Durability of bioprosthetic aortic valve replacement in patients under the age of 60 years – 1-year follow-up from the prospective INDURE registry

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ABSTRACT

Objectives: We report 1-year safety and clinical outcomes in patients <60 years undergoing bioprosthetic surgical aortic valve intervention.

Methods: The INSPIRIS RESILIA Durability Registry (INDURE) is a prospective, multicentre registry to assess clinical outcomes of patients <60 years. Patients with planned SAVR with or without concomitant replacement of the ascending aorta and/or coronary bypass surgery were included. Time-related valve safety, haemodynamic performance, and quality of life (QoL) at 1 year were assessed.

Results: 421 patients were documented with a mean age of 53.5 years, 76.5% being male, and 27.2% in NYHA class III/IV. Outcomes within 30 days included cardiovascular-related mortality (0.7%), time-related valve safety (VARC-2; 5.8%), thromboembolic events (1.7%), valve-related life-threatening bleeding (VARC-2; 4.3%), and permanent pacemaker implantation (3.8%). QoL was significantly increased at 6 months and sustained at 1 year. Freedom from all-cause mortality at 1 year was 98.3% (95%CI 97.1;99.6) and 81.8% were NYHA I vs. 21.9% at baseline. No patient developed structural valve deterioration Stage 3 (VARC-3). Mean aortic pressure gradient was 12.6 mmHg at 1 year and effective orifice area was 1.9 cm^2.

Conclusions: The 1-year data from the INSPIRIS RESILIA valve demonstrate good safety and excellent haemodynamic performance as well as an early QoL improvement.

Keywords: Surgical aortic valve replacement, structural valve degeneration, valve durability

INTRODUCTION

While mechanical valves have traditionally been preferred over bioprosthetic valves in younger patients, the use of bioprosthetic valves has expanded due to its durability, decreased risk of reoperation, and a possibility of undergoing transcatheter valve-in-valve procedure [1]. Retrospective observational studies have reported comparable long-term benefits in patients 50 to 69 years undergoing mechanical versus bioprosthetic valve replacement [2, 3]. As a result, current American and European guidelines recommend lower age cut-offs (50 to 65 years of age) for the use of bioprostheses emphasizing the importance of considering individual patient factors and informed shared decision-making [4, 5].

The INSPIRIS RESILIA aortic valve (Edwards Lifesciences, Irvine, USA) is a stented bioprosthetic, tri-leaflet valve comprised of bovine pericardial tissue. To date, one pre-clinical randomized controlled trial (RCT) [6] and several clinical trials [7-12] involving the RESILIA tissue were performed. Flameng reported significantly improved hemodynamic and anticalcification properties of the RESILIA tissue compared with the standard Perimount valve in the juvenile sheep model [6]. The findings from a single-arm registry and the COMMENCE trial have shown excellent safety and effectiveness at 5 years, with no structural valve deterioration (SVD) [7, 11]. The INSPIRIS RESILIA valve has also demonstrated improved hemodynamic performance in early results of smaller cohorts [10, 12].

Although data on safety and effectiveness of the RESILIA tissue are accumulating, studies focusing specifically on younger patients less than 60 years are lacking. The prospective INSPIRIS RESILIA Durability Registry (INDURE) aims to provide data on short-term clinical effectiveness, as well as on long-term hemodynamic and structural performance in patients <60 years. Here, we report 1-year data of patients enrolled.

METHODS

INDURE is a prospective, open-label, multicentre, international registry to assess the clinical outcomes of patients younger than 60 years of age who undergo SAVR with the INSPIRIS RESILIA aortic valve [13]. Patients were enrolled at 21 sites across Austria, Belgium, France, Germany, Italy, the Netherlands, Spain, UK, and Canada.

Ethics statement

The ethics committee responsible for each site granted approval and written informed consent was obtained.

Patients

Adult patients 60 years of age or younger, undergoing SAVR and receiving the INSPIRIS RESILIA aortic valve (AV) prosthesis were enrolled. In addition to the stipulations of the device Instructions for Use (IFU), inclusion criteria included a planned replacement of the native valve as indicated based on a preoperative evaluation. The AVR was either isolated or with concomitant replacement of the ascending aorta and/or coronary artery bypass graft (CABG). Patients undergoing pulmonary vein isolation were also allowed if it was not a full cox-maze procedure. Patients with 1) no possibility of valve implantation in accordance with the IFU; 2) presence of active or within the last three months of the scheduled SAVR endocarditis/myocarditis; 3) previous AVR; 4) a Bentall (root) procedure or any surgery on other valves; or 5) life expectancy of less than 12 months were excluded.

Objectives

The primary objective was to determine the time-related valve safety at 1-year depicted as freedom from events in patients undergoing SAVR and receiving the INSPIRIS RESILIA AV prosthesis. Time-related valve safety was defined as composite endpoint according to the VARC-2 criteria (requiring of repeat procedure; prosthetic valve endocarditis, prosthetic valve thrombosis, thromboembolic events [e.g. stroke], and life-threatening bleeding) [14]; however, due to more precise definitions compared to VARC-2, SVD Stage 3 was presented according to VARC-3 criteria comparing 1-year vs. discharge echo (increase in mean AV PG ≥20 mmHg resulting in mean AV PG ≥30 mmHg with

concomitant decrease in EOA ≥0.6 cm^2 or ≥50% and/or decrease in DVI ≥0.2 or ≥40%, OR new occurrence, or increase of ≥2 grades, of intraprosthetic AR resulting in severe AR) [15].

The secondary objective was the assessment of haemodynamic performance of the INSPIRIS RESILIA AV and further durability parameters, clinical outcomes, and quality-of-life (QoL). Further clinical outcomes of interest were all-cause, cardiovascular, and valve-related mortality, [15], valve-related dysfunction, requirement of repeat procedure due to any cause, permanent pacemaker implantation (PPI), acute kidney injury AKIN Stage 2/3, and NYHA functional class compared to baseline. QoL was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Short Form-12 Health Survey Version 2 (SF-12v2).

