



Incidence, pathophysiology, predictive factors and prognostic implications of new onset atrial fibrillation following transcatheter aortic valve implantation

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1 Introduction

Atrial fibrillation (AF) constitutes the most frequent cardiac arrhythmia with an increasing prevalence and incidence in the general population, demonstrating a significant impact on cardiovascular morbidity and mortality.^[1,2] AF has been correlated with an increased risk of stroke, systemic embolism and long term morbidity compared to individuals with sinus rhythm.^[3] The highest prevalence of AF is reported in elderly as well as in patients with severe aortic stenosis, ranging between 16% and 40% in the latter.^[4] In the general population, AF scales the death risk up to 1.5 and 1.9 fold in men and women, respectively.^[2,5]

AF and aortic stenosis can coexist as there is a dynamic interplay and causal correlation between these pathologic processes. Especially, AF impairing atrioventricular synchrony results in irregular ventricular contraction, increased filling pressures and reduced cardiac output that may further deteriorate in case of severe aortic stenosis. On the other side, the left ventricular outflow obstruction and left ventricular hypertrophy precipitated by severe aortic stenosis, result in diastolic dysfunction, elevated left atrial pressure and further AF induction.

AF has been associated with late adverse cardiac and cerebrovascular events following surgical aortic valve replacement, such as heart failure, stroke and mortality, proven to be an independent poor prognostic factor by several surgical series.^[5–7] Transcatheter aortic valve implantation (TAVI) has been considered as the appropriate treatment in high risk patients with severe aortic valve stenosis and other comorbidities that are rendered inoperable. How-

ever, the incidence, the prevalence, the pathophysiologic mechanisms as well as the impact of pre-existing or new onset AF on early and late outcomes have not been elucidated. Several studies and meta-analysis have been performed with conflicting results. The aim of this review is a comprehensive approach to characteristics and prognostic implications of pre-existing or new onset AF in TAVI patients.

2 Epidemiology and pathophysiology of AF in patients undergoing TAVI

The term pre-existing AF refers either to previous history of AF (paroxysmal, permanent, persistent) or to the documentation of arrhythmia during hospital admission or TAVI procedure.^[8,9] New onset AF is characterized the presence of arrhythmia within 30 days after TAVI procedure in patients with negative previous history, recorded on 12 lead ECG or on a rhythm strip lasting at least 30 s.^[10,11] According to a recent meta-analysis,^[5] pre-existing AF demonstrated an average prevalence of 33.4% ± 9.6% (data derived from 23 studies, overall population = 13,241), whereas new onset AF had an incidence of 17.5% ± 8.7% (nine studies, total population = 4749).

In general, a significantly higher prevalence of pre-existing AF has been reported in TAVI treated patients compared to those having undergone surgical aortic valve replacement (SAVR), a fact that could be attributed to the worse clinical profile of TAVI patients.^[8,12] According to a study of Motloch, *et al.*,^[12] the prevalence of post-procedural AF in TAVI patients has been significantly lower versus SAVR patients (6% vs. 33.7%, $P < 0.05$) in contrast to the higher pre existing reported rate of AF in TAVI vs. SAVR patients (32.1% vs. 12.8%, $P < 0.05$). The lower

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incidence of new onset AF in TAVI versus SAVR patients (3.5% vs. 30.7%), reflects the known high incidence of AF after SAVR that can be attributed to adverse surgical-related factors such as pericardiectomy, aortic cross clamping and cardiopulmonary bypass.^[12,13] Accordingly, new onset AF in TAVI patients has been higher after transapical (6%–38%) versus transfemoral access (< 1%–16%).^[12,14] However, this effect has not been validated in a recent meta-analysis, as there was no significant differences regarding new onset AF incidence between transapical and transfemoral implantation.^[5]

Several co-morbidities coexist in AF and aortic stenosis such as advanced age, hypertension, diabetes, obesity, left ventricular dysfunction or even heart failure that might explain the pathophysiologic mechanisms of new onset AF in TAVI patients.^[8] However, the underlying pathophysiology of new onset AF in TAVI patients remains unclarified, while it can be speculated that post-operative AF may share common triggers with post-TAVI AF.^[12]

