“One-Stop Shop”: safety of combining transcatheter aortic valve replacement and left atrial appendage occlusion

Attinger-Toller, Adrian; Maisano, Francesco; Senn, Oliver; Taramasso, Maurizio; Shakir, Samera; Possner, Mathias; Gloekler, Steffen; Windecker, Stephan; Stortecky, Stefan; Lüscher, Thomas F; Meier, Bernhard; Nietlispach, Fabian

Abstract: OBJECTIVES: The aim of this study was to investigate the safety and efficacy of combining transcatheter valve replacement (TAVR) and left atrial appendage occlusion (LAAO) versus TAVR alone. BACKGROUND: Patients with severe aortic stenosis and atrial fibrillation undergoing TAVR are at increased risk for stroke and bleeding complications. METHODS: A cohort of 52 patients undergoing concomitant TAVR and LAAO were compared with 52 patients undergoing isolated TAVR. A primary safety endpoint at 30 days, a clinical efficacy endpoint from day 30 to last follow-up, and an LAAO efficacy endpoint from the first post-interventional day to the last follow-up were chosen. RESULTS: The mean age of the study population was 85 ± 5 years. The mean CHA2DS2-VASc score and HAS-BLED score were 3.9 ± 1.1 and 2.6 ± 0.9, respectively. The mean Society of Thoracic Surgeons score was 7.8 ± 5.5. The median follow-up duration of the study population was 9.4 months (range 0 to 48 months). The primary safety endpoint occurred in 10 patients in the concomitant group and in 7 patients in the isolated TAVR group (19% vs. 14%; 95% confidence interval: 0.59 to 4.06). The clinical and LAAO efficacy endpoints were achieved in 81 (79%) (75% vs. 82%; 95% confidence interval: 0.49 to 2.92) and 75 (73%) patients (69% vs. 76%; 95% confidence interval: 0.54 to 2.51), respectively. CONCLUSIONS: This pilot study shows that concomitant TAVR and LAAO is feasible and seems to be safe among patients with severe aortic stenosis and atrial fibrillation. Larger trials and longer follow-up are needed to confirm the safety and efficacy of such an approach.

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‘One-stop-shop’: safety of combining transcatheter aortic valve replacement and left atrial appendage occlusion

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Abstract

Objectives: We investigated safety and efficacy of combining transcatheter valve replacement (TAVR) and left atrial appendage occlusion (LAAO) versus TAVR alone.

Background: Patients with severe aortic stenosis and atrial fibrillation undergoing TAVR are at increased risk for stroke and bleeding complications.

Methods: A cohort of 52 patients undergoing concomitant TAVR and LAAO were compared to 52 patients undergoing isolated TAVR. A primary safety endpoint at 30 days, a clinical efficacy endpoint from day 30 to last follow-up and a LAAO efficacy endpoint from the first postinterventional day to the last follow-up were chosen.

Results: Mean age of the study population was 85 ± 5 years. Mean CHA2DS2-Vasc-score and HASBLED score were 3.9 ± 1.1 and 2.6 ± 0.9, respectively. Mean STS score was 7.8 ± 5.5. Median follow-up of the study population was 9.4 (range 0-48) months. The primary safety endpoint occurred in 10 patients in the concomitant and in 7 patients in the isolated TAVR group (19% vs. 14%, 95% confidence interval, [CI] 0.59 to 4.06). The clinical and LAAO efficacy endpoints were achieved in 81 (79%; 75% vs. 82%, 95% confidence interval, [CI] 0.49 to 2.92) and 75 patients (73%; 69% vs. 76%, 95% confidence interval, [CI] 0.54 to 2.51), respectively.

Conclusion: This pilot study shows that concomitant TAVR and LAAO is feasible and seems to be safe among patients with severe aortic stenosis and atrial fibrillation. Larger trials and longer follow-up is needed to confirm safety and efficacy of such an approach.

Key words: atrial appendage, atrial fibrillation, stroke prevention, TAVR, LAAO
**Condensed abstract**

Patients with severe aortic stenosis and atrial fibrillation undergoing transcatheter valve replacement (TAVR) are at increased risk for stroke and bleeding complications.

We investigated clinical outcome (safety and efficacy) of concomitant TAVR and left atrial appendage occlusion (LAAO) in 104 patients (52 undergoing TAVR/LAAO, 52 undergoing isolated TAVR).

This pilot study shows that concomitant TAVR and LAAO is feasible and seems to be safe. However larger trials and longer follow-up is needed to confirm these results.

