Ruzina E. V., Berdibekov B. Sh., Bulaeva N. I., Kubova M. Ch., Golukhova E. Z.
Bakulev National Medical Research Center, Moscow, Russia

Comparison of Various Regimens of Antithrombotic Therapy in Patients With Valvular Heart Disease and Coronary Artery Disease After Surgical and Interventional Interventions

Aim — To evaluate the postoperative incidence of bleeding, incidence of thromboembolic complications, and all-cause mortality in patients with valvular heart disease and ischemic heart disease (IHD) associated with various regimens of the antithrombotic treatment during one year after surgery.

Material and methods — This study included 271 patients with valvular heart disease and IHD after heart valve replacement and myocardial revascularization from 2009 through 2018. However, during the follow-up period (12 months), contact with 12 patients was lost, and therefore these patients were excluded from the study. Further analysis included 259 patients. Coronary artery bypass grafting (CABG) in combination with heart valve intervention was performed in 217 (83.8%) patients, and percutaneous coronary interventions (PCIs) were performed in 42 (16.2%) patients. There were 197 (72.7%) male participants; median age was 64.0 [58.0; 67.5] years. The patients were divided into two groups. Group 1 consisted of 113 patients who received postoperative dual antithrombotic therapy (DAT) with acetylsalicylic acid (ASA)/clopidogrel+vitamin K antagonist (VKA). Group 2 included 146 patients receiving postoperative triple antithrombotic therapy (TAT) with ASA+clopidogrel+VKA. Follow-up duration was 12 months after surgery. Due to significant intergroup differences in major clinical anamnestic data, the data were adjusted using pseudo-randomization (Propensity Score Matching, PSM). In result, 109 patients were selected for each group.

Results — The incidence of adverse hemorrhagic outcomes was significantly higher in the group treated with TAT than with DAT. Minor bleedings were observed in 19 (17.4%) vs. 8 (7.3%) cases; moderate, clinically significant bleedings in 16 (14.7%) vs. 6 (5.5%) cases; and the total number of bleedings was 35 (32.1%) vs. 14 (12.8%; p=0.02, p=0.02, and p=0.001, respectively). Comparing the incidence of major bleedings did not show and significant intergroup differences (p=1.000). The incidence rate of any bleeding during the follow-up period was 32.1% in patients treated with TAT (n=109) and 12.8% in patients treated with DAT (n=109; p=0.005). The incidence of no bleeding during one year after surgery was 87% in the DAT treatment group and 67% in the TAT treatment group (p=0.005). The incidence of secondary endpoints, including ischemic stroke, myocardial infarction, prosthetic valve thrombosis, and death, was statistically non-significant.

Conclusion — Administration of DAT vs. TAT after heart valve replacement and myocardial revascularization significantly decreases the incidence of any bleedings in the absence of significant differences in the incidence of thromboembolic events and mortality.

Keywords — Ischemic heart disease; heart valve replacement; percutaneous coronary intervention; coronary artery bypass grafting; vitamin K antagonists; antiplatelet therapy

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Corresponding author — Ruzina E. V. E-mail: kykyryzinka2@yandex.ru

Introduction

Continuous administration of vitamin K antagonists (VKAs) is indicated for all patients after heart valve replacement (HVR) with mechanical prosthetic valve [1, 2]. In 20–30% of cases, these patients have concomitant coronary artery disease (CAD), which also requires surgical treatment – percutaneous coronary intervention (PCI) with stenting or coronary artery bypass grafting (CABG) [3, 4]. Coronary artery interventions, whether PCI or CABG, require the administration of antiplatelet drugs as monotherapy or dual therapy [5]. The co-administration of dual antiplatelet therapy (DAT) and VKA, versus VKA monotherapy, leads

