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ORIGINAL ARTICLE

Transcatheter Aortic Valve Replacement and Atrial Fibrillation: Impact of Antithrombotic Strategy on Clinical Outcomes

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Background Antithrombotic recommendations following transcatheter aortic valve replacement (TAVR) are largely based on previous trial protocols. The efficacy and risk of anticoagulation has not been systematically assessed. The aim of this study was to determine the efficacy and safety of oral anticoagulation in patients with atrial fibrillation (AF) following TAVR with the Lotus Valve System (Boston Scientific, Marlborough, MA, USA).

Methods Consecutive patients with severe aortic stenosis who underwent Lotus valve implantation were prospectively recruited (n = 164). Atrial fibrillation patients prescribed oral anticoagulation (standard AF therapy) were compared to non-AF patients prescribed aspirin and clopidogrel (standard non-AF therapy). Twenty (20) of 164 patients were excluded, as they were not prescribed standard therapy. The primary endpoint was 6-month incidence of death, myocardial infarction, stroke/transient ischaemic attack (TIA) or major/life-threatening bleeding. Secondary endpoints included each component of the primary endpoint, defined according to VARC-2.

Results Overall, the primary endpoint occurred in 20.8% and 17.7% of the standard AF and standard non-AF therapy groups respectively (p = 0.82). There was no statistically significant difference in bleeding (12.5% versus 9.4%, p = 0.77) or stroke/TIA (2.1% versus 8.3%, p = 0.27) between the standard AF and standard non-AF therapy groups respectively.

Conclusions This study supports the safety of anticoagulation in AF patients, which did not result in excess risk of bleeding or stroke/TIA compared with dual antiplatelet therapy in non-AF patients.

Keywords Bleeding • Stroke • Transcatheter aortic valve replacement • Anticoagulation

Introduction

Transcatheter aortic valve replacement (TAVR) is an accepted treatment for patients with severe aortic stenosis (AS) at high surgical risk. Following TAVR, the incidence of ischaemic stroke and transient ischaemic attack (TIA) is estimated to be between 1.5 and 6% [1]. Furthermore, over one-third of TAVR patients have a history of atrial fibrillation

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(AF) and approximately 5–9% develop new onset AF with the additional risk of cerebrovascular events [2–4]. Most of these patients meet guideline recommendations for oral anticoagulation based on CHA_2DS_2-VASc criteria.

The efficacy and risks of antiplatelet versus anticoagulation therapy post-TAVR has not been well described. In post-TAVR patients, the American College of Cardiology guidelines recommend clopidogrel 75 mg daily for 3–6 months in conjunction with lifelong aspirin 75–100 mg. This recommendation has come under scrutiny as it is based on previous trial protocol rather than evidence of its efficacy [5,6]. There is very limited evidence to guide anticoagulation therapy in post-TAVR patients who have concurrent pre-existing or new onset AF.

The aim of the current study was to determine the efficacy and safety of oral anticoagulation with or without antiplatelet therapy in patients with pre-existing or new onset atrial fibrillation (AF) post-TAVR. This approach was compared to standard dual antiplatelet therapy in non-AF post-TAVR patients with a clinical outcome of stroke/TIA and major bleeding events.

Material and Methods

Patient Selection

Consecutive patients (n = 164) undergoing TAVR with the repositionable Lotus valve system (Boston Scientific, Marlborough, MA, USA) were prospectively recruited from a large tertiary TAVR referral centre in Melbourne (April 2012–October 2016). This centre has performed over 400 TAVR procedures, with an average of 80 TAVR procedures annually. Aside from the Lotus valve, the centre also implanted smaller numbers of the Sapien 3 valve (Edwards Lifesciences, Irvine, CA, USA) and the Medtronic Corevalve/Evolut R valve systems (Medtronic Incorporated, Minneapolis, MN, USA), however, only Lotus valve recipients were included in the current study. Patients with symptomatic severe aortic stenosis were determined to be at high or extreme surgical risk based on agreement within a heart valve team through clinical assessment of comorbidities, or a Society of Thoracic Surgeons score $\geq$8%.

