Antiplatelet versus oral anticoagulant therapy as antithrombotic prophylaxis after mitral valve repair

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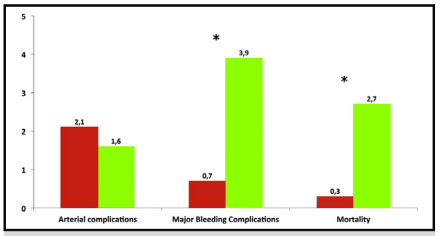
ABSTRACT

Objective: To verify the rate of thromboembolic and hemorrhagic complications during the first 6 months after mitral valve repair and to assess whether the type of antithrombotic therapy influenced clinical outcome.

Methods: Retrospective data were retrieved from 19 centers. Inclusion criteria were isolated mitral valve repair with ring implantation. Exclusion criteria were ongoing or past atrial fibrillation and any combined intraoperative surgical procedures. The study cohort consisted of 1882 patients (aged 58 ± 15 years; 36% women), and included 1517 treated with an oral anticoagulant (VKA group) and 365 with antiplatelet drugs (APLT group). Primary efficacy outcome was the incidence of arterial thromboembolic events within 6 months and primary safety outcome was the incidence of major bleeding within 6 months. Propensity matching was performed to obtain 2 comparable cohorts (858 vs 286).

Results: No differences were detected for arterial embolic complications in matched cohort (1.6% VKA vs 2.1% APLT; $P = .50$). Conversely, patients in the APLT group showed lower incidence of major bleeding complications (3.9% vs 0.7%; $P = .01$). Six-month mortality rate was significantly higher in the VKA group (2.7% vs 0.3%; $P = .02$). Multivariable analysis in the matched cohort found VKA as independent predictor of major bleeding complications and mortality at 6 months.

Conclusions: Vitamin K antagonist therapy was not superior to antiplatelet therapy to prevent thromboembolic complications after mitral valve repair. Our data suggest that oral anticoagulation may carry a higher bleeding risk compared with antiplatelet therapy, although these results should be confirmed in an adequately powered randomized controlled trial. (J Thorac Cardiovasc Surg 2016;151:1302-8)



Main 6-months events in patients receiving vitamin K antagonists (*green*) and antiplatelet therapy (*red*) in matched cohorts.

Central Message

Oral anticoagulation is not superior to antiplatelet therapy to prevent thromboembolic complications after mitral valve repair.

Perspective

Antithrombotic prophylaxis after mitral valve repair is debated. Our study shows that vitamin K antagonists are not superior to antiplatelet therapy during the first 6 postoperative months to prevent thromboembolic complications. Our data suggest that oral anticoagulation may carry a higher bleeding risk compared with antiplatelet therapy. A large prospective randomized trial is needed.

See Editorial Commentary page 1309.

Mitral regurgitation is the most frequent pathology of the mitral valve in Western countries[1] and mitral valve repair (MVR) is the surgical treatment of choice.[2] In fact, MVR is now being performed more frequently than mitral valve replacement with biological or mechanical prosthesis[3] and should be preferred to mitral valve replacement even in complex anatomic situations.[4] MVR is performed using a variety of techniques depending on the etiology. In degenerative mitral insufficiency (type II, according to Carpentier classification), leaflet resections, artificial chorda tendinae implant, chordal transposition, or edge-to-edge technique are among the most frequently used. An annuloplasty ring is almost invariably implanted during MVR to reduce annular dimensions, improve leaflet coaptation, and stabilize MVR results. The artificial surface of newly implanted mitral rings takes generally 3 months to be covered by endothelium. Theoretically during this period, the ring, together with surgical knots, scarred tissue of the left atrium, and

Abbreviations and Acronyms
APLT = antiplatelet therapy
MVR = mitral valve repair
VKA = vitamin K antagonist

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arrhythmias may increase the risk of thromboembolic complications and therefore an antithrombotic prophylaxis is usually prescribed. Whether to use oral anticoagulation with a vitamin K antagonist (VKA) or antiplatelet therapy (APLT) is still debated and current guidelines are discordant on this topic.[5,6]

In a retrospectively collected large cohort of consecutive patients who had undergone mitral valve repair in different hospitals, we aimed to verify the rate of thromboembolic and hemorrhagic complications during the first 6 months after hospital discharge, and whether the type of antithrombotic therapy influenced the clinical outcome.