to at least a two-fold or three-fold increase in the likelihood of hemorrhagic complications. The VKA and antiplatelet treatments is associated with a high risk of bleeding in the group of patients who have had HVR and myocardial revascularization [6–9]. There are very few studies in the world literature that have examined the safety and efficacy of antithrombotic therapy (ATT) in the specified category of patients. The randomized study WOEST (2012), which included 573 patients, is one of those [10]. However, only 10% of patients with mechanical heart valves were included in the study; 70% were patients with atrial fibrillation (AF) and the remaining 20% had pulmonary embolism and left ventricular thrombosis. The study of two ATT regimens (warfarin + clopidogrel + acetylsalicylic acid (ASA) versus warfarin + clopidogrel) demonstrated the superiority of dual therapy with warfarin and clopidogrel over triple therapy in terms of achieving the primary endpoint – hemorrhagic complications (19.5% vs.44.4%; hazard ratio (HR) 0.36; 95% confidence interval (CI) 0.26–0.50; $p < 0.001$). The WOEST study gave rise to further large studies (PIONEER AF-PCI, REDUAL-PCI, RE-LY, AUGUSTUS, WOEST 2) [11–15], which aimed to determine the optimal balance of efficacy and safety of the simultaneous administration of anticoagulant and antiplatelet drugs.

We have tested the hypothesis that DAT (VKA + ASA/clopidogrel) versus triple antithrombotic therapy (TAT; VKA + ASA + clopidogrel) is associated in patients subjected to HVR and myocardial revascularization with a significant reduction in the risk of bleeding without an increase in the risk of thromboembolic and ischemic complications.

Material and Methods

The retrospective cohort study included patients who had been treated in the Bakulev National Medical Research Center of Cardiovascular Surgery from 2009 to 2018.

Inclusion criteria were the following: condition after scheduled mitral valve (MV)/aortic valve (AV) interventions in combination with coronary artery stenting/bypass grafting; continuous use of anticoagulant drugs (VKA) and antiplatelet agents (ASA, clopidogrel).

Exclusion criteria: absolute contraindications to ATT, chronic kidney disease (3b, stage 5); active infectious process; other decompensated extracardiac pathology; patient's refusal to participate in the study.

The study included 271 patients, 197 (72.7%) of them were male; the median age was 64.0 [58.0; 67.5] years. The median follow-up was 12 months (minimum 1 month and maximum 12 months). During this period, 12 (4.4%) patients were lost to follow up, and their data on the development of endpoints was missing. These patients were excluded from the analysis.

All patients included in the further analysis (n = 259) underwent AV and/or MV replacement with mechanical prostheses with simultaneous myocardial revascularization by CABG or PCI, which had been performed 24 hours before the heart valve surgery. The replacement of AV, MV, and both was performed in 215 (83.0%), 32 (12.4%), and 12 (4.6%) patients, respectively. Modern Russian and foreign low-thrombogenicity mechanical prostheses were used (Miks, Karboniks, Medeng, St.Jude, On-X, Medtronic, ATS). CABG and PCI combined with a valve intervention was performed in 217 (83.8%) and 42 (16.2%) patients, respectively. In the postoperative period, all patients received VKA as anticoagulant therapy; due to myocardial revascularization, ASA monotherapy was added VKA in 82 (31.7%) patients, clopidogrel monotherapy was ordered for 31 (12.0%) patients, and 146 (56.4%) patients received the combination of ASA and clopidogrel. The choice of an ATT regimen in the postoperative period was up to the patient's attending physician. To assess the effectiveness of the international normalized ratio (INR) control, the time it was within the target range – time in therapeutic range (TTR) – was calculated using to the Rosendaal method. The median TTR was 70.0 [55.5; 80.0] %.

The development of hemorrhagic complications, such as minor, clinically significant minor, and major bleeding, was the primary safety endpoint of ATT. The secondary efficacy endpoint was the development of thromboembolic and/or ischemic complications, and death.

The outcome data were collected by remote questioning of patients or by telephone survey of patients or family members. The duration of follow-up was 12 months from the date of surgery to the onset of an endpoint. If a patient did not have an endpoint during follow-up, the patient's data was censored by the date of the last contact.

