

A single dose of aprotinin prevents platelet hyporeactivity after coronary artery bypass graft surgery

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KEY WORDS

aprotinin, coronary artery bypass graft, platelet function

ABSTRACT

INTRODUCTION Bleeding after coronary artery bypass graft (CABG) surgery is associated with a significant increase in mortality. Even though aprotinin significantly reduces bleeding in patients undergoing cardiac surgery, its use has been recently substantially limited because of serious cardiovascular complications. The exact mechanism of its action, particularly its effect on platelet function, remains unclear.

OBJECTIVES The aim of the study was to assess the effect of aprotinin on platelet function in patients undergoing CABG.

PATIENTS AND METHODS In a randomized placebo-controlled double-blind study, we investigated the effect of a single dose of aprotinin on platelet function in 24 patients who underwent CABG between 2005 and 2006. Before surgery and in the postoperative period, we measured platelet activation markers (P-selectin and activated form of glycoprotein IIb/IIIa) at baseline and following in vitro platelet activation with adenosine diphosphate (ADP) or protease-activated receptor 1 (PAR-1) agonist – thrombin receptor activator for peptide 6 (TRAP-6). Perioperative bleeding and urinary metabolites of thromboxane A₂ were also determined.

RESULTS Aprotinin reduced perioperative bleeding by 26% ($P < 0.01$) and prevented a decrease in platelet sensitivity to ADP immediately after CABG. In vitro platelet reactivity to TRAP-6 remained unchanged. Aprotinin did not affect blood platelet count or urinary thromboxane A₂ metabolite excretion after CABG.

CONCLUSIONS Our results indicate that aprotinin may reduce perioperative bleeding by its interference with ADP pathway of platelet activation, thereby preventing postoperative hyporeactivity of platelets to ADP. Platelet reactivity to PAR-1 receptor agonist was not affected by aprotinin.

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INTRODUCTION Bleeding after coronary artery bypass graft (CABG) surgery results from severe coagulopathy caused by extensive physical contact between blood and synthetic surfaces of extracorporeal circulation; it seriously increases mortality after the surgery.¹ As a serine protease inhibitor, aprotinin inhibits kallikrein, thus leading to the inhibition of factor XIIa formation. Finally, it inhibits both the intrinsic pathway of coagulation and fibrinolysis. It has been shown to be effective

in reducing bleeding associated with CABG surgery.² Recently, protective action of aprotinin has been also observed in an ischemia-reperfusion injury in animal model.³

The exact mechanisms underlying the effects of aprotinin on platelet function remain unknown. It has been proposed that in cardiac surgery aprotinin could protect against thrombin-mediated depletion of platelets and subsequent impairment of their function.⁴ While aprotinin remains one

of the most potent drugs available in such clinical situations, its use was substantially limited in 2007, as a consequence of major adverse cardiovascular events reported in clinical trials.^{5,6}

Activation of blood platelets and their increased consumption during the course of cardiopulmonary bypass (CPB) often result in bleeding after CABG surgery.⁷

During CPB, platelets are activated not only by contact with artificial surfaces and increased shear stress, but also by signaling through a platelet protease-activated receptors 1 (PAR-1), stimulated by thrombin.⁸ Once activated, they are quickly sequestered from the circulation and replaced with the new ones. This dynamic process is reflected by a decrease in platelet count after CPB, and their gradual return to preoperative values during recovery period.

There are no laboratory assays that can accurately predict postoperative bleeding after cardiac surgery.⁹ Flow cytometry tests, analyzing the expression of platelet activation receptors, could evaluate their sensitivity to various agonists during CABG. Flow cytometric assessment of platelet function has been recently used in patients with coronary artery disease (CAD).¹⁰ On the other hand, urinary excretion of 11-dehydro-thromboxane B₂ (11-dehydro-TXB₂, a thromboxane A₂ metabolite) was found to be a good marker of an overall platelet activation in the systemic circulation.¹¹

In this study, we used both methods to investigate the effect of aprotinin on platelet function during the CABG surgery. The study was conducted before aprotinin use in cardiac surgery had been limited. It may provide information on how aprotinin and similar protease inhibitors can prevent blood loss during cardiac surgery.

PATIENTS AND METHODS **Patients and study protocol** Between 2005 and 2006, 24 patients were enrolled into a prospective randomized double-blind study. All patients were scheduled for elective CABG due to stable CAD. Their clinical and demographic characteristics are summarized in the [TABLE](#).

