death in two more patients (all-cause mortality at FU: 37%). The 20 patients still alive were all in good clinical condition, with respect to their age, and were all in New York Heart Association (NYHA) class 1–2 without history of rehospitalization for cardiac decompensation: to note, this includes the 2 patients on preoperative chronic haemodialysis and 4 'valve-in-valve' cases. Signs of valve dysfunction were not reported. The actuarial survival estimates from all-cause confounded mortality at 6 months, 1 year, 18 months and 2 years are 68, 57, 54 and 54%, respectively (Fig. 2B).

Concerning the risk factors for all-cause mortality at FU, we analysed the same variables we used for the hospital mortality and our findings are that there were one preprocedural and two postprocedural variables with statistical relevance: the presence of previous coronary angioplasty/stent ($P = 0.01$) and the presence of a postoperative paravalvular leak ($P = 0.02$) were

Table 4: Clinical endpoints following the VARC[a] definitions, *n* = 40

Device success	40 (100)
All-cause mortality	8 (20)
Cardiovascular mortality	4 (10)
Myocardial infarction (periprocedural)	1 (2.5)
Stroke (major)	2 (5)
Bleeding (life-threatening)	2 (5)
Access site complications (vascular–major)	1 (2.5)
Acute kidney injury (RIFLE 3)	2 (5)
PVL (moderate/severe)	1 (2.5)
Valve-related failure/dysfunction	0

PVL: paravalvular leak.
Data are presented as mean ± SD or number (%).
[a]Standardized endpoints for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. Eur Heart J 2011;32:205–217.

Table 5: Follow-up (32 discharged patients)

Variables	TA-TAVR (*n* = 32)
Mean FU time (months)	24 (range 9–40)
FU completeness	100%
Patients alive at FU	20 (63)
All-cause mortality	12 (37)
Cardiovascular mortality (cardiac failure: 7; cardiac arrest: 1; cerebrovascular accident: 2)	10 (31)
Other cause of death	
MOF (in sepsis)	1 (3)
Pneumonia	1 (3)
Valve dysfunction	0
Valve-related cardiovascular procedures	0

TA-TAVR: transapical aortic valve replacement; FU: follow-up; MOF: multiorgan failure.
Data are presented as mean ± SD or number (%).

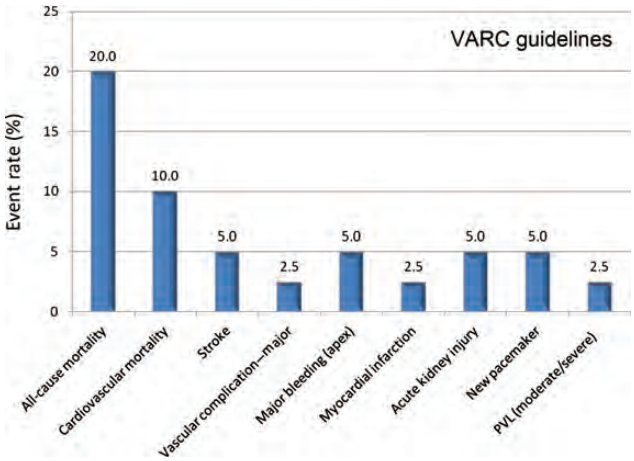

Figure 1: Hospital outcome: clinical endpoints following the VARC definition. (Standardized endpoints for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. Eur Heart J 2011;32:205–217.)