Pre-TAVR Work-Up

All patients underwent baseline clinical assessment, laboratory investigations, electrocardiograph (ECG), echocardiography and coronary angiography prior to implantation [7]. Electrocardiographs were analysed at baseline, immediately post procedure and prior to discharge from hospital. ECGs were also reviewed where available at subsequent follow up. ECGs were analysed by a consultant cardiologist.

TAVR Implantation

The Lotus valve system was used for all patients with an 18-F or 20-F proprietary delivery sheath. TAVR implantation was conducted by two interventional cardiologists, who were experienced TAVR operators prior to commencement of this study. The heart valve team consisted of at least two interventional cardiologists, echocardiologist, anaesthetist and a cardiothoracic or vascular surgeon when required. General anaesthesia or intravenous sedation was used at the discretion of the operator according to standard local practice. All procedures involved balloon valvuloplasty with rapid ventricular pacing prior to the deployment of the valve system whilst post-dilatation was operator dependent.

Data Collection

Baseline demographic and procedural data was collected prospectively at time of enrolment in a dedicated TAVR database. Antithrombotic strategies and clinical outcomes were determined and tracked through retrospective chart analysis. The antithrombotic strategy was defined as the first strategy chosen following TAVR, prior to the occurrence of a primary or secondary endpoint. Formal 6-month follow-up was also performed for the majority of patients within our centre. For those who were followed up externally, outcomes were determined through medical records from external cardiologists. All ECGs were reported by a cardiologist with regard to presence of AF. All outcomes were defined according to the Valve Academic Research Consortium (VARC) 2 criteria [8].

Study Design

Patients were retrospectively divided into two groups for the purpose of data analysis—a standard AF therapy group (pre-existing or new onset) and standard non-AF therapy group. The standard AF therapy group were prescribed oral anticoagulation (vitamin K antagonist or novel oral anticoagulant [NOAC]), usually in addition to a single antiplatelet medication. The standard non-AF therapy group were prescribed dual antiplatelet therapy (DAPT) with aspirin and clopidogrel. Analysis was performed on an intention-to-treat basis, based on the first antithrombotic strategy prescribed for the patient post-TAVR.

Patients who were not prescribed standard therapy (n = 20) had other clinical factors influencing the clinician's decision to prescribe antithrombotic medication and were excluded from analysis. This included patients without AF who required anticoagulation or patients with AF who were contraindicated from anticoagulation. Ethics approval was obtained from the institutional Human Research Ethics Committee.

Endpoints

The primary endpoint was defined as a composite endpoint of death, myocardial infarction (MI), stroke/transient ischaemic attack (TIA), or major/life threatening bleeding between 24 hours and 6 months post-TAVR. Events occurring within the first 24 hours were excluded, as these were considered procedure related complications and usually occurred before the commencement, or recommencement, of antithrombotic medication. Patients who experienced multiple endpoints

were counted as one event for the composite endpoint. Secondary endpoints included each individual component of the primary endpoint.

In accordance with VARC-2, stroke was defined as an acute neurological deficit producing cerebral tissue damage on imaging with symptoms lasting more than 24 hours. Transient ischaemic attack was defined as a transient episode of focal neurological dysfunction with no tissue damage on imaging. Life threatening bleeding was defined as fatal bleeding, bleeding in a critical organ, bleeding causing hypovolaemic shock or an overt source of bleeding with a drop in serum haemoglobin ≥5.0 g/dL. Major bleeding was defined as overt bleeding with a drop in serum haemoglobin ≥3.0 g/dL and not meeting criteria for life threatening or minor bleeding. Myocardial infarction was defined as symptoms of cardiac ischaemia, detection of rise and fall of cardiac biomarkers or new ECG changes indicative of new ischaemia.