Patients were randomly assigned to a single dose of aprotinin 2,000,000 of kallikrein inhibitor units, intravenously) just before skin incision, or to a placebo (saline infusion). None of the patients were treated with any other antiplatelet drug within 10 days before the operation. The study was approved by the Ethics Committee of the Medical University of Silesia, Katowice, Poland. All patients gave their written informed consent to participate in the study.

General anesthesia was used in all patients according to the same protocol. CABG was performed by a standardized method through median sternotomy, with normothermic CPB and intermittent antegrade warm blood cardioplegia. Intravenous heparin was administered before cannulation of the ascending aorta (300 U/kg) with additional doses (100 U/kg) given every

60 minutes to maintain activated clotting time (ACT) above 480 seconds. Once the CPB was weaned off, protamine sulfate (3 mg/kg) was given to reverse heparin action. The following data were recorded: CPB time, cross-clamp time, number of grafts, use of the left internal thoracic artery, need for inotropic (dopamine, adrenaline) or mechanical (intra-aortic balloon pump) support. Perioperative myocardial infarction was diagnosed according to the current criteria.¹² The following complications were recorded in the course of hospitalization (up to 7 days after CABG): reexploration because of bleeding, postoperative renal failure (serum creatinine level >2.0 mg/dl or its increase by >50%), deep sternal wound infection, and prolonged mechanical ventilation (>3 days). Intraoperative blood loss was recorded as the volume of blood in the external sucker reservoir and the weight of the swabs. The volume of chest drainage to a four-chamber Sherwood collection bag was measured after the operation. First dose of aspirin (325 mg orally) was administered within the first 6 hours after the surgical procedure. Both the intensive care unit and total hospitalization days were recorded.

Laboratory measurements Laboratory tests were performed 2 hours before the surgery (before CABG), 10 minutes after the surgery (after CABG), and 72 hours after the surgery (recovery). They included routine laboratory measurements, platelet activation tests, prothrombin time, and ACT. At the same time points, urine samples were collected and stored in -80°C for future measurements of 11-dehydro-TXB₂.

Transfusions of packed red blood cells, fresh frozen plasma (FFP) or pooled platelet concentrate (PPC) were recorded. When excessive bleeding persisted after the correction of clotting abnormalities or if platelet count was less than 80,000/μl, PPC was transfused.

Platelet function tests Blood samples were collected and processed at the patient bedside in order to minimize nonspecific platelet activation. Venous blood was drawn using a 19-gauge needle into 5 ml tubes (Vacutainer, BD Biosciences, Franklin Lakes, NJ, United States) containing 3.8% sodium citrate. Aliquots of blood were diluted 10-fold in phosphate buffer saline (PBS, 0.2% bovine albumin), containing platelet agonists and monoclonal antibodies (all from BD Biosciences): PerCP-CD61, PE-CD62P (P-selectin), and fluorescein-isothiocyanate-PAC-1 (detecting activated glycoprotein [GP] IIb/IIIa). Decimal dilution series of platelet activators were used at the final concentrations of 0.001 to 10 μM of adenosine diphosphate (ADP) and 0.2 to 20 μM of thrombin receptor activator for peptide 6 (TRAP-6) (PAR-1 activating peptide; both from Sigma-Aldrich, St. Louis, MO, United States). After 15 minutes of incubation at room temperature, the samples were fixed with 250 μl of FACS Lysing Solution (BD Biosciences), diluted 10-fold in 1.5% para-

