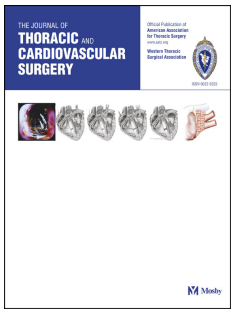
# Accepted Manuscript




The Freedom SOLO bovine pericardial stentless valve: Single-center experience, outcome and long-term durability

Olaf Stanger, MD, MBA, FETCS, Irina Bleuel, MD, Fabian Gisler, MD, Volkhard Göber, MD, Sylvia Reineke, MD, Brigitta Gahl, MSc, Thierry Aymard, MD, Lars Englberger, MD, Thierry Carrel, MD, Hendrik Tevaearai, MD, MBA

PII: S0022-5223(15)00123-3

DOI: 10.1016/j.jtcvs.2015.01.060

Reference: YMTC 9362

To appear in: *The Journal of Thoracic and Cardiovascular Surgery*

Received Date: 7 November 2014

Revised Date: 8 January 2015

Accepted Date: 24 January 2015

Please cite this article as: Stanger O, Bleuel I, Gisler F, Göber V, Reineke S, Gahl B, Aymard T, Englberger L, Carrel T, Tevaearai H, The Freedom SOLO bovine pericardial stentless valve: Single-center experience, outcome and long-term durability, *The Journal of Thoracic and Cardiovascular Surgery* (2015), doi: 10.1016/j.jtcvs.2015.01.060.

# The Freedom SOLO bovine pericardial stentless valve: Single-center experience, outcome and long-term durability

Olaf Stanger, MD, MBA, FETCS[1], Irina Bleuel, MD[1], Fabian Gisler, MD[1], Volkhard Göber, MD[1], Sylvia Reineke, MD[1], Brigitta Gahl, MSc[1], Thierry Aymard, MD[1], Lars Englberger, MD[1], Thierry Carrel, MD[1], Hendrik Tevaearai, MD, MBA[1]

[1] Department of Cardiovascular Surgery, Inselspital University Hospital Berne, Switzerland

Correspondence:
Olaf Stanger, MD, MBA, FETCS
Clinic for Cardiovascular Surgery, Inselspital University Hospital and University of Berne
Freiburgstrasse 18
CH-3010 Berne, Switzerland
Tel: 0041 79 193251
FAX: 0041 31 6329766
oh.stanger@gmail.com

**There is no ethical problem, source of funding, or conflict of interest, particularly as relationship with industry, associated with the manuscript for all authors.**

word count: abstract (240); ultramini abstract (49); text (3529), references [33]

**Abstract**

**OBJECTIVES:** We report our institutional experience and long-term results with the Sorin Freedom **SOLO** bovine pericardial stentless bioprosthesis.

**METHODS:** Between January 2005 and November 2009, 149 patients (mean age 73.6±8.7 years, 68 [45.6%] female) underwent isolated (n=75) or combined (n=74) aortic valve replacement (AVR) using the **SOLO** in our institution. Follow-up was 100% complete with an average follow-up time of 5.9±2.6 years (maximum 9.6 years) and a total of 885.3 patient years.

**RESULTS:** Operative (30-day) mortality was 2.7% (1.3% for isolated AVR [n=1] and 4.0% for combined procedures [n=3]). All causes of death were not valve-related. Preoperative peak (mean) gradients of 74.2±23.0 mmHg (48.6 ± 16.3 mmHg) decreased to 15.6±5.4 (8.8±3.0) after AVR, and remained low for up to 9 years. The postoperative effective orifice area (EOA) was 1.6 ±0.57 $cm^2$, 1.90±0.45 $cm^2$, 2.12±0.48 $cm^2$ and 2.20±0.66 $cm^2$ for the valve sizes 21, 23, 25 and 27, respectively; with absence of severe prosthesis-patient-mismatch (PPM) and 0.7% (n=1) moderate PPM. During follow-up, Twenty-six patients experienced structural valve deterioration (SVD) and 14 patients underwent explantation. Kaplan-Meier estimates for freedom from death, explantation and SVD at 9 years averaged 0.57 [0.47–0.66], 0.82 [0.69–0.90] and 0.70 [0.57–0.79], respectively.

**CONCLUSIONS:** The Freedom SOLO stentless aortic valve is safe to implant and shows excellent early and mid-term hemodynamic performance. However, SVD was observed in a substantial number of patients after only 5−6 years and the need for explantation increased markedly, suggesting low durability.

**Ultramini abstract**

We report our institutional outcome in 149 patients receiving the Freedom SOLO bioprosthesis and up to 9.6 years of follow-up. The SOLO valve is safe to implant with excellent early hemodynamic performance. However, SVD and need for explantation increased markedly after only 5−6 years, suggesting low durability.

**Keywords**: aortic valve • stentless • bioprosthesis • cardiac surgery • valve surgery

Stentless bioprostheses were introduced as an attractive alternative to stented valves, combining the advantages of non-obstructive effective orifice area (EOA) and a flexible aortic root that was believed to be essential for natural leaflet stress distribution. Correspondingly, unstented xenografts, with minimal disruption of the aortic root anatomy and function, are expected to reduce dynamic stress on leaflets, and thereby limit valve degeneration and failure [1]. Whereas some earlier stentless porcine root prostheses showed unsatisfactory results with premature failure [2–4], more advanced models were aimed at optimizing the tissue type, preservation and anticalcification treatments, as well as valve design.

The third-generation bovine pericardium Freedom SOLO (henceforth SOLO) stentless bioprosthesis (Sorin Group, Saluggia, Italy) emerged as a modified version of the Pericarbon Freedom stentless valve in 2004 [5], and has recently received FDA approval for use in the US (June 24, 2014). The prosthesis is made of two bovine pericardial sheets for supra-annular subcoronary implantation using only one single suture line, thus reducing cross-clamp time. Furthermore, the SOLO is manufactured with a unique process that includes homocysteic acid (HCA) as an anticalcification treatment, to bind and neutralize free glutaraldehyde (GA) residues for optimal durability.

