European Journal of Cardio-Thoracic Surgery 50 (2016) 1139–1148
doi:10.1093/ejcts/ezw218 Advance Access publication 12 July 2016

ORIGINAL ARTICLE

Cite this article as: Salizzoni S, D'Onofrio A, Agrifoglio M, Colombo A, Chieffo A, Cioni M *et al*. Early and mid-term outcomes of 1904 patients undergoing transcatheter balloon-expandable valve implantation in Italy: results from the Italian Transcatheter Balloon-Expandable Valve Implantation Registry (ITER). Eur J Cardiothorac Surg 2016;50:1139–48.

Early and mid-term outcomes of 1904 patients undergoing transcatheter balloon-expandable valve implantation in Italy: results from the Italian Transcatheter Balloon-Expandable Valve Implantation Registry (ITER)[†]

Stefano Salizzoni[a,*], Augusto D'Onofrio[b], Marco Agrifoglio[c], Antonio Colombo[d,e], Alaide Chieffo[d], Micaela Cioni[d], Laura Besola[b], Tommaso Regesta[f], Filippo Rapetto[f], Giuseppe Tarantini[b], Massimo Napodano[b], Davide Gabbieri[g], Francesco Saia[h], Corrado Tamburino[i], Flavio Ribichini[j], Diego Cugola[k], Marco Aiello[l], Francesco Sanna[m], Alessandro Iadanza[n], Esmeralda Pompei[o], Pierluigi Stefàno[p], Antioco Cappai[q], Alessandro Minati[r], Mauro Cassese[s], Gian Luca Martinelli[s], Andrea Agostinelli[t], Rosario Fiorilli[u], Francesco Casilli[v], Maurizio Reale[w], Francesco Bedogni[x], Anna Sonia Petronio[y], Rosa Alba Mozzillo[z], Roberto Bonmassari[aa], Carlo Briguori[ab], Armando Liso[ac], Gennaro Sardella[ad], Giuseppe Bruschi[ae], Claudia Fiorina[af], Claudia Filippini[a], Claudio Moretti[a], Maurizio D'Amico[ag], Michele La Torre[ag], Federico Conrotto[ag], Roberto Di Bartolomeo[h], Gino Gerosa[b] and Mauro Rinaldi[a]

[a] Department of Surgical Sciences, University of Turin, Turin, Italy
[b] Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy
[c] Centro Cardiologico Monzino—Department of Clinical Sciences and Community, University of Milan, Milan, Italy
[d] Ospedale San Raffaele, Milano, Italy
[e] Casa di Cura Columbus, Milano, Italy
[f] Divisione di Cardiochirurgia, IRCCS San Martino-IST, Genova, Italy
[g] Hesperia Hospital, Modena, Italy
[h] Cardio-Thoraco-Vascular Department, University Hospital Policlinico S. Orsola - Malpighi, Bologna, Italy
[i] Ospedale Ferrarotto, Università di Catania, Catania, Italy
[j] AOU Integrata Verona, Verona, Italy
[k] AO Papa Giovanni XXIII, Bergamo, Italy
[l] IRCCS Policlinico S. Matteo, Pavia, Italy
[m] AO Brotzu, Cagliari, Italy
[n] AOU Policlinico Le Scotte, Siena, Italy
[o] AOUD Santa Maria della Misericordia, Udine, Italy
[p] AOU Careggi, Firenze, Italy
[q] Humanitas Research Hospital, Rozzano, Italy
[r] Ospedale Cattinara, Trieste, Italy
[s] Clinica S. Maria, Bari, Italy
[t] Azienda O.U. Ospedale Maggiore di Parma, Italy
[u] AO San Camillo Forlanini, Roma, Italy
[v] IRCCS Policlinico San Donato, Milano, Italy
[w] A.O. Cesare Biagio e Arrigo, Alessandria, Italy
[x] Istituto Clinico Sant'Ambrogio, Milano, Italy
[y] AOU Pisana, Pisa, Italy
[z] AOU Federico II, Napoli, Italy
[aa] Ospedale S. Chiara, Trento, Italy
[ab] Clinica Mediterranea, Napoli, Italy
[ac] Città di Lecce Hospital, Lecce, Italy
[ad] Policlinico Umberto I, Roma, Italy
[ae] Ospedale Niguarda, Milano, Italy
[af] Spedali Civili, Brescia, Italy
[ag] Città della Salute e della Scienza—Molinette, Torino, Italy

* Corresponding author. Corso Bramante 88, 10126 Torino, Italy. Tel: +39-011-6335511; fax: +39-011-6336130; e-mail: salizzonis@gmail.com (S. Salizzoni).

Received 29 June 2015; received in revised form 8 April 2016; accepted 13 April 2016

[†]Presented at the 28th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Milan, Italy, 11–15 October 2014.

Abstract

OBJECTIVES: The aim of this multicentre study is to report the clinical experiences of all patients undergoing transcatheter aortic valve implantation (TAVI) with a balloon-expandable device in Italy.

METHODS: The Italian Transcatheter balloon-Expandable valve Registry (ITER) is a real-world registry that includes patients who have undergone TAVI with the Sapien (Edwards Lifesciences, Irvine, CA, USA) bioprosthesis in Italy since it became available in clinical practice. From 2007 to 2012, 1904 patients were enrolled to undergo TAVI in 33 Italian centres. Outcomes were classified according to the updated Valve Academic Research Consortium (VARC-2) definitions. A multivariable analysis was performed to identify independent predictors of all-cause mortality.

RESULTS: Mean age was 81.7 (SD:6.2) years, and 1147 (60.2%) patients were female. Mean Logistic EuroSCORE was 21.1% (SD:13.7). Transfemoral, transapical, transaortic and transaxillary TAVI was performed in 1252 (65.8%), 630 (33.1%), 18 (0.9%) and 4 (0.2%) patients, respectively. Operative mortality was 7.2% (137 patients). The VARC-2 outcomes were as follows: device success, 88.1%; disabling stroke, 1.0%; life-threatening and major bleeding 9.8 and 10.5%, respectively; major vascular complication, 9.7%; acute kidney injury, 8.2%; acute myocardial infarction ≤72 h, 1.5%. Perioperative pacemaker implantation was necessary in 116 (6.1%) patients. At discharge, the mean transprosthetic gradient was 10.7 (SD:4.5) mmHg. Incidence of postoperative mild, moderate or severe paravalvular leak was, respectively, 32.1, 5.0 and 0.4%. A total of 444/1767 (25.1%) deaths after hospital discharge were reported: of these, 168 (37.8%) were classified as cardiac death. Preoperative independent predictors of all-cause mortality were male gender (HR: 1.395; 95% CI:1.052–1.849); overweight, BMI 25–30 kg/m^2 (HR: 0.775; 95% CI: 0.616–0.974); serum creatinine level (every 1 mg/dl increase; HR: 1.314; 95% CI:1.167–1.480); haemoglobin level (every 1 g/dl increase; HR: 0.905; 95% CI:0.833–0.984); critical preoperative state (HR: 2.282; 95% CI: 1.384–3.761); neurological dysfunction (HR: 1.552; 95% CI:1.060–2.272); atrial fibrillation (HR: 1.556; 95% CI:1.213–1.995); pacemaker rhythm (HR: 1.948; 95% CI:1.310–2.896); NYHA Class III or IV (HR: 1.800; 95% CI:1.205–2.689 or HR: 2.331; 95% CI:1.392–3.903, respectively).