Outcomes according to the VARC-2 criteria were adjudicated by an independent clinical event committee. Digital imaging and communication in medicine (DICOM) files of echocardiograms generated at 1-year follow-up were collected for analysis by the Echo Core Laboratory to ensure unbiased and consistent analysis of the diagnostic data.

Statistical analysis

Data were analyzed using descriptive statistics, with categorical variables presented as absolute values and frequencies (%) and the continuous variables presented as means (standard deviation [SD]) and/or median (interquartile range [IQR]). Test for normal distribution was carried using Kolmogorov-Smirnov-test. Wilcoxon signed ranks test for paired data was used for comparing QoL scores between baseline and follow-up visits. For outcome reporting Kaplan-Meier estimates were provided. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS Version 28.0 (Armonk, NY, IBM Corp.) [16].

RESULTS

A total of 457 patients were enrolled between April 2019 and May 2021. For the present analysis, 36 patients with a Bentall procedure and mitral/pulmonary valve replacement were excluded, resulting

in a total of 421 patients. Within the first-year post SAVR, 17 patients were lost to follow-up (4.0%). Of the remaining 404 patients, 7 (1.7%) patients died, which resulted in a total of 397 (94.3%) patients alive with available data at 1 year (**Figure 1**).

Patient characteristics

Patients had a mean age of 53.5 (SD: 6.9) years (median 55 [IQR: 51, 58]), primarily male (76.5%) with a mean BMI of 28.2 (SD: 5.1) kg/m^2. 27.2% had NYHA class III/IV and 5.3% had Angina CCS III/IV (**Table 1**). Mean EuroScore II was 1.5% (SD: 1.6%; median 0.95% [IQR: 0.67, 1.83]) and STS-Risk-Score 1.1% (SD: 1.0%; median 0.75% [IQR: 0.50, 1.20]). Common comorbidities included arterial hypertension, coronary artery disease, and type II diabetes. Mean left ventricular ejection fraction (LVEF) was 59.3 %, EOA index was 0.54 cm^2/m^2, mean AV PG was 45.3 (SD: 21.5) mmHg, and left ventricular outflow tract (LVOT) diameter was 23.8 (SD: 10.6) mm. In patients with pure AS, mean aortic PG at 1 year was 52.9 (SD: 16.3) mmHg and EOA index was 0.41 (SD: 0.14) cm^2/m^2.

Procedural details

The prevalence of bicuspid valves was 73.2% (**Table 2**). A total of 346 (82.4%) patients in the overall population had AS of any severity and 277 (66.0%) had AR. AS was dominating in 304 (72.4%) patients while AR was dominating in 98 (23.3%) patients. Pure forms of AS and AR were present in 142 (33.8%) and 73 (17.4%) patients. The etiology of valve pathology in the overall population was: 73.6% were congenital, 22.8% were degenerative, 1.0% were rheumatic, 0.7% were endocarditic, and 1.9% (n=8) were other/unknown (n=5 unknown, n=2 prolaps/pocket rupture, and n=1 dilation of aortic root).

The common surgical approach was full sternotomy (71.7%), followed by upper hemisternotomy (26.6%), and right anterior minithoracotomy (1.7%) (**Table 2**). Isolated AVR was performed in 255 (60.6%) patients, of which 163 (63.4%) received full sternotomy. In the total cohort, the median valve size was 25 mm as the majority of patients received either a 23 mm valve (31.1%) or a 25 mm valve (29.7%) (**Figure 2A**). A total of 5 (1.2%) 19 mm valve were implanted with all patients being female.

Intraoperative complications were as follows: 3 (0.7%) patients had aortic rupture or dissection, 2 (0.5%) patients required conversion to full sternotomy, and 1 (0.2%) patient had coronary artery obstruction. There were no cases of intraoperative death.

Procedural and in-hospital outcomes

Patients stayed for 8.4 (SD: 4.3) days in the hospital and 50.4 (SD: 55.9) hours in the ICU. Mean duration of mechanical ventilation was 10.1 (SD: 31.0) hours (**Table 2**). There was a decrease in mean aortic pressure gradient (PG) and increase in EOA depending on valve size: patients receiving a 19 mm valve had the highest mean aortic PG at discharge (21.3 mmHg) and smallest EOA (1.3 cm^2), while those receiving a 29 mm valve had lowest mean aortic PG (8.2 mmHg) and largest EOA (2.9 cm^2) (**Figure 2B**). Severe patient-prosthesis mismatch (PPM) was present in 4 (1.0%) patients. One (0.2%) patient died in the hospital, over a half of the patients were discharged home (n=245 [58.0%]), while 156 (37.1%) were referred to cardiac rehabilitation.

Compared to discharge, mean aortic PG was only slightly higher at 1 year while EOA was lower in patients (**Figure 2B**). In addition, 81.8% of patients were in NYHA class I at 1 year compared to 21.9% at baseline and only 3.6% were in NYHA class III/IV compared to 27.2% at baseline (**Figure 3**). There were no cases of mild/severe PVL at 1 year.

Quality of life outcomes

SF-12v2 and KCCQ were used for assessing QoL in patients (**Table 3** and **Supplementary Table 1**). Mean SF-12v2 physical summary score at 3-6 months was 47.7 points ($p<0.001$) compared to baseline (41.5 points) with a further increase at 1 year (49.2 points; $p<0.001$]). Mean SF-12v2 mental summary score at 3-6 months was 50.0 points ($p<0.001$) from baseline (45.6 points) and remained relatively stable at 1 year (49.9 points; $p<0.001$). Both physical and mental summary scores at 1 year were near the general population mean (50.0 points). Overall, changes in PCS and MCS at 1 year compared to baseline were classified as follows: 39.6% and 29.8% of patients had a large improvement in QoL. 1.9% for both died (**Figure 4**).