Statistical analysis was performed using SPSS Statistics v. 26.0. Quantitative indicators were evaluated for the distribution normality using the Kolmogorov-Smirnov test and asymmetry and excess coefficients. Normally distributed quantitative indicators were presented as the arithmetic means (M) and standard deviations (SD). Non-normally distributed quantitative indicators were described using the medians (Me) and the lower and upper quartiles ([Q1; Q3]). Nominal data were expressed by the absolute values and percentages. Non-normally distributed independent sets were compared using the Mann-Whitney U-test. Nominal data were compared using Pearson's chi-squared test. When at least one cell of the $2x^2$ table contained less than 5 expected observations, the significance level of differences was estimated using Fisher's exact test. The odds ratios (OR) were used as a quantitative measure of the effect when the relative variables were compared. Kramer's V test was used to evaluate the correlation of the nominal variables.

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The baseline data was corrected by pseudo-randomization (propensity score matching (PSM)). Patient survival was assessed using the Kaplan-Meier method. Patient survival was analyzed by Cox regression analysis. The differences were considered to be statistically significant with $p < 0.05$.

Results

Depending on the ATT regimen used, patients were divided into 2 groups: DAT (VKA + ASA/clopidogrel) and TAT (VKA + ASA +clopidogrel). The main clinical and anamnestic data of patients are presented depending on the ATT regimen in Table 1.

The analysis showed a statistically significantly larger number of female patients in the TAT group ($p = 0.012$) and a higher frequency of PCI procedures for myocardial revascularization ($p = 0.032$); at the same time, a higher frequency of CABG procedures ($p = 0.032$) was observed in the DAT group. There were no statistically significant differences in other characteristics in the groups compared ($p > 0.05$).

The data were corrected using the pseudo-randomization method in connection with the detected statistically significant differences between the TAT and DAT groups in sex composition and myocardial revascularization methods applied.

The main clinical and anamnestic data and methods of surgical intervention did not differ statistically significantly ($p > 0.05$) in the groups of 109 patients formed after pseudorandomization. The results of the comparative analysis of the patient groups after pseudorandomization are presented in Table 2.

During the follow-up period, the primary endpoint (any bleeding) was reported in 49 (22.5%) patients: minor bleeding in 27 (12.4%) cases, clinically significant minor bleeding in 22 (10.1%) cases, and major bleeding in 2 (0.9%) cases. We estimated the incidence of various hemorrhagic complications depending on the ATT regimen administered. The results are presented in Table 3.

According to the analysis, the incidence of adverse hemorrhagic outcomes, specifically, minor, clinically significant minor, and all bleeding events, was statistically significantly higher in the TAT group ($p = 0.02$, $p = 0.02$, and $p = 0.001$, respectively). The odds of developing these adverse hemorrhagic outcomes during TAT increased 2.66 (95% CI 1.11–6.38), 2.95 (95% CI 1.11–7.86), and 3.21 times (95% CI 1.61–6.40), respectively. The closeness of the correlations identified between the ATT regimen and the development of the specified hemorrhagic outcomes as assessed using the Kramer V-test, was weak for minor and clinically significant minor bleeding events ($V = 0.153$ and $V = 0.152$, respectively) and moderate for all bleeding events ($V = 0.231$). At the same time, no statistically significant differences were found when comparing the frequency of major bleeding between the ATT regimen groups.

During the follow-up period, the composite secondary endpoint was reported in 21 (9.6%) patients: 14 (6.4%) cases of ischemic stroke, 2 (0.9%) cases of prosthetic valve thrombosis, 4 (1.8%) cases of myocardial infarction (MI), and 13 (6.0%) patients died.

