

# Antitrombotik Ajanların Preoperatif Kesilmesinin Tromboz ve Kanama Riski Üzerine Etkileri

## Withdrawal of Antithrombotic Agents and Its Impact on Thrombosis and Bleeding in Patients Undergoing Cardiac Surgery

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### ÖZ

**GİRİŞ ve AMAÇ:** Amacımız açık kalp ameliyatı geçiren hastalarda preoperatif antikoagülanların kesilmesi ile ilişkili olabilecek trombotik komplikasyonların insidansını belirlemektir.

**YÖNTEM ve GEREÇLER:** Elektif açık kalp ameliyatı geçiren 512 erişkin hastanın verileri değerlendirildi. İkili antiplatelet tedavisi alan hastalar dahil edildi ve iki gruba ayrıldı. Grup 1'deki hastalar (n = 255) cerrahi öncesi aspirin tedavilerini askıya almış olup, Grup 2'deki hastalarda (n = 257) askıya alınmamıştır. Demografik özellikler, kalp rezervleri, preoperatif ve postoperatif Htc düzeyleri, antikoagülan türleri, kan ürünlerinin transfüzyonu, olası komplikasyonlar ve mortalite oranları kaydedildi.

**BULGULAR:** Demografik özellikler, ameliyat süresi, hastane ve yoğun bakımda kalış süresi, Kardiyopulmoner Bypass zamanı, mortalite oranı, re-eksplorasyon oranı, transfüzyon ihtiyacı gruplar arasında farklılık göstermedi. Antitrombotik gruptaki transfüze edilen trombosit süspansiyonu miktarı, antitrombotik ajan içermeyen gruptan anlamlı olarak daha yüksekti (p < 0.05).

**TARTIŞMA ve SONUÇ:** Aspirin tedavisindeki kardiyak hastalar için ne re-eksplorasyon ne de transfüzyon oranları farklılık göstermemiştir. Üstelik aspirin, heparinizasyon ve ekstra korporeal dolaşımın gerekli olduğu kardiyak cerrahi için postoperatif komplikasyon insidansını artırmamıştır. Aspirinin hasta sonuçları üzerinde olumsuz bir etkisi bulunmadığından, major cerrahi geçiren hastalarda kesilmemesi gerektiği kanısına varılmıştır.

**Anahtar Kelimeler:** kardiyak cerrahi, tromboz, kanama

### ABSTRACT

**INTRODUCTION:** Our aim is to determine the incidence of thrombotic complications that may be associated with discontinuation of preoperative anticoagulants in patients undergoing open heart surgery.

**METHODS:** The data of 512 adult patients undergoing elective open hearth surgery were evaluated. Patients treated with dual antiplatelet therapy were included and divided into two groups. Group 1 patients (n=255) have suspended their aspirin therapy prior to surgery. Group 2 patients (n=257) have not suspended. Demographics, cardiac reserves, preoperative and postoperative Htc levels, the types of anticoagulants, the transfusion of blood products, possible complications and mortality rates were recorded.

**RESULTS:** The demographics, the duration of surgery, hospital and internal care unit (ICU) stay, cardiopulmonary bypass (CPB) time, mortality rate, reexploration rate, the need for transfusion did not differ between groups. The amount of platelet suspension in antithrombotic group was significantly higher than in group without antithrombotic agent (p < 0.05).

**DISCUSSION AND CONCLUSION:** Neither reexploration nor transfusion rates were different for cardiac patients on aspirin therapy. Therefore, aspirin did not increase the incidence of postoperative complications even for cardiac surgery, where heparinization and extra corporeal circulation are necessary. As aspirin has not a negative effect on patient outcomes, should not be discontinued in patients undergoing major surgery.

**Keywords:** cardiac surgery, thrombosis, bleeding

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## INTRODUCTION

Antiplatelet agents inhibit platelet aggregation. Aspirin and clopidogrel, which are oral antiplatelet agents, form the basis for cardiovascular protection and are the most frequently prescribed drugs in this category. Drug withdrawal in the preoperative period may give rise to the risks, such as rebound phenomenon or thrombosis. On the other hand, continuation of anticoagulant agent is associated with bleeding risk (1).

