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Long-Term Outcomes of Anticoagulation for Bioprosthetic Valve Thrombosis

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ABSTRACT

BACKGROUND Early in the prevention and treatment of bioprosthetic valve thrombosis (BPVT), anticoagulation is effective, but the long-term outcome after BPVT is unknown.

OBJECTIVES The goal of this study was to assess the long-term outcomes of patients with BPVT treated with anticoagulation.

METHODS This analysis was a matched cohort study of patients treated with warfarin for suspected BPVT at the Mayo Clinic between 1999 and 2017.

RESULTS A total of 83 patients treated with warfarin for suspected BPVT (age 57 ± 18 years; 45 men [54%]) were matched to 166 control subjects; matching was performed according to age, sex, year of implantation, and prosthesis type and position. Echocardiography normalized in 62 patients (75%) within 3 months (interquartile range [IQR]: 1.5 to 6 months) of anticoagulation; 21 patients (25%) did not respond to warfarin. Median follow-up after diagnosis was 34 months (IQR: 17 to 54 months). There was no difference in the primary composite endpoint between the patients with BPVT and the matched control subjects (log-rank test, $p = 0.79$), but the former did have a significantly higher rate of major bleeding (12% vs. 2%; $p < 0.0001$). BPVT recurred (re-BPVT) in 14 (23%) responders after a median of 23 months (IQR: 11 to 39 months); all but one re-BPVT patient responded to anticoagulant therapy. Patients with BPVT had a higher probability of valve re-replacement (68% vs. 24% at 10 years' post-BPVT; log-rank test, $p < 0.001$).

CONCLUSIONS BPVT was associated with re-BPVT and early prosthetic degeneration in a significant number of patients. Indefinite warfarin anticoagulation should be considered after a confirmed BPVT episode, but this strategy must be balanced against an increased risk of bleeding. (J Am Coll Cardiol 2020;75:857-66) © 2020 by the American College of Cardiology Foundation.

Bioprosthetic valve thrombosis (BPVT) is an increasingly recognized entity. We (1-4) and others (5-7) have previously reported on the response to anticoagulant therapy and outlined the role of echocardiography in its diagnosis. Other groups have reported a high incidence of valve thrombosis after transcatheter aortic valve replacement and outlined the role of computed tomography (CT) cardiac angiography as a diagnostic tool in these patients (8-10). These observations led to an update in the 2017 American College of Cardiology/American Heart Association valvular heart disease guidelines, now recommending anticoagulant therapy with warfarin for 3 months after all bioprosthetic valve implantations (11).

Although the beneficial effect of anticoagulation in the prevention and treatment of BPVT is widely accepted, the intensity, optimal duration of therapy, and additive risk of anticoagulant therapy are largely unknown. In a former prospective study completed by our group, 83% of patients with suspected BPVT diagnosis responded to anticoagulation and thus avoided early re-operation/re-intervention (3). This response was predicted with reasonable sensitivity

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ABBREVIATIONS AND ACRONYMS

BPVT = bioprosthetic valve thrombosis

CT = computed tomography

HR = hazard ratio

INR = international normalized ratio

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

and specificity using our proposed BPVT score. The analysis was limited, however, by the short follow-up time and was primarily focused on surrogate endpoints (e.g., change in transvalvular gradient) rather than on clinical endpoints (e.g., survival, bleeding, valve re-intervention). Furthermore, the long-term effect of an episode of BPVT on bioprosthetic longevity is unknown, and there is no formal treatment recommendation for duration of anticoagulation after an episode of BPVT. We and others have speculated that BPVT may precede bioprosthetic degeneration, but whether successful treatment of a BPVT episode prevents this process cannot be answered from the existing literature.

The goal of the current study was to evaluate the impact of BPVT on prosthesis longevity, as well as to define the long-term clinical outcomes in patients with BPVT treated with warfarin, with a focus on rethrombosis, thromboembolic phenomena, and all-cause mortality. Our hypotheses were that: 1) successful anticoagulation for BPVT restores expected prosthetic valve longevity; and 2) anticoagulation with warfarin for BPVT is safe and effective.

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METHODS

STUDY DESIGN. This single-center, retrospective analysis was conducted at the Mayo Clinic (Rochester, Minnesota). Patients age ≥18 years who underwent surgical or transcatheter replacement with bioprosthetic valves between January 1999 and April 2017 were identified from the electronic clinical and echocardiographic databases (Figure 1). Patients who underwent a trial of anticoagulation for a tentative clinical diagnosis of BPVT and had at least 1 follow-up transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) study after initiation of anticoagulation therapy were identified; some of them had been included in previous analyses (1–4). Two control patients were randomly selected for each patient with BPVT from a matched candidate list. Matching was performed for age, sex, date of original implantation (±3 years), type of replacement (surgical or transcatheter), and valve position and type (porcine or pericardial). Control subjects had to be event-free for an interval equal to or greater than the interval between implantation and BPVT occurrence in their matched patient (i.e., control subjects could not experience events before their corresponding match experienced BPVT). The Mayo Clinic Institutional Review Board approved the study protocol.

