Comparison of Outcomes of Transcatheter Aortic Valve Implantation in Patients ≥85 Years Versus Those <85 Years

Martino Pepe, MD, PhD[a,*], Nicola Corcione, MD[b], Giuseppe Biondi-Zoccai, MD, MStat[c,d], Alberto Morello, MD[b], Sergio Berti, MD[e], Francesco Bedogni, MD[f], Alessandro Iadanza, MD[g], Fabrizio Tomai, MD[h], Gennaro Sardella, MD[i], Enrico Romagnoli, MD, PhD[j], Paolo Ferraro, MD[k], Sirio Conte, MD[k], Palma Luisa Nestola, MD[a], Marcello De Giosa, Mmaths[l], Michele Cimmino, MD[k], Giacomo Frati, MD, MSc[c,m], and Arturo Giordano, MD, PhD[b]

The differential outcomes across the age spectrum of transcatheter aortic valve implantation (TAVI) recipients are still debated. Aim of the study was to evaluate the clinical outcomes of oldest-old patients undergoing TAVI in the large "Registro Italiano GISE sull'impianto di Valvola Aortica Percutanea (RISPEVA)" registry. A total of 3,507 patients were stratified according to age: 1,381 were ≥85 years, 2,126 were <85 years. Primary endpoints were death at 30-days and complete follow-up (FU) (medium 368 days). Cerebrovascular events, myocardial infarction, bleedings, vascular complications at 30-days and complete FU were considered. In the unadjusted analysis, 30-days mortality in the oldest-old group was higher than in younger patients (4.2% vs 2.4%; p = 0.007); this difference kept true also at complete FU (19.6% vs 15.9%; p = 0.014). After propensity score (PS) matching, the oldest-old population showed a higher mortality solely at 30-days (4.7% vs 2.4%; p = 0.016), while the survival at complete FU was similar to that of younger patients (20.1% vs 18.0%; p = 0.286). The incidence of non-fatal outcomes resulted comparable between the 2 groups, also after propensity score matching. At the multivariate logistic regression analysis procedural major or disabling bleedings, cerebrovascular events, cardiogenic shock resulted predictors of 30-days death in the oldest-old cohort. In conclusion, patients ≥85 years can safely undergo TAVI being not more exposed to procedural complications than those <85 years; nevertheless they showed worse 30-days mortality, probably driven by reduced tolerance to complications. Passed the critical periprocedural phase, patients ≥85 years had a similar survival to those <85 years with comparable risk profile.
 (Am J Cardiol 2020;129:60−70)

Due to the population aging phenomenon aortic stenosis (AS) is nowadays one of the most common valvular heart disease.[1] Early recognition and management of AS are of utmost importance because severe, symptomatic, untreated AS is associated with a dismal prognosis: aortic valve replacement is indeed the only treatment shown to improve both survival and quality of life.[1,2] The introduction of transcatheter aortic valve implantation (TAVI) has revolutionized the treatment of severe AS, especially in high-risk patients, often deemed ineligible for conventional surgical aortic valve replacement (SAVR) for either comorbidities or advanced age. Elderly patients in particular are known to face high postoperative morbidity and mortality following major cardiac surgery.[3] Since refinements in valve design and delivery systems have led to a widespread diffusion of TAVI, the differential outcomes across the age spectrum of treated patients are still debated. Cause the prevalence of AS increases with age and affects up to 10% of the population by the eighth decade, the assessment of TAVI outcomes in the category of the "oldest-old" appears of great interest.[4] Current literature is controversial and the single-handed clinical weight of age remains uncertain; moreover, elderly patients have represented only a small fraction in the pivotal randomized clinical trials on TAVI versus SAVR. As such, the aim of this study was to evaluate in a large "real world" registry the clinical outcomes of the oldest-old patients undergoing TAVI in comparison with the younger counterpart.

[a]Division of Cardiology, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy; [b]Invasive Cardiology Unit, "Pineta Grande" Hospital, Castel Volturno, Caserta, Italy; [c]Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; [d]Mediterranea Cardiocentro, Napoli, Italy; [e]Fondazione C.N.R. G. Monasterio Ospedale del Cuore, Massa, Italy; [f]Department of Cardiology, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy; [g]Divisione di Emodinamica, Dipartimento di Scienze Cardiache, Toraciche e Vascolari, Policlinico Santa Maria alle Scotte, Siena, Italy; [h]European Hospital, Rome, Italy; [i]Department of Cardiovascular Sciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; [j]Institute of Cardiology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; [k]Department of Invasive Cardiology, Casa di Salute "Santa Lucia", San Giuseppe Vesuviano, Napoli, Italy; [l]Department of Mathematics, University of Bari "Aldo Moro", Bari, Italy; and [m]IRCCS NEUROMED, Pozzilli, Isernia, Italy. Manuscript received March 6, 2020; revised manuscript received and accepted May 19, 2020.

See page 68 for disclosure information.

*Corresponding author: Tel: 0039-0805592996; fax: 0039-0805592819.
E-mail address: drmartinopepe@libero.it (M. Pepe).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.05.033

METHODS

This was a retrospective analysis of data accrued in the prospective multicenter "Registro Italiano GISE sull'impianto di Valvola Aortica Percutanea (RISPEVA)" registry. Details of the RISPEVA study have been reported elsewhere.[5–9] The study is an ongoing Italian multicenter observational registry approved by all ethics committees of participating centers, with all patients providing written informed consent. The study is registered online at clinicaltrials.gov (NCT02713932). All patients in whom TAVI was attempted at participating centers and willing to provide consent were offered inclusion in the study, without any additional selection criterion. Accordingly, patient selection and procedural strategy were at physician's discretion. Nonetheless, subject selection, preprocedural management, procedural technique, device choice, and subsequent management were all largely guided by contemporary best practice recommendations from national and European scientific societies. In detail, a heart-team was available in all participating centers, even though a preliminary heart-team evaluation was not mandatory. The RISPEVA registry collects clinical information including patient demographics, comorbidities, and procedural details in a dedicated electronic case report form. After TAVI, follow-up assessments were planned at 30-days, 6 months, 12 months, and yearly afterward. The present analysis is focused on patients treated from March 2008 to November 2018.

The oldest-old population was defined as patients aged 85 years or more at the time of the procedure.[10] The definition of high and/or prohibitive surgical risk for SAVR was based on current practice standards at the time of patient enrollment; some centers relied on heart team appraisal (including a cardiac surgeon) for all their cases, while others referred to surgical evaluation only those patients whose prohibitive risk was doubtful. Frailty was assessed by the treating physician based on a body mass index <20 kg/m^2, serum albumin <3.5g/dl, cachexia, any neurological disability, scarce mobility. However, information on physical performance such as gait speed and grip strength, perhaps more objective measures also mentioned in the current Valve Academic Research Consortium recommendations, were not available.[11] Severe chronic kidney disease was defined as an estimated glomerular filtration rate ≤30 ml/min calculated by means of the Cockcroft-Gault formula. New generation and old generation devices were defined according to the latest evidences in literature: Corevalve (Medtronic, Medtronic Parkway, Minneapolis, Minnesota) and Sapien XT (Edwards Lifesciences, Irvine, California) prostheses were intended as old generation.[8,12]

Follow-up data at 30-days after TAVI were available for 2,887 patients, whereas data at complete follow-up (medium 368.8 ± 438.1 days) were available for 2704 patients. The primary endpoints were death from any cause occurring within the first 30-days and at complete follow-up. Among secondary endpoints, procedural success, cerebrovascular events (including both stroke and transient ischemic attack), myocardial infarction, bleedings (major or disabling and minor), vascular complications (major or disabling and minor) were defined according the current Valve Academic Research Consortium recommendations and assessed at the time of procedure, at 30-days, and at complete follow-up.[11] The database was built up by Excel software (Microsoft Corporation, Redmond, Washington); data were analyzed by SPSS version 22 (IBM Research, Armonk, New York) and R version 3.5.3 (R Foundation, Wirtschaftsuniversität Wien-Welthandelsplatz, Vienna, Austria). The study population was divided into 2 groups: oldest-old patients (≥85 years) and patients younger than 85 years. Baseline characteristics of the study population and procedural findings were presented according to age category. Continuous variables were summarized as medians with standard deviations and categorical variables as percentages. Cumulative incidence of death and nonfatal outcomes at procedure time, at 30-days, and at complete follow-up were estimated for patients ≥85 years and <85 years of age. Baseline characteristics, procedural findings, and clinical outcomes of the study were compared between age groups using the Pearson chi-square test or Fisher exact test, when appropriated, for categorical variables and the Student's *t* test for continuous variables.