However, a retrospective study including 10000 Coronary artery bypass grafting (CABG) patients indicated that acetylsalicylic acid (ASA) therapy does not increase bleeding (2). There are other studies reporting decreased mortality with ASA therapy (3). Another study investigating 4143 patients reported that patients, who continued taking aspirin till 5 day prior to CABG, required significantly higher intraoperative and postoperative blood transfusion as compared to those, who discontinued aspirin therapy 6 days before the procedure (4). Continuing ASA therapy till the time of CABG has been also associated with decreased inflammatory and oxidative response (5). Moreover, ASA has been reported to have a potentially positive effect on myocardial damage.

Excessive bleeding is known to impair post-CABG outcomes. In patients undergoing cardiac surgery, the withdrawal of antithrombotic agents may prevent bleeding preoperatively, but may also increase the risk of cardiac complications. In a meta-analysis involving six studies, a three-fold increase in the incidence of major cardiac side-effects was observed in patients who quit daily aspirin therapy (4).

Our aim in this retrospective cohort study is to determine the incidence of thrombotic complications that may be associated with discontinuation of preoperative antithrombotic in patients undergoing open heart surgery. We also evaluated the possible association with significant bleeding risk in patients with ongoing medication.

## MATERIAL AND METHODS

Following the Ethics Committee (No: 44140529/2017-61, date: 30.05.2017) approval, the data of 512 adult patients undergoing elective open heart surgery with cardiopulmonary bypass between

2013 and 2017 were evaluated. Patients treated with dual antithrombotic therapy were included.

Patients were divided into two groups. Group 1 patients (n=255) have suspended their aspirin therapy prior to surgery. Group 2 patients (n=257) have not suspended their aspirin therapy. Heart transplantation, left ventricular assist device implantation and repair of congenital heart malformations were excluded. Demographics, cardiac reserves, preoperative and postoperative Hematocrit levels, the types of anticoagulants, the transfusion of blood products, possible complications and mortality rates were recorded.

### Statistical Analysis

The SPSS 22.0 program was used for the analysis of the study data. The descriptive statistics employed in the study were mean, standard deviation, median, minimum, maximum, frequency, and ratio. The Kolmogorov-Smirnov test was used to measure the distribution of variables. The Mann-Whitney U test was used to analyze quantitative independent data while the Chi-square test was used to assess the qualitative independent data. In cases where the Chi-square conditions were not met, the Fisher test was used for the qualitative data. A value of  $P < 0.05$  was considered statistically significant.

## RESULTS

Patients receiving antithrombotic agents did not significantly differ from those, who did not use antithrombotics, in terms of age, gender distribution and Body Mass Index (BMI) values ( $p > 0.05$ , Table 1). There was no significant difference between patients receiving antithrombotic agents and those not receiving antithrombotic agents regarding duration of surgery, CPB (cardiopulmonary bypass) time and operation type ( $p > 0.05$ ). Drainage amount at the Intensive Care Unit (ICU), length of ICU stay were similar ( $p > 0.05$ , Table 1). The number of patients staying in hospital for 7 and 8 days was significantly higher in patients receiving antithrombotic agents ( $p = 0.007$ , Table 1). The mortality rate did not significantly differ between the groups receiving and not receiving antithrombotics. Furthermore, there was no significant difference between patients regarding the amount of Red Blood Cell (RBC), Fresh Frozen Plasma (FFP), and cryoprecipitate transfusions ( $p > 0.05$ , Table 1).

Table 1: The comparison of demographics, perioperative values, hospital and ICU stay time, bleeding and transfusion rate and postoperative complications in groups