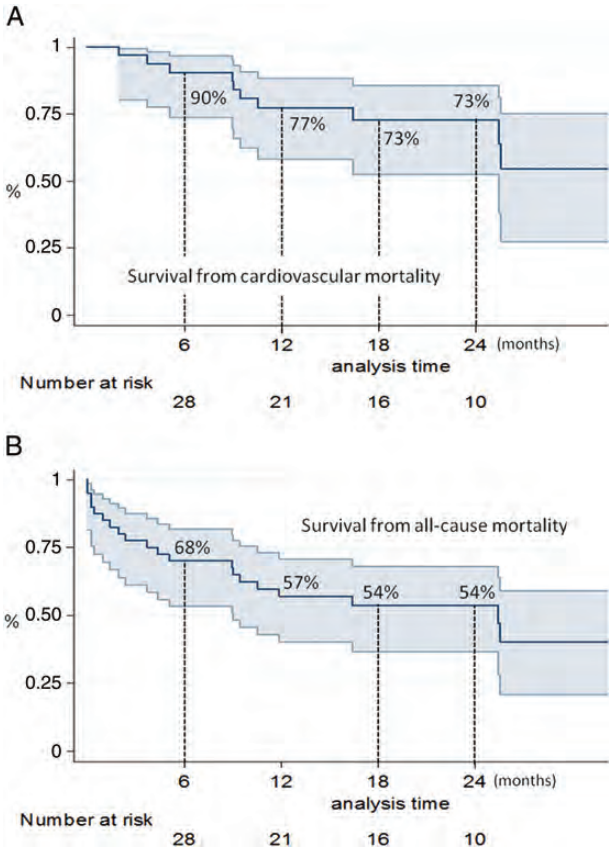

Figure 2: (**A**) Kaplan–Meier survival estimate for cardiovascular mortality [with confidence intervals (95% CI) in blue]. (**B**) Kaplan–Meier survival estimate for all-cause mortality (with 95% CI in blue).

identified as risk factors for late mortality (Fig. 3A and B), whereas the early extubation had a positive impact on long-term survival ($P = 0.03$). The multivariate analysis applied to the variables 'previous coronary stenting' and 'postoperative paravalvular leak' (Cox regression model) showed a 3.6 times and a 3 times higher risk of long-term all-cause mortality, respectively, for patients having these characteristics.

With regard to the risk factors for late cardiovascular mortality, we identified variables with statistical significance: systemic hypertension ($P < 0.00$), previous coronary bypass grafting ($P = 0.02$), previous coronary angioplasty/stent ($P = 0.01$) (Fig. 3C) and postoperative paravalvular leak ($P = 0.01$) (Fig. 3D).

DISCUSSION

TAVR is a minimally invasive technique for elderly patients with symptomatic AS and at high-risk for conventional surgery. Moreover, those with an 'extreme-risk' profile are very fragile elderly patients with a very poor outcome in the absence of appropriate treatment, and we were interested in evaluating the efficacy of transcatheter aortic valve procedures in this selected subgroup of patients.

Although TAVR procedures in high-risk patients with logistic EuroSCORE around 20% have already shown good hospital outcomes with 1-year mortality rates ranging from 25 to 30%

