Clinical Research in Cardiology (2019) 108:763–771
https://doi.org/10.1007/s00392-018-1404-2

ORIGINAL PAPER

Characteristics and outcomes of patients ≤ 75 years who underwent transcatheter aortic valve implantation: insights from the SOURCE 3 Registry

Derk Frank[1,12] · Mohamed Abdel-Wahab[2] · Martine Gilard[3] · Franck Digne[4] · Geraud Souteyrand[5] · Christophe Caussin[6] · Frédéric Collart[7] · Vincent Letocart[8] · Jochen Wöhrle[9] · Christian Kuhn[1,12] · Tomas Hovorka[10] · Helmut Baumgartner[11]

Received: 26 August 2018 / Accepted: 10 December 2018 / Published online: 14 December 2018

Abstract

Background Current trials and registries of transcatheter valve implantation (TAVI) mostly include patients older than 75 years. Little is known about younger patients who undergo this treatment. We investigated comorbidities among patients < 75 years old who underwent TAVI in the SAPIEN 3™ European post-approval SOURCE 3 Registry, and analysed outcomes at 30 days and 1 year.

Methods and results Three age groups of patients were analysed for outcomes and characteristics: < 75 ($n = 235$), 75–80 ($n = 391$) and ≥ 80 years ($n = 1320$). Overall, the mean age was 81.6 ± 6.7 years; transfemoral access was used in 87.1% of patients treated with SAPIEN 3 transcatheter heart valves. The mean logistic EuroSCORE increased according to age group (12.6%, 17.3% and 19.7%, respectively, $p < 0.001$). Younger patients had a higher incidence of comorbidities, particularly those not included in surgical risk score assessment tools, e.g., severe liver disease, previous radiation therapy, and porcelain aorta. Mortality rates were similar between age groups at 30 days (1.7%, 2.0% and 2.3%, respectively, $p = 0.79$) and 1 year (14.2%, 9.3% and 13.3%, respectively, $p = 0.08$). However, sudden cardiac death rates were higher in the < 75 years age group compared with the ≥ 85 years age group (20.7% vs. 4.8%, $p = 0.010$).

Conclusions In current TAVI practice, patients younger than 75 years are a minority (12%). Despite younger age and lower surgical risk scores, this cohort was characterized by comorbidities not accounted for by traditional surgical risk scores. More data are needed for this age group to guide the appropriate decision between surgery and TAVI.

Clinicaltrial.gov number NCT02698956.

Keywords Aortic stenosis · Transcatheter aortic valve implantation · Balloon-expandable valve · SAPIEN 3 · Predictors of mortality · Causes of death

Abbreviations

BAV	Balloon aortic valvuloplasty
COPD	Chronic obstructive pulmonary disease
CABG	Coronary artery bypass graft
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Society of Cardiology
KM	Kaplan–Meier
NYHA	New York Heart Association functional class
SOURCE 3	SAPIEN 3 Aortic Bioprosthesis European Outcome
STS	Society of Thoracic Surgeons
SAVR	Surgical aortic valve replacement
TAVI	Transcatheter aortic valve implantation

Introduction

Transcatheter aortic valve implantation (TAVI) has become the standard treatment for patients with severe, symptomatic aortic stenosis who are considered inoperable [1] or at high

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00392-018-1404-2) contains supplementary material, which is available to authorized users.

✉ Derk Frank
derk.frank@uksh.de

Extended author information available on the last page of the article

operative risk [2–5]. The recently revised European Society of Cardiology (ESC)/European Association of Cardiothoracic Surgeons (EACTS) guidelines on valvular heart disease recommend considering TAVI as an alternative to surgical aortic valve replacement (SAVR) in patients at intermediate surgical risk (logistic EuroSCORE > 10% and Society of Thoracic Surgeons [STS] score > 4% or other risk factors not included in the scores) [6]. The guidelines emphasize, however, that the population currently being studied has a mean age of approximately 80 years (e.g., intermediate risk trials, such as PARTNER 2 [7] or SURTAVI [8]), with patients rarely younger than 75 years, and that data reported for this population cannot simply be applied to younger patients.

Currently available data on the impact of age on outcomes after TAVI are mostly restricted to analyses within the population older than 75 years [9, 10]. Given the limited outcome data on patients younger than 75 years treated with TAVI, we have systematically investigated the potential impact of younger age on clinical outcomes at 30 days and 1 year in the large SOURCE 3 cohort implanted with a balloon-expandable THV. Overall data on 30-day [11] and 1-year [12] outcomes have recently been published. Herein, we present a detailed analysis of a large cohort of patients younger than 75 years compared with older patients.

Methods

Registry design and purpose of this analysis

From July 2014 to October 2015, 1946 patients with severe aortic stenosis who underwent TAVI with the third generation SAPIEN 3 THV (Edwards Lifesciences, Irvine, CA, USA) were included in the SOURCE 3 Registry. The SOURCE 3 (SAPIEN 3 Aortic Bioprosthesis European Outcome) European, post-approval, multicenter, observational, and non-randomized registry was approved by each of the 80 participating centre's institutional ethical review board in 10 European countries (centres listed in Supplemental Table). Treatment with TAVI in all centres was supported by a local heart team. The patients were not necessarily enrolled consecutively. The trial conformed to the principles outlined in the Declaration of Helsinki, and each patient signed an informed consent for data collection and analysis. The 30-day [11] and 1-year results [12] have been published previously.

