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Anticoagulation After Surgical or Transcatheter Bioprosthetic Aortic Valve Replacement

Tarun Chakravarty, MD,[a] Akshar Patel, MD,[a] Samir Kapadia, MD,[b] Matthias Raschpichler, MD,[a] Richard W. Smalling, MD,[c] Wilson Y. Szeto, MD,[d] Yigal Abramowitz, MD,[a] Wen Cheng, MD,[a] Pamela S. Douglas, MD,[e] Rebecca T. Hahn, MD,[f] Howard C. Herrmann, MD,[d] Dean Kereiakes, MD,[g] Lars Svensson, MD, PhD,[b] Sung-Han Yoon, MD,[a] Vasilis C. Babaliaros, MD,[h] Susheel Kodali, MD,[f] Vinod H. Thourani, MD,[i] Maria C. Alu, MS,[f] Yangbo Liu, PhD,[j] Thomas McAndrew, PhD,[j] Michael Mack, MD,[k] Martin B. Leon, MD,[f,j] Raj R. Makkar, MD[a]

ABSTRACT

BACKGROUND There is paucity of evidence on the impact of anticoagulation (AC) after bioprosthetic aortic valve replacement (AVR) on valve hemodynamics and clinical outcomes.

OBJECTIVES The study aimed to assess the impact of AC after bioprosthetic AVR on valve hemodynamics and clinical outcomes.

METHODS Data on antiplatelet and antithrombotic therapy were collected. Echocardiograms were performed at 30 days and 1 year post-AVR. Linear regression model and propensity-score adjusted cox proportional model were used to assess the impact of AC on valve hemodynamics and clinical outcomes, respectively.

RESULTS A total of 4,832 patients undergoing bioprosthetic AVR (transcatheter aortic valve replacement [TAVR], n = 3,889 and surgical AVR [SAVR], n = 943) in the pooled cohort of PARTNER2 (Placement of Aortic Transcatheter Valves) randomized trials and nonrandomized registries were studied. Following adjustment for valve size, annular diameter, atrial fibrillation, and ejection fraction at the time of assessment of hemodynamics, there was no significant difference in aortic valve mean gradients or aortic valve areas between patients discharged on AC vs. those not discharged on AC, for either TAVR or SAVR cohorts. A significantly greater proportion of patients not discharged on AC had an increase in mean gradient >10 mm Hg from 30 days to 1 year, compared with those discharged on AC (2.3% vs. 1.1%, p = 0.03). There was no independent association between AC after TAVR and adverse outcomes (death, p = 0.15; rehospitalization, p = 0.16), whereas AC after SAVR was associated with significantly fewer strokes (hazard ratio [HR]: 0.17; 95% confidence interval [CI]: 0.05-0.60; p = 0.006).

CONCLUSIONS In the short term, early AC after bioprosthetic AVR did not result in adverse clinical events, did not significantly affect aortic valve hemodynamics (aortic valve gradients or area), and was associated with decreased rates of stroke after SAVR (but not after TAVR). Whether early AC after bioprosthetic AVR has impact on long-term outcomes remains to be determined. (Placement of AoRTic TraNscathetER Valves [PARTNERII A]; NCT01314313)
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From the [a]Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California; [b]Cleveland Clinic, Cleveland, Ohio; [c]University of Texas Health Science Center at Houston, Houston, Texas; [d]University of Pennsylvania, Philadelphia, Pennsylvania; [e]Duke University Medical Center/Duke Clinical Research Institute, Durham, North Carolina; [f]Columbia University Irving Medical Center/NewYork-Presbyterian Hospital, New York, New York; [g]The Christ Hospital, Cincinnati, Ohio; [h]Emory University, Atlanta, Georgia; [i]Medstar Heart & Vascular Institute, Washington Hospital Center, Washington, DC; [j]Cardiovascular Research Foundation, New York, New York; and [k]Baylor Scott & White Health, Plano, Texas. The PARTNER 2 Trial was funded by Edwards Lifesciences. Dr. Chakravarty has been a proctor and consultant for Edwards Lifesciences and Medtronic. Dr. Szeto has received grant support from Edwards Lifesicences and Metronic; and has served as a consultant for MicroInterventional Devices. Dr. Douglas has core lab contracts with Edwards Lifesciences. Dr. Hahn has core lab contracts with Edwards Lifesciences. Dr. Herrmann has received grant support from Abbott Vascular, Boston Scientific, Edwards Lifesciences, and Medtronic; and has served as a

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Transcatheter aortic valve replacement (TAVR) is the standard of care for intermediate- to high-risk patients with severe symptomatic aortic stenosis (AS) (1-8). The ongoing randomized clinical trials are further evaluating TAVR in low-risk patients with severe symptomatic AS; in patients with asymptomatic AS; as well as in patients with moderate AS and heart failure. There has also been a shift from mechanical to bioprosthetic aortic valves during surgical aortic valve replacement (SAVR) due to the aging population with severe AS and higher surgical-risk profile; bleeding risk associated with lifelong anticoagulation; and availability of transcatheter valve-in-valve as a treatment option for degenerative surgical bioprostheses (9). With expanding indications for TAVR, increasing use of bioprosthetic surgical valves, and recent reports on subclinical leaflet thrombosis in both transcatheter and surgical bioprosthetic valves (10-15), there is considerable interest in adjunctive pharmacotherapy with antiplatelet and anticoagulant (AC) agents after bioprosthetic AVR for the prevention of bioprosthetic valve thrombosis and to further optimize valve hemodynamics, durability, and clinical outcomes.

