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Short communication

# Dual antiplatelet therapy after TAVR: A drop in the bucket?

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ABSTRACT

Current guidelines recommend a three- to six-months dual antiplatelet therapy (DAPT) in patients undergoing transcatheter aortic valve replacement (TAVR) or to continue with oral anticoagulant agents (OAC) if already indicated before procedure. However, recent studies showed that treatment with aspirin has the same efficacy of DAPT but it was associated with a significant reduction of major bleeding.
Furthermore, half of cerebrovascular events, occurring >24 h after procedure, may be related to new onset of atrial fibrillation or to subclinical leaflets thrombosis and they may be prevented by use of OAC rather than antiplatelet therapy.
In absence of very high bleeding risk and of recent percutaneous coronary intervention, the use of OAC over SAPT or DAPT might theoretically be considered in patients undergoing TAVR waiting for results of ongoing clinical trials.


## 1. Introduction

Transcatheter aortic valve replacement (TAVR) is the treatment of choice in patients with severe symptomatic aortic stenosis at prohibitive surgical risk, and an alternative to surgical valve replacement (SAVR) in patients at high or intermediate risk [1].

However, TAVR may be associated with peri-procedural myocardial infarction (MI) and transient ischemic attack (TIA)/stroke [2]. Reduced aortic-valve motion and leaflets thrombosis at follow-up may affect valve haemodynamic and increase the risk of cerebrovascular events (CVEs) [3,4].

According to European guidelines, that will be our main reference, single antiplatelet therapy (SAPT) with aspirin, dual antiplatelet therapy (DAPT) with aspirin and clopidogrel, or oral anticoagulant agents (OAC) may be considered after TAVR [5]. As major late bleeding complications are not unfrequent and are associated with an increased risk of total mortality [6], a careful risk/benefit evaluation is warranted to identify the most appropriate antithrombotic regimen.

The present review will provide insights on the optimal antithrombotic therapy in patients undergoing TAVR, with an overview on the ongoing trials.

### 1.1. Current recommendation

In patients undergoing TAVR with no other indication to receive OAC, DAPT including lifelong aspirin plus clopidogrel for 3–6 months should be considered and is the most used strategy [5,7]. OAC are recommended lifelong after TAVR if required for a different clinical indication [e.g. atrial fibrillation (AF)] [5]; the addition of antiplatelet agents for concomitant coronary artery disease or recent stent implantation should be based on specific guidelines [8]. US guidelines consider anticoagulation with vitamin k inhibitor (VKA) for at least 3 months after TAVR in patients at low bleeding risk (IIb B); despite previous indication is similar to that for surgical bioprosthesis, it has never been investigated in TAVR setting [1].

Safety and efficacy of DAPT in this setting has never been demonstrated in a randomized clinical trial (RCTs) and received a IIa C recommendation, whereas, SAPT may be considered in patients at high bleeding risk [5]. Notably, patients undergoing TAVR are usually per se at high bleeding risk due to advanced age and comorbidities and the identification of patients in whom SAPT should be preferred over DAPT is challenging [6].

### 1.2. SAPT versus DAPT

The rationale for DAPT administration after TAVR derives from the empirical assumption that transcatheter prosthesis (provided of metallic ring) is similar to a coronary stent. As DAPT was associated with a significant increase of major bleeding [9], recent studies investigated the net clinical benefit of DAPT compared to SAPT after TAVR. The prospective randomized ARTE trial showed no additional benefit on death, stroke and MI with addition of clopidogrel for 3 months to aspirin in patients undergoing TAVR. Furthermore, DAPT was associated to a significant 3-fold increase of major or life-threatening bleeding [10]. Previous results should be considered as hypothesis generating due to the open-label design, the small sample size, and the use of only balloon

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expandable valves. A meta-analysis including 26 studies (mostly observational) reported that, after TAVR, aspirin was equivalent to DAPT in terms of stroke prevention, death and bleeding. [11]. A patient-level meta-analysis of 3 RCTs, including only 421 patients, showed that DAPT for 3–6 months compared to aspirin significantly increased major or life-threatening bleedings, with no benefit on ischemic events [12].