For the primary endpoints of the study the association with several clinical characteristics and procedural findings (known from the literature as predictors of poor outcome after TAVI) was tested in the general unmatched population with a univariate logistic regression model; the odd ratio (OR) values were calculated with confidence interval (CI) 95% and test Z score. Subsequently, a multivariate logistic regression model was built, using as determinants the parameters associated with the single outcome in the linear regression; the adjusted OR values were calculated with CI 95% and test Z score. Because of the nonrandomized nature of the study, a propensity score (PS) analysis was used to adjust for differences in patients' baseline characteristics, balancing them for gender, body mass index, frailty, New York Heart Academy (NYHA) class, diabetes mellitus, insulin-treated diabetes mellitus, arterial hypertension, peripheral artery disease, prior stroke or transient ischemic attack, history of coronary artery disease, prior cardiac surgery, estimated glomerular filtration rate, chronic obstructive pulmonary disease, left ventricular ejection fraction, pre-TAVI mean aortic gradient; these variables were selected because associated with worse short to midterm prognosis, as demonstrated by the previous literature or by our regression analysis. The 1:1 nearest neighbor matching without replacement method was used. Standardized mean differences for assessing covariate balance after PS matching were calculated.[13] For mortality at 30-days the association with non-fatal procedural complications was tested in the 2 age groups generated in the PS-matched population with a univariate logistic regression model, followed by a multivariate logistic regression model according to the same above described method. The Kaplan-Meier curve was used to evaluate the survival at 30-days and at complete follow-up in the propensity matched population and the log-rank test was used to evaluate the differences between the 2 age groups. For all tests significance was set for a 2-tailed value of $p < 0.05$.

RESULTS

From March 2008 through November 2018 a total of 3,507 patients undergoing TAVI at the participating hospitals

were included in the RISPEVA registry. The median age was 82.56 ± 6.26 years, 59% of patients were female, and the median STS score was 6.55 ± 6.21%. The study population was stratified according to the age: 1,381 (39.4%) patients were classified as oldest-old, the remaining 2,126 patients constituted the younger cohort. The baseline demographic and clinical characteristics of the 2 age groups are presented in Table 1. Compared to the younger group, the oldest-old patients were more frequently women, had lower body mass index, worse renal function, and degree of heart failure (expressed as NYHA class). Oldest-old also showed smaller aortic valve area and higher mean gradient. In contrast, the oldest-old group had significantly lower prevalence of diabetes mellitus, dyslipidemia, history of coronary artery disease, carotid artery disease, peripheral vascular disease, prior stroke or transient ischemic attack, prior cardiac surgery, prior coronary artery bypass grafting, chronic obstructive pulmonary disease, and more preserved left ventricle ejection fraction. Despite fewer comorbidities, the oldest-old patients presented with much higher values of Logistic EUROSCORE, EUROSCORE II, and STS score, relative to younger patients. Procedural features are described in Table 2. The TAVI procedure was conducted under local anesthesia, with pre- or periprocedural transesophageal echocardiography, and with the use of new generation devices in the 70.2%, 15.0%, and 56.4% of the RISPEVA population respectively, with no differences between the 2 groups; the oldest-old conversely received smaller sized prostheses, implanted through lower sized sheaths, and more often via a transfemoral access. After PS matching, a population of 1,648 patients was selected: 824 per group; baseline clinical and procedural findings are shown in Supplementary Table 3 and Supplementary Table 4.

Procedural outcomes are shown in Table 3. In the unmatched population, compared with the younger counterpart, oldest-old patients suffered from higher incidence of procedural death and cardiogenic shock. Contrariwise, no differences in cerebrovascular events, myocardial infarction, bleedings, vascular complications, cardiac tamponade, coronary occlusion were found. In the PS-matched population procedural death reflected the same trend as in the whole study population, but only approached threshold for statistical significance; the other non-fatal adverse events showed no significant differences between the 2 groups. Data on 30-days follow-up are shown in Table 4. In the overall population 30-days mortality in the oldest-old group was higher as well as the incidence of renal failure; on the other hand no between age groups differences in all the other non-fatal outcomes were observed. After PS matching, the incidence of all the other adverse events was similar between the 2 groups with exception for the survival rate that persisted lower in oldest-old (Figure 1). Data on complete follow-up (medium 368.82 ± 438.14 days) are shown in Table 5. In the overall population mortality in the oldest-old cohort kept resulting higher, together with the rate of renal failure. Divergently, after PS matching between the 2 age groups no difference in terms of mortality rate was observed (Figure 1). At the multivariate logistic regression analysis major or disabling procedural bleedings and cardiogenic shock resulted predictors of 30-days death in the younger cohort, whereas also cerebrovascular events, together with the same 2 above mentioned parameters, were predictors of 30-days mortality in the oldest-old cohort (Supplementary Table 5 and Table 6).

DISCUSSION

Aim of this analysis was to evaluate the clinical outcomes of the oldest-old patients undergoing TAVI; the main findings of the present study can be summarized as follows:

- 30-days mortality rate in patients ≥85 years of age was low;
- in the unmatched population mortality rates at 30-days and at complete follow-up (medium 368.82 ± 438.14 days) were higher in the oldest-old group relative to the younger patients;
- after PS matching the oldest-old population showed a higher mortality solely at 30-days, while the survival at complete follow-up was similar to that of younger patients;
- the incidence of non-fatal outcomes resulted essentially comparable between the oldest-old and younger arm at both 30-days and complete follow-up, also after PS matching.

As stated above, the low 30-days mortality in the oldest-old cohort demonstrates the safe feasibility of TAVI procedures in this category of patients. Our 30-days mortality in the oldest-old population was 4.2%, inferior than the rate observed in other multicenter observational registries that ranges around 10% (9.9% from Vlastra et al report, 8.8% from Arsalan et al, 11.3% in >90 years old patients from Yamamoto et al).[14–16] This can be due to different age limits used in other studies (e.g., nonagenarians), but can also reflect the impact of different patients' selection, of the elevated number of high volume centers participating to the RISPEVA Registry, and of the over the last years improvements in devices and techniques. In details, in our oldest-old population 86.3% of patients were treated in high-volume centers, mostly after 2015 (67.1%), with new generation devices in more than half of cases (56.8%), and prevalently through the transfemoral access (86.9%). Not by chance, Mentias et al recently analyzed the outcome of TAVI procedures performed in the sole year 2016 describing a 30-days death rate comparable to ours (3.6%) and similar short-term mortality between nonagenarians and younger patients when the analysis was limited to high-volume centers.[17]

Despite low, the 30-days mortality of the very elderly group was higher relative to the younger group, and in the unmatched population this difference in disfavor of the oldest-old kept true also at midterm follow-up. This result is in line with several recent observational reports.[14,15,17,18] Nevertheless, divergently from the above-cited researches, in the FRANCE-2 Registry 30-days mortality after TAVI between nonagenarians and younger groups did not differ significantly.[16] Also results on long-term survival are contradictory. Arsalan et al (through the investigation of the STS/ACC TVT

Table 1
Baseline characteristics of the RISPEVA population divided according to age

