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Routine use of anticoagulation after transcatheter aortic valve replacement: Initial safety outcomes from a single-center experience☆,☆☆

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ABSTRACT

Background: Subclinical leaflet thrombosis (SCLT) can be seen in up to 12% of patients after transcatheter aortic valve replacement (TAVR). Anticoagulation appears to prevent and reverse SCLT but concerns exist about bleeding risk.
Methods: Our program adopted a strategy of routine anticoagulation after TAVR, starting warfarin on post-procedure day 0 and continuing for 3 months in 10/2015. We report the initial safety and efficacy outcomes of this approach. Bleeding events were assessed using Valve Academic Research Consortium (VARC) and Bleeding Academic Research Consortium (BARC) definitions.
Results: The median (IQR) age of the population ($n = 191$) was 82 years (72–87) and the median (IQR) STS score was 5.6% (3–8). A total of 101 (53%) patients were discharged on anticoagulation (warfarin 97%) while 90 (47%) received antiplatelet therapy alone. The mean duration of anticoagulation therapy was 81 ± 17 days. During follow-up 7 patients (4%) had a stroke or TIA, 3 (3%) in the anticoagulation group and 4 (4%) in the antiplatelet group ($p = 0.71$). A total of 8 patients (4.2%) had BARC bleeding events during follow-up, 3 patients in the anticoagulation group (2.9%) and 5 in the antiplatelet group (5.5%, $p = 0.48$). All bleeding events (VARC and BARC) were numerically lower in the anticoagulation group (8% versus 13%, $p = 0.20$).
Conclusions: A strategy of routine anticoagulation for 3-months after TAVR is well tolerated and associated with similar or lower bleeding risk compared to antiplatelet therapy.

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1. Introduction

In 2015 Makkar et al. reported the first case series of reduced aortic-valve leaflet motion among patients undergoing surgical and transcatheter aortic valve replacement (TAVR) in a clinical trial and two registries [1]. Among patients receiving antiplatelet therapy the incidence of reduced leaflet motion was 55% in the clinical trial and 29% in the pooled registries [1]. In contrast, among patients treated with warfarin the incidence of reduced leaflet motion was 0%. Of the 11 patients with reduced leaflet motion that underwent follow-up computed tomography (CT), and were prescribed warfarin, restoration of leaflet motion was noted in all. Although the clinical significance of this imaging finding remains under investigation, the prevailing view is that it represents subclinical leaflet thrombosis (SCLT) of bioprosthetic aortic valves [1,2]. In a follow-up study Chakravarty et al. showed that SCLT is associated with increased trans-valvular gradients, increased risk of stroke and transient ischemic attack (TIA) [3].

The risk of thromboembolism after surgical aortic valve replacement (SAVR) is highest in the first 90 days after the operation (up to 41% in the first 10 days) and then decreases to 1.9%/year beyond 90 days [4]. Given these considerations our heart team decided to change the antithrombotic regimen after TAVR in October 2015; from dual antiplatelet therapy with clopidogrel and aspirin (ASA) to warfarin therapy to a goal international normalized ratio (INR) between 2 and 3 for 90 days and

Abbreviations: TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; NOAC, novel oral anticoagulant; CT, computed tomography; SCLT, subclinical leaflet thrombosis; VARC, valve Academic Research Consortium; BARC, bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy.

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life-long ASA, unless contraindications to anticoagulation were present. In this manuscript we report our early experience with this approach.

2. Methods

2.1. Setting

The Minneapolis VA Healthcare System (MVAHCS) is a tertiary, 250-bed hospital within the VA Midwest Heath Care Network (Veterans Integrated Service Network VISN 23). The network serves >440,000 enrolled Veterans residing in the states of Iowa, Minnesota, Nebraska, North Dakota, South Dakota, and portions of Illinois, Kansas, Missouri and Wyoming. The MVAHCS is the only approved TAVR program in a nine state area and has an academic affiliation with the University of Minnesota Medical Center (UMMC) [5]. The TAVR program at the Minneapolis VAMC was established in April of 2015. Prior to that date, all of TAVR procedures were performed at the University of Minnesota Medical Center.

2.2. Patients, study intervention and outcomes

We included 191 patients treated with TAVR at MVAHCS and the University of Minnesota Medical Center (UMMC) from April 2015 to February 2017. We excluded patients that underwent transcatheter valve replacement in a non-aortic position (i.e. mitral valve in valve procedures or pulmonary). Patients that underwent TAVR procedures for off label indications (bicuspid valve, aortic insufficiency) and/or valve-in-valve (VIV) procedures were included in the analysis.

Prior to October 2015 (**Period 0 or pre-intervention**) our antithrombotic regimen consisted of dual antiplatelet therapy with clopidogrel 75 mg daily for 6 months and life-long ASA 81 mg daily. After October 2015 (**Period 1 or post-intervention**) the antithrombotic regimen consisted of warfarin (without bridging) starting on postoperative day 0 and continuing for 90 days or longer (if indicated for other reasons such as deep venous thrombosis, pulmonary embolism, or atrial fibrillation) in conjunction with life-long ASA 81 mg daily. The decision to use low-dose aspirin is consistent with current ACC/AHA guidelines. Patients with contraindications to anticoagulation were discharged on antiplatelet therapy and were included in the control group. Patients treated at UMMC in 2015 were included in the control group since this program never adopted the anticoagulation regimen. Therefore, the control group was comprised of patients treated at the MVAHCS pre- intervention as well as post-intervention as long as they had relative or absolute contraindications to anticoagulation, and patients treated at our University affiliate in 2015 (Supplementary Appendix Table 3). We compared the outcomes of patients discharged on anticoagulation versus antiplatelet therapy.