CONCLUSIONS: TAVI with a balloon-expandable device in the 'real world' shows good mid-term outcomes in terms of survival, technical success, valve-related adverse events and haemodynamic performance.

Keywords: TAVI • Registry • Aortic stenosis

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is an established procedure for patients suffering from severe symptomatic aortic valve stenosis who are considered inoperable or with serious comorbidities that generate a high-risk surgical profile [1–9].

Clinical data are still needed to further support expansion of TAVI to moderate-risk patients [10]. Controlled trials and 'real-world' experience from single centres and multicentre registries are crucial to share results and complications to improve patient selection and outcomes.

ITER (Italian Transcatheter Balloon-Expandable Valve Implantation Registry) is a Latin word that stands for the new 'path' we are searching for in the treatment of stenotic aortic valve disease.

ITER is an 'all-comers', real-world, independent multicentre registry that virtually includes all TAVI procedures with a balloon-expandable prosthesis performed in Italy since the beginning of the activity in 2007. The study device is the only balloon-expandable transcatheter bioprosthesis available for clinical use so far, the Sapien (Edwards Lifesciences, Irvine, CA, USA) and all its following generations (Sapien XT and Sapien 3). The aim of this registry is ultimately to assess long-term clinical and haemodynamic results of patients undergoing TAVI with a balloon-expandable bioprosthesis in a real-world national scenario. However, in this first report of the ITER, we aim to evaluate patients' characteristics as well as to assess early and medium-term clinical and haemodynamic outcomes of all patients undergoing balloon-expandable TAVI in our country.

PATIENTS AND METHODS

The ITER includes 33 Italian centres performing balloon-expandable TAVI. All patients undergoing balloon-expandable TAVI in each centre between 2007 and 2012 were enrolled in this registry regardless of the access. Data were collected from each study site and then anonymously sent to the University of Torino for storage and analysis. Ethic committees from the partipating centres approved data collection, and patient informed consent was always collected. As this is a real-world, all-comers' experience, patient selection and procedure strategies were done according to single-site policies, experience and protocols. All procedures were performed using the Edwards Sapien and Sapien XT prostheses with retrograde or antegrade approaches. The Sapien 3 valve was not yet available during the study period of this first ITER report.

Data and definitions

Preoperative risk factors were defined according to the EuroSCORE (ES) classification [11, 12].

The presence of preoperative coronary artery disease was considered according to the STS Score definitions as left anterior descending system, circumflex system and/or right system with greater than or equal to 50% narrowing of any vessel.

Postoperative outcomes were defined according to the updated Valve Academic Research Consortium (VARC-2) definitions [13].

In particular, 'operative mortality' is defined as all deaths that occurred within 30 days from the procedure or longer if the patient was not discharged from the treatment hospital or a secondary rehabilitation facility. The echocardiographic measurements were performed according to the current recommendations of the European and American Societies of Echocardiography. In particular, aortic regurgitation was classified as absent/trivial (0), mild (1+), moderate (2+) and severe (3+).

Follow-up

Patients underwent clinical and echocardiographic assessment at the study site before the operation, at hospital discharge and then according to each centre's protocol.

Follow-up time points were requested after 3–6 months, 1 year and every year thereafter.

Data on late mortality were collected in different ways according to the various centres. Mainly follow-up data were collected by direct contact with patients, telephone and registry office. Few centres had data linkage with regional registers for data on mortality. The last census date varies between centres, and it is between January and March 2014.

Statistical analysis

Data are presented as frequency and percentages as well as mean and standard deviation or median and first and third quartiles. A univariable analysis was performed to test which covariates would be considered in a further multivariable analysis: a hazard ratio and its 95% confidence interval were estimated for each variable; a log-rank test was used for categorical variables. Multivariable analysis was used to determine risk factors for the occurrence of total mortality.

A Cox proportional hazards regression model was fitted to determine the relative risk for death from the procedure until the end of follow-up: the results were expressed as hazard ratios with 95% confidence interval.

Clinical significant variables were then entered in the model; we chose the variables with a 0.2 significance level. Only variables missing for less than 5% of the records were considered for inclusion in the multivariable model and for these it was made imputation with the mean of the observed values. The logistic EuroSCORE was not included in the model because the individual factors had been already included.

The assumption of proportional hazards was assessed by including and testing time-dependent covariates defined as the interaction between the predictor and a function of survival time. All time-dependent covariates were not significant. A plot of the Kaplan–Meier estimator was performed for all patients. All data were analysed using SAS release 9.03 by SAS Institute Inc. (Cary, NC, USA).

RESULTS

Study population

The study population comprises 1904 patients enrolled in ITER from November 2007 to December 2012. Enrolment at each centre is summarized in supplementary Figure A. Mean age was 81.7 (SD:6.2) years; 1147 (60.2%) patients were female; mean Logistic EuroSCORE, EuroSCORE II and STS score were 21.1 (SD:13.7)%, 7.3 (SD:6.7)% and 9.2 (SD:7.6)%, respectively. The New York Heart Association (NYHA) functional class was III or IV in 1536 (80.7%) patients. Preoperative clinical variables of patients are listed in Table 1.

Baseline echocardiography

Indication for TAVI was severe symptomatic aortic stenosis, with or without concomitant insufficiency, in all patients. In particular, 47 (2.5%) patients suffered from concomitant severe aortic regurgitation. Mean aortic gradient was 50.2 (SD: 15.0) mmHg, and the aortic valve area index was 0.46 (SD: 0.14) cm^2/m^2. Mean left ventricle ejection fraction was 53.5% (SD: 12.4). Detailed echocardiographic data are summarized in Table 2.

Procedural results

The antegrade transapical approach was used in 630 (33.1%) patients. Retrograde access was achieved in the remaining cases: 1252 (65.8%) underwent transfemoral, 18 (1.0%) transaortic and 4 (0.2%) transaxillary TAVI. The Sapien XT valve has been implanted in 1303 (68.4%) patients since mid-2010.

The 23- and 26-mm prostheses were equally used: 902 (47.3%) and 906 (47.6%), respectively. The 29-mm valve was used in 96 (5.1%) patients.

A total of 223 operative complications occurred in 143 (7.5%) patients. A detailed description of intraoperative complications is depicted in Table 3.

Perioperative outcomes

Outcomes according to VARC-2 definitions are summarized in Table 4.

Device success was 88.1%; life-threatening bleeding occurred in 186 (9.8%) patients and major vascular complications happened in 177 (9.3%) patients. Heart rhythm conduction disturbances occurred in 286 (15%) patients, 116 (6.1%) of whom needed a pacemaker (PM) implantation before discharge and 170 (8.9%) of whom had at least one episode of atrial fibrillation.