The KCCQ total symptom score and clinical summary score significantly increased both at 3-6 months (87.6 points; p<0.001 and 88.4 points; p<0.001) and at 1 year (90.0 points; p<0.001 and 89.2 points; p<0.001) compared to baseline (74.6 and 75.1 points) (**Table 3**). Similarly, there was an increase in mean overall summary score already at 3-6 months (85.2 points; p<0.001) and further at 1 year (87.1 points; p<0.001) in comparison to baseline (66.1 points). Overall, 1-year changes in patient overall summary score from baseline were classified as follows: 43.7% of patients had a large improvement in QoL and 1.9% died (**Figure 4**).

Outcome events at 30 days and 1 year

At 30 days, a total of 3 (0.7%) patients had died, with all cases being due to cardiovascular reasons: (**Table 4**). At 1 year, further 4 (1.0%/valve years [vy]) patients died (total n=7 at one year): 2 (0.5%/vy) deaths were due to cardiovascular causes and 2 (0.5%/vy) were related to non-cardiovascular factors. There were no cases of valve-related death. Freedom from all-cause mortality at 6 months and 1 year was 98.8% (95% confidence interval [CI] 97.8;99.8) and 98.3% (95%CI 97.1;99.6). Freedom from valve-related mortality was 100% at all timepoints.

Time-related valve safety events (VARC-2) were reported in 25 (5.9%) patients as early (≤30 days) and 9 (2.2%/vy) patients as late outcome (>30 days to 1 year) with freedom from event of 91.8% (95%CI 89.1; 94.4) at 1 year. None of the patients developed SVD Stage 3 according to VARC-3 criteria within the first year post AVR. No patient developed prosthetic valve endocarditis and valve thrombosis as early outcomes, but at 1 year the incidence was 1 (0.2%/vy) and 4 (1.0%/vy), respectively. Two of the patients with valve thrombosis, the patient with endocarditis, and two further patients (mild PVL post AVR due to severe annular calcification [n=1] and new onset of mild AV regurgitation [n=1]) developed valve-related dysfunction at 1 year (total n=5); re-AVR was needed solely in the patient with endocarditis. Thromboembolic events were documented in 7 (1.7%) patients as early outcome (of which 3 [0.7%] were strokes), and in 5 (1.2%/vy) patients as late outcome. Valve-related life-threatening bleeding according to VARC-2 occurred in 18 (4.3%) patients as early outcome (mainly being revision for bleeding) with no incidence at 1 year.

Total valve-related bleeding (categorized in minor, major and life-threatening) occurred in 45 (10.7%) patients as early outcome and there were no further cases at 1 year. 16 (3.8%) patients required a PPI as early outcome and further 3 (0.7%/vy) patients required it as late outcome. 6 (1.4%) patients developed acute kidney injury AKIN Stage 2/3 at 30 days with no further incidence at 1 year.

DISCUSSION

The 1-year results of the INDURE registry demonstrate 1) high hospital and 1-year survival rates with an absence of valve-related mortality; 2) satisfactory and stable performance of the INSPIRIS RESILIA with complete freedom from Stage 3 SVD based on a standardized CoreLab adjudicated assessment; and 3) an improvement in the patients' QoL early after the intervention which was sustained at 1 year.

Hospital and 1-year survival rates

In-hospital all-cause mortality rate in our study (0.7%) was lower than the rates reported in the trials by Useini (2.5%) and Fukunaga (3.4%), which both evaluated hospital outcomes after AVR using the INSPIRIS RESILIA bioprosthesis in smaller cohorts [10, 12]. The reported in-hospital mortality rates for the Carpentier-Edwards Perimount Magna Ease bioprosthesis with RESILIA tissue range between 1.2% and 2.3% [7, 8].

We report excellent survival rates at 1 year: overall survival was 98.3% and valve-related survival was 100%. Although survival may vary depending on patient characteristics, the survival rates in our patient cohort are comparable or potentially even slightly better to those reported in previous trials using bioprostheses with RESILIA tissue [7, 8]. Puskas reported a 1-year overall survival of 97.6% and valve-related survival of 98.8% with the Carpentier-Edwards Perimount Magna Ease bioprosthesis (Model 11000A) in the COMMENCE trial [7]. Bartus reported an overall mortality rate of 6.8% for the same bioprosthesis [9]. Furthermore, Didier reported higher mortality rates after TAVR with balloon-expandable transcatheter heart valves at 1 year (23.2%) [17].

Performance of the INSPIRIS RESILIA

One-year hemodynamic performance of INSPIRIS RESILIA, evaluated by an independent CoreLab, was favourable. Mean aortic PG (12.5 [SD: 5.3] mmHg) and EOA (1.9 [SD: 0.6] cm^2) at 1 year were within the ranges reported in other studies. In the COMMENCE trial, mean aortic PG and EOA at 1 year were 10.4 (SD: 4.9) mmHg and 1.7 (SD: 0.5) cm^2 [7]. Bartus reported mean aortic PG and EOA at 1 year to be 13.9 (SD: 6.1) mmHg and 1.8 (SD: 0.6) cm^2 [8]. Mean aortic PG and EOA reported in a Japanese cohort undergoing AVR with INSPIRIS RESILIA were 11.2 (SD: 3.2) mmHg and 1.8 (SD: 0.4) cm^2. In the recently published early results after INSPIRIS RESILIA AVR (including only discharge data), mean aortic PG was 10.2 (SD: 4.1) mmHg, which is slightly lower than mean aortic PG at discharge in our cohort (11.7 [SD: 4.3] mmHg). It should be noted, however, that patients receiving 19 mm valves (n=5; all female) in our study exhibited elevated mean aortic PG at both discharge (21.3 mmHg) and 1 year (21.8 mmHg). Increased aortic PG may lead to risks associated with PPM as well accelerated degeneration of the implanted valve. Therefore, it is important to provide reduced gradients to patients requiring smaller valves, particularly those requiring a 19 mm valve.