		Aspirin (-)		Aspirin (+)		P	
		mean±sd/n(%)	median	mean±sd/n(%)	median		
Age (years)		64.7 ± 10.8	66.0	63.9 ± 11.2	64.0	0.342	<sup>m</sup>
Gender	Female	70	27.5%	68	26.5%	0.800	<sup>x<sup>2</sup></sup>
	Male	185	72.5%	189	73.5%		
BMI		26.7 ± 1.8	26.0	26.6 ± 1.9	26.0	0.389	<sup>m</sup>
Duration of surgery (min)		217.4 ± 33.7	215.0	211.6 ± 36.9	205.0	0.111	<sup>m</sup>
CPB time (min)		99.3 ± 37.9	90.0	96.6 ± 36.4	90.0	0.378	<sup>m</sup>
CX time (min)		75.5 ± 26.8	70.0	74.6 ± 28.6	70.0	0.535	<sup>m</sup>
Drainage in ICU (mL)		440.9 ± 203.3	450.0	462.8 ± 286.5	450.0	0.752	<sup>m</sup>
Length of stay in ICU (days)	1 day	204	80.0%	202	78.6%	0.630	<sup>x<sup>2</sup></sup>
	≥ 2 days	51	20.0%	55	21.4%		
Length of stay in hospital (days)	7 days	180	70.6%	209	81.3%	<b>0.007</b>	<sup>x<sup>2</sup></sup>
	8 days	43	16.9%	73	28.4%		
	9 days	2	0.8%	2	0.8%		
Mortality rate	(-)	255	100.0%	256	99.6%	1.000	<sup>x<sup>2</sup></sup>
	(+)	0	0,0%	1	0,4%		
RBC		4.0 ± 5.4	3.0	3.9 ± 6.2	3.0	0.323	<sup>m</sup>
FFP	not transfused	29	11.4%	26	10.1%	0.646	<sup>x<sup>2</sup></sup>
	transfused	226	88.6%	231	89.9%		
Platelet	not transfused	103	40.4%	104	40.5%	0.986	<sup>x<sup>2</sup></sup>
	transfused	152	59.6%	153	59.5%		
Cryoprecipitate	not transfused	210	82.4%	217	84.4%	0.527	<sup>x<sup>2</sup></sup>
	transfused	45	17.6%	40	15.6%		
Perioperative bleeding (mL)	not transfused	8.3 ± 5.0	6.0	8.6 ± 3.6	6.0	0.534	<sup>m</sup>
	transfused	246	96.5%	250	97.3%		
EF (%)	not transfused	246	96.5%	250	97.3%	0.600	<sup>x<sup>2</sup></sup>
	transfused	9	3.5%	7	2.7%		
EF (%)		50.3 ± 4.9	50.0	50.4 ± 5.0	50.0	0.729	<sup>m</sup>
Extubation time (h)		6.4 ± 1.3	6.0	6.5 ± 1.3	6.0	0.650	<sup>m</sup>
Postoperative DVT/PE	(-)	255	100.0%	256	99.6%	-	
	(+)	0	0.0%	0	0.0%		
Postoperative stroke	(-)	255	100.0%	257	100.0%	-	
	(+)	0	0.0%	0	0.0%		
Reexploration	(-)	248	97.3%	248	96.5%	0.623	<sup>x<sup>2</sup></sup>
	(+)	7	2.7%	9	3.5%		

<sup>m</sup> Mann-whitney u test / <sup>x<sup>2</sup></sup> Chi-square test

BMI: Body Mass Index, CPB: Cardiopulmonary Bypass, CX: Cross Clamp, ICU: Intensive Care Unit, RBC: Red Blood Cell, FFP: Fresh Frozen Plasm, EF: Ejection Fraction, DVT: Deep Vein Thrombosis, PE: Pulmonary Embolism

However, the amount of platelet transfusion was significantly higher in patients receiving antithrombotics ( $p < 0.05$ , Table 1). The amount of hemorrhage, Ejection Fraction (EF) value, extubation time and re-exploration rate did not differ significantly between groups ( $p > 0.05$ ). Preoperative and postoperative platelet levels were similar in groups ( $p > 0.05$ ). Nevertheless, postoperative platelet level was significantly lower than preoperative platelet level in group receiving antithrombotics ( $p < 0.05$ , Table 1).

There was no significant difference between patients receiving antithrombotic agents and those, who did not use antithrombotics, in terms of preoperative and postoperative hemoglobin (Hb) level ( $p > 0.05$ ). Postoperative Hb level was significantly lower than the preoperative level in both groups ( $p < 0.05$ , Table 2). There was no significant difference between patients receiving antithrombotic and non-antithrombotic groups regarding the Hematocrit, INR and creatinine levels in preoperative and postoperative periods ( $p > 0.05$ ). Postoperative Hematocrit level was significantly lower than the preoperative level in both groups ( $p < 0.05$ , Table 2). INR and creatinine levels significantly increased in the postoperative period as compared to the preoperative period in both groups regardless of antithrombotic agents use ( $p < 0.05$ , Table 2).

## DISCUSSION

This study analyzed patients undergoing CABG in two separate groups as patients receiving antiplatelet agents and those not receiving antiplatelet agents, and indicated higher platelet transfusion and extended hospital stay in the former. Nevertheless, no significant difference was detected between these two groups regarding the risks for complications, such as extubation time, re-exploration, DVT and stroke.