Clinical and echocardiographic data were collected at baseline, discharge, 30-days, and 1-year post index procedure. All clinical events were adjudicated according to Valve Academic Research Consortium 2 (VARC-2) criteria by an independent committee. Adverse events adjudicated included THV in THV, conversion to open heart surgery, life-threatening bleeding, and coronary obstruction to 30 days post-procedure; acute kidney injury to 7 days post-procedure; and cardiovascular death, stroke, myocardial infarction, and new permanent pacemaker to 1 year post-procedure. Echocardiographic data presented were site-reported. The investigators answered a "yes/no" question to document the frailty of patients in the study.

For the purpose of the present analysis, patients were categorized into three groups according to their age at enrolment, i.e., < 75, 75–80, and ≥ 80 years. The < 75-year-old cut-off was selected according to the current guidelines [6], while the 75- to 80-year-old group was chosen to further differentiate the results. Baseline characteristics, 30-day and 1-year outcomes were analysed according to age groups.

Data collection and statistical analysis

All data were entered in the electronic data capture system by the participating centres and was monitored by the Sponsor.

Continuous variables are presented as mean ± standard deviation (SD). Kaplan–Meier (KM) estimates were computed for clinical outcomes at 30 days and 1 year.

A landmark analysis was conducted to investigate the impact of age from 30 days to 1 year. Differences between age groups were tested using the Wilcoxon rank sum test for continuous variables, Fisher´s exact test for categorical variables, and log rank test for clinical outcomes. For variables with a statistically significant difference among the three groups, a pairwise comparison was conducted using Wilcoxon test for continuous variables, Fisher´s exact test for categorical variables, and log rank test for clinical outcomes. Kaplan–Meier survival curves for each group were plotted up to 1 year. In addition, a sub-analysis of the < 65-year-old subgroup ($n = 40$) was performed to identify other drivers of poor prognosis.

All statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Most patients were 80 years old or older; followed by patients between 75 and 80 years old; 12% of patients were younger than 75 years at enrolment (Table 1). As age is one of the main drivers of the logistic EuroSCORE (log ES) calculation, the mean log ES increased significantly with age. The proportion of males was approximately 60% in each group, except in the ≥ 80-year-old group, where males represented half of the population ($p < 0.001$).

While the age groups did not differ in several baseline characteristics (eg, NYHA class IV, coronary artery disease,

Table 1 Demographic and baseline characteristics

Characteristic	< 75 years old (*N* = 235)	75–80 years old (*N* = 391)	≥ 80 years old (*N* = 1320)	*p* value
Mean ± SD				
Age, years	68.8 ± 5.62	77.3 ± 1.40	85.1 ± 3.49	
Log ES	12.6 ± 11.45 (*n* = 209)	17.3 ± 13.04 (*n* = 367)	19.7 ± 13.20 (*n* = 1209)	< 0.001
EuroSCORE II	4.6 ± 4.68 (*n* = 189)	5.4 ± 5.83 (*n* = 308)	5.8 ± 5.56 (*n* = 1002)	< 0.0001
STS	6.0 ± 8.21 (*n* = 138)	5.3 ± 5.98 (*n* = 227)	7.9 ± 7.59 (*n* = 719)	< 0.0001
n/*N* (%)				
Female	89/235 (37.9)	149/391 (38.1)	696/1320 (52.7)	< 0.001
Log ES < 10%	120/209 (57.4)	129/367 (35.1)	269/1209 (22.2)	< 0.001
NYHA class IV	20/226 (8.8)	30/382 (7.9)	119/1271 (9.4)	0.686
LVEF	53.9 ± 14.9 (*n* = 193)	53.2 ± 13.4 (*n* = 391)	55.3 ± 13.6 (*n* = 1320)	0.035
LVEF < 30%	17/193 (8.8)	20/328 (6.1)	63/1129 (5.6)	0.218
Hypertension	182/235 (77.4)	342/391 (87.5)	1067/1320 (80.8)	0.002
Dyslipidaemia	128/235 (54.5)	236/391 (60.4)	690/1320 (52.3)	0.019
History of smoking	109/235 (46.4)	143/390 (36.7)	333/1320 (25.2)	< 0.001
Diabetes	89/235 (37.9)	140/391 (35.8)	346/1320 (26.2)	< 0.001
Insulin-dependent	44/235 (18.7)	59/391 (15.1)	107/1320 (8.1)	< 0.001
Coronary artery disease	124/235 (52.8)	213/391 (54.5)	665/1320 (50.4)	0.334
Myocardial infarction	42/235 (17.9)	52/391 (13.3)	134/1320 (10.2)	0.002
Stroke	21/235 (8.9)	41/391 (10.5)	102/1320 (7.7)	0.211
Coronary bypass grafting	48/235 (20.4)	59/391 (15.1)	114/1319 (8.6)	< 0.001
Prior sternotomy	41/235 (17.4)	48/391 (12.3)	83/1319 (6.3)	< 0.001
Prior aortic valvuloplasty	10/235 (4.3)	13/391 (3.3)	67/1319 (5.1)	0.353
Prior mitral valvuloplasty	6/235 (2.6)	6/391 (1.5)	6/1319 (0.5)	0.003
Prior tricuspid valvuloplasty	0/235 (0)	1/391 (0.3)	3/1319 (0.2)	> 0.999
Prior peripheral stent (femoral, iliac)	13/235 (5.5)	13/391 (3.3)	24/1319 (1.8)	0.003
Prior carotid stent or carotid endarterectomy	8/235 (3.4)	17/391 (4.3)	45/1319 (3.4)	0.657
Congestive heart failure	96/235 (40.9)	143/391 (36.6)	468/1320 (35.5)	0.280
Mitral regurgitation (moderate to severe)	26/208 (12.5)	45/368 (12.2)	178/1198 (14.9)	0.378
Tricuspid regurgitation (moderate to severe)	21/204 (10.3)	37/342 (10.8)	122/1104 (11.1)	0.970
Atrial fibrillation	36/220 (16.4)	81/370 (21.9)	307/1283 (23.9)	0.040
Prior pacemaker	24/235 (10.2)	31/391 (7.9)	175/1319 (13.3)	0.010
COPD	54/235 (23.0)	75/391 (19.2)	184/1320 (13.9)	< 0.001
Renal insufficiency	59/235 (25.1)	105/391 (26.9)	371/1320 (28.1)	0.625
Creatinine, mg/dL, mean ± SD (*n*)	7.1 ± 24.3 (234)	4.1 ± 19.4 (388)	6.5 ± 23.9 (1315)	0.741
n/*N* (%)				
Liver disease	17/235 (7.2)	7/391 (1.8)	11/1320 (0.8)	< 0.001
Porcelain aorta	25/235 (10.6)	19/391 (4.9)	32/1320 (2.4)	< 0.001
Hostile chest	25/235 (10.6)	19/391 (4.9)	32/1320 (2.4)	< 0.001
Frailty	35/235 (14.9)	71/391 (18.2)	161/1320 (12.2)	0.010
Previous cancer	62/235 (26.4)	99/391 (25.3)	246/1320 (18.6)	0.002
Mean ± SD (*n*)				
BNP	822 ± 1710 (*n* = 32)	1578 ± 3418 (*n* = 51)	1666 ± 3387 (*n* = 215)	0.063
N-terminal BNP	3854 ± 6620 (*n* = 68)	4770 ± 7865 (*n* = 107)	4485 ± 7600 (*n* = 338)	0.378
Creatinine kinase	94.8 ± 72.3 (*n* = 129)	89.3 ± 66.1 (*n* = 268)	88.9 ± 73.4 (*n* = 696)	0.632
CK-MB, U/L	17.4 ± 11.0 (*n* = 35)	19.8 ± 18.3 (*n* = 93)	20.0 ± 30.4 (*n* = 194)	0.766
Troponin I, ng/mL	1.9 ± 7.1 (*n* = 36)	6.0 ± 13.1 (*n* = 59)	4.0 ± 12.8 (*n* = 227)	0.152
Troponin T, ng/mL	11.1 ± 28.3 (*n* = 61)	8.2 ± 37.3 (*n* = 118)	10.6 ± 59.6 (*n* = 329)	0.664
Haemoglobin, g/dL	16.5 ± 21.3 (*n* = 235)	14.9 ± 16.4 (*n* = 386)	16.7 ± 21.9 (*n* = 1307)	0.063