Table 1. Clinical and anamnestic characteristics of patients

Parameter	DAT (n = 113)	TAT (n = 146)	p
Female, n (%)	22 (19.5)	49 (33.6)	0.012
Age, years, Me [Q1; Q3]	64.0 [58.0; 67.0]	64.0 [58.0; 68.0]	0.654
BMI, kg/m^2, M ± SD	27.4 ± 3.9	28.3 ± 4.5	0.084
Arterial hypertension, n (%)	92 (81.4)	129 (88.4)	0.117
Atrial fibrillation, n (%)	41 (36.3)	41 (28.1)	0.159
Diabetes mellitus, n (%)	16 (14.2)	26 (17.8)	0.429
PICS, n (%)	27 (23.9)	36 (24.7)	0.887
History of PCI, n (%)	11 (9.7)	25 (17.1)	0.088
History of CABG, n (%)	2 (1.8)	3 (2.1)	1.000
History of stroke, n (%)	6 (5.3)	8 (5.5)	1.000
CHF NYHA class III–IV, n (%)	101 (89.4)	130 (89.0)	0.930
History of valve surgery, n (%)	0	1 (0.7)	1.000
HAS-BLED score, n (%)			
1	5 (4.4)	4 (2.7)	0.509
2	24 (21.2)	36 (24.7)	0.518
3	55 (48.7)	57 (39.0)	0.055
4	25 (22.9)	37 (33.9)	0.121
5	3 (2.7)	7 (4.8)	0.521
TTR, %, Me [Q1; Q3]	70.0 [55.5; 83.3]	66.6 [50.0; 80.0]	0.316
Aortic valve replacement, n (%)	90 (79.6)	125 (85.6)	0.204
Mitral valve replacement, n (%)	15 (13.3)	17 (11.6)	0.693
Aortic + mitral valve replacement, n (%)	8 (7.1)	4 (2.7)	0.136
PCI, n (%)	12 (10.6)	30 (20.5)	0.032
CABG, n (%)	101 (89.4)	116 (79.5)	0.032

DAT, dual antithrombotic therapy; TAT, triple antithrombotic therapy; BMI, body mass index; PICS, post-infarction cardiosclerosis; CABG, coronary artery bypass grafting; HAS-BLED, a scoring system to estimate bleeding risk; TTR, time in therapeutic range.

Table 2. Comparative characteristics of the main clinical and anamnestic data and techniques of surgical intervention after pseudorandomization

Parameter	DAT (n = 109)	TAT (n = 109)	p
Female, n (%)	22 (20.2)	30 (27.5)	0.204
Age, years, Me [Q1; Q3]	64.0 [58.5; 67.0]	65.0 [58.5; 69.0]	0.310
BMI, kg/m2, M ± SD	27.4 ± 3.9	28.1 ± 4.3	0.221
Arterial hypertension, n (%)	88 (80.7)	96 (88.1)	0.135
Atrial fibrillation, n (%)	39 (35.8)	29 (26.6)	0.144
Diabetes mellitus, n (%)	14 (13.8)	13 (11.9)	0.837
PICS, n (%)	26 (23.9)	28 (25.7)	0.754
History of PCI, n (%)	11 (10.1)	15 (13.8)	0.403
History of CABG, n (%)	2 (1.8)	2 (1.8)	1.000
History of stroke, n (%)	6 (5.5)	7 (6.4)	1.000
CHF NYHA class III–IV, n (%)	98 (89.9)	99 (90.8)	0.818
History of valve surgery, n (%)	0	1 (0.9)	1.000
HAS-BLED score, n (%)			
1	5 (4.6)	3 (2.8)	0.721
2	23 (21.1)	24 (22.0)	0.869
3	53 (48.6)	39 (35.8)	0.055
4	25 (22.9)	37 (33.9)	0.072
5	3 (2.8)	6 (5.5)	0.499
TTR, %, Me [Q1; Q3]	70.0 [55.5; 83.3]	70.0 [50.0; 80.0]	0.368
Aortic valve replacement, n (%)	86 (78.9)	95 (87.2)	0.104
Mitral valve replacement, n (%)	15 (13.8)	12 (11.0)	0.537
Aortic + mitral valve replacement, n (%)	8 (7.3)	2 (1.8)	0.101
PCI, n (%)	12 (10.6)	4 (3.7)	0.066
CABG, n (%)	97 (89.0)	105 (96.3)	0.066

DAT, dual antithrombotic therapy;
TAT, triple antithrombotic therapy; BMI, body mass index;
PICS, post-infarction cardiosclerosis; HAS-BLED, a scoring system to estimate bleeding risk; TTR, time in therapeutic range.

