Nonusefulness of Antithrombotic Therapy After Surgical Bioprosthetic Aortic Valve Replacement

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Controversy persists regarding the advisability of anticoagulation for the early period after biological surgical aortic valve replacement (AVR). We aim to examine the impact of various antithrombotic regimens on outcomes in a large cohort of biological AVR patients. Records of 1,111 consecutive adult patients who underwent surgical biological AVR at our institution between 2013 and 2017 were reviewed. Outcomes included stroke, bleeding, and death at 3 and 12 months. Treatment regimens included (1) no therapy, (2) anticoagulants (warfarin or Factor Xa inhibitors), (2) antiplateles (various), and (4) anticoagulants + antiplatelets. Kaplan-Meier analysis was used to track outcomes, and Cox-proportional hazards regression models were conducted to analyze effects of different therapies on adverse events.

At 3 months, thromboembolic events were low and not significantly different between the no therapy group (2.2%) and anticoagulation (2.8%) or anticoagulation + antiplatelet (3.6%) or all groups (3.7%). The antiplatelet group was just significantly lower, at 2.2%. However, this was driven by non-stroke cardiovascular events in patients with coronary artery disease. The incidence of death at 3 months was low and not significantly different between all groups. At 12 months, there were no thromboembolic benefits between groups, but bleeding events were significantly higher in the anticoagulation group (no therapy (1.4%), anticoagulation (8.4%), antiplatelet (4.5%), anticoagulation + antiplatelet (7.9%)). In conclusion, none of the antithrombotic regimens showed benefits in stroke or survival at 3 or 12 months after biological AVR. Anticoagulation increased bleeding events. Routine anticoagulation after biological AVR appears to be unnecessary and potentially harmful. **(Am J Cardiol 2020;129:71−78)**

Valvular heart disease is one of the most common pathologic disorders, affecting 1.8% of people in United States and millions worldwide.[1,2] Aortic valve stenosis (AS) is the most common cardiac valvular pathology.[3] Severe AS is typically treated surgically with aortic valve replacement (AVR). Biological prosthetic valves, albeit less durable, are often preferred over mechanical valves for being less thrombogenic and not requiring life-long anticoagulation.[2,4] The recent societal guidelines recommend postoperative anticoagulation treatment with a vitamin K antagonist or acetylsalicylic acidfor patients after biological AVR for at least 3-months postoperatively.[5-7] However, level of evidence is suboptimal and there is currently no unequivocal consensus.[8-12] In fact, multiple studies question the benefit of using anticoagulation agents after a surgical bioprosthesis is placed and uncertainty persists.[13-18] In this study, we evaluate the efficacy of (and clinical need for) early antithrombotic therapy in patients undergoing surgical bioprosthesis AVR

Methods

We reviewed electronic medical records (EPIC software) of 1,734 consecutive adult patients who underwent AVR from February 2013 through November 2017. 623 patients were excluded due to: mechanical valve implantation (n = 606), patients who expired after surgery, but before hospital discharge (n = 10), and patients lost to follow-up (n = 7) (Figure 1). The resulting 1,111 patients were included, all of whom underwent primary AVR with a biologic prosthesis [ICD-10-CM]).

This study was approved by the Human Investigation Committee of Yale University. Requirement for informed consent was waived due to the retrospective nature of this medical record review.

In-hospital and outpatient data included following variables: bleeding during follow-up (any type of bleeding

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See page 77 for disclosure information.

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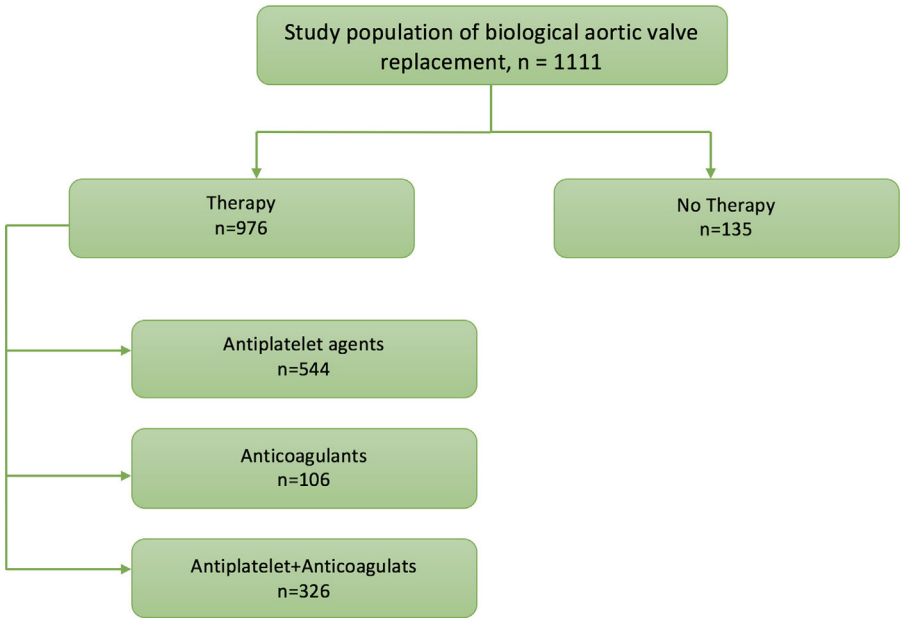