TABLE Demographic and clinical characteristics of the patients

	Aprotinin group n = 12	Placebo group n = 12
sex, M:F	10:2	10:2
age, y	55.6 ± 6.9	59.6 ± 6.8
BMI, m/kg ²	27.7 ± 3.0	28.0 ± 3.2
CCS class	2.5 ± 0.6	2.1 ± 0.6
hypertension, n (%)	9 (75)	12 (100)
LVEF, %	52.5 ± 9.4	50 ± 10.7
current or past smokers, n (%)	7 (58)	6 (50)
diabetes mellitus, n (%)	0	3 (25)
hypercholesterolemia, n (%)	11 (92)	12 (100)
positive family history of CAD, n (%)	6 (50)	6 (50)
intermittent claudication, n (%)	1 (8)	3 (25)
renal insufficiency, n (%)	1 (8)	0
history of stroke, n (%)	0	1 (8)
history of MI, n (%)	9 (75)	7 (58)
preoperative statin use, n (%)	11 (92)	12 (100)
preoperative β-blockers use, n (%)	11 (92)	12 (100)
preoperative ACEI use, n (%)	8 (67)	9 (75)
basic laboratory results		
leukocyte count, × 10 ³ cells/μl	7.7 ± 2.3	7.7 ± 1.7
HgB before surgery, g/dl	13.8 ± 1	14.5 ± 1.1
HgB on the 3rd day after surgery, g/dl	10.3 ± 1.1	11.1 ± 1.2
creatinine, mg/dl	0.9 ± 0.1	1.1 ± 0.2
glucose, mg/dl	126.4 ± 51.2	107.1 ± 20.7
fibrinogen, g/l	3 ± 0.4	2.8 ± 0.2
CRP above normal range, n (%)	2 (17)	2 (17)

Data are presented as mean values ± standard deviation; no significant differences were observed

Abbreviations: ACEI – angiotensin-converting enzyme inhibitor, BMI – body mass index, CAD – coronary artery disease, CCS – Canadian Cardiovascular Society, CRP – C-reactive protein, F – female, HgB – hemoglobin, LVEF – left ventricular ejection fraction, M – male, MI – myocardial infarction

formaldehyde-PBS and stored at 4°C before the analysis (completed within 24 hours). The samples were spun down, resuspended in PBS, and counted by flow cytometry (EPICS XL, Beckman Coulter, Fullerton, CA, United States). The percentage of activated platelets and mean fluorescence intensities (MFI) were acquired separately for PAC-1 and CD62P markers using 10,000 events within CD61 positive gate. The results were expressed as the index of platelet activation (IPA+), calculated using the following formula: IPA+ = f+ × MFI+, where f+ is a fraction of marker positive platelets and MFI+ is mean fluorescence intensity of the studied marker.

Thromboxane A₂ metabolite in urine 11-dehydro-TXB₂ was measured directly in diluted urine samples using a commercially available enzyme-linked immunoassay kit (Cayman Chemicals, Ann Arbor, MI, United States) according to the manufacturer's instructions. Metabolite levels are expressed per 1 mg of urinary creatinine to compensate for urine dilution.

Statistical analysis Statistical analysis was performed using the STATISTICA software, version 8.0 (StatSoft, Inc., Poland). Data are presented as medians and interquartile range or means and standard deviation. Hypothesis testing was done using the analysis of variance (ANOVA). Data collected on consecutive days were analyzed by repeated ANOVA measurements, and planned comparisons were tested by post hoc tests. Platelet activation in a wide range of agonist concentrations was analyzed with nonlinear regression models using the GraphPad Prism 4.0 software (GraphPad Software, San Diego, CA, United States). The effective concentration of ADP resulting in 50% expression (EC₅₀) of P-selectin or PAC-1 was also calculated. A P value <0.05 was considered statistically significant.

RESULTS Group characteristics A total of 24 subjects were randomly assigned to the aprotinin (n = 12) or placebo groups (n = 12). Preoperative patient characteristics did not differ between the groups (TABLE). There were no known predisposing factors for surgical bleeding in any

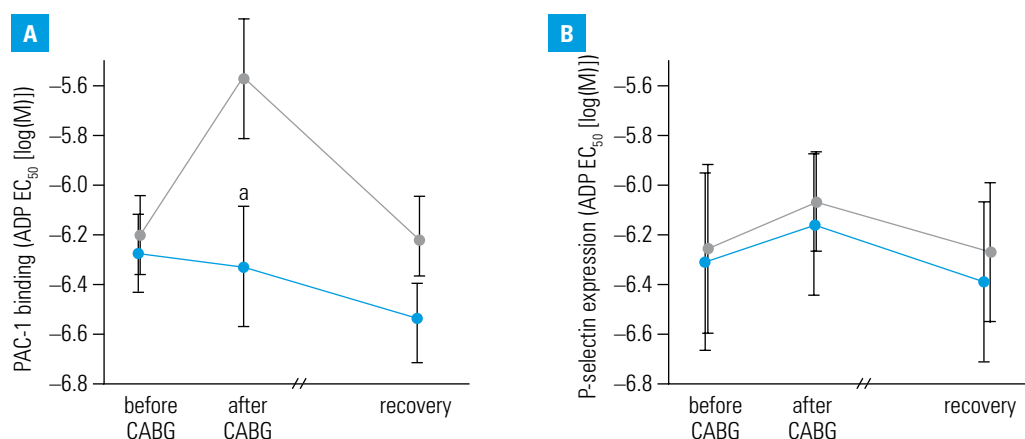
FIGURE 1 A time course of in vitro blood platelet activation kinetics in subjects undergoing coronary artery bypass graft (CABG) surgery