We assessed the frequency of various secondary endpoints depending on the ATT regimen, the resulting data are presented in Table 4.

According to the analysis, there were no statistically significant differences in the incidence of adverse secondary endpoints (death, ischemic stroke, prosthetic valve thrombosis, MI) ($p > 0.05$).

Predictors of hemorrhagic complications

Cox regression analysis was conducted to predict the risk of hemorrhagic complications and assess the effect of certain predictors on this risk. Such factors as the presence of diabetes mellitus (HR 2.48; 95% CI 1.20–5.12), HAS-BLED score (HR 1.98 per point; 95 CI 1.07–3.66), and DAT (HR 0.39; 95% CI 0.20–0.74) showed an independent correlation with the risk of hemorrhagic complications in multivariate Cox regression analysis. These results are presented in Table. 5.

Patient survival was assessed using the Kaplan-Meier method. The dependence of the risk of bleeding on ATT regimens (DAT or TAT) was compared using the Kaplan-Meier curves. The cumulative risk of bleeding during the observation period is plotted on the Kaplan-Meier curves (Figure 1).

The incidence of any bleeding events during the follow-up (365 days) was 32.1% in the TAT group (n = 109) and 12.8% in the DAT group (n = 109). Within 1 year after surgery, there was no bleeding in 87% and 67% of cases in the DAT group and the TAT group, respectively The differences in the incidence of hemorrhagic complications over time, estimated using the Mantel-Cox log-rank test, were statistically significant ($p = 0.001$; Figure 2).

The incidence of secondary endpoints, including ischemic stroke, MI, prosthetic valve thrombosis, and death during the follow-up (365 days) was 11.9% in the TAT group (n = 109) and 7.3% in the DAT group (n = 109). Within 1 year after surgery, 93% and 88% of patients did not develop secondary endpoints in the DAT and TAT groups, respectively The differences in the incidence of secondary endpoints, estimated using the Mantel-Cox log-rank test, were statistically insignificant ($p = 0.24$; Figure 3).

Discussion

Our study clearly demonstrated the significant superiority of the DAT regimen over TAT in terms of safety, specifically reducing the risk of hemorrhagic complications. At the same time, there were no differences in the incidence of thromboembolic and ischemic outcomes between these regimens.

During the follow-up period, the primary endpoint of any bleeding occurred in 49 (22.5%) patients – 14 (12.8%) cases in patients receiving DAT and 35 (32.1%) cases in patients on TAT. The incidence of hemorrhagic complications was slightly lower than in the WOEST study, in which the incidence of bleeding was 19.4% and 44.4% in the DAT group and the TAT group, respectively. The higher bleeding rate in the WOEST study is likely due to the fact that all patients underwent PCI for myocardial revascularization, which required longer administration of combination ATT.

It should be noted that the differences in the incidence of hemorrhagic complications observed in our study between the DAT group and the TAT group are mainly due to differences in the incidence of minor and clinically significant minor bleeding events.

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Table 3. Comparison of bleeding rates depending on the antithrombotic regimen

Type of hemorrhagic complications	Antithrombotic regimen				p	OR (95 %CI)
	DAT (n = 109)		TAT (n = 109)			
	n	%	n	%		
Minor bleeding	8	7.3	19	17.4	0.021	2.66 (1.11–6.38)
Clinically significant minor bleeding	6	5.5	16	14.7	0.024	2.95 (1.11–7.86)
Major bleeding	1	0.9	1	0.9	1.001	1.00 (0.06–16.19)
All bleeding events	14	12.8	35	32.1	0.001	3.21 (1.61–6.40)

DAT, dual antithrombotic therapy; TAT, triple antithrombotic therapy; OR, odds ratio; CI, confidence interval.