It is known that the use of bioprosthetic valves is associated with higher rates of SVD, particularly in younger patients. Although high freedom from SVD at 1 year in the current study further highlights the durability of RESILIA tissue reported in previous studies [7-9], it is important to note that the rates of SVD in the first years are generally very low and the incidence rises in later years. However, SVD is caused by degenerative calcification over time in the majority of cases, which can be permanently reduced by the novel integrity preservation technology applied during the preparation of RESILIA tissue [6]. This preservation technology is described as a capping process, which permanently blocks residual aldehyde content known to bind with calcium. Further glycerolization preserves the tissue in dry storage, which provides a persistent protection of collagen.

The rates of prosthetic valve endocarditis and prosthetic valve thrombosis at 1 year were 0.2% and 1.0%. A recent meta-analysis concluded that bioprosthetic valves may be associated with a higher risk of endocarditis than mechanical valves [18]. However, freedom from prosthetic valve

endocarditis in our patient cohort was still very high (99.8%) and comparable to the rates previously reported for RESILIA tissue [7-9]. The prevalence of prosthetic valve thrombosis in our study (1.0%) is comparable with that reported in the literature (0.6 – 0.7%), although the authors state that their prevalence is currently underestimated since routine prospective follow-up imaging is frequently not performed in the absence of symptoms or hemodynamic changes noted by echocardiography [19]. It has also been reported that the risk of thrombosis is higher with stented bioprosthetis, such as INSPIRIS RESILIA, compared to stentless valves [20]. In addition, we did not differentiate (or did not assess?) between clinical valve thrombosis and subclinical leaflet thrombosis characterized by hypoattenuated leaflet thickening (HALT), which is defined as incidental finding of an increase in the thickness of the prosthetic valve leaflets without associated symptoms. HALT may be an early indicator of valve thrombosis, although its relationship to clinical events is still not clear [21, 22]. Therefore, we feel the prevalence of prosthetic valve thrombosis after valve implantation in our study is acceptable.

Quality of life

We assessed QoL in patients in this study, which hasn't been reported in previous trials on valves with the RESILIA tissue [7-9]. Myken assessed the differences between patients receiving mechanical and bioprosthetic valve for heart valve surgery and found no differences in [23]. Repack also compared postoperative QoL in patients undergoing aortic root replacement with mechanical vs. bioprosthetic valves and reported similar outcomes in QoL between two patient groups [24]. In our study, there was a significant improvement in QoL already at six months post-surgery with further improvement at 1 year, suggesting that SAVR with INSPIRIS RESILIA improves QoL in young patients.

Limitations

The INDURE registry provides real-world data of a large patient cohort with the applicability of findings to clinical practice across Europe and Canada. However, as we did not include an active control group, different bioprosthetic valves or valve generations could not be compared and selection bias cannot be excluded. Furthermore, there is no comparison of the bioprosthetic valve

data with the outcomes and performance of mechanical valves. Lastly, although the results presented here are limited to 1-year data and may not reflect the ultimate safety outcomes and performance of the valve prosthesis, the present cohort will be followed up for 5 years, indicating the reporting of long-term outcomes in the future.

CONCLUSION

The results of this study showed good safety outcomes, early improved QoL, and high survival at 1 year in patients under the age of 60 receiving the INSPIRIS RESILIA valve.

Competing interests

All authors except for BB have received lecture fees and/or research support from Edwards Lifesciences. The institutions of most authors, except for BB and PB, received patient inclusion-based funding. BB has no conflict of interest to disclose.

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Authors' contributions

BM, RdP, TB, BB, PB and MB were involved in the conception and design of the study. PB and BB drafted the manuscript and all other authors revised the article for important intellectual content. All authors gave approval for the final version.

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Data availability statement

All relevant data within this manuscript will be shared upon reasonable request to the corresponding author.

TABLES

Table 1: Patient characteristics

	Total population Mean (SD) or n (%)
Age [years]	53.5(SD: 6.9)
Female gender	99(23.5)
Body Mass Index [kg/m^2]	28.2(SD: 5.1)
NYHA class III/IV	113(27.2)
Angina CCS class III/IV	22(5.3)
EuroScore II [%]	1.5(SD: 1.6) 0.95(IQR: 0.67, 1.83)
STS Risk Score [%]	1.06(SD: 0.99) 0.75(IQR: 0.50, 1.20)
Medical history	
Coronary artery disease	99(23.5)
Hypertension	209(49.6)
Prior MI	16(3.8)
Prior PPI	12(2.9)
Prior PCI	24(5.7)
Diabetes	55(13.1)
Peripheral vascular disease	16(3.8)
Prior stroke/TIA	24(5.7)
COPD	32(7.6)
Renal failure (eGFR>50)/dialysis	5(1.2)
Echocardiographic variables	
Severe AV stenosis	294(70.0)
Severe AV regurgitation	92(21.9)
LVEF [%]	59.3(SD: 10.1)
EOA [cm^2]	1.07(SD: 0.76)
EOA index [cm^2/m^2]	0.54(SD: 0.39)
Peak AV pressure gradient [mmHg]	70.6(SD: 33.3)
Mean AV pressure gradient [mmHg]	45.3(SD: 21.5)
Vmax [m/sec]	4.0(SD: 1.1)
Severe pulmonary hypertension, >55 [mmHg]	6(1.6)

EuroScore=European System for Cardiac Operative Risk Estimation; SD=standard deviation