Numerous reports have documented superior early and mid-term hemodynamic results for stentless valve prostheses, including the SOLO, in comparison to stented bioprostheses [6–10]. Although the SOLO stentless valve has been used since 2004, no long-term outcome data (beyond mean 1.2 ± 0.8 years) is available [10]. Thus, we are only now reaching an observation period that allows evaluation of long-term outcome, particularly durability, which will eventually define non-inferiority compared to available alternative stented bioprostheses. As our institution introduced the SOLO stentless bioprosthesis at a particularly early stage, we report our operative results with the aim of assessing long-term clinical results, i.e. durability and freedom from major adverse events after up to 9.6 years of follow up.

## MATERIALS AND METHODS

### PATIENT POPULATION

Between January 2005 and November 2009, 149 patients (mean age 73.6 ± 8.7 years, 68 [45.6%] female) underwent isolated (n=75) or combined (n=74) AVR using the SOLO bovine pericardial stentless valve bioprosthesis in our institution. The decision to use the SOLO stentless valve or an alternative, conventional stented prosthesis was at the surgeon's discretion. The SOLO stentless valve was not considered suitable in cases with severe calcification of the aortic root, and in patients with true bicuspid valve and ectasia of the ascending aorta. The local ethics committee approved the review of patient data and patient consent was waived for the retrospective analysis. The patients'

characteristics are shown in Table 1. One patient was operated with acute bacterial endocarditis (staphylococcus aureus), and four cases were re-do procedures. At the time of surgery, left ventricular ejection fractions (LVEF) ≤ 40% was present in 24 patients (16.1%).

**Surgical and postoperative management**

AVR procedures were all performed under routine general anesthesia and with a median sternotomy, using standard cardiopulmonary bypass and mild hypothermia (34°C). Cold blood cardioplegia was routinely used for myocardial protection. Aortotomy was performed approximately 1cm above the sinotubular junction (STJ). The diseased valve was then excised and the annulus carefully decalcified. The SOLO valve was implanted without rinsing in the supra-annular subcoronary position, with 3 continuous suture lines using 4/0 prolene monofilament as reported in detail elsewhere [11]. In brief, sutures started at the base of each sinus, continued to the top of the commissures, and ended with extraaortic fixation. Transesophageal echocardiography (TEE) was routinely performed intraoperatively before and after AVR to assess the function of the prosthesis. No oral anticoagulation after hospital discharge was required in patients with the SOLO valve.

**Data collection, follow-up and definitions**

Perioperative data were retrieved from our prospectively managed institutional database (Dendrite Clinical Systems LTD, Henley-on-Thames, UK). Closing date for all follow-up investigations was Oct. 1st, 2014. Follow-up was 100% complete with an average follow-up time of 5.9 ± 2.6 years (maximum 9.6 years) and a total of 885.3 patient years.

All patients were routinely examined with transthoracic echocardiography (TTE) before hospital discharge, at 6 months post-operatively and yearly thereafter. Intervals were shortened when changes or signs of degeneration were observed. Transvalvular pressure gradients and EOA were calculated using the modified Bernoulli equation and the continuity equation, respectively. Clinical status and adverse events were carefully assessed at each visit or by consultation with the referring physician. Dates of death were confirmed with data from local public authorities.

Data analysis was performed as follows. Baseline characteristics and risk factors were defined according to EuroScore II criteria. Mortality and morbidity (rate of adverse events) were reported according to established guidelines [12, 13]. These guidelines define structural valve deterioration (SVD) as change in function or deterioration of an operated valve resulting from an intrinsic abnormality of the valve that causes stenosis or regurgitation, exclusive of infection or thrombosis. SVD includes wear, fracture, poppet escape, calcification, leaflet tear, stent creep, and suture line disruption of an operated valve [12, 13]. In absence of established reference values for prosthetic SVD, particularly for stentless valves, we defined intrinsic prosthetic stenosis, under normal flow conditions (EF>50%) and after normal postoperative function, when echocardiographic evidence of distinctive

and pronounced degenerative changes (such as severely impaired cusp movements due to thickened, sclerosed or calcified leaflets) was present (repeat measurements with different investigators) and at least two of the following criteria were met: (i) ≥ 3-fold increase of mean gradients compared to early postoperative measurements (before discharge) in (ii) ≥ 25 mmHg mean gradient; (iii) EOA of <1.5 $cm^2$ *and* iEOA < 0.9 $cm^2/m^2$ *and* peak velocity ≥3 m/sec *or* velocity time integral (VTI) of 0.5–0.25 (VTI was measured in the left ventricular outflow tract (LVOT) and the aortic valve (AoV) and expressed as LVOT/AoV). SVD due to regurgitation was defined as at least moderate regurgitation with pressure half time (PHT) ≤500ms *and* width of vena contracta (VC) ≥5 mm (if limited to one jet) *or* diastolic flow reversal in the descending or abdominal aorta in combination with echocardiographic evidence of abnormal prosthesis structure or motion. According to the generally accepted concept of prosthesis-patient-mismatch (PPM), the best variable for defining PPM is the ratio of prosthetic EOA to the patient's body surface area (BSA) [14]. PPM mismatch was defined as an indexed EOA (iEOA) between 0.85 $cm^2/m^2$ and 0.65 $cm^2/m^2$ (moderate) and less than 0.65 $cm^2/m^2$ (severe), which are the established cut-off values for all types of prosthetic valves [14].

**Statistical analysis**

Demographic data are presented as mean values and standard deviation for continuous variables, and by number and percentages for categorical variables. Outcome data are presented as operative mortality, defined as death from any cause during or after surgery within 30 days if the patient was discharged, or within any interval if the patient was not discharged [12], or as Kaplan-Meier estimates of freedom from the following endpoints: death, SVD, explantation, thrombosis, endocarditis, or a combination of all. We used multivariate Cox proportional hazard ratio models to identify associations between patient- or procedure-related factors and endpoints. We used two linear mixed models, the first to analyze the effect of the valve replacement on the mean gradient, and the second to analyze the time effect on the mean gradient. Inspecting the residual plots with respect to the random and fixed effects, we detected outliers in the second model corresponding to those patients who developed SVD. As these patient provide particularly important information, we accepted the larger variance. All p-values and confidence intervals are two-sided. All statistical analyses were performed using Stata (version 12, StataCorp, College Station, Texas USA).

## RESULTS

### Operative data, mortality and early complications

The mean extracorporeal circulation (ECC) and cross-clamp times were, respectively, 64 ± 14min (47 ± 13 min) and 95 ± 31 (71 ± 23 min) for isolated and combined procedures, with no significant differences among sizes 21, 23, 25 and 27. All patients left the operating room with no or trivial regurgitation.