Figure 1. Population flow diagram.

severe enough to require medical attention, such as transfusions or surgical intervention), hemorrhagic strokes, thromboembolic events (ischemic strokes, transient ischemic attacks (TIA)), and mortality. All variables were registered at 3 and 12-months postoperatively. We also collected anthropometric data: age, gender and race.

Use of postdischarge medications was recorded from discharge summaries in electronic medical records (EPIC). Patients were stratified into four groups based on postdischarge therapy: antiplatelet-only (n = 544, 48.9%)(acetylsalicylic acid 81 mg to 325 mg daily), anticoagulant therapy (warfarin or factor Xa inhibitors (rivaroxapan or apixaban, n = 106, 9.5%)), antiplatelet plus anticoagulants (n = 326, 29.3%), and no therapy (n = 135, 12.5%) (Figure 2). In addition to aspirin, 36 patients (6.6%) were also taking a P2Y12 receptor antagonist (clopidogrel 75 mg or ticagrelor 90 mg). Only four patients (0.7%) were solely only P2Y12 antagonists.The patients receiving anticoagulants were discharged on warfarin (1.5 mg to 10 mg daily) with target INR 2.0 to3.0 (n = 96; 90.6%). The remaining patients in that group (n = 10; 9.4%) received Xa inhibitors: rivaroxaban 10 mg to 20 mg daily, or apixaban 2.5 mg to 5 mg one or two times daily.

In the antiplatelet + anticoagulants group, in antiplatelet agents, 97.54% (n = 318) of patients were on aspirin oral therapy, and the rest (2.46% n = 8) on clopidogrel (P2Y12 antagonist). Warfarin was prescribed to 89.99% (n = 293) of patients in that group, whereas factor Xa inhibitors were used in only 9.99% (n = 33) (Figure 3). The "no therapy group" received no any antiplatelet agents or anticoagulation therapy throughout the follow-up period.

Statistical analysis was performed using R 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).[19] Continuous variables are presented as mean± standard deviation, or median with range, whereas categorical variables are presented as values and percentages.

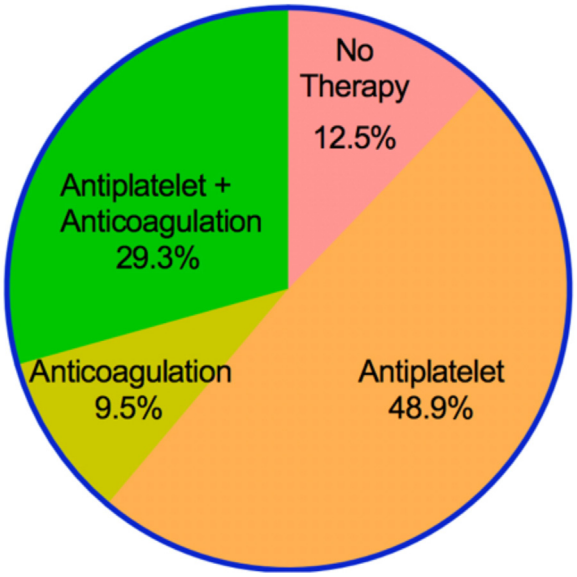

Figure 2. Prevalence of antithrombotic therapy strategies after discharge.

Kaplan-Meier (K-M) curves display the survival probability in all groups. Cumulative risks for definite, possible, and total events were plotted. Cox-proportional hazards regression models were conducted to analyze effects of different therapies on various adverse events, including mortality, bleeding, thrombosis, and stroke. Patient age at surgery, gender, and atrial fibrillation were taken into account in the Cox regression as control variables.