Variable	Overall (n = 3507)	Age (years-old) <85 (n = 2126)	Age (years-old) ≥85 (n = 1381)	p
Age (years)	82.56 ± 6.26	73.07 ± 5.53	87.93 ± 2.20	<0.001
Women	2070 (59.0%)	1168 (54.9%)	902 (65.3%)	<0.001
Body mass index (m/kg^2)	26.13 ± 4.44	26.74 ± 4.77	25.20 ± 3.70	<0.001
Body surface area (m^2)	1.74 ± 0.19	1.77 ± 0.20	1.70 ± 0.18	<0.001
Frailty	953 (27.2%)	551 (25.9%)	402 (29.1%)	0.038
Diagnosis				
Aortic stenosis	3038 (86.63%)	1823 (85.7%)	1215 (88.0%)	0.058
Combined aortic stenosis and regurgitation	316 (9.0%)	196 (9.2%)	120 (8.7%)	0.592
Risk profile				
Intermediate risk	231 (6.6%)	162 (6.6%)	69 (5.0%)	0.002
High risk	3061 (87.3%)	1830 (86.1%)	1231 (89.1%)	0.008
Inoperable risk	215 (6.13%)	134 (6.3%)	81 (5.9%)	0.598
Logistic EuroSCORE	17.54 ± 12.67	16.02 ± 12.06	19.83 ± 13.21	<0.001
EuroSCORE II	5.53 ± 5.80	5.28 ± 5.84	5.90 ± 5.71	0.004
STS-score	6.55 ± 6.21	5.69 ± 5.72	7.67 ± 6.65	<0.001
NYHA class III/IV	2454 (70.0%)	1441 (67.8%)	1013 (73.4%)	<0.001
Syncope	253 (7.2%)	122 (5.7%)	131 (9.5%)	<0.001
Arterial hypertension	2711 (77.3%)	1648 (77.5%)	1063 (77.0%)	0.707
Diabetes mellitus	823(23.5%)	570 (26.8%)	253 (18.3%)	<0.001
Insulin treatment	281(8.0%)	201 (9.5%)	80 (5.8%)	<0.001
Dyslipidemia*	1564 (44.6%)	1012 (47.6%)	552 (40.0%)	<0.001
Current smoker	252 (7.19%)	190 (8.9%)	62 (4.5%)	<0.001
Carotid artery disease	550 (15.68%)	356 (16.7%)	194 (14.0%)	0.032
Peripheral artery disease	654 (18.7%)	428 (20.1%)	226 (16.4%)	0.005
Prior stroke/transient ischemic attack	245 (7.00%)	169 (7.9%)	76 (5.5%)	0.005
Prior acute pulmonary edema	513 (14.63%)	290 (13.6%)	223 (16.1%)	0.040
History of coronary artery disease	921 (26.3%)	585 (27.5%)	336(24.3%)	0.036
Prior myocardial infarction	444 (12.7%)	284 (13.4%)	160(11.6%)	0.123
Prior percutaneous coronary intervention	790 (22.5%)	501 (23.6%)	289(20.9%)	0.068
Prior coronary bypass	229 (6,53%)	187 (8.8%)	42(3.0%)	<0.001
Prior cardiac surgery	483 (13.8%)	38 (17.9%)	103(7.5%)	<0.001
Prior aortic valve surgery procedure	102 (2.91%)	67 (3.2%)	35 (2.5%)	0.288
Prior valvuloplasty	200 (5.7%)	106 (5.0%)	94 (6.8%)	0.023
Temporary ventricular assist device	8 (0.2%)	8 (0.4%)	0 (0.0%)	0.026
Permanent ventricular assist device	2 (0.1%)	2 (0.1%)	0 (0.0%)	0.522
Prior iliofemoral percutaneous transluminal angioplasty	59 (1.7%)	43 (2.0%)	16 (1.2%)	0.052
Severe chronic kidney disease	396 (11.3%)	172 (8.1%)	224 (16.2%)	<0.001
Serum creatinine (mg/dl)	1.21 ± 0.73	1.23 ± 0.84	1.17 ± 0.53	0.013
eGFR (ml/min)	53.88 ± 23.84	59.28 ± 26.45	45.82 ± 16.28	<0.001
Hemoglobin (g/dl)	12.07 ± 1.65	12.13 ± 1.70	11.96 ± 1.57	0.003
Hematocrit (%)	36.78 ± 4.73	36.98 ± 4.85	36.48 ± 4.52	0.011
Serum albumin (g/dl)	4.04 ± 0.96	4.11 ± 1.10	3.94 ± 0.71	0.010
Chronic obstructive pulmonary disease	649 (18.5%)	445 (20.9%)	204 (14.8%)	<0.001
Chronic oxygen therapy	60 (1.7%)	42 (2.0%)	18 (1.3%)	0.134
Porcelain aorta	163 (4.7%)	112 (5.3%)	51 (3.7%)	0.389
History of cancer	383 (10.9%)	250 (11.8%)	133 (9.6%)	0.048
Cirrhosis	52 (1.5%)	50 (2.4%)	2 (0.1%)	<0.001
Cachexia	110 (3.1%)	86 (4.0%)	24 (1.7%)	<0.001
Left ventricular ejection fraction <50%	927 (26.4%)	585 (27.5%)	342 (24.8%)	0.071
Echocardiography				
Peak aortic gradient (mm Hg)	78.07 ± 22.68	76.18 ± 22.82	80.90 ± 22.18	<0.001
Mean aortic gradient (mm Hg)	48.61 ± 15.16	47.55 ± 15.12	50.23 ± 15.10	<0.001
Orifice aortic area (cm^2)	0.63 ± 0.23	0.66 ± 0.24	0.59 ± 0.21	<0.001
Peak aortic velocity (m/s^2)	4.34 ± 0.75	4.26 ± 0.73	4.45 ± 0.75	<0.001
Left ventricular ejection fraction (%)	52.90 ± 10.96	52.61 ± 11.23	53.36 ± 10.53	0.049
Aortic annulus (mm)	22.51 ± 2.99	22.61 ± 2.86	22.34 ± 3.09	0.072
Valsalva sinus diameter (mm)	32.54 ± 3.93	32.68 ± 3.97	32.34 ± 3.86	0.170
Sinotubular junction (mm)	28.67 ± 4.39	28.62 ± 4.46	28.74 ± 4.27	0.725
Ascending aorta (mm)	34.61 ± 4.38	34.68 ± 4.34	34.51 ± 4.43	0.485
Moderate or severe aortic calcification	1814 (51.7%)	1074 (50.5%)	740 (53.6%)	0.076

(*continued*)

Table 1 (***Continued***)

Variable	Overall (n = 3507)	Age (years-old)		p
		<85 (n = 2126)	≥85 (n = 1381)	
Aortic regurgitation	2319 (66.1%)	1418 (66.7%)	901 (65.2%)	0.374
Mild aortic regurgitation	1576 (44.9%)	957 (45.0%)	619 (44.8%)	0.911
Moderate aortic regurgitation	595 (17.0%)	359 (16.9%)	236 (17.1%)	0.876
Severe aortic regurgitation	148 (4.2%)	102 (4.8%)	46 (3.3%)	0.035
Mitral regurgitation	3153 (89.9%)	1893 (89.0%)	1260 (91.2%)	0.035
Mild mitral regurgitation	1685 (48.0%)	1067 (50.2%)	618 (44.8%)	0.002
Moderate mitral regurgitation	1371(39.1%)	773 (36.4%)	598 (43.3%)	<0.001
Severe mitral regurgitation	97(2.77%)	53 (2.5%)	44 (3.2%)	0.221
Systolic pulmonary artery pressure (mmHg)	41.88 ± 12.66	41.95 ± 12.71	41.77 ± 12.59	0.735
Multidetector computer tomography				
Mean aortic annulus diameter (mm)	23.51 ± 2.43	23.65 ± 2.54	23.31 ± 2.25	0.035
Left iliac artery diameter (mm)	8.69 ± 3.43	8.65 ± 3.13	8.74 ± 3.82	0.713
Right iliac artery diameter (mm)	8.63 ± 4.06	8.49 ± 2.96	8.82 ± 5.25	0.220
Left femoral artery diameter (mm)	7.23 ± 1.70	7.24 ± 1.77	7.214 ± 1.616	0.725
Right femoral artery diameter (mm)	7.25 ± 1.69	7.25 ± 1.71	7.28 ± 1.67	0.404
Moderate or severe tortuosity vessel	771 (22.0%)	453 (21.3%)	318 (23.0%)	0.230
Moderate or severe wall calcification	1359 (38.8%)	810 (38.1%)	549 (39.8%)	0.326

Values are expressed as mean ± standard deviation or n (%).

eGFR = Estimated glomerular filtration rate; NYHA = New York Heart Association.