**Abbreviation list**

ACP = AMPLATZER Cardiac Plug  
AF = atrial fibrillation  
LAA = left atrial appendage  
LAAO = left atrial appendage occlusion  
OAC = oral anticoagulation  
TAVR = transcatheter aortic valve replacement  
TEE = transesophageal echocardiography  
TIA = transient ischemic attack  
TTE = transthoracic echocardiography  
VARC = Valve Academic Research Consortium
Introduction

Over the past decade, transcatheter aortic valve replacement (TAVR) has emerged as preferred treatment modality for patients with severe aortic stenosis at high surgical risk and is now expanding to lower risk patients(1-3). Atrial fibrillation (AF) occurs in more than 10% in octogenarians and is the most common arrhythmia in the TAVR population. It is associated with substantial morbidity and mortality, particularly due to early and late embolic stroke(4-7), bleeding complications(8) and impaired overall outcome(7,8).

To prevent thromboembolic strokes in patients with AF, oral anticoagulation (OAC) is the standard treatment, for patients with a CHA2DS2-VASc score of ≥1(9). However, OAC carries a substantial risk of major bleeding complications(10). The combination of OAC with antiplatelet agents after TAVR potentiates the risk for major bleeding complications(11). In AF patients undergoing TAVR, bleeding complications were reported to be as high as 50% and in those who suffer a bleeding complication during the first year, 1-year mortality is doubled(8). Therefore, the increased risk for serious bleeding precludes the use of OAC in a significant proportion (30% to 50%) of eligible patients due to relative or absolute contraindications or due to physician or patient preference(12).

Balancing the risk of embolic and bleeding events in this high-risk population represents a major clinical challenge. Left atrial appendage occlusion (LAAO) offers a non-pharmacologic stroke protection, obviating the need for OAC. It may therefore be an attractive treatment for the AF TAVR population(13,14) (Figure 1).

We investigated safety and short-term efficacy of combined procedures (TAVR and LAAO) versus TAVR alone in a contemporary TAVR population suffering from AF.
Methods

Patients
This is an observational study on consecutive patients undergoing TAVR at the university hospitals of Zurich (463 patients) and Bern (707 patients) from February 2011 to June 2015. Decision on whether to perform concomitant LAAO or not was random, based on patients’ wish, operator and treating Cardiologists’ preference. All patients suffered from severe aortic stenosis (mean transaortic systolic pressure gradient of $\geq 40\text{mmHg}$, or an aortic valve area of $<1.0\text{cm}^2$ or $<0.6\text{cm}^2/\text{m}^2$) and were deemed appropriate candidates for TAVR as assessed by the local Heart Team. All patients had AF with a CHA2DS2-Vasc score of $\geq 1$. Patients were dichotomized into a “concomitant group” (TAVR and LAAO during the same procedure) and an “isolated TAVR group” (TAVR alone and medical therapy for stroke prevention). All patients gave written informed consent for the procedure and data collection. Patients were followed within the nationwide Swiss TAVR registry, which was approved by the local ethics committees.

Device
The AMPLATZER Cardiac Plug (ACP) (St. Jude Medical, Plymouth, MN, USA) is made of nitinol mesh and filled by polyester to enhance endothelialization and to prevent blood flow through the device. The ACP consists of a lobe with tiny anchoring hooks and a sealing disc. Lobe and disk are connected by a thin, stretchable waist. The ACP is available in lobe sizes from 16 to 30mm, requiring a 9 to 13 French TorqVue delivery sheath (St. Jude Medical, Plymouth, MN, USA). The second generation device ACP (Amulet) has a recessed screw on the disc to prevent clot
formation. Additionally, the lobe comes in larger size ranges (16 - 34mm) and requires a 12 or 14 French sheath. The larger sizes also feature more anchoring hooks.

Procedure

TAVR was performed using either a transfemoral procedure or in case of limiting peripheral arterial disease, a transapical, subclavian, or direct aortic access. Balloon-expandable as well as self-expandable valve systems were used. Prosthesis size was selected on the basis of annulus measurements by multislice computed tomography or transesophageal echocardiography (TEE).