Results

1 111 patients who survived to hospital discharge after surgical biological AVR between 2013 and 2017. Median

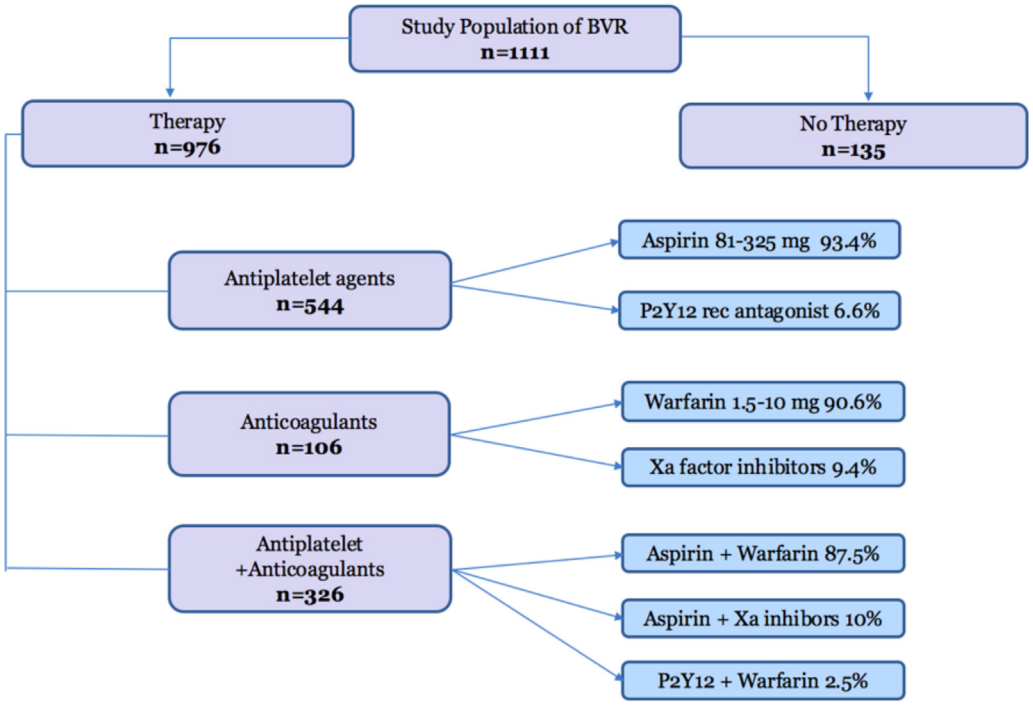

Figure 3. Antithrombotic therapy strategies at discharge.

age was 69.86 ± 10.86 (range 22 to 87), with 64.4% men and 35.6% women. 69.8% of patients had aortic stenosis, 19.1% had aortic insufficiency, and 8.2% had mixed disease. Bicuspid aortic valve was found in 20.1% of patients, ascending aortic aneurysm in 23.1%, and descending aortic aneurysm in 1.7% (Table 1). (Frequency of ascending aortic aneurysms reflects the concentration of our Aortic Institute.)

Table 1
Patient characteristics stratified by discharge antithrombotic strategy

Parameter	No therapy group (n = 135)	Post-discharge Therapy Groups				p - Value	Total (n = 1,111)
		Therapy (all 3 subgroups) (n = 976)	Antiplatelet (n = 544)	Anticoagulants (n = 106)	Antiplatelet + Anticoagulants (n = 326)		
Age (years)	69.09 ± 10.52	70.64 ± 11.21	69.97 ± 11.23	70.44 ± 12.99	71.82 ± 10.48	-	69.86 ± 10.86
Male	84 (62.2%)	632 (64.7%)	350 (64.3%)	71 (66.9%)	211 (64.7%)	0.564603	716 (64.4%)
Female	51 (37.8%)	344 (35.3%)	194 (35.7%)	35 (33.1%)	115 (35.3%)	0.564603	395 (35.6%)
White	123 (91.1%)	865 (88.6%)	475 (87.3%)	96 (90.5%)	294 (90.1%)	0.388608	988 (88.9%)
Black	9 (6.6%)	49 (5.0%)	32 (5.8%)	5 (4.7%)	12 (3.6%)	0.420284	58 (5.2%)
N. American	3 (2.2%)	2 (0.2%)	1 (0.1%)	0	1 (0.3%)	0.00103*	5 (0.5%)
Asian	0 (0%)	11 (1.0%)	8 (1.4%)	0	3 (0.9%)	-	11 (1%)
Hispanic	0 (0%)	39 (3.9%)	24 (4.4%)	3 (2.8%)	12 (3.6%)	-	39 (3.5%)
Unknown	0 (0%)	10 (1.0%)	4 (0.7%)	2 (1.8%)	4 (1.2%)	-	10 (0.9%)
Aortic Stenosis (AS)	76 (54.8%)	699 (71.6%)	402 (73.8%)	68 (64.1%)	229 (70.2%)	0.00028*	775 (69.8%)
Aortic Insufficiency (AI)	44 (32.5%)	157 (16.0%)	78 (14.3%)	28 (26.4%)	51 (15.6%)	<0.001*	201 (19.1%)
Combined AS & AI	6 (4.4%)	85 (8.7%)	45 (8.2%)	7 (6.6%)	33 (10.1%)	0.090347	91 (8.2%)
Bicuspid aortic valve	24 (17.7%)	209 (21.4%)	121 (22.2%)	27 (25.4%)	61 (18.7%)	0.330717	233 (20.1%)
Ascending aortic aneurysm	69 (51.1%)	188 (19.2%)	100 (18.3%)	38 (35.8%)	50 (15.3%)	<0.001*	257 (23.1%)
Descending aortic aneurysm	3 (2.2%)	16 (1.6%)	11 (2.0%)	3 (2.8%)	2 (0.6%)	0.624419	19 (1.7%)
Dissection Type A	1 (0.7%)	17 (1.7%)	11 (2.0%)	1 (0.9%)	5 (1.5%)	0.387861	18 (1.6%)
Dissection Type B	4 (2.9%(	1 (0.1%)	1 (0.1%)	0	0	<0.001*	5 (0.4%)
CAD	38 (28.1%)	501 (51.3%)	277 (50.9%)	38 (35.8%)	186 (57.0%)	<0.001*	539 (48.5%)
PAD	4 (2.9%)	63 (6.4%)	36 (6.6%)	6 (5.6%)	21 (6.4%)	0.110163	67 (6%)
Atrial fibrillation	47 (34.8%)	430 (44.0%)	152 (27.9%)	73 (68.8%)	205 (62.8%)	0.042005*	477 (42.9%)

