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► **To cite this version:**

Osama Abou-Arab, Saïd Kamel, Stephane Bar, Christophe Beyls, Pierre Huette, et al.. Original Article Changes in Plasma Angiotensin Levels After Transcatheter Aortic Valve Replacement and Surgical Aortic Valve Replacement: A Prospective Cohort Study. *Journal of Cardiothoracic and Vascular Anesthesia*, 2021, 35 (11), pp.3215-3222. 10.1053/j.jvca.2021.03.025 . hal-03565098

HAL Id: hal-03565098

<https://u-picardie.hal.science/hal-03565098>

Submitted on 16 Oct 2023

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Changes in plasma angiotensin levels following TAVR and SAVR: a prospective cohort study

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Conflicts of interest: none

Financial support: institutional

Introduction

Severe aortic stenosis requires valve replacement. For decades, the standard treatment has been surgical aortic valve replacement (SAVR). However, transcatheter aortic valve replacement (TAVR) has become increasingly popular, and is now the primary alternative to SAVR because the peripheral vascular approach is less invasive and associated with better outcomes¹. A number of large studies have validated TAVR with regard to SAVR - particularly in high- and intermediate-risk surgical patients^{2 3}. The current guidelines on aortic valve management recommend (i) TAVR as the first-line treatment for elderly patients or those with a high surgical risk, and (ii) SAVR for patients with a lower surgical risk⁴.

Although TAVR appears to have several advantages over SAVR, various aspects (such as endothelial function) have yet to be fully explored. In particular, the members of the angiotensin (Ang) family have a major role in endothelial cell stabilization.

Ang-1 and 2 are both implied in the regulation of endothelial permeability and angiogenesis⁵. Ang-1 promotes endothelial expression of adhesion proteins and preserves endothelial integrity. Ang-2 increases endothelial permeability and loss in endothelial integrity. Mechanistically, they are both competitive on the binding of Tie2 receptor and endothelial cell but induce a different signal. Cardiac surgery is known to lead to an imbalance between Ang-1 and Ang-2 with an over expression of Ang-2⁶. The consequence is a compromised endothelial permeability with multiple organs failure (acute kidney injury, prolonged mechanical ventilation and mortality)^{7 8 9}. Cardiopulmonary bypass use (CPB) during cardiac surgery is associated with inflammation, endothelial alterations, and microcirculatory perfusion disturbance^{10 11}. The use of CPB may be the main trigger of Ang-2 expression and Ang-1/Ang-2 ratio imbalance. No study has demonstrated that angiotensin dysregulation is associated with the use of CPB. On contrary, TAVR that do not use CPB may be associated with less microcirculatory disturbance and endothelial injury¹². Moreover endothelial improvement following TAVR may be compromised in case of paravalvular leaks¹³.

To date, none study has evaluated the effects of SAVR and TAVR on Ang-1 and Ang-2 homeostasis. We made the hypothesis that Ang homeostasis is less altered in TAVR than in

SAVR. The primary objective of this study was to compare the expression of Ang-1 and Ang-2 in patients suffering of aortic stenosis treated with SAVR (with CPB) and TAVR (without CPB). Because angiopoietins are involved in endothelial homeostasis, we evaluated the association between paravalvular leakage and angiopoietin expression.

Material and methods

Ethics

This prospective, single-centre study was conducted in accordance with the Declaration of Helsinki and the French legislation on clinical research ¹⁴. The procedures were approved by the local independent ethics committee (Mr Arnaud Collin, CPP Nord Ouest II, Amiens, France, December 2016; reference: PI2016_843_0029; ClinicalTrial.gov registration NCT03135496). All participants provided their written, informed consent. The present report was drafted according to the STROBE statement for cohort studies ¹⁵.

Participants

Consecutive patients scheduled for SAVR or TAVR with a bioprosthetic valve at Amiens Picardie Hospital University (Amiens, France) were included. The exclusion criteria were as follows: combined cardiac surgery, surgical replacement of a mechanical prosthesis valve, permanent atrial fibrillation, pre-operative sepsis or endocarditis, and permanent anticoagulation. No hemofiltration was performed in the population study.

Angiopoietin assays

Blood samples were collected at three point times: immediately prior to valve replacement (T0), immediately after valve replacement (T1) and at 8.00 am on the day after valve replacement (T2). After centrifugation of the blood at 3000 g during 5 minutes, plasma was stored at -80°C. The plasma Ang level was measured using an ELISA (R&D Systems, Minneapolis, MN, USA). Levels of Ang-1 and Ang-2 were determined in 5-fold diluted plasma samples using commercially available ELISA kits, according to the manufacturer's instructions. Each sample was detected in duplicate. The assay sensitivity is 30 pg ml⁻¹ for Ang-1 and 10 pg ml⁻¹ for Ang-2. The inter-assay and intra-assay coefficients of variation for Ang-1 and Ang-2 are all <12%. We reported in the results the level of Ang-1, Ang-2. We expressed Ang-2/Ang-

1 ratio to describe the interaction between Ang-1 and Ang-2 as mentioned in previous reports¹⁶
¹⁷.

Procedures for TAVR and SAVR

For TAVR, the patient was sedated and received local anaesthesia. Femoral vascular access was preferred, in line with our standard procedures. The prosthetic valve was the Sapiens XT (Edwards Lifesciences, Irvine, CA, USA). Transfemoral placement was performed using an introducer sheath with an internal calibre of 22 or 24 French, depending on the size of the valve. After accessing the femoral vascular site, balloon aortic valvuloplasty was performed during rapid ventricular pacing. Once the correct position had been checked under fluoroscopic guidance, the expandable valve was deployed during ventricular pacing. At the end of procedure, patients were admitted to the intensive care unit for 24 hours (or longer, if required).