METHODS

Patient Cohort and Data Collection

Nineteen centers from Italy, Spain, Canada, Israel, and Saudi Arabia participated in the study. Data were collected from institutional databases or patient charts for preoperative, operative, and postoperative details. Follow-up was achieved through direct or telephone interview with survivors, with relatives, with general practitioners, or with hospital doctors in the case of patients hospitalized for any cause after surgery. The study was conducted according to the Declaration of Helsinki. Ethics committee approval was obtained initially from the coordinating center (Policlinico of Bari University Hospital No. 759 2013-09-24) and subsequently from each participating site.

The choice of antithrombotic prophylaxis was based solely on center or surgeon preference; there were no other indication for APLT or oral anticoagulant therapy.

Study Design

This is a retrospective analysis of patients having MVR as the sole valvular procedure done at participating centers during a 3-year period (from 2011-2013), with a follow-up of at least 6 months after surgery. Study cohort (Figure 1) consisted of 1882 patients and included 1517 treated with oral anticoagulant (VKA group) for first postoperative 3 months and 365 with antiplatelet drugs (aspirin 100 mg daily, APLT group).

Inclusion Criteria

Included patients were aged ≥18 years at time of surgery underwent isolated MVR with mitral ring implantation to treat mitral regurgitation, and in sinus rhythm at hospital discharge.

Exclusion Criteria

Exclusion criteria included any history of atrial fibrillation, any combined surgical procedure associated with mitral valve repair, and treatment with both oral anticoagulation and APLT (80 or 100 mg once daily).

Primary Outcomes

Efficacy. This primary outcome was defined as real incidence of arterial thromboembolic events within 6 months after mitral valve repair, including cerebrovascular accidents, transient ischemic attack, and limb or mesenteric ischemic events.

Safety. This primary outcome was defined as real incidence of major bleeding up to 6 months after mitral valve repair or the stop of VKA anticoagulation +1 day, whichever came first.

Definitions of Study Outcomes

Arterial event. An arterial event was defined as the presence of 1 of the following within 6 months of the mitral valve operation: cardiac valvular or mural thrombus confirmed by echocardiogram, intracranial event confirmed by computed tomography/magnetic resonance imaging, transient ischemic attack, or limb or mesenteric thromboembolic event confirmed by arteriogram, magnetic resonance imaging, or computed tomography.

Bleeding. Major bleeding within the first 48 hours after surgery was defined per the Bleeding Academic Research Consortium[7]: perioperative intracranial bleeding within 48 hours, and/or reoperation after closure of sternotomy for the purpose of controlling bleeding, and/or transfusion of ≥5 units whole blood or packed red blood cells within a 48-hour period (cell saver products were not counted), and/or chest tube output ≥2 L within a 24-hour period.

Major bleeding that occurred at least 48 hours after surgery was defined per the International Society of Thrombosis and Haemostasis definition[8]: fatal bleeding; and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal,

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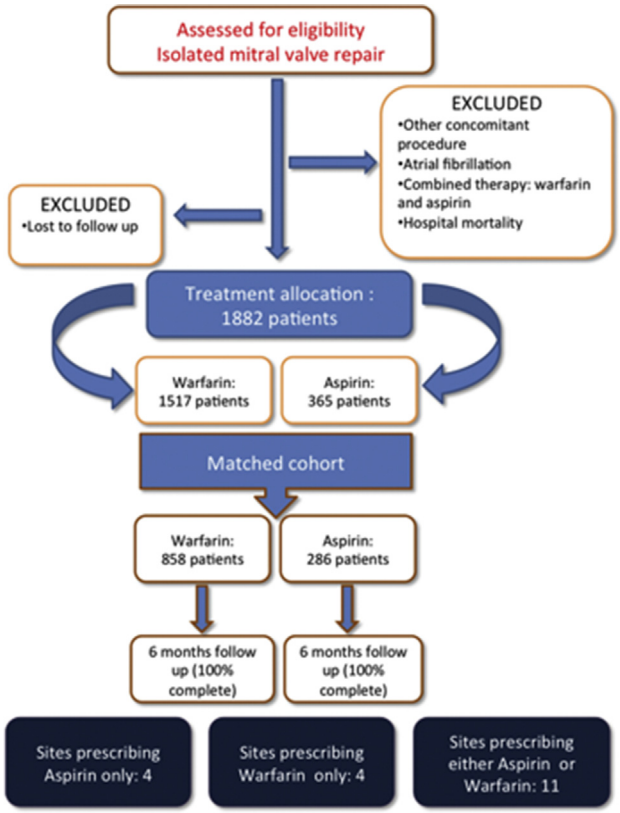

FIGURE 1. Consort diagram of the study.

intra-articular or pericardial, or intramuscular with compartment syndrome; and/or bleeding causing a fall in hemoglobin level of 3.0 g/dL or more or leading to transfusion of 2 or more units of whole blood or red cells.