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The optimal antithrombotic and antiplatelet strategy following bioprosthetic AVR is not clear. Adjunctive pharmacotherapy after TAVR originally consisted of dual-antiplatelet therapy (DAPT) with aspirin and clopidogrel, as this was the regimen used in the PARTNER (Placement of Aortic Transcatheter Valves) and CoreValve IDE trials (1-5,7,8). But there is significant variation in the type and duration of pharmacotherapy after TAVR (16) and SAVR. The 2014 American College of Cardiology and American Heart Association guidelines for the management of valvular heart disease recommended DAPT with aspirin and clopidogrel for 6 months after TAVR and anticoagulation for 3 months after SAVR (17). The guidelines were recently updated, in the absence of supporting evidence, recommending 3 months of anticoagulation not only after SAVR but also after TAVR in patients at low risk of bleeding (18). Although bioprosthetic valve thrombosis is less prevalent in patients on anticoagulation (10,11), the impact of routine anticoagulation after bioprosthetic AVR on valve hemodynamics and clinical outcomes is not known. Moreover, bleeding complications after TAVR are associated with significant morbidity and mortality (19,20). Recently, the randomized controlled GALILEO (Global Study Comparing a rivaroxaban-based Antithrombotic Strategy to an anti-platelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes [NCT02556203]) trial (21) was prematurely halted because of increased risk of adverse events with anticoagulation compared with dual antiplatelet therapy. In the current substudy of PARTNER 2 trials and registries, we evaluated the impact of AC after bioprosthetic AVR by comparing valve hemodynamics and clinical outcomes between patients who were discharged on AC with those who were not discharged on AC.

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVR = aortic valve replacement

DAPT = dual antiplatelet therapy

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

TIA = transient ischemic attack

METHODS

STUDY DESIGN AND PATIENT POPULATION. The analysis presented in this manuscript includes the pooled cohort of all patients undergoing bioprosthetic AVR in the PARTNER 2 randomized trials and the nonrandomized registries. The PARTNER2 trial was a prospective, multicenter study that enrolled patients with severe symptomatic AS. The pooled cohort included the randomized PARTNER 2A (intermediate risk) (8) and PARTNER 2B (inoperable) (22) trials as well as the nonrandomized registries of Sapien-XT for valve-in-valve (23) and alternate access; and Sapien 3 valve in intermediate-risk (7) and high-risk (24) patients. The design of the randomized PARTNER 2A and 2B trials as well as the

consultant for Edwards Lifesciences. Dr. Kereiakes has served as a consultant for Boston Scientific, Abbott Vascular, and REVA Medical Inc. Dr. Svensson has served as an unpaid member of the PARTNER Trial Executive Committee (Edwards Lifesciences); holds equity in Cardiosolutions and ValvXchange; and holds intellectual property rights for Posthorax. Dr. Babaliaros has served as a consultant for Edwards Lifesciences and Abbott Vascular. Dr. Kodali has served as a consultant for Abbott Vascular, Merrill Lifesciences, and Claret Medical; and has served on the Scientific Advisory Boards of Thubrikar Aortic Valve, Inc., Dura Biotech, and Biotrace Medical. Dr. Thourani has served on the Advisory Boards of Abbott Vascular, Gore Vascular, Bard Medical, JenaValve, and Boston Scientific. Dr. Mack has served as an unpaid member of the PARTNER Trial Executive Committee (Edwards Lifesciences). Dr. Leon has served as an unpaid member of the PARTNER Trial Executive Committee (Edwards Lifesciences). Dr. Makkar has received grant support from Edwards Lifesciences and St. Jude Medical; and has served as a consultant for Abbott Vascular, Cordis, and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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TABLE 1 Baseline Demographics and Clinical Characteristics

	TAVR			SAVR		
	AC (n = 1137)	No AC (n = 2,752)	p Value	AC (n = 342)	No AC (n = 601)	p Value
Age, yrs	82.6 ± 7.1	81.8 ± 8.0	0.005	82.2 ± 6.1	81.2 ± 7.1	0.03
Male	696 (61.2)	1551 (56.4)	0.005	208 (60.8)	311 (51.7)	0.007
Hypertension	1053 (92.6)	2550 (92.7)	0.96	326 (95.3)	568 (94.5)	0.59
Dyslipidemia	887 (78.0)	2251 (81.8)	0.007	275 (80.4)	497 (82.7)	0.38
Diabetes mellitus	389 (34.2)	994 (36.1)	0.09	108 (31.6)	220 (36.6)	0.12
Previous/current smoker	600 (52.8)	1380 (50.1)	0.14	162 (47.4)	300 (49.9)	0.45
Body mass index, kg/m^2	28.9 ± 6.6	28.3 ± 6.5	0.12	28.4 ± 6.0	28.4 ± 6.3	0.98
COPD	402 (35.4)	875 (31.8)	0.03	103 (30.3)	180 (30.2)	0.96
Chronic kidney disease	102 (9.0)	242 (8.8)	0.86	17 (5.0)	34 (5.7)	0.65
Anemia	240 (21.1)	575 (20.9)	0.88	60 (17.5)	128 (21.3)	0.17
Thrombocytopenia	61 (5.4)	137 (5.0)	0.69	14 (4.1)	18 (3.0)	0.37
Coagulopathy	39 (3.4)	37 (1.3)	<0.0001	7 (2.0)	8 (1.3)	0.40
Previous/current bleeding	80 (10.2)	203 (11.0)	0.59	38 (11.1)	66 (11.1)	0.99
STS score	7.9 ± 4.3	7.3 ± 4.0	<0.0001	5.8 ± 1.9	5.8 ± 1.8	0.88
Congestive heart failure	996 (87.6)	2359 (85.7)	0.12	293 (85.7)	500 (83.2)	0.32
Coronary artery disease	784 (69.0)	1953 (71.0)	0.21	235 (68.7)	392 (65.2)	0.28
Cardiomyopathy	155 (13.6)	317 (11.5)	0.07	37 (10.8)	65 (10.8)	1.00
Peripheral arterial disease	349 (30.7)	846 (30.7)	0.98	101 (29.5)	203 (33.8)	0.18
Carotid disease	227 (20.0)	570 (20.7)	0.60	64 (18.7)	122 (20.3)	0.56
Previous myocardial infarction	209 (18.4)	490 (17.8)	0.67	55 (16.1)	112 (18.6)	0.32
Ejection fraction, %	54.3 ± 13.4	55.4 ± 13.1	0.02	54.5 ± 11.4	54.1 ± 12.1	0.60
Previous stroke/TIA	234 (20.6)	487 (17.7)	0.04	67 (19.6)	90 (15.0)	0.07
Stroke	137 (12.0)	277 (10.1)	0.07	42 (12.3)	55 (9.2)	0.13
TIA	109 (9.6)	245 (8.9)	0.50	32 (9.4)	37 (6.2)	0.11
Atrial fibrillation/flutter	872 (76.7)	636 (23.1)	<0.0001	208 (60.8)	125 (20.8)	<0.0001
Atrial fibrillation	848 (74.6)	604 (21.9)	<0.0001	207 (60.5)	121 (20.1)	<0.0001
Atrial flutter	104 (9.1%	82 (3.0)	<0.0001	22 (6.4)	18 (3.0)	0.01