BNP B-type natriuretic peptide, *CK* creatinine kinase, *COPD* chronic obstructive pulmonary disease, *Log ES* logistic EuroSCORE, *LVEF* left ventricular ejection fraction, *NYHA* New\ York Heart Association

Table 1 (continued)

p value: Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables

congestive heart failure, moderate or severe mitral and tricuspid regurgitation, and chronic obstructive pulmonary disease [COPD]), other parameters differed significantly across age groups (Table 1 and Supplemental Table A). For example, younger patients had higher rates of a history of smoking ($p < 0.001$), diabetes ($p < 0.001$), previous myocardial infarction ($p = 0.002$), coronary artery bypass graft (CABG; $p < 0.001$), and COPD ($p < 0.001$). Of particular note, the rate of risk factors not considered in surgical risk scores [e.g., severe liver disease ($p < 0.001$), hostile chest ($p < 0.001$), and porcelain aorta ($p < 0.001$)] were remarkably high in the youngest age group (< 75 years) compared with the older age groups. A few risk factors had a higher incidence in the 75–80-year-old group (eg, hypertension, dyslipidaemia, and frailty) compared with the other groups, while atrial fibrillation and pacemaker implantation had a higher incidence in the ≥ 80-year-old group compared with the other two age groups. Interestingly, the percentage of frailty was numerically higher in the < 75-year-old group than in the > 80-year-old group, although the difference was not statistically significant. A higher proportion of patients had cancer at baseline in the younger group compared with older patients ($p = 0.002$, Table 1). It translated to a slightly higher numerical death rate for malignancy during the study in younger patients versus older patients but did not reach the level of statistical significance ($p = 0.65$, Supplemental Table C). A higher proportion of patients had a peripheral stent, mitral valvuloplasty, and sternotomy in the younger group compared with the older groups (Table 1 and Supplemental Table A).

Intra- and periprocedural parameters

Most patients (87.1%) were treated using the transfemoral (TF) approach, while 12.9% of patients underwent TAVI through non-TF access, mainly transapical. Regarding intraprocedural parameters (Table 2), similar among age groups was the rate of transfemoral approach, no BAV in approximately half of patients, correct valve positioning in most patients, post-dilatation in approximately 10% of patients, surgical vascular closure in approximately 6% of patients, procedure time of approximately 75 min, and amount of contrast volume used.

While slightly more than half of the patients in the < 75- and 75–80-year-old groups had general anaesthesia, only 45% of patients ≥ 80 years had general anaesthesia ($p = 0.011$). The percentage of patients implanted per valve size (i.e., 23 mm, 26 mm, and 29 mm) differed among age groups (comparison between the 3 groups: $p < 0.001$). Fluoroscopy time was slightly, but significantly, longer in the ≥ 80-year-old group ($p = 0.008$).

