# Low-dose aprotinin infusion is not clinically useful to reduce bleeding and transfusion of homologous blood products in high-risk cardiac surgical patients

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A high-dose regimen of aprotinin 5–6 million KIU is effective in reducing bleeding and the need for homologous blood products (HBP) associated with cardiopulmonary bypass (CPB). These high doses aim at achieving plasmin and plasma kallikrein concentrations which in vitro are inhibitory but, theoretically, smaller doses could suffice in vivo. Also, aprotinin is an expensive drug, so efficiency requires using the smallest effective dose. Therefore, the efficacy of prophylactic aprotinin 1 million KIU (the maximal dose approved currently) was evaluated in a patient population at high risk of bleeding and of being transfused. Forty-one patients undergoing reoperation or a complex surgical procedure were included in a prospective, randomized, placebo-controlled, double-blind study. Before skin incision, a bolus of 200,000 KIU aprotinin was administered in 20 min, followed by an infusion of 100,000 KIU· hr⁻¹ over eight hours. Control patients received an equal volume of saline. Dryness of the operative field, chest drainage, transfusion of HBP, haemoglobin concentrations, and coagulation variables (including bleeding time) were compared. There were no differences between aprotinin and placebo-treated patients for all clinical and laboratory variables. The apparent ineffectiveness of aprotinin may be explained by the use of an insufficient dose, by a different protocol of administration (e.g., no bolus in CPB prime), or by the inability of aprotinin to decrease bleeding and transfusions any further. Also, the number of patients studied does not exclude the possibility of a Type II error. However, based on the small differences observed, we conclude that low-dose aprotinin infusion is not useful clinically to reduce chest drainage and transfusions in a patient population at high risk of being exposed to HBP.

**Key words**

ANAESTHESIA: cardiac;
BLOOD: coagulation; antifibrinolytics, aprotinin;