A effective concentration of adenosine diphosphate (ADP) resulting in a 50% increase (EC_{50}) of the activation marker (activated glycoprotein IIb/IIIa detected with PAC-1 antibody)

B effective concentration of ADP resulting in a 50% increase (EC_{50}) in P-selectin expression

a indicates significant P level (<0.05); data presented as mean $\pm$ standard deviation

Subjects were grouped as treated with aprotinin (blue line) or placebo (grey line)



of the groups; coagulation pathway markers: prothrombin time (international normalized ratio) and activated partial thromboplastin time were in normal ranges in all patients; none of the patients had low blood platelet count prior to the study. There were also no differences between the groups with respect to CABG-related clinical procedures (number of grafts, CPB time, aorta cross-clamp time). No deaths or major cardiovascular events were recorded in the course of the study. There was no need for surgical reexploration because of bleeding. Both the length of hospital stay (mean 7.4 ± 1.1 days) and time spent in the intensive care unit did not differ between the groups.

Blood loss related to the surgery was significantly greater (by 35.3%) in the placebo group as compared to aprotinin group (1034 ± 172 vs. 764 ± 234 ml, respectively; $P < 0.01$). In the aprotinin group, 1 patient received packed red blood cells, and another 2 received both PPC and FFP. In the control group, 2 patients received PPC and 1 patient received FFP. There were no differences in blood platelet count between the groups.

There was a significant ($P < 0.01$) decrease in platelet count after CABG surgery in both the aprotinin (from 193 ± 51 to $131 \pm 29/\mu\text{l}$) and placebo (from 211 ± 62 to $156 \pm 38/\mu\text{l}$) groups. The consumption of platelets was similar in both groups (decrease by an average of $29 \pm 14\%$ and $23 \pm 9\%$, respectively), and did not correlate with the intensity of CABG-related bleeding. The platelet count increased during recovery in both groups.

Urinary excretion of thromboxane A_2 metabolite Following CABG, there was a marked, over 20-fold increase in the urinary excretion of 11-dehydro-TXB₂, from preoperative 1.52 ± 0.67 ng/mg of creatinine to 31.29 ± 32.59 ng/mg after surgery ($P < 0.001$). Urinary 11-dehydro-TXB₂ excretion returned to the baseline level on the third day after CABG (1.22 ± 0.58 ng/mg of creatinine). There was no difference in 11-dehydro-TXB₂ excretion between the aprotinin and placebo groups. An increase of 11-dehydro-TXB₂ in urine did not correlate with postoperative bleeding or the decrease in blood platelet count after CABG.

Platelet activation studies Ex vivo studies of platelet activation revealed rather minimal

expression of P-selectin and PAC-1 binding at baseline conditions; $3.3 \pm 1.9\%$ resting platelets positive for P-selectin and $12.2 \pm 9.8\%$ expressing activated form of GP IIb/IIIa (PAC-1). After CABG, there was a 2-fold increase in the expression of P-selectin and 1.5-fold increase in PAC-1 binding as compared to the preoperative values. This increase was significant only for P-selectin ($P < 0.01$). CABG procedure resulted in a significant ($P < 0.01$) decrease in platelet reactivity, when analyzing the expression of P-selectin upon stimulation with ADP agonist (EC_{50} for ADP: 0.75 ± 0.58 μM at baseline vs. 0.9 ± 0.49 μM after CABG) followed by the return of reactivity during the recovery period (0.55 ± 0.28 μM , $P = 0.01$). Similar changes in platelet reactivity were evidenced by measuring PAC-1 binding (baseline EC_{50} for ADP: 0.58 ± 0.05 μM , post CABG: 1.12 ± 0.16 μM , and 0.42 ± 0.04 μM during recovery; influence of CABG: $P = 0.05$).