Acute kidney injury (AKI) occurred in 156 (8.2%) patients, 53 (2.8%) of whom needed dialysis support in the perioperative period. Operative mortality occurred in 137 (7.2%) patients. The 60-day and 90-day mortality rates, using the Kaplan–Meier estimator, were, respectively, 7.1 and 8.1%.

The early safety (at 30 days) composite end-point was reached in 1418 (74.5%) patients.

Echocardiographic outcomes

Peak and mean transvalvular gradients at discharge were 19.9 (SD: 7.8) and 10.8 (SD: 4.5) mmHg ($P < 0.001$), respectively, and after 1 year were 20.5 (SD: 8.4) and 10.9 (SD: 4.8) mmHg.

More than mild aortic regurgitation was detected in 99 (5.2%) patients, 8 (0.4%) of whom had severe insufficiency. Detailed echocardiographic measurements are summarized in Table 5.

Hospital and intensive care unit stay

After TAVI, 1153 patients (60.6%) were admitted into an intensive care unit: 618 (49.4% of all TF) transfemoral; 519 (82.5%) transapical; 16 (84.2%) transaortic. Average stay was 24 (IQR1 18; IQR3 48) h. The average length of in-hospital stay was 7 (IQR1 5; IQR3 11) days after the procedure.

Follow-up

Median follow-up was 773 days (IQR1 468; IQR3 1126; longest 2319). A total of 10 patients were lost to follow-up.

After hospital discharge, a total of 444/1767 (25.1%) deaths were reported: of these, 168 (37.8%) were classified as cardiac death. Figure 1 shows the Kaplan–Meier curve of all-cause mortality.

Table 1: Baseline characteristics of the patients

	All patients (n = 1904)	Patients who survived (n = 1323)	Patients who died (n = 581)	HR (CI 95%)	P-value
Age (years)	81.7 (6.2)	81.7 (6.1)	81.4 (6.8)	0.998 (0.985;1.012)	0.812
Gender (male)	39.8% (757/1904)	36.8% (487/1323)	46.5% (270/581)	1.420 (1.206;1.672)	**<0.001**
Body mass index, kg/m^2	25.8 (4.5)	26.0 (4.6)	25.4 (4.4)	0.970 (0.951;0.988)	**0.001**
Underweight (BMI < 18.5 kg/m^2)	3.5% (58/1904)	3.1% (35/1323)	4.0% (23/581)	1.289 (0.842;1.973)	**0.027**
Overweight (25 ≤ BMI < 30 kg/m^2)	37.6% (716/1904)	38.9% (515/1323)	34.6% (201/581)	0.808 (0.672;0.970)	
Obese (BMI ≥ 30 kg/m^2)	16.2% (308/1904)	16.9% (223/1323)	14.6% (85/581)	0.800 (0.627;1.020)	
Hypertension	81.6% (1553/1904)	81.3% (1075/1323)	82.3% (478/581)	1.088 (0.879;1.346)	0.436
Diabetes mellitus	25.8% (491/1904)	24.3% (322/1323)	29.1% (169/581)	1.268 (1.060;1.517)	**0.011**
Insulin-dependent diabetes mellitus	9.6% (182/1904)	8.2% (108/1323)	12.7% (74/581)	1.503 (1.177;1.919)	**0.002**
Creatinine (mg/dl) [0.6% missing values]	1.3 (0.9)	1.2 (0.7)	1.5 (1.1)	1.285 (1.223;1.351)	**<0.001**
Glomerular filtration rate (ml/min/1.73 m^2) [1% missing values]	44.4 (19.8)	46.8 (19.7)	38.8 (18.8)	0.977 (0.973;0.982)	**<0.001**
Haemoglobin (g/dl) [11% missing values]	11.8 (1.6)	11.9 (1.6)	11.7 (1.5)	0.912 (861;0.966)	**0.002**
Log EuroSCORE (%)	21.1 (13.7)	19.6 (12.3)	24.6 (15.9)	1.021 (1.015;1.026)	**<0.001**
Log EuroSCORE II (%) [53% missing values]	7.3 (6.7)	6.7 (5.8)	8.6 (8.2)	1.030 (1.017;1.043)	**<0.001**
STS mortality score (%) [43% missing values]	9.2 (7.6)	8.8 (7.4)	10.1 (8.0)	1.018 (1.005;1031)	**0.010**
Peripheral vascular disease	35.4% (674/1904)	32.4% (428/1323)	42.3% (246/581)	1.439 (1.220;1.696)	**<0.001**
COPD	24.6% (468/1904)	22.5% (298/1323)	29.3% (170/581)	1.315 (1.100;1.573)	**0.003**
Neurological dysfunction	9.0% (171/1904)	8.2% (108/1323)	10.4% (63/581)	1.220 (0.938;1.586)	0.148
Critical preoperative state	3.2% (61/1904)	2.2% (29/1322)	5.5% (32/581)	2.362 (1.653;3.376)	**<0.001**
Previous cardiac surgery	18.5% (352/1904)	18.4% (244/1323)	18.6% (108/581)	0.989 (0.802;1.219)	0.917
Systolic pulmonary artery pressure					
31–55 mmHg	49.4% (941/1904)	49.5% (655/1323)	49.2% (286/581)	0.958 (0.804;1.142)	0.282
>55 mmHg	10.9% (207/1904)	10.2% (135/1323)	12.4% (72/581)	1.188 (0.911;1.550)	
LVEF < 30	4.2% (80/1904)	3.0% (40/1323)	6.9% (40/581)	2.177 (1.577;3.004)	**<0.001**
LVEF ≥30 and ≤50	32.9% (627/1904)	31.1% (411/1323)	37.2% (216/581)	1.322 (1.117;1.564)	**0.001**
Creatinine >2.2 mg/dl or dialysis	8.0% (152/1904)	4.3% (57/1323)	16.4% (95/581)	3.104 (2.489;3.872)	**<0.001**
Dialysis	3.1% (59/1904)	1.2% (16/1323)	7.4% (43/581)	3.366 (2.465;4.596)	**<0.001**
Previous acute myocardial infarction	19.5% (371/1904)	18.2% (241/1323)	22.4% (130/581)	1.202 (0.989;1.462)	0.069
AMI < 90 days	24.3% (90/371)	22.4% (54/241)	27.7% (36/130)		
AMI ≥ 90 days	75.8% (281/371)	77.6% (187/241)	72.3% (94/130)		
Conduction rhythm					
Atrial fibrillation	21.7% (414/1904)	19.7% (261/1323)	26.3% (153/581)	1.459 (1.213;1.756)	**<0.001**
Pacemaker	7.0% (133/1904)	5.7% (75/1323)	10.0% (58/581)	1.760 (1.341;2.308)	**<0.001**
History of any CAD	45.2% (860/1904)	42.6% (564/1323)	51.0% (296/581)	1.209 (1.027;1.423)	**0.023**
Previous coronary intervention	34.9% (665/1904)	33.8% (447/1323)	37.5% (218/581)	1.073 (0.907;1.270)	0.412
CAD at the time of intervention	26.2% (498/1904)	24.5% (324/1323)	30.0% (174/581)	1.156 (0.967;1.380)	0.114
Revascularization for planned TAVI	14.0% (267/1904)	13.3% (176/1323)	15.7% (91/581)	1.112 (0.901;1.410)	0.302
Porcelain aorta	9.7% (185/1904)	9.8% (129/1323)	9.6% (56/581)	0.953 (0.723;1.256)	0.732
Aortic balloon valvuloplasty	11.6% (221/1904)	10.4% (13771323)	14.5% (84/581)	1.336 (1.060;1.683)	**0.018**
New York Heart Association functional class (class reference NYHA ≤ II)					
III	68.0% (1294/1904)	67.4% (892/1323)	69.2% (402/581)	1.588 (1.235;2.041)	**<0.001**
IV	12.7% (242/1904)	10.2% (135/1323)	18.4% (107/581)	2.642 (1.958;3.564)	