* Dyslipidemia was defined as having plasma triglyceride concentration or total and/or low-density lipoprotein (LDL) cholesterol levels higher than local laboratory cutoff levels.

Registry), as well as Deharo et al, demonstrated higher mortality rates in the nonagenarians at longer follow-up after TAVI[15,18]; conversely other studies reported a comparable mid to long-term survival between the elderly and younger populations.[16,18,20] These limited and controversial results highlight how prognosis of very elderly patients is still a matter of debate, also because the available data are potentially jeopardized by the unequal distribution of clinical and echocardiographic variables. Also in the present analysis, relative to the younger counterpart, several comorbidities (Table 1) were less often present in the oldest-old population.[14,15,19,20] On the other hand, despite less comorbidities, the very elderly group had lower body mass index and more frequently presented severe chronic kidney disease, worse symptoms (prior pulmonary edema, syncope, class NYHA III/IV), and more advanced valvular disease as expressed by higher mean aortic gradient, higher peak velocity, and smaller aortic valve area. Oldest-old patients had also significantly higher predicted surgical risk as expressed by different scores (logistic EUROSCORE, EUROSCORE II, STS-PROM) which are currently adapted, perhaps inadequately, to assess the "surgical" risk of patients undergoing TAVI.[14,20] These population characteristics, similar to other observational studies, reflect a selection custom that can be licitly summarized as follows: in the first decade since TAVI introduction, heart teams have selected the healthiest among the oldest-old patients in whom TAVI procedure was motivated by more severe and symptomatic AS. This obviously creates a selection bias driven by clinical and echocardiographic differences.[21–23] In our population, when tested, age did not result an independent predictor of the primary endpoints, as conversely other comorbidities or the functional status were (Supplementary Table1 and Supplementary Table 2).

In order to adjust for the different risk profiles of elderly and younger patients, we performed, at variance with most previous studies, a PS matching analysis.[24] Notwithstanding being a statistical tool thought to compare therapeutic interventions in observational studies, the PS analysis has been recently widely used to balance unequal distribution of prognostic determinants in different age groups.[25] In the PS-matched population, divergently from the whole cohort, no significant difference in terms of mortality at complete follow-up was detected between the 2 age groups, as well as in terms of the other non-fatal adverse events. This finding, in line with a recent study by Atizzani et al, confirms that raw data from real-world registries are possibly hampered by an age-driven different risk profile and suggests that the mid-term prognostic relevance of age should probably be resized down.[26]

Differently from the results at 1-year, after PS correction the oldest-old population continued to show higher 30-days mortality, as in the whole population (Figure 2). Noteworthy, the higher 30-days mortality is not coupled with higher non-fatal adverse events either procedural or at 30-days (Table 4). As a consequence, the hypothesis of higher short-term mortality driven by higher procedural deaths or rates of procedural complications is questioned by our data. It may be conversely assumed that, even though advanced age standing alone does not trigger more procedural adverse events during TAVI, the oldest-old patients have poorer tolerance to periprocedural complications. This postulation is confirmed in our multivariate logistic analysis: in the oldest-old matched population procedural cerebrovascular events, major procedural bleeding, and cardiogenic shock resulted independent predictors of 30-days mortality, in line with the few available literature data.[17,27] We can speculate that the higher vulnerability of very elderly patients in case of procedural complications may be associated with

Table 2
Procedural features and discharge data in the RISPEVA population divided according to age

Variable	Overall (n = 3507)	Age (years-old)		p
		<85 (n = 2126)	≥85 (n = 1381)	
≥ 2015	2290 (65.3%)	1363 (64.1%)	927 (67.1%)	0.067
Local anesthesia	2463 (70.2%)	1486 (69.9%)	977 (70.7%)	0.591
Transesophageal echocardiography	526 (15.0%)	328 (15.4%)	198 (14.3%)	0.377
Femoral access	2978 (84.9%)	1778 (83.6%)	1200 (86.9%)	0.008
Percutaneous only approach	2601 (74.2%)	1553 (73.0%)	1048 (75.9%)	0.061
Sheathless	234 (6.7%)	145 (6.8%)	89 (6.4%)	0.663
Sheath size (F)	16.59 ± 2.31	16.73 ± 2.28	16.36 ± 2.35	<0.001
Prosthesis size (mm)	26.33 ± 2.77	26.56 ± 2.78	25.97 ± 2.72	<0.001
Aortic valve gradient (mmHg)	61.31 ± 26.25	59.42 ± 25.47	64.36 ± 27.21	<0.001
Device				
Old generation devices*	1091 (31.1%)	684 (32.2%)	407 (29.5%)	0.091
New generation devices †	1977 (56.4%)	1192 (56.1%)	785 (56.8%)	0.651
Corevalve	476 (13.6%)	322 (15.1%)	154 (11.2%)	0.001
Acurate	234 (6.7%)	131 (6.2%)	103 (7.5%)	0.133
Directflow	35 (1.0%)	18 (0.8%)	17 (1.2%)	0.263
Lotus	151 (4.3%)	97 (4.6%)	54 (3.9%)	0.352
Portico	347 (9.9%)	223 (10.5%)	124 (9.0%)	0.143
Sapien XT	615 (17.6%)	362 (17.0%)	253 (18.3%)	0.325
Sapien3	541 (15.4%)	298 (14.0%)	243 (17.6%)	0.004
Evolute Pro	107 (3.1%)	65 (3.1%)	42 (3.0%)	0.978
Evolute R	597 (17.0%)	378 (17.8%)	219 (15.9%)	0.139
Allegra	10 (0.3%)	4 (0.2%)	6 (0.4%)	0.181
Jena	2 (0.1%)	1 (0.0%)	1 (0.1%)	0.758
Undefined	392 (11.2)	227 (10.7%)	165 (11.9%)	0.243
Embolic protection device	52 (1.5%)	37 (1.7%)	15 (1.1%)	0.117
Valve-in-valve	100 (2.9%)	69 (3.2%)	31 (2.2%)	0.082
Predilation	2251 (64.2%)	1341 (63.1%)	910 (65.9%)	0.089
Postdilation	676 (19.3%)	429 (20.2%)	247 (17.9%)	0.093
Contrast volume (mL)	173.79 ± 100.91	169.10 ± 95.28	180.88 ± 108.83	0.002
Procedural time (minutes)	107.35 ± 49.44	106.93 ± 50.03	107.97 ± 48.55	0.577
Closure device use	1987 (56.7%)	1208 (56.8%)	779 (56.4%)	0.810
Proglide	913 (26.0%)	554 (26.1%)	359 (26.9%)	0.922
Prostar	1074 (30.6%)	654 (30.8%)	420 (30.4%)	0.922
Device success	3075 (87.7%)	1860 (87.5%)	1215 (88.0%)	0.655
Discharge data				
Hospital stay (days)	7.46 ± 7.31	7.54 ± 7.93	7.33 ± 6.23	0.419
Discharge left ventricular ejection fraction (%)	53.60 ± 9.77	53.28 ± 10.00	54.10 ± 9.40	0.018
Discharge peak aortic gradient (mmHg)	18.30 ± 11.3	18.52 ± 11.37	17.97 ± 11.25	0.243
Mean aortic gradient (mmHg)	9.78 ± 5.40	9.81 ± 5.21	9.75 ± 5.66	0.756
Discharge orifice aortic area (cm^2)	1.34 ± 0.50	1.33 ± 0.48	1.36 ± 0.53	0.462
Discharge aortic regurgitation	1657 (47.2%)	983 (46.2%)	674 (48.8%)	0.137
Moderate or severe discharge aortic regurgitation	267 (7.6%)	150 (7.1%)	117 (8.5%)	0.122
Moderate discharge mitral regurgitation	293 (8.4%)	157 (7.4%)	136 (9.8%)	0.010
Severe discharge mitral regurgitation	51 (1.5%)	25 (1.2%)	26 (1.9%)	0.088
Discharge pericardial effusion	137 (3.9%)	77 (3.6%)	60 (4.3%)	0.280
Discharge systolic pulmonary artery pressure (mmHg)	37.55 ± 11.00	37.49 ± 11.28	37.63 ± 10.61	0.799

