EuroIntervention

Title: Balloon Aortic Valvuloplasty for Severe Aortic Stenosis Before Urgent Noncardiac Surgery.

Authors: Nicolas Debry, M.D; Alexandre Altes, M.D; Flavien Vincent, M.D, PhD; Cédric Delhaye, M.D; Guillaume Schurtz, M.D; Farid Nedjari, M.D; Gabin Legros, M.D; Sina Porouchani, M.D; Augustin Coisne, M.D, PhD; Marjorie Richardson, M.D; Alessandro Cosenza, M.D; Basile Verdier, M.D; Tom Denimal, M.D; Thibault Pamart, M.D; Hugues Spillemaeker, M.D; Habib Sylla, M.D; Arnaud Sudre, M.D; Dany Janah, M.D; David Aouate, M,D; Wassima Marsou, M.D; Ludovic Appert, M.D; Gilles Lemesle, M.D, PhD; Julien Labreuche, Sylvestre Maréchaux, M.D, PhD; Eric Van Belle, M.D, PhD

DOI: 10.4244/EIJ-D-20-01423

Citation: Debry N, Altes A, Vincent F, Delhaye C, Schurtz G, Nedjar F, Legros G, Porouchani S, Coisne A, Richardson M, Cosenza A, Verdier B, Denimal T, Pamart T, Spillemaeker H, Sylla H, Sudre A, Janah D, Aouate D, Marsou W, Appert L, Lemesle G, Labreuche J, Maréchaux S, Van Belle E. Balloon Aortic Valvuloplasty for Severe Aortic Stenosis Before Urgent Noncardiac Surgery. *EuroIntervention* 2021; Jaa-906 2021, doi: 10.4244/EIJ-D-20-01423

Manuscript submission date: 22 December 2020

Revisions received: 10 May 2021

Accepted date: 03 June 2021

Online publication date: 08 June 2021

Balloon Aortic Valvuloplasty for Severe Aortic Stenosis Before Urgent Noncardiac Surgery

Authors: Nicolas Debry MD[1,2,3], Alexandre Altes MD[2], Flavien Vincent MD-PhD[1,3,4], Cédric Delhaye MD[1], Guillaume Schurtz MD[1], Farid Nedjari MD[2], Gabin Legros MD[2], Sina Porouchani MD[1], Augustin Coisne MD-PhD[3,4,5], Marjorie Richardson MD[5], Alessandro Cosenza MD[1], Basile Verdier MD[1], Tom Denimal MD[1], Thibault Pamart MD[1], Hugues Spillemaeker MD[1], Habib Sylla MD[1], Arnaud Sudre MD[1], Dany Janah MD[1], David Aouate MD[1], Wassima Marsou MD[2], Ludovic Appert MD[2], Gilles Lemesle MD-PhD[1,34], Julien Labreuche[6], Sylvestre Maréchaux MD-PhD[2], Eric Van Belle MD-PhD[1,3,4]

[1] CHU Lille, Institut Coeur Poumon, Cardiology, Department of Interventional Cardiology for Coronary, Valves and Structural Heart Diseases, Lille, France;

[2] Groupement des Hôpitaux de l'Institut Catholique de Lille (GHICL), Cardiology Department and Heart valve center, Faculté libre de médecine/université catholique de Lille, F-59000 Lille, France

[3] INSERM, U1011, F-59000 Lille, France

[4] Université de Lille, Lille, France

[5] CHU Lille, Department of Clinical Physiology and Echocardiography, Lille, France.

[6] Univ. Lille, CHU Lille, ULR 2694-METRICS : évaluation des technologies de santé et des pratiques médicales, F59000-Lille, France

Short title: **BAV for severe AS before urgent noncardiac surgery**

Corresponding author: Eric Van Belle, ericvanbelle@aol.com, Cardiology Department, Institut Coeur-Poumons, CHUU Lille, F-59000 Lille, France.

No funding.

No conflict of interest.

Abstract

Aims: Balloon aortic valvuloplasty (BAV) has been proposed as a therapeutic option in patients suffering from severe aortic stenosis (SAS) who need urgent noncardiac surgery (NCS). Whether this strategy is better than medical therapy in this very peculiar population is unknown. We evaluated the clinical benefit of an invasive strategy (IS) with preoperative BAV in patients with SAS requiring urgent NCS.

Methods and Results: From 2011 to 2019, a registry conducted in 2 centers included 133 patients with SAS undergoing urgent NCS, of whom n=93 underwent preoperative BAV (IS) and n=40 a conservative strategy (CS) without BAV. All analyses were adjusted for confounding using inverse probability of treatment weighting (IPTW) (10 clinical and anatomical variables). The primary outcome was the MACE at 1-month follow-up after NCS including mortality, heart-failure, and other cardiovascular outcomes.

In patients managed conservatively, occurrence of MACE was 20.0%(n=8) and death was 10.0%(n=4) at 1 month. In patients undergoing BAV, occurrence of MACE was 20.4%(n=19) and death was 5.4%(n=5) at 1-month. Among patients undergoing conservative management, all events were observed after NCS while in patients undergoing BAV, 12.9%(n=12) had events between BAV and NCS including 3 deaths and 7.5% (n=7) after NCS including 2 deaths.

In IPTW-propensity analyses, the incidence of the primary outcome (20.4% vs. 20.0%;OR=0.93;95%CI:0.38-2.29) and 3-months survival (89.2% vs. 90.0%;IPTW-adjustedHR=0.90;95%CI:0.31-2.60) were similar in both groups.

Conclusions: Patients with SAS managed conservatively before urgent NCS are at high risk of events. A systematic invasive strategy using BAV does not provide a significant improvement in clinical outcome.

Classifications: balloon aortic valvuloplasty, aortic stenosis, noncardiac surgery

Condensed Abstract

From 2011 to 2019, a prospective registry included n=93 patients with SAS treated with preoperative BAV (invasive strategy,IS), and n=40 with SAS without preoperative BAV (conservative strategy,CS) before urgent noncardiac surgery(NCS). Patients treated with the invasive strategy were compared to those treated with conservative strategy using IPTW propensity score (10 clinical and anatomical variables). In CS patients, occurrence of MACE was 20.0%(n=8) and death 10.0%(n=4) at 1-month after NCS. In IS patients, occurrence of MACE was 20.4%(n=19) and death 5.4%(n=5) at 1-month. In IPTW-propensity analyses, the incidence of the primary outcome (20.4% vs. 20.0%;OR=0.93;95%CI:0.38-2.29) and 3-months survival (89.2% vs. 90.0%;IPTW-adjusted HR=0.90;95%CI:0.31-2.60) were similar in both groups.