Values are mean ± SD or n (%).

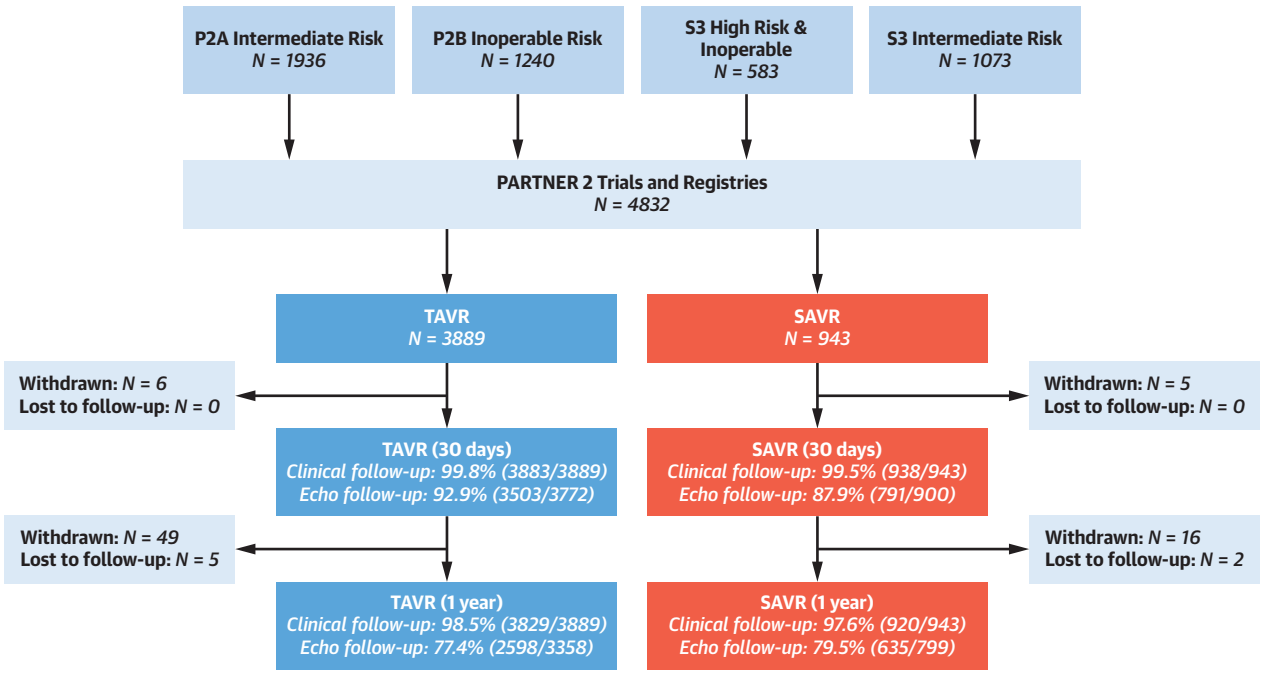
AC = anticoagulation; COPD = chronic obstructive pulmonary disease; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgery; TAVR = transcatheter aortic valve replacement; TIA = transient ischemic attack.

nonrandomized registries of Sapien-XT and Sapien 3 (Edwards Lifesciences, Irvine, California) valves has been published previously (7,8,22-24). In PARTNER 2A, intermediate-risk patients with severe symptomatic AS were randomized to TAVR with Sapien-XT or SAVR. In the PARTNER 2B trial, inoperable patients with severe symptomatic AS were randomized to Sapien-XT or Edwards-Sapien valves. Enrolled patients had severe symptomatic AS of native trileaflet aortic valve (aortic valve area of <0.8 cm^2 with either a mean aortic valve gradient of ≥40 mm Hg or a peak aortic jet velocity of ≥4.0 m/s) or symptomatic degeneration of surgical aortic bioprostheses. Patients were categorized as intermediate-risk, high-risk, or inoperable by the heart team, based on the Society of Thoracic Surgery (STS) score and/or the presence of coexisting conditions.

The as-treated patient population surviving up to discharge after TAVR or SAVR was used for all analyses. Data on clinical events, antiplatelet and antithrombotic therapy were collected in case-report forms at discharge and at every protocol-mandated follow-up clinic visit. Clinical events occurring up to the time of discharge were excluded from the analysis, as those events are primarily related to the index procedure. The PARTNER 2 trial protocol did not mandate administration of AC after bioprosthetic AVR: either TAVR or SAVR. The administration of AC at discharge was based on the clinical indications, as determined by the treating physicians. Following TAVR, treatment for 6 months with aspirin and clopidogrel was recommended. Serial echocardiograms were performed at 30 days and 1 year after AVR and analyzed independently by an echocardiographic core laboratory. All clinical events were adjudicated by the clinical-events committee, and a data and safety-monitoring board reviewed all adverse events.