### 1.3. Atrial Fibrillation in patients undergoing TAVR

In patients undergoing TAVR, CVEs occur 24 h after procedure in half of the cases, and new onset or chronic AF has been reported as their strongest predictor [13]. One third of patients treated with TAVR presented baseline AF, and, new onset occurred in 10–15% of the cases [10,13,14].

As most of CVEs occurring 24 h after procedure seem to be AF-related, a lack of protection by antiplatelet therapy is not unexpected. In patients with AF, DAPT has been shown to be less effective than VKA in the reduction of all vascular events with no difference in the rate of major bleeding [15], and, apixaban compared to aspirin significantly reduced the rate of stroke/systemic embolism with a similar rate of major bleeding [16].

In the recent French TAVI registry, history of AF was an independent predictor of 3-year mortality, and OAC at discharge (prescribed to 70.8% of patients with AF) was significantly related to long-term mortality independently of AF [17]. These data should be interpreted with caution: OAC prescription might identify patients with a basal, higher risk, thus representing a marker of comorbidities rather than the cause of adverse events [17].

### 1.4. Valve deterioration or leaflet thrombosis and antithrombotic therapy

Hemodynamic deterioration of bioprosthetic valve contributes to failure of surgical valve replacement, with an incidence increasing over time, as result of leaflets calcification or thrombosis [18]. Data about valve dysfunction after TAVR are lacking, despite an increase of transvalvular gradient may be related to thrombosis of the bioprosthesis [19].

In patients treated with transcatheter or surgical bioprosthesis, a CT scan, performed within 3 months after procedure, revealed a reduced leaflet motion in 13% of the cases; despite a very small number of events, reduced leaflet motion was associated with a significant increase in the rate of TIA/stroke, but its occurrence was reduced by warfarin compared to DAPT [3].

In a multicenter registry, echocardiographic examinations performed after TAVR, showed a valve hemodynamic deterioration (VHD, defined as an increase in transprosthetic mean gradient during follow-up ≥10 mm Hg) in 4.5% of the cases: lack of OAC prescription at hospital discharge was the main independent predictor of VHD, followed by valve-in-valve procedure, valve size ≤ 23 mm, and body mass index [20].

In a pooled analysis of two recent registries, CT scan post SAVR or TAVR revealed subclinical leaflet thrombosis in 12% of cases at a median of 83 days from procedure. Subclinical leaflet thrombosis was significantly associated with an increased rate of all stroke or TIAs, and, a beneficial effect of OAC in their prevention or treatment was obtained both with warfarin and NOACs, but not with SAPT or DAPT [4]. In the French TAVI registry, OAC at discharge was independently associated to a half rate of early valve dysfunction [17].

### 1.5. Gap in evidence and ongoing studies

In TAVR patients, the protective role of OAC in patients without AF and the association of OAC and antiplatelet therapy need further investigation.

Optimal antithrombotic regimen after TAVR, including the use of direct OAC, is the target of ongoing clinical studies. The AUREA trial (NCT01642134) is recruiting patients randomized to 3 months DAPT or OAC for prevention of cerebral thromboembolism. The POPular-TAVI trial (NCT02247128) is assessing whether aspirin or OAC vs additional clopidogrel after TAVR reduces bleeding with a favorable net-clinical benefit.

The GALILEO trial (NCT02556203) enrolled patients undergoing TAVR with no indication to OAC and randomized to 3-months therapy with rivaroxaban 10 mg up to 25 months plus low-dose aspirin or DAPT with aspirin plus clopidogrel, followed by aspirin alone. The trial