Abbreviations:

Acute kidney injury:AKI
Aortic regurgitation:AR
Balloon aortic valvuloplasty:BAV
Chronic obstructive pulmonary disease:COPD
Coronary artery bypass surgery:CABG
Conservative strategy:CS
Invasive strategy:IS
Left ventricular ejection fraction:LVEF
Major advert cardiac event:MACE
Noncardiac surgery:NCS
Severe Aortic stenosis:SAS
Society of thoracic surgeons score:STS score
Transcatheter aortic valve implantation:TAVI
Transient ischemic attack:TIA
Transthoracic echocardiography:TTE

Introduction

Management of severe aortic stenosis (SAS) patients undergoing noncardiac surgery (NCS) is a challenging and relatively frequent topic [1], with no clear evidence-based strategy.

Performing elective NCS in patients with SAS has been associated with a relatively high rate of MACE (18.8%) and mortality (5.9%) at 1-month [2]. In that context an invasive strategy based on balloon aortic valvuloplasty (BAV) before NCS has been proposed as an option to reduce this risk [3,4]. The 2017 ESC and 2014 ESC/AHA/ACC recommendations, which are largely based on small and observational studies that are now more than three decades old [5,6,7], suggest to differ the NCS whenever it is possible, while BAV can be proposed with a low level of evidence class IIbC [7].

For the specific subgroup of SAS patients requiring urgent non-elective NCS, clinical data are even more scarce [8,9]. The risk of performing urgent (< 7days) or emergency (<48hr) NCS is not well known as these high-risk surgical conditions are usually under-represented (around 10%) in studies investigating the risk of NCS in SAS patients [2,10]. Besides, the utility of preoperative BAV in this particular setting is unknown. No randomized study comparing the outcomes of SAS patients undergoing urgent NCS under conservative or invasive approach has been conducted to date and the net benefit of BAV as a preparation for urgent NCS is uncertain because of the potential high complication rate of BAV in these conditions [11,12]. This explains why the practice is very wide with some centers using an invasive strategy-percutaneous balloon aortic valvuloplasty (BAV) in all SAS patients before urgent NCS while others in none (conservative strategy).

In the current study we set forth to re-evaluate in the contemporary era the outcomes of SAS patients requiring urgent non-elective NCS and the potential benefit of an invasive strategy (preoperative BAV for urgent NCS) vs. conservative strategy. This was conducted by comparing the outcomes of SAS patients undergoing BAV prior urgent NCS to the outcomes of SAS undergoing urgent NCS without prior BAV and used as a control group.

Methods.

Patient selection

In this retrospective study, we involved two centers with different strategy regarding the management of SAS patients before urgent noncardiac surgery from 2011-2019.

(i) One center with a default *invasive strategy* using routine BAV before NCS,

(ii) One center with a default *conservative strategy* without BAV before NCS.

Severe aortic stenosis was considered to be present at the time of surgery if documented within 12 months before surgery. Severe aortic stenosis was defined using current trans-thoracic echocardiography (TTE) criteria (aortic valve area ≤1 cm^2, peak systolic flow velocity ≥4 m/s, mean gradient ≥40 mmHg) in conjunction with typical 2D echocardiographic appearance of severe AS[13]. Patients undergoing aortic valve replacement before non-cardiac surgery were excluded. Patients with high gradients or velocities attributable to increased cardiac output (anaemia, septic shock, etc.), as well as those with concomitant diseases that may have influenced Doppler indexes of SAS (hypertrophic obstructive cardiomyopathy, sub- or supravalvular aortic stenosis, coarctation of the aorta, or complex congenital heart diseases) were excluded.

Baseline demographic data, type of surgical intervention, comorbidities, symptoms potentially associated with SAS (dyspnoea), and echocardiographic data just before surgery were extracted from the electronic medical record.

Regarding BAV procedure, the size of the balloon was chosen according to the annulus measurement according to the TTE before BAV. NuMed Nucleus® and ZMed Braun® balloons were used for transfemoral BAV, and VACS II Osypka® balloons for transradial BAV. Valvuloplasty was considered successful if significant reduction (≥50%) of the mean transaortic gradient assessed by hemodynamic measures was obtained.

This study was approved by the institutional ethics committee.

Echocardiography

All echocardiograms were performed as clinically indicated, and in accordance with current European and American Society of Echocardiography recommendations [13]. In patients with multiple echocardiograms, the study closest to the time of surgery was selected. Aortic valve parameters (valve area and valve area index, peak aortic velocity and mean aortic valve gradient), as well as left ventricular size, ejection fraction, and estimated pulmonary artery systolic pressure (based on tricuspid regurgitant velocity) were extracted from the echocardiography database.

Non-elective non-cardiac surgery (NCS)

Surgical interventions were classified according to current ESC/ACC/AHA guidelines into low, intermediate, and high risk [5]. Patients undergoing low (transurethral resection of the prostate, superficial, eye, breast surgery…; reported cardiac risk <1%), intermediate (intraperitoneal and intrathoracic surgery, carotid endarterectomy, head and neck surgery, orthopaedic surgery, prostate surgery; reported cardiac risk 1–5%) and high-risk procedures (aortic and other major vascular surgery, peripheral vascular surgery; reported risk >5%) [5] under general or locoregional anaesthesia were included. Semi-urgent NCS included patients who were operated within 2 to 7 days and emergency NCS those who were operated within 48hr. Ambulatory, ophthalmological and percutaneous interventions were excluded.

Clinical endpoints

We compared the outcomes after NCS of invasive vs. conservative strategy of management of SAS patients. The primary endpoint (MACE) was a composite endpoint of 1-month mortality, heart failure, myocardial infarction, stroke/transient ischemic attack, new atrial fibrillation, acute kidney injury (rise of >2 fold of baseline creatinine and/or <0.5ml/kg/hr urine output), and life-threatening bleeding (hypovolemic shock or severe hypotension requiring vasopressors or surgery, or packed red blood cells (RBCs) transfusion ≥4 units) after NCS. The secondary outcome included predictive factors of 1-month MACE. Other analyses included 3-months survival after NCS. All medical files were carefully reviewed and in case of doubts clinical events were adjudicated by a medical committee of two physicians.

Statistical Analysis

Quantitative variables are expressed as means (standard deviation) in the case of normal distribution or medians (interquartile range) otherwise. Categorical variables are expressed as numbers (percentage). Normality of distributions was assessed using histograms and the Shapiro-Wilk test. Patients were divided in two groups according to the strategy used. Baseline characteristics were described according to the two study groups and the magnitude of the between-group differences in pre-specified confounders was assessed by calculating the absolute standardized difference; an absolute standardized difference >10% was interpreted as a meaningful difference [14]. Between-group comparisons in surgical procedure characteristics, and association of potential predictors of primary clinical endpoint (1-month MACE) were done using Chi-square test or Fisher's exact in case of expected cell frequencies <5. Comparison in outcomes between the two study groups was done using logistic regression model for MACE, linear regression model for length of hospital stay (after log-transformation values to satisfy the residual normality) and Cox's proportional hazard model for 3-month all-cause mortality; effect sizes and their 95% confidence intervals were derived from regression models using patients treated with conservative strategy (without preoperative BAV) as control group. In order to take into account the pre-specified confounders, comparisons in outcomes were further done by using pre- inverse probability of treatment weighting (IPTW) propensity score method (using stabilized inverse propensity score as weighty in regression models). The propensity score was estimated using a multivariable logistic regression model, with study groups as the dependent variable and a pre-specified confounders as covariates (Table 1). Statistical testing was conducted at the two-tailed α-level of 0.05. Data were analyzed by J.L. using the SAS software version 9.4. (SAS Institute, Cary, NC).