Using a CPB circuit causes tissue trauma. Also, cardiac surgery itself is a strong coagulation stimulus (6). CPB creates a complex clinical scenario resulting in widespread activation and dysregulation of the hemostatic system (7). At the beginning of CPB, heparinization reduces total thrombin and fibrin production, but soluble fibrin formation shows

a 5-10 fold increase and remains high during CPB (8).

Relevant guidelines recommend cessation of clopidogrel for 5-7 days prior to CABG (9). However, in the Timing Based on Platelet Function Strategy to Reduce Clopidogrel-Associated Bleeding Related to CABG [TARGET-CABG] study, clopidogrel responsiveness was determined via thrombelastography using the ADP-induced platelet-fibrin clot strength [MAADP] (10) CABG was performed within 1 day, 3-5 days, and more than 5 days. Clopidogrel arm was compared with clopidogrel-naive patients. As a result, no significant difference was detected in any of the 3 clopidogrel sub-groups regarding re-sternotomy for bleeding, chest tube output or total transfusion requirements. So, in contrast to relevant guidelines, the mean total waiting period in was found to be 2.7 days per patient for clopidogrel. Similarly, recent guidelines of the European Society of Anesthesiologists (ESA) recommends aspirin to be continued in patients undergoing cardiac surgery (11) and also underlines that if to be discontinued, 3 days would be enough before major surgeries. In this study, we demonstrated extended hospitalization in patients, who were on antithrombotic therapy and discontinued prior to CABG.

Discontinuation of aspirin in patients undergoing cardiac surgery increases the risk of coronary thrombosis; however, continuation of aspirin increases the risk of bleeding. As recommended by the ESA guidelines, administration of tranexamic acid prior to CPB in patients undergoing CABG may reduce the risk of bleeding (11). Topical application of tranexamic acid into the thoracic cavity is recommended to reduce postoperative blood loss after cardiac surgery. For this reason, all our patients were given prophylactic intravenous tranexamic acid during the study period. We believe that this prophylactic administration was the reason why perioperative need for RBC and FFP transfusions did not increase in our study.

Table 2: The changes in Hemoglobin, Hematocrit, Platelet, INR and Creatinine levels according to the groups

	Aspirin (-)			Aspirin (+)			p
	mean±sd	Median		mean±sd	Median		
<i>Platelet</i>							
Preoperative	233.2 ± 73.6	220.0		239.4 ± 71.4	231.0		0.121 <sup>m</sup>
Postoperative	176.5 ± 58.4	173.0		181.2 ± 73.4	169.0		0.986 <sup>m</sup>
Pre/Post Change (p)	<b>0.000</b>	w		<b>0.000</b>	w		
<i>Hemoglobin (g/dL)</i>							
Preoperative	13.3 ± 1.7	13.3		13.2 ± 1.6	13.4		0.549 <sup>m</sup>
Postoperative	10.5 ± 1.1	10.5		10.3 ± 1.1	10.1		0.004 <sup>m</sup>
Pre/Post Change (p)	<b>0.000</b>	w		<b>0.000</b>	w		
<i>Hematocrit (%)</i>							
Preoperative	38.9 ± 4.5	39.0		38.5 ± 4.3	38.9		0.536 <sup>m</sup>
Postoperative	30.7 ± 3.1	30.6		30.1 ± 3.0	29.7		0.052 <sup>m</sup>
Pre/Post Change (p)	<b>0.000</b>	w		<b>0.000</b>	w		
<i>INR</i>							
Preoperative	1.1 ± 1.0	1.2		1.3 ± 1.5	1.0		0.856 <sup>m</sup>
Postoperative	1.2 ± 2.0	1.0		1.4 ± 1.1	1.2		0.417 <sup>m</sup>
Pre/Post Change (p)	<b>0.000</b>	w		<b>0.000</b>	w		
<i>Creatinine (mg/dL)</i>							
Preoperative	1.0 ± 0.6	0.9		1.2 ± 2.2	0.9		0.392 <sup>m</sup>
Postoperative	1.3 ± 1.9	1.0		1.3 ± 1.3	1.0		0.647 <sup>m</sup>
Pre/Post Change (p)	<b>0.000</b>	w		<b>0.000</b>	w		
<sup>m</sup> Mann-whitney u test / <sup>w</sup> Wilcoxon test							

Hansson et al. (12) investigated the effects of the discontinuation of clopidogrel (n=978) and ticagrelor (n=1266) in patients scheduled for CABG. CABG-associated bleeding incidence was found to be high when ticagrelor/clopidogrel was discontinued 24 hour before the surgery. Discontinuation 3 days before surgery, as opposed to 5 days, did not increase the incidence of major bleeding complications with ticagrelor, but increased the risk with clopidogrel. The overall risk of major CABG-related bleeding complications was reported to be lower with ticagrelor than with clopidogrel.