Values are expressed as mean ± standard or n (%).
* COREVALVE, SAPIEN XT were defined as old generation devices.
† SAPIEN3, ACURATE, EVOLUTE R-PRO, PORTICO, LOTUS were defined as new generation devices.

the frailty status, naturally correlated to oldness. Even if no consensus exists, the most comprehensive definition of frailty is indeed the decreased ability of resisting to stressors.[28–30] Although there is growing attention on frailty as an outcome predictor after TAVI, the lack of an unequivocal and objective measure of frailty is the major barrier limiting the esteem of its prognostic impact. In current clinical practice frailty is frequently assessed subjectively based upon an informal "eyeball test"; such an evaluation was also made in our population on the basis of characteristics such as scarce mobility, neurological disability, and malnutrition, along with laboratory findings (i.e., low serum albumin).[11]

The present analysis could not avoid certain limitations. First, given the nonrandomized nature of the registry, data would result in selection bias, even though our dataset was large and prospectively collected from high-volume centers. Indeed, we observed differences in baseline clinical

Table 3
Procedural complications in the RISPEVA unmatched and propensity score-matched population divided by age

	Unmatched population				Propensity score-matched population			
		Age (years-old)				Age (years-old)		
Variable	Overall (n = 3507)	<85 (n = 2126)	≥85 (n = 1381)	p	Overall (n = 1648)	<85 (n = 824)	≥85 (n = 824)	p
Procedural Death	25 (0.7%)	10 (0.5%)	15 (1.1%)	0.034	19 (1.2%)	5 (0.6%)	14 (1.7%)	0.062
Procedural Cerebrovascular events	28 (0.8%)	14 (0.7%)	14 (1.0%)	0.248	18 (1.1%)	8 (1.0%)	10 (1.2%)	0.814
Procedural stroke	24 (0.7%)	11 (0.5%)	13 (0.9%)	0.137	15 (0.9%)	6 (0.7%)	9 (1.1%)	0.606
Procedural transient ischemic attack	5 (0.1%)	3 (0.1%)	2 (0.1%)	1.000	4 (0.2%)	2 (0.2%)	2 (0.2%)	1.000
Procedural myocardial infarction	7 (0.2%)	3 (0.1%)	4 (0.3%)	0.444	6 (0.4%)	2 (0.2%)	4 (0.5%)	0.687
Procedural vascular complications	305 (8.7%)	180 (8.5%)	125 (9.1%)	0.548	186 (11.3%)	91 (11.0%)	95 (11.5%)	0.815
Procedural minor vascular complications	184 (5.2%)	104 (4.9%)	80 (5.8%)	0.242	115 (7.0%)	55 (6.7%)	60 (7.3%)	0.699
Procedural major vascular complications	121 (3.5%)	76 (3.6%)	45 (3.3%)	0.616	71 (4.3%)	36 (4.4%)	35 (4.2%)	1.000
Procedural bleeding	173 (4.9%)	97 (4.6%)	76 (5.5%)	0.209	110 (6.7%)	50 (6.1%)	60 (7.3%)	0.374
Procedural minor bleeding	116 (3.3%)	66 (3.1%)	50 (3.6%)	0.404	69 (4.2%)	32 (3.9%)	37 (4.5%)	0.623
Procedural major or disabling bleeding	57 (1.6%)	31 (1.5%)	26 (1.9%)	0.331	41 (2.5%)	18 (2.2%)	23 (2.8%)	0.527
Procedural cardiac tamponade	34 (1.0%)	16 (0.8%)	18 (1.3%)	0.104	22 (1.3%)	9 (1.1%)	13 (1.6%)	0.521
Procedural coronary occlusion	6 (0.2%)	3 (0.1%)	3 (0.2%)	0.686	5 (0.3%)	2 (0.2%)	3 (0.4%)	1.000
Procedural valve migration	24 (0.7%)	17 (0.8%)	7 (0.5%)	0.304	9 (0.5%)	4 (0.5%)	5 (0.6%)	1.000
Missed implantation	11 (0.3%)	6 (0.3%)	5 (0.4%)	0.680	5 (0.3%)	1 (0.1%)	4 (0.5%)	0.374
Retrieved device	17 (0.5%)	11 (0.5%)	6 (0.4%)	0.730	7 (0.4%)	1 (0.1%)	6 (0.7%)	0.124
Annulus or aortic rupture	6 (0.2%)	3 (0.1%)	3 (0.2%)	0.686	4 (0.2%)	2 (0.2%)	2 (0.2%)	1.000
Conversion to open surgery	12 (0.3%)	6 (0.3%)	6 (0.4%)	0.451	8 (0.5%)	3 (0.4%)	5 (0.6%)	0.726
Unplanned surgery	210 (6.0%)	129 (6.1%)	81 (5.9%)	0.805	131 (7.9%)	67 (8.1%)	64 (7.8%)	0.856
Cardiogenic shock	37 (1.1%)	14 (0.7%)	23 (1.7%)	0.004	26 (1.6%)	8 (1.0%)	18 (2.2%)	0.073

and procedural characteristics between the 2 age groups. Although we sought to reduce potential biases using the PS-matched analysis, we were not able to correct for unmeasured variables. Second, the use of the type of device, as well as procedural strategy were at physicians' discretion. Accordingly, our findings should mainly be regarded as hypothesis-generating and require further confirmation from a large pragmatic randomized trial.

In conclusion, our findings suggest that patients ≥85 years can safely undergo TAVI procedures being not more exposed to procedural complications than younger patients; they showed both worse short-term prognosis and reduced tolerance to complications. However, after the critical peri-procedural phase, patients ≥85 years proved a midterm survival rate comparable to younger patients with comparable risk profile.

Table 4
30-days clinical outcomes in the RISPEVA unmatched* and propensity score-matched population divided by age

	Unmatched population				Propensity score-matched population			
		Age (years-old)				Age (years-old)		
Variable	Overall (n = 2887)	<85 (n = 1758)	≥85 (n = 1129)	p	Overall (n = 1648)	<85 (n = 824)	≥85 (n = 824)	p
All cause death	89 (3.1%)	42 (2.4%)	47 (4.2%)	0.007	59 (3.6%)	20 (2.4%)	39 (4.7%)	0.016
Cerebrovascular events	43 (1.5%)	24 (1.4%)	19 (1.7%)	0.492	26 (1.6%)	11 (1.3%)	15 (1.8%)	0.554
Stroke	39 (1.4%)	20 (1.1%)	19 (1.7%)	0.216	23 (1.4%)	8 (1.0%)	15 (1.8%)	0.207
Transient ischemic attack	6 (0.2%)	4 (0.2%)	2 (0.2%)	1.000	5 (0.3%)	3 (0.4%)	2 (0.2%)	1.000
Myocardial infarction	8 (0.3%)	4 (0.2%)	4 (0.4%)	0.719	7 (0.4%)	3 (0.3%)	4 (0.5%)	1.000
Bleedings	303 (10.5%)	169 (9.6%)	134 (11.9%)	0.054	186 (11.3%)	85 (10.3%)	101 (12.3%)	0.243
Minor bleedings	198 (6.9%)	110 (6.3%)	88 (7.8%)	0.111	115 (7.0%)	49 (5.9%)	66 (8.0%)	0.122
Major or disabling bleedings	105 (3.6%)	59 (3.4%)	46 (4.1%)	0.314	71 (4.3%)	36 (4.4%)	35 (4.2%)	1.000
Vascular complications	327 (11.3%)	192 (10.9%)	135 (12.0%)	0.391	200 (12.1%)	97 (11.8%)	103 (12.5%)	0.706
Minor vascular complications	202 (7.0%)	113 (6.4%)	89 (7.9%)	0.135	126 (7.6%)	59 (7.2%)	67 (8.1%)	0.517
Major vascular complications	125 (4.3%)	79 (4.5%)	46 (4.1%)	0.589	74 (4.5%)	38 (4.6%)	36 (4.4%)	0.905
PM implantation	451 (15.6%)	282 (16.0%)	169 (15.0%)	0.439	280 (17.0%)	148 (18.0%)	132 (16.0%)	0.325
Renal failure	308 (10.7%)	171 (9.7%)	137 (12.1%)	0.041	218 (13.2%)	103 (12.5%)	115 (14.0%)	0.424
Valve thrombosis	3 (0.1%)	1 (0.1%)	2 (0.2%)	0.565	2 (0.1%)	0 (0.0%)	2 (0.2%)	0.500
Surgical aortic valve repair	13 (0.5%)	7 (0.4%)	6 (0.5%)	0.602	9 (0.5%)	4 (0.4%)	5 (0.6%)	1.000