Results

Study Population

(i) SAS patients undergoing conservative strategy before NCS

As presented in Central Illustration, from 2011 to 2019, we identified 40 patients with SAS (Aortic valve area=0.77 ± 0.22cm^2) undergoing NCS without BAV before NCS.

(ii) SAS patients undergoing invasive strategy (BAV) procedure before NCS

We also identified 93 patients with severe aortic stenosis (Aortic valve area=0.72 ± 0.15cm^2) treated with preoperative BAV before NCS (**Central Illustration**). BAV was performed 4 (2-11) days before noncardiac surgery.

Baseline Characteristics

Baseline characteristics and comorbidities of the different groups are presented in **Table 1** (main pre-specified confounders for IPTW score) and in **Table 2**.

When comparing TTE characteristics in both groups at baseline (**Table 1),** there was no significant difference in mean aortic gradient (45.0mm±13.6mmHg vs. 42.3±8.1mmHg; P=0.24) or maximal velocity (4.2±0.6m/s vs. 4.1±0.4m/s; P=0.45), and aortic valve area (0.72±0.15cm^2 vs. 0.77±0.22cm^2; P=0.16).

After IPTW using propensity score, the between-group differences in main confounders (**Table 1**) were reduced as shown in **supplemental Figure 1**.

BAV procedure and outcomes in the invasive strategy group before urgent NCS

Mean Balloon size was 21.6±1.7mm and mean number of inflations was 1.6±0.6. N=5 (5.3%) were performed through the radial artery. Complications (n=12, 12.9%) of BAV included: 2 (2.1%) perprocedural death due to cardiac arrest after crossing the valve for BAV, 1 (1.0%) death following a major stroke, 3 (3.2%) patients requiring a permanent pace-maker implantation after the procedure, 4 (4.3%) patients had a clinical hematoma at the femoral puncture site without need of transfusion, 1 (1.0%) patient presented a transient (<24h) hemiplegia after the BAV, and 1 (1.0%) patient had a homolateral acute limb ischemia requiring an urgent reperfusion. BAV was successful in most severe AS cases (70% had a significant reduction (≥50%) of the mean transaortic gradient assessed by hemodynamic measures) with a significant reduction of the transaortic gradient: 45.0±13.6mmHg vs. 32.4±11.4 P<0.001, the aortic maximal velocity: 4.2±0.6m/s vs. 3.6±0.6 P<0.001, and the

AVA: 0.72±0.15 cm^2 vs. 0.91±0.2 P<0.001 evaluated by transthoracic echocardiography. Finally, out of the 93 patients undergoing BAV, 90 underwent NCS.

Non-elective Noncardiac surgery

Period of NCS (before or after 2015), timing of surgery (emergency or semi-urgent) and type of anaesthesia (general or not) were well balanced in the two groups (**Table 2)**. Details about noncardiac surgery procedures are depicted in **Table 3**.

Outcomes after non-elective noncardiac surgery (NCS)

(i) Primary endpoint

The rate of MACE at 1-month was 20.4% in the invasive strategy group and 20.0% in the conservative strategy group, unadjusted analysis OR=1.03; 95%CI:0.40-2.59 and IPTW-adjusted analysis OR=0.93; 95%CI:0.38-2.29. Details in individual events included in MACE are available in **Table 4**. Reasons for death in the CS group were limb ischemia (n=1) and multiple organ failure (n=1) after vascular surgery, cardiac arrest (asystole) after hip repair, and critical sepsis (n=1) after abdominal surgery. Other causes of death in the IS group after NCS included n=1 mitral endocarditis after acute gonarthritis, and n=1 digestive cancer.

(iii) Predictive factors of 1-month MACE

In the global cohort, univariate predictive factors of primary endpoint included higher ASA score≥3 (28.3% vs. 4.7%; P=0.001) and preoperative pulmonary hypertension>35mmHg (33.0% vs. 14.7%; P=0.007).

In the invasive strategy group, univariate predictive factors of primary endpoint included ilio-femoral artery disease (38% vs. 15%; P=0.02), higher ASA score ≥3 (29.1% vs. 3.6%; P=0.003) and preoperative pulmonary hypertension>35mmHg (37.2% vs. 11.8% P=0.003).

(iii) Other outcomes

Among events occurring at 1 month, heart failure, life-threatening bleeding, stroke/TIA and acute kidney injury occurred at the same rate in the two groups (**Table 4**). Regarding length of hospital stay for NCS, invasive strategy was associated with a non-significant shorter duration (median 6 days; IQR 4 to 9) than conservative strategy (median 8 days; IQR 4 to 16, **Table 4**). In the overall cohort 34 (25.5%) patients had a TAVI procedure after NCS (invasive strategy 31.2% vs. conservative strategy SAS 12.5%) with a median delay of 103 days (52;200). No patient had surgical aortic valve replacement.

As shown in the **Figure 1,** there was no difference in 3-months survival between CS and IS (89.2% vs. 90.0%) with an IPTW-adjusted HR of 0.90 (95%CI:0.31-2.60).

Among subgroups of interest, there was no difference in 1-month MACE (26.1% vs. 23.4%; P=0.82) or 1-month mortality (15.2% vs. 8.9%; P=0.39) between conservative and invasive strategies before emergency NCS (<48hr).

There was also no difference in 1-month MACE (33.9% vs. 40.0%; P=0.82) or 1-month mortality (33.5% vs. 20.8%; P=0.61) between conservative and invasive strategies before high-risk NCS(aortic and other major vascular surgery, peripheral vascular surgery; reported risk >5%).

Discussion

The best preoperative management of SAS patients before urgent NCS is unknown. This study is the first (i) to provide the largest set of SAS patients undergoing urgent NCS, and to include a large proportion (>60%) of emergent (<48h) NCS, and (ii) to compare conservative and invasive strategy before urgent NCS using IPTW analysis. Overall it reflects the real life of managing old patients with SAS who suffer, for example, from hip fracture which requires emergency surgery to preserve their autonomy [8].