Bold value indicates statistical significance (P < 0.05).
AMI: acute myocardial infarction; BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; HR: heart rate; LVEF: left ventricle ejection fraction; TAVI: transcatheter aortic valve implantation.

Two patients underwent late open-heart surgery for prosthetic failure: (i) aortic valve replacement (AVR) because of endocarditis 108 days after TAVI and (ii) AVR for severe perivalvular leak (PVL) on the 41st postoperative day.

Three other patients underwent transcatheter reintervention on the aortic prosthesis: (i) valve-in-valve for severe intraprosthetic regurgitation 10 months after the index procedure, (ii) valve-in-valve for moderate intraprosthetic regurgitation 7 months after the index procedure and (iii) prosthesis balloon expansion on the 18th postoperative day for severe circumferential periprosthetic regurgitation. All procedures resulted in a good final result. Six late endocarditic events on the implanted prosthesis were treated medically.

Three other patients underwent elective reintervention for mitral valve disease: (i) mitral valve annuloplasty 5 months after TAVI; (ii) mitral valve replacement after 7 months and (iii) Mitraclip (Abbott Vascular, Menlo Park, CA, USA) procedure 8 months after TAVI.

Hospital readmission for heart failure occurred in 252/1767 (14.3%) patients. At the last clinical assessment, 7.9% of patients were in NYHA class higher than II.

Clinical efficacy (after 30 days) composite end-point was observed in 1030 (54.1%) patients. After 1 year, a total of 286/1904 (15.0%) patients died.

Univariable analysis of all-cause mortality

Univariable analysis was performed to assess associations between preoperative risk factors and overall mortality. Patients who died were more frequently female, had lower body mass

Table 2: Baseline echocardiographic data

	All (*n* = 1904)	Patients who survived (*n* = 1323)	Patients who died (*n* = 581)	HR (CI 95%)	*P*-value
Peak aortic gradient (mmHg)[a]	81.6 (22.5)	82.4 (22.1)	79.9 (23.4)	0.994 (0.990;0.998)	**0.002**
Mean aortic gradient (mmHg)[b]	50.2 (15.0)	50.9 (14.7)	48.6 (15.5)	0.989 (0.983;0.994)	**<0.001**
Aortic functional area index (cm^2/mq)[c]	0.46 (0.14)	0.45 (0.14)	0.47 (0.15)	1.579 (0.874;2.852)	0.133
Aortic annulus (mm)[d]	22.0 (2.1)	22.0 (2.1)	22.1 (2.1)	1.035 (0.990;1.082)	0.134
Left ventricle ejection fraction (%)	53.5 (12.4)	54.3 (11.7)	51.6 (13.6)	0.981 (0.975;0.987)	**<0.001**
LVDV index (ml/mq)[e]	79.8 (37.5)	81.1 (38.2)	77.4 (36.0)	0.997 (0.994;1.001)	0.096
Interventricular septum (mm)[f]	13.9 (2.3)	13.9 (2.3)	14.0 (2.4)	1.015 (0.961;1.071)	0.595
sPAP (mmHg)[g]	42.1 (13.0)	41.5 (13.0)	44.0 (12.7)	1.010 (1.003;1.017)	**0.007**
Mitral regurgitation, *n* (%)					
≥Moderate	23.8% (454/1904)	22.5% (297/1323)	27.0% (157/581)	1.344 (1.118;1.614)	**0.002**
Aortic regurgitation, *n* (%)					
≥Moderate	18.7% (356/1904)	18.3% (242/1323)	19.6% (114/581)	1.158 (0.943;1.421)	0.167

Bold value indicates statistical significance ($P < 0.05$).
[a]10.3% missing values.
[b]2.3% missing values.
[c]16.7% missing values.
[d]19% missing values.
[e]LVDV: left ventricle diastolic volume; 51% missing values.
[f]61.3% missing values.
[g]sPAP: systolic pulmonary artery pressure, measured in 77% of the patients.

Table 3: Operative data and complications

	All (*n* = 1904)	Patients who survived (*n* = 1323)	Patients who died (*n* = 581)	HR (CI 95%)	*P*-value
Access, *n* (%)					
Transapical	630 (33.1)	361 (27.3)	269 (46.3)	1.733 (1.470;2.044)	**<0.001**
Transaortic	18 (0.9)	12 (0.9)	6 (1.0)	2.204 (0.981;4.953)	
Transaxillary	4 (0.2)	2 (0.2)	2 (0.3)	2.168 (0.540;8.712)	
Planned valve-in-valve, *n* (%)	49 (2.6)	44 (2.7)	5 (1.8)	0.602 (0.299;1.210)	0.121
Sapien XT, *n* (%)	1303 (68.4)	993 (75.1)	310 (53.4)	0.761 (0.640;0.904)	**0.002**
Valve size, *n* (%)					
26 mm	906 (47.6)	771 (47.7)	135 (47.2)	1.222 (1.032;1.447)	**<0.001**
29 mm	96 (5.0)	69 (4.3)	27 (9.4)	2.016 (1.412;2.878)	
Prosthesis embolization, *n* (%)	12 (0.6)	6 (0.4)	6 (2.1)	3.099 (1.385;6.931)	**0.020**
Need for extracorporeal circulation, *n* (%)	32 (1.7)	9 (0.6)	23 (8.0)	7.488 (5.005;11.203)	**<0.001**
Conversion to sternotomy, *n* (%)	32 (1.7)	15 (0.9)	17 (5.9)	3.650 (2.310;5.769)	**<0.001**
Apex complications, *n* (%)	15/630 (2.4)	8/499 (1.6)	7/131 (5.3)	2.857 (1.463;5.578)	**0.008**
Need for external cardiac massage, *n* (%)	63 (3.3)	22 (1.4)	41 (14.3)	5.613 (4.147;7.597)	**<0.001**
Coronary occlusion, *n* (%)	22 (1.2)	10 (0.6)	12 (4.2)	2.705 (1.525;4.796)	**0.003**
Aortic dissection, *n* (%)	26 (1.4)	5 (0.3)	21 (7.3)	8.232 (5.363;12.637)	**<0.001**
Bail-out valve-in-valve, *n* (%)	10 (0.5)	6 (0.4)	4 (1.4)	1.658 (0.687;4.001)	0.299
Conversion to AVR	11 (0.6)	6 (0.4)	5 (1.8)	2.848 (1.180;6.875)	**0.047**

Bold value indicates statistical significance ($P < 0.05$).
AVR: aortic valve replacement.

index, poorer renal function, and worse functional class and more frequently presented a critical preoperative state. In addition, patients who died had a history of diabetes, neurological dysfunction, peripheral vascular disease, previous cardiac surgery, previous coronary artery disease or previous balloon angioplasty. Lastly, also atrial fibrillation and pacemaker rhythm were associated with mortality. Owing to these dissimilarities in comorbidities, logistic EuroSCORE, logistic EuroSCORE II and STS were significantly higher in patients who died (Table 1).