Clinical outcomes at 30 days and 1 year

Overall and cardiovascular mortality at 30 days were low and similar in the three age groups (1.7%, 2.0%, 2.3% and 0.9%, 1.0%, 1.9%, respectively, in the < 75-, 75–80-, and > 80-year-old age groups). At 1 year, overall and cardiovascular mortality were also similar in patients < 75 years compared with those 75–80 years (14.2% vs. 9.3% and 7.6% vs. 5.3%, respectively) as well as with patients > 80 years (13.3% overall and 8.9% cardiovascular mortality; Table 3).

Nevertheless, when analysing the Kaplan–Meier event rates of all-cause mortality, it appeared that while the rates were rather superimposed up to 30 days, the three curves dissociated beyond this point (Fig. 1). This analysis confirmed that all-cause mortality was similar ($p = 0.54$) between < 75-year-old patients (12.7% [95% CI 9.02, 17.80]) and those older than 80 years (11.3% [95% CI 9.72, 13.20]); while mortality appeared significantly lower in the 75–80-year-old group: 7.4% [95% CI 5.16, 10.53] ($p = 0.024$ compared with the < 75-year-old group and $p = 0.025$ compared with the ≥ 80-year-old group). No other significant differences were observed between 30 days and 1 year on any other clinical outcomes, including cardiac mortality (see Supplemental Table B). To identify factors involved in the cardiac mortality results, we conducted an analysis on the cause of cardiac death. Sudden cardiac death appeared to be the main driver of differences among age groups for all-cause mortality ($p = 0.006$). The sudden cardiac death rate was 20.7% in the < 75-year-old group, while it was reported in less than 5% of patients in the two older age groups ($p = 0.102$ when compared with the 75- to 80-year-old group and $p = 0.010$ when compared with the ≥ 80-year-old group) (Supplementary Files—Table C).

No other statistically significant differences were seen between age groups for any other clinical outcomes, i.e., disabling stroke (Supplementary Figure A), bleeding, myocardial infarction (MI), new onset of atrial fibrillation (AF) and new pacemaker implantation (Supplementary Figure B).

Subgroup of patients < 65 years

Expectedly, the analysis conducted on the subgroup of very young patients (< 65 years, 62.5% males, $n = 40$) revealed a much lower surgical risk score (mean log ES: 7.3 ± 7.5%, $p < 0.001$) as compared with other groups (Table D in Supplementary Files). Hostile chest occurred significantly

Table 2 Procedural characteristics, by age group

Characteristic	< 75 years old (*N* = 235)	75–80 old (*N* = 391)	≥ 80 years old (*N* = 1320)	*p* value
n/*N* (%)				
Transfemoral approach	196/235 (83.4)	335/391 (85.7)	1163/1320 (88.1)	0.092
General anaesthesia	118/235 (50.2)	204/391 (52.2)	592/1320 (44.8)	0.011
No BAV	114/235 (48.5)	192/391 (49.1)	677/1319 (51.3)	0.593
Valve size				< 0.001
23 mm	68/235 (28.9)	116/391 (29.7)	523/1320 (39.6)	
26 mm	93/235 (39.6)	169/391 (43.2)	540/1320 (40.9)	
29 mm	74/235 (31.5)	106/391 (27.1)	257/1320 (19.5)	
Correct positioning	233/235 (99.1)	386/391 (98.7)	1297/1314 (98.7)	0.698
Post-dilatation	27/235 (11.5)	48/389 (12.3)	132/1319 (10.0)	0.359
Vascular closure-surgical	13/194 (6.7)	20/331 (6.0)	62/1155 (5.4)	0.809
Vascular closure-device	178/194 (91.8)	309/331 (93.4)	1076/1155 (93.2)	0.809
Procedure time, mean ± SD in min	77.8 ± 51.49 (*n* = 194)	74.1 ± 38.74 (*n* = 329)	71.4 ± 33.66 (*n* = 1081)	0.463
Mean ± SD				
Fluoroscopy time, min	13.2 ± 8.78 (*n* = 200)	13.6 ± 6.94 (*n* = 357)	14.2 ± 7.42 (*n* = 1152)	0.008
Contrast volume, ml	213, 117.4 ± 55.46	374, 129.0 ± 69.20	1251, 119.0 ± 57.00	0.173
Total length of stay, min	13.4 ± 9.2 (*n* = 235)	12.6 ± 7.0 (*n* = 391)	12.7 ± 9.0 (*n* = 1320)	0.351
Length of stay in the intensive cardiac unit, min	2.2 ± 4.1 (*n* = 235)	1.9 ± 3.4 (*n* = 391)	2.1 ± 4.1 (*n* = 1320)	0.837
THV in THV	2 (0.9)	5 (1.3)	7 (0.5)	0.228
Conversion to open heart surgery	1 (0.4)	3 (0.8)	7 (0.5)	0.891
Coronary obstruction	0 (0.0)	1 (0.3)	6 (0.5)	0.853
Aortic root/annulus rupture[a]	0 (0.0)	0 (0.0)	3 (0.2)	> 0.999
Major vascular complication	7 (3.0)	12 (3.1)	39 (3.0)	0.979

BAV balloon aortic valvuloplasty, *THV* transcatheter heart valve

p values were calculated using Wilcoxon sum rank for continuous variables and Fisher's exact test for categorical variables. *p* values for THV in THV and conversion to open heart surgery were calculated using Fisher's exact test; *p* values for coronary obstruction, aortic root/annulus rupture, and major vascular complication were calculated using log rank test

[a]Site reported

greater frequency in the younger patient group than in the older patient groups ($p < 0.001$, Table D in Supplementary File). In patients < 65 years, 17.5% reported complications from previous surgery or had evidence of thoracic radiation therapy vs. 2.8% in the 75–80-year-old group ($p < 0.001$) and 1.4% in the ≥ 80-year-old group ($p < 0.001$). Radiation therapy related to previous cancer was also reported in 17.5% of < 65-year-old patients with hostile chest (Table D in Supplementary File). All-cause mortality in this subgroup of < 65-year-old patients (Table E in Supplementary File) appeared to be the higher than for all other age groups (15.4% vs. 7.4% in the 75- to 80-year-old and 11.3% in the ≥ 80-year-old group; *p* value between groups = 0.044).