For SAVR procedures, general anaesthesia and cardiopulmonary bypass management was standardised as previously described¹⁸. The Trifecta prosthetic valve (St Jude Medical, Saint Paul, MN, USA) was implanted. Cardiopulmonary bypass was performed using a heart-lung machine (LivaNova PLC, London, United Kingdom) and a blood flow rate of $2.5 \text{ ml min}^{-1} \text{ m}^{-2}$. The mean arterial pressure during CBP was maintained at 65 mmHg using a vasopressor, if required. Anterograde or retrograde cardioplegia was with blood or crystalloid solution, depending on the procedure or the surgeon's habits. During CBP, the goal was to maintain normothermia at 37°C and a haemoglobin value over 8 g.dl^{-1} by using red blood cell transfusion, if necessary. The CBP circuit was anticoagulated with 400 UI kg^{-1} heparin, to achieve a clotting time of 400 milliseconds. None of the included patients underwent intraoperative hemofiltration. After surgery, patients were admitted to the intensive care unit for 48 hours (or longer, if required), in line with our standard procedures. Upon discharge from ICU, the patient was transferred to the cardiology unit of our centre.

Study protocol

Usual cares were delivered to patients included in the study. Blood samples were collected as mentioned before. Echocardiography was performed on day 5 by a cardiologist who was not involved in the clinical trial and was blinded to the Ang assay results. Last follow up ended at one year after the procedure to collect one year mortality.

Data collection, and definition of paravalvular leakage (PVL)

The following data were collected for each patient: age, body mass index, sex, body surface area, aortic valve characteristics (mean valve gradient (mmHg), aortic peak velocity (cm s^{-1}), aortic surface (cm^2) and left ventricular ejection fraction), length of stay in the intensive care unit, and overall length of hospital stay (days). For SAVR, the durations of CPB and aortic clamping (in min) were noted. The following postoperative outcomes were documented: new-onset atrial fibrillation, acute kidney injury according to the KDIGO criteria (diuresis $<0.5 \text{ ml kg}^{-1} \text{ h}^{-1}$ or an increase in plasma creatinine greater than $26.5 \mu\text{mol l}^{-1}$), stroke, vascular complications (acute lower limb ischemia or vascular access bleeding requiring vascular surgery), and atrial ventricular block requiring implantation of a pacemaker.

Paravalvular leakage was defined according to Valve Academic Research Consortium-2 standardized endpoints, based on the circumferential extent of prosthetic valve regurgitation¹⁹: grade 1: $<10\%$ (mild); grade 2: $10\text{-}29\%$ (moderate); grade 3: $>30\%$ (severe:).

Statistical analysis

Changes in Ang-1 and Ang-2 levels after SAVR and TAVR have not been studied previously; hence, the sample size was set arbitrary to 60 consecutive patients (30 in the SAVR group and 30 in the TAVR group). Variables were expressed as the median [interquartile range (IQR)] or the number (percentage), and values were compared using the Mann-Whitney test, the chi-squared test or Fischer's exact test, as appropriate. After a univariate between-groups analysis, we calculated Spearman's coefficient for the correlation between continuous variables and Ang levels in order to identify confounding variables. An analysis of variance for

repeated measures was used to compare Ang levels at the different time points. Bonferroni's *post hoc* correction was used for multiple comparisons. To predict PVL following TAVR, receiver-operating characteristic (ROC) curves were built for Ang-1 and Ang-2 levels and the Ang-2/Ang-1 ratio. The P value for statistical significance was set to $p < 0.05$. All statistical analyses were performed using SPSS® software for Mac (version 22, SPSS Inc., Chicago, IL, USA).

Results

Characteristics of the patients and procedures (Table 1)

Between January and June 2017, 60 consecutive patients were included in the study (30 in the SAVR group and 30 in the TAVR group). The patients' characteristics are summarized in Table 1. All patients met the criteria for severe aortic stenosis. The median [IQR] surgical risk (Euroscore II) was higher in the TAVR group (2.5 [1.9-4.9]) than in the SAVR group (1.4 [1.1-1.8]; $p < 0.0001$).

The prosthesis diameter after the procedure was greater in the TAVR group than in the SAVR group. The two groups did not differ significantly with regard to the median transprosthesis gradient and aortic peak velocity (Table 2). Eighteen patients (60%) in the TAVR group and none of the patients in the SAVR group (0%; $p < 0.0001$) presented PVL.

Changes in Ang levels after SAVR and TAVR (Table 2 and figure 2)

The Ang-1 level was higher at baseline (T1: 3663 [2602-4262] vs 1603 [975-2849] ng ml⁻¹; $p = 0.001$) and after valve replacement (T2: 1611 [981-2409] vs 783 [547-1024] ng ml⁻¹; $p < 0.0001$) in the TAVR group (relative to the SAVR group) but was similar on Day 1 (1082 [652-1589] vs 828 [460-1227] ng ml⁻¹; $p = 0.088$) (Table 2). In both groups, the Ang-1 level significantly decreased after the procedure but the intergroup difference in this decrease was not significant (Figure 1). *Post hoc* comparisons showed that the Ang-1 level decreased significantly at each time point.

The baseline Ang-2 level was higher in the SAVR group than in the TAVR group. After the procedure, the Ang-2 level increased significantly in the SAVR group (T0: 2472 [1502-3622]; T1: 2997 [1759-3839] and T2: 5421 [3557-7087] ng ml⁻¹; $p < 0.0001$) but remained similar to the

baseline value in the TAVR group (T0: 3343 [2661-6272]; T1: 3788 [2574-5016] and T2: 3446 [3029-6313] ng ml⁻¹; p=0.066).

For the SAVR group, *post hoc* comparisons revealed a significant increase at each time point (2472 [1502-3622] at T1 vs 2997 [1759-3839] ng ml⁻¹ at T2; p=0.001; and 2997 [1759-3839] at T2 vs. 5421 [3557-7087] ng ml⁻¹ at T3; p<0.0001).