Overall operative (in-hospital) mortality was 2.7% (1.3% for isolated AVR [n=1] and 4.0% for combined procedures [n=3]). The corresponding EuroScore II overestimated the observed mortality considerably (Table 1). Causes of early death were not valve-related, i.e. low cardiac output and myocardial infarction (n=3) and embolism of the basilar artery (n=1) (Table 2). The four non-surviving patients were older (77.9 ± 2.6 years vs. 73.4 ± 0.7 years, p=0.038) and had a significantly higher EuroScore II risk score (20.42 ± 20.74 vs. 5.29 ± 8.12, p<0.001) as compared to the 145 surviving patients.

In total, 25 patients experienced in-hospital complications (multiple complications possible), including temporary hemofiltration (HF) therapy for renal failure (of which four patients had renal impairment preoperatively). There were eight cerebral events, seven of which were fully reversible by the time of hospital discharge (three patients had previously suffered cerebral events). Five patients required drainage for pericardial or pleural effusions. There were two sternal re-explorations for impaired sternal healing. One permanent pacemaker was implanted due to complete AV-block. Including all patients with these early complications combined, the discharge from hospital occurred after a median length of stay (LOS) of 10.0 and 10.5 days for isolated and combined procedures, respectively.

**Hemodynamic and hematologic data**

The mean preoperative LVEF of 55.4 ± 12.3 improved to 58.6 ± 11.1, 61.5 ± 12.7, 61.7 ± 10.1, 62.4 ± 10.1 and 63.0 ± 8.5 at 6 months, 1, 2, 3 and 4 years postoperatively (p<0.001). Preoperative peak gradients of 76.3 ± 25.3 mmHg decreased to 17.9 ± 9.8 mmHg postoperatively. Mean gradients decreased by -39.2 mmHg [p<0.001, 95% confidence interval from -42.4 to -35.9 mmHg] on average in every patient following AVR (Figure 1). Following the first postoperative measurement, the mean gradient increased by .94 mmHg [p<0.001, 95% confidence interval from .74 to 1.1] per year, but this was driven by 12 patients who reached a mean gradient >30 mmHg. Gradients showed a non-significant trend for lower values with increasing valve size. The postoperative EOA (mean ± SD) for the valve sizes 21, 23, 25 and 27 were 1.67 ± 0.57 $cm^2$, 1.90 ± 0.45 $cm^2$, 2.12 ± 0.48 $cm^2$ and 2.20 ± 0.66 $cm^2$, respectively. With the definition of PPM as the ratio of prosthetic EOA to the patient's body surface area (BSA) and the use of established cut-off values [14], severe PPM was completely absent, and moderate PPM occurred in one patient (0.7%), however BMI was 37.7 and BSA was 2.02.

Daily platelet counts were performed as part of the standard patient management protocol. Excluding patients with HF, infection and re-exploration, minimum platelet counts occurred following an average decrease of 59.9%. After reaching a nadir on the second postoperative day, platelet count

returned to baseline value, on average, on the 8th postoperative day. No excess or unexpected bleeding or re-exploration was associated with the SOLO valve.

**Long-term survival and freedom from major adverse events**

54 patients died during the follow-up period. The survival rate at 7, 8 and 9 years was 66%, 59% and 57%, respectively (Table 3, Figure 2). Multivariate Cox regression analysis identified age (HR=1.06 [1.02–1.11], p=0.008) and renal dysfunction (HR=1.94 [1.02–3.68], p=0.044) as parameters independently associated with survival, in contrast to arterial hypertension (HR=2.75 [0.85–8.85], p=0.091), concomitant coronary artery bypass grafting (CABG) (HR=1.18 [0.70–2.05], p=0.544), combined procedures (HR=1.12 [0.65–1.93], p=0.680) and indexed PPM (EOA/BSA as continuous variable; HR=1.00 [0.73–13.76], p=1.000).

In 14 patients, the SOLO prostheses required explantation due to valve-independent dysfunction (n=5; i.e. thrombus formation, oversizing, aortic dilatation, endocarditis and suture dehiscence) or valve-dependent failure (n=9). Of these, five SOLO required explantation due to severe functional stenosis and gross calcification that was always strikingly severe and included the entire aortic root. Four cases presented with acute regurgitation due to leaflet rupture, all of which were size 23 and 25 prostheses. In all these cases of non-sclerotic SVD, vertical tears were notably located in close proximity to the non-coronary/right-coronary commissure (NCC/RCC), and in our series they occurred, on average, 1.5 years (6.0 vs. 7.5 years) earlier than explantation for degenerative stenosis. Two patients (14.3%) did not survive reoperation; one due to sudden cardiac arrest of unknown cause on the 8th postoperative day, and the second, because of right ventricular failure.

There were 26 cases of SVD documented during the follow-up period (Figure 2, Table 3), of which only 10 underwent reoperation. The remaining 16 patients were not re-operated because of presumed excessive surgical risk, stable valve dysfunction or because the patient declined surgical treatment. Multivariate Cox regression analysis identified younger age (HR=0.93 [0.89–0.97], p=0.002) as an independent predictor for SVD, but not renal dysfunction (HR=1.15 [0.26–5.14], p=0.855), diabetes (HR=1.39 [0.54–3.55], p=0.495), arterial hypertension (HR=2.60 [0.62–10.80], p=0.189), nor PPM (EOA/BSA) as continuous variable (HR=0.10 [0.10–7.26], p=0.855).

Four patients experienced endocarditis, two of which underwent valve explantation and replacement, and the two other patients did not undergo re-operation and died 3 and 8 months after diagnosis, respectively. One patient presented with a large thrombotic adhesion on the NCC and underwent reoperation 5 months after the primary AVR.

Combining all endpoints, 78 (52%) patients experienced an event. We included age, gender, isolated procedure, hypertension, indexed EOA, renal dysfunction, diabetes and EuroScore II in a Cox regression analysis with the combined endpoint; only EuroScore II showed an association (HR=1.02 [0.02–1.00], p=0.018), suggesting heterogeneous associations between independent variables and

individual endpoints, and indicating that no patient- or procedure-specific parameter alone permits prediction of prosthesis failure.