In patients with concomitant interventions, LAAO was performed during the same sitting, usually after TAVR. Preprocedural imaging of the left atrial appendage (LAA) comprised a TEE in all patients. Procedural guidance, for both TAVR and LAAO was strictly based on fluoroscopy, to avoid general anesthesia (except in cases of a transapical or transaortic access). Safety of fluoroscopy-guided LAAO has been previously described by our group(15). The left atrium was accessed by transseptal puncture or through a patent foramen ovale (PFO) or atrial septal defect (ASD)(16). Using a Backup Meier wire (Boston Scientific, Natick, MA, USA) the transseptal sheath was exchanged for the 13 French Amplatzer 45°-45°-TorqVue sheath (St. Jude Medical, Plymouth, MN, USA) for delivery of the ACP. Device sizing relied on contrast injections to the LAA in different angulations. Given the known outer diameter of the delivery sheath (e.g., 5.5mm) an adequately sized ACP was chosen, aiming for at least 20% oversizing. After device deployment, a stable device position was confirmed by a tug test and contrast injections. Finally the device was released. A transthoracic echocardiogram (TTE) was performed before hospital discharge to confirm a stable position of the ACP.
In the concomitant TAVI and LAAO group, oral anticoagulation was discontinued immediately after LAAO, and patients received dual antiplatelet therapy with long-term acetylsalicylic acid (100mg) and clopidogrel (75mg) for 1–6 months. Patients undergoing isolated TAVR were continued on oral anticoagulation in combination with dual or single antiplatelet therapy.

**Follow-up**

Patients with combined interventions underwent a TEE after 3-6 months to confirm a proper sealing of the LAA and to identify residual leaks or thrombi on the device. All patients had TTE performed at 1 and 12 months after the intervention to confirm proper functioning of the aortic valve prosthesis. Clinical follow-up was performed at the time of TEE and TTE visits. In case of an event, hospital charts were reviewed, or the cardiologist or primary care physician was contacted. An independent clinical event committee adjudicated all adverse events according to current criteria.

**Endpoints**

Three primary endpoints were adapted from Valve Academic Research Consortium (VARC)-2 standardized endpoint definitions(17) by including LAAO-specific events.

The primary safety endpoint at 30-days was a composite of all-cause mortality, stroke (disabling and non-disabling) and TIA, bleeding (life-threatening), acute kidney injury stage 2-3 (according to the AKIN system), major vascular complications, clinically significant pericardial effusion requiring pericardiocentesis or resulting in cardiac tamponade, device embolization, and valve failure.
The efficacy endpoints were divided into a ‘clinical efficacy endpoint’ and a ‘LAAO efficacy endpoint’. The clinical efficacy endpoint included events from day 30 to last follow-up and was defined as freedom from all-cause mortality, all-cause stroke (disabling and non-disabling), and bleeding (life threatening and major) events. The LAAO efficacy endpoint was defined as freedom from all-cause mortality, all-cause stroke (disabling and non-disabling) and TIA, and bleeding (life-threatening and major) occurring from the first postinterventional day to the last follow-up.

**Statistical analysis**

Data are presented as mean (±SD) or frequency as appropriate. Baseline patient characteristics between groups (e.g., concomitant TAVR/LAAO vs. isolated TAVR) were compared by unpaired parametric and non-parametric tests as appropriate. For the composite endpoints, time-to-event after intervention was estimated by the Kaplan-Meier method. 95%-confidence intervals estimated by bivariate cox regression are presented for the composite and single endpoints between groups. Multivariable Cox regression analysis controlling for age at intervention, sex, and CHA2DS2-Vasc, HAS-BLED, and STS scores was used to further assess the effect of concomitant LAAO on the composite endpoints. A two-sided p-value ≤0.05 was considered statistically significant for the comparison of the baseline patient characteristics between groups. We did not attempt inferential hypothesis testing for the composite and single endpoint comparisons, thus 95%-confidence intervals rather than p-values are presented. Statistical analyses were performed using STATA version 13.1 (Stata Corp, TX, USA).
Results

Patient Characteristics

The study population comprised 104 patients (59 males; mean age 85 ± 5 years). Mean CHA₂DS₂-Vasc score was 3.9 ± 1.1, mean HASBLED score was 2.6 ± 0.9, and mean STS score was 7.8 ± 5.5. A history of arterial hypertension was present in 81 (78%), diabetes mellitus in 33 (32%), prior ischemic stroke or TIA in 14 (14%), and coronary heart disease in 53 patients (51%). Five patients (5%) were on dialysis. No significant differences in baseline characteristics were present between the two groups (Table 1).