Table 4. Comparison of the estimates of secondary endpoint incidence depending on the antithrombotic regimen

Secondary endpoint	Antithrombotic regimen				p	OR (95 %CI)
	DAT (n = 109)		TAT (n = 109)			
	n	%	n	%		
Death	5	4.6	8	7.3	0.569	1.65 (0.52–5.20)
Ischemic stroke	4	3.7	10	9.2	0.165	2.65 (0.80–8.73)
Prosthetic valve thrombosis	0	0	2	1.8	0.498	–
Myocardial infarction	0	0	4	3.7	0.122	–
Composite endpoint	8	7.3	13	11.9	0.251	1.71 (0.68–4.31)

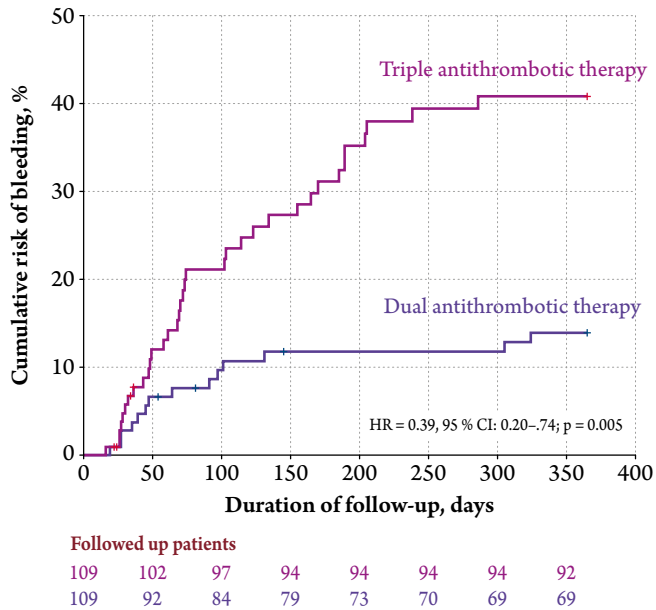
DAT, dual antithrombotic therapy; TAT, triple antithrombotic therapy; OR, odds ratio; CI, confidence interval.

Table 5. Results of Cox multivariate logistic regression analysis

Parameter	HR	95 % CI	p
Age	1.01	0.95–1.08	0.716
Sex, male	1.38	0.71–2.67	0.346
BMI	0.93	0.86–1.01	0.081
CHF NYHA class III-IV	1.18	0.45–3.10	0.741
AH	1.23	0.33–4.61	0.760
PCI	2.39	0.87–6.57	0.092
DM	2.48	1.20–5.12	0.014
AF	0.86	0.45–1.66	0.658
DAT	0.39	0.20–0.74	0.005
HAS-BLED	1.98	1.07–3.66	0.030
TTR	0.99	0.97–1.01	0.423

HR, hazard ratio; CO, confidence interval; BMI, body mass index; DAT, dual antithrombotic therapy; TAT, triple antithrombotic therapy; HAS-BLED, a scoring system to estimate bleeding risk; TTR, time in therapeutic range.

Figure 1. Graph of cumulative risk of bleeding during the follow-up depending on the antithrombotic regimen



HR, hazard ration; CI, confidence interval.

There were no statistically significant differences between the groups in the rate of thromboembolic and ischemic complications, including ischemic stroke, MI and prosthetic valve thrombosis, and all-cause death. The absence of differences in the incidence of ischemic complications between the DAT group and the TAT group is probably due to the fact that VKAs have antiplatelet properties as well as the anticoagulant effect; the former are implemented by inhibiting thrombin, which is a leading factor of increased platelet aggregation. Thus, the use of the combination of VKA + antiplatelet produces a sufficient antiplatelet effect, and the additional administration of another antiplatelet probably is unlikely to result in the expected significant reduction in the incidence of ischemic complications, and this strategy significantly increases the incidence of bleeding. Cox's multivariate regression analysis showed that the DAT regimen was an independent factor that reduced the risk of all bleeding events by 61 % versus the TAT regimen.