Hemodynamics and functional evaluation

Mean gradient and effective orifice area (EOA) were substantially improved after valve implantation, but no statistically significant differences were found between age groups (Fig. 2).

Similarly, the quality of life assessed according to EQ-5D was improved by the THV implant with no statistically significant differences found between age groups. While most patients were in NYHA class II/III at baseline; they were in NYHA class I/II after the THV implant (Fig. 3).

Discussion

While a huge amount of data is available now on the outcomes of TAVI in patients older than 75 years of age, little is known about TAVI outcomes in younger patients. In our analysis of the SOURCE 3 Registry, only 12% of patients were younger than 75 years. These younger patients had higher rates of smoking, diabetes, myocardial infarction, previous CABG procedure, and COPD at enrolment. Of particular note, there was a remarkably higher rate of comorbidities not reflected by surgical risk scores in the younger than 75 years, such as severe liver disease, hostile chest, severe

Table 3 Clinical outcomes on the overall cohort and by age

Endpoints	Time point	< 75 years old ($N = 235$)	75–80 old ($N = 391$)	≥ 80 years old ($N = 1320$)	p value
All-cause mortality	30 days	1.7 [0.64, 4.47]	2.0 [1.03, 4.05]	2.3 [1.66, 3.32]	0.793
	1 year	14.2 [10.32, 19.41]	9.3 [6.79, 12.64]	13.3 [11.62, 15.31]	0.076
Cardiovascular mortality	30 days	0.9 [0.21, 3.37]	1.0 [0.39, 2.72]	1.9 [1.29, 2.79]	0.299
	1 year	7.6 [4.76, 11.88]	5.3 [3.43, 8.05]	8.9 [7.43, 10.55]	0.068
All stroke	30 days	0.4 [0.06, 2.98]	1.0 [0.39, 2.70]	1.8 [1.17, 2.63]	0.217
	1 year	1.4 [0.45, 4.29]	3.5 [2.05, 5.98]	3.2 [2.38, 4.35]	0.283
Disabling stroke	30 days	0.4 [0.06, 2.98]	0.5 [0.13, 2.03]	0.5 [0.25, 1.11]	0.978
	1 year	0.9 [0.22, 3.53]	1.9 [0.92, 4.00]	1.3 [0.78, 2.08]	0.584
Life-threatening bleedings	30 days	4.7 [2.62, 8.29]	3.1 [1.76, 5.34]	5.8 [4.70, 7.25]	0.089
Major vascular complication (%)	30 days	5.5 [3.25, 9.35]	4.9 [3.13, 7.51]	4.0 [3.09, 5.23]	0.509
Myocardial infarction	30 days	0.0 NA	0.8% [0.25, 2.36]	0.2% [0.07, 0.71]	0.160
	1 year	0.9 [0.23, 3.65]	1.9 [0.89, 3.86]	0.6 [0.32, 1.29]	0.098
New onset of atrial fibrillation	30 days	3.4 [1.72, 6.69]	7.2 [5.00, 10.21]	6.6 [5.41, 8.12]	0.139
	1 year	4.3 [2.34, 7.87]	8.5 [6.12, 11.75]	8.4 [6.97, 10.01]	0.106
New permanent pacemaker	30 days	9.8 [6.62, 14.37]	10.7 [8.06, 14.26]	12.9 [11.24, 14.88]	0.246
	1 year	10.7 [7.35, 15.40]	12.1 [9.23, 15.78]	13.9 [12.17, 15.93]	0.299
Acute kidney injury	7 days	2.1 [0.89, 5.04]	1.0 [0.39, 2.70]	1.0 [0.58, 1.70]	0.309

All events are CEC adjudicated; values are Kaplan–Meier estimates (%) [95% confidence interval]

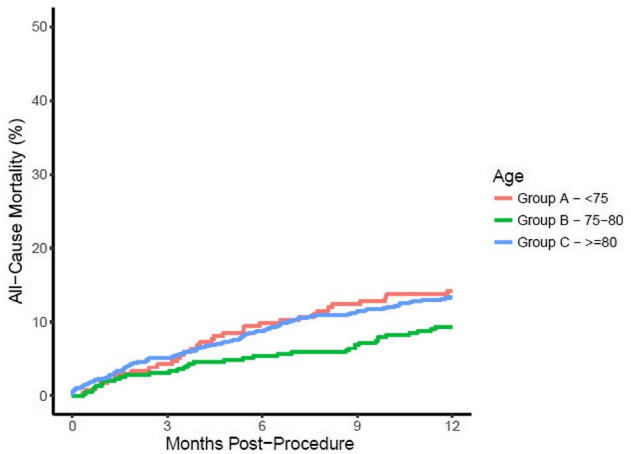

Fig. 1 All-cause mortality per age group, up to 1 year

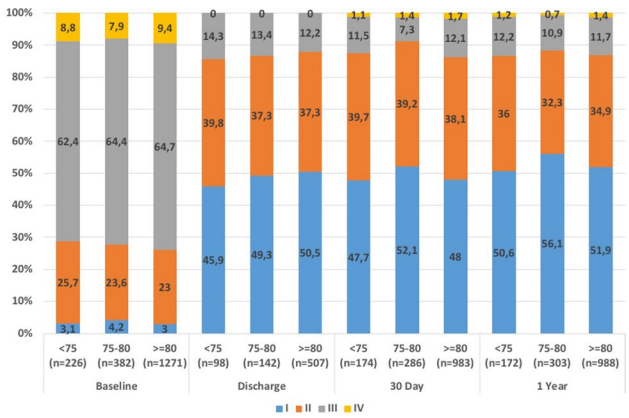

Fig. 3 Symptoms assessed using the New York Heart Association per age group, up to 1 year