Statistical Analysis

The categorical variables are expressed as percentages, whereas the continuous variables tested for type of distribution by means of Kolmogorov-Smirnov test and were reported as the mean ± standard deviation in case of normal distribution or as median and quartiles in case of nonnormal distribution. The comparison between the 2 groups was made by Student *t* test for independent variables or Mann-Whitney *U* test in case of continuous variables. Frequencies were compared using the χ^2 or Fisher exact test.

A not parsimonious propensity score model was built having APLT as the treatment (area under the curve, 0.96).

A 1:3 sample matching was performed using propensity score caliper matching with a caliper of 0.2. The final propensity model is reported in Appendix 1. To validate the matching, standardized mean differences after matching as well as *P* values are reported in Table 1. Standardized mean difference ≤20% was considered a threshold for a good balance.[9]

All the variables reported in Table 1 were tested using univariate analysis to predict either major bleeding or mortality; when the *P* value was <0.2, the variable was included in the initial logistic regression models. The results of multivariable analyses were reported as odds ratios and 95% confidence intervals, and *P* value. Receiver operating characteristic curve analysis was used to assess the calibration of the final models. SPSS version 20 software (IBM-SPSS Inc, Chicago Ill) integrated with R software version 2.1 (R Foundation for Statistical Computing, Vienna, Austria) was used to obtain automatically the best-matched samples.

RESULTS

The study cohort consisted of 1882 patients (aged 58 ± 15 years; 36% women), and included 1517 patients treated with VKA (VKA group) and 365 treated with antiplatelet drugs (APLT group).

After propensity matching the 2 groups consisted of 858 VKA and 286 APLT patients, respectively.

Table 1 shows patient characteristics according to the groups in the matched cohort. As reported, the final matching made the resulting groups comparable because all the standardized mean differences were below 20%. The only differences between the 2 groups concerned are technical: patients in VKA group received more commonly complete ring but lower chordal implantation (Table 1), even if the standardized difference between the 2 groups concerning complete ring implantation was slightly under 20%. However, these unbalanced variables had no influence on the clinical outcomes.

The overall rate of arterial complication was 1.7% (19 cases) with no differences between groups (n = 6 [2.1% APLT] vs n = 13 [1.6% VKA]; *P* = .50), but patients treated with APLT had a significantly lower incidence of major bleeding complications than the VKA group, (overall n = 32 [2.8%] and n = 2 [0.7%] APLT vs n = 30 [3.9%] VKA; *P* = .01) (Table 2); this finding was mainly due to patients experiencing hemoglobin drop >3 g/dL or necessitating blood transfusion (Figure 2).

In the matched cohort, 6-month mortality was 2.1% (24 cases), significantly higher in patients treated with VKA than APLT drugs (n = 1 [0.3%] APLT vs n = 23 [2.7%] VKA; *P* = .02) (Table 2); this result was mainly due to the association between VKA therapy and major bleeding: mortality occurred in 3 patients (9.4%) with major bleeding versus 21 patients (1.9%) without major bleeding (*P* = .027). Stratifying in 4 groups according to the type of therapy and occurrence of major bleeding, mortality occurred in 0.4% of APLT group patients without major bleeding, in none of the APLT group patients with major bleeding, in 2.4% of the VKA group patients without major bleeding, and in 10% of the VKA group patients with major bleeding (*P* = .03).

Multivariable Analyses in the Matched Cohort

VKA therapy was confirmed to be associated with higher likelihood of major bleeding along with ischemic time (ie, crossclamp time) and female gender (Table 3); moreover, VKA therapy was associated with a higher rate of 6-month mortality, along with age and creatinine (Table 3).