n= number, % = percentage, CAD = coronary artery disease, PAD =peripheral artery disease.
* $p < 0.05$.

Table 2
Clinical outcomes of antithrombotic therapy at 3-months after bioprosthetic aortic valve replacement

Group	No therapy (n = 135)	Therapy group								Total (n = 1,111)
		Total (n = 976)	p - Value	Antiplatelet (n = 544)	p - Value	Anticoagulants (n = 106)	p -Value	Antiplatelet + anticoagulants (n = 326)	p - Value	
Hemorrhage	2 (1.4%)	31 (3.1%)	0.276973	11 (2.0%)	0.681621	6 (5.6%)	0.072258	14 (4.2%)	0.013399*	33 (2.97%)
Hemorrhagic stroke	0 (0%)	6 (0.6%)	-	2 (0.9%)	-	1 (1%)	-	3 (0.9%)	-	6 (0.545)
Other	2 (1.4%)	25 (2.5%)	0.444993	9 (1.6%)	0.886718	5 (4.7%)	0.137647	11 (3.3%)	0.026393*	27 (2.43%)
Thromboembolic events	5 (3.7%)	22 (2.2%)	0.305276	7 (1.2%)	0.056428	3 (2.8%)	0.70718	12 (3.6%)	0.990601	27 (2.43%)
Embolic Stroke	3 (2.2%)	15 (1.5%)	0.554412	7 (1.2%)	0.419304	1 (0.9%)	0.4405516	7 (1.2%)	0.95989	18 (1.62%)
Other	2 (1.4%)	7 (1.1%)	0.353147	0 (0%)	-	2 (1.8%)	0.856102	5 (1.5%)	0.606457	9 (0.81%)
Mortality	2 (1.4%)	11 (1.1%)	0.719648	2 (0.3%)	0.130102	5 (4.7%)	0.137647	4 (1.2%)	0.826348	13 (1.17%)

Thromboembolic events (thrombosis, ischemic stroke, TIA); Hemorrhage (hemorrhage stroke, any bleeding).
* $p < 0.05$.

Clinical characteristics and comorbidities are listed in Table 1.: coronary artery disease (CAD) (48.5%) and atrial fibrillation (both previous and postoperative) were common

The 3-months incidence of death after hospital discharge was low (no therapy 1.4%; antiplatelet 0.3%; anticoagulants 4.7%; antiplatelet + anticoagulant 1.2%) and not significant different ($p = 0.13$, $p = 0.13$, $p = 0.82$ respecttively). Also, there is no significant difference between no-therapy (1.4%) versus all three antithrombic groups 1.1% ($p = 0.71$) (Table 2).

We excluded patients with perioperative mortality since the study concerned impact of anticoagulation on postdischarge events. At the 3-months evaluation, survival rates were no different between the no therapy and the three therapy groups (antiplatelet, anticoagulants, and antiplatelet plus anticoagulant) ($p = 0.24$, $p = 0.15$ and $p = 0.79$, respectively).