The main findings from this IPTW analysis are: (i) Patients with SAS managed conservatively before NCS are at high risk of events: high 1-month MACE (20.0%) and 1-month mortality (10.0%), (ii) Performing BAV in such population is not "benign" and is associated with 3.2% mortality and 9.6% non-fatal complications at 7 days, (iii) While "immediate" one-month mortality after NCS might be lower in "survivors" of the invasive strategy, overall one month MACE and 3-months survival are similar in SAS patients treated with or without BAV, (iv) ASA score≥3 or preoperative pulmonary hypertension>35mmHg seems to impact prognosis after NCS.

Some studies have previously described the outcomes of AS patients vs. non-AS patients undergoing NCS (**Table 5**). Patients with AS undergoing non-cardiac surgery have not been shown to be at increased risk of mortality, but have significantly higher rates of adverse cardiovascular events compared to patients without AS [16], especially those with symptomatic SAS have more MACE (acute myocardial infarction, acute heart failure, arrhythmia) than asymptomatic SAS (36% vs. 16% respectively) and higher mortality rates than moderate AS (16% vs. 4%) [17].

We report higher 1-month mortality (10.0%) and MACE (20.0%) rates with conservative strategy after urgent NCS, than *Tashiro et al.* from the Mayo Clinic, but the latter explored only asymptomatic patients with AS after scheduled NCS (1-month mortality 3.3% and MACE 12%) [2].

No randomized study comparing the outcomes of SAS patients undergoing urgent NCS under conservative or invasive approach has been conducted to date. Invasive strategy reduced "immediate" 1-month mortality rate after NCS (3.2% vs. 10.0%;P=0.04) but not if we take into account the mortality induced by the BAV itself (5.4% and 10.0%; P=0.33). Partly because of the insufficient "hemodynamic result" and the complications linked to the invasive strategy, both attitudes have similar one-month MACE after NCS. While we confirm that using a routine invasive strategy using for SAS patients is not recommended, it may be beneficial in selected patients.

Asymptomatic SAS patients, or patients requiring low-intermediate risk NCS could be managed conservatively [10]. As the *Tashiro* study reminds us, urgent and scheduled NCS have not the same morbidity as emergency NCS alone is also a strong predictor of 30-day mortality [2]. Published reports indicates that on the basis of TTE adverse events during NCS occurred primarily in AS patients with an AVA ≤0.7 cm^2 and a mean gradient ≥50 mm Hg [9]. In our study, because of a small cohort and the presence of severe AS in both groups, we were not able to identify anatomical aortic criteria that should encourage us to perform BAV before NCS. However preoperative pulmonary hypertension>35mmHg and ASA score ≥3 are associated with higher short-terms MACE and mortality rates. Invasive strategy in patients with these criteria could be discussed to improve prognosis after NCS.

The first way to decrease morbi-mortality after NCS may be to reduce the morbidity related to the BAV procedure. Using smaller unilateral [18] or bilateral sheath slender [19] transradial access for BAV is safe and feasible. BAV with low-profile compliant balloons [20], without pace maker back-up [21], or with pacing on the left ventricular guidewire [22] has also recently been described.

The second way is to improve the hemodynamic result of the BAV procedure. In our study, 30% of the patients did not experienced a significant improvement of the hemodynamic parameters following BAV. In addition, in the remaining 70% with some improvement, the mean residual gradient was 30.0+/-4.0mmHg. The best means to achieve a consistent hemodynamic improvement, and possibly to decrease morbi-mortality after NCS, is to perform direct TAVI before NCS. However, TAVI can be technically difficult to perform in the specific setting of urgent NCS because it requires a dedicated technical platform with on-site multislice CT-scan and available catherization laboratory. It requires at least a 14F vascular access, larger than for a transradial BAV (9F), and may be associated with more complications. Performing TAVI before NCS can also be at very high risk of endocarditis, in particular when the surgery is associated with bacteriemia (e.g. urgent digestive surgery, or septic orthopaedic surgery). In addition, in our study, only 25% of the global SAS cohort had a TAVI procedure within 3 months after urgent NCS. This is highlighting that this population is not a typical TAVI population, as it includes a combination of frailty and multiple comorbidities including cancer, disabilities, which in the end may postpone or even cancel the TAVI procedure. On the other hand, studies have reported that cancer patients with severe AS who underwent AVR had an improved survival, regardless of cancer status [23]. When compared to aortic surgery, TAVI under local anaesthesia is less invasive and may avoid the possibility of cancer dissemination due to extracorporeal circulation for patients with malignancy.

Large-scale prospective cohort studies are needed to clarify the above interrogations and delineate the role of direct TAVI in this population. For the time being, a case-by-case pluridisciplinary Heart-Team discussion remains the best option to choose the optimal strategy in those SAS requiring urgent NCS.

Limitations

Limitations to this study are inherent to the non-randomized design. The present findings are derived from observational analyses, which are subject to well-known limitations. The main is the potential for confounding by measured or unmeasured variables, which cannot be ruled out, even after IPTW adjustment. In particular, we could not exclude a residual bias related to age or NCS risk since both remained not completely balanced in IPTW-adjusted analysis, as well as to other patient's characteristics not included in propensity score calculation. No formal sample size calculation was done and we therefore caution that we could not excluded a lack of adequate statistical power to detect the between-group differences. In a posteriori power calculation, our study sample size (93 patients with invasive strategy and 40 patients with conservative strategy) allows, with 80% power, to detect with type-1 error of 5%, an odd ratio of MACE at 1-month of 3.2 (or 0.19 for protective effect) for patients with invasive strategy versus conservative strategy. These calculations were done by considering the observed rate of MACE at 1-month in conservative group (20%), a 80% power and two-sided type-1 error of 5%.

Conclusions

Patients with SAS managed conservatively before urgent NCS are at high risk of events. A systematic invasive strategy using BAV does not provide a significant improvement in clinical outcome.

Impact on daily practice

The presence of SAS in patients requiring urgent non-elective NCS (including 62% emergency surgery performed <48hr) is at high risk of mortality and clinical events. Our study suggests that the performance of BAV before NCS does not provide enough safety and hemodynamic benefit to be performed in a systematic fashion. The indication of BAV needs to be discussed on an individual basis. Large-scale prospective cohort studies are needed to delineate the role of minimally-invasive BAV procedure or "direct" TAVI in selected high-risk patients before NCS.

No funding

No disclosures to declare for all authors

REFERENCES

1. Alkhouli M, Zack CJ, Sarraf M, Bashir R, Nishimura RA, Eleid MF, Nkomo VT, Sandhu GS, Gulati R, Greason KL, Holmes DR, Rihal CS. Morbidity and Mortality Associated With Balloon Aortic Valvuloplasty: A National Perspective. *Circ Cardiovasc Interv* 2017;**10**.

2. Tashiro T, Pislaru SV, Blustin JM, Nkomo VT, Abel MD, Scott CG, Pellikka PA. Perioperative risk of major non-cardiac surgery in patients with severe aortic stenosis: a reappraisal in contemporary practice. *Eur Heart J* 2014;**35**:2372–2381.