Regarding preoperative echocardiographic parameters, left ventricle ejection fraction, systolic pulmonary artery pressure and mitral regurgitation were statistically different among patients who died or survived (Table 2).

Access and valve size seem also to influence the procedural outcomes (Table 3); in fact, quite often patients who died had a transapical approach.

The influences of procedural complications on mortality are given in Table 4. Device failure, acute myocardial infarction within 72 h, any stroke, life-threatening bleeding, major vascular

Table 4: Perioperative outcomes according to the updated Valve Academic Research Consortium (VARC-2) definitions

	All (*n* = 1904)	Patients who survived (*n* = 1323)	Patients who died (*n* = 581)	HR (CI 95%)	*P*-value
Device in success, *n* (%)	226 (11.9)	123 (9.4)	103 (17.7)	2.088 (1.687;2.584)	**<0.001**
Intraoperative mortality	37 (1.9)	–	37 (6.4)		
>1 valve implanted (TAVI or surgical)	27 (1.4)	13 (1.0)	14 (2.4)	2.575 (1.514;4.377)	**0.002**
Aortic regurgitation ≥moderate	99 (5.2)	61 (4.6)	38 (6.5)	1.450 (1.043;2.015)	**0.036**
Mean aortic gradient ≥20 mmHg	63 (3.3)	50 (3.8)	13 (2.2)	0.595 (0.343;1.032)	**0.044**
Acute myocardial infarction (≤72 h), *n* (%)	29 (1.5)	11 (0.8)	18 (3.1)	3.924 (2.452;6.278)	**<0.001**
Stroke, *n* (%)	54 (2.8)	22 (2.0)	32 (7.7)	2.849 (1.994;4.072)	**<0.001**
Disabling	18 (1.0)	3 (0.2)	15 (2.6)	6.094 (3.636;10.214)	**<0.001**
Not disabling	36 (1.9)	19 (1.4)	17 (2.9)	1.890 (1.167;3.063)	**0.019**
Bleeding, *n* (%)	499 (26.2)	306 (23.1)	193 (33.2)	1.536 (1.292;1.825)	**<0.001**
Life threatening	191 (10.0)	86 (6.5)	105 (18.1)	2.499 (2.021;3.090)	**<0.001**
Major	200 (10.5)	139 (10.5)	61 (10.5)	0.972 (0.745;1.267)	0.829
Minor	108 (5.7)	81 (6.1)	27 (4.7)	0.831 (0.564;1.223)	0.333
Vascular complication, *n* (%)	314 (16.5)	206 (15.6)	108 (18.6)	1.304 (1.057;1.608)	**0.016**
Major	185 (9.7)	112 (8.5)	73 (12.6)	1.513 (1.183;1.936)	**0.002**
Minor	129 (6.8)	94 (7.1)	35 (6.0)	0.967 (0.687;1.361)	0.844
Acute kidney injury (AKIN) Grade 2–3[a], *n* (%)	155 (8.6)	77 (6.0)	78 (15.0)	2.186 (1.718;2.782)	**<0.001**
PM implantation (before discharge), *n* (%)	116 (6.1)	74 (5.6)	42 (7.2)	1.216 (0.888;1.664)	0.236
New onset of atrial fibrillation, *n* (%)	170 (9.0)	113 (8.6)	57 (10.0)	1.021 (0.776;1.343)	0.882

Bold value indicates statistical significance ($P < 0.05$).
PM: pacemaker; TAVI: transcatheter aortic valve implantation.
[a]5.2% missing values.

Table 5: Available echocardiographic data at discharge (whether the patient was dead or alive)

	All (*n* = 1867)	Patients who survived (*n* = 1323)	Patients who died (*n* = 544)	HR (CI 95%)	*P*-value
PG (mmHg), mean (SD) (*n* = 1364)	19.9 (7.8)	20.0 (7.6) *n* = 971	19.4 (8.9) *n* = 393	0.995 (0982;1.008)	0.422
MPG (mmHg), mean (SD) (*n* = 1484)	10.8 (4.5)	10.9 (4.4) *n* = 1067	10.4 (4.9) *n* = 417	0.980 (0.957;1.003)	0.086
LVEF (%), mean (SD) (*n* = 1665)	54.5 (11.1)	54.8 (10.7) *n* = 1184	51.7 (13.3) *n* = 481	0.976 (0.969;0.984)	**<0.001**
sPAP (mmHg), mean (SD) (*n* = 797)	38.0 (10.7)	37.6 (10.5) *n* = 554	40.8 (11.6) *n* = 243	1.024 (1.014;1.035)	**<0.001**
Mitral regurgitation, *n* (%) (*n* = 1394)					
Mild	688 (49.3)	494/1008 (49.0)	74/386 (50.3)	1.233 (0.989;1.537)	**0.044**
Moderate	164 (11.8)	113/1008 (11.2)	51/386 (13.2)	1.542 (1.116;2.131)	
Severe	21 (1.5)	15/1008 (1.5)	6/386 (1.6)	1.631 (0.719;3.701)	
Aortic regurgitation, *n* (%) (*n* = 1820)					
Mild	582 (32.0)	396/1299 (30.5)	186/521 (35.7)	1.344 (1.118;1.615)	**<0.001**
Moderate	91 (5.0)	60/1299 (4.6)	31/521 (6.0)	1.518 (1.048;2.198)	
Severe	8 (0.4)	1/1299 (0.1)	7/521 (1.3)	9.800 (4.619;20.792)	

Bold value indicates statistical significance ($P < 0.05$).
LVEF: left ventricular ejection fraction; MPG: mean pressure gradient; PG: pressure gradient; sPAP: systolic pulmonary artery pressure.

complication and AKI Grade 2–3 were associated with higher mortality rates. Post-procedural echocardiographic variables are given in Table 5.