Procedural information

Procedures were performed at the University Hospital Zurich (80 patients, 77%) and at Bern University Hospital (24 patients, 23%) between October 2009 and March 2015. Of the 104 patients, 52 underwent TAVR and LAAO in the same procedure (concomitant group), whereas 52 patients underwent TAVR alone (isolated TAVR group). For TAVR, a transfemoral approach was chosen in 92% (85% in the concomitant group, 90% in the isolated TAVR group), a transapical access in 6% (12% in the concomitant group, 8% in the isolated TAVR group), a direct aortic access in 1% (0% in the concomitant group, 2% in the isolated TAVR group), and a left subclavian access in 1% (2% in the concomitant group, 0% in the isolated TAVR group). The CoreValve prosthesis (Medtronic, Minneapolis, MN) was implanted in 21 (40%) patients, an Edwards SAPIEN XT in 19 (36%) patients, an Edwards SAPIEN 3 (Edwards Lifesciences, Irvine, CA) in 7 (14%) patients, a Lotus valve (Boston Scientific, Marlborough, MA) in 2 (4%) patients, and an Acurate TA valve (Symetis SA, Ecublens, Switzerland), a St. Jude Portico valve (St. Jude Medical, Inc,
St Paul, MN), and a Direct Flow Medical valve (Direct Flow Medical Inc., Santa Rosa, CA) each in 1 (2%) patient. No differences in valve distribution between the ‘concomitant group’ and the ‘single TAVR group’ (p=0.439) was observed. Besides TAVR and LAAO, 18 patients (17%) had additional interventions: 15 patients (29%) in the concomitant group (percutaneous coronary intervention in 8 patients (15%), iliofemoral stenting in 3 patients (6%), PFO or ASD closure in 3 patients (6%), and MitraClip in 1 patient (2%)) and three patients (6%) in the isolated TAVR group (percutaneous coronary intervention in 2 patients (4%) and PFO closure in 1 patient (2%)).

**Procedural and safety outcome at 30 days**

The primary safety endpoint occurred in 10 patients in the concomitant group and in 7 patients in the isolated TAVR group (19% vs. 14%, 95% confidence interval, [CI] 0.59 to 4.06, Table 2, Figure 2). Multivariate analysis did not reveal any evidence for a difference between groups (95% confidence interval, [CI] 0.59 to 4.29).

There was no procedural neurologic complication. Three patients died during the first 30 days after the intervention, 1 in the concomitant and 2 in the isolated TAVR group. Of those, 2 were cardiovascular (1 in each group) and 1 was a non-cardiovascular death. The non-cardiovascular death occurred 3 weeks after TAVR and was due to urosepsis complicated by multi-organ failure. One cardiovascular death (isolated TAVR group) occurred directly after successful TAVR due to global ischemia with sustained ventricular fibrillation resistent to defibrillation. The other cardiovascular death (concomitant group) happened two weeks after the procedure and was due to worsening heart failure. None of the deaths was associated with LAA occlusion.

During the first month of follow-up, 1 disabling stroke of ischemic origin (persistent
hemiparesis, dysarthria, and dysphagia presumably due to a thromboembolic event arising from a thrombus on the LAAO) occurred in the concomitant group and 3 neurologic events in the isolated TAVR group (1 TIA and 2 minor ischemic strokes). In the patient with the disabling ischemic stroke, OAC was restarted and continued. In both groups there was 1 life-threatening bleeding complication: 1 bleeding was due to femoral arteriovenous fistula (concomitant group), and in 1 patient gastrointestinal bleeding occurred 4 days after the initial intervention due to multiple duodenal ulcers (isolated TAVR group). As expected, use of contrast dye was higher in the concomitant group when compared to the isolated TAVR group (312 ± 148ml in the concomitant group vs. 98 ± 74ml in the isolated TAVR group). Five patients suffered from acute kidney injury (2 patients with AKIN stage 1 and 3 patients with AKIN stage 3), 4 in the concomitant and 1 in the isolated TAVR group. Three procedural access site complications occurred in the concomitant group (1 femoral perforation and 1 arteriovenous fistula with a relevant hematoma, both treated with a Fluency covered stent; and 1 dissection of the femoral artery, that was treated with uncovered stents).

Cardiac tamponade occurred in 1 patient directly after LAAO and was successfully treated with pericardiocentesis without any long-term sequelae. In 1 patient transthoracic echocardiography 1 day after the intervention revealed an embolized LAA occluder in the left ventricle. The device was percutaneously snared and removed. The patient then underwent successful implantation of another device.

**Follow-up and efficacy outcome**

Median (range) follow-up of the study population was 9.4 (0-48) months. The composite clinical efficacy endpoint was achieved in 39 patients in the concomitant
group and in 42 patients in the isolated TAVR group (75% vs. 82%, 95% confidence interval, [CI] 0.49 to 2.92, Table 3, Figure 3). The LAAO efficacy endpoint was achieved in 36 patients in the concomitant, and in 39 patients in the isolated TAVR group (69% vs. 76%, 95% confidence interval, [CI] 0.54 to 2.51, Table 3, Figure 4). Multivariate analysis did not reveal a difference between concomitant and isolated interventions for the composite clinical efficacy (95% confidence interval, [CI] 0.55 to 3.71) and the LAAO efficacy endpoint (95% confidence interval, [CI] 0.52 to 2.63).