## COMMENT

In the present study, we report our clinical results in a cohort of 149 patients with the longest follow-up available to date for the third generation SOLO stentless bioprosthesis. Our data suggest that the valve is safe to implant, and provides an excellent early hemodynamic performance. However, freedom from SVD and explantation decreased markedly in our single center study after only 5–6 years, implying that the SOLO durability is considerably lower than that of conventional stented prostheses.

The SOLO represents the most advanced stentless bioprosthesis that combines the single-suture, subcoronary implantation technique with the latest-generation bovine pericardial tissue and a novel anticalcification treatment. Consistent with previous reports [7–10], we demonstrate excellent early results of the SOLO, relatively easy implantation with acceptable cross-clamp times, low gradients and large EOA, as well as near absence of PPM.

As a unique SOLO-dependent side-effect, and consistent with previous reports [7, 8, 10, 15, 16], we observed postoperative thrombocytopenia following implantation, with a mean decrease of 59.9% in platelet numbers on the second postoperative day, followed by full recovery within 8 days. Importantly, and unexpectedly, SOLO-related excess bleeding complications, thromboemboli or increased re-exploration rates have not been observed despite this transient thrombocytopenia. Furthermore, there is no evidence for excess platelet activation, platelet consumption, or change in postoperative platelet function [17]. Causal hemodynamic flow-dependent mechanical damage appears highly unlikely given the large EOA and low gradients with correctly sized SOLO valves, with performances similar to native aortic valves at rest and under stress conditions [9, 18]. Contrary to observation, the platelet-damaging effect would be expected to persist if SOLO-related hemodynamic stress was causal. In agreement with the suggestion of a patient-independent effect derived from a study with propensity matched design [16], we hypothesize that a temporary, chemistry-induced lysis leads to lower platelet counts in patients with the SOLO, although the precise mechanism of thrombocytopenia remains to be identified.

A number of stentless valve prostheses have been developed and introduced, but all have been fundamentally different with respect to design, tissue type and anticalcification treatment, rendering comparisons difficult. Concerns have been raised for stentless prostheses regarding long-term durability; most likely resulting from experiences with earlier (porcine root) models, for which, after approximately 10 years, freedom from SVD and reoperation dropped dramatically, e.g. the O`Brien

(CryoLife, Atlanta, GA) [2], Shelhigh (Shelhigh, Inc, Millburn, NJ) [3], Biocor [19] and Toronto SPV (both St. Jude Medical, St. Paul, MN) [4].

In our single institution experience freedom from thromboembolism and endocarditis was high and comparable to that reported for other stentless and stented bioprosthesis [20–24], but freedom from SVD and explantation in our series was much lower than expected. Freedom from explantation after 9 years was only 0.82 in our cohort is, comparing to 0.97 and 0.98 reported for the conventional stented Hancock II (Medtronic Inc, Minneapolis, MN) [21, 22], and Perimount Magna (Edwards Lifesciences, Irvine, CA) [22, 23] bioprostheses at 10 years. Prostheses with tears and cusp ruptures in our series were relatively easy to replace; however, cases with severe calcification turned out to require very difficult and demanding re-operations. The freedom from SVD in our series was only 0.70 after 9 years, substantially lower than rates of 0.86 to 0.97 reported for conventional stented valves at 10 years, i.e. the Hancock II [21, 22], Mosaic (Medtronic Inc, Minneapolis, MN) [24], and Perimount Magna [22].

The morphological and hemodynamic criteria defined in this study for SVD indicate intrinsic changes in the valve suggesting at least moderate aortic stenosis associated with left ventricular hypertrophy [26], substantial complications and event rates from AS [27], impaired event-free survival and increased overall mortality [28]. Thus the definition for SVD in our study is rather conservative considering the generally larger EOA and lower gradients of stentless vs. stented valves.

In general, SVD is influenced by the tissue structure (e.g. bovine vs. porcine), the design of the valve, as well as its mechanical wear and stress absorption properties. Notably, chemical fixation and the anticalcification treatment are considered key elements in valve manufacturing aimed at enhancing valve durability, and avoiding premature calcification, SVD and reoperation [29]. All biological tissue valves including the SOLO primarily undergo chemical fixation with GA to provide mechanical stability, at the expense of susceptibility to calcification. In a unique treatment, Sorin uses HCA featuring strong electronegative sulfonic groups as post-fixation treatment bonding to neutralize free toxic aldehyde groups in the SOLO valve [30]. In a subcutaneous rat model, GA-HCA-treated bovine pericardium showed less calcification than GA alone after explantation (14-84 days) [30]. The effectiveness, however, has been questioned because this model ignores mechanical and dynamic stress or blood-surface contact [31]. In fact, results from the subcutaneous rat model were the exact opposite of those from the blood contact and the pulsatile models, emphasizing the necessity of blood contact in preclinical valve testing [31]. Furthermore, and perhaps even more important, stentless valve implantation techniques are generally more demanding, less reproducible and standardized, and more dependent on the surgeon’s skill and experience. Importantly, the ideal concept of a stentless valve prosthesis assumes that it can replace and imitate a native valve, thus adopting nearly identical functional durability. However, this theoretical idea ignores that the stentless valve may not seat adequately in the native aortic root. In detail, correct sizing and perfectly symmetrical implantation to

ensure low leaflet stress is only rarely obtained with heterogeneous strain and elongation, compression, shear, and torsional deformation for the three sinuses [32], whereas the SOLO is constructed perfectly symmetrical and thereby causes stress variations on the leaflets [1, 33]. In the sheep model, the left- and non-coronary sinuses were found to undergo clockwise torsion during the ejection phase, while the right sinus undergoes counterclockwise torsion [32]. This puts stress on the NCC/RCC commissure and could explain why tears were predominantly seen close to this particular location. Any malpositioning and asymmetry between the native anatomy and the stentless tissue valve may cause small distortions with eccentric regurgitation, increased chronic mechanical stress, potentially leading to fatigue over time and premature valve deterioration [33]. Given the large individual variability in root anatomy, particularly of the non-coronary sinus, which is usually larger than left- and right-coronary sinuses (with a larger volume, increased height, width, leaflet size and thickness) [1, 32], symmetric implantation and tension-free positioning can hardly be guaranteed. As a consequence, the observation of root anatomy, correct sizing and symmetric implantation of the SOLO must be given particular attention.