3. Roth RB, Palacios IF, Block PC. Percutaneous aortic balloon valvuloplasty: its role in the management of patients with aortic stenosis requiring major noncardiac surgery. *J Am Coll Cardiol* 1989;**13**:1039–1041.

4. Hayes SN, Holmes DR, Nishimura RA, Reeder GS. Palliative percutaneous aortic balloon valvuloplasty before noncardiac operations and invasive diagnostic procedures. *Mayo Clin Proc* 1989;**64**:753–757.

5. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, Ford I, Gonzalez-Juanatey JR, Gorenek B, Heyndrickx GR, Hoeft A, Huber K, Iung B, Kjeldsen KP, Longrois D, Lüscher TF, Pierard L, Pocock S, Price S, Roffi M, Sirnes PA, Sousa-Uva M, Voudris V, Funck-Brentano C, Authors/Task Force Members. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J* 2014;**35**:2383–2431.

6. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;**130**:e278–333.

7. Baumgartner H, Falk V, Bax JJ, Bonis M De, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–2791.

8. Keswani A, Lovy A, Khalid M, Blaufarb I, Moucha C, Forsh D, Chen D. The effect of aortic stenosis on elderly hip fracture outcomes: A case control study. *Injury* 2016;**47**:413–418.

9. Leibowitz D, Rivkin G, Schiffman J, Rott D, Weiss AT, Mattan Y, Kandel L. Effect of severe aortic stenosis on the outcome in elderly patients undergoing repair of hip fracture. *Gerontology* 2009;**55**:303–306.

10. Calleja AM, Dommaraju S, Gaddam R, Cha S, Khandheria BK, Chaliki HP. Cardiac risk in patients aged >75 years with asymptomatic, severe aortic stenosis undergoing noncardiac surgery. *Am J Cardiol* 2010;**105**:1159–1163.

11. Lieberman EB, Bashore TM, Hermiller JB, Wilson JS, Pieper KS, Keeler GP, Pierce CH, Kisslo KB, Harrison JK, Davidson CJ. Balloon aortic valvuloplasty in adults: failure of procedure to improve long-term survival. *J Am Coll Cardiol* 1995;**26**:1522–1528.

12. Percutaneous balloon aortic valvuloplasty. Acute and 30-day follow-up results in 674 patients from the NHLBI Balloon Valvuloplasty Registry. *Circulation* 1991;**84**:2383–2397.

13. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B, Otto CM, Pellikka PA, Quiñones M, American Society of Echocardiography, European Association of Echocardiography. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr* 2009;**22**:1–23; quiz 101–102.

14. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;**28**:3083–3107.

15. Austin PC. A comparison of 12 algorithms for matching on the propensity score. *Stat Med* 2014;**33**:1057–1069.

16. Kwok CS, Bagur R, Rashid M, Lavi R, Cibelli M, Belder MA de, Moat N, Hildick-Smith D, Ludman P, Mamas MA. Aortic stenosis and non-cardiac surgery: A systematic review and meta-analysis. *Int J Cardiol* 2017;**240**:145–153.

17. MacIntyre PA, Scott M, Seigne R, Clark A, Deveer F, Minchin I. An observational study of perioperative risk associated with aortic stenosis in non-cardiac surgery. *Anaesth Intensive Care* 2018;**46**:207–214.

18. Tumscitz C, Campo G, Tebaldi M, Gallo F, Pirani L, Biscaglia S. Safety and Feasibility of Transradial Mini-Invasive Balloon Aortic Valvuloplasty: A Pilot Study. *JACC Cardiovasc Interv* 2017;**10**:1375–1377.

19. Vassileva A, Valsecchi O, Guagliumi G, Fiocca L, Canova PA, Cereda AF. Bilateral Slender Transradial Aortic Balloon Valvuloplasty. *J Invasive Cardiol* 2018;**30**:E48–E49.

20. Rau EM, El-Hajjar M. Aortic valvuloplasty via the radial artery: Case reports and review of the literature. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 2018;**92**:597–600.

21. Rigatelli G, Dell'Avvocata F, Conte L, Lanza D, Giatti S, Santo P Del, Roncon L, Faggian G. Modified balloon aortic valvuloplasty in fragile symptomatic patients unsuitable for both surgical and percutaneous valve replacement. *Cardiovasc Revascularization Med Mol Interv* 2018;**19**:444–447.

22. Faurie B, Souteyrand G, Staat P, Godin M, Caussin C, Belle E Van, Mangin L, Meyer P, Dumonteil N, Abdellaoui M, Monségu J, Durand-Zaleski I, Lefèvre T, EASY TAVI

Investigators. Left Ventricular Rapid Pacing Via the Valve Delivery Guidewire in Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv* 2019;**12**:2449–2459.

23. Yusuf SW, Sarfaraz A, Durand J-B, Swafford J, Daher IN. Management and outcomes of severe aortic stenosis in cancer patients. *Am Heart J* 2011;**161**:1125–1132.

Figures legends

Central Illustration. Study flow chart

Figure 1. 3-months survival after NCS in patients with invasive (BAV) or conservative (without BAV) strategy

Table 1. Main Baseline Characteristics(pre-specified confounders) in aortic stenosis patients before urgent NCS

Characteristics	*(n=133)*		
	Severe AS **Invasive strategy (n=93)**	**Conservative strategy (n=40)**	**ASD, %**
Patient's characteristics			
Age (years)	79.9 ± 9.5	83.0 ± 8.0	35.4
Male gender	38 (40.9)	19 (47.5)	13.4
Surgery Period > 2015	45 (48.4)	19 (47.5)	1.8
ASA score			
-2	31 (33.3)	13 (32.5)	5.0
-3	37 (39.8)	15 (37.5)	
-4	25 (26.9)	12 (30.0)	
STS score (nov. 2018 %)	3.0 ± 1.3	3.2 ± 1.4	10.9
TTE characteristics[1]			
LVE fraction (%)	56.6 ± 12.2	59.2 ± 9.3	23.7
AVA (cm2)	0.72 ± 0.15	0.77 ± 0.22	24.8
Mean Transaortic gradient (mmHg)	45.0 ± 13.6	42.3 ± 8.1	24.1
Aortic Maximal Velocity (m/s)	4.2 ± 0.6	4.1 ± 0.4	15.6
Surgery characteristics			
Noncardiac surgery risk[2]			
-Low	21 (22.6)	9 (22.5)	29.1
-Intermediate	57 (61.3)	28 (70.0)	
-High	15 (16.1)	3 (7.5)	

Values expressed as numbers (%) unless otherwise indicated. These variables were used for the IPTW score.