The value of the **Ang-2/Ang-1** ratio increased after the procedure in the SAVR group (T0: 1.6 [0.8-2.6]; T1: 4.0 [2.6-5.4]; T2: 5.5 [3.9-11.2]; p<0.0001) but not in the TAVR group (T0: 0.8 [0.5-1.4]; T1: 1.8 [0.9-3.8]; T2: 4.3 [2.9-6.6] ng ml⁻¹; p=0.364). *Post hoc* comparisons in the SAVR group revealed a significant increase in the Ang-2/Ang-1 ratio at each time point (1.6 [0.8-2.6] at T1 vs. 4.0 [2.6-5.4] at T2; p=0.008; and 4.0 [2.6-5.4] at T2 vs. 5.5 [3.9-11.2] at T3; p=0.001)

Correlations between the baseline plasma Ang levels, age, and the Euroscore II

The baseline plasma **Ang-1** level was moderately correlated with age (Rho=0.322; p=0.012) but not correlated with the Euroscore II (Rho=0.237; p=0.068). The baseline plasma **Ang-2** level was not correlated with age (Rho=0.095; p=0.471) or the Euroscore II (Rho=0.109; p=0.408).

Change over time in the plasma Ang level as a function of the presence or absence of PVL after TAVR (Table 3 and figure 2)

Following the TAVR procedure, the plasma **Ang-1** level decreased in both the PVL subgroup (T0: 3663 [3266-3981], T1: 1793 [836-2409] and T2: 852 [651-1386]; p<0.0001) and the non-PVL subgroup (T0: 3755 [2322-4948], T1: 1347 [1181-2085] and T2: 1368 [997-1734] ng ml⁻¹; p=0.007) (Table 3). The levels were similar at each observation time point.

Following the TAVR procedure, the plasma **Ang-2** level increased in the PVL subgroup (T0: 2660 [1545-3211], T1: 4026 [2651-4712] and T2: 5366 [3644-8403] ng ml⁻¹; p<0.0001) but remained close to the baseline value in the non-PVL group (T0: 3719 [2397-4592], T1: 4025

[2651-4712] and T2: 3369 [2675-4491]; $p=0.073$). *Post hoc* comparisons in the PVL subgroup revealed a continuous increase after the procedure (3719 [2397-4592] at T1 vs. 4025 [2651-4712] ng ml⁻¹ at T2; $p=0.010$; and 4025 [2651-4712] at T2 vs. 3369 [2675-4491] at T3; $p<0.0001$).

Ability of plasma Ang levels to detect PVL following TAVR (Figure 3)

On day 1 (T2), Ang-2 detected the post-TAVR occurrence of PVL with an area under the ROC curve (AUC) [95% confidence interval (CI)] of 0.801 [0.634-0.987] ($p=0.005$). The cut-off was 4914 ng ml⁻¹, with a sensitivity of 78% and a specificity of 83%. At the same time point, the Ang-2/Ang-1 ratio detected PVL with an AUC of 0.815 [0.661-0.968] ($p=0.004$). The cut-off was 3.3, with a sensitivity of 83% and a specificity of 67%. The Ang-1 level on day 1 did not detect PVL (AUC [95% CI]: 0.681 [0.483-0.878]; $p=0.099$).

Discussion

Our study demonstrated an increase of Ang-2 and Ang-2/Ang-1 ratio following SAVR. We observed an increase in the Ang-2/Ang-1 ratio reflecting both a decrease in Ang-1 and an increase in Ang-2. Because TAVR do not use CPB, we did not demonstrate an increase of Ang-2 values whereas Ang-1 value decreased. However, Ang-2 significantly increased in case of PVL following TAVR. That latter observation could find a clinical application of Ang-2 as a biological sensor of PVL.

Based on the literature, cardiac surgery with CPB leads to an endothelial injury with specific change in circulating Ang levels. We confirmed an increase in the Ang2/Ang1 ratio reflecting both a decrease in Ang-1 and an increase in Ang-2⁸. Because TAVR do not use CPB, we did not observe similar Ang changes in the TAVR group.

Angiopoietins are considered to be biomarkers of microcirculation. Recent reports have showed that Ang-2 is involved in impairments of the microcirculation. Dekker *et al.* confirmed the association between a high Ang-2 level and excessively high endothelial permeability after cardiac surgery¹⁶. By studying plasma samples taken from patients after surgery, the researchers highlighted the role of Ang-2 in endothelial permeability on kidney and lung capillaries *in vitro*. Koning *et al.* also compared Ang levels in on-pump and off-pump cardiac surgery without any protective effect of on pump surgery²⁰. In our study, all patients went for on pump cardiac surgery. The increase in Ang-2 is associated with adverse clinical outcomes. Following cardiac surgery, the Ang-2 level is correlated with high-volume fluid resuscitation, respiratory failure, and acute kidney injury^{7 21}. In a lower extent TAVR can induce an increase in Ang-2. To date, only one referenced study has also reported an increase in Ang-2²². However, our comparison confirms the major role of CPB use in Ang-2 increase.

The role of Ang-2 is to promote angiogenesis. However, there are no published data on Ang levels and PVL. To explain our findings, we hypothesize that Ang-2 expression is induced by wall shear stress, i.e. the force per unit area acting on the endothelial wall in the direction of flow (expressed in dynes.cm⁻²)²³. Wall shear stress is known to alter gene expression and

endothelial protein expression^{24 25}. Angiopoietin 2 is normally stored in endothelial inclusions – the so-called Weibel-Palade bodies. When exposed to high wall shear stress, the Weibel-Palade bodies release Ang-2²⁶. Vincentelli *et al.* clearly demonstrated that high wall shear stress occurs in severe aortic stenosis²⁷. Von Willebrand factor (stored in Weibel-Palade inclusions) was monitored in cases of moderate and severe aortic stenosis, and it was associated with clinical haemostatic abnormalities related to the loss of von Willebrand factor multimers under high shear stress conditions (i.e. severe aortic stenosis). In a cohort of patients undergoing TAVR, the level of von Willebrand factor was used to monitor PVL¹³. The researchers showed that a low level of von Willebrand multimers factor was predictive of PVL. In patients with mechanical circulatory support, pulsatile flow induces less endothelial damage than continuous flow does²⁸. In the present study, PVL might induce high shear stress (with Ang-2 release followed by endothelial cell quiescence)²⁹. Furthermore, we observed a high transprosthetic gradient pressure in patients with PVL (Table 3) but it does not provide information on the level of wall shear stress. We did not perform Ang assays after day 1, and so could not assess a longer time course.