STUDY ENDPOINTS. The primary objective of the study was to assess the impact of AC after bioprosthetic AVR on valve hemodynamics and clinical outcomes. Outcomes were evaluated separately for

FIGURE 1 Flowchart of Cohort Assembly



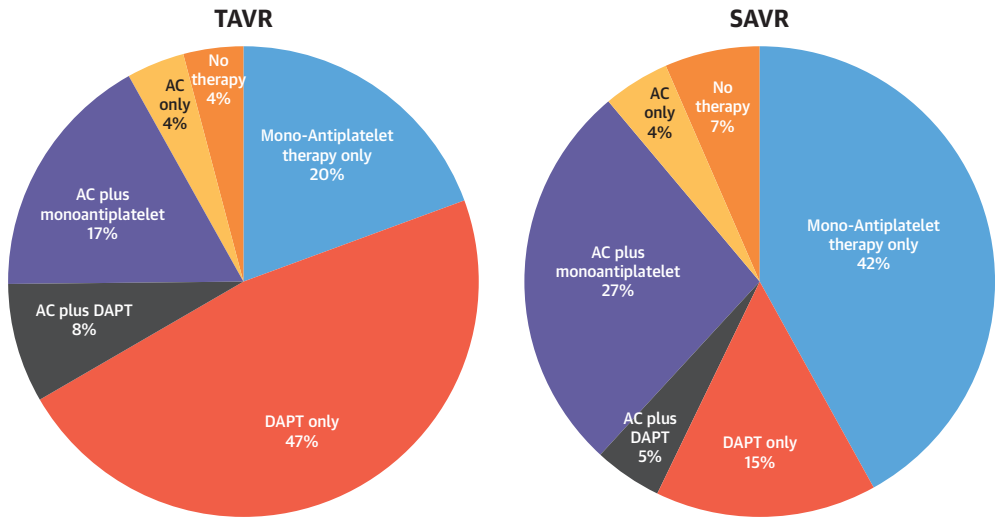
Flowchart of the total number of as-treated patients in the PARTNER 2 randomized controlled trials and nonrandomized registries. Patients were further categorized according to transcatheter or surgical aortic valve replacement to evaluate the impact of anticoagulation at discharge on valve hemodynamics and clinical outcomes at 30 days and 1 year.

the TAVR and SAVR populations. The mean transvalvular gradients and aortic valve areas were used to assess valve hemodynamics. The following clinical endpoints were included in the analysis: death, myocardial infarction, rehospitalization, stroke, transient ischemic attack (TIA), bleeding, aortic valve reintervention, and prosthetic valve dysfunction (stenosis or regurgitation). All clinical endpoints were defined according to the VARC2 criteria (25).

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD and were compared using 2-sided Student's *t*-tests or Wilcoxon rank sum tests, as appropriate. Categorical variables are expressed as number (%) and were compared using the chi-square or Fisher exact test, as appropriate. Event rates are reported as Kaplan-Meier estimates and compared using the log-rank test. The impact of AC on valve hemodynamics was assessed at 30 days and 1 year in TAVR and SAVR patients separately. Linear regression model was used for adjusted comparison between patients who were discharged on AC vs. those who were not discharged on AC. Baseline mean annular diameter, valve size, baseline atrial fibrillation, and left ventricular ejection fraction (LVEF) at the time of endpoint were used for adjustments for both TAVR and SAVR patients. A sensitivity analysis was performed with endpoint observed at discharge added to regression model. We estimated 53.8% and 38.0% correlation between baseline mean annular dimension and valve size among TAVR and SAVR patients separately by Pearson Correlation Coefficient; thus, it was determined appropriate to include both in the same model.

The impact of AC on clinical outcomes after discharge to 1 year was assessed in TAVR and SAVR patients separately by propensity-score adjusted cox proportional model. A propensity score was calculated by logistic regression with AC at discharge as a binary outcome. All covariates listed in **Table 1** plus LVEF (%) at baseline, high-risk versus intermediate-risk, and transfemoral versus alternative access were included in the model. As some of the procedural complications also have impact on the choice of the antithrombotic regimen as well as midterm clinical outcomes, the occurrence of any in-hospital complication (including stroke/TIA, myocardial infarction, major vascular complication, major/life-

FIGURE 2 Distribution of Anticoagulation and Antiplatelet Therapy at Discharge



The antiplatelet and anticoagulation regimens were categorized as anticoagulation only, mono- or dual-antiplatelet therapy only, anticoagulation plus mono- or dual-antiplatelet therapy, or no anticoagulation or antiplatelet therapy.

threatening bleeding, stage 3 acute kidney injury, and coronary occlusion) was included as an additional covariate in the Cox proportional model. Receiver-operating curve analysis was performed to confirm the validity of the propensity model (Online Figure 1). The Cox proportional models in TAVR patients were further adjusted for post-dilatation. All statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, North Carolina).

RESULTS

The study schematics are summarized in **Figure 1**. A total of 4,832 patients surviving up to discharge were included in the analysis. Of those, 3,889 patients underwent TAVR, and 943 underwent SAVR. Among 3,889 patients undergoing TAVR, 993 intermediate-risk and 1,240 inoperable patients received Sapien-XT valves, and 583 high-risk/inoperable and 1,073 intermediate-risk patients received Sapien 3 valves. The mean follow-up was 1.7 ± 0.8 years for the TAVR cohort and 2.1 ± 0.9 years for the SAVR cohort. Of the 3,889 patients undergoing TAVR and surviving up to discharge, TAVR for native AS was performed in 3,523 (90.6%) patients, and aortic valve-in-valve procedure for degenerative bioprosthetic surgical aortic valve was performed in 366 (9.4%) patients. Baseline clinical and echocardiographic characteristics are summarized in **Table 1**. Patients who were discharged on AC after TAVR had significantly more comorbidities, including higher STS scores and higher incidence of chronic obstructive pulmonary disease, previous strokes/TIAs, and atrial fibrillation/flutter. Similarly, surgical patients discharged on anticoagulation had higher incidence of previous strokes/TIAs and atrial fibrillation/flutter. Larger bioprosthetic valve size was more frequently used in patients discharged on anticoagulation compared with those not discharged on anticoagulation in both TAVR (20/23 mm: 35.1% vs. 43.5%, $p < 0.0001$; and 26/29 mm: 64.9% vs. 56.5%, $p < 0.0001$) and surgical patients (17/19/21 mm: 27.5% vs. 48.0%, $p = 0.002$; 23/25 mm: 55.7% vs. 49.7%, $p = 0.08$ and 27/29 mm: 6.7% vs. 2.4%, $p = 0.001$). Patients discharged on anticoagulation after TAVR had larger mean aortic annular diameter compared with those not discharged on anticoagulation (25.0 ± 2.5 mm vs. 24.2 ± 2.2 mm, $p < 0.001$).