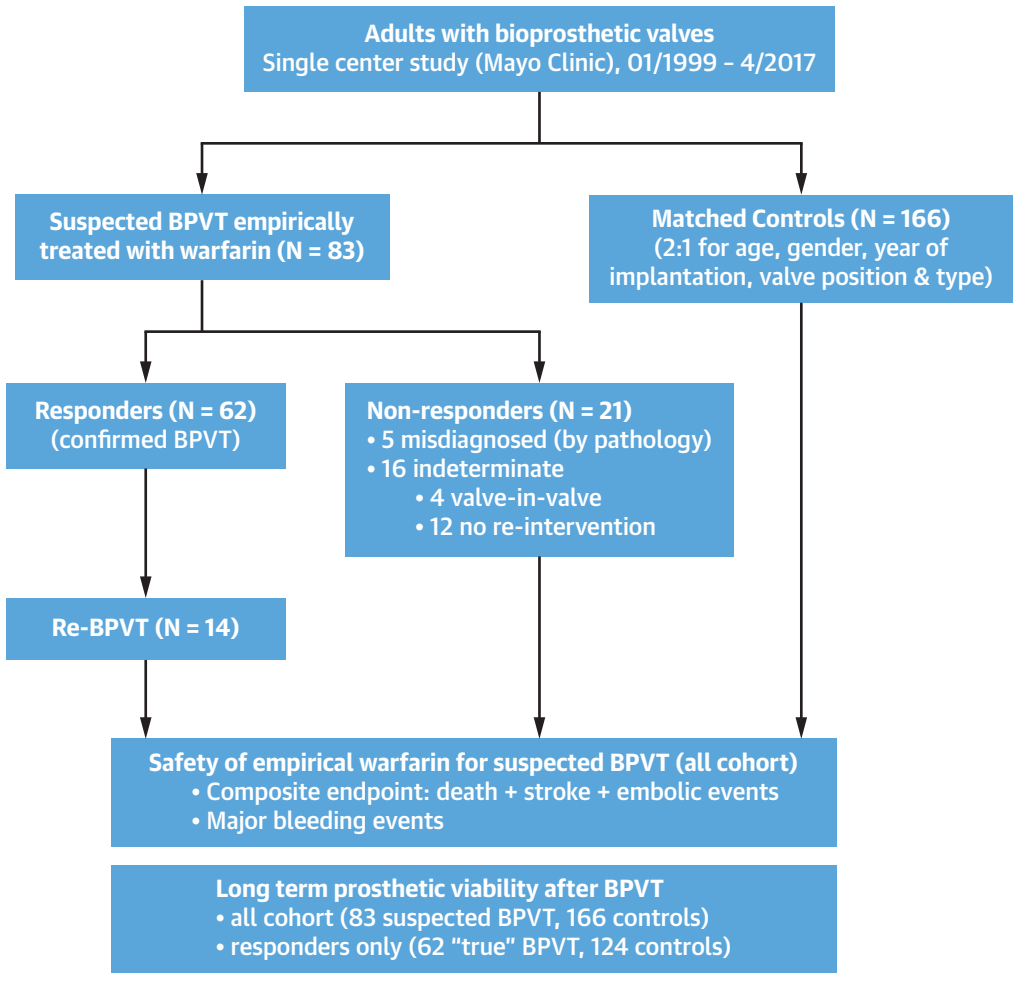
Patients who responded to warfarin ("responders" [discussed in the following Echocardiography section]) were considered to have empirically confirmed BPVT. Patients who were treated for BPVT but did not have a response were classified as either misdiagnosed (confirmed degeneration/pannus/infection according to pathologic evaluation of the explanted bioprosthesis), with BPVT resistant to warfarin (persistent thrombus at pathology), or as indeterminate (i.e., transcatheter valve replacement, no additional intervention performed).

The overall long-term clinical outcome after BPVT was assessed with a composite endpoint consisting of stroke, peripheral embolic events, or death of any cause determined from the electronic medical record, autopsy reports, and/or the Social Security Death Index. The risk of warfarin anticoagulation was estimated from analysis of major bleeding episodes (defined as intracranial bleeding or any bleeding requiring transfusion or percutaneous/surgical intervention).

To address our second hypothesis that successful anticoagulation restores normal prosthetic valve longevity, we evaluated the need for valve re-replacement at long-term follow-up. Two separate analyses were performed, one including the entire cohort of presumed patients with BPVT and their matched control subjects, and one using only responders and their corresponding control subjects.

ECHOCARDIOGRAPHY. All echocardiography reports, beginning with the immediate post-surgical implantation to the suspected diagnosis of BPVT and beyond, were directly reviewed. Transvalvular gradients, presence of morphologically abnormal valves (e.g., increased cusp thickness, calcification), and subjective assessments regarding cusp mobility were re-assessed by experienced echocardiographers (A.C.E., H.M.C., and S.V.P.). The BPVT risk score was calculated from post-implantation echocardiography data, based on the 3 criteria previously described by our group (gradient increase of >50% over baseline, presence of thick noncalcified cusps, and reduced cusp mobility) (2). Successful response to warfarin was defined as significant reduction of transprosthetic gradient (>30% decrease or return to post-implantation gradient ±2 mm Hg) and resolution of other abnormal findings (e.g., improved cusp mobility, normalized cusp thickness). Additional imaging with TEE or CT scanning for assessment of presumed BPVT was performed at the discretion of the attending cardiologists; results were reviewed when available. The baseline gradients were obtained

FIGURE 1 Study Design and Outcomes



Long-term effects of anticoagulant therapy for presumed bioprosthetic valve thrombosis (BPVT) were assessed in a retrospective, matched cohort study. Details are presented in the text.

from the pre-discharge TTE after initial surgical or transcatheter implantation.