There was no difference in platelet reactivity between the aprotinin and placebo groups before CABG. However, we noticed a protective effect of aprotinin on platelet function immediately after the surgery, as evidenced by sustained reactivity of platelets to ADP in the aprotinin group (no increase in EC_{50} for ADP-induced PAC-1 binding), when compared to placebo ($P = 0.04$, **FIGURE 1A**). Platelet reactivity data indicate that when patients were administered aprotinin, blood platelets remained as sensitive to ADP agonist as before the surgery, while in the placebo group, a 4.2-fold higher concentration of ADP was required to achieve the same platelet activation. During recovery, platelet reactivity to ADP returned to preoperative values. The protective effect of aprotinin was restricted only to the earliest events of platelet activation (activation of GP IIb/IIIa), as ADP-induced platelet degranulation (P-selectin expression) was comparable in both groups (**FIGURE 1B**).

CABG-related dynamics of platelet activation with PAR-1 agonist, TRAP-6, was quite similar. A reduction in platelet reactivity was observed immediately after CABG. P-selectin expression decreased by 13.6% ($P = 0.03$) and PAC-1 by 18.6% ($P = 0.02$). However, aprotinin had no protective effect on the reduction in platelet reactivity, because both PAC-1 binding and P-selectin expression were similar in both groups.

DISCUSSION Perioperative blood loss requiring reexploration for bleeding and/or a large amount of transfused blood products are both associated with increased mortality and serious cardiovascular events in cardiac surgery patients.^{1,13} Therefore, adequate management aimed at reducing bleeding complications is needed. Aprotinin, a protease inhibitor, was found to be effective in reducing postoperative bleeding and the amount of transfused blood,^{2,14} with higher efficacy than other antifibrinolytic agents.^{6,15} Moreover, administration of aprotinin reduced postoperative complications and length of stay in the intensive care unit, possibly by decreasing the inflammatory reaction and oxidative stress associated with ischemia-reperfusion injury during CPB surgery.^{3,16}

However, the evidence concerning the safety of aprotinin has risen serious concerns. It has been found that treatment with aprotinin during CABG procedure is associated with increased risk of renal failure, stroke, myocardial infarction, and heart failure.^{5,17} Additionally, results from large randomized trials indicate that administration of aprotinin is associated with higher mortality rate in comparison with lysine analogue-derived antifibrinolytic drugs, even though it decreased the incidence of major bleeding.⁶ The latter study conducted by the BART trial investigators⁶ led to serious restrictions in aprotinin use in cardiac surgery patients. In Europe, the European Medicines Agency Committee has stated that “benefits of ‘systemic’ formulations of aprotinin no longer outweigh their risks” and suspended its authorization for aprotinin use throughout Europe.¹⁸

Based on the above-mentioned cardiovascular risk aggravation, aprotinin should not be used any more in cardiac surgery; however, there is a considerable need for a drug that would be as potent as aprotinin in preventing surgical bleeding but free of its adverse events. Therefore, our work, conducted before the restriction of aprotinin use, may help develop such a drug by highlighting the mechanism of aprotinin action on platelets.

CABG surgery with extracorporeal blood oxygenation is a potent stimulus for platelet activation. This is reflected by an enormous increase in urinary excretion of the 11-dehydro-TXB₂ and decrease in platelet count after CABG surgery. Flow cytometric tests measuring the expression of platelet activation markers at rest and on stimulation with agonists showed that CABG led to an increase in the number of circulating activated platelets, although aprotinin had no direct effect on platelet depletion during CABG procedure. After the surgery, platelets failed to respond adequately to agonists, as evidenced by the lower expression of activated form of GP IIb/IIIa on ADP-stimulated platelets. Though aprotinin seemed to protect against postoperative platelet hyporeactivity to ADP, it had no effect on platelet reactivity to TRAP-6. This is at variance with

the findings of Day et al.,^{3,19} who described inhibitory effect of aprotinin on PAR-1-mediated activation of platelets, both in vivo and in vitro. This difference could be partially explained by the differences in the study design. We looked for kinetics of platelet activation with 2 direct platelet agonists, TRAP-6 and ADP, in the whole blood, while Day et al.¹⁹ measured the formation of platelet-leukocyte aggregates upon stimulation with PAR-1 agonist, in an in vitro setting. Also Kozek-Langenecker et al.²⁰ observed the reduction of platelet aggregation upon addition of aprotinin to ADP- or TRAP-6-stimulated platelets. However, they did not observe any significant change in the expression of activated form of GP IIb/IIIa or P-selectin. Ex vivo functional assays have the advantage of reflecting a steady state in the functional status of circulating platelets, where their activation and sequestration (associated with CABG) is balanced by a release of new platelets from the bone marrow.