Co-existing risk factors between AF and aortic stenosis, like hypertension and advanced age, in combination with co morbidities accompanying aortic stenosis such as obesity, obstructive sleep apnoea and increased pericardial fat, contribute to atrial fibrosis induction.^[8] In addition, the systemic inflammatory response observed after TAVI, which is more pronounced in transapical implantation consistently with SAVR, enhances further atrial oxidative stress.^[15,16] Both atrial fibrosis and oxidative stress can result in slow atrial conduction, short refractoriness, early after depolarization and endoepicardial dissociation, favouring re-entry and ectopic activity.^[16,17] Re-entry and ectopic activity lead to anatomical and electrical atrial remodeling which in turn contributes to maintenance of re-entry and ectopic activity, rendering AF permanent. Peri-procedural factors such as hemodynamic instability, balloon valvuloplasty, local inflammation and pain can stimulate autonomic nervous system. Autonomic system has been strongly correlated with early after depolarization and triggered activity in animal models, further contributing to AF initiation and recurrence.^[13,18] Notably, aortic stenosis itself may cause atrial fibrillation. Especially, left ventricular outflow obstruction in case of severe aortic stenosis provokes left ventricle hypertrophy and dysfunction, increased filling pressures, diastolic dysfunction, elevated left atrial pressures, atrial dilatation and fibrosis facilitating further re-entry, ectopic activity and AF onset.^[8,19,20]

3 Predictive factors of new onset AF following TAVI

Both clinical and peri-procedural risk factors have been

identified as potential triggers of new onset AF after TAVI, favoring its maintenance.

In SOURCE XT study, 2688 patients were enrolled and underwent TAVI via transfemoral (62.7%), transapical (33.3%), trans-subclavian (0.3%) and direct transaortic (3.8%) with the deployment of Sapien XT valve.^[9] New onset AF was reported in 7.2% of patients following TAVI and related with the following procedural characteristics: transapical access, large prosthetic valve size, general anesthesia, pre- or post-balloon dilatation, technical and device success.^[9] Notably independent risk factors for new AF were age, NYHA III-IV, non transfemoral access and balloon post dilatation of the prosthetic valve.

In FRANCE-2 registry,^[21] 3933 patients undergoing TAVI were enrolled, while 174 patients (6%) demonstrated new onset AF post-valve implantation. Independent factors correlated with the new onset AF were previous history of stroke, non transfemoral approach (surgical transapical and transaortic), as well as cardiological and hemorrhagic procedure-related events.

Amat Santos, *et al.*,^[10] enrolled 138 patients with severe aortic stenosis without previous history of AF to undergo TAVI with a balloon expandable valve (Edwards SAPIEN, SAPIEN XT). New onset AF observed in 44 patients (31.9%) within 30 days post TAVI. A large atrial size > 27 mm/m² assessed by echocardiography was considered the cut-off point with the best sensitivity (67%) and specificity (61%) for the prediction of new onset AF. An additional independent procedural predictor for AF was the transapical approach.

Barbash, *et al.*^[22] analyzed 371 consecutive patients underwent TAVI either with the balloon expandable Edwards SAPIEN or SAPIEN XT transcatheter valves or the self expandable Medtronic Core-Valve via transfemoral, transapical or transaortic routes. The patients were divided based on the presence ($n = 143$) or absence ($n = 281$) of baseline AF. New onset AF post-TAVI was reported in 46 patients (20%) and was associated with procedural factors as transapical approach (57%), use of general anesthesia (74%), deployment of SAPIEN valve (87%), and hemodynamic deterioration requiring inotropic or chronotropic support (12%). Notably, the strongest predictor of new AF was hemodynamic compromise followed by transapical access—with a 9-fold and 5-fold increased risk for new AF.^[22]

Consequently, transapical access has been proven to increase significantly the risk of the new onset AF incidence compared to transfemoral route.^[9,10,12,21] This fact could be attributed to the worse clinical profile of patients undergoing transapical TAVI, but a direct pathogenetic mechanism of transapical approach as a triggering cause for post procedure AF should be considered.^[8]

Finally, procedural factors such as paravalvular regurgitation, implantation depth, prosthesis to annulus size ratio, left ventricular outflow diameter, type of prosthesis (balloon or self expandable), as well as clinical parameters, which including age, gender, pre-existing conduction abnormalities, have not been correlated with the new onset AF post TAVI.^[8,23–25] This is in contrast to the fact that pre-existing AF is predicted by clinical entities such as moderate to severe mitral and tricuspid regurgitation as well as pulmonary hypertension.^[8,9]

4 Prognostic implications and distinctions of pre-existing and new onset AF following TAVI

4.1 Mortality

Several studies have analyzed the impact of pre-existing or new onset AF on early and late mortality, reporting conflicting results. In the afore-mentioned large meta-analysis,^[5] pre-existing AF increased significantly the overall and cardiovascular long term mortality risk post-TAVI compared to sinus rhythm, whereas the overall mortality risk at 30 day follow up was not significantly elevated. Conversely, patients with new onset AF revealed no increased risk in 30 day or long term all cause mortality. On the contrary, a meta analysis of Gargiulo, *et al.*^[26] including nine studies with 4959 patients, reported a mean incidence of new onset AF of 10.1%. Interestingly, patients with new onset AF revealed a borderline increase at 30 day all-cause mortality, and a significant 1-year increase of the overall mortality compared to sinus rhythm patients.