STATISTICAL ANALYSIS. All statistical analysis was performed using JMP version 14 (SAS Institute, Inc., Cary, North Carolina). Categorical variables are expressed as number (percentage) and continuous variables as mean ± SD or median (interquartile range [IQR]) for skewed data. Categorical variables were compared by using the chi-square test or Fisher exact test. Continuous variables were compared by using a 2-sided unpaired Student's *t*-test or Wilcoxon rank sum test, as appropriate. Survival analysis was performed by using the Kaplan-Meier method.

For all endpoints, time to various events was measured starting at the initial diagnosis of BPVT (or from the corresponding time point in their matched control subjects). Patients who did not reach the study endpoints were censored at the time of their last clinical follow-up. The Cox proportional hazards method was used to assess the impact of various factors on the need for valve re-replacement. All p values were 2-sided, and p values <0.05 were considered to indicate statistical significance.

RESULTS

BASELINE CHARACTERISTICS AT INITIAL IMPLANTATION. Between January 1999 and April 2017, a total of 83 patients with suspected BPVT who received anticoagulant therapy were identified. The mean age was

TABLE 1 Baseline Characteristics

	BPVT (n = 83)	Control Subjects (n = 166)	p Value
Age, yrs	57 ± 18	58 ± 19	0.7
Male	45 (54)	90 (54)	NA
Prosthesis position			NA
Aortic	40 (48)	80 (48)	
Mitral	18 (22)	36 (22)	
Tricuspid	21 (25)	42 (25)	
Pulmonary	4 (5)	8 (5)	
Prosthesis type			NA
Porcine	54 (65)	108 (65)	
Pericardial	22 (27)	44 (27)	
Transcatheter replacement	7 (8)	14 (8)	
Clinical and echocardiographic data			
LVEF <40%	10 (12)	23 (14)	0.6
Persistent atrial fibrillation	18 (22)	45 (27)	0.3
Hypertension	54 (65)	113 (68)	0.6
Diabetes	10 (12)	31 (19)	0.2
Coronary artery disease	32 (39)	97 (58)	0.003
CKD grade ≥3	17 (21)	31 (19)	0.7
Intracardiac device	15 (18)	41 (25)	0.3
Antiplatelet at BPVT diagnosis	78 (96)	NA	NA
Anticoagulant at BPVT diagnosis	9 (11)	NA	NA
Previous thromboembolic events	11 (13)	17 (10)	0.4

Values are mean ± SD or n (%).

BPVT = bioprosthetic valve thrombosis; CKD = chronic kidney disease; LVEF = left ventricular ejection fraction; NA = not applicable.

57 ± 18 years; 45 (54%) were men. Most initial valve replacements were surgical, with only 7 (8.4%) having transcatheter replacements. The most common prosthesis position was aortic in 40 (48%) patients, followed by tricuspid in 21 (25%), mitral in 18 (22%), and pulmonary in 4 (5%). Porcine valves accounted for 65% of all prostheses; 27% were pericardial prostheses, and the remaining 8% were transcatheter bioprosthetic valves.

The baseline characteristics of the BPVT cohort and their matched control subjects are summarized in Table 1. The 2 cohorts did not differ significantly in terms of comorbid conditions except for coronary artery disease, which was slightly more prevalent in the control subjects. Notably, there was no difference in the prevalence of previous thromboembolic events (13% vs. 10%; p = 0.40).

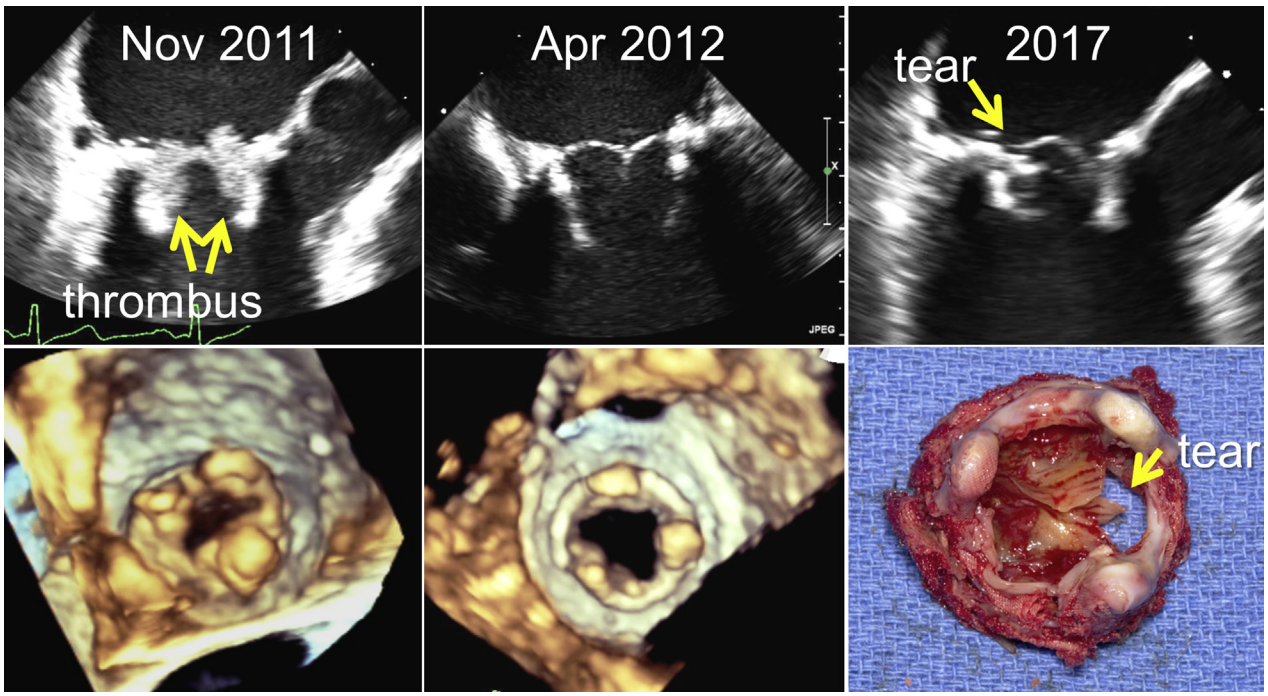
The median time from implantation to suspected BPVT diagnosis was 23 months (IQR: 9 to 68 months). At the time of presumed BPVT diagnosis, 78 (96%) patients with BPVT were receiving antiplatelet medication, 9 (11%) were taking warfarin, and 3 (4%) were taking direct oral anticoagulants (rivaroxaban 2; apixaban 1). Four of the nine patients taking warfarin had a subtherapeutic international normalized ratio (INR; <2) at BPVT diagnosis. The main indication for anticoagulation in these patients was atrial fibrillation (7) or hypercoagulable state (antiphospholipid syndrome 4; active malignancy 1).