DISTRIBUTION OF ANTICOAGULATION AND ANTIPLATELET THERAPY AFTER BIOPROSTHETIC AVR. The distribution of AC and antiplatelet therapy is presented in **Figure 2**. A greater proportion of patients after SAVR, compared with TAVR, were discharged on AC (36.3% vs. 29.2%, $p < 0.0001$). Similar trends were observed at 30 days (35.5% vs. 28.0%, $p < 0.0001$) and 1 year (30.8% vs. 27.3%, $p = 0.049$). Monoantiplatelet therapy in the absence of AC was more likely to be prescribed at discharge after SAVR (42.0% vs. 19.4%, $p < 0.0001$), whereas patients after TAVR were more likely to be discharged on DAPT alone (47.2% vs.

TABLE 2 Comparison of Valve Hemodynamics Between Patients Discharged on Versus Those Not Discharged on Anticoagulation After Bioprosthetic Aortic Valve Replacement

	AC		No AC		Unadjusted p Value	Adjusted p Value*	Sensitivity Analysis†
Transcatheter aortic valve replacement: mean gradients							
30 days	1,018	10.6 ± 5.0	2,484	11.4 ± 5.4	<0.0001	0.83	0.55
1 yr	732	11.1 ± 5.1	1,865	12.0 ± 5.7	0.0001	0.85	0.82
Transcatheter aortic valve replacement: aortic valve area							
30 days	971	1.64 ± 0.46	2,344	1.60 ± 0.44	0.004	0.049	0.02
1 yr	681	1.61 ± 0.45	1,735	1.56 ± 0.43	0.03	0.10	0.22
Surgical aortic valve replacement: mean gradients							
30 days	285	10.4 ± 4.5	506	11.2 ± 4.3	0.009	0.89	0.98
1 yr	231	11.1 ± 4.4	401	11.8 ± 4.4	0.05	0.56	0.89
Surgical aortic valve replacement: aortic valve area							
30 days	264	1.50 ± 0.44	466	1.46 ± 0.43	0.23	0.30	0.25
1 yr	221	1.42 ± 0.41	371	1.42 ± 0.41	0.88	0.43	0.68

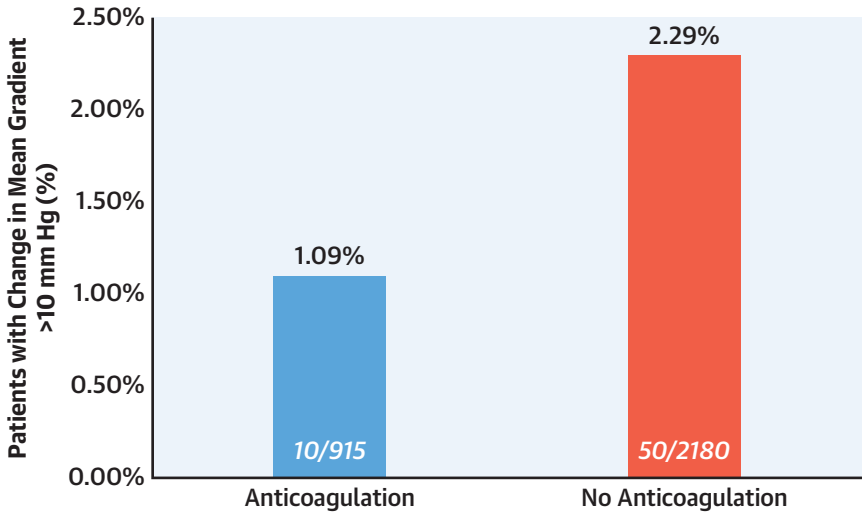
Values are n or mean ± SD. *p values adjusted for baseline mean annular diameter, valve size, baseline atrial fibrillation, left ventricular ejection fraction at the time of endpoint. †p values adjusted for baseline mean annular diameter, valve size, baseline atrial fibrillation, left ventricular ejection fraction at the time of endpoint and endpoint observed at discharge.

AC = anticoagulation.

15.2%, p < 0.0001). Among patients undergoing TAVR, a similar proportion of high-risk and intermediate-risk patients were on AC at discharge (29.7% vs. 28.8%, p = 0.52), 30 days (29.3% vs. 27.0%, p = 0.11) and 1 year (27.3% vs. 27.3%, p = 0.98).

ANTICOAGULATION AND VALVE HEMODYNAMICS. Valve hemodynamics are summarized in Table 2. Patients discharged on AC after TAVR had significantly lower aortic valve mean gradients at 30 days (10.6 ± 5.0 mm Hg vs. 11.4 ± 5.4 mm Hg, p < 0.0001) and 1 year (11.1 ± 5.1 mm Hg vs. 12.0 ± 5.7 mm Hg, p = 0.0001), compared with those not discharged on AC. AC at discharge after TAVR was also associated with greater aortic valve areas at 30 days (1.64 ± 0.46 cm^2 vs. 1.60 ± 0.44 cm^2, p = 0.004) and 1 year (1.61 ± 0.45 cm^2 vs. 1.56 ± 0.43 cm^2, p = 0.03), compared with no AC. Lower aortic valve mean

FIGURE 3 Proportion of Patients With Change in Mean Gradient >10 mm Hg



The proportion of patients with change in mean gradient >10 mm Hg during follow-up after bioprosthetic aortic valve replacement was greater in patients who were not discharged on anticoagulation compared with those discharged on anticoagulation.