Recent significant trials as SOURCE XT,^[9] FRANCE-2,^[21] and data derived from PARTNER trial,^[27] have demonstrated a significant increase in early and late all cause mortality in case of both pre-existing and new onset AF. Specifically, in SOURCE XT both pre-existing and new onset AF correlated with worse outcomes regarding all cause and cardiovascular mortality compared to sinus rhythm patients. Also, new onset AF showed a numerically higher rate of all cause and cardiovascular mortality, compared to pre existing AF, without difference in terms of statistical significance.^[9]

4.2 Stroke

Cerebrovascular events (CVE) early after TAVI have been correlated with an 11% mortality rate in the first 30 day period post procedure,^[28] accounting for half of all stroke cases.^[9,29] The impact of pre-existing AF on early stroke after the procedure has not been documented by several studies, while heterogenous results have been reported

regarding the effect of pre-existing AF on long term CVEs.^[30–32] A recent large meta-analysis demonstrated that pre-existing AF in TAVI patients could not predict CVE at long term follow up (4604 patients, HR = 1.68, 95% CI: 0.86–3.30, $P = 0.13$).^[5] On the contrary, new onset AF revealed significantly increased short term CVE (2025 patients, HR = 2.86, 95% CI: 1.88–4.34, $P < 0.00001$), but no significant impact on the incidence of long term CVE (3997 patients, HR = 1.44, 95% CI: 0.50–4.10, $P = 0.50$).^[5] Similarly, another meta-analysis reported that new onset AF increased significantly CVE at 30 day period (4647 patients, HR = 2.52, 95% CI: 1.76–3.62, $P < 0.00001$) only, but not thereafter (4277 patients, HR = 1.82, 95% CI: 0.86–3.84, $P = 0.12$).^[26]

Considering that TAVI itself is correlated with an important increase of CVE incidence due to large catheter manipulation in calcified aortas and the subsequent risk of embolization combined with the fact that pre-existing AF does not increase early CVE incidence, it might be speculated that technical factors account for the main risk of early stroke.

4.3 Bleedings

Several studies have demonstrated the impact of new or preexisting AF on bleeding risk in TAVI patients. In France-2 study,^[21] hemorrhagic events occurred peri-procedurally were higher in new onset AF compared to sinus rhythm patients (27 out of 174 versus 219 out of 2448 patients, $P = 0.006$), whereas there was no difference in pre-existing AF and sinus rhythm (SR) patients (85 out of 1002 versus 287 out of 2873 patients, $P = 0.17$). However, major bleedings at 30 day and 1 year demonstrated no significant difference in both pre-existing and new onset AF patients compared to overall population. Similarly, in PARTNER trial, major bleeding events demonstrated no significant differences among new onset AF, pre-existing AF and SR patients, although a trend of increased events reported in new onset AF.^[27] In addition, Barbash, *et al.*^[22] observed no difference regarding in hospital post TAVI major bleeding events between pre-existing AF and SR patients (10% vs. 8%, $P = 0.53$).

On the contrary, in SOURCE-XT study,^[9] both pre-existing and new onset AF correlated with significantly higher total bleeding events at 1 year post TAVI compared to SR patients (163/685 and 46/138 vs. 212/1102; $P = 0.01$ and $P < 0.0001$, respectively). Notably, patients with new onset AF correlated with higher total bleeding events at 1 year post TAVI versus those with pre-existing AF (34.2% vs. 25%, $P = 0.02$).

Finally, future large controlled randomized trials such as POPular-TAVI,^[33] and GALILEO,^[34] investigating aspi-

rin/oral anticoagulant as monotherapy or combined with clopidogrel, as well as rivaroxaban and aspirin versus double antiplatelet therapy respectively, will further clarify the optimal treatment for thromboembolic event protection and major bleeding reduction.

5 Conclusions

A dynamic and causal correlation exist between aortic stenosis and AF, rendering pre-existing or new onset AF the most frequent arrhythmia in patients undergoing TAVI. Pre-existing and new onset AF constitute two different entities characterized by different predictors and prognosis. As AF is correlated with increased mortality and adverse ischemic or hemorrhagic events, the prompt diagnosis, optimal treatment and proper prevention should be pursued. Pre-existing and new onset AF in TAVI consist in individual pathophysiological processes with potential overlapping mechanisms, rendering crucial to clarify if AF constitute an independent risk factor or an index of increased risk in TAVI patients.

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