A combination of TTE followed by TEE was most often used for diagnosis (n = 55 [66%]), with the remaining cases diagnosed by using TTE (n = 26 [31%]) or TEE alone (n = 2 [2%]). Forty-seven (57%) patients had new valvular stenosis on the diagnostic echocardiogram, 33 (40%) had valvular regurgitation, and 3 (4%) had both. Of the diagnostic criteria previously described (50% increase in baseline gradient, increase in cusp thickness, restricted cusp mobility), all 83 (100%) patients met at least 2 criteria, and 63 (80%) met all 3 criteria. For 3 patients, the baseline post-implantation gradient was not available, and the increase in gradient criterion could not be assessed; the other 2 criteria were present in these patients. In the remaining 17 subjects, the most common criterion present was an increase in cusp thickness (12), followed by restricted cusp mobility (8) and a 50% increase in gradient (6).

SHORT-TERM RESPONSE TO ANTICOAGULANT THERAPY. All 83 patients received treatment with warfarin at the time of suspected BPVT diagnosis; 35 (43%) of these underwent bridging with unfractionated or low-molecular-weight heparin initially. The median follow-up time after BPVT diagnosis was 34 months (IQR: 17 to 54 months). The median duration of treatment to demonstrated echocardiographic response was 3 months (IQR: 1.5 to 6 months). Mortality data were available in 100% of patients. Complete data on other events (bleeding, stroke, embolism, and redo surgery) were available in 98% of patients and control subjects at 1 year, 83% at 3 years, 71% at 5 years, and 44% at 10 years.

The outcomes after BPVT therapy are summarized in Figure 1. Sixty-two (75%) patients achieved a positive response to anticoagulant therapy (28 aortic, 18 mitral, 14 tricuspid, and 2 pulmonary). In these patients, BPVT diagnosis was made earlier after surgical implantation (median time: 20 [IQR: 9 to 28] months vs. 54 [IQR: 21 to 86] months; p = 0.03), and they met all 3 echocardiographic criteria more often (54 of 62 [87%]) compared with nonresponders (9 of 21 [43%]; p < 0.001). Overall, the combined 3 echocardiographic criteria had a sensitivity of 87%, specificity of 57%, and accuracy of 80% in predicting a response to anticoagulant therapy. Of all responders, 9 (15%) were already receiving anticoagulant therapy at the time of diagnosis (warfarin 6; rivaroxaban 2; apixaban 1). An example of a patient responding to warfarin is provided in Figure 2.

FIGURE 2 Bioprosthetic Thrombosis Followed by Prosthetic Degeneration



Patient presenting in November 2011 with mitral bioprosthetic valve thrombosis (BPVT) **(left panels)**; note presence of soft echodensities on the prosthetic cusps **(top left, arrows)** resulting in restricted systolic opening on the 3-dimensional left ventricular view **(bottom left)**. The patient was known to have antiphospholipid syndrome but used warfarin only sporadically. After appropriate anticoagulation with warfarin, the appearance, gradients, and valve opening normalized by April 2012 **(middle panels)**. In 2017, the patient underwent redo valve replacement for severe regurgitation due to a torn prosthetic cusp **(top right panel)**. At pathologic evaluation, 1 cusp was torn **(bottom right)**, and the other 2 had evidence of degeneration.