It can be concluded that a single dose of aprotinin (2,000,000 units) administered immediately before CABG procedure, efficiently decreases postoperative bleeding. This effect could be related, at least in part, to the preserved platelet reactivity to ADP. In the placebo group, immediately after CABG procedure, this reactivity was significantly decreased. Providing that ADP is the major secondary mediator amplifying virtually all platelet activation pathways initiated in vivo, our observation seems to fit well with clinical data on the efficacy of aprotinin administration during cardiac surgery. Further studies are needed to explain detailed mechanisms of aprotinin interference with other platelet activation pathways.

In summary, our results indicate that treatment with aprotinin interacts favorably with the processes of platelet activation. A single dose of aprotinin could prevent postoperative hyporeactivity of platelets, and in this way reduce bleeding.

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Pojedyncza dawka aprotyniny zapobiega upośledzeniu reaktywności płytek krwi po zabiegu pomostowania aortalno-wieńcowego

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SŁOWA KLUCZOWE

aprotynina,
krwawienie
okołooperacyjne,
płytki krwi,
pomostowanie
aortalno-wieńcowe

STRESZCZENIE

WPROWADZENIE Krwawienie pooperacyjne u pacjentów poddawanych zabiegom pomostowania aortalno-wieńcowego (*coronary artery bypass graft – CABG*) istotnie zwiększa śmiertelność. Pomimo znacznego zmniejszenia ryzyka krwawienia u pacjentów poddawanych zabiegom kardiologicznym, w ostatnim czasie użycie aprotyniny znacznie ograniczono z uwagi na wywoływanie poważnych powikłań sercowo-naczyniowych. Dokładny mechanizm działania aprotyniny, a w szczególności jej wpływ na funkcję płytek krwi, nie jest znany.

CELE Celem badania była ocena wpływu aprotyniny na funkcję płytek krwi u pacjentów poddawanych zabiegom CABG.

PACJENCI I METODY W badaniu z randomizacją, z podwójnie ślełą próbą, oceniono wpływ podania pojedynczej dawki aprotyniny na funkcję płytek krwi u 24 pacjentów poddawanych zabiegowi CABG w latach 2005–2006. Przed zabiegiem oraz w okresie pooperacyjnym mierzono ekspresję markerów aktywacji płytek krwi (selektyna P oraz aktywowana forma glikoproteiny IIb/IIIa) w warunkach spoczynkowych oraz *in vitro* po aktywacji za pomocą adenosynodifosforanu (*adenosine diphosphate – ADP*) lub agonisty receptora aktywowanego peptydem 1 – peptydu aktywującego receptor trombiny (*thrombin receptor activator for peptide 6 – TRAP-6*). Oceniano również okołooperacyjną utratę krwi oraz stężenie metabolitów tromboksanu A_2 w moczu.

WYNIKI Aprotynina spowodowała zmniejszenie krwawienia okołooperacyjnego o 26% ($P < 0,01$) oraz zapobiegła zmniejszeniu reaktywności płytek po zabiegu CABG w odpowiedzi na ADP. Efektu tego nie obserwowano po stymulacji płytek *in vitro* za pomocą TRAP-6. Nie zaobserwowano również działania aprotyniny na liczbę płytek krwi ani też na wydzielanie metabolitów tromboksanu A_2 z moczem po zabiegu CABG.

WNIOSKI Wyniki przedstawionych badań wskazują, że jednym z mechanizmów odpowiedzialnych za zmniejszenie krwawienia okołooperacyjnego po podaniu aprotyniny może być wpływ na reaktywność płytek krwi w odpowiedzi na ADP poprzez zapobieganie jej upośledzeniu w okresie pooperacyjnym. Aprotynina nie ma natomiast wpływu na szlak aktywacji płytek zależny od aktywacji receptora trombinowego.

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