[1] evaluated by TTE before BAV and before noncardiac surgery. [2] according to ESC 2014 and 2017 recommendations

Abbreviations: ASA=American society of anesthesiologists score; ASD=absolute standardized difference; AVA=aortic valve area (cm^2); BAV=balloon aortic valvuloplasty;

LVE=left ventricular ejection; SAS=severe aortic stenosis; TTE=transthoracic echocardiogram.

Table 2. Baseline Characteristics (considered as non- specified confounders) in aortic stenosis patients

	Invasive strategy (n=93)	Conservative strategy (n=40)
Patient's characteristics	-	-
Hypertension	72(77)	30(75)
Diabetes mellitus	27(29)	12(30)
Obese (BMI>30)	13(14)	5(12)
Ilio-femoral artery disease	21(23)	15(37)
Coronary disease	33(35)	12(30)
Previous CABG	2(2)	2(0.5)
Active cancer	33(35)	3(7)
Renal dysfunction, n (%)	24(26)	10(25)
COPD	13(14)	6(15)
Atrial fibrillation	29(31)	12(32)
Prior Stroke/TIA	11(12)	9(22)
Preoperative pacemaker	8(9)	4(1)
Dyspnea III-IV before NCS	72(77)	12(30)
Medication at the time of surgery	-	-
Anticoagulant	24(25)	10(25)
Antiplatelet	60(64)	34(85)
Statins	56(60)	27(67)
CEI/ARAII	45(48)	19(47)
B-blockers	25(27)	10(25)
Other TTE characteristics before surgery	-	-
LVE fraction (%)	57.5+/-12.1[1]	59.2 ± 9.3
AVA (cm^2)	0.91+/-0.21[1]	0.77 ± 0.22
Mean Transaortic gradient (mmHg)	32.4+/-11.4[1]	42.3 ± 8.1
Aortic Maximal Velocity (m/s)	3.6+/-0.6[1]	4.1 ± 0.4
Bicuspid aortic valve	7(7)	4(10)
Left ventricle volume (mL), mean±SD	100.6 ± 28.4[1]	105.4 ± 30.2
Mitral regurgitation	31(33)[1]	14(35)
Left atrium volume (mL), mean±SD	45.7 ± 17.9[1]	44.8 ± 19.3
Sdti (cm/s), mean±SD	10.8 ± 2.1[1]	11.1 ± 3.0
Systolic PAP (mmHg), mean±SD	35.5 ± 11.1[1]	33.5 ± 10.7
Surgery characteristics	-	-
Timing of surgery	-	-
-Emergency(<48hr)	61(65)	22(55)
-Semi-urgent(2-7days)	32(35)	18(45)
General anesthesia	84(90)	33(83)

Values expressed as numbers (%) unless otherwise indicated. Renal dysfunction defined as GFR ≤60ml/min/m2.

[1] evaluated by TTE after BAV and before noncardiac surgery.

Abbreviations: ARAII=angiotensin II receptor antagonist; ASA=American society of anesthesiologists score; AVA=aortic valve area; CABG= coronary artery bypass graft; BAV=balloon aortic valvuloplasty; CEI=converting enzyme inhibitors; COPD= chronic obstructive pulmonary disease; IQR=interquartile range; LVE= left ventricular ejection; PAP=pulmonary artery pressure; SAS=severe aortic stenosis; SD=standard deviation; Sdti= tricuspid lateral *annular* systolic velocity; TIA=transient Ischemic Attack; TTE= transthoracic echocardiogram

Table 3: Surgical procedures according to 2014 ESC recommendations

	Severe AS (n=133)		
	Invasive strategy (n=93)	**Conservative strategy (n=40)**	**P value**
High-risk surgery	*15(16.1)*	*3(7.5)*	*0.18*
Aortic and major vascular surgery	5(5.3)	2(5.0)	0.93
Pneumonectomy	2(2.1)	0(0.0)	0.35
Major digestive surgery[1]	8(8.6)	1(2.5)	0.20
Intermediate-risk surgery	*57(61.3)*	*28(70.0)*	*0.34*
Major orthopaedic surgery	21(22.5)	9(22.5)	0.99
Major urological/renal surgery	6(6.4)	2(5.0)	0.75
Major neurological surgery	4(4.3)	1(2.5)	0.62
Major gynecologic surgery	3(3.2)	1(2.5)	0.82
Minor vascular surgery [2]	5(5.3)	7(17.5)	0.03
Intraperitoneal surgery [3]	18(19.3)	8(20.0)	0.93
Low-risk surgery	*21(22.6)*	*9(22.5)*	*0.99*
Superficial surgery	2(2.1)	2(5.0)	0.38
Minor orthopaedic surgery	14(15.0)	6(15.0)	0.99
Minor gynecologic surgery	3(3.2)	1(2.5)	0.82
Minor urological surgery	2(2.1)	0(0.0)	0.35

[1] duodena-pancreatic, liver, bile-duct, perforated bowel surgery or esophagectomy; [2] carotid symptomatic, endovascular aneurysm, peripheral arterial surgery; [3] splenectomy, hiatal hernia repair, cholecystectomy

Table 4. One-month outcomes after urgent NCS in patients with SAS after IPTW Propensity-Score

			Unadjusted analysis		**IPTW-adjusted analysis**	
	Severe AS (n=133)					
Outcomes	**Invasive strategy (n=93)**	**Conservative strategy (n=40)**	**Effect size (95%CI)**	**P**	**Effect size (95%CI)**	**P**
Composite cardiovascular outcome (MACE)	19 (20.4)*#	8 (20.0)	1.03 (0.40 to 2.59)[1]	0.96	0.93 (0.38 to 2.29)[1]	0.88
Heart Failure	*8 (8.6)*	*4 (10.0)*				
Myocardial infarction	*1 (1.1)*	*1 (2.5)*				
New atrial fibrillation	*7 (7.5)*	*2 (5.0)*				
Life-Threatening bleeding	*3 (3.2)*	*0 (0.0)*				
Stroke/TIA	*1 (1.1)#*	*0 (0.0)*				
Acute kidney injury	*5 (5.4)*	*5 (12.5)*				
Mortality	*5 (5.4)**	*4 (10.0)*				
Length of hospital stay, days, median (IQR)	6 (4 to 9)	8 (4 to 16)	-0.20 (-0.53 to 012)	0.22	-0.29 (-0.62 to 0.04)	0.082

The propensity score was estimated using a multivariable logistic regression model, with study groups as the dependent variable and a pre-specified confounders as covariates (age, sex, surgery period, ASA score, STS score, LVEF, AVA, mean transaortic gradient, maximal velocity, NCS risk).

[1] odds ratio calculated using unweighted (unadjusted analysis) and weighted (IPTW-adjusted analysis) logistic regression models using conservative strategy group as reference.