* Follow up data available for 2887 patients.

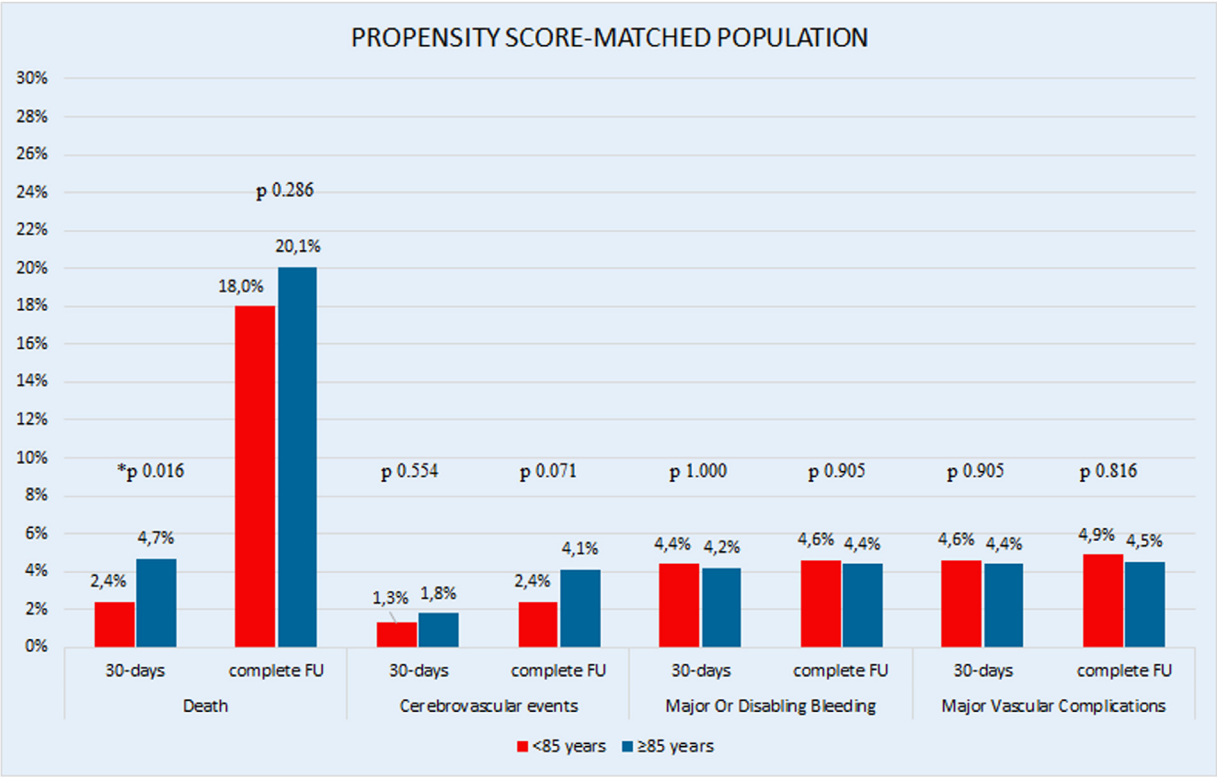

Figure 1. Clinical outcomes at 30-days and complete follow-up (FU) in the propensity score-matched population divided by age.

Table 5
Clinical outcomes at complete follow-up in the RISPEVA unmatched* and propensity score-matched population divided by age

	Unmatched population				Propensity score-matched population			
		Age (years-old)				Age (years-old)		
Variable	Overall (n = 2704)	<85 (n = 1646)	≥85 (n = 1058)	p	Overall (n = 1648)	<85 (n = 824)	≥85 (n = 824)	p
All cause death	469 (17.3%)	262 (15.9%)	207 (19.6%)	0.014	314 (19.1%)	148 (18.0%)	166 (20.1%)	0.286
Cerebrovascular events	83 (3.1%)	44 (2.7%)	39 (3.7%)	0.136	54 (3.3%)	20 (2.4%)	34 (4.1%)	0.071
Stroke	67 (2.5%)	36 (2.2%)	31 (2.9%)	0.225	42 (2.5%)	15 (1.8%)	27 (3.3%)	0.084
Transient ischemic attack	19 (0.7%)	8 (0.5%)	11 (1.0%)	0.093	14 (0.8%)	5 (0.6%)	9 (1.1%)	0.422
Myocardial infarction	20 (0.7%)	12 (0.7%)	8 (0.8%)	0.936	12 (0.7%)	6 (0.7%)	6 (0.7%)	1.000
Bleeding	316 (11.7%)	177 (10.8%)	139 (13.1%)	0.060	194 (11.8%)	89 (10.8%)	105 (12.7%)	0.252
Minor bleeding	206 (7.6%)	114 (6.9%)	92 (8.7%)	0.090	120 (7.3%)	51 (6.2%)	69 (8.4%)	0.107
Major or disabling bleeding	110 (4.1%)	63 (3.8%)	47 (4.4%)	0.430	74 (4.5%)	38 (4.6%)	36 (4.4%)	0.905
Vascular complications	335 (12.4%)	198 (12.0%)	137 (12.9%)	0.479	206 (12.5%)	101 (12.3%)	105 (12.7%)	0.823
Minor vascular complications	206 (7.6%)	116 (7.0%)	90 (8.5%)	0.163	129 (7.8%)	61 (7.4%)	68 (8.3%)	0.582
Major vascular complications	129 (4.8%)	82 (5.0%)	47 (4.4%)	0.521	77 (4.7%)	40 (4.9%)	37 (4.5%)	0.816
PM implantation	490 (18.1%)	303 (18.4%)	187 (17.7%)	0.629	304 (18.4%)	157 (19.1%)	147 (17.8%)	0.568
Endocarditis	18 (0.7%)	15 (0.9%)	3 (0.3%)	0.055	10 (0.6%)	8 (1.0%)	2 (0.2%)	0.108
Renal failure	308 (11.4%)	171 (10.4%)	137 (12.9%)	0.041	218 (13.2%)	103 (12.5%)	115 (14.0%)	0.424
Surgical aortic valve repair	14 (0.5%)	8 (0.5%)	6 (0.6%)	0.774	10 (0.6%)	5 (0.6%)	5 (0.6%)	1.000
Valve degeneration	10 (0.4%)	9 (0.5%)	1 (0.1%)	1.000	7 (0.4%)	6 (0.7%)	1 (0.1%)	0.124
Valve explantation	16 (0.6%)	10 (0.6%)	6 (0.6%)	0.894	11 (0.7%)	6 (0.7%)	5 (0.6%)	1.000
Valve-in-valve	8 (0.2%)	4 (0.2%)	4 (0.4%)	0.719	6 (0.4%)	3 (0.4%)	3 (0.4%)	1.000

* Follow up data available for 2704 patients.