325 **Table 2:** Interventional details and discharge

	Mean (SD), Median (IQR) or n (%)
Bicuspid valve	308(73.2)
Pure stenosis	142(33.8)
Pure regurgitation	73(17.4)
Mixed disease (stenosis and regurgitation)	205(48.8)
Etiology of valve pathology	
Degenerative	96(22.8)
Congenital	310(73.6)
Rheumatic	4(1.0)
Endocarditic	3(0.7)
Other*/unknown	8(1.9)
Surgical approach	
Full sternotomy	302(71.7)
Upper hemisternotomy	112(26.6)
Right anterior mini thoracotomy	7(1.7)
Isolated aortic valve replacement	255(60.6)
Concomitant procedure	
Coronary artery bypass graft	53(12.6)
1 graft	23
2 grafts	19
3 grafts	11
Root replacement	6(1.4)
Supracoronary tube graft	78(18.5)
Other	59(14.0)
Implantation details	
First attempt successful**	417(99.0)
Paravalvular leakage (visible)	7(1.7)
Second attempt needed	
Successful	4
2nd cross clamp	2
Valve size Edwards INSPIRIS	25(IQR: 23, 25)
Intraoperative complication	
Aortic rupture/dissection	3(0.7)
Coronary artery obstruction	1(0.2)
Conversion to full sternotomy	2(0.5)
Duration of intervention	
Procedure time, min	197(SD: 59) 186(IQR: 155, 230)
Cross clamp time, min	74.2(SD: 25.2) 70(IQR: 55, 88)
Cardiopulmonary bypass, min	96.4(SD: 33.8) 89(IQR: 72, 116)
Length of stay	
Hospital stay (implant to discharge) [days]	8.4(SD: 4.3) 7(IQR: 6, 10)
Intensive care unit length of stay [hours]	50.4(SD: 55.9) 30(IQR: 22, 56)
Duration of mechanical ventilation [hours]	10.1(SD: 31.0)

	6(IQR: 4, 9)

IQR=interquartile range; SD=standard deviation

*Prolaps/pocket rupture (n=2), aortic root dilation (n=1)

**aortic rupture/dissection (n=1), coronary artery obstruction (n=1), multiple complications (n=1), and paravalvular leakage (n=1)

Table 3: Quality of life

	Baseline (N=397)	3-6 months (N=394)	(N=378)	1 Year (N=380)	(N=365)
	Mean (SD)	Mean (SD)	p-value* (vs. Baseline)	Mean (SD)	p-value* (vs. Baseline)
SF-12v2					
Physical component summary	41.5(SD: 10.5)	47.7(SD: 9.7)	<0.001	49.2(SD: 9.5)	<0.001
Mental component summary	45.6(SD: 11.2)	50.0(SD: 10.5)	<0.001	49.9(SD: 10.6)	<0.001
KCCQ	**(N=401)**	**(N=399)**	**(N=384)**	**(N=385)**	**(N=371)**
Total symptom score	74.6(SD: 22.6)	87.6(SD: 17.2)	<0.001	90.0(SD: 17.1)	<0.001
Overall summary score	66.1(SD: 22.7)	85.2(SD: 17.5)	<0.001	87.1(SD: 18.0)	<0.001
Clinical summary score	75.1(SD: 21.2)	88.4(SD: 15.6)	<0.001	89.2(SD: 16.4)	<0.001

SD=standard deviation

*Based on paired cases

Table 4: Early and late outcomes

	Early (≤30 days) n(%)	Late (>30 days to 1 year) n(%/vy)†	Freedom from event 6 months %(95%CI)	Freedom from event 1 year %(95%CI)
All-cause mortality	3(0.7)	4(1.0)	98.8(97.8, 99.8)	98.3(97.1, 99.6)
Cardiovascular	3(0.7)	2(0.5)	99.3(98.5, 100.0)	98.8(97.7, 99.8)
Valve-related*	0(0)	0(0)	100.0	100.0
Time-related valve safety (VARC-2)	25(5.9)	9(2.2)	93.1(90.6, 95.5)	91.8(89.1, 94.4)
SVD Stage 3 (VARC-3)**	-	0(0)	-	100.0
Prosthetic valve endocarditis	0(0)	1(0.2)	99.8(99.3, 100.0)	99.8(99.3, 100.0)
Prosthetic valve thrombosis	0(0)	4(1.0)	99.5(98.9, 100.0)	99.0(98.1, 100.0)
Thromboembolic event	7(1.7)	5(1.2)	98.1(96.8, 99.4)	97.1(95.4, 98.7)
Stroke	3(0.7)	0(0)	99.3(98.5, 100.0)	99.3(98.5, 100.0)
Valve-related bleeding				
Life-threatening	18(4.3)	0(0)	95.7(93.8, 97.7)	95.7(93.8, 97.7)
Other outcomes				
Valve-related dysfunction	1(0.2)	4(1.0)	99.8(99.3, 100.0)	98.7(97.6, 99.8)
Requirement of repeat procedure (all-cause)***	0(0)	1(0.2)	99.8(99.3, 100.0)	99.8(99.3, 100.0)
Valve-related bleeding (total)****	45(10.7)	0(0)	89.3(86.4, 92.3)	89.3(86.4, 92.3)
Permanent pacemaker implantation	16(3.8)	3(0.7)	95.7(93.7, 97.6)	95.4(93.4, 97.4)
Acute kidney injury AKIN Stage 2/3	6(1.4)	0(0)	98.6(97.4, 99.7)	98.6(97.4, 99.7)

AKIN=Acute Kidney Injury Network; CI=confidence interval; SVD=structural valve deterioration

† 406 valve years

*Within the first year, it was unknown in a total of 4 patients whether the death was valve-related

338 **SVD Stage 3 according to VARC-3 comparing 1-year vs. discharge echo (increase in mean AV PG ≥20 mmHg resulting in mean AV PG ≥30 mmHg with
339 concomitant decrease in EOA ≥0.6 cm^2 or ≥50% and/or decrease in DVI ≥0.2 or ≥40%, OR new occurrence, or increase of ≥2 grades, of intraprosthetic AR
340 resulting in severe AR)

341 ***Requiring repeat procedure of the prosthetic valve due to prosthetic endocarditis

342 ****Valve-related bleeding reported as minor, major and life-threatening according to VARC-2