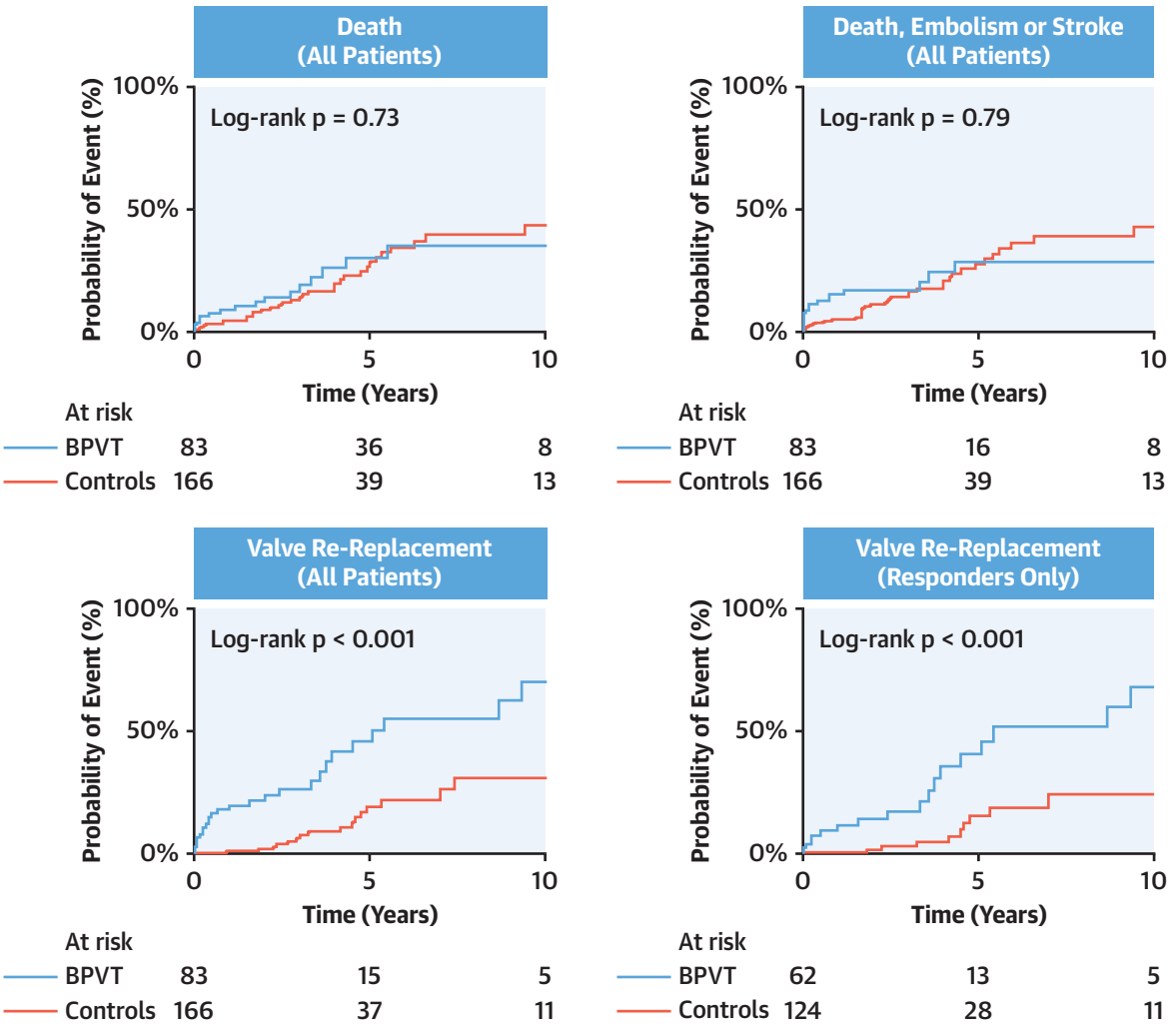
Twenty-one (25%) patients did not respond to warfarin (14 aortic, 2 mitral, 4 tricuspid, and 1 pulmonary). Of these, 9 (43%) patients underwent valve re-replacement shortly after failure of medical therapy. Pathologic examination of the explanted bioprostheses was available in 5 patients undergoing surgical re-replacement and revealed misdiagnosis in all (endocarditis 1; leaflet calcification 2; pannus formation 2). Four patients who underwent transcatheter valve-in-valve implantation and 12 patients who did not have an additional intervention to date were classified as indeterminate. Direct oral anticoagulants were not used as initial anticoagulant strategy for BPVT.

RISK OF ANTICOAGULANT THERAPY FOR PRESUMED BPVT. Patients with BPVT treated with anticoagulation had a significantly higher number of major bleeding events compared with the matched control subjects (12% vs. 2%; $p < 0.001$), but no intracerebral or fatal bleeding was noted in either the patients or the control subjects. Warfarin was discontinued in all patients who experienced a major bleed; none of these patients developed ischemic stroke or peripheral embolism for the remainder of the study period.

Long-term outcomes of patients with BPVT treated with warfarin are presented in Figure 3. During the observation period, the combined endpoint of death or stroke or embolic event occurred to a similar extent in patients with BPVT and their matched control subjects (log-rank test, $p = 0.79$). Similarly, there was no difference for the endpoint of mortality ($p = 0.73$).

RECURRENCE OF BPVT. A recommendation to continue warfarin indefinitely was made in 51 (82%) of 62 patients who responded to anticoagulation for the initial BPVT episode. A second episode of BPVT (re-BPVT) was noted in 14 (23%) of the responders (aortic 8; mitral 2; tricuspid 3; pulmonary 1) (Table 2). The median time from the initial episode of BPVT to re-BPVT was 23 months (IQR: 11 to 39 months). Importantly, 9 patients were still taking warfarin at the time of re-BPVT, but INR values were subtherapeutic in 5 patients within 30 days of diagnosis. A hypercoagulable state (already identified at first BPVT

FIGURE 3 **Long-Term Outcomes After BPVT**



Warfarin anticoagulation did not increase the risk of death **(top, left)** or of the combined primary endpoint of death, stroke, or embolic events **(top, right)** at long term. However, patients treated for BPVT were at increased risk of needing valve re-replacement. This difference was noted when analyzing the entire cohort **(bottom, left)**, and it remained significant when including only the patients who initially responded to warfarin **(bottom, right)**.

episode) was present in 4 of the 14 patients with re-BPVT (antiphospholipid syndrome in 2, hypereosinophilic syndrome in 1, active malignancy in 1; all these patients were receiving chronic anticoagulation). Two patients had 3 episodes of BPVT (1 due to discontinuation of warfarin at patient's request, and 1 due to a hypercoagulable state and re-BPVT associated with subtherapeutic INR).