AUTHORS' CONTRIBUTION

Martino Pepe: Conceptualization, Methodology, Writing-Original draft preparation; Nicola Corcione: Investigation: Giuseppe Biondi-Zoccai: Conceptualization, Validation; Alberto Morello: Investigation; Sergio Berti: Investigation, Supervision; Francesco Bedogni: Investigation, Supervision; Alessandro Iadanza: Investigation, Writing - Review & Editing; Fabrizio Tomai: Investigation, Supervision; Gennaro Sardella: Investigation, Supervision; Enrico Romagnoli: Investigation, Supervision; Paolo Ferraro: Investigation;

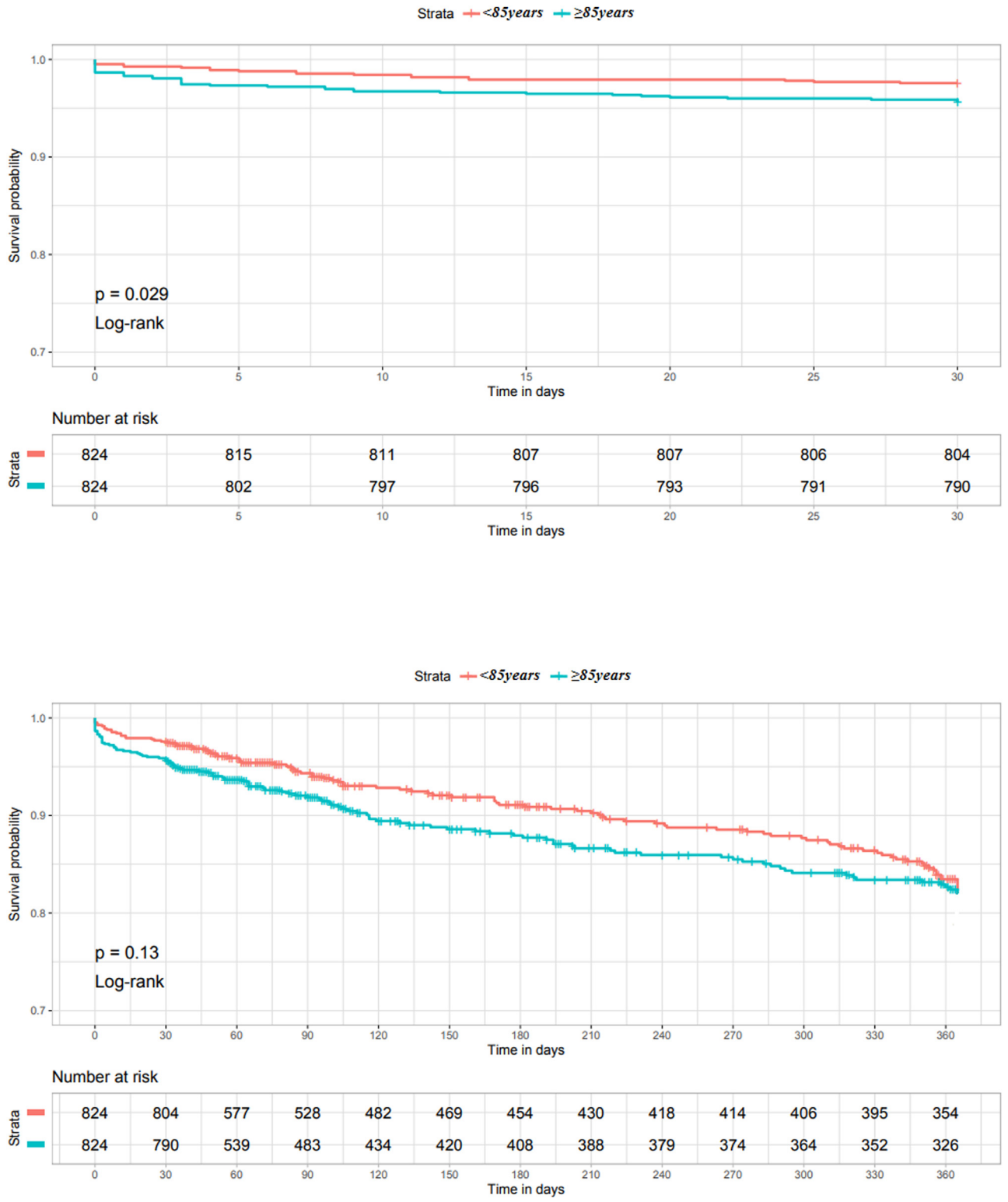

Figure 2. Kaplan-Meier survival probability at 30-days (above) and complete follow-up (below) in the propensity score-matched population divided by age.

Sirio Conte: Investigation; Palma Luisa Nestola: Writing-Original draft preparation, Visualization; Marcello De Giosa: Formal analysis; Michele Cimmino: Investigation; Giacomo Frati: Supervision; Arturo Giordano: Supervision, Project administration.

Disclosures

The RISPEVA study was supported by unrestricted grants from Edwards Lifesciences and Medtronic to the Società Italiana di Cardiologia Invasiva (SICI-GISE). G. Sardella

has received proctor fees from Edwards Lifesciences, Boston Scientific and Biosensors, and speaker fees from AstraZeneca, Terumo, OrbusNeich, Biosensors, Boston Scientific, Abbott Vascular, Stentys, and Alvimedica. The other authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.05.033.

1. Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, Bogers AJ, Piazza N, Kappetein AP. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol* 2013;62:1002–1012.
2. Marquis-Gravel G, Redfors B, Leon MB, Généreux P. Medical treatment of aortic stenosis. *Circulation* 2016;134:1766–1784.
3. Turrentine FE, Wang H, Simpson VB, Jones RS. Surgical risk factors, morbidity, and mortality in elderly patients. *J Am Coll Surg* 2006;203:865–877.
4. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis. the Tromsø study. *Heart* 2013;99:396–400.
5. Giordano A, Corcione N, Biondi-Zoccai G, Berti S, Petronio AS, Pierli C, Presbitero P, Giudice P, Sardella G, Bartorelli AL, Bonmassari R, Indolfi C, Marchese A, Brscic E, Cremonesi A, Testa L, Brambilla N, Bedogni F. Patterns and trends of transcatheter aortic valve implantation in Italy: insights from RISPEVA. *J Cardiovasc Med (Hagerstown)* 2017;18:96–102.
6. Giordano A, Corcione N, Ferraro P, Bedogni F, Testa L, Sardella G, Mancone M, Tomai F, De Persio G, Iadanza A, Frati G, Biondi-Zoccai G. RISPEVA (Registro Italiano GISE sull'impianto di Valvola Aortica Percutanea) StudyInvestigators. Outcome of patients undergoing transcatheter aortic valve implantation after prior balloon aortic valvuloplasty. *J Invasive Cardiol* 2018;30:380–385.
7. Giordano A, Corcione N, Ferraro P, Morello A, Conte S, Bedogni F, Testa L, Iadanza A, Sardella G, Mancone M, Tomai F, De Persio G, Attisano T, Pepe M, Frati G, Biondi-Zoccai G. RISPEVA (Registro Italiano GISE sull'impianto di Valvola Aortica Percutanea) Study Investigators. Impact of predilation before transcatheter aortic valve implantation with new-generation devices. *Cardiovasc Revasc Med* 2019;20:1096–1099.
8. Giordano A, Corcione N, Ferraro P, Morello A, Conte S, Testa L, Bedogni F, Iadanza A, Berti S, Regazzoli D, Romagnoli E, Trani C, Burzotta F, Pepe M, Frati G, Biondi-Zoccai G. Registro Italiano GISE sull'impianto di Valvola Aortica Percutanea (RISPEVA) Study Investigators. Comparative one-month safety and effectiveness of five leading new-generation devices for transcatheter aortic valve implantation. *Sci Rep* 2019;9:1–12.
9. Giordano A, Corcione N, Ferraro P, Morello A, Conte S, Testa L, Iadanza A, Sardella G, Mancone M, Berti S, Petronio AS, Romagnoli E, Pepe M, Frati G, Biondi-Zoccai G. Registro Italiano GISE sull'impianto di Valvola Aortica Percutanea (RISPEVA) StudyInvestigators. Comparison of ProGlide vs. Prostar in patients undergoing transcatheter aortic valve implantation. *Minerva Cardioangiol* 2019;67:443–449.
10. Lee SB, Oh JH, Park JH, Choi SP, Wee JH. Differences in youngest-old, middle-old, and oldest-old patients who visit the emergency department. *Clin Exp Emerg Med* 2018;5:249–255.
11. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol* 2012;60:1438–1454.
12. Cahill TJ, Chen M, Hayashida K, Latib A, Modine T, Piazza N, Redwood S, Søndergaard L, Prendergast BD. Transcatheter aortic valve implantation: current status and future perspectives. *Eur Heart J* 2018;39:2625–2634.
13. Zhang Z, Kim HJ, Lonjon G, Zhu Y. written on behalf of AME Big-Data Clinical Trial Collaborative Group. Balance diagnostics after propensity score matching. *Ann Transl Med* 2019;7:16.
14. Vlastra W, Chandrasekhar J, Vendrik J, Gutierrez-Ibanes E, Tchétché D, de Brito FS, Barbanti M, Kornowski R, Latib A, D'Onofrio A, Ribichini F, Baan J, Tijssen JGP, Pan M, Dumonteil N, Mangione JA, Sartori S, D'Errigo P, Tarantini G, Lunardi M, Orvin K, Pagnesi M, Sanchez Gila J, Modine T, Dangas G, Mehran R, Piek JJ, Delewi R. Transfemoral TAVI in nonagenarians: from the CENTER collaboration. *JACC Cardiovasc Interv* 2019;12:911–920.
15. Arsalan M, Szerlip M, Vemulapalli S, Holper EM, Arnold SV, Li Z, DiMaio MJ, Rumsfeld JS, Brown DL, Mack M. Should transcatheter aortic valve replacement be performed in nonagenarians?: Insights from the STS/ACC TVT registry. *J Am Coll Cardiol* 2016;67:1387–1395.
16. Yamamoto M, Mouillet G, Meguro K, Gilard M, Laskar M, Eltchaninoff H, Fajadet J, Iung B, Donzeau-Gouge P, Leprince P, Leuguerrier A, Prat A, Lievre M, Chevreul K, Dubois-Rande JL, Teiger E. FRANCE-2 Registry Investigators. Clinical results of transcatheter aortic valve implantation in octogenarians and nonagenarians: insights from the FRANCE-2 registry. *Ann Thorac Surg* 2014;97:29–36.
17. Mentias A, Saad M, Desai MY, Horwitz PA, Rossen JD, Panaich S, Elbadawi A, Qazi A, Sorajja P, Jneid H, Kapadia S, London B, Vaughan Sarrazin MS. Temporal trends and clinical outcomes of transcatheter aortic valve replacement in nonagenarians. *J Am Heart Assoc* 2019;8:e013685.
18. Yokoyama H, Tobaru T, Muto Y, Hagiya K, Higuchi R, Saji M, Takamisawa I, Shimizu J, Takanashi S, Takayama M, Tomita H, Tamura H, Doi S, Okazaki S, Isobe M. Long-term outcomes in Japanese nonagenarians undergoing transcatheter aortic valve implantation: a multicenter analysis. *Clin Cardiol* 2019;42:605–611.
19. Deharo P, Bisson A, Herbert J, Lacour T, Saint Etienne C, Theron A, Porto A, Collart F, Bourguignon T, Cuisset T, Fauchier L. Outcomes in nonagenarians undergoing transcatheter aortic valve implantation (TAVI): data from a nationwide analysis. *EuroIntervention* 2019;15:1489–1496.
20. Vendrik J, van Mourik MS, van Kesteren F, Henstra MJ, Piek JJ, Henriques JPS, Wykrzykowska JJ, de Winter RJ, Vis MM, Koch KT, Baan J. Comparison of outcomes of transfemoral aortic valve implantation in patients <90 with those >90 years of age. *Am J Cardiol* 2018;121:1581–1586.
21. Arnold SV, Reynolds MR, Lei Y, Magnuson EA, Kirtane AJ, Kodali SK, Zajarias A, Thourani VH, Green P, Rodés-Cabau J, Beohar N, Mack MJ, Leon MB, Cohen DJ, PARTNER Investigators. Predictors of poor outcomes after transcatheter aortic valve replacement: results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. *Circulation* 2014;129:2682–2690.
22. Arnold SV, Zhang Y, Baron SJ, McAndrew TC, Alu MC, Kodali SK, Kapadia S, Thourani VH, Miller DC, Mack MJ, Leon MB, Cohen DJ. Impact of short-term complications on mortality and quality of life after transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2019;12:362–369.
23. Capodanno D, Barbanti M, Tamburino C, D'Errigo P, Ranucci M, Santoro G, Santini F, Onorati F, Grossi C, Covello RD, Capranzano P, Rosato S, Seccareccia F, OBSERVANT Research Group. A simple risk tool (the OBSERVANT score) for prediction of 30-day mortality after transcatheter aortic valve replacement. *Am J Cardiol* 2014;113:1851–1858.
24. Elze MC, Gregson J, Baber U, Williamson E, Sartori S, Mehran R, Nichols M, Stone GW, Pocock SJ. Comparison of propensity score methods and covariate adjustment: evaluation in 4 cardiovascular studies. *J Am Coll Cardiol* 2017;69:345–357.
25. Wilson JRF, Badhiwala JH, Jiang F, Wilson JR, Kopjar B, Vaccaro AR, Fehlings MG. The impact of older age on functional recovery and quality of life outcomes after surgical decompression for degenerative cervical myelopathy: results from an ambispective, propensity-matched analysis from the CSM-NA and CSM-I international, multicenter studies. *J Clin Med* 2019;8:1708.
26. 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. 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* 2016;118:1024–1030.
27. Vlastra W, Jimenez-Quevedo P, Tchétché D, Chandrasekhar J, de Brito FS, Barbanti M, Kornowski R, Latib A, D'Onofrio A, Ribichini F, Baan J, Tijssen JGP, De la Torre Hernandez JM, Dumonteil N, Sarmento-Leite R, Sartori S, Rosato S, Tarantini G, Lunardi M, Orvin K, Pagnesi M, Hernandez-Antolin R, Modine T, Dangas G, Mehran R, Piek JJ, Delewi R. Predictors, incidence, and outcomes of patients undergoing transfemoral transcatheter Aortic Valve Implantation complicated by stroke. *Circ Cardiovasc Interv* 2019;12:e007546.
28. Anand A, Harley C, Visvanathan A, Shah ASV, Cowell J, MacLullich A, Shenkin S, Mills NL. The relationship between preoperative frailty and outcomes following transcatheter aortic valve implantation: a systematic review and meta-analysis. *Eur Heart J Qual Care Clin Outcomes* 2017;3:123–132.
29. Afilalo J, Lauck S, Kim DH, Lefèvre T, Piazza N, Lachapelle K, Martucci G, Lamy A, Labinaz M, Peterson MD, Arora RC, Noiseux N, Rassi A, Palacios IF, Généreux P, Lindman BR, Asgar AW, Kim CA, Trnkus A, Morais JA, Langlois Y, Rudski LG, Morin JF, Popma JJ, Webb JG, Perrault LP. Frailty in older adults undergoing aortic valve replacement: the FRAILTY-AVR study. *J AmCollCardiol* 2017;70:689–700.
30. Petronio AS, Giannini C. Frailty in patients undergoing TAVI: how can we measure it? *EuroIntervention* 2019;15:652–655.