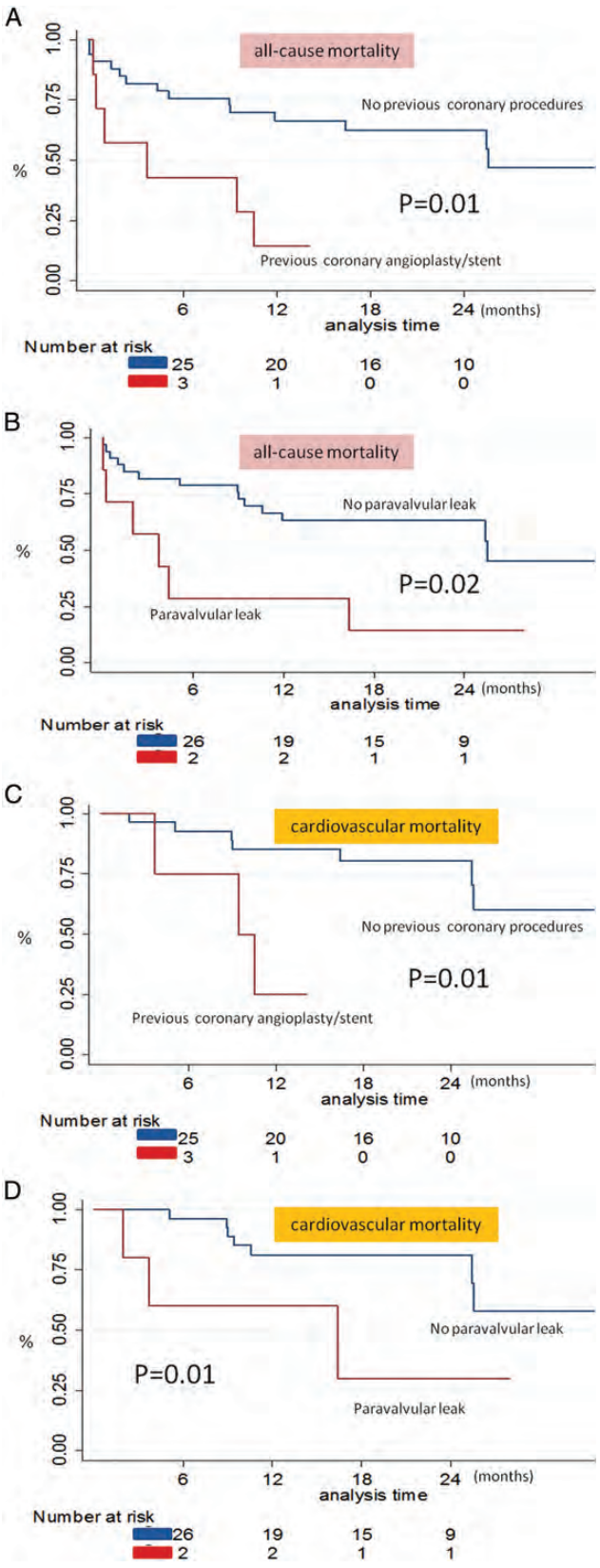

Figure 3: (**A**) Survival from all-cause mortality in patients with and without preoperative coronary angioplasty/stent. (**B**) Survival from all-cause mortality in patients with and without paravalvular leaks. (**C**) Survival from cardiovascular mortality in patients with and without preoperative coronary angioplasty/stent. (**D**) Survival from cardiovascular mortality in patients with and without paravalvular leaks.

[13, 14], we do not know yet if the same procedure in extreme-risk profile patients also guarantees acceptable results in terms of procedural risk, ameliorated quality of life and, perhaps, longer life-expectancy. Therefore, we studied 40 consecutive TA-TAVR patients with logistic EuroSCORE above 35%. In comparing our results with the (limited) literature, we observe that Thielmann *et al.* [15] also identified 39 patients at extreme risk who underwent TAVR (24 transapical and 15 transfemoral) with a mean logistic EuroSCORE of 44 ± 12%. They showed a 30-day mortality of 18% in the entire group and 21% in the transapical group (in our experience, the 30-day mortality was 15% and the hospital mortality 20%), a 6-month survival rate of 74% in the entire group and 70% in the transapical group, and a 12-month survival rate of 64% in the entire group and 62% in the transapical group. Moreover, the transfemoral and the transapical populations showed different mean EuroSCORE profiles: 38 and 52%, respectively. This difference was statistically significant ($P < 0.001$) and confirmed the higher challenges in performing TA-TAVR than transfemoral TAVR.

If we compare our group with standard TA-TAVR patients, we observe that there are better hospital outcomes and mid-term results as soon as the mean logistic EuroSCORE decreases from above 40 to ~30%. A paper from Walther *et al.* [16] describes the mid-term outcome of 299 standard transapical patients with a mean EuroSCORE of 31 ± 16%: the 30-day mortality was reported at 9%, and the 1- and 2-year survival rates were 73 and 68%, respectively. Similarly, the PARTNER trial in its transapical arm (104 patients) with a mean logistic EuroSCORE of 32% showed a 30-day mortality of 4% with a 1-year survival rate of 71% [14].

With respect to predictors for hospital mortality, we did not observe a statistical significance for any of the collected preoperative variables (due, probably, to the limited amount of patients), and this confirms that in very high-risk patients groups, the patient selection performed by the TAVR-team remains the main predictor for hospital outcomes. Nevertheless, we observed significant *P*-values for intraoperative and postoperative complications such as conversion to sternotomy, intraprocedural life-threatening bleeding, postoperative renal failure with dialysis and prolonged ICU stay. These findings are in line with results from other groups and underline the fragility of these extreme-risk profile patients: this should always guide the medical community to carefully evaluate patients who are candidates for TAVR with a reasonable use of bailout procedures in case of very severe intraprocedural complications. In particular, the use of contrast for angiographies should be reduced as much as possible in order to reduce the risk of postoperative kidney injury, whereas the CPB stand-by can have a remarkable positive effect for recovery in case of severe haemodynamic instability after an otherwise uncomplicated procedure (typically, in redo patients after the rapid cardiac pacing).