All but 1 patient with re-BPVT responded to anticoagulant therapy either at the original target (INR 2 to 3 for those with subtherapeutic INR) or at the increased target (INR 2.5 to 3.5 for those who were at target during re-BPVT). Bridging anticoagulation with unfractionated or low-molecular-weight heparin was used in 9 patients with re-BPVT. Peripheral embolism was recorded in 2 patients.

THE NEED FOR PROSTHETIC VALVE RE-REPLACEMENT. Presumed patients with BPVT required valve re-replacement (surgical or transcatheter) more often within the observation period (28 of 83 vs. 18 of 166 control subjects); at 10 years after BPVT, the probability of needing valve re-replacement was 70% in patients with BPVT versus 31% in matched control subjects (log-rank test, $p < 0.001$) (Figure 3). Re-replacement was performed after a median of

26 months (IQR: 3 to 64 months) after the initial BPVT episode.

When patients with "true" BPVT (i.e., those who responded to warfarin) were analyzed separately, this difference remained significant (19 of 62 patients with true BPVT vs. 11 of 124 control subjects; 68% probability of re-replacement at 10 years vs. 24% in matched control subjects; log-rank test, $p < 0.001$) (**Figure 3**). Of these 19 patients, 12 underwent surgical re-replacement; pathologic evaluation showed degenerative changes in 7 (calcified, retracted, or torn cusps), pannus in 3, and a combination of fresh and old thrombus in 2 (both patients had antiphospholipid syndrome). The differences between patients with true BPVT and control subjects remained significant even after excluding all patients with BPVT on transcatheter-implanted valves (Online Tables 1 and 2, Online Figure 1).

At univariate proportional hazards analysis, the only factors significantly associated with the need for valve re-replacement were BPVT (hazard ratio [HR]: 4.3; $p < 0.001$) and presence of a prothrombotic state (HR: 7.5; $p < 0.001$). The prosthesis type, valve position, and comorbid conditions showed no significant association with the need for re-replacement. At multivariate analysis, both BPVT (HR: 3.2; $p = 0.007$) and prothrombotic state (HR: 4.5; $p = 0.009$) remained independent predictors after adjustment for age and sex. The need for valve re-replacement seemed higher among patients with >1 episode of BPVT (50%; 7 of 14 patients) versus those with a single episode (25%; 12 of 48 patients), and among patients who underwent a limited course of warfarin (44%; 8 of 18 patients) versus those who were recommended to continue warfarin indefinitely (25%; 11 of 44 patients); however, neither difference reached statistical significance at proportional hazards analysis.

TABLE 2 Recurrent BPVT

	Age (yrs)	Sex	Hypercoagulable*	Warfarin†	Response‡	Redo§
Aortic	33	Female	+	+	+	+
	67	Male	-	-	+	-
	69	Female	-	+	+	+
	69	Female	-	+	+	+
	72	Male	-	+	+	+
	76	Male	-	-	+	-
	80	Male	-	-	+	+
	95	Male	-	-	+	-
Pulmonary	19	Male	-	-	+	-
Mitral	44	Female	-	+	+	-
	76	Female	+	+	+	-
Tricuspid	40	Female	+	+	+	+
	40	Female	-	+	-	+
	69	Female	+	+	+	-

*Presence of known hypercoagulable state. †Patient on warfarin at time of re-bioprosthetic valve thrombosis (BPVT). ‡Echocardiographic resolution with adjustment to warfarin anticoagulation (details are given in the text). §Needing valve re-replacement at long-term follow-up.