The 3-months incidence of thromboembolic events after discharge was low and not significantly different between the no-therapy group and the therapy groups combined (3.7%, $p = 0.30$) or indivicually: anticoagulants (2.8%, $p = 0.71$) and antiplatelet + anticoagulants (3.6%, $p = 0.99$). However, we did identify significantly lower events in the antiplatelet group (1.2%, $p = 0.05$) (Table 2), also seen in the K-M plot (1.2%, $p = 0.042$) (Figure 4) compared with no therapy (2.2%). Interestingly, anticoagulants-only and antiplatelet +anticoagulants showed no significant differences at 2.8% ($p = 0.70$), and 3.6% ($p = 0.99$) respectively. We stratified the antiplatelet group into 2 subgroups: patients with and without history of CAD or CABG. K-M analysis showed a trend toward lower rates of thrombosis in patients with CAD on antiplatelets versus non-CAD group ($p = 0.099$) (Figure 5). The benefit trend appeard after bioprosthesis AVR only in patients with CAD.

For the thromboembolic subgroup of stroke, there was no difference in incidence rates between no therapy and therapy, or between no therapy and any therapy subcategory (Table 2).

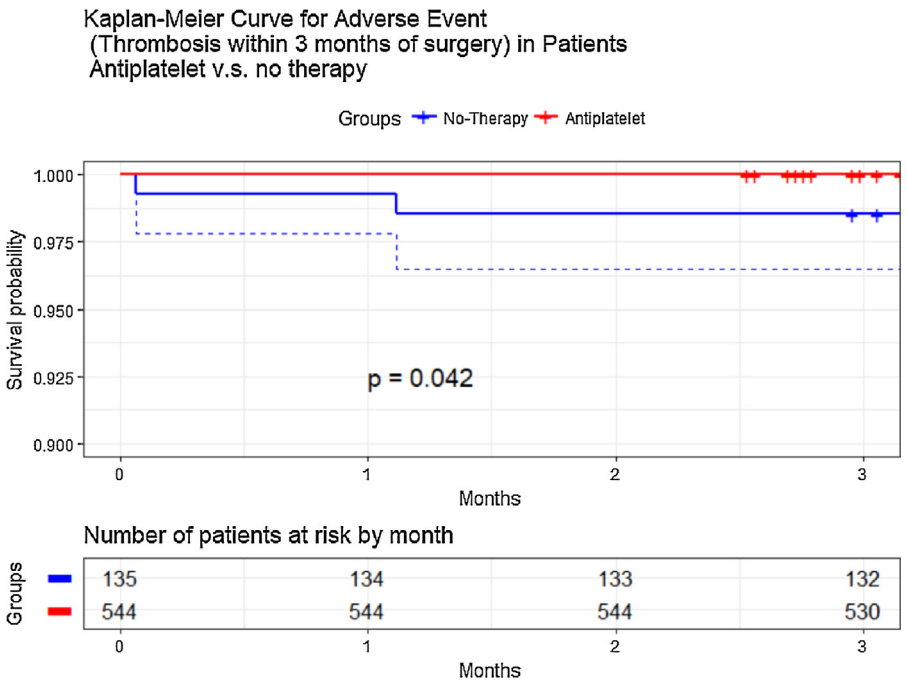

Figure 4. Kaplan-Meier curve for thrombosis in the no therapy and antiplatelet group.

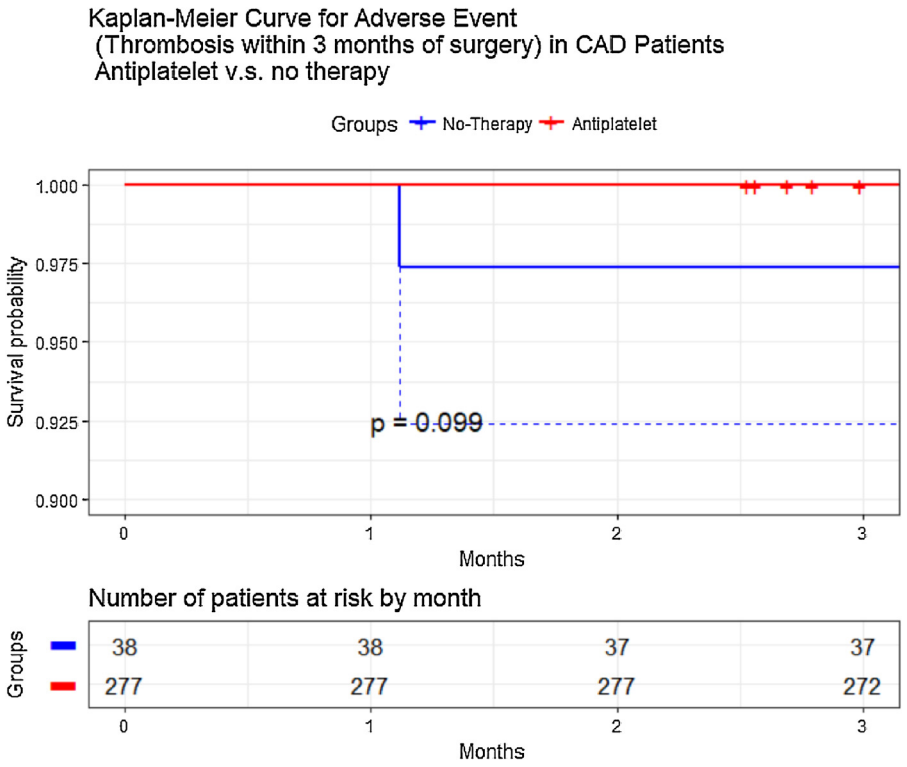

Figure 5. Kaplan-Meier curve for thrombosis in patients of the no therapy and antiplatelet group with CAD .