**Limitation**

At the time of introduction of the SOLO stentless prosthesis, no prior experience was available, and surgeons were engaged in proctoring and teaching, which could have influenced patient selection and technical precision. This study was neither designed to investigate the cause of SOLO-associated postoperative thrombocytopenia, nor the structural cardiac changes, i.e. the mass regression and its influence on survival. With regard to long-term adverse events, not all causes of death could be clarified. However, it must be expected that SVD in some patients contributed to premature death, particularly because 2/3 of patients diagnosed with SVD did not undergo re-operation for various reasons, and concomitant procedures do not fully explain the difference in mortality between isolated and combined procedures. Thus, competing events may potentially have influenced the assessment of other aortic-valve related adverse events. Alternatively, we combined all endpoints to evaluate overall successful AVR with the SOLO stentless prosthesis; albeit at the cost of losing clinically relevant information. Because our data reports outcomes from a single institution, we caution a premature final conclusion regarding the SOLO; additional data from other centers are warranted to help to determine long-term durability of the SOLO prosthesis.

In conclusion, the SOLO stentless valve is safe to implant, shows excellent hemodynamic performance as well as early- and mid-term results. There were 26 cases of SVD during the follow-up period. Multivariate Cox regression analysis identified only younger age as an independent predictor for SVD, but not renal dysfunction, diabetes, arterial hypertension, nor PPM as continuous variable. However, actuarial freedom from SVD and explantation decreased markedly after only 5–6 years and

was only 70% and 82% at 9 years, implying that the SOLO durability is lower than that of conventional stented prostheses in our institution.

**Acknowledgements**: The authors are thankful to Sarah Longnus, Dorothee Keller, Marija Trojancevic, Laetitia Krummen-Bayard, Monika Sperisen, Bettina Kohler, and Sara Baumberger for valuable support in conducting this study and preparation of the manuscript.

**REFERENCES**


1. Dagum P, Green GR, Nistal FJ, Daughters GT, Timek TA, Foppiano LE, et al. Deformational dynamics of the aortic root: modes and physiologic determinants. *Circulation.* 1999;100:II54-62.
2. Pavoni D, Badano LP, Ius F, Mazzaro E, Frassani R, Gelsomino S, et al. Limited long-term durability of the Cryolife O'Brien stentless porcine xenograft valve. *Circulation.* 2007;116:I307-13.
3. Carrel TP, Schoenhoff FS, Schmidli J, Stalder M, Eckstein FS, Englberger L. Deleterious outcome of No-React-treated stentless valved conduits after aortic root replacement: why were warnings ignored? *J Thorac Cardiovasc Surg*. 2008;136:52–7.
4. David TE, Feindel CM, Bos J, Ivanov J, Armstrong S. Aortic valve replacement with Toronto SPV bioprosthesis: optimal patient survival but suboptimal valve durability. *J Thorac Cardiovasc Surg*. 2008;135:19-24.
5. Repossini A, Kotelnikov I, Bouchikhi R, Torre T, Passaretti B, Parodi O, et al. Single-suture line placement of a pericardial stentless valve. *J Thorac Cardiovasc Surg*. 2005;130:1265-9.
6. Funder JA. Current status on stentless aortic bioprosthesis: a clinical and experimental perspective. *Eur J Cardiothorac Surg*. 2012;41:790-9.
7. Thalmann A, Kaiblinger J, Krausler R, Pisarik H, Veit F, Taheri N, et al. Clinical experience and mid-term results with the Freedom SOLO stentless aortic valve in 277 consecutive patients. *Ann Thorac Surg., in press*
8. Iliopoulos DC, Deveja AR, Androutsopoulou V, Filias V, Kastelanos E, Satratzemis V, et al. Single-center experience using the Freedom SOLO aortic bioprosthesis. *J Thorac Cardiovasc Surg*. 2013;146:96-102.
9. Repossini A, Rambaldini M, Lucchetti V, Da Col U, Cesari F, Mignosa C, et al. Early clinical and haemodynamic results after aortic valve replacements with the Freedom SOLO bioprosthesis (experience of Italian multicenter study). *Eur J Cardiothorac Surg*. 2012;41:1104-10.
10. Beholz S, Repossini A, Livi U, Schepens M, El Gabry M, Matschke K, et al. The Freedom SOLO valve for aortic valve replacement: clinical and hemodynamic results from a prospective multicenter trial. *J Heart Valve Dis*. 2010;19:115-23.
11. Stanger O, Tevaerarai H, Carrel T. The Freedom SOLO bovine pericardial stentless valve. *Res Rep Clin Cardiol*. 2014;5:1-13.
12. Edmunds LH, Clark RE, Cohn LH, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after vardiac valvular operations. *Ann Thorac Surg*. 1988;46:257-59.
13. Vahanian A, Alfieri O, Andreotti F, Artunes MJ, Baron Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg*. 2012;42:S1-44.