DISCUSSION

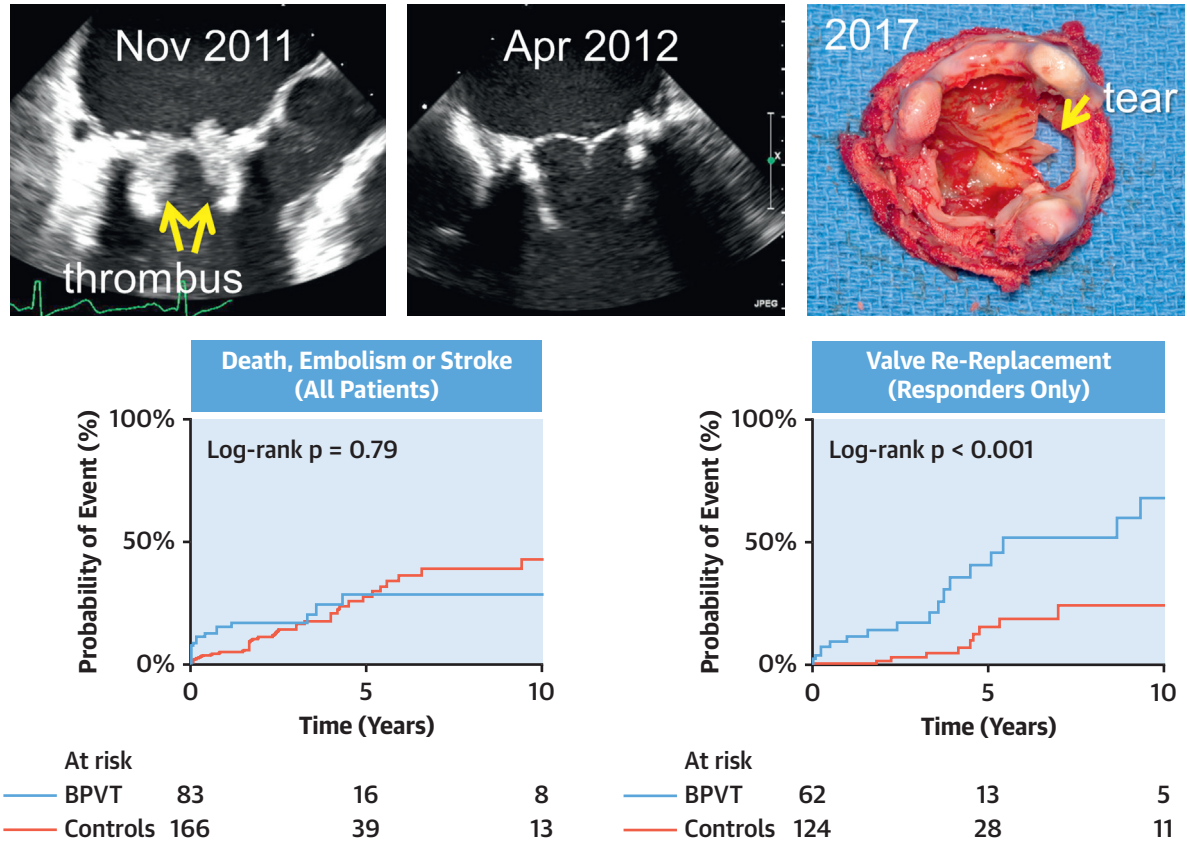
To the best of our knowledge, this study is the first to investigate the long-term outcomes of warfarin therapy for presumed BPVT. Our main findings are as follows: 1) 23% of patients had a second episode of BPVT, frequently related to inadequate INR, discontinuation of warfarin, or hypercoagulable state, suggesting that tightly controlled chronic warfarin anticoagulation may be required for this condition; 2) patients with BPVT had a 3.2-fold increased risk of needing valve re-replacement during long-term follow-up; and 3) warfarin anticoagulation for BPVT was effective and did not result in excess morbidity or mortality except for an increased risk of major bleeding (**Central Illustration**).

RECURRENT BPVT IS NOT AN ISOLATED EVENT. A common unanswered question relates to how long anticoagulation should be continued after an initial episode of BPVT. In this study, 23% of patients who responded to warfarin experienced a second episode of BPVT after a median of 23 months. The second BPVT episode occurred despite continued warfarin anticoagulation in 9 of the 14 patients, albeit with a subtherapeutic INR in 5 patients and with a hypercoagulable state in 4 patients.

The exact risk factors for BPVT remain poorly understood, with a hypercoagulable state identified only in a minority of patients. Given that nearly 1 in 4 patients had a recurrent episode in this series, we propose that warfarin anticoagulation should be maintained indefinitely after an episode of BPVT, except in those patients at prohibitive risk of bleeding. Whether tight monitoring of INR and/or higher INR targets (similar to those used for mechanical valves) could prevent re-BPVT remains to be determined.

It is important to note that 21 patients with presumed BPVT did not respond to anticoagulant therapy. To minimize the chance of misdiagnosis, we propose that confirmatory TEE and CT angiography be performed in all patients suspected of BPVT before initiation of anticoagulant therapy. Furthermore, meticulous follow-up should be arranged to document response to therapy. Only those patients with "true" BPVT should then be considered for lifelong anticoagulation.

CENTRAL ILLUSTRATION **Bioprosthetic Thrombosis and Risk of Valve Re-Replacement**



Petrescu, I. et al. J Am Coll Cardiol. 2020;75(8):857–66.

(Top) Patient with bioprosthetic thrombosis shortly after initial implantation **(left panel)**. Despite successful treatment with warfarin **(middle panel)**, the patient subsequently experienced prosthetic degeneration and required surgery for a torn cusp **(right panel)** 6 years after implantation. **(Bottom)** Warfarin anticoagulation did not increase the risk of the combined endpoint of death, stroke, or peripheral embolism **(left)**. However, patients who responded to warfarin anticoagulation experienced an increased risk of valve re-replacement **(right)**. BPVT = bioprosthetic valve thrombosis.

The role of direct oral anticoagulants in BPVT remains unclear. A registry analysis of surgical or transcatheter implanted aortic valves suggested that warfarin and direct oral anticoagulants are equally effective in treating subclinical leaflet thrombosis (12). On the other hand, the GALILEO (Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) trial of rivaroxaban versus antiplatelet therapy after transcatheter aortic valve replacement was stopped early due to increased risks of all-cause mortality, thromboembolic events, and bleeding (13,14). Furthermore, isolated reports of valve thrombosis while taking direct oral anticoagulants have recently been published (15,16). In our series, neither warfarin nor direct oral anticoagulants were able to completely eliminate the risk of BPVT, with 9 of 62 confirmed patients already undergoing anticoagulation at the time of their initial event (6 on warfarin, 3 on direct oral anticoagulants). Our current clinical approach is to use warfarin or heparin for BPVT until more data accumulate regarding direct oral anticoagulants.