Statistical Analysis

Statistical analysis was conducted using RStudio for Windows (Version 0.99.903, 2016). Two-tailed tests with a significance level of 5% were used throughout. The independent t-test was used as a test for association between continuous variables. The chi-squared test was used as a test for association between categorical variables. The log-rank test was used as a test for association between survival distributions.

Results

A total of 164 patients underwent Lotus valve implantation. Antithrombotic strategies used for the entire cohort are summarised in Figure 1 for AF patients and Figure 2 for non-AF patients. From the total cohort, 59/164 (36%) had AF, 4.3% new onset and 31.7% pre-existing. A total of 20 patients were not prescribed standard therapy and were therefore excluded from the primary analysis.

Out of 144 patients prescribed standard therapy, the mean age was 84 ± 6 years and 45% were male. Baseline characteristics for the standard therapy cohort are shown in Table 1. Patients in the standard AF therapy group were more likely to have a permanent pacemaker ($p < 0.01$). There were no other statistically significant differences in baseline characteristics between groups. Patients in the standard AF therapy group had a mean CHA_2DS_2-VASc score of 3.8 ± 1.2.

For the 48 patients in the standard AF therapy group, 18 (37.5%) were prescribed NOACs and 30 (62.5%) were prescribed warfarin. From the standard AF therapy group 46/48 (95.8%) patients were prescribed anticoagulation in addition to a single antiplatelet medication (Table 2). One patient from the standard AF therapy group was prescribed aspirin, clopidogrel and anticoagulation at discharge, although this was shortly changed to aspirin and anticoagulation post-discharge. None of the endpoints were met in this patient. All patients in the standard non-AF therapy group were prescribed aspirin and clopidogrel only.

At a mean follow up of 5.4 ± 1.4 months, the primary composite endpoint occurred in 10 patients (20.8%) in the standard AF therapy group, compared with 17 patients (17.7%) in the standard non-AF therapy group ($p = 0.82$) (Table 3). The secondary endpoint of major or life threatening bleeds did not differ between the two groups (12.5% versus 9.4%, $p = 0.77$). The incidence of stroke or TIA was lower in the standard AF therapy compared with the standard non-AF therapy group, although this did not reach statistical significance (2.1% versus 8.3%, $p = 0.27$). Overall, the composite endpoint as well as bleeding events occurred more frequently in the first 3 months following TAVR (Figures 3 and 4).