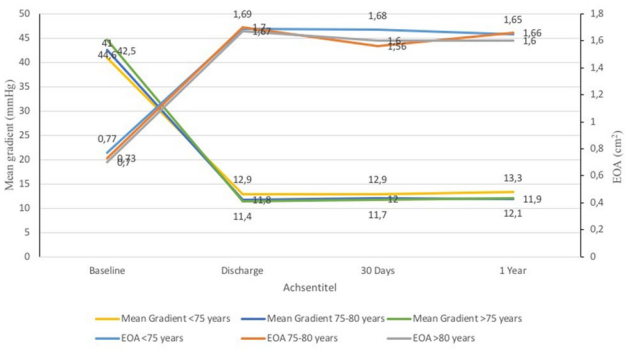

Fig. 2 Mean gradient and effective orifice area per age group, up to 1 year

radiation damage, and porcelain aorta. These findings were even more pronounced in patients younger than 65 years.

The higher rate of pre-existing comorbidities in younger than average TAVI patients are consistent with reports from the German TAVI registry [13], as well as other reports. Attizzani et al. [14] analysed data from a large, prospective, multi-centre, Italian registry to assess age-related differences in clinical outcomes at 30 days and 12 months follow-up in consecutive patients who underwent TAVI with a self-expanding TAVI prosthesis focussing on patients of very advanced age (i.e., > 85 years). The results of their study suggested that higher age is not associated with a worse outcome post-TAVI. Despite a higher overall risk profile, as

determined by higher EuroSCORE and Society of Thoracic Surgeons score. Older patients had similar periprocedural 30-day and 1-year outcomes compared with their younger (i.e., 75–85 years old) counterparts.

Conversely, Regev and colleagues [15] recently published an outcome analysis of a small subgroup of patients < 70 years from a three-centre TAVI registry. The authors found a higher rate of comorbidities in this subgroup, including significantly higher use of corticosteroids, COPD, diabetes, and peripheral artery disease. Despite the higher prevalence of risk factors, the 1-year mortality was lower in the 70-year-old subgroup than in the octogenarians.

In our study, most procedural parameters did not differ among age groups, except for the percentage of patients implanted per valve size and fluoroscopy time. Despite a higher overall risk profile, as described by higher logistic EuroSCORE and EuroSCORE II, older patients (≥ 75 years) experienced periprocedural, 30-day and 1-year outcomes comparable to younger patients (< 75 years). More 23 mm valves were used in the eldest age group; presumably because of the higher proportion of female patients in this group compared with the two younger groups; and also, potentially, because women are generally smaller than men.

We applied a landmark analysis for mortality from 30 days to 1 year, which excludes most of the periprocedural mortality and complications. Of note, mortality appeared to be similar between the < 75-year-old group and the oldest group (≥ 80 years), but significantly higher than the 75- to 80-year-old group. Additionally, in concordance with the available literature, younger patients experienced less atrial fibrillation [16] and required fewer permanent pacemaker implantations to 1 year [17, 18]. In addition, low numbers of life-threatening bleeding and low-risk scores (e.g., STS score) might have contributed to this finding.

Various hypotheses could be proposed to support these observations. As described above, in our analysis, younger patients (< 75 years) appeared to suffer more frequently from comorbidities not accounted for in "classical" surgical risk scores, such as hostile chest, in part, secondary to radiation therapies for cancer treatment, porcelain aorta and liver disease. These comorbidities could contribute to the mortality observed from 30 days to 1 year in this subgroup. This notion is in line with the findings from Theut and co-workers [19] that confirmed that "late" mortality in TAVI patients (in their case > 90 days post-TAVI) is mostly driven by non-cardiovascular, comorbidity-associated mortality.

However, the rather high rate of sudden cardiac death in the < 75-year-old patient group in our analysis remains unexplained; although, high numbers of previous myocardial infarction and/or a history of relevant coronary artery disease treated with CABG might partially contribute to this finding. In a large cohort ($N > 3700$), Urena and colleagues [20] could not identify age as an independent risk factor for late sudden cardiac death after TAVI. In their analyses, sudden cardiac death accounted for 8.6% of all deaths, with reduced ejection fraction (EF; < 40%) being the strongest predictor. Yet, the latter point was not reproduced in our patient cohort: we found no significant differences in the frequency of severely impaired EF between age groups. A potential explanation for the high number of sudden cardiac deaths could be the significantly higher number of young patients who had undergone irradiation [21].

It must be mentioned that our 30-day mortality results were low and did not differ between age groups. Thus, despite the relevant comorbidities, TAVI was feasible in all patient groups with a high degree of procedural safety.

Recently, Eggebrecht and colleagues [22] published a study from the German AQUA registry comparing the in-hospital outcomes of patients under 75 years who underwent transfemoral TAVI or SAVR. In their study, similar factors, such as frailty, had driven the decision to perform TAVI in this young patient cohort. Of note, after propensity matching, no differences were found for in-hospital mortality or stroke. Patients who underwent TAVI had fewer incidences of delirium but needed more permanent pacemakers.