TABLE 3 Impact of Anticoagulation on Adjusted Outcomes After Transcatheter and Surgical Aortic Valve Replacement

	Transcatheter Aortic Valve Replacement		Surgical Aortic Valve Replacement	
	Adjusted HR	p Value	Adjusted HR	p Value
Death or stroke or rehospitalization	1.26 (1.01–1.58)	0.05	1.05 (0.76–1.46)	0.75
Death	1.26 (0.92–1.74)	0.15	0.97 (0.61–1.53)	0.88
Rehospitalization	1.21 (0.93–1.58)	0.16	0.97 (0.65–1.45)	0.89
Stroke/TIA	1.48 (0.89–2.45)	0.13	0.27 (0.11–0.68)	0.006
Stroke	1.30 (0.68–2.48)	0.43	0.17 (0.05–0.60)	0.006
TIA	1.66 (0.76–3.63)	0.20	0.56 (0.14–2.28)	0.42
Myocardial infarction	0.71 (0.20–2.53)	0.60	0.59 (0.11–3.02)	0.52
Any bleeding	1.21 (0.83–1.77)	0.32	2.43 (0.65–9.10)	0.19
Life-threatening or disabling bleeding	1.55 (0.94–2.57)	0.09	1.95 (0.73–5.22)	0.18
Major bleeding	1.03 (0.56–1.90)	0.91	0.93 (0.43–2.02)	0.85
Minor bleeding	1.72 (1.13–2.61)	0.01	1.48 (0.91–2.42)	0.11
Aortic valve reintervention	1.34 (0.39–4.65)	0.64	N/A	N/A
Prosthetic valve dysfunction				
Moderate to severe AR*	1.14 (0.46–2.81)	0.78	N/A	N/A
Significant aortic stenosis†	N/A	N/A	N/A	N/A

*Presence of moderate or severe regurgitation and clinical findings, symptoms or events indicating impaired cardiovascular or valvular function (e.g., new or worsening congestive heart failure, rehospitalization for worsening symptoms, reoperation, or death). †Presence of possible or significant stenosis and clinical findings, symptoms or events indicating impaired cardiovascular or valvular function (e.g., new or worsening congestive heart failure, rehospitalization for worsening symptoms, reoperation, or death).

AR = aortic regurgitation; HR = hazard ratio; N/A = not applicable; TIA = transient ischemic attack.

gradients at 30 days (10.4 ± 4.5 mm Hg vs. 11.2 ± 4.3 mm Hg, p = 0.009) and 1 year (11.1 ± 4.4 mm Hg vs. 11.8 ± 4.4 mm Hg, p = 0.05) were noted in the surgical patients who were discharged on AC compared with those not discharged on AC. The aortic valve areas did not differ significantly in the surgical cohort between patients discharged on AC versus those not discharged on AC. As valve hemodynamics are affected by valve size, aortic annular dimensions, and atrial fibrillation and LVEF at the time of assessment of hemodynamics, we evaluated hemodynamics after adjustment for these covariates. The differences in aortic valve gradients or aortic valve areas in the transcatheter or surgical cohorts were no longer significant after adjustment for these covariates. A significantly greater proportion of patients not discharged on AC had an increase in mean gradient >10 mm Hg from 30 days to 1 year, compared with those discharged on AC (2.3% [95% CI: 1.71% to 3.01%] vs. 1.1% [95% CI: 0.005% to 2.00%], p = 0.03) (**Figure 3**).

ANTICOAGULATION AND CLINICAL OUTCOMES. Unadjusted clinical outcomes. The unadjusted clinical outcomes are presented in Online Tables 1 and 2. There was no difference in the incidence of aortic valve reintervention or prosthetic valve dysfunction (regurgitation or stenosis) among patients discharged on AC compared with those not discharged on AC, either in the transcatheter or surgical population. Patients who were discharged on AC after TAVR had increased incidence of death (p = 0.002), rehospitalization (p < 0.0001) and bleeding (p = 0.002), with no difference in the incidence of strokes/TIAs (4.9% vs. 4.1%, p = 0.24). AC at discharge after SAVR was associated with significantly decreased rates of stroke (1.7% vs. 5.5%, p = 0.01), with no difference in the rates of death or rehospitalization.