At last follow-up, 83 patients (81%) of the total study population were alive. Deaths occurred in 21 patients (20%), of which 18 (86%) were late deaths (>30 days after the initial procedure). Ten patients died in the concomitant and 8 in the isolated TAVR group (19% vs. 15%). None of the deaths was directly associated with LAAO. Eight deaths were cardiovascular (5 patients in the concomitant and 3 patients in the isolated group) and 10 were non-cardiovascular (5 patients in each group). Cardiovascular deaths included 1 patient with coronary triple-vessel disease with sudden cardiac death (concomitant group), 1 patient with progressive heart failure (3 patients in the concomitant and 2 in the isolated TAVR group), and 2 unknown deaths (1 patient in each group). Non-cardiovascular deaths occurred due to multi-organ failure caused by sepsis in 4 patients (2 patients in each group), progressive renal failure in 2 patients (both in the concomitant group), subdural hematoma due to recurrent falls 10 months after the initial procedure in 1 patient (concomitant group), tongue carcinoma in 1 patient (isolated TAVR group), progressive dementia in 1 patient (isolated TAVR group), and 1 patient decided to discontinue dialysis due to his co-morbidities (isolated TAVR group).
Two patients (1 in each group) suffered from late life threatening bleeding and 3 patients (concomitant group) had major bleeding complications (all due to gastrointestinal bleeding).

At the time of bleeding 2 of these patients received acetylsalicylic acid therapy alone and 1 was under dual antiplatelet therapy (acetylsalicylic acid therapy and clopidogrel). Life threatening bleeding included the patient with subdural hematoma due to recurrent falls (concomitant group) and 1 patient with upper gastrointestinal bleeding under supratherapeutic oral anticoagulation with warfarin.

OAC was continued for some additional period after LAAO in 5 (10%) of the 52 patients. The reasons varied among patients: thrombus on the device (2 patients), physician order (1 patient), heparin induced thrombocytopenia (1 patient), and unknown reasons (1 patient). The 2 patients with a thrombus on the device continued with OAC due to physician order and patient wish. In the patient with heparin-induced thrombocytopenia, OAC with rivaroxaban 20 mg was continued for 6 weeks after the intervention. Eight patients (16%) in the isolated TAVR group received no OAC. Duration and type of antiplatelet therapy varied among patients and depended on physician order. In the isolated TAVR group, 8 patients (16%) at discharge were treated with triple therapy (acetylsalicylic acid, clopidogrel, and OAC); 24 patients (47%) received dual therapy (either acetylsalicylic acid or clopidogrel and OAC), 11 patients (22%) received oral anticoagulation alone; 7 patients (14%) were treated with acetylsalicylic acid and clopidogrel or ticagrelor, 1 patient was on clopidogrel alone. Of those patients receiving OAC most were treated with warfarin (86%) and additional antiplatelet therapy was prescribed for 1 to 12 months.
Discussion

The goal of this pilot study in patients with severe aortic stenosis was to investigate outcomes of combined procedures (TAVR and LAAO) and TAVR alone. The main findings were that (1) combining TAVR with LAAO was safe and did not result in adverse procedural outcome; (2) there was no difference in efficacy after a mean follow-up of 9.4 months; and (3) these findings held true after multivariate analysis adjusted for age, sex, and CHA2DS2-Vasc, HASBLED, and STS scores; and (4) most (88%) safety events occurred in the first 7 days after the intervention.

Procedural and clinical safety outcome

As previously shown, LAAO has the potential to prevent ischemic stroke as well as bleeding complications in patients with AF(13,14,18). Since patients in AF undergoing TAVR are at high risk for bleeding and thromboembolic events, combining TAVR and LAAO appears as a reasonable approach to prevent these complications. However, LAAO is a technically demanding procedure with a flat learning curve(15,16). Therefore, complication rates of LAAO are clinically significant and strongly related to operator experience(19,20). Due to the additional venous access, the transseptal puncture, the increased procedural time, and the extra contrast-dye required, LAAO after TAVR potentially bears an increased risk of adverse procedural events. However, our results suggest, that the procedure can be performed safely in addition to TAVR in experienced hands.

In line with recently published data, most safety events (88%) in the present study were a result of periprocedural complications or occurred early after the intervention (<7 days)(13,21). Safety events strictly related to LAAO, such as cardiac tamponade and embolization of the LAA closure device, occurred in only 2 patients (5%). Device
embolization was previously reported in 0.8 - 3.9% and is mainly limited to the early post procedural period(18,22). Cardiac tamponade in our patient cohort was low (2%) in line with published data (1.2 - 5%)(13,18,19) and neither device embolization(23) nor tamponade did result in any long-term sequelae.