The 3-months incidence of bleeding (all types except hemorrhagic stroke) was slightly higher in the antiplatelet and anticoagulant group versus no therapy, although not significantly (2.0%; 5.6%; versus 1.4 p = 0.68; p = 0.07%). However, antiplatelet + anticoagulants increased risk of hemorrhage significantly (p = 0.01), Table 2.

Thus, none of the therapy groups showed benefit after biological AVR during the first 3-months, except fewer thromboembolic events (stroke, deep venous thrombosis or pulmonary embolism) in patients on antiplatelet agents with CAD. Furthermore, antiplatelet + anticoagulant therapy was associated with a higher risk of hemorrhage.

We assessed postoperative adverse events also aftter the first year following AVR. Overall, 1-year mortality occurred in 3.7% (n = 5) of patients in the no-therapy group, 2.2% (n = 12) (p = 0.31) in patients on antiplatelet agents, 6.6% (n = 7) (p = 0.30) in patients on anticoagulants, and 4.6% (n = 15) (p = 0.66) in patients on antiplatelet therapy and anticoagulants. Thromboembolic events or ischemic or hemorrhagic strokes were not significantly different at 12-months follow-up in no therapy group (4.4%) versus therapy groups (3.8%)(p = 071). However, bleeding and hemorrhagic events were significantly higher in the therapy groups compared with no therapy (no therapy 1.4%, antiplatelets 4.5% p = 0.09, anticoagulants 8.4% p = 0.01, antiplatelets + anticoagulation 7.9% p = 0.006 (Table 3) and (Figure 6).

Thus, 12-months antithrombotic therapy after AVR conferred no advantage in prevention of early cerebral ischemic events after biological AVR. Moreover, anticoagulants put patients at higher risk of bleeding.

Table 3
One-year outcomes of antithrombotic therapy after bioprosthetic aortic valve replacement

Group	No therapy (n = 135)	Therapy group								Total (n = 1,111)
		Total (n = 976)	p - Value	Antiplatelet (n = 544)	p -Value	Anticoagulants (n = 106)	p - Value	Antiplatelet + anticoagulants (n = 326)	p - Value	
Hemorrhage	2 (1.4%)	60 (6.4%)	0.026851*	25 (4.5%)	0.097437	8 (8.4%)	0.019039*	27 (7.9%)	0.006204*	62 (5.58%)
Hemorrhagic stroke	0 (0%)	9 (1.4%)	-	5 (0.9%)	-	1 (1.0%)	-	3 (0.9%)	-	9 (0.81%)
Other	2 (1.4%)	51 (5.5%)	0.055759	20 (3.6%)	0.197309	7 (7.2%)	0.037366*	24 (7.0%)	0.012752*	53 (4.77%)
Thromboembolic events	6 (4.4%)	37 (3.8%)	0.712771	16 (2.9%)	0.377255	4 (4.1%)	0.795472	17 (5.2%)	0.729584	43 (3.87%)
Embolic Stroke	3 (2.2%)	26 (2.7%)	0.762881	13 (2.3%)	0.90858	3 (3.1%)	0.763662	10 (3.0%)	0.617855	29 (2.61%)
Other	3 (2.2%)	11 (1.1%)	0.284974	3 (0.5%)	0.063361	1 (1.0%)	0.440516	7 (2.1%)	0.95989	14 (1.26%)
Mortality	5 (3.7%)	34 (3.4%)	0.896379	12 (2.2%)	0.31875	7 (6.6%)	0.304245	15 (4.6%)	0.666858	39 (3.51%)

Thromboembolic events (thrombosis, ischemic stroke, TIA); Hemorrhage (hemorrhage stroke, any bleeding).
* $p < 0.05$.