14. Pibarot P, Dumesnil JG. Prosthesis-patient mismatch: definition, clinical impact, and prevention. Heart 2006;92:1022–9.
15. Pozzoli A, De Maat GE, Hillege HL, Boogaard JJ, Natour E, Mariani MA. Severe thrombocytopenia and its clinical impact after implant of the stentless Freedom Solo bioprosthesis. *Ann Thorac Surg*. 2013;96:1581-6.
16. Piccardo A, Rusinaru D, Petitprez B, Marticho P, Vaida I, Tribouilloy C, et al. Thrombocytopenia after aortic valve replacement with freedom solo bioprosthesis: a propensity study. *Ann Thorac Surg*. 2010;89:1425-30.
17. Tarzia V, Bottio T, Buratto E, Spiezia L, Simioni P, Gerosa G. Freedom Solo Stentless Aortic Valve: Quantitative and Qualitative Assessment of Thrombocytopenia. *Ann Thorac Surg*. 2011;92:1935.
18. Khoo JP, Davies JE, Ang KL, Galinanes M, Chin DT. Differences in performance of five types of aortic valve prostheses: haemodynamic assessment by dobutamine stress echocardiography. *Heart*. 2013;99:41-7.
19. Dellgren G, Eriksson MJ, Brodin LA, Rådegran K. Eleven years' experience with the Biocor stentless aortic bioprosthesis: clinical and hemodynamic follow-up with long-term relative survival rate. *Eur J Cardiothorac Sur*g. 2002;22:912-21.
20. Desai ND, Merin O, Cohen GN, Herman J, Mobilos S, Sever JY, et al. Long-term results of aortic valve replacement with the St. Jude Toronto stentless porcine valve. *Ann Thorac Surg*. 2004;78:2076-83.
21. David TE, Armstrong S, Maganti M. Hancock II bioprosthesis for aortic valve replacement: the gold standard of bioprosthetic valves durability? *Ann Thorac Surg*. 2010;90:775-81.
22. Chan V, Kulik A, Tran A, Hendry P, Masters R, Mesana TG, et al. Long-term clinical and hemodynamic performance of the Hancock II versus the Perimount aortic bioprostheses. *Circulation*. 2010;122:S10-6.
23. Dellgren G, David TE, Raanani E, Armstrong S, Ivanov J, Rakowski H. Late hemodynamic and clinical outcomes of aortic valve replacement with the Carpentier-Edwards Perimount pericardial bioprosthesis. *J Thorac Cardiovasc Surg*. 2002;124:146-54.
24. Celiento M, Ravenni G, Milano AD, Pratali S, Scioti G, Nardi C, et al. Aortic valve replacement with the Medtronic Mosaic bioprosthesis: a 13-year follow-up. *Ann Thorac Surg*. 2012;93:510-5.
25. Borger MA, Prasongsukarn K, Armstrong S, Feindel CM, David TE. Stentless aortic valve reoperations: a surgical challenge. *Ann Thorac Surg*. 2007;84:737-44.
26. Cramariuc D, Rieck AE, Staal EM, Wachtell K, Eriksen E, Rossebø AB, et al. Factors influencing left ventricular structure and stress-corrected systolic function in men and women with asymptomatic aortic valve stenosis (a SEAS Substudy). *Am J Cardiol*. 2008;101:510-15.
27. Kennedy KD, Nishimura RA, Holmes DR, Bailey KR. Natural history of moderate aortic stenosis. *J Am Coll Cardiol.* 1991;17:313-9.

28. Rosenhek R, Klaar U, Schemper M, Scholten C, Heger M, Gabriel H, et al. Mild and moderate aortic stenosis. Natural history and risk stratification by echocardiography. *Eur Heart J*. 2004;25:199-205.
29. Schoen FJ, Levy RJ. Calcification of tissue heart valve substitutes: progress towards understanding and prevention. *Ann Thorac Surg*. 2005;79:1072–80.
30. Valente M, Pettenazzo E, Thiene G, Molin GM, Martignago F, De Giorgi G, et al. Detoxified glutaraldehyde cross-linked pericardium: tissue preservation and mineralization mitigation in a subcutaneous rat model. *J Heart Valve Dis*. 1998;7:283-91.
31. Ozaki S, Herijgers P, Flameng W. Influence of blood contact on the calcification of glutaraldehyde-pretreated porcine aortic valves. *Ann Thorac Cardiovasc Surg*. 2003;9:245-52.
32. Dagum P, Green GR, Nistal FJ, Daughters GT, Timek TA, Foppiano LE, et al. Deformational dynamics of the aortic root: modes and physiologic determinants. *Circulation*. 1999;100:II54-62.
33. Grande KJ, Cochran RP, Reinhall PG, Kunzelmann KS. Stress variations in the human aortic root and valve: The role of anatomic asymmetry. *Ann Biomed Eng*. 1998;26;534-45.

**Table 1:** Patient preoperative characteristics

| | |
|---|---|
| Number of patients | 149 |
| Age (y) | 73.6 ± 8.7 (46.1-87.4) |
| Gender | |
| Male (n, %) | 81 (54.4) |
| Female (n, %) | 68 (45.6) |
| BMI (kg/m$^2$) | 27.0 ± 5.9 (16.9-29.4) |
| BSA (Dubois) m$^2$ | 1.82 ± 0.29 (1.27-2.20) |
| Diabetes mellitus (n, %) | 34 (22.8) |
| Arterial hypertension (n, %) | 130 (87.2) |
| Renal impairment (n, %) | 24 (16.1) |
| Peripheral artery disease (n, %) | 62 (14.1) |
| Carotid stenosis (n, %) | 14 (10.1) |
| COPD (n, %) | 25 (9.4) |
| LVEF (%) | 55.4 ± 12.3 |
| History of cerebral events (n, %) | 17 (11.4) |
| NYHA class | |
| NYHA I | 14 (9.4) |
| NYHA II | 62 (41.6) |
| NYHA III | 54 (36.2) |
| NYHA IV | 19 (12.8) |
| Valve pathology | |
| Stenosis | 126 (84.6) |
| Regurgitation | 10 (6.7) |
| Combined | 13 (8.7) |
| Preoperative rhythm | |
| Sinus Data as mean ± SD | 120 (80.5) |
| Chronic atrial fibrillation | 21 (14.1) |
| Heart block | 2 (1.3) |
| Paced | 6 (4.0) |
| EuroScore II, total | 5.70 ± 8.88 |
| EuroScore II, isolated AVR | 2.69 ± 3.36 |
| EuroScore II, combined procedures | 8.67 ± 11.34 |

BMI=body mass index, BSA=body surface area, COPD=chronic obstructive pulmonary disease, LVEF=left ventricular ejection fraction, NHYA=New York Heart Association, Data as mean ± SD