Our study had some limitations. **Unsurprisingly, the TAVR and SAVR groups differed with regard to the baseline demographic characteristics: the patients in the TAVR group were older and had a higher surgical risk. Most importantly, the baseline plasma Ang-1 level was higher in the TAVR group.** We then confirmed the presence of a moderate correlation between the plasma Ang-1 level and age but not between Ang-1 and the Euroscore II. **Thus, we cannot totally exclude effects of other factors than CPB use for the observed difference in Ang values.** The two groups had similar severities of aortic valvular disease and similar comorbidity burdens. Another limitation relates to differences in prosthesis implantation in the two groups. We standardized the devices, with a Trifecta valve for SAVR and a Sapiens XT for TAVR. However, prosthesis diameter size is different in both group and may induce different turbulent blood flow. Furthermore, we hypothesized that flow characteristics had a role in endothelial Ang expression but did not have any quantitative data on the flow. Advanced techniques (e.g.

four-dimensional flow MRI) can quantify flow displacement, wall shear stress, turbulent kinetic energy, and pressure, and would be valuable tools in further investigations ³⁰.

Although it is known that PVL increases long term morbidity, the echocardiographic diagnosis and grading of PVL remain challenging. In a recent study, 30-day and 1-year mortality were higher in patients with PVL - probably due to the persistence of myocardial remodelling; the more severe the PVL, the higher the morbidity rate ³¹. Only 2 patients in our cohort had grade II PVL, so we could not assess the possible association between the plasma Ang levels and the severity of PVL. Nevertheless, one can hypothesize that Ang-2 levels increase with the severity grade.

Quantification of PVL is an important goal ³². The mechanism underlying PVL is unknown, although MRI studies have shown that left ventricle reverse modelling does not always occur. There are many limitations to techniques for quantifying PVL; although echocardiography it is the mainstay diagnostic technique, it usually underestimates the severity of PVL. The current international guidelines specify that PVL quantification cannot be based on a single parameter ^{19 33}. In further perspective, we intend to validate Ang as a biomarker of PVL in a larger (and PVL-only) patient population. The present study was not designed to address that question.

Conclusion

Because of CPB use, SAVR induces alterations of Ang homeostasis. On contrary, TAVR seems to lesser affect Ang homeostasis. However, the presence of paravalvular leakage following TAVR can induce alterations of Ang homeostasis close to those observed with SAVR. These preliminary data require further explorations, particularly on the application of Ang-2 as a biological sensor of paravalvular leakage.

Authors' contributions

Concept and design: OAA, SK, EL and PGG.

Data acquisition: OAA, SB, PH.

Angiotensin assays: CG, CA.

Echocardiography procedure: CB and CT.

Statistical analysis: OAA, EL and PGG.

Manuscript draft: OAA and PGG.

Manuscript revision: OAA, SK, EL and PGG.

All the authors approved the last version of the manuscript.

Acknowledgements We thank all the personal staff of MP3CV laboratory for their warming welcome.