ACCELERATED BIOPROSTHETIC FAILURE. Contrary to our working hypothesis, successful medical therapy for BPVT did not fully restore the expected prosthetic longevity. Indeed, one-third of the patients who responded to anticoagulation eventually required valve re-replacement during the observation period, with BPVT being independently associated

with a 3.2-fold increase in the risk of reintervention. Patients who had >1 BPVT episode seemed more vulnerable (50% re-replacement), as did those in whom a short course of warfarin was used for the initial episode (44% re-replacement), but neither difference reached statistical significance. However, the unfavorable numbers observed in these subgroups further supports recommending lifelong anticoagulation with warfarin after BPVT.

The mechanism linking BPVT and accelerated prosthetic degeneration remains to be explained, but common comorbid conditions (atrial fibrillation, renal dysfunction, hypertension, presence of ventricular dysfunction, and type of prosthesis) did not seem to be a factor in our cohort. A recent study of explanted bioprostheses suggested that fibrinogen and plasminogen play a key role in prosthetic degeneration (17). The authors hypothesized that deposition of fibrinogen from circulating blood leads to focal accumulation of plasminogen-rich macrophages on the surface of bioprosthetic cusps, and triggers focal calcification. To what extent the presence of immobile leaflets at the time of implantation and/or agents used during the manufacturing process play a part remains unknown.

EFFECTIVENESS, LONG-TERM RISKS OF WARFARIN THERAPY, AND THE RISK OF OVERDIAGNOSIS OF BPVT. The current study complements the findings of our previous prospective analysis of the efficacy of warfarin treatment in BPVT (3). In this larger study, and with a significantly longer follow-up, we confirm that warfarin anticoagulation was a reasonable initial strategy for BPVT. Indeed, there was no excess burden of ischemic stroke, peripheral embolism, or death in the BPVT cohort compared with matched control subjects.

Bleeding was significantly more frequent with warfarin, with episodes requiring transfusion or intervention occurring roughly in 1 in 8 patients treated. Clearly, anticoagulation is not benign, and shared decision-making between the patient and the cardiologist remains crucial in this situation (18).

More concerning was the fact that 21 of 83 patients tentatively diagnosed with BPVT did not respond to warfarin, with misdiagnosis confirmed in all 5 patients in whom pathology specimens were available. Although the other 16 patients are technically indeterminate, one could reasonably assume that a significant proportion were also misdiagnosed. The incidence of bleeding was low in the 21 nonresponders (3 episodes of bleeding attributable to anticoagulation for presumed BPVT, all within the first 3 months of empirical therapy), but potentially all could have been avoided by a correct initial diagnosis. This finding highlights that empirical anticoagulation does come at a risk, even when used for a short time.

Confirmatory TEE or CT imaging was not used in all patients; it is possible their systematic use may increase the diagnostic yield. Indeed, progress in CT angiography now allows accurate differentiation of BPVT from pannus and prosthetic degeneration in left-sided valves; much less is known about CT imaging for right-sided bioprostheses. Recent studies on CT follow-up after transcatheter valve implantation suggest that hypoattenuating leaflet thickening and hypoattenuation affecting motion (both CT hallmarks of BPVT) are present in a significant number of patients (9,10,12), highlighting the role of CT imaging, especially for TAVR valves, which are difficult to image by using TEE. We propose that confirmatory TEE and/or CT imaging be used systematically whenever BPVT is suspected. To what extent this strategy will reduce the chance of misdiagnosis, and implicitly the associated risk of unnecessary anticoagulant therapy, remains to be shown in prospective studies.

STUDY LIMITATIONS. This retrospective observational study reflects the experience at a large tertiary center. Without pathology confirmation, a BPVT diagnosis cannot be made with absolute certainty, and a number of patients may have been misclassified. However, we believe that a typical rise in prosthetic gradients associated with abnormal bioprosthetic appearance followed by gradient resolution with anticoagulation constitute a reasonable empirical diagnosis of true BPVT. The sample size was relatively small owing to the rarity of BPVT. The setting of a large tertiary center with experience in valve replacement surgery and postoperative management may have resulted in referral bias. Although mortality data were available in 100% of patients and control subjects, other events (stroke, peripheral embolic events, bleeding, and redo valve interventions) may have been treated at outside institutions and therefore underestimated in our analysis. However, this factor should have affected patients and control subjects to a similar extent. Despite all these limitations, this population is the largest of BPVT studied to date, and it generated interesting and clinically relevant results that help formulate pertinent hypotheses for future investigations. Prospective studies to further understand the long-term outcomes of BPVT are warranted.

CONCLUSIONS

This study presents evidence that BPVT is not a benign condition, with re-BPVT and early prosthetic degeneration occurring in a significant number of patients. Indefinite warfarin anticoagulation should be considered after an initial BPVT episode, but this strategy must be balanced against an increased risk of bleeding.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: BPVT is associated with the need for early valve re-replacement. TEE or CT imaging should confirm the diagnosis before anticoagulant therapy with warfarin, which is usually effective in reducing the risks of systemic embolism and death but should be continued long-term, since nearly one-quarter of patients experience recurrence.

TRANSLATIONAL OUTLOOK: Further studies are required to investigate the safety and efficacy of more intensive anticoagulation with warfarin (as used for mechanical valve [prosthesis]) target-specific oral anticoagulants for treatment and prevention of recurrent BPVT.

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