FIGURE LEGENDS

INDURE Registry Central image

Figure 1: Study flowchart

FU=follow-up

Figure 2: A) Valve size distribution and B) Hemodynamics over time by valve size

PG=pressure gradient; AV=atrioventricular; EOA=effective orifice area

Figure 3: NYHA functional class vs. baseline

NYHA=New York Heart Association

Figure 4: Quality of Life changes vs. baseline A) SF-12v2 B) KCCQ

PCS=physical component summary; MCS=mental component summary

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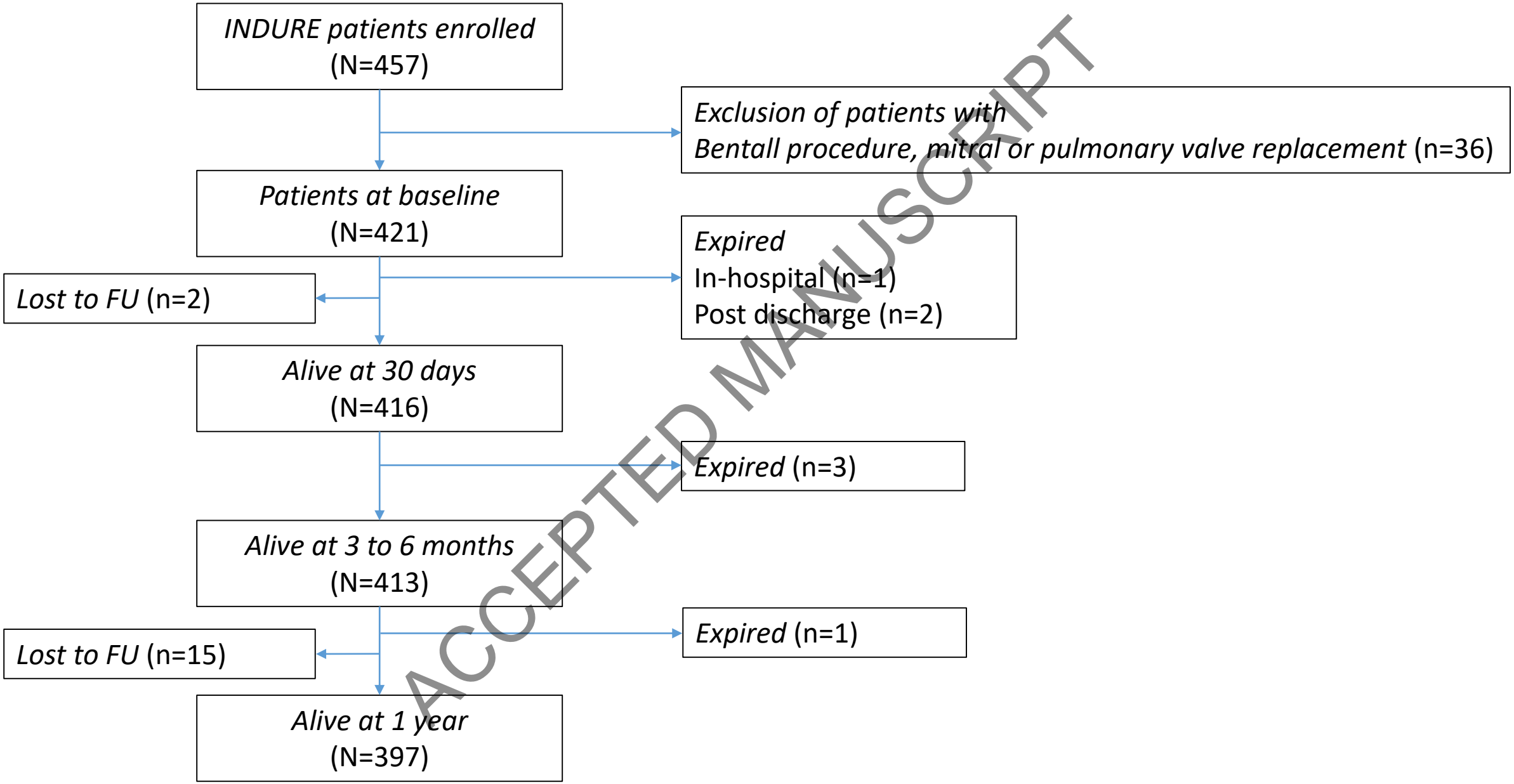
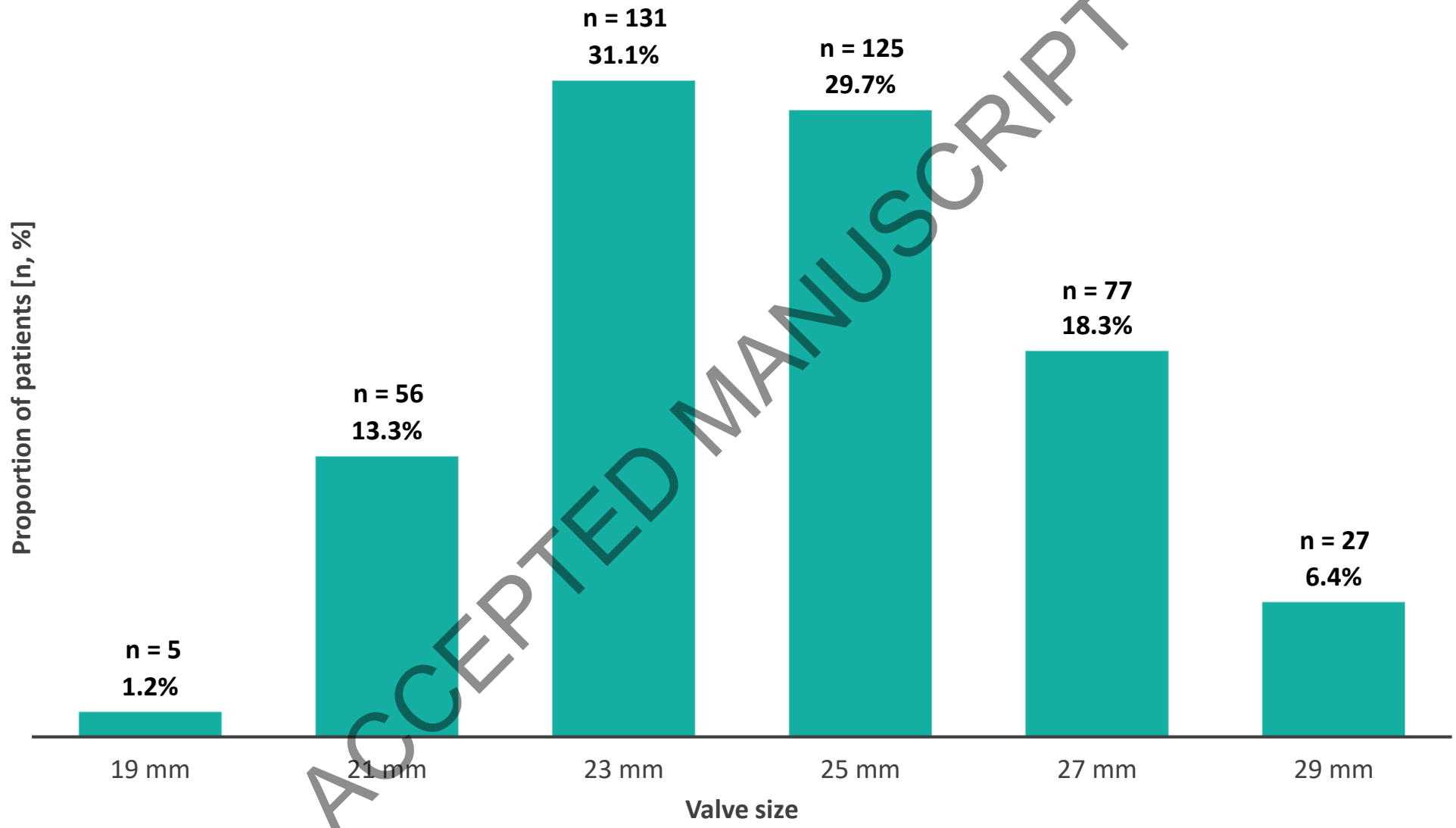
Figure 1