[2] mean difference (95%CI) calculated on log-transformed values among patients discharged alive (n=129) by using unweighted (unadjusted analysis) and weighted (IPTW-adjusted analysis) linear regression models

*including 3 deaths after BAV before NCS; #including 1 TIA after BAV before NCS

Abbreviations: AR=aortic regurgitation ; BAV=balloon aortic valvuloplasty ; CI=confidence interval ; MACE=major advert cardiovascular event; NCS=noncardiac surgery, SAS=severe aortic stenosis; TIA=transient ischemic attack.

Table 5. Summary of studies with AS patients and noncardiac surgery

Study	N	Urgent non elective NCS(n,%)	Preop BAV(n)	Type of NCS	NCS requiring General anesthesia (%)	NCS within 7 days	ASA score	Risk score of NCS[1]	Comparative group	Ref.
Hayes et al. Mayo Clin Proc(1989)	15	9(60%)	15(100%)	Miscellaneous	60%	80%	NA	NA	No comparison	4
Leibowitz et al. Gerontology(2009)	32	32(100%)	0(0%)	Hip fracture	30%	100%	NA	NA	Matched control comparison without AS	9
Calleja et al. AJC(2010)	30	3(10%)	0(0%)	Miscellaneous	73%	NA	NA	Intermediate-low	Matched control comparison without AS	10
Tashiro et al. EHJ(2014)	256	24(10%)	0(0%)	Miscellaneous	NA	NA	NA	High-intermediate	Matched control comparison without AS	2
Keswani et al. Injury(2016)	65	65(100%)	0(0%)	Hip fracture	60%	100%	ASA3,4 100%	NA	Matched control comparison without AS	8
MacIntyre et al. Anaesth Intensive Care(2018)	147	30%	0(0%)	Miscellaneous	NA	NA	ASA 4=18-37%	High: 4-15%	Comparison moderate vs. severe AS (no propensity)	17
Debry et al. (2020)	133	133(100%)	93(70%)	Miscellaneous	90%	100%	ASA 4=15-24%	High:10-15%	IPTW comparison between invasive(BAV) and conservative strategy	-

Abbreviations: AS=aortic stenosis, BAV=balloon aortic valvuloplasty, GA=general anesthesia, NCS=noncardiac surgery, TC=transcarotid, TAx=transaxillary, Tao=transaortic, TF=transfemoral, Tap=transapical, NA not available

[1] according to ESC 2014 recommendations

Central Illustration

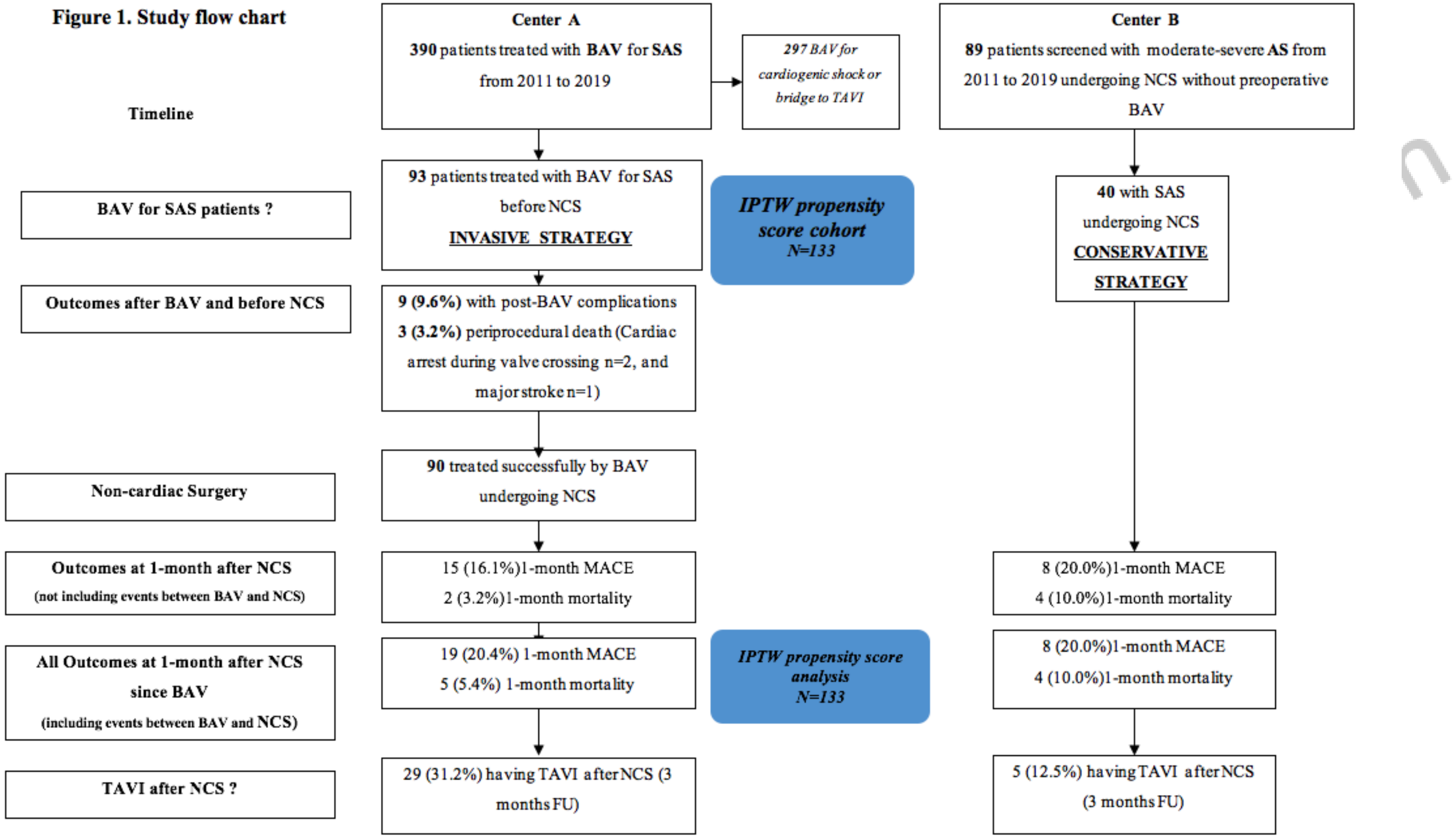
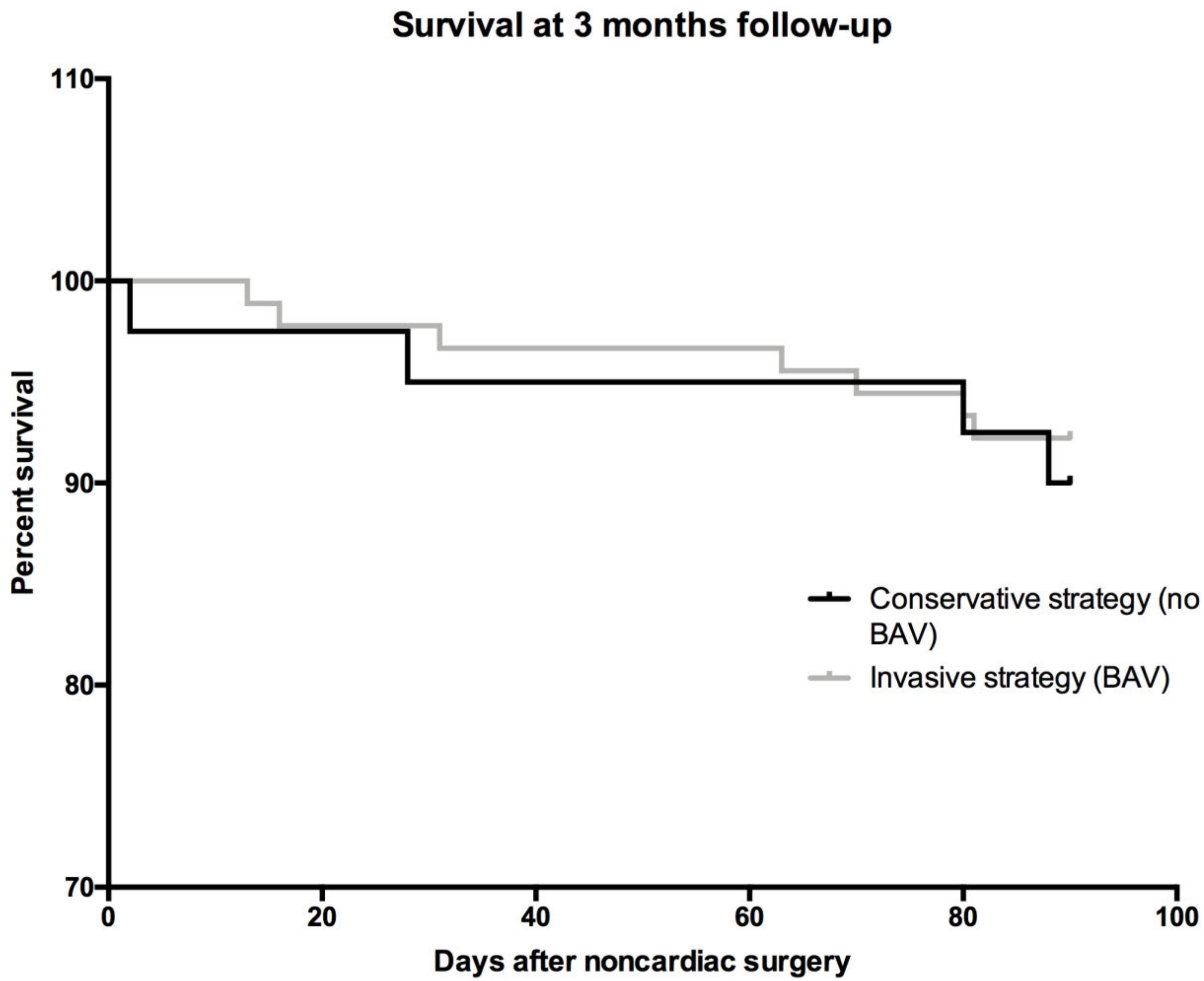