Multivariable analysis of all-cause mortality

In the multivariable analysis, the independent preoperative predictors of cumulative all-cause mortality were male gender (HR: 1.395; 95% CI: 1.052–1.849); overweight, BMI 25–30 kg/m^2 (HR: 0.775; 95% CI: 0.616–0.974); serum creatinine level (every 1 mg/dl increase; HR: 1.314; 95% CI: 1.167–1.480); haemoglobin level (every 1 g/dl increase HR: 0.905; 95% CI: 0.833–0.984); critical preoperative state (HR: 2.282; 95% CI: 1.384–3.761); neurological dysfunction (HR: 1.552; 95% CI: 1.060–2.272); atrial fibrillation (HR: 1.556; 95% CI: 1.213–1.995); pacemaker rhythm (HR: 1.948; 95% CI: 1.310–2.896); NYHA Class III or IV (HR: 1.800; 95% CI: 1.205–2.689 or HR: 2.331; 95% CI: 1.392–3.903, respectively). All data are listed in Table 6.

DISCUSSION

Several single-centre and multicentre studies have already evaluated early, mid-term and long-term outcomes of patients who underwent TAVI [3–9]. These reports are very important not only

to understand the clinical outcome of patients who have been treated with TAVI, but also to clarify the behaviour of TAVI at long-term follow-up. This point is crucial to define the real possibility to extend TAVI to younger and intermediate-risk patients. Another important element is the identification of independent preoperative risk factors for poor outcome in this population to perform TAVI only in patients who will likely benefit from it.

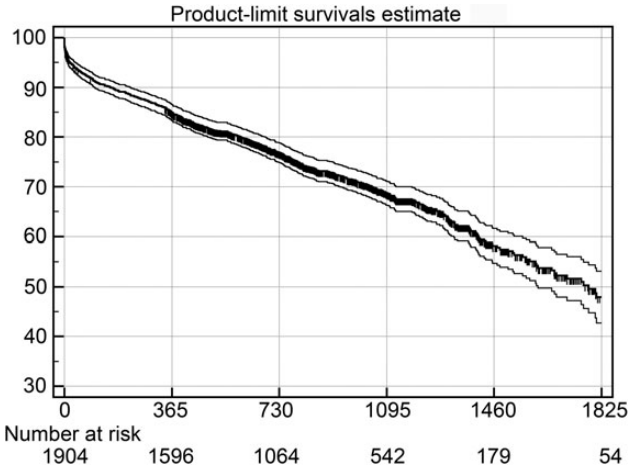

Figure 1: Kaplan–Meier survival curve for all-cause mortality.

The ITER is a voluntarily independent registry reporting the Italian experience of balloon-expandable TAVI. Its independence from industry allows an objective evaluation of 'real-world' outcomes excluding potential bias derived from patient selection. Different from many other single- and multicentre experiences, our registry collects data only from patients who received a balloon-expandable Sapien valve prosthesis.

This first ITER report includes the experience of 33 Italian centres that have implanted the Sapien aortic transcatheter prosthesis through 2012.

Table 7 summarizes and compares nine major registries. In our study, mean age, Logistic EuroSCORE, periprocedural complications as at least moderate PVL, life-threatening bleeding, PM implantation and strokes at 30 days were consistent with paravalvular leak results from previously published studies. Also, operative mortality and 1-year mortality rates were comparable. The rate of moderate to severe paravalvular leak was slightly lower than that in other reports. This difference might be explained by the use of only balloon-expandable prostheses in our registry compared to those that collect data about both self-expandable and balloon-expandable prostheses. The same reason could explain the minimal difference in PM implantation rate as well. PM was necessary in 116 patients (6.1%); most studies report a rate of PM implantation that ranges between 5 and 40%, with lower rates among patients who received a balloon-expandable bioprosthesis (5–22%) [14]. Described rates of PM implantation after TAVI with self-expandable prosthesis are higher than those using balloon-expandable valves probably because of the mechanical features of the device. Indeed, the radial

Table 6: Proportional risk survival model

	HR	95% CI	*P*-value
Age (years)	1.003	(0.979;1.026)	0.829
Gender (male)	1.395	(1.052;1.849)	**0.021**
BMI*,[a]			
Underweight	1.442	(0.873;2.383)	0.083
Overweight	0.775	(0.616;0.974)	
Obese	0.813	(0.567;1.164)	
Diabetes mellitus	1.038	(0.778;1.386)	0.799
Creatinine (mg/dl)	1.314	(1.167;1.480)	**<0.001**
Left ventricle ejection fraction (%)	0.994	(0.984;1.004)	0.265
Haemoglobin (g/dl)	0.905	(0.833;0.984)	**0.020**
Critical preoperative state	2.282	(1.384;3.761)	**0.001**
Chronic obstructive pulmonary disease	1.160	(0.873;1.542)	0.306
Neurological dysfunction	1.552	(1.060;2.272)	**0.024**
Peripheral vascular disease	1.272	(0.971;1.667)	0.081
Previous acute myocardial infarction	0.981	(0.780;1.234)	0.870
Conduction rhythm disturbances[b]			
Atrial fibrillation	1.556	(1.213;1.995)	**<0.001**
Pacemaker	1.948	(1.310;2.896)	**<0.001**
Mitral regurgitation (≥moderate)[c]	1.001	(0.740;1.354)	0.995
History of any coronary artery disease	1.212	(0.908;1.618)	0.193
Previous aortic valvuloplasty	1.082	(0.748;1.566)	0.675
New York Heart Association functional class[d]			
NYHA III	1.800	(1.205;2.689)	**0.006**
NYHA IV	2.3331	(1.392;3.903)	

Bold value indicates statistical significance ($P < 0.05$).
BMI: body mass index; normal weight ($18.5 \leq$ BMI < 25 kg/m^2); underweight (BMI < 18.5 kg/m^2); overweight ($25 \leq$ BMI < 30 kg/m^2); obese (BMI ≥ 30 kg/m^2).
[a]Referral category: normal weight.
[b]Referral category: sinus rhythm.
[c]Referral category: mitral regurgitation ≤mild.
[d]Referral category: NYHA ≤ II.

Table 7: Summary and schematic table of periprocedural outcomes of nine of the most important national registries or trials

Study Author Journal	Prosthesis Year enrolled	No. of pts	No. of centres in Country	Age	Log. ES	30-day all-cause mortality	1-year all-cause mortality	Aortic regurgitation ≥ moderate	LT + major bleeding	Major vascular compl.	Stroke 30 day/1 year	PM
PIVOTAL [3] Popma *JACC* 2014	**CV** 2011–12	**489**	**41 USA**	**83**	**23**	**8**	**24**	**11**	**13 + 25**	**8**	**2/4**	**22**
CV Trial [4] Adams *NEJM* 2014	**CV** 2011–12	**390**	**45 USA**	**83**	**18**	**8**	**14**	**10**	**14 + 28**	**6**	**5/9**	**20**
FRANCE-2 [2] Gilard *NEJM* 2012	**Edw & CV** 2010–11	**3195**	**34 FR**	**83**	**22**	**10**	**24**	**16**	**1 + 5**	**5**	**NA/4**	**16**
GARY [5] Mohor *EJCTS* 2014	**All** 2011	**3876**	**78 DE**	**81**	**25**	**7**	**24**	**NA**	**NA**	**NA**	**NA/5**	**19**
SWISS [6] Wenaweser *EuroInt* 2014	**All CE** 2011–13	**697**	**8 CH**	**82**	**20**	**5**	**NA**	**9**	**6 + 8**	**NA**	**3/NA**	**21**
UK [7] Blackman *JIC* 2014	**Edw & CV** 2007–10	**1620**	**30 UK**	**82**	**20**	**7**	**23**	**10**	**23**[a]	**6**	**3/NA**	**15**
ADVANCE [8] Linke *EHJ* 2014	**CV** 2010–11	**1015**	**44 EU**	**81**	**19**	**2**	**18**	**16**	**4 + 10**	**11**	**3/NA**	**26**
EUROSentinel [9] Di Mario *EUROint* 2013	**Edw & CV** 2011–12	**4571**	**137 EU**	**81**	**20**	**7**	**NA**	**NA**	**17**[a]	**3**	**NA**	**13**
ITER Salizzoni	**Edw** 2007–12	**1904**	**33 ITA**	**82**	**21**	**7**	**16**	**5**	**10 + 11**	**9**	**3 / NA**	**6**