Although periprocedural complications are thought to be higher in patients undergoing concomitant TAVR and LAAO, we did not observe higher 30-day event rates of clinical significant bleeding (2%), access site complications (6%), and acute kidney injury stage 2-3 (8%) when compared to studies with patients undergoing TAVR alone. 30-day outcome of recent trials with patients undergoing TAVR show event rates of major vascular complications of 5.3 - 6.5%, clinically significant bleeding of 4.0 - 13.6%, and acute kidney injury of 2.7 - 18.7%(3,24,25). A word of caution is needed for patients with reduced kidney function, since concomitant procedures required a higher procedural amount of contrast dye. On the other hand, patients with kidney failure are exposed to a higher bleeding risk and may particularly benefit from concomitant LAAO. Of note, in the concomitant patient population additional procedures (besides LAAO) were performed much more frequently than in the isolated TAVR group (29% vs. 6%).

In summary, concomitant LAAO in patients undergoing TAVR does not seem to affect the success rate or outcome of TAVR.

Clinical and LAAO efficacy outcome

After 3.8 years of follow-up, superiority of LAAO as compared to OAC with warfarin was shown in a randomized trial(14), which was in line with a large multi-center registry with ACP(18) with a follow-up of 13 months. The potential advantage of
LAAO over vitamin K antagonists (i.e. reduction of bleeding and ischemic stroke) became more prominent with longer follow-up(15,26).

In our study we could not show any difference in efficacy outcomes between the two groups, presumably due to a too short follow-up and small patient number (9.4 months as compared to 3.8 years and 13 months, respectively in the previously mentioned studies including a larger number of patients). However, it is likely that the advantage of LAAO becomes only evident after longer follow-up. Furthermore, ischemic strokes were a relatively rare event in our study population, thereby further limiting statistical power.

The second composite LAAO efficacy endpoint was chosen to assess early efficacy, excluding procedural events, which account for the largest share according to the PROTECT-AF trial. Although warfarin was stopped directly after LAAO in most patients, no difference in the composite of mortality, neurological events, and bleeding complications was noted. As mentioned above, this finding supports the evidence that the benefit of LAAO over vitamin K antagonists materializes, if at all, only after a longer follow-up period.

Another interesting finding is the diversity of antithrombotic regimens in the isolated TAVR group. Given the high-risk population, treating physicians seem reluctant to put TAVR patients on oral anticoagulation. This in return puts those patients at very high risk for stroke complications(27), indicating the dilemma we are facing in these patients.

LAAO seems to be a valuable alternative for oral anticoagulation especially in these high-risk patients. The question remains, however, if concomitant procedures are preferable to a staged approach, as described in a case report by Bogunovic et al.(28).

In our opinion concomitant procedures are not only feasible in experienced hands but
also have several advantages: patients undergoing TAVR and LAAO in the same sitting are immediately protected from stroke and bleeding complications and a single session approach seems patient-friendly for elderly and multimorbid patients(29).

**Study limitations**

The main goal of this pilot study was an initial proof of concept to demonstrate the safety of combining TAVR with LAAO. Conclusions on safety and efficacy are only hypothesis generating, since the main limitation of the study arises from the relatively small number of patients and the short follow-up, which limits the power of the analysis. Certain design limitations are inherent, including the retrospective nature of this study and the possible selection bias due to the lack of selecting a propensity matched cohort. However, comparison of the ‘isolated TAVR group’ to the remaining patients with atrial fibrillation in the TAVR cohort of the University hospital Zurich shows no remarkable difference in risk factors (STS score, sex, diabetes, hypertension, stroke and coronary artery disease).

LAAO is considered an intricate procedure, coming along with a flat learning curve. Therefore, our results may represent the outcomes of high-volume centres with many years of experience with LAAO and may therefore not be generalizable. Further, the diversity of therapeutic regimens for OAC might have influenced outcomes of the presented study population. Therefore, a larger, randomized study is needed to show safety and efficacy of combined interventions. For a future study, the total estimated sample size for the composite safety endpoint based on 80% power to confirm non-inferiority (one-sided confidence level of 97.5%) would be 484 (assuming an event rate of 19% and considering that a difference in the composite safety event rate as large as 10% in favour of the single TAVI procedure would allow
the concomitant TAVI procedure to be non-inferior).