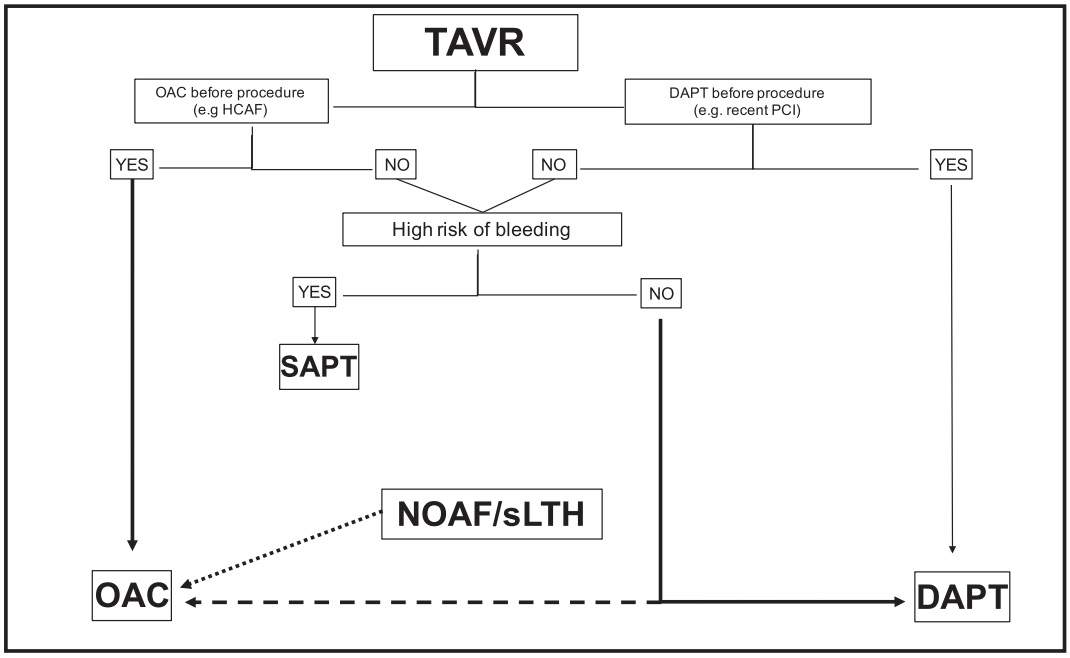


**Fig. 1.** Current antithrombotic therapy in patients undergoing TAVR. OAC: oral anticoagulant agents. DAPT: dual oral antiplatelet therapy. SAPT: single oral antiplatelet therapy. HCAF: history of chronic atrial fibrillation. NOAF: new onset of atrial fibrillation. sLHT: subclinical valve leaflet thrombosis. Dotted arrow indicates the recommend therapy in case of NOAF/sLHT. Dashed arrow suggests the potential use of OAC instead of DAPT.

was prematurely stopped after an interim analysis on 1644 patients showing a higher rate of death or first thromboembolic event (11.4% vs 8.8%), all-cause death (6.8% vs 3.3%), and bleeding events (4.2% vs 2.4%) in patients treated with rivaroxaban [https://www.tctmd.com/news/galileo-trial-rivaroxaban-after-tavr-stopped-early-harm].

The aim of the ATLANTIS trial (NCT02664649) was to assess if apixaban 5 mg (with dose adjustment, if required) bid for 12 months, was superior to the standard of care in patients undergoing TAVR; randomization will be stratified based on the need of OAC: if present, VKA will be the comparator, and if not, DAPT will be the control arm. The ENVISAGE-TAVI AF (NCT02943785) will compare edoxaban versus warfarin in patients with AF and indication to long term OAC undergoing TAVR.

### *1.6. Conclusion and future perspectives*

Guidelines recommendations do not seem to be consistent with recent data that failed to demonstrate that DAPT can confer an incremental protection over SAPT in long-term prevention of CVEs, with a concomitant increased of bleeding [11].

On the other hand, subacute and late CVEs in patients undergoing TAVR seem to be strongly related to new onset AF or history of persistent AF. In this setting, OAC should be considered mandatory as its superiority over antiplatelet therapy has been widely demonstrated in stroke prevention. Of note, it has to be pointed out that antiplatelet therapy seems to have a null effect in the prevention subclinical leaflet valve thrombosis [4,5].

As current recommendation of antithrombotic therapy after TAVR are not based on results of RCTs, the use of OAC should be carefully considered in these patients, particularly in subgroups at high risk of leaflet thrombosis and in case of known AF.

Theoretically, for the prevention of leaflets thrombosis and cardioembolic events in subclinical AF, OAC might be considered after TAVR in patients who do not require antiplatelet therapy for recent PCI [Fig. 1], while awaiting for the results of ongoing clinical trials.

## Disclosure

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