Edw: Edwards; CV: CoreValve; ES: EuroSCORE; NA: not available.
[a]Bleeding classification was not specified and not reported as VARC-2 definition.

force applied on the aortic annulus, adjacent to the conduction system, and the lower extension of the stent inside the left ventricle outflow tract could explain the difference in PM rate.

A similar distribution is described for PVL rates. The literature reports rates that vary between 10 and 40% regardless of prosthesis type [15, 16]. However, most authors report a lower incidence of at least moderate PVL after TAVI using a balloon-expandable bioprosthesis [15]. In our series, the rate of moderate-to-severe PVL was 5.2% (99 patients) at discharge, slightly lower than that reported in the literature. The explanation of this rate could be the exclusive employment of the Sapien prostheses.

Several studies and meta-analyses showed that sex seems to be related to the outcome after TAVI, despite baseline features [17]. Our registry confirmed that female sex has a protective role for all-cause mortality in TAVI patients.

Interestingly, our study supports the 'obesity paradox': patients with an increased body mass index have better outcomes, in particular, than those considered overweight (BMI ranging between 25 and 30 kg/m^2). This was already demonstrated by several studies in conventional cardiac surgery patients, but only the FRANCE-2 registry supported this conclusion in the TAVI population [18].

Preoperative data analysis showed that chronic kidney disease (CKD) is a predictor of mortality. Several studies have demonstrated the negative impact of survival of CKD on the survival of patients who underwent surgical AVR for aortic disease. CKD is frequent in patients with AS, in particular in elderly high-risk patients screened for transcatheter treatment. Authors reported higher rates of acute kidney disease requiring temporary haemofiltration in patients with CKD [19–21]. Also early and long-term survival of patients undergoing AVR is negatively influenced by CKD. On the other hand, it is widely demonstrated that survival after TAVI is reduced by preoperative impaired renal function and consequent onset of acute kidney disease. Renal impairment is an independent risk factor for worse survival in most studies [19–21]. Nguyen *et al.* [20] described the association between different degrees of CKD and mortality after TAVI and AVR. They found increasing in-hospital mortality only in the AVR group with mild, moderate and severe renal dysfunction. Also mid-term and long-term mortalities were higher only in AVR patients with CKD. These contradictory findings suggest the need for an accurate preoperative evaluation of other risk factors besides CKD of each patient to identify the surgical strategy between TAVI and AVR.

Previous studies have shown a significant association between preprocedural anaemia and mortality [22]. This study confirms that a low haemoglobin level is significantly related to mortality and suggests that preprocedural haemoglobin levels should be carefully evaluated prior to the procedure.

Cockburn *et al.* [23] recently reported that poor mobility (defined as severe impairment of mobility secondary to musculoskeletal or neurological dysfunction) predicts adverse outcome better than other frailty indices in patients undergoing TAVI. Also in our study patients with poor mobility or else defined neurological dysfunction suffered a worse outcome.

Heart rhythm conduction disturbances (defined as patient with atrial fibrillation at the time of intervention or previous PM implantation) were also identified as predictors of mortality. They are already considered as risk factors in currently used risk scores, as for example the STS, and they have been just recently associated with the TAVI population [24]. The presence of a PM before the procedure is probably associated with higher mortality because it represents a sign of heart performance deterioration or pre-existing chronic ischaemic heart disease [14]. On the other hand, conduction disturbances such as atrial fibrillation or complete or incomplete bundle blocks should not be underestimated, in particular in patients with severe valve calcifications since there is a high risk of progression towards a complete A/V block [25].

Reported transprosthesis gradients are lower and the incidence of at least moderate PVL is 5.2%. This rate is inferior to that most reported in the literature, which is probably justified by the use of only balloon-expandable prostheses that are usually associated with a lower rate of significant PVL [5, 7, 13]. The analysis of post-procedural PVL is particularly important considering the large number of studies that report this complication as an independent risk factor for early and late death and worse clinical status [4–9].

We reported few cases of endocarditis or valve degeneration needing reoperation within follow-up. However, data reported in the literature are not conclusive about TAVI durability. Longer follow-up on larger series is needed to confirm these findings to extend the indication for TAVI also to younger or intermediate-risk patients and, on the other hand, to avoid futile procedures [26].

LIMITATIONS

Data were self-adjudicated, and there was no external event adjudication. The number of patients operated at each centre was heterogeneous, ranging from 1 to 358. Different physicians using different machines performed echocardiographic examinations. Clinical follow-up was done either by phone or clinical assessment depending on centre policies.

Because of the nature of the registry, several important variables (such as catheterization and CT-scan measurement) were not included, leading to an 'omitted variable bias'.

Data on quality of life and geriatric assessment were collected only in a few centres.

CONCLUSIONS

According to ITER, the results of a real-world experience with only a balloon-expandable device, TAVI shows good early and mid-term outcomes in terms of survival, technical success, valve-related adverse events and haemodynamic performance. Male gender, preoperative renal function and haemoglobin level, lower BMI, critical preoperative state, neurological dysfunction, NYHA Classes III–IV and heart rhythm disturbances (atrial fibrillation and previously implanted PM) were independently associated with mortality.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: Augusto D'Onofrio, Marco Aiello and Davide Gabbieri report consulting fees from Edwards Lifesciences. Mauro Cassese reports consulting fees from Edwards Lifesciences and Medtronic, as well as lecture fees from Medtronic. Mauro Rinaldi reports consulting fees from Edwards Lifesciences and lecture fees from Edwards Lifesciences, Medtronic, and Novartis. Gino Gerosa reports consulting fees from AstraZeneca, lecture fees from HeartWare and St Jude Medical, and grant support from Edwards. Giuseppe Bruschi reports consulting for Medtronic and Direct Flow. Gian Luca Martinelli is a speaker for Edwards. Francesco Bedogni reports consulting for Medtronic, Boston Scientific and St. Jude Medical. Antonio Colombo is a minor shareholder in

Direct Flow Medical. Corrado Tamburino receives speaker honorara from Abbott, Medtronic and St Jude Medical. All other authors none declared.

REFERENCES

[1] Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG *et al*. for the PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.

[2] Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J *et al*. Registry of transcatheter aortic-valve implantation in high-risk patients. N Engl J Med 2012;366:1705–15.