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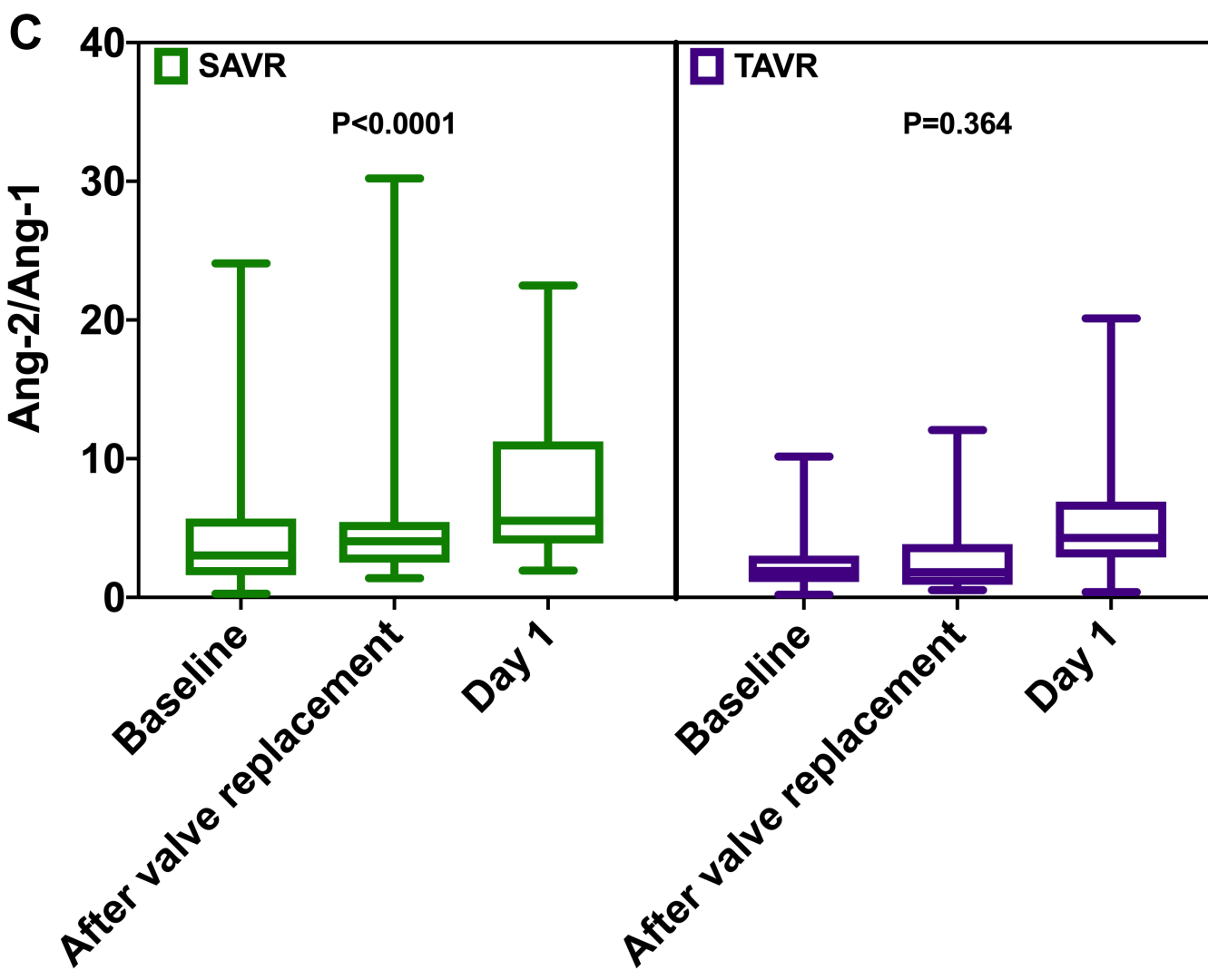
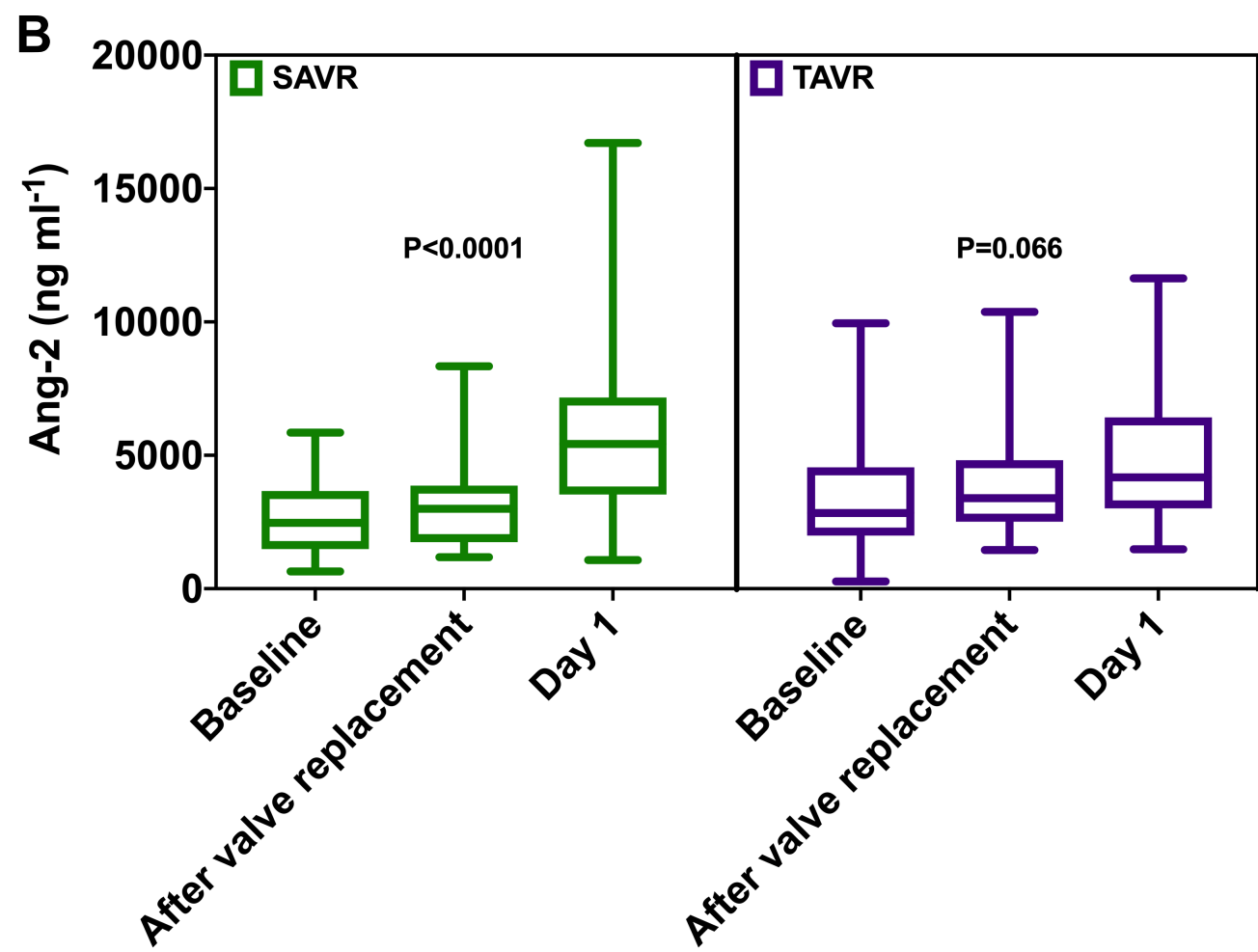
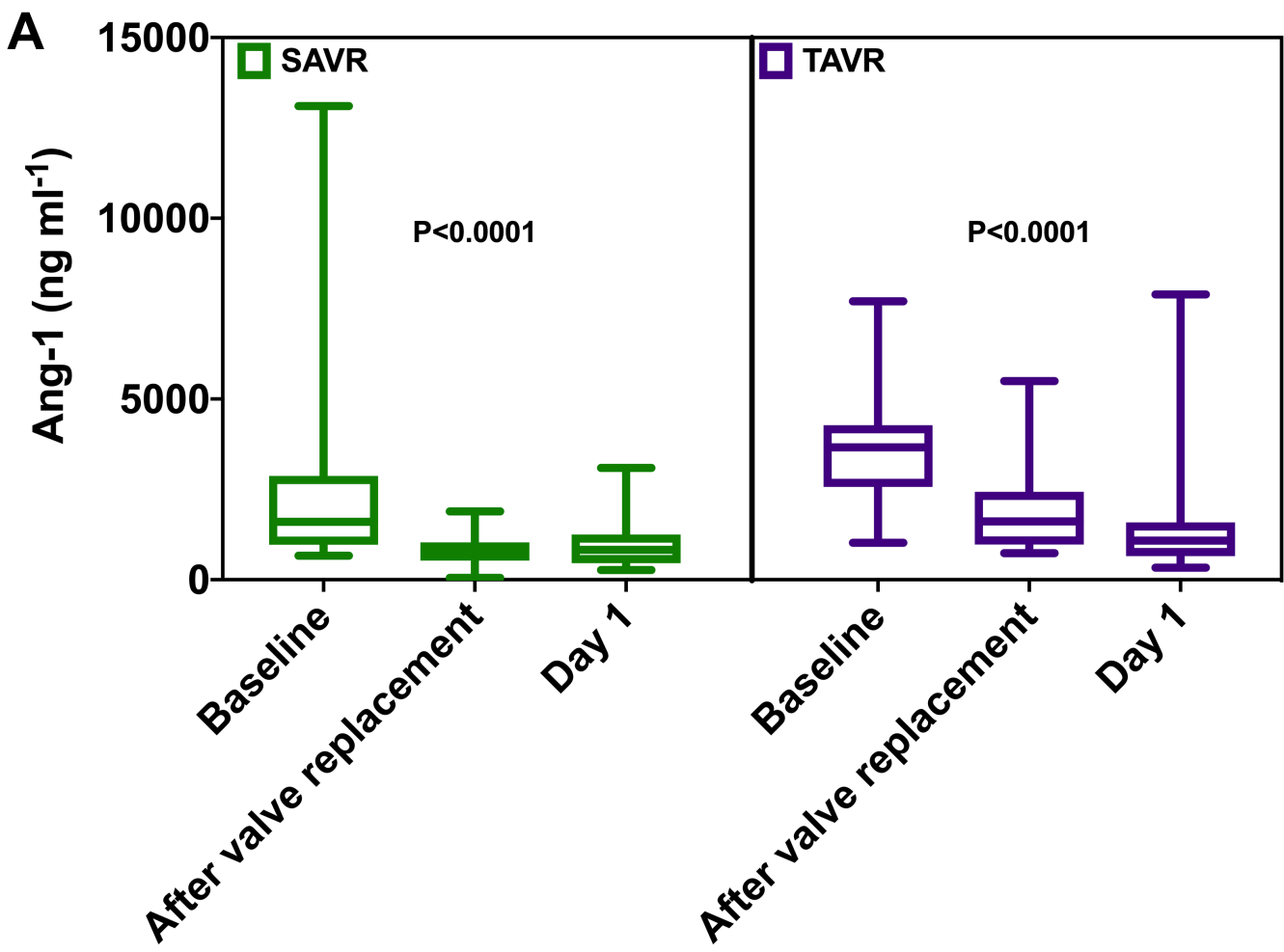
33. Zoghbi WA, Chambers JB, Dumesnil JG, et al: Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report From the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 22:975–1014; quiz 1082–4, 2009