DISCUSSION

We performed the largest study to date regarding the incidence of short-term thromboembolic and hemorrhagic complications in patients undergoing MVR. We demonstrated

TABLE 1. Patient characteristics in matched cohorts

	Antiplatelet therapy group (n = 286)	Vitamin K antagonist group (n = 858)	*P* value	Standardized difference (%)
Female gender	106 (37.1)	319 (37.2)	.97	0.21
Age (y)	56.3 ± 17.3	57.7 ± 12.9	.22	13.1
Body mass index	25.4 ± 4.0	25.0 ± 4.8	.15	9.0
Chronic obstructive pulmonary disease	29 (10.1)	61 (7.1)	.20	10.7
Malignancy	5 (1.7)	24 (2.8)	.33	7.4
Prior stroke	5 (1.7)	11 (1.3)	.56	3.3
Other than cerebrovascular disease	8 (2.8)	13 (1.5)	.16	9.0
Hypertension	145 (50.7)	404 (47.1)	.29	7.2
Noninsulin dependent diabetes mellitus	12 (4.2)	30 (3.5)	.59	3.6
Insulin dependent diabetes mellitus	4 (1.4)	12 (1.4)	1.00	0
Peripheral vascular disease	11 (3.9)	24 (2.8)	.37	6.1
Previous gastrointestinal bleeding	7 (2.4)	17 (2.0)	.63	2.7
Creatinine (mg/dL)	0.90 ± 0.22	0.90 ± 0.23	.54	0
Closed ring	165 (58.3)	583 (67.9)	<.001	19.9
Resective plasty	118 (41.3)	376 (43.8)	.45	5.0
Chordal implantation	70 (24.5)	84 (9.8)	<.001	39.7
Chordal transposition	6 (2.7)	14 (1.6)	.64	7.6
Edge-to-edge	33 (11.5)	108 (12.6)	.64	3.4
Cardiopulmonary bypass time (min)	109.7 ± 27.8	109.6 ± 34.7	.96	0.3
Crossclamp time (min)	83.0 ± 22.1	82.3 ± 28.9	.72	2.7

Values are presented as mean ± standard deviation or n (%).

that thromboembolic complications are rare, with an overall incidence of 1.4% during the first 6 months after surgery. The type of antithrombotic therapy did not influence arterial thromboembolic complications.

A higher incidence of major bleeding was also observed in patients receiving oral anticoagulants during the first 3 months. In addition, the incidence of hemorrhagic complications was relatively more frequent (overall, 2.8%) than thromboembolic ones.

The relevance of these findings is not negligible because most of the information available in the literature for patients undergoing MVR are gathered from large series with long-term follow-up. David and colleagues[10] reported 50 thromboembolic events (10.2%) out of 488 patients during 15 years of follow-up. Carpentier and colleagues[11] described only 4 thromboembolic events in his original series of 162 patients followed for 29 years (2.5%). In both series patients underwent anticoagulation therapy with VKA during the first 3 and 2 months, respectively, and the incidence of thromboembolic or hemorrhagic complications during the early period after surgery was not specified. Postoperative oral anticoagulation therapy should theoretically abolish the risk of thrombosis on newly implanted prosthetic material and scarred tissue, avoiding systemic embolization. However, oral anticoagulation therapy carries a bleeding risk, and such hemorrhagic events associated with this therapy are not insignificant. Adequately powered trials have clearly demonstrated that a higher

TABLE 2. Outcomes in matched cohorts

	Antiplatelet therapy group (n = 286)	Vitamin K antagonist group (n = 858)	*P* value
Length of stay (d)	7 (6-9)	7 (6-8)	.45
Arterial complications	6 (2.1)	13 (1.6)	.50
Cardiac valvular or mural thrombus	0	2 (0.2)	1.00
Ischemic stroke	3 (1.0)	9 (1.0)	1.00
Transient ischemic attack	1 (0.3)	6 (0.7)	.51
Peripheral thromboembolism	1 (0.3)	1 (0.1)	.44
Major bleeding complications	2 (0.7)	30 (3.9)	.01
Hemorrhagic stroke	1 (0.3)	5 (0.6)	.64
Symptomatic bleeding into critical organ	0	8 (0.9)	.21
Drop in hemoglobin >3 g/dL or necessitating blood transfusion	2 (0.7)	27 (3.1)	.02
Fatal bleeding	0	2 (0.2)	.41
6-mo Mortality	1 (0.3)	23 (2.7)	.02

Values are presented as median (range) or n (%).