Figure 1. Study flow chart

Abbreviations: SAS= severe aortic stenosis; BAV=Balloon aortic valvuloplasty; FU=follow-up; NCS=noncardiac surgery; SAS=severe aortic stenosis, TTE=transthoracic echocardiography

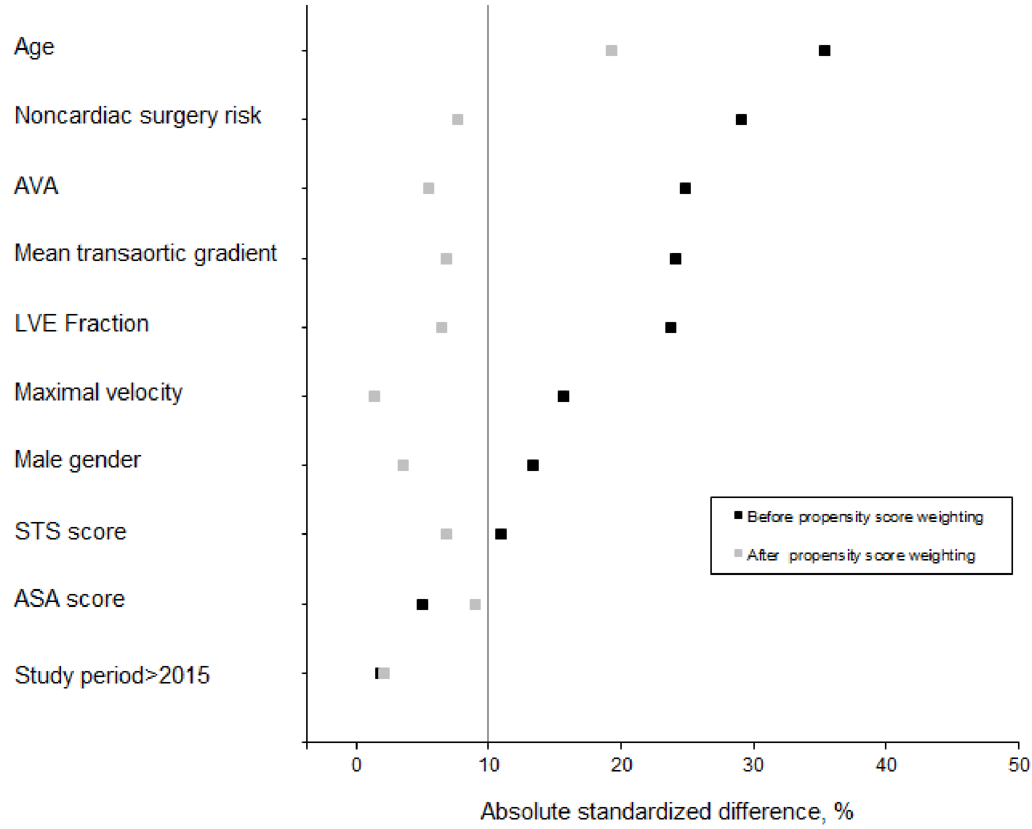
Figure 1



Survival at 3 months follow-up
110
100
90
80
70
Percent survival
0
20
40
60
80
100
Days after noncardiac surgery
Conservative strategy (no BAV)
Invasive strategy (BAV)

Supplementary data

Supplemental Figure 1. Absolute Standardized differences between invasive or conservative strategies before and after IPTW Propensity Score



Abbreviations: ASA= american society of anesthesiologists; AVA=aortic valve area; BAV=balloon aortic valvuloplasty; LVEF= left ventricular fraction; STS= society of thoracic surgeons;