**Conclusions**

Combining TAVR with LAAO is feasible and seems to be safe. A larger randomized trial with longer follow-up is needed to confirm safety and to further show efficacy of combining these two interventions.
Clinical Perspectives

Patients with severe aortic stenosis and atrial fibrillation undergoing transcatheter aortic valve replacement (TAVR) are at increased risk for stroke and bleeding complications. Left atrial appendage occlusion (LAAO) offers a non-pharmacologic stroke protection, obviating the need for oral anticoagulation. Combining TAVR and LAAO in the same sitting is feasible and seems to be safe. However, to show safety and efficacy of combining TAVR and LAAO in these patients, a larger randomized trial with longer follow-up is needed.
References


### Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Overall population (n = 104)</th>
<th>Concomitant (n = 52)</th>
<th>Isolated TAVR (n = 52)</th>
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<td>Age, yrs</td>
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<td>Male</td>
<td>59 (57)</td>
<td>29 (56)</td>
<td>30 (58)</td>
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<td>CHA2DS2-Vasc score</td>
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<td>HAS-BLED score</td>
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<td>2.7 ± 1.0</td>
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<td>STS score</td>
<td>7.8 ± 5.5</td>
<td>8.0 ± 5.3</td>
<td>7.5 ± 5.7</td>
<td>0.301</td>
</tr>
<tr>
<td>Hypertension</td>
<td>81 (78)</td>
<td>40 (77)</td>
<td>41 (79)</td>
<td>0.813</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>33 (32)</td>
<td>18 (35)</td>
<td>15 (29)</td>
<td>0.527</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>45 (43)</td>
<td>24 (46)</td>
<td>21 (40)</td>
<td>0.553</td>
</tr>
<tr>
<td>NYHA functional Class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>28 (27)</td>
<td>12 (23)</td>
<td>16 (31)</td>
<td>0.225</td>
</tr>
<tr>
<td>III</td>
<td>56 (54)</td>
<td>33 (64)</td>
<td>23 (44)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>18 (17)</td>
<td>6 (12)</td>
<td>12 (23)</td>
<td></td>
</tr>
<tr>
<td>Prior ischemic stroke or TIA</td>
<td>14 (14)</td>
<td>6 (12)</td>
<td>8 (15)</td>
<td>0.566</td>
</tr>
<tr>
<td>CHD</td>
<td>53 (51)</td>
<td>26 (50)</td>
<td>27 (52)</td>
<td>0.844</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>53.2 ± 12.4</td>
<td>53.9 ± 11.2</td>
<td>52.6 ± 13.5</td>
<td>0.599</td>
</tr>
<tr>
<td>Mean aortic valve gradient, mmHg</td>
<td>44.3 ± 17.1</td>
<td>44.3 ± 17.6</td>
<td>44.3 ± 16.8</td>
<td>0.997</td>
</tr>
<tr>
<td>Aortic valve Area, cm²</td>
<td>0.70 ± 0.2</td>
<td>0.69 ± 0.2</td>
<td>0.72 ± 0.2</td>
<td>0.473</td>
</tr>
<tr>
<td>Dialysis</td>
<td>5 (5)</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td>0.647</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%).

CHD = coronary heart disease; CHA2DS2-Vasc = congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke of transient ischemic attack; CHD = coronary heart disease; HAS-BLED = uncontrolled hypertension > 160 mmHg, renal disease (dialysis, transplant, creatinine > 200µmol/l), liver disease (cirrhosis or bilirubin >2x normal or AST/ALT/AP > 3x normal), prior stroke, prior major bleeding or predisposition to bleeding, labile INR (time in therapeutic range < 60%), age > 65 years, medication usage predisposing to bleeding (antiplatelet agents, non-steroidal antirheumatic drugs), alcohol or drug usage (≥8 drinks/week); LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; STS score = The Society of Thoracic Surgeons risk score; TIA = transient ischemic attack.
<table>
<thead>
<tr>
<th></th>
<th>Overall (n=104)</th>
<th>Concomitant (n=52)</th>
<th>Isolated TAVR (n=52)</th>
<th>95% conf. interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Composite safety endpoint</td>
<td>17 (16)</td>
<td>10 (19)</td>
<td>7 (14)</td>
<td>0.59 - 4.06</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3 (3)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>0.46 - 5.59</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0.06 - 15.99</td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Stroke and TIA</td>
<td>4 (4)</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td>0.33 - 3.06</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>3 (3)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>0.044 - 5.37</td>
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<tr>
<td>Hemorrhagic stroke</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0.06 - 15.83</td>
</tr>
<tr>
<td>Acute kidney injury (stage 2-3)</td>
<td>5 (5)</td>
<td>4 (8)</td>
<td>1 (2)</td>
<td>0.45 - 36.24</td>
</tr>
<tr>
<td>Major vascular complication</td>
<td>3 (3)</td>
<td>3 (6)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Pericardial tamponade</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Device embolization</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Valve failure</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%).