In the present study, we did not observe an elevation in the amount of RBC, FFP or cryoprecipitate transfusions, whereas there was a significant increase in the incidence of platelet transfusion. We benefited from platelet transfusions in order to reverse the effect of aspirin discontinued

5 days. However, no significant difference was detected between these patients regarding morbidity and mortality rates, re-exploration, cross clamp time and CPB time, duration of ICU stay or drainage amount. While the only potentially expected complication was increased platelet transfusion, it did not occur.

#### Limitations:

The major limitation of this study was its retrospective nature. Another limitation was failure to perform the platelet function test for all patients. Also, as there is no standardization in this regard, we were not able to make an evaluation.

#### Conclusions:

Neither reexploration nor transfusion rates were different for cardiac patients on aspirin therapy. Therefore, aspirin did not increase the incidence of postoperative complications even for cardiac

surgery, where heparinization and extracorporeal circulation are necessary. In conclusion, we believe that aspirin has not a negative effect on patient outcomes and should not be discontinued in patients undergoing major surgery.

### REFERENCES

1. Le Manach Y, Kahn D, Bachelot-Loza C, Le Satche F, Smadja DM, Remones V, et al. Impact of aspirin and clopidogrel interruption on platelet function in patients undergoing majorvascular surgery. *PLoS One* 2014; 9: e104491. doi: 10.1371/journal.pone.0104491.
2. Gulbins H, Malkoc A, Ennker IC, Ennker J. Preoperative platelet inhibition with ASA does not influence postoperative blood loss following coronary artery bypass grafting. *Thorac Cardiovasc Surg* 2009; 57: 18-21. doi: 10.1055/s-2008-1038791.
3. Bybee KA, Powell BD, Valeti U, Thomas RJ, Kopecky SL, Mullany CJ, et al. Preoperative aspirin therapy is associated with improved postoperative outcomes in patients undergoing coronary artery bypass grafting. *Circulation* 2005; 112: 286-92.
4. Biondi-Zoccai G, Lotrionte M, Agostoni P, Abbate A, Fusaro M, Burzotta F, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50 279 patients at risk for coronary artery disease. *Eur Heart J* 2006; 27: 2667-74.
5. Berg K, Langaas M, Ericsson M, Pleym H, Basu S, Nordrum IS, et al. Acetylsalicylic acid treatment until surgery reduces oxidative stress and inflammation in patientsundergoing coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2013; 43: 1154-63. doi: 10.1093/ejcts/ezs591.
6. Jacob M, Smedira N, Blackstone E, Williams S, Cho L. Effect of timing of chronic preoperative aspirin discontinuation on morbidity and mortality in coronary artery bypass surgery. *Circulation* 2011;123:577-83. doi: 10.1161/CIRCULATIONAHA.110.957373.
7. Dhir A. Antifibrinolytics in cardiac surgery. *Ann Card Anaesth* 2013; 16: 117-25.
8. Sniecinski RM, Chandler WL. Activation of the hemostatic system during cardiopulmonary bypass. *Anesth Analg* 2011; 113: 1319-33. doi: 10.1213/ANE.0b013e3182354b7e.
9. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC guideline for the management of patients with non-ST elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation* 2014; 130: 2354-94. doi: 10.1161/CIR.000000000000133.
10. Mahla E, Suarez TA, Bliden KP, Rehak P, Metzler H, Sequeira AJ, et al. Platelet function measurement-based strategy to reduce bleeding and waiting time in clopidogrel-treated patients undergoing coronary artery bypass graft surgery: the timing based on platelet function strategy to reduce clopidogrel-associated bleeding related to CABG (TARGET-CABG) study. *Circ Cardiovasc Interv* 2012; 5: 261-9. doi: 10.1161/CIRCINTERVENTIONS.111.967208.
11. Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016. *Eur J Anaesthesiol* 2017; 34: 332-95. doi: 10.1097/EJA.0000000000000630.
12. Hansson EC, Jidéus L, Åberg B, Bjursten H, Dreifaldt M, Holmgren A, et al. Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: a nationwide study. *Eur Heart J* 2016; 37: 189-97. doi: 10.1093/eurheartj/ehv381.