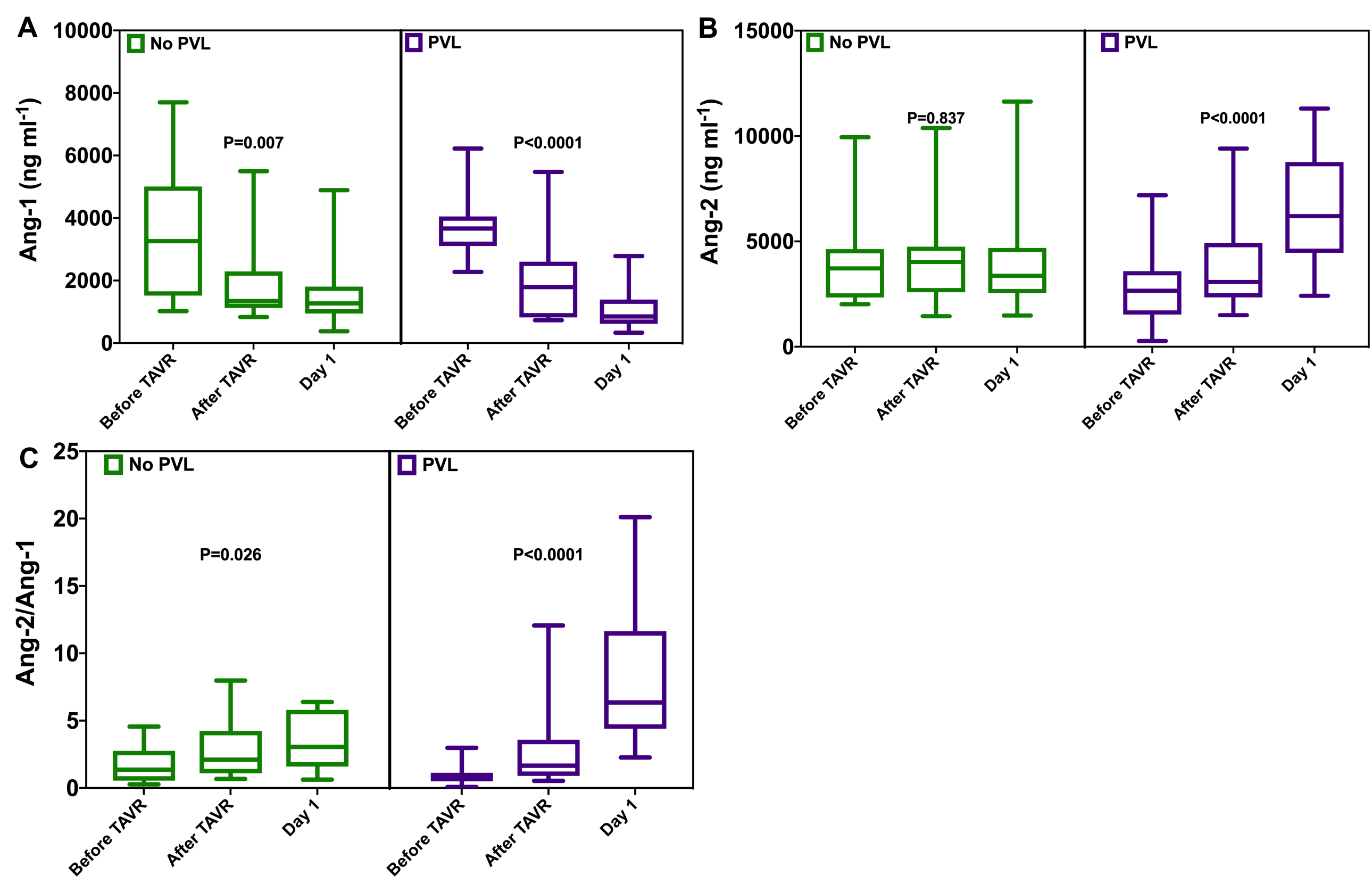
Legends to figure

Figure 1. Plasma Ang-1 (A) and Ang-2 (B) levels and the Ang-2/Ang-1 ratio (C) for SAVR vs. TAVR immediately at baseline, after valve replacement (T1), and on Day 1. Within group comparisons were performed using an ANOVA test for repeated measures.

Figure 2. Time course of circulating concentrations of Ang-1 (A), Ang-2 (B) and the ratio Ang-2/Ang-1 before and following TAVR according to the presence of paravalvular leakage (PVL). Within group comparisons were performed using an ANOVA test for repeated measures.

Figure 3. Receiver operating characteristic curve for the plasma Ang-1 level, the plasma Ang-2 level and the Ang-2/Ang-1 ratio on the day 1 after TAVR (T2) for the prediction of PVL following valve replacement. All three parameters were significantly predictive of the occurrence of PVL.





ROC Curve

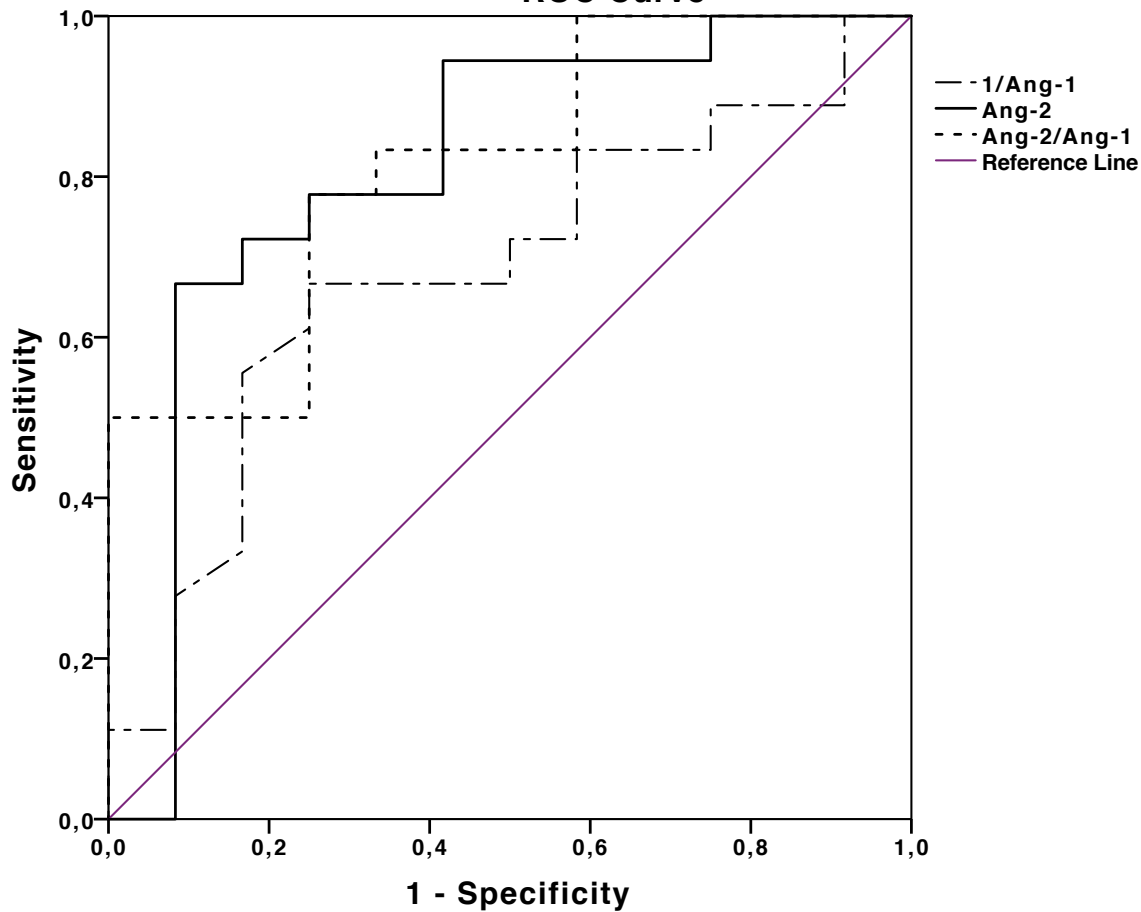


Table 1 Patient characteristics. BMI: body mass index; LVEF: left ventricular ejection fraction. Data were presented as number (percentage) or as median [interquartile range]