A)



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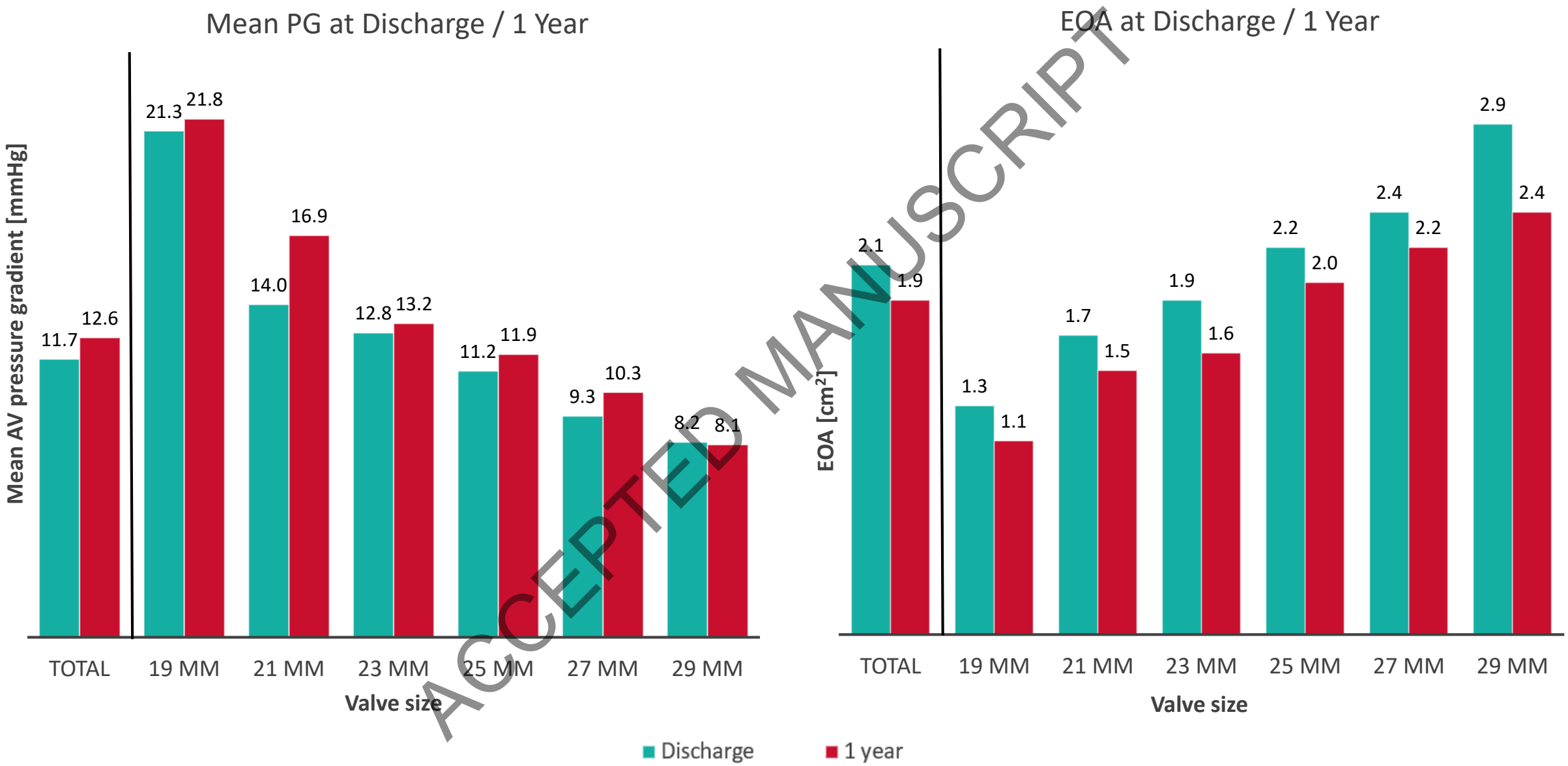