**Table 2:** Operative data

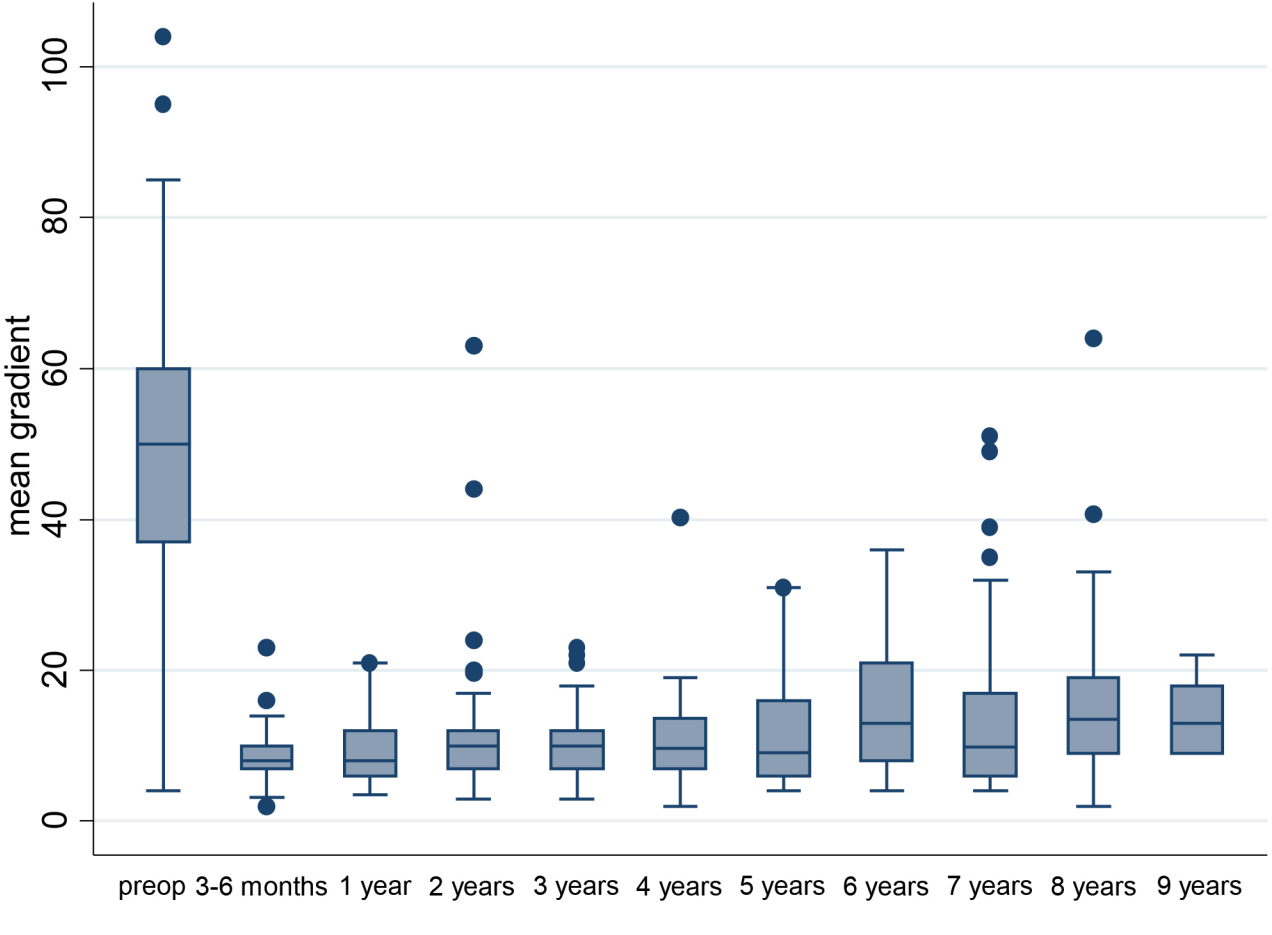
| | |
|---|---|
| Procedures | 149 |
| Isolated AVR | 75 |
| Combined procedures* | 74 |
| CABG, n | 59 |
| Grafts, n | 1.9 ± 1.0 |
| CABG+MVR, n | 5 |
| CABG+TVR, n | 1 |
| MVR (DVR), n | 1 |
| MVR (DVR)+TVR, n | 1 |
| Tricuspid annuloplasty, n | 1 |
| Ascendens tube graft, n | 3 |
| Ablation, n | 2 |
| PFO-closure, n | 8 |
| Other, n | 4 |
| Labeled valve size | |
| #19 | 3 (2.0) |
| #21 | 28 (18.8) |
| #23 | 44 (29.5) |
| #25 | 39 (26.2) |
| #27 | 35 (23.5) |
| CPB time (min) | |
| Isolated procedures | 64 ± 14 |
| Combined procedures | 95 ± 31 |
| Cross-clamp time (min) | |
| Isolated procedures | 47 ± 13 |
| Combined procedures | 71 ± 23 |
| RBC units[a] | |
| Isolated procedures | 2.4 ± 1.3 |
| Combined procedures | 3.2 ± 2.1 |
| platelets[b] | |
| Isolated procedures | 1.5 ± 0.9 |
| Combined procedures | 1.8 ± 1.1 |
| 30-day mortality | |
| Isolated procedures | 1/75 (1.3) |
| Combined procedures | 3/74 (4.0) |
| Overall | 4/149 (2.7) |

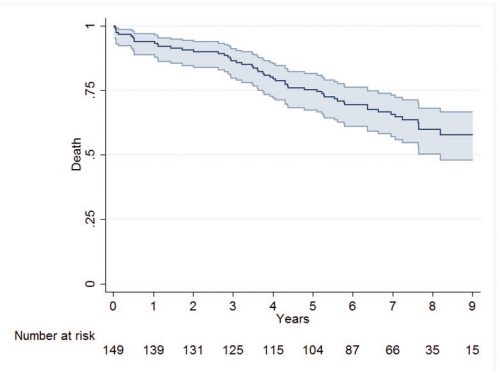
*one or more concomitant procedures, AVR=aortic valve replacement, MVR=mitral valve repair/replacement, CABG=coronary artery bypass grafting, TVR=tricuspid valve repair (tricuspid annuloplasty), DVR=double valve replacement, PFO=persistent foramen ovale, CPB=cardiopulmonary bypass, RBC=red blood cells, [a] 51.1% of patients received one or more RBC units, [b] 14.4% of patients received one or more platelet units, values are n (%)

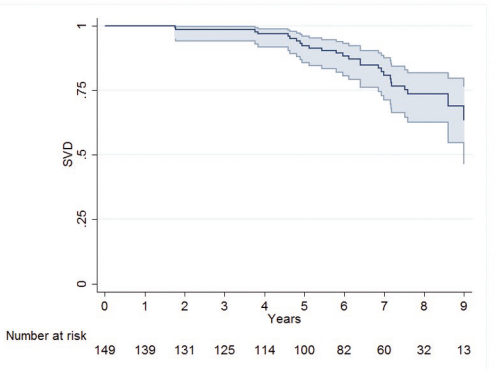
**Table 3:** Estimates on freedom from major adverse events