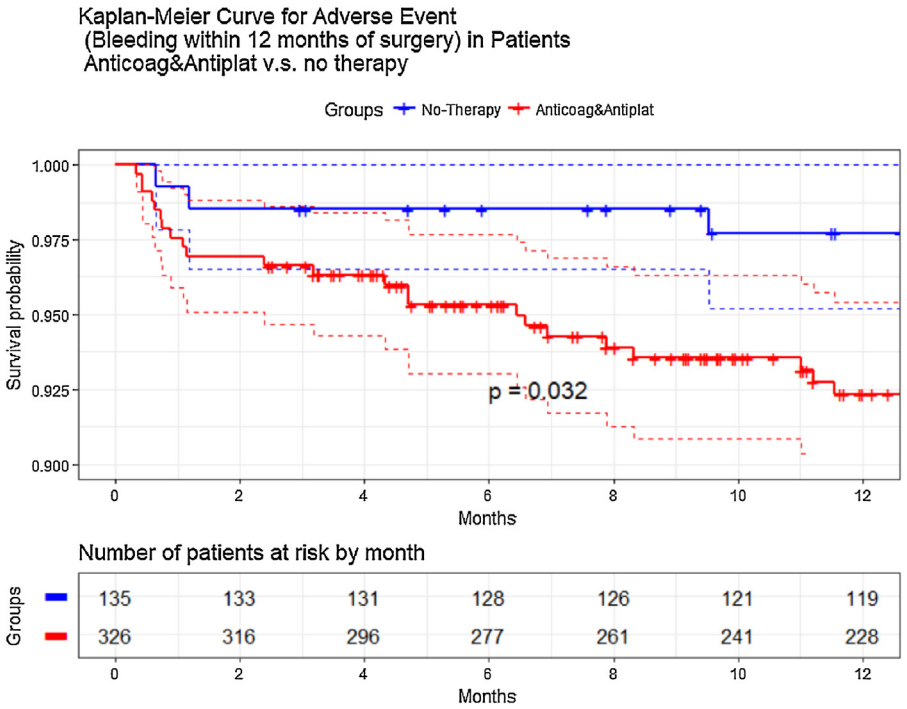

Figure 6. Kaplan-Meier curve for bleeding events in the no therapy and antiplatelet group.

Table 4
Cox proportional hazard regression analysis results of mortality

Risk factor	Parameter estimate	p - Value	Hazard ratio (HR) (95% CI for HR)
Therapy	−0.226235	0.64376	0.79 (0.3057−2.080)
Age at surgery	0.002298	0.89162	1.00 (0.9697−1.036)
Female	−0.264823	0.47004	0.76 (0.3741−1.574)
Coronary artery disease	0.150140	0.66284	1.16 (0.5917−2.282)
Atrial fibrillation	0.997740	0.00448	2.71 (1.363−5.397)

Risk factors like patient age at surgery, gender, and atrial fibrillation are taken into account in the Cox regression as control variables. In general, we did not find evidence of significantly different outcomes between all treatment groups and no-treatment group. However, patients with atrial fibrillation, regardless of therapy, were at nearly 3-fold higher increased risk of mortality (HR = 2.71, 95% CI 1.36 to 5.40, p = 0.0045) (Table 4).

Disscussion

Optimal anticoagulation strategy after bioprosthetic AVR still remains questionable.[7,13] Clinicians may be infuenced to anticoagulate by virtue of a catastrophic anectodal experience or fear of potential medicolegal repurcussions of not anticoagulating. Our study provides evidence in a large number of patients to clarify real world benefits and demerits of anticoagulation.

Coli demonstrated that patients treated with warfarin as compared with aspirin received no benefit in postoperative ischemic events, bleeding, and overall survival in the first 3 months after biological AVR.[20] Recently, Rafiq found no significant advantage of warfarin over aspirin for thromboembolism prevention in patients with biological AVR during the first 3 months after surgery.[17] Multiple other studies have questioned the utility of anticoagulation after biological AVR.[15,18,21,22] Even 20 years ago, our own group compared warfarin to no-therapy after biological AVR, finding that early anticoagulation after a bioprosthesis seemed unnecessary.[16] Moreover, a meta-analysis by Riaz et al. showed that anticoagulation in the setting of an aortic bioprosthesis significantly increases bleeding risk.[23]

This present study (over 1,000 patients with biological AVR) was designed to clarify whether early anthithrombotic therapy is necessary after biologic AVR, Does anticoagulation reduce thromboembolism or improve survival? Even within our 1 institution, post-AVR anticoagulation management varied greatly in clinicians. Strategies included: antiplatelet, anticoagulant, antiplatelet and anticoagulant treatment, and no therpay.

The risk of stroke events in our series was quite low. Further, we found no significant difference in thromboembolic events or survival at 3 and 12 months in patients on anticoagulants, aspirin, or both, compared with no-therapy after biological AVR.

We also demonstrated that anticoagulation strategies did increase the risk of hemorrhage during the observation period (See summary of study in Figure 7).