The concept of 'frailty' requires further evaluations also in order to better quantify the procedural risk: in our experience, elderly, slim females were reputed to be too fragile to survive standard surgery but, perhaps, also the adverse events that can complicate transapical TAVR. In fact, the same phenotype of patients badly tolerated, in our experience, prolonged ICU stay and prolonged mechanical ventilation because of the limited muscular reserve (cachexia) and the consequent higher risk of pneumonia and MOF. However, after having considered a body mass index below 20 as a very simple, indirect sign of fragility, we did not find any statistical significance for hospital mortality in our study (limited by the small number of patients) [17].

Concluding, in future TAVR reports, more patients and a more frailty-focused analysis, with specific scores, are required to better define this point and, in general, we believe that in the process of adjudicating very high-risk patients to this minimally invasive procedure we will benefit from new and simple score systems specifically designed for the evaluation of frail candidates.

Concerning the mid-term survival of this limited cohort of patients (comparable to patients with severe symptomatic AS in medical therapy [1, 2]), our findings are in line with the cohort B of the PARTNER trial, and we can comment that this can be related to the presence of multiple severe concomitant comorbidities and the AVR plays a marginal role in increasing life expectancy. However, patients alive at FU recall were all in NYHA class 1–2 with an acceptable quality of life (with respect of their age), and they were never rehospitalized for cardiac failure (this reached the goal of the Combined Efficacy Endpoint at 1 year of the VARC classification, together with absence of signs of stent-valve malfunction).

With respect to risk factors for mid-term all-cause and cardiovascular mortality, two characteristics were significant for both: the presence of previous coronary angioplasty and stenting ($P = 0.01$) and the presence of a residual paravalvular leak after the TAVR ($P = 0.02$ and $P = 0.01$). Moreover, systemic hypertension ($P < 0.00$) and previous surgical myocardial revascularization ($P = 0.02$) have a negative effect on late cardiovascular mortality in our cohort. Thus, we can assume that the concomitant presence of a severe coronary disease that already required percutaneous or surgical revascularization, plays a key role in increasing the risk of death in very fragile patients treated for AS. On the other hand, if we take into consideration the paravalvular leak, this is not the first time that residual leaks are related to a higher risk of mid-term mortality in a group of TA-TAVR patients [18, 19]. In particular, in our experience the degree of the leakage was evaluated by echocardiography both intraoperatively and before the patient's discharge and we measured only one Grade 2 and six Grade 1 leaks: in standard patients, these findings would not have represented a severe complication affecting mid-term survival, whereas very diseased patients do not have the reserve to support any degree of aortic valve insufficiency. Therefore, further investigations in bigger groups are mandatory to well define this crucial point, and we must be more aggressive in treating leakages.

At the end of these considerations, we should extrapolate a lesson learned from this cohort of patients at extreme risk, operated on during a pioneering phase of TAVR procedures. Firstly, as is well known, all patients must be evaluated by a multidisciplinary TAVR-team composed, when the risk score is above 20% (by EuroSCORE), of a cardiac surgeon, a cardiologist, an anaesthetist, and also by an intensivist who evaluates the risk of prolonged ICU stay and long intubation time. This first phase is crucial, and doctors should carefully evaluate the 'biological age' of these patients using their experience. Secondly, following our experience, elderly slim women represent a pool of bad candidates even for TAVR because of their increased fragility and absence of the muscular reserve required to recover in case of complications or long mechanical ventilation time in ICU. Thirdly, if the apical access represents a risk of untreatable haemorrhage (difficult to evaluate preoperatively, but the surgeon's experience plays a role) the TA-TAVR can be aborted and other access sites, such as the ascending aorta (trans-aortic approach), should be taken into consideration. Fourthly, the CPB support can be precious in some critical situations, and the injection of contrast has to be reduced as much as possible to prevent renal injury. Fifthly, a more-than trivial paravalvular leak requires tentative treatment.

In conclusion, TA-TAVR for extreme-risk patients carries a moderate procedural risk, and patients surviving surgery have a good quality of life with a low risk of rehospitalization for cardiac failure. Nevertheless, mid-term survival is affected by multiple comorbidities and by the presence of residual paravalvular leakages, and is comparable to patients with severe symptomatic AS under medical treatment.

Limitations of the study

This study has important limitations: (1) it is a retrospective study; (2) there is no control group because patients with the same characteristics undergoing standard AVR or transfemoral TAVR do not exist given the extreme-high risk profile; (3) the number of patients is small with a relatively short FU time (2 years).

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Conflict of interest: Enrico Ferrari is a consultant for Edwards Lifesciences.

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