Variable	SAVR (n=30)	TAVR (n=30)	p value
Age (years)	76 [68-8]	83 [76-89]	<0.0001
Male sex (n; %)	18 (60)	16 (53)	0.602
BMI (kg m ⁻²)	28.4 [25.7-29.4]	29.3 [26.6-31.2]	0.589
Body surface area (m ²)	2.0 [1.9-2.2]	2.0 [1.8-2.2]	0.964
<i>Medical history (n; %)</i>			
Diabetes	10 (33)	16 (53)	0.192
Hypertension	18 (60)	25 (80)	0.158
Dyslipidaemia	14 (47)	17 (57)	0.606
Smoking	7 (23)	7 (23)	1.000
Coronary disease	13 (43)	13 (43)	1.000
Vascular disease	2 (7)	8 (27)	0.08
<i>Echocardiography data</i>			
Mean aortic gradient (mmHg)	52 [43-56]	52 [40-65]	0.203
Valve aortic surface (cm ²)	0.75 [0.65-0.85]	0.74 [0.60-0.90]	0.617
Aortic peak velocity (m s ⁻¹)	4.2 [3.9-4.4]	4.2 [3.9-4.4]	0.947
LVEF (%)	63 [60-68]	60 [60-65]	0.511
<i>Plasma concentrations</i>			
Creatinine (μmol l ⁻¹)	82 [76-94]	85 [77-104]	0.594
Haemoglobin (g dl ⁻¹)	13.1 [12.0-14.5]	12.1 [11.4-12.9]	0.011
Total protein (g l ⁻¹)	75 [71-78]	75 [71-78]	0.926
EuroSCORE II	1.4 [1.1-1.8]	2.5 [1.9-4.9]	<0.0001

Table 2 Post-operative course and angiotensin levels for SAVR vs. TAVR.

CPB: cardiopulmonary bypass; **AKI:** acute kidney injury; **Ang-1** and **2:** angiotensins 1 and 2, ICU: intensive care unit. ^a: P value <0.005 for T0 vs. T1, ^b: P value<0.005 for T0 vs. T2. **Data** were presented as number (percentage) or as median [interquartile range].

Variables	SAVR (n=30)	TAVR (n=30)	P value
Duration of CPB (min)	84 [63-106]	NA	NA
Duration of aortic clamping (min)	65 [51-81]	NA	NA
Echocardiography data			
Aortic peak velocity (m s ⁻¹)	2.2 [1.9-2.4]	2.4 [2.1-2.6]	0.109
Mean valvular gradient (mmHg)	10 [8-14]	12 [10-15]	0.089
Prosthesis diameter (mm)	23 [21-25]	29 [26-29]	< 0.0001
Outcomes (n; %)			
New-onset atrial fibrillation	7 (23)	1 (3)	0.052
Stroke	0	4 (13)	0.112
Auricular ventricular block	2 (7)	3 (10)	1.000
AKI	2 (7)	1 (3)	1.000
Vascular complications	0 (0)	2 (7)	0.492
Paravalvular leakage (n, %)	0 (0)	18 (60)	0.0001
Length of ICU stay (days)	2 [2-2]	1 [1-1]	<0.0001
Length of hospital stay (days)	10 [9-12]	7 [6-8]	<0.0001
1-year mortality (n; %)	1 (3)	7 (23)	0.052
Plasma Ang-1 level (ng ml⁻¹)			
Baseline (T0)	1603 [975-2849]	3663 [2602-4262]	0.001
After valve replacement (T1)	783 [547-1024] ^a	1611 [981-2409] ^a	<0.0001
Day 1 (T2)	828 [460-1227] ^b	1082 [652-1589] ^b	0.088
Plasma Ang-2 level (ng ml⁻¹)			
Baseline (T0)	2472 [1502-3622]	3343 [2661-6272]	0.167
After valve replacement (T1)	2997 [1759-3839] ^a	3788 [2574-5016]	0.162
Day 1 (T2)	5421 [3557-7087] ^b	3446 [3029-6313]	0.359
Plasma Ang-2/Ang-1			
Baseline (T0)	1.6 [0.8-2.6]	0.8 [0.5-1.4]	0.052
After valve replacement (T1)	4.0 [2.6-5.4] ^a	1.8 [0.9-3.8]	0.001
Day 1 (T2)	5.5 [3.9-11.2] ^b	4.3 [2.9-6.6]	0.044

Table 3 Plasma angiotensin (Ang) concentrations following TAVR, according to the presence or absence of paravalvular leakage (PVL). ^a: P value<0.05 for T0 vs. T1, ^b: P value <0.05 for T0 vs. T2. **Data were presented as number (percentage) or as median [interquartile range].**

Variable	No PVL (n=12)	PVL (n=18)	P value
<i>Echocardiography</i>			
Mean valvular gradient (mmHg)	10 [10-12]	13 [11-15]	0.007
Aortic peak velocity (m s ⁻¹)	2.1 [1.9-2.3]	2.5 [2.3-2.6]	0.043
Plasma angiotensin 1 (ng ml⁻¹)			
Baseline (T0)	3755 [2322-4948]	3663 [3266-3981]	0.662
After valve replacement (T1)	1347 [1181-2085]	1793 [836-2409]	0.851
Day 1 (T2)	1368 [997-1734]	852 [651-1386]	0.104
Plasma angiotensin 2 (ng ml⁻¹)			
Baseline (T0)	3719 [2397-4592]	2660 [1545-3211]	0.124
After valve replacement (T1)	4025 [2651-4712] ^a	4026 [2651-4712]	0.573
Day 1 (T2)	3369 [2675-4491] ^b	5366 [3644-8403]	0.004
Plasma Ang-2/Ang-1			
Baseline (T0)	1.4 [0.6-2.4]	0.7 [0.5-1.1]	0.065
After valve replacement (T1)	2.1 [1.2-4.1]	2.2 [1.9-3.5]	0.545
Day 1 (T2)	3.0 [1.6-5.4] ^b	6.0 [3.4-10.1]	0.003