Figure 3

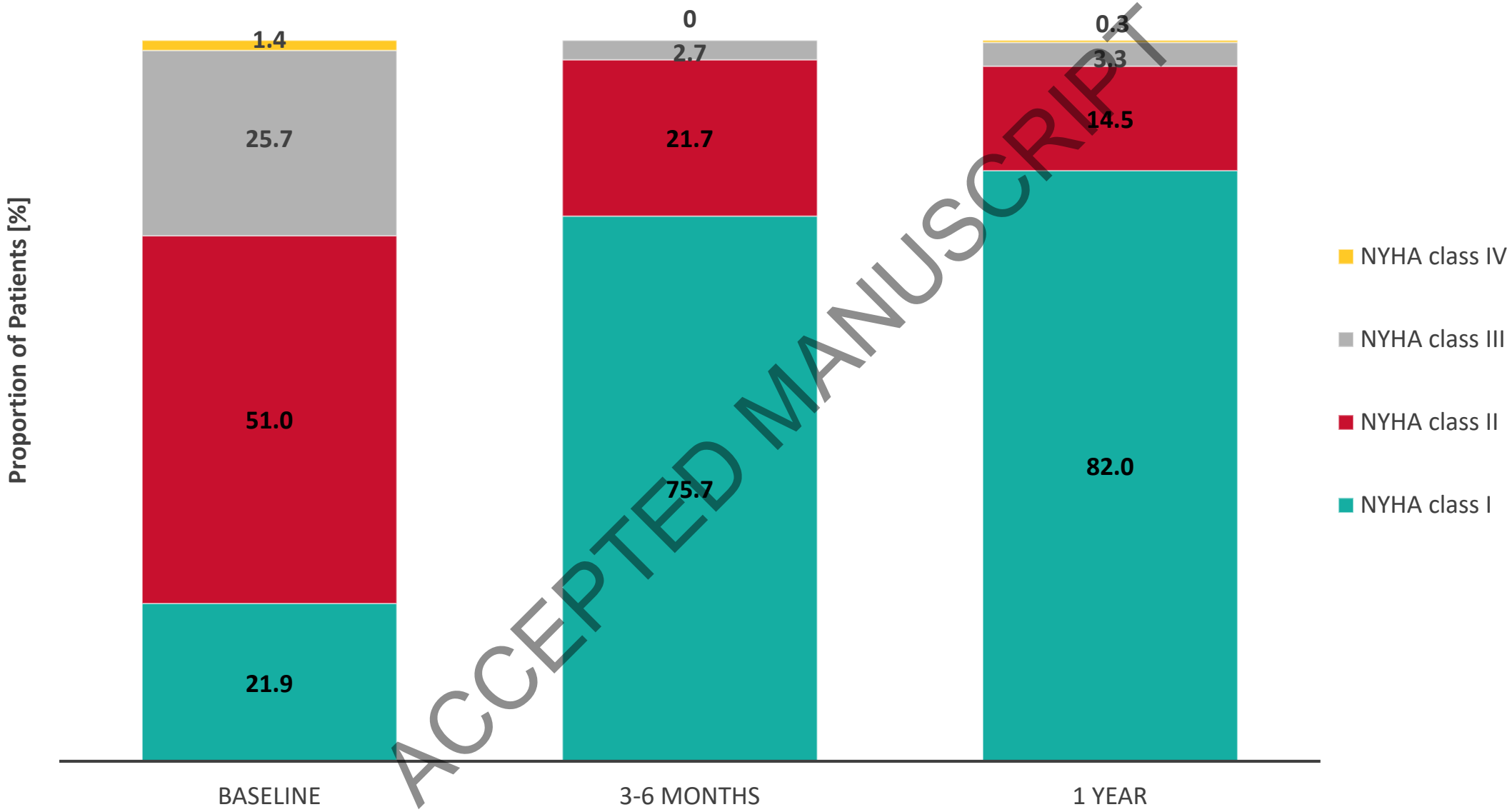


Figure 4

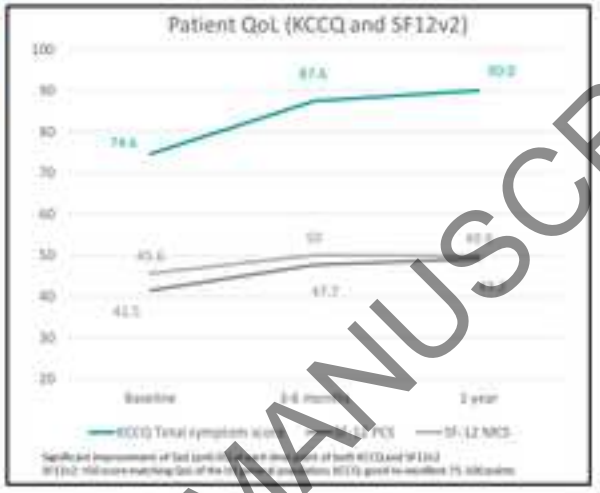
A)

B)

Safety of SAVR with a biosprosthesis in young patients (<60 years old)

Summary

In a prospective study of 421 patients <60 years old undergoing SAVR with a bioprosthetic valve at 21 sites in Europe and Canada, we assessed 1-year valve safety and performance as well as clinical outcomes in patients. Our results demonstrate good safety, excellent hemodynamic performance and early improvements in patient quality of life.



Legend: SAVR, surgical aortic valve replacement; QoL, quality of life; KCCQ, Kansas City Cardiomyopathy Questionnaire; PCS, physical component score; MCS, mental component score