Limitations

The SOURCE 3 Registry is limited by its non-randomized design. Additionally, although our data had low numbers of events that may preclude definitive conclusions from our analyses, the study represents a large cohort of real-life TAVI patients. One should also consider that the parameters we analysed were available in high but not complete percentages.

Conclusions

In contemporary TAVI practice, patients under the age of 75 years represent a minority of cases. Here, we presented the largest cohort of TAVI patients under 75 years published to date. Despite younger age and a significantly lower surgical risk score, their periprocedural, 30-day outcomes did not markedly differ from older, higher-risk patients, but outcomes from 30 days to 1 year were worse for younger patients than for patients between 75 and 80 years. The 1-year outcomes in younger patients were mainly driven by a higher rate of sudden cardiac death compared with older patients. The results of this study may be partially, but not entirely, explained by comorbidities not accounted for by traditional scores, which was particularly prominent in a subgroup of patients < 65 years. Our results confirm current guidelines and emphasize the need for further research. We suggest conducting randomized trials in this age group

before recommendations are made to choose TAVI over conventional aortic valve surgery.

Acknowledgements The authors would like to acknowledge the patients, the CEC members and SOURCE 3 investigators. Frédérique Maneval, MS, Edwards Lifesciences provided manuscript drafting services. Tracey Fine, MS, ELS of Edwards Lifesciences provided manuscript editing services.

Funding The SOURCE 3 Registry is funded by Edwards Lifesciences, LLC (Irvine, CA, USA).

Compliance with ethical standards

Conflict of interest All authors have received fees from Edwards Lifesciences as Investigators of the SOURCE 3 Registry. In addition, Christophe Caussin is a proctor for Edwards Lifesciences and has received speaker fees and travel support from Edwards Lifesciences. Derk Frank and Helmut Baumgartner are consultants and proctors for Edwards Lifesciences and have received speaker fees and travel support from Edwards Lifesciences.

Responsibility for the scientific content The first and last author wrote the first draft of the manuscript, which was revised and approved by all co-authors. This manuscript was prepared using a clinical extract of completed and adjudicated 1-year follow-up results from the SOURCE 3 Registry. The Registry is in active follow-up and interim analyses were completed for this report.

References

1. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S, Investigators PT (2010) Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 363:1597–1607. https://doi.org/10.1056/NEJMoa1008232
2. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK, Investigators USCC (2014) Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 370:1790–1798. https://doi.org/10.1056/NEJMoa1400590
3. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ, Investigators PT (2011) Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 364:2187–2198. https://doi.org/10.1056/NEJMoa1103510
4. Kim WK, Hamm CW (2018) Transcatheter aortic valve implantation in Germany. Clin Res Cardiol 107:81–87. https://doi.org/10.1007/s00392-018-1297-0
5. Gaede L, Blumenstein J, Kim WK, Liebetrau C, Dorr O, Nef H, Hamm C, Elsasser A, Mollmann H (2017) Trends in aortic valve replacement in Germany in 2015: transcatheter versus isolated surgical aortic valve repair. Clin Res Cardiol 106:411–419. https://doi.org/10.1007/s00392-016-1070-1
6. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Munoz D, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, Group ESCSD (2017) 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 38:2739–2791. https://doi.org/10.1093/eurheartj/ehx391
7. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG, Investigators P (2016) Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 374:1609–1620. https://doi.org/10.1056/NEJMoa1514616
8. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PW, Kappetein AP, Investigators S (2017) Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med 376:1321–1331. https://doi.org/10.1056/NEJMoa1700456
9. Yamamoto M, Meguro K, Mouillet G, Bergoend E, Monin JL, Lim P, Dubois-Rande JL, Teiger E (2012) Comparison of effectiveness and safety of transcatheter aortic valve implantation in patients aged ≥ 90 years versus < 90 years. Am J Cardiol 110:1156–1163. https://doi.org/10.1016/j.amjcard.2012.05.058
10. Abramowitz Y, Chakravarty T, Jilaihawi H, Kashif M, Zadikany R, Lee C, Matar G, Cheng W, Makkar RR (2015) Comparison of outcomes of transcatheter aortic valve implantation in patients ≥ 90 years versus < 90 years. Am J Cardiol 116:1110–1115. https://doi.org/10.1016/j.amjcard.2015.06.033
11. Wendler O, Schymik G, Treede H, Baumgartner H, Dumonteil N, Ihlberg L, Neumann FJ, Tarantini G, Zamarano JL, Vahanian A (2017) SOURCE 3 registry: design and 30-day results of the European postapproval registry of the latest generation of the SAPIEN 3 transcatheter heart valve. Circulation 135:1123–1132. https://doi.org/10.1161/CIRCULATIONAHA.116.025103
12. Wendler O, Schymik G, Treede H, Baumgartner H, Dumonteil N, Neumann FJ, Tarantini G, Zamorano JL, Vahanian A (2017) SOURCE 3: 1-year outcomes post-transcatheter aortic valve implantation using the latest generation of the balloon-expandable transcatheter heart valve. Eur Heart J 38:2717–2726. https://doi.org/10.1093/eurheartj/ehx294
13. Buellesfeld L, Gerckens U, Erbel R, Zahn R, Linke A, Sievert H, Figulla HR, Kuck KH, Hauptmann KE, Hambrecht R, Richardt G, Naber C, Voehringer M, Mudra H, Senges J, Grube E, German TRI (2012) Age-stratified baseline and outcome characteristics of patients undergoing transcatheter aortic valve implantation: results from the German multicenter registry. J Invasive Cardiol 24:531–536
14. Attizzani GF, Ohno Y, Latib A, Petronio AS, Giannini C, Ettori F, Fiorina C, Bedogni F, Brambilla N, Bruschi G, Colombo P, Presbitero P, Fiorilli R, Poli A, Barbanti M, Colombo A, Tamburino C (2016) Age-related differences in 1- and 12-month outcomes in patients undergoing transcatheter aortic valve implantation (from a large multicenter data repository). Am J Cardiol 118:1024–1030. https://doi.org/10.1016/j.amjcard.2016.07.018
15. Regev E, Finkelstein A, Assali A, Barbash I, Fefer P, Ben-Shoshan J, Orvin K, Konigstein M, Guetta V, Kornowski R, Segev A (2017) Comparison of outcome of transcatheter aortic valve implantation for severe aortic stenosis in 3 age groups (≤ 70; 71