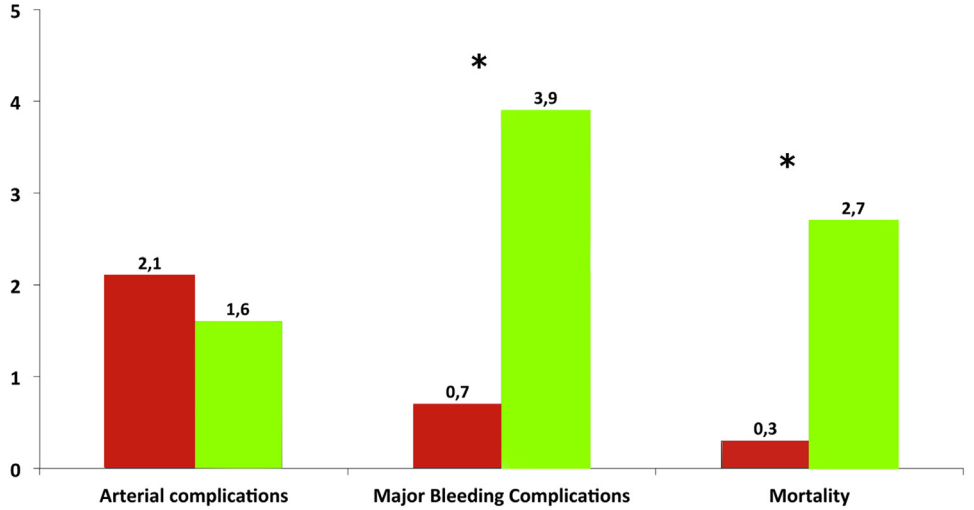

FIGURE 2. Main 6-month events in vitamin K antagonist (*green columns*) and antiplatelet therapy (*red columns*) in matched cohorts. *$P < .05$.

rate of major bleeding is directly related to increased risk of death.[12] Our observation of major bleeding events during the first 3 months of oral anticoagulation therapy is in accordance with previous publications. Recently, the Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients After Heart Valve Replacement (RE-ALIGN) trial[13] (conducted among patients with prosthetic heart valves) reported major bleeding complications in 2% of patients during the first 3 months. Major bleeding complications were found in 2.8% in patients receiving warfarin therapy during the first 3 months following mitral valve replacement with bioprosthesis.[14]

Guidelines are discordant in their recommendations for antithrombotic prophylaxis during the first 3 months following MVR. In 2008, the Committee of the European Association of Cardio-Thoracic Surgery produced guidelines on antiplatelet and anticoagulation management in cardiac surgery.[15] This document included a specific chapter for anticoagulation during the first 3 months after MVR; it takes into consideration the few studies reporting thrombembolic events and a Best Evidence Topic review published by Dunning and colleagues.[16] The Committee recommendations are most influenced by the Dunning review,[16] which supported warfarin anticoagulation therapy during the first 3 months after MVR. The 2012 joint European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines[5] on heart valve disease recommend oral anticoagulation during the first 3 months after MVR (Class IIa, Level C) with no references supporting the recommendation. In 2012, the American College of Chest Physicians guidelines on antithrombotic therapy suggested antiplatelet therapy for the first 3 months after MVR in patients in sinus rhythm (Grade 2C).[6] This recommendation is based on a single retrospective study by Aramendi and colleagues[17] who reported on the thromboembolic risk of 235 patients undergoing mitral replacements or repairs from 1990 to 1995. In total, 6 episodes of thromboembolism were reported. All occurred during the first postoperative year, and 4 of these events occurred during the first 3 months of follow-up. Two patients were taking ticlopidine and 4 were taking warfarin.

More recently Schwann and colleagues[18] performed a single-center, retrospective evaluation of 249 patients who underwent MVR (144 patients) or replacement with bioprosthesis (105 patients), including also patients receiving concomitant procedures such as coronary artery bypass grafting, aortic bioprosthesis implants, and atrial fibrillation surgery. Patients discharged taking warfarin (77%) were compared with those discharged without warfarin; no difference in thromboembolic or hemorrhagic events was demonstrated.