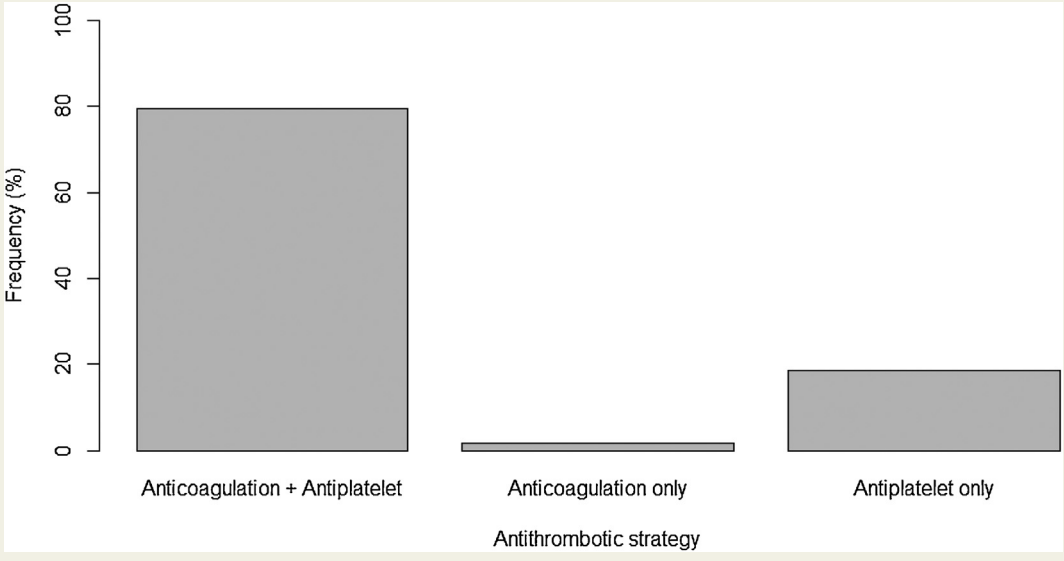

Figure 1 Antithrombotic strategies amongst all atrial fibrillation patients (n = 59).

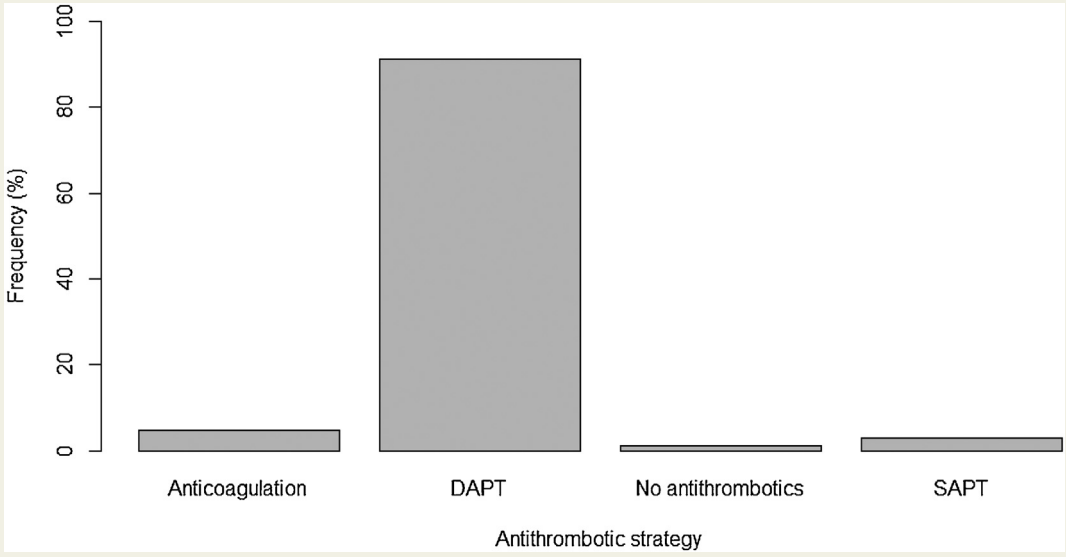

Figure 2 Antithrombotic strategies amongst all non-atrial fibrillation patients (n = 105).

One patient from the standard AF therapy group (2.1%) developed both major/life threatening bleeding in addition to stroke or TIA. Two patients from the standard non-AF therapy group (2.1%) developed both complications. Three patients from the standard AF therapy group died at 6 months (4.2%) and one patient had a myocardial infarction (2.1%). Two patients from the standard non-AF therapy group died at 6 months (2.1%) with no myocardial infarctions recorded.

Discussion

In the current study, a strategy of oral anticoagulation in post-TAVR patients with AF resulted in no increased risk of bleeding, with numerically lower but statistically similar rates of cerebrovascular events to patients without AF treated with DAPT. The overall rate of stroke/TIA was low (2.1% within the first 6 months) in patients post-TAVR with pre-existing or new onset AF treated with oral anticoagulation. This is despite a mean CHA_2DS_2-VASc of 3.8 in post-TAVR patients with AF. Most significant bleeding or cerebrovascular events occurred early following TAVR (usually within the first 3 months).

Pre-existing AF was present in 31.7% and new onset AF occurred in 4.3% of our TAVR cohort. This is comparable to other studies, which typically report a prevalence of pre-existing AF between 30–40% and new onset AF between 5–9% [2–4,9]

There have been several observational studies comparing a DAPT strategy to single antiplatelet therapy (SAPT) strategy

Table 1 **Baseline Characteristics.**

	Total (n = 144)	Standard AF therapy with OAC (n = 48)	Standard non-AF therapy with DAPT (n = 96)	P-value
Age, mean ± SD	84 ± 6	85 ± 5	83 ± 6	0.08
Male gender	66, 45%	24, 50%	42, 44%	0.60
Prior MI	13, 9%	3, 6%	10, 10%	0.61
Prior AVR	5, 4%	3, 6%	2, 2%	0.42
Prior stroke/TIA	15, 10%	5, 10%	10, 10%	1.0
Prior PPM	16, 11%	11, 23%	5, 5%	<0.01
COPD	27, 19%	8, 17%	19, 20%	0.82
Hypertension	113, 79%	34, 71%	79, 82%	0.17
Diabetes	30, 21%	7, 15%	23, 24%	0.28
CHA_2DS_2-VASc (±SD)	3.9 ± 1.1	3.8 ± 1.2	3.9 ± 1.1	0.64
Pre-TAVR serum Creatinine (mmol/L), mean ± SD	103 ± 70	107 ± 36	101 ± 81	0.66

Abbreviations: OAC, oral anticoagulation; DAPT, dual antiplatelet therapy; MI, myocardial infarction, AVR, aortic valve replacement; TIA, transient ischaemic attack; PPM, permanent pacemaker; COPD, chronic obstructive pulmonary disease

Table 2 Antithrombotic strategies in standard AF therapy cohort (n = 48).

	Frequency
OAC + Clopidogrel	19 (39.6%)
OAC + Aspirin	27 (56.2%)
OAC + Aspirin + Clopidogrel	1 (2.1%)
OAC only	1 (2.1%)
Total	48 (100%)

Abbreviation: OAC = oral anticoagulation; AF, atrial fibrillation

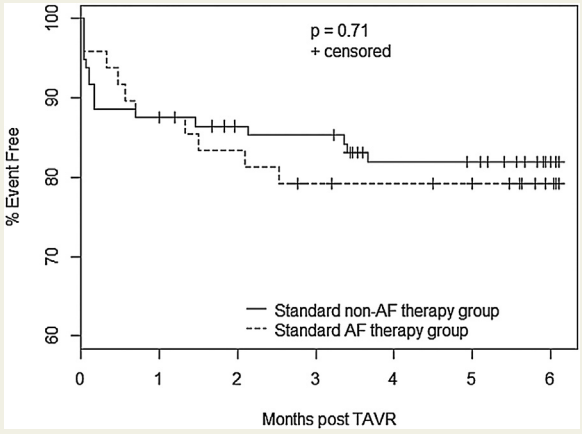

Figure 3 Kaplan–Meier curve for composite endpoint (n = 144).

following TAVR. Results from these studies have largely suggested no difference in stroke risk or MI with a trend towards excess bleeding in the DAPT strategy group [10–13]. Similar findings have been noted in three small randomised trials [14–16]. The POPular-TAVI (NCT02247128) trial will continue to compare the efficacy of these two strategies.

Few studies, however, have previously compared the use of oral anticoagulation to antiplatelets following TAVR. A small retrospective review previously compared three strategies—SAPT, DAPT and warfarin [17]. The combined endpoint of death, coronary events, stroke or bleeding was worse in the DAPT group compared with the other two strategies, with no excess bleeding noted in the warfarin group. It was suggested that DAPT did not appear to offer protection from adverse events whilst exposing the patient to excess bleeding risk.

Recent studies using four-dimensional computed tomography (CT) have suggested that subclinical leaflet thrombosis in transcatheter valves occurs more frequently than previously recognised [18,19]. Makkar et al. found a significantly reduced incidence in patients prescribed anticoagulation compared to those on DAPT [18]. These findings were correlated in a recent study of 931 patients following surgical and transcatheter bioprosthetic valve implantation. Reduced leaflet motion occurred in 15% of patients on DAPT compared to 4% on anticoagulation (with similar outcomes between NOAC and warfarin). Furthermore, reduced leaflet motion occurred more frequently in transcatheter valves (13%) compared with surgical valves (4%) [19]. With these recent findings, there may be an increased emphasis on using anticoagulation following TAVR, potentially even in patients without AF. This hypothesis is being examined by the GALILEO randomised trial (NCT02556203), which will compare rivaroxaban/SAPT to a DAPT strategy while the ATLANTIS randomised trial (NCT02664649) will similarly compare apixaban to the current standard of care (vitamin K antagonist if anticoagulation indicated, or DAPT if anticoagulation not indicated).

Our findings add to the literature supporting the use of oral anticoagulation post-TAVR in that it is effective and safe in patients with concurrent AF.

Table 3 Clinical outcomes between standard AF therapy and standard non-AF therapy groups.

6-month outcomes	Standard AF therapy with OAC (n = 48)	Standard non-AF therapy with DAPT (n = 96)	P-value
Composite endpoint (death OR MI OR stroke/TIA OR major/life threatening bleed)	10 (20.8%)	17 (17.7%)	0.82
Major/life threatening bleed	6 (12.5%)	9 (9.4%)	0.77
Stroke/TIA	1 (2.1%)	8 (8.3%)	0.27
Both major/life threatening bleeds AND stroke/TIA	1 (2.1%)	2 (2.1%)	1
Death	3 (6.3%)	2 (2.1%)	0.42
MI	1 (2.1%)	0 (0%)	
Follow up (months, mean ±SD)	5.2 ± 1.7	5.5 ± 1.2	0.21

Abbreviations: TIA, transient ischaemic attack; MI, myocardial infarction; AF, atrial fibrillation; OAC, oral anticoagulation

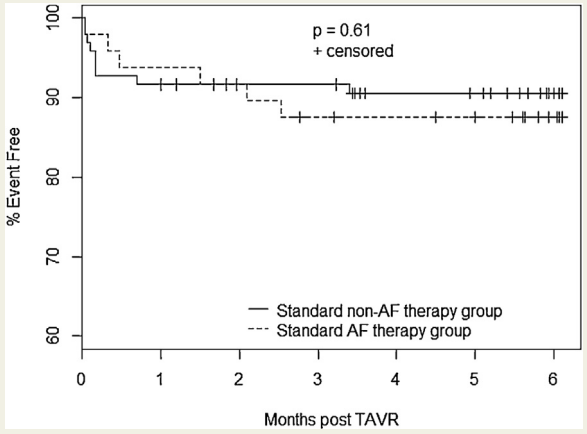

Figure 4 Kaplan–Meier curve for major/life threatening bleeding events (n = 144).

Limitations

Recent studies have reported a high frequency of subclinical valve thrombosis post-TAVR [18,19]. Within our cohort however, valve leaflet thrombosis is not reported as an endpoint, as not all patients underwent follow up CT scan.

While patients were prospectively recruited in a consecutive fashion, our analysis was limited to a single centre with small numbers of clinical events. Only the Lotus valve system was included in this analysis, which as of early 2017 has undergone a voluntary recall by Boston Scientific. Subsequently, this limits the generalisability of our results. Our findings require confirmation in a larger multi-centre prospective study.

Conclusion

Our study directly compares a strategy incorporating oral anticoagulation therapy in AF patients with a strategy of DAPT in non-AF patients following TAVR. Given our low rate of observed ischaemic and bleeding events, the use of oral anticoagulation in AF patients post-TAVR appears to be safe and effective.

Disclosures

Dr Robert Gooley has received proctor fees from Boston Scientific. All other authors have no potential conflict of interest.

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