[3] Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D *et al*. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 2014;63:1972–81.

[4] Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM *et al*. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790–8.

[5] Mohr FW, Holzhey D, Möllmann H, Beckmann A, Veit C, Figulla HR *et al*. The German Aortic Valve Registry: 1-year results from 13,680 patients with aortic valve disease. Eur J Cardiothorac Surg 2014;46:808–16.

[6] Wenaweser P, Stortecky S, Heg D, Tueller D, Nietlispach F, Falk V *et al*. Short-term clinical outcomes among patients undergoing transcatheter aortic valve implantation in Switzerland: the Swiss TAVI registry. EuroIntervention 2014;10:982–9.

[7] Blackman DJ, Baxter PD, Gale CP, Moat NE, Maccarthy PA, Hildick-Smith D *et al*. Do outcomes from transcatheter aortic valve implantation vary according to access route and valve type? The UK TAVI Registry. J Interv Cardiol 2014;27:86–95.

[8] Linke A, Wenaweser P, Gerckens U, Tamburino C, Bosmans J, Bleiziffer S *et al*. Treatment of aortic stenosis with a self-expanding transcatheter valve: the International Multi-centre ADVANCE Study. Eur Heart J 2014;35:2672–84.

[9] Di Mario C, Eltchaninoff H, Moat N, Goicolea J, Ussia GP, Kala P *et al*. The 2011-12 pilot European Sentinel Registry of Transcatheter Aortic Valve Implantation: in-hospital results in 4,571 patients. EuroIntervention 2013;8:1362–71.

[10] Kappetein AP, Osnabrugge RL, Head SJ. Patient selection for TAVI in 2014: is there a justification for treating low or intermediate-risk patients? The surgeon's view. EuroIntervention 2014;10(Suppl. U):U11–5.

[11] Roques F, Nashef SAM, Michel P, Gauducheau E, de Vincentiis C, Baudet E *et al*. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardio-Thoracic Surg 1999;15:816–22; discussion 822–3.

[12] Nashef SAM, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR *et al*. Eur J Cardio-Thoracic Surg 2012;41:1–12.

[13] Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH *et al*. Updated standardized end-point definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). Eur J Cardiothorac Surg 2012;42:S45–60.

[14] Buellesfeld L, Stortecky S, Heg D, Hausen S, Mueller R, Wenaweser P *et al*. Impact of permanent pacemaker implantation on clinical outcome among patients undergoing transcatheter aortic valve implantation. J Am Coll Cardiol 2012;60:493–501.

[15] Kodali S, Pibarot P, Douglas PS, Williams M, Xu K, Thourani V *et al*. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards Sapien valve in the PARTNER trial: characterizing patients and impact on outcomes. Eur Heart J 2015;36:449–56.

[16] Gotzmann M, Pljakic A, Bojara W, Lindstaedt M, Ewers A, Germing A *et al*. Transcatheter aortic valve implantation in patients with severe symptomatic aortic valve stenosis-predictors of mortality and poor treatment response. Am Heart J 2011;162:238–45.

[17] Conrotto F, D'Ascenzo F, Presbitero P, Humphries KH, Webb JG, O'Connor SA *et al*. Effect of gender after transcatheter aortic valve implantation: a meta-analysis. Ann Thorac Surg 2015;99:809–16.

[18] Yamamoto M, Mouillet G, Oguri A, Gilard M, Laskar M, Eltchaninoff H *et al*. Effect of body mass index on 30- and 365-day complication and survival rates of transcatheter aortic valve implantation (from the FRench Aortic National CoreValve and Edwards 2 [FRANCE 2] registry). Am J Cardiol 2013;112:1932–7.

[19] Thourani VH, Keeling WB, Sarin EL, Guyton RA, Kilgo PD, Dara AB *et al*. Impact of preoperative renal dysfunction on long-term survival for patients undergoing aortic valve replacement. Ann Thorac Surg 2011;91:1798–806.

[20] Nguyen TC, Babaliaros VC, Razavi SA, Kilgo PD, Guyton RA, Devireddy CM *et al*. Impact of varying degrees of renal dysfunction on transcatheter and surgical aortic valve replacement. J Thorac Cardiovasc Surg 2013;146:1399–406.

[21] D'Ascenzo F, Moretti C, Salizzoni S, Bollati M, D'Amico M, Ballocca F *et al*. 30 days and midterm outcomes of patients undergoing percutaneous replacement of aortic valve according to their renal function: a multicenter study. Int J Cardiol 2013;167:1514–8.

[22] Arai T, Morice MC, O'Connor SA, Yamamoto M, Eltchaninoff H, Leguerrier A *et al*. Impact of pre- and post-procedural anemia on the incidence of acute kidney injury and 1-year mortality in patients undergoing transcatheter aortic valve implantation (from the French Aortic National CoreValve and Edwards 2 [FRANCE 2] Registry). Catheter Cardiovasc Interv 2015;85:1231–9.

[23] Cockburn J, Singh MS, Rafi NH, Dooley M, Hutchinson N, Hill A *et al*. Poor mobility predicts adverse outcome better than other frailty indices in patients undergoing transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2015;86:1271–7.

[24] Giordana F, D'Ascenzo F, Nijhoff F, Moretti C, D'Amico M, Biondi Zoccai G *et al*. Meta-analysis of predictors of all-cause mortality after transcatheter aortic valve implantation. Am J Cardiol 2014;114:1447–55.

[25] Salizzoni S, Anselmino M, Fornengo C, Giordana F, La Torre M, Moretti C *et al*. One-year follow-up of conduction disturbances following transcatheter aortic valve implantation. J Cardiovasc Med (Hagerstown) 2015;16:296–302.

[26] D'Onofrio A, Salizzoni S, Agrifoglio M, Lucchetti V, Musumeci F, Esposito G *et al*. When does transapical aortic valve replacement become a futile procedure? An analysis from a national registry. J Thorac Cardiovasc Surg 2014;148:973–9.

APPENDIX. CONFERENCE DISCUSSION

Dr J. Kempfert *(Bad Nauheim, Germany):* I have two questions for you. The first one is, can you confirm, based on new data, an association between the occurrences of mild or more than mild paravalvular leak on 1—year survival, as it has been shown with other registries and trials?

My second question is in regard to a potential learning curve. You have shown in one of the very first slides that here, your registry, your centers have a rather high volume and also some that were more or less low volume centers. So also in the context of the political ongoing discussion, it would be very interesting for us to see if there is any difference in regard to the volume that a center does.

Dr Salizzoni*:* For the third question, yes, we find that moderate to severe is a predictor of mortality. We are doing deeply the analysis, especially for the mild, because we want to understand it like the partner trial is a risk factor for early mortality too. So in this registry for sure, to have the moderate or severe, aortic regurgitation of the procedure is a risk factor for early mortality. Then for the learning curve, there is an analysis we will do in the next weeks, I hope, with a statistician and we will have that for the paper for sure. Because I think it is important, as we discussed it before, the volume of the center and the learning curve of each center.