Suri and colleagues[19] recently reported on 13,082 patients from the Society of Thoracic Surgeons Database undergoing mitral valve repair in North America from 2008 to 2010. Their study aimed to determine the incidence and predictors

TABLE 3. Multivariate analyses in the matched cohort

	Odds ratio	95% Confidence interval	*P* value
6-mo Major bleeding*			
Vitamin K antagonist therapy	5.2	1.2-15.7	.03
Female gender	2.5	1.2-5.1	.01
Crossclamp time (min)	1.02	1.01-1.03	.04
6-mo Mortality†			
Vitamin K antagonist therapy	11.1	1.4-25.2	.02
Age (y)	1.09	1.05-1.14	<.01
Creatinine (mg/dL)	6.4	2.2-15.7	<.01

*Area under the curve of the model was 0.75. †Area under the curve of the model was 0.86.

of VKA use immediately after isolated MVR. They showed an extreme variability in VKA prescription, which is predominantly driven by surgeon or center preference rather than patients' clinical variables. VKA prescription was associated with a significantly longer length of stay in hospital after surgery. No data regarding thromboembolic or hemorrhagic complications were available in this study. Based on the paucity of information from published series on the short-term antithromboembolic prophylaxis after MVR, our findings are consistent with the need of reappraisal in terms of adequate therapeutic strategies and effects.

Several limitations should be emphasized regarding our study: the retrospective nature of data collection and the absence of randomized criteria for treatment allocation, antithrombotic prophylaxis chosen mainly by center or surgeon's preference, the lack of information regarding the incidence of atrial fibrillation after the operation, the international normalized ratio values at the time of bleeding or thrombotic events and the time in therapeutic range, and the limited number of patients receiving aspirin therapy.

Propensity scores are often used to reduce bias in observational and retrospective studies.[20,21] Ideally, a prospective, randomized controlled trial should be performed comparing warfarin therapy to APLT during the first 3 months after MVR. However, given the small number of events occurring in the short period of observation after surgery, such a trial would be difficult to perform. In our study, overall arterial and bleeding complications rate was 0.7% and 3.9%, respectively. Accordingly, more than 5000 patients per group would be needed to obtain a 95% confidence interval lower than 1% under the hypothesis of similar arterial and bleeding event rates between treatment arms. While we wait for such an endeavour to be accomplished, our study offers the best evidence so far regarding the initial antithrombotic prophylaxis in patients undergoing mitral valve repair. We observed similar thromboembolic rates for patients undergoing isolated MVR who are at low risk of thromboembolic complications. Given that the incidence of hemorrhagic complication in our series was double the incidence of thromboembolic events, these data should be considered when choosing antithrombotic therapy in these patients. Compared with previous publications, we selected a large and homogeneous group of patients, excluding concomitant procedures that might lead to a different clinical profile (ie, coronary artery disease and risk of atherosclerosis-related events as well as atrial fibrillation ablation surgery) and carefully excluding patients with preoperative chronic, paroxysmal, or permanent atrial fibrillation.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: mitral valve repair, anticoagulation, bleeding, stroke, antiplatelet

APPENDIX 1. Propensity score model

Variables	β	Standard error	*P* value
Closed ring	−.627	.241	.009
Age	−.010	.009	.266
Female gender	.306	.245	.212
Chronic obstructive pulmonary disease	1.342	.323	.000
Malignancy	−.308	.630	.625
Prior stroke	.902	.771	.242
Other than Cerebrovascular disease	−.226	.810	.781
Hypertension	.483	.227	.033
Noninsulin-dependent diabetes mellitus	−.089	.585	.879
Insulin-dependent diabetes mellitus	2.149	.586	.000
Peripheral vascular disease	1.076	.604	.075
Previous gastrointestinal bleeding	.293	.655	.655
Resective plasty	.496	.241	.040
Chordal implantation	.398	.322	.216
Edge-to-edge	1.147	.335	.001
Chordal Transposition	−1.217	.668	.069
Creatinine	−.093	.469	.843
Body mass index	.007	.027	.783
Cardiopulmonary bypass time (min)	.005	.006	.423
Crossclamp time (min)	−.010	.008	.239
Center volume*			.000
Medium vs low	3.247	.372	.000
High vs low	−2.907	.256	.000
Continent			.000
North America vs Europe	.635	.561	.257
Middle Asia vs Europe	2.625	.503	.000
Constant	−.487	.971	.616
	Area under the curve	**Standard error**	
Model	0.96	0.004	

*Low-volume center: <50 cases (9 centers), medium-volume center: 51-100 cases (3 centers) and high-volume center: >100 cases (7 centers).