Figure 2. Graph of cumulative survival (probability of no bleeding) during the follow-up depending on the antithrombotic regimen

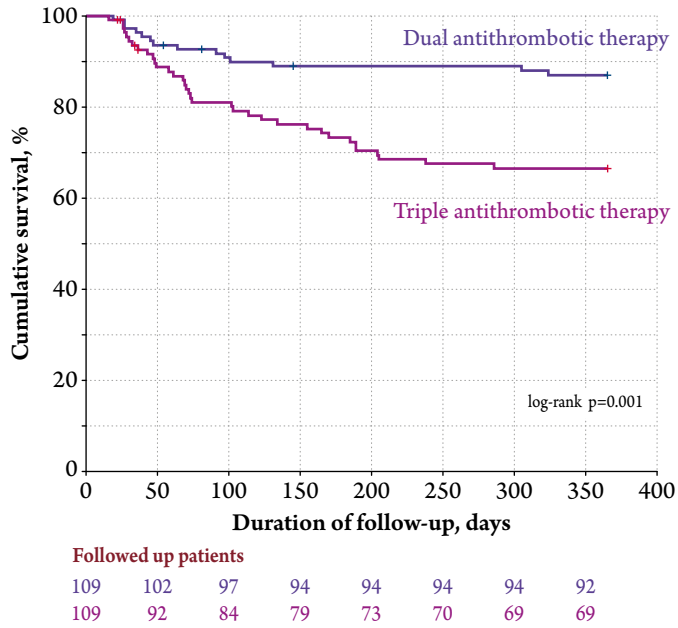
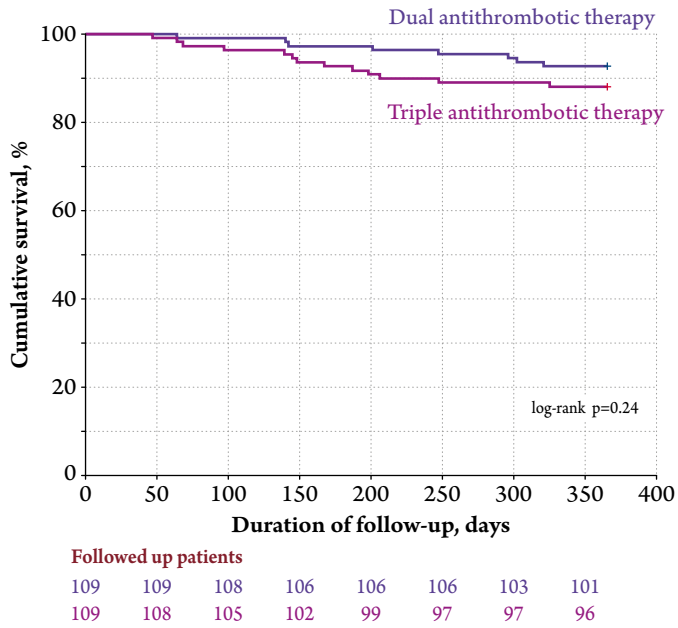


Figure 3. Graph of cumulative survival (probability of no secondary endpoints) during the follow-up depending on the antithrombotic regimen



There are no randomized clinical trials published in the world literature that assess the efficacy and safety of the combination use of antiplatelet agents and VKA in patients after heart valve replacement and myocardial revascularization. Further thought should perhaps be given to achieving a balance between the risk of bleeding and the risk of thromboembolic complications in the cohort of interest comprising patients who often have severe comorbidity.

The advantage of our study is a detailed description of a relatively large cohort of patients. To the best of our knowledge, our study is the first of its kind to evaluate adverse outcomes depending on the ATT regimen. Of course, the main limitation of our study is its retrospective design – its results reflect only existing trends and are intended to develop hypotheses. Moreover, we did not analyze the incidence of endpoints in individual patient subgroups, such as patients with AF; patients after PCI or CABG separately; depending on the heart valve disease, or position of prosthetic valve, etc. Further randomized studies in this patient cohort will allow more confidently recommending a particular ATT regimen.

Conclusion

Thus, a dual antithrombotic regimen may be a preferred strategy with the best possible safety and efficacy profile for patients with heart valve disease and coronary artery disease who have undergone heart valve replacement and myocardial revascularization by coronary artery bypass grafting or percutaneous coronary intervention.

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