*Composite of all-cause mortality, all-cause stroke and TIA, bleeding (life-threatening), acute kidney injury (Stage 2-3), major vascular complication, pericardial tamponade, device embolization, and valve failure.

TIA = transient ischemic attack.
Table 3. Efficacy outcome of combined interventions vs. TAVR alone.

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=103)</th>
<th>Concomitant (n=52)</th>
<th>Isolated TAVR (n=51)</th>
<th>95% conf. interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Composite clinical efficacy EP</td>
<td>81 (79)</td>
<td>39 (75)</td>
<td>42 (82)</td>
<td>0.49 - 2.92</td>
</tr>
<tr>
<td>Late all-cause mortality</td>
<td>85 (83)</td>
<td>42 (81)</td>
<td>43 (84)</td>
<td>0.37 - 2.67</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>95 (92)</td>
<td>47 (90)</td>
<td>48 (94)</td>
<td>0.28 - 5.78</td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>93 (90)</td>
<td>47 (90)</td>
<td>46 (90)</td>
<td>0.22 - 3.08</td>
</tr>
<tr>
<td>Late all-cause stroke and TIA</td>
<td>103 (100)</td>
<td>52 (100)</td>
<td>51 (100)</td>
<td></td>
</tr>
<tr>
<td>Late bleeding</td>
<td>98 (95)</td>
<td>48 (92)</td>
<td>50 (98)</td>
<td>0.41 - 34.21</td>
</tr>
<tr>
<td>†Composite LAAO efficacy EP</td>
<td>75 (73)</td>
<td>36 (69)</td>
<td>39 (76)</td>
<td>0.54 - 2.51</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>83 (81)</td>
<td>41 (79)</td>
<td>42 (82)</td>
<td>0.39 - 2.53</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>95 (92)</td>
<td>47 (90)</td>
<td>48 (94)</td>
<td>0.28 - 5.78</td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>91 (88)</td>
<td>46 (88)</td>
<td>45 (88)</td>
<td>0.26 - 2.82</td>
</tr>
<tr>
<td>Stroke and TIA</td>
<td>99 (96)</td>
<td>51 (98)</td>
<td>48 (94)</td>
<td>0.03 - 3.06</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>99 (96)</td>
<td>51 (98)</td>
<td>48 (94)</td>
<td>0.33 - 3.06</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>103 (100)</td>
<td>52 (100)</td>
<td>51 (100)</td>
<td></td>
</tr>
<tr>
<td>Postprocedural bleeding</td>
<td>92 (89)</td>
<td>45 (87)</td>
<td>47 (92)</td>
<td>0.53 - 6.18</td>
</tr>
</tbody>
</table>

Values are n (%).

*Freedom from all-cause mortality, all-cause stroke (disabling and non-disabling) and TIA, and bleeding (life threatening and major). †Freedom from all-cause mortality, all-cause stroke (disabling and non-disabling) and TIA, and bleeding (life threatening and major).

EP = endpoint; LAAO = left atrial appendage occlusion; TIA = transient ischemic attack.
Figures

**Figure 1.** Fluoroscopic image of a combined procedure (left anterior oblique 20°, caudal 20°).
Arrow A: Amulet 25 mm left atrial appendage occluder; Arrow B: Edwards Sapien 3 26 mm transcatheter heart valve.

**Figure 2.** Kaplan-Meier survival curve for each group: Freedom from composite safety outcome; 95% confidence interval 0.59 to 4.06.

**Figure 3.** Kaplan-Meier survival curve for each group: Freedom from composite clinical efficacy outcome; 95% confidence interval 0.49 to 2.92.

**Figure 4.** Kaplan-Meier survival curve for each group: Freedom from composite LAAO efficacy outcome; 95% confidence interval 0.54 to 2.51.
Figure 1

Figure 2

<table>
<thead>
<tr>
<th></th>
<th>Isolated TAVR</th>
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<tbody>
<tr>
<td>Number at risk:</td>
<td>52</td>
<td>44</td>
<td>44</td>
<td>43</td>
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<tr>
<td>Concomitant</td>
<td>52</td>
<td>41</td>
<td>39</td>
<td>37</td>
</tr>
</tbody>
</table>
Figure 3

Cumulative Event-free Survival (%)

Time in days

Number at risk:

<table>
<thead>
<tr>
<th></th>
<th>Isolated TAVR</th>
<th>Concomitant</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>52</td>
<td>26</td>
<td>14</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Figure 4

Cumulative Event-free Survival (%)

Time in days

Number at risk:

<table>
<thead>
<tr>
<th></th>
<th>Isolated TAVR</th>
<th>Concomitant</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>52</td>
<td>23</td>
<td>12</td>
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<tr>
<td>0</td>
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<td>4</td>
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