to 80, and ≥ 81 years). Am J Cardiol 120:1607–1611 https://doi.org/10.1016/j.amjcard.2017.07.060
16. Tarantini G, Mojoli M, Windecker S, Wendler O, Lefevre T, Saia F, Walther T, Rubino P, Bartorelli AL, Napodano M, D'Onofrio A, Gerosa G, Iliceto S, Vahanian A (2016) Prevalence and impact of atrial fibrillation in patients with severe aortic stenosis undergoing transcatheter aortic valve replacement: an analysis from the SOURCE XT prospective multicenter registry. JACC Cardiovasc Interv 9:937–946. https://doi.org/10.1016/j.jcin.2016.01.037
17. Fadahunsi OO, Olowoyeye A, Ukaigwe A, Li Z, Vora AN, Vemulapalli S, Elgin E, Donato A (2016) Incidence, predictors, and outcomes of permanent pacemaker implantation following transcatheter aortic valve replacement: analysis from the U.S. Society of Thoracic Surgeons/American College of Cardiology TVT Registry. JACC Cardiovasc Interv 9:2189–2199. https://doi.org/10.1016/j.jcin.2016.07.026
18. Martinez-Selles M, Bramlage P, Thoenes M, Schymik G (2015) Clinical significance of conduction disturbances after aortic valve intervention: current evidence. Clin Res Cardiol 104:1–12. https://doi.org/10.1007/s00392-014-0739-6
19. Theut M, Thygesen JB, De Backer O, Sondergaard L (2017) Survival and cause of death after transcatheter aortic valve replacement as compared to an age- and sex-matched background population. EuroIntervention 13:e1058–e1066. https://doi.org/10.4244/EIJ-D-17-00147
20. Urena M, Webb JG, Eltchaninoff H, Munoz-Garcia AJ, Bouleti C, Tamburino C, Nombela-Franco L, Nietlispach F, Moris C, Ruel M, Dager AE, Serra V, Cheema AN, Amat-Santos IJ, de Brito FS, Lemos PA, Abizaid A, Sarmento-Leite R, Ribeiro HB, Dumont E, Barbanti M, Durand E, Alonso Briales JH, Himbert D, Vahanian A, Imme S, Garcia E, Maisano F, del Valle R, Benitez LM, Garcia del Blanco B, Gutierrez H, Perin MA, Siqueira D, Bernardi G, Philippon F, Rodes-Cabau J (2015) Late cardiac death in patients undergoing transcatheter aortic valve replacement: incidence and predictors of advanced heart failure and sudden cardiac death. J Am Coll Cardiol 65:437–448. https://doi.org/10.1016/j.jacc.2014.11.027
21. Jaworski C, Mariani JA, Wheeler G, Kaye DM (2013) Cardiac complications of thoracic irradiation. J Am Coll Cardiol 61:2319–2328. https://doi.org/10.1016/j.jacc.2013.01.090
22. Eggebrecht H, Bestehorn K, Rassaf T, Bestehorn M, Voigtlander T, Fleck E, Schachinger V, Schmermund A, Mehta RH (2018) In-hospital outcomes after transcatheter or surgical aortic valve replacement in younger patients less than 75 years old: a propensity-matched comparison. EuroIntervention 14:50–57. https://doi.org/10.4244/EIJ-D-17-01051

Affiliations

Derk Frank[1,12] · Mohamed Abdel-Wahab[2] · Martine Gilard[3] · Franck Digne[4] · Geraud Souteyrand[5] · Christophe Caussin[6] · Frédéric Collart[7] · Vincent Letocart[8] · Jochen Wöhrle[9] · Christian Kuhn[1,12] · Tomas Hovorka[10] · Helmut Baumgartner[11]

1 Department of Internal Medicine III (Cardiology, Angiology, and Critical Care), University Medical Center Schleswig-Holstein (UKSH), Campus Kiel, Arnold-Heller-Str. 3, Building 6, 24105 Kiel, Germany

2 Cardiology Department, Heart Center, Leipzig, Germany

3 Public Hospital La Cavale Blanche, Brest, France

4 Centre Cardiologique du Nord, Saint-Denis, France

5 Public Hospital Clermont-Ferrand, Clermont-Ferrand, France

6 Institut Mutualiste Montsouris, Paris, France

7 Public Hospital La Timone, Marseille, France

8 Institut du thorax, Public Hospital Nantes, Nantes, France

9 Department of Internal Medicine II, University Hospital of Ulm, Ulm, Germany

10 Statistics, Edwards Lifesciences, Prague, Czech Republic

11 Division of Adult Congenital and Valvular Heart Disease, Department of Cardiovascular Medicine, University Hospital Muenster, Muenster, Germany

12 DZHK (German Centre for Cardiovascular Research), Partner Site Kiel/Hamburg/Lübeck, Kiel, Germany