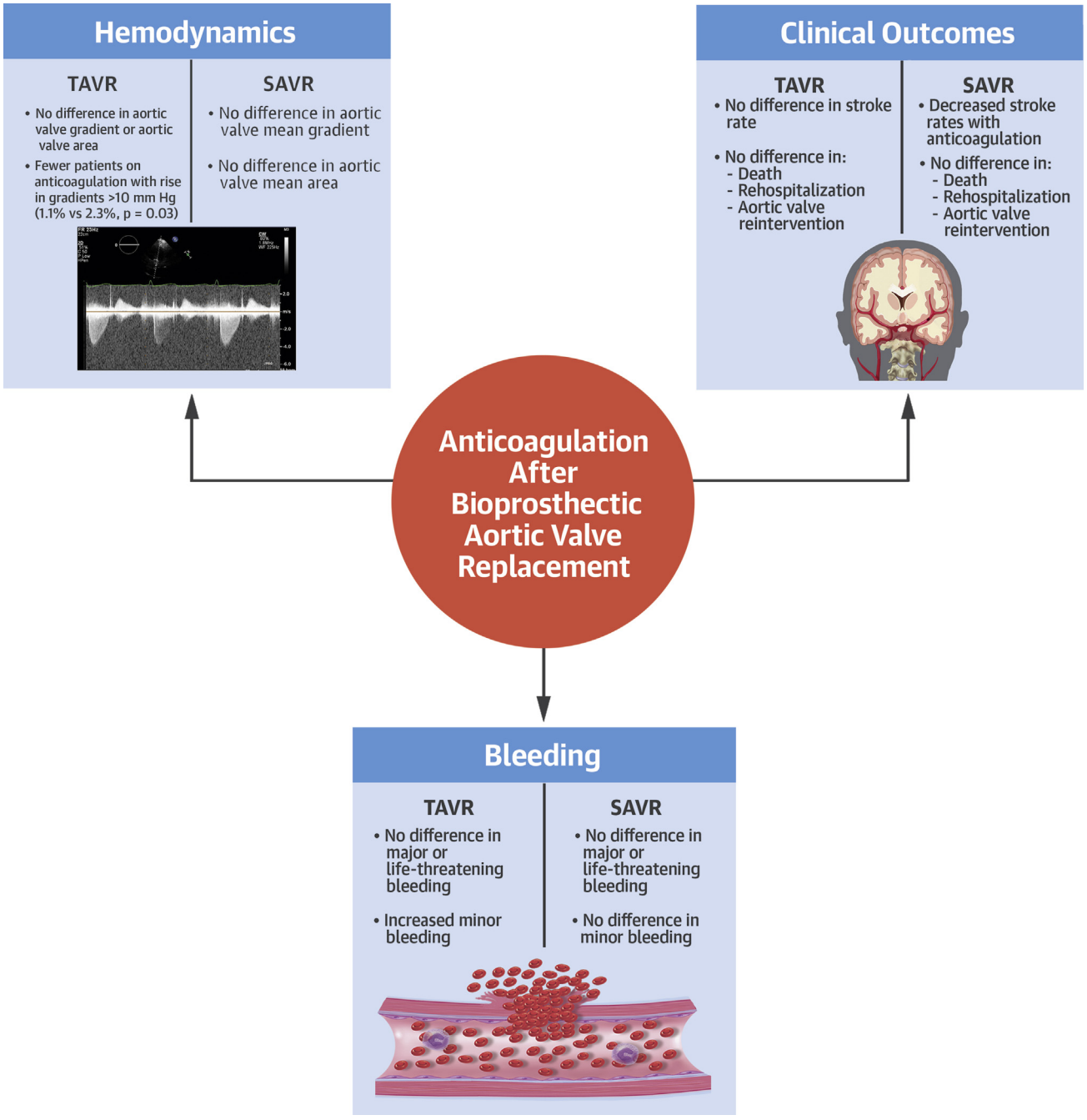
ADJUSTED CLINICAL OUTCOMES. A propensity score-adjusted Cox proportion model was used to determine the independent association between AC after TAVR/SAVR and clinical outcomes (**Table 3, Central Illustration**). Online Table 3 summarizes the balancing of baseline variables after adjustment of propensity score. Following adjustment for covariates, there was no independent association between AC after TAVR and adverse outcomes (death, p = 0.15; rehospitalization, p = 0.16), except significantly increased rates of minor bleeding (HR: 1.72; 95% CI: 1.13 to 2.61; p = 0.01). Despite adjustment for differences in baseline characteristics, AC after SAVR continued to be associated with significantly lower rates of stroke compared with no AC (HR: 0.17; 95% CI: 0.05 to 0.60; p = 0.006).

DISCUSSION

This study has the following principal findings: AC after discharge did not significantly affect aortic-valve hemodynamics; at least in the short term, AC was not associated with differences in the rates of aortic valve reintervention or structural valve degeneration; AC after bioprosthetic AVR did not affect clinical outcomes, except for fewer strokes in surgical patients discharged on AC.

AC after bioprosthetic aortic valve replacement (TAVR or SAVR) was not independently associated with overall improved aortic valve gradients or aortic valve area. The mean aortic valve gradients were lower in the AC group after TAVR at 30 days; however, these results were likely driven by lower aortic valve gradients at discharge in the AC cohort, as suggested by the sensitivity analysis by including the mean gradients at discharge in the adjustment model. The study demonstrated excellent durability of both transcatheter and surgical bioprostheses up to 1 year. Severe increase in gradients that would be suggestive of valve thrombosis or stenosis was not noted in any patient. Only 2% of patients experienced rise in gradients >10 mm Hg at 1 year. A significantly greater proportion of patients not discharged on AC had an

CENTRAL ILLUSTRATION **Impact of Anticoagulation on Valve Hemodynamics and Clinical Outcomes After Bioprosthetic Aortic Valve Replacement**



Chakravarty, T. et al. J Am Coll Cardiol. 2019;74(9):1190-200.

Anticoagulation at discharge after bioprosthetic aortic valve replacement was not associated with adverse clinical outcomes, did not significantly impact valve hemodynamics, and was associated with decreased rates of stroke after SAVR (but not after TAVR). SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

increase in mean gradient >10 mm Hg from 30 days to 1 year, compared with those discharged on AC. These results are consistent with the previously published studies reporting an association between the lack of AC therapy and increase in mean transvalvular gradients during follow-up (26–28). The reports on bioprosthetic aortic valve thrombosis have led to significant interest in studying the association between AC and aortic valve hemodynamics after AVR. Bioprosthetic valve thrombosis represents a spectrum ranging from the presence of hypo-attenuated leaflet thickening (HALT) (with normal leaflet motion) to subclinical leaflet thrombosis (associated with HALT and reduced leaflet motion) to clinically significant leaflet thrombosis (with increased gradients or symptoms). Although multiple large studies have reported increased transvalvular gradients in patients with bioprosthetic valve thrombosis (11,12,15), a few underpowered studies with small sample size did not notice an impact of subclinical leaflet thrombosis on valve gradients (14,29). AC, but not DAPT, is effective in the prevention as well as treatment of bioprosthetic valve thrombosis (10,11). The difference in aortic valve gradients between patients with or without subclinical leaflet thrombosis, albeit statistically significant, is small (11). Our study findings do not support the hypothesis that the decreased incidence of subclinical leaflet thrombosis of transcatheter heart valves observed in patients on AC translates into decreased aortic valve gradients or improved aortic valve areas, at least in the short term.