Outcomes measures included stroke, transient ischemic attack (TIA), vascular complications, bleeding, and in-hospital mortality. Outcomes were prospectively defined according to the Valve Academic Research Consortium (VARC) definitions [6]. Rates of bleeding 90-days after the index TAVR procedure were assessed using Bleeding Academic Research Consortium (BARC) definitions [7]. All patients treated with anticoagulation were enrolled in a dedicated anticoagulation clinic staffed by trained pharmacist and hematologists. All patients underwent echocardiograms for assessment of trans-valvular gradients and routine clinic visits between 30 and 90 days post procedure.

2.3. Statistical methods

Continuous variables are presented as mean ± SD, or as median with interquartile range when appropriate. Categorical variables are reported as frequencies and percentages. Continuous variables were compared using the unpaired Student *t*-test or Mann-Whitney *U* test as appropriate. Discrete variables were compared with the chi-square test or Fisher exact test as appropriate. A 2-sided p value <0.05 was considered to be statistically significant. Medcalc® version 17.2 was used for analysis.

This study was approved by the Institutional Review Board of the Minneapolis VA Medical Center and University of Minnesota. Individual consent requirement was waived.

3. Results

The study population consisted 191 consecutive patients undergoing TAVR between 2015 and 2017. The median (interquartile range) age of the patients was 82 years (72–87) and the median (IQR) Society of Thoracic Surgeons (STS) risk score was 5.6 (3–8). Baseline characteristics are presented in Table 1. A total of 101 patients (53%) were discharged on anticoagulation and 90 (47%) on antiplatelet therapy alone. Of the 101 patients treated with anticoagulation, 97 received warfarin and 3 received a novel oral anticoagulant (NOAC) for a mean (±SD) duration of 81 days (17). In addition, 76 (84%) received antiplatelet therapy with ASA or clopidogrel. Of the patients discharged on antiplatelet therapy alone 83 (92%) received ASA and 76 (84%) received dual antiplatelet therapy (DAPT) for 6 months (Table 2). Thirteen patients underwent TAVR after the intervention but were discharged on antiplatelet therapy alone because of real or perceived contraindications to anticoagulation. A summary of contraindications to anticoagulation, as listed in the medical record, is presented in Table 1 of the Supplemental Appendix. The median time to therapeutic INR in the anticoagulation group was 11 days (IQR: 16 days). The proportion of therapeutic INRs (between 2.0 and 3.0) relative to the total number of INRs measured was 43% (±19) among patients followed the VA. Atrial fibrillation was more prevalent in the anticoagulation group (44% versus 17%, $p <$ 0.01). The mean (±SD) HASBLED score was 2.9 (0.7) in the control group and 3.5 (1.2) in the anticoagulation group ($p < 0.01$). Otherwise there were no significant inter-group differences (Table 1).

Transfemoral (TF) access was used in 155 patients (81%) and alternative access in 36 (19%). Alternative access included transapical 7.3%, transaortic 0.5%, transilliac 1%, axillary 4%, and subclavian 6%. A balloon-expandable valve (SAPIEN XT or SAPIEN 3, Edwards Life sciences, Irvine, CA) was used in 153 (80%) patients and a self-expandable valve (Corevalve or Evolut R, Medtronic, Minneapolis, MN) in the remaining 38 patients (20%). No inter-group differences in

Table 1
Baseline characteristics.

Parameter	Overall ($n = 191$)	Control ($n = 90$)	AC ($n = 101$)	P
Age–years median- IQR	82 (72–87)	82 (73–87)	81 (72–87)	0.90
Male gender	83%	72% (65)	92% (93)	1.00
STS score median- IQR	5.6 (3–8)	6.7 (3–9)	5 (3–7)	0.16
Weight (kg)	90 ± 23	85 ± 25	94 ± 20	<0.01
COPD	40% (76)	38% (34)	42% (42)	0.18
Dialysis	6% (11)	3% (3)	8% (8)	0.13
Prior PCI	30% (57)	42% (38)	19% (19)	<0.01
Prior CABG	27% (52)	23% (21)	31% (31)	0.27
Prior AF	31% (59)	17% (15)	44% (44)	<0.01
Home O2	13% (25)	12% (11)	14% (14)	0.60
TIA	12% (22)	9% (8)	14% (14)	0.21
Prior CVA	15% (29)	9% (8)	21% (21)	0.01
Prior myocardial infarction	19% (36)	30% (27)	9% (9)	<0.01
Prior heart failure	29% (56)	36% (32)	24% (24)	0.20
EF- % mean ± SD	51 ± 11	52 ± 12	50 ± 11	0.25
Immunocompromised	11% (21)	12% (11)	10% (10)	0.74
BMI	31 ± 7	30 ± 8	32 ± 6	0.06
Creatinine median- IQR	1.1 (0.9–1.4)	1 (0.8–1.4)	1.1 (0.9–1.4)	0.13
Hemoglobin (g/dl) median- IQR	13 (11–14)	12 (11–14)	13 (11–14)	0.02
Platelets	196 ± 79	202 ± 90	191 ± 64	0.35
Albumin	3.5 ± 0.5	3.5 ± 0.4	3.4 ± 0.5	0.53
HASBLED score, mean (±SD)	3.2 ± 1	2.9 ± 0.7	3.5 ± 1.2	<0.01

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