In one small subgroup of patients, those with history of CAD/CABG, a very small but statistically significant benefit of anticoagulation was seen at 3 and 12 months, manifested as decreased thrombotic events, but not strokes. Aspirin has long been recommended for secondary prevention after myocardial infarction or stroke.[24-27] In a sub-analysis, we stratified patients receiving aspirin into 2 groups: with CAD/CABG or without CAD or previous heart surgery. In this sub-analysis, we simply redemonstrated the well-known fact

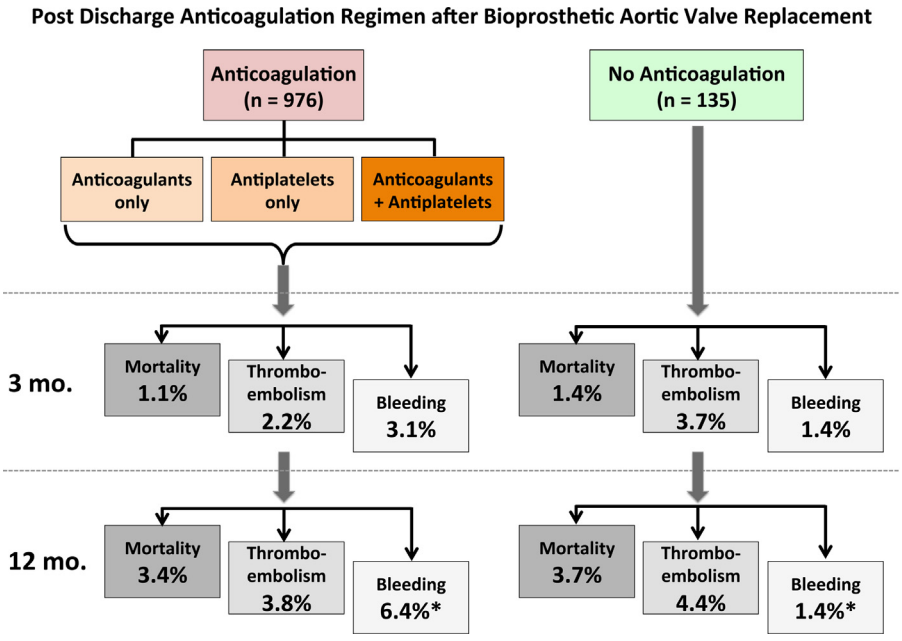

Figure 7. Summary of study results (* – Indicates significant increase in bleeding with anticoagulation. Note no significant difference in mortality or thromboembolism).

that aspirin reduces cardiovascular events in patients with CAD/CABG, but not in patients without CVD.

Another interesting finding in our study is that atrial fibrillation raises the mortality risk of AVR by nearly 3-fold. Concomitant atrial fibrillation may in its own right indicate anticoagulation therapy. That topic is beyond the scope of this study.

There are several limitations of the present study. 1. This is a retrospective, observational investigation, not a randomized, controlled trial. 2. Although we have precise discharge anticoagulation presecriptions, we do not have detailed information about drug compliance. 3. This study is limited by its single center nature. 4. We have limited our outcome analysis the first year after surgery. 5. Our findings in a tertiary referral center may not be representative.

In conclusion, this study of the antithrombotic therapy after surgical AVR with a bioprosthesis permits the following conclusions:

1) Antithrombotic regimens vary, even at a single institution.
2) The risk of cerebral embolic events is low in patients receiving bioprosthetic AVR.
3) Early and 1-year follow-up results reveal no significant difference in survival and thromboembolic events between four antithrombotic regimens (no antithrombotic medications, aspirin, oral anticoagulants, and aspirin plus oral anticoagulants).
4) Patients with CAD receiving aortic valve bioprostheses show benefit from antiplatelet therapy in period of 3 months postoperatively (in the form of reduction of thromboembolic events).
5) Antiplatelet and anticoagulant therapy were associated with increased risk of hemorrhage.
6) Atrial fibrillation regardless of therapy, increased the odds of adverse events (mortality).
7) Anticoagulation and antiplatelet therapy does not appear to offer benefit in patients without CAD undergoing surgical bioprosthetic AVR.

Author contributions

Anton A. Gryaznov: Writing – Original draft, validation. Ayman Saeyeldin: Visualization, Investigation. Mohamed Abdelbaky: Investigation. Mohammad A. Zafar: Methodology. Maryam Tanweer: Investigation. Mahnoor Imran: Data Curation. Dimitra Papanikolaou: Data Curation. Yupeng Li: Software, formal analysis. Bulat A. Ziganshin: Project administration, Resources. John A. Elefteriades: Conceptualization, Supervision, Reviewing and Editing.

Disclosures

Dr. John Elefteriades sits on the Data and Safety Monitoring Board of Terumo, consults for CryoLife, and is a principal of CoolSpine. The other authors have nothing to disclose.

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