AC did not affect the incidence of aortic valve reintervention or prosthetic valve dysfunction (stenosis or regurgitation). We used the VARC2 definition of prosthetic valve dysfunction in our study, as these endpoints were blindly adjudicated by the clinical-events committee. Recently, Dvir et al. (30) proposed a new classification of structural valve degeneration built into stages to reflect the process of bioprosthetic degeneration. This classification may be more sensitive at detecting prosthetic valve dysfunction. In an unadjusted analysis, the clinical outcomes (death, rehospitalization, bleeding) were worse in patients on AC after TAVR or SAVR. AC after AVR was prescribed not as routine pharmacotherapy but for coexisting medical conditions. Patients discharged on AC had significantly greater comorbidities. This patient population with comorbidities requiring AC, especially atrial fibrillation, is inherently at increased risk for adverse outcomes. The incidence of pre-existing atrial fibrillation ranges from 30% to 40% in patients undergoing bioprosthetic AVR (1,2,4,5,31). An additional 8% to 9% of patients after TAVR and 15% to 25% of patients after SAVR develop new-onset atrial fibrillation (2,5,6,31). Both pre-existing atrial fibrillation (32) and new-onset atrial fibrillation (33,34) are independent predictors of mortality and thromboembolic events after bioprosthetic AVR. Following adjustment for these differences in baseline characteristics, there were no differences in clinical outcomes in patients who were treated with AC. Rates of stroke continued to be lower among patients on AC after SAVR but not after TAVR. The association between AC and decreased rates of stroke after SAVR is intriguing. This is possibly due to the greater incidence of new-onset atrial fibrillation after SAVR (2,5,6,31). It is also possible that decreased incidence of subclinical leaflet thrombosis in surgical patients on AC contributed to the decreased stroke rates. In nonrandomized registries, subclinical leaflet thrombosis was associated with increased risk of TIAs (10,11).

CLINICAL IMPLICATIONS. Our study findings suggest that in patients with clinical indications for AC and acceptable bleeding risks undergoing bioprosthetic AVR, it is safe to initiate AC at discharge. AC may not affect valve hemodynamics but offers a significant benefit in rates of stroke after SAVR. Studies have previously evaluated the impact of AC after bioprosthetic AVR (both TAVR and SAVR); however, the studies have been limited by inconsistent results, incomplete follow-up, lack of core laboratory assessment of echocardiograms, and lack of systematic adjudication of clinical events (35–38). The PARTNER2 trials and registries, owing to their rigorous study design and study monitoring, overcome these limitations and provide a robust model to evaluate the impact of adjunctive pharmacotherapy after bioprosthetic AVR (35,37–41). To the best of our knowledge, this is the first study evaluating the impact of AC after bioprosthetic AVR (TAVR or SAVR) on valve hemodynamics in a large patient cohort, using an echocardiographic core laboratory and adjudication of clinical outcomes by a clinical-events committee.

Our study only included balloon-expandable Sapien valves; thus, the findings cannot be extrapolated to other valve types. Our study findings cannot be generalized to initiate AC in all patients after TAVR. We did not address whether routine initiation of AC after TAVR in patients without a pre-existing clinical indication for AC affects clinical outcomes. This is especially relevant, as the GALILEO trial comparing treatment strategy of routine AC with rivaroxaban after TAVR vs. dual antiplatelet therapy in patients without clinical indications for AC was recently halted prematurely because of the increased risk of adverse events observed with AC. The impact of

routine AC after TAVR is currently being evaluated in the ongoing ATLANTIS (Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis [NCT02664649]) trials (42).

STUDY LIMITATIONS. The study does not address the impact of direct oral anticoagulants after bioprosthetic AVR. Only 5% of the patients were discharged on direct oral anticoagulants. Post-AVR computed tomography imaging was not performed to evaluate the impact of AC on subclinical leaflet thrombosis. Only a small percentage of patients treated by TAVR or SAVR were discharge on AC only. Thus, the true effect of such a regimen is difficult to assess in the current study. Although the echocardiograms at follow-up were not available in a proportion of patients, the missing echocardiograms were not related to any systematic bias in the PATNER trials and registries; thus, it is unlikely that the missing echocardiograms would affect study results. The study is not powered to assess the impact of different antiplatelet and AC regimens or the impact of only AC in the absence of antiplatelet therapy on valve hemodynamics or clinical outcomes. The study did not address the impact of AC crossover on outcomes. There was significant concordance between the presence of atrial fibrillation and use of AC; however, the clinical indication for initiation of AC after bioprosthetic AVR was not captured in the case-report forms. Only a randomized clinical trial would provide a true assessment of the impact of anticoagulation on valve hemodynamics and clinical outcomes.

CONCLUSIONS

In this PARTNER2 trial analysis of intermediate and high-risk patients undergoing bioprosthetic AVR, at least in the short term, early AC after bioprosthetic AVR did not significantly affect valve hemodynamics or valve durability/degeneration, was not associated with adverse clinical events, and was associated with decreased rates of stroke after SAVR (but not after TAVR). Longer-term follow-up will determine whether AC after discharge is associated with clinically meaningful differences in valve hemodynamics and/or have impact on valve durability.

ADDRESS FOR CORRESPONDENCE: Dr. Raj R. Makkar, Cedars-Sinai Heart Institute, 8700 Beverly Boulevard, Los Angeles, California 90048. E-mail: makkarr@cshs.org.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Anticoagulation reduces the risk of stroke after surgical AVR, but not transcatheter AVR, with negligible impact on valve hemodynamics.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to evaluate the effect of anticoagulation after TAVR on valve hemodynamics, durability, and clinical outcomes.

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KEY WORDS anticoagulation, bioprosthetic aortic valve replacement, transcatheter aortic valve replacement

APPENDIX For supplemental tables and a figure, please see the online version of this paper.