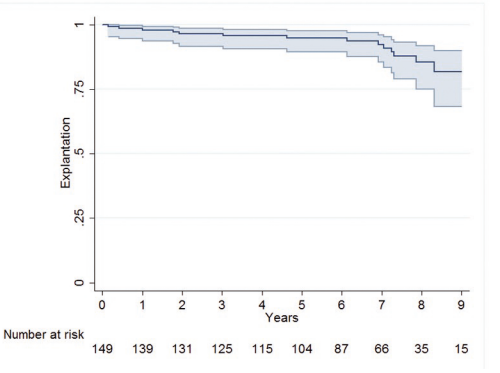
| estimate | year 1 | year 2 | year 3 | year 4 | year 5 | year 6 | year 7 | year 8 | year 9 | year 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| freedom from | | | | | | | | | | |
| death | 0.94 [0.89–0.97] | 0.91 [0.85–0.94] | 0.86 [0.80–0.91] | 0.80 [0.73–0.86] | 0.75 [0.67–0.81] | 0.69 [0.61–0.76] | 0.66 [0.57–0.73] | 0.59 [0.50–0.68] | 0.57 [0.47–0.66] | 0.57 [0.47–0.66] |
| SVD | 1.00 [1.00–1.00] | 0.99 [0.94–1.00] | 0.99 [0.94–1.00] | 0.97 [0.92–0.99] | 0.92 [0.86–0.96] | 0.88 [0.81–0.93] | 0.81 [0.72–0.88] | 0.73 [0.62–0.81] | 0.70 [0.57–0.79] | 0.60 [0.37–0.77] |
| explantation | 0.99 [0.95–1.00] | 0.96 [0.92–0.99] | 0.96 [0.92–0.99] | 0.96 [0.91–0.98] | 0.95 [0.89–0.97] | 0.95 [0.89–0.97] | 0.92 [0.86–0.96] | 0.85 [0.75–0.92] | 0.82 [0.69–0.90] | 0.82 [0.69–0.90] |
| explantation for SVD | 1.00 [1.00–1.00] | 0.99 [0.94–1] | 0.99 [0.94–1.00] | 0.99 [0.94–1.00] | 0.98 [0.93–0.99] | 0.98 [0.93–0.99] | 0.95 [0.88–0.98] | 0.88 [0.77–0.94] | 0.84 [0.71–0.92] | 0.84 [0.71–0.92] |
| endocarditis | 0.99 [0.95–1.00] | 0.99 [0.95–1.00] | 0.98 [0.93–0.99] | 0.98 [0.93–0.99] | 0.98 [0.93–0.99] | 0.98 [0.93–0.99] | 0.97 [0.93–0.99] | 0.97 [0.91–0.99] | 0.97 [0.91–0.99] | 0.97 [0.91–0.99] |
| thromboembolism | 0.99 [0.99 0.93] | 0.99 [0.95–1.00] | 0.99 [0.95–1.00] | 0.99 [0.95–1.00] | 0.99 [0.95–1.00] | 0.99 [0.95–1.00] | 0.99 [0.95–1.00] | 0.99 [0.95–1.00] | 0.99 [0.95–1.00] | 0.99 [0.95–1.00] |
| combined overall failure | 0.93 [0.87–0.96] | 0.88 [0.82–0.92] | 0.84 [0.77–0.89] | 0.77 [0.69–0.83] | 0.69 [0.61–0.76] | 0.60 [0.52–0.68] | 0.53 [0.45–0.61] | 0.45 [0.36–0.53] | 0.41 [0.31–0.50] | 0.35 [0.22–0.48] |

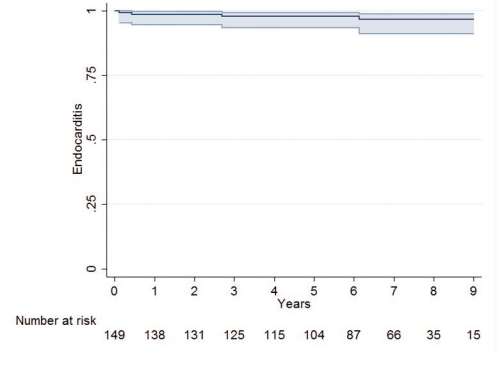
SVD = structural valve deterioration

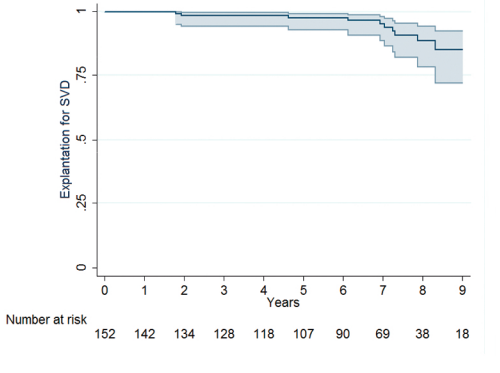

mean gradient
0
20
40
60
80
100
preop
3-6 months
1 year
2 years
3 years
4 years
5 years
6 years
7 years
8 years
9 years

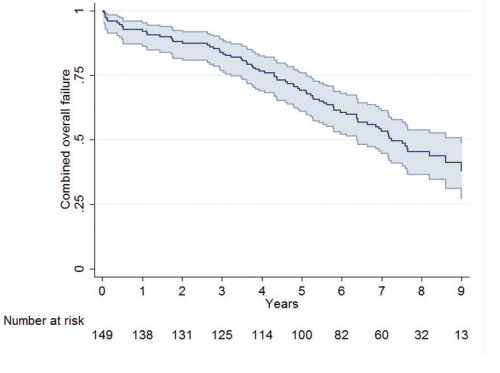

Death
0
.25
.5
.75
1
0 1 2 3 4 5 6 7 8 9
Years
Number at risk
149 139 131 125 115 104 87 66 35 15


SVD
0
.25
.5
.75
1
0 1 2 3 4 5 6 7 8 9
Years
Number at risk
149 139 131 125 114 100 82 60 32 13


Explantation
0
.25
.5
.75
1
0 1 2 3 4 5 6 7 8 9
Years
Number at risk
149 139 131 125 115 104 87 66 35 15


Endocarditis
0
.25
.5
.75
1
0 1 2 3 4 5 6 7 8 9
Years
Number at risk
149 138 131 125 115 104 87 66 35 15


Explantation for SVD
0
.25
.5
.75
1
0 1 2 3 4 5 6 7 8 9
Years
Number at risk
152 142 134 128 118 107 90 69 38 18


Combined overall failure
0
.25
.5
.75
1
0 1 2 3 4 5 6 7 8 9
Years
Number at risk
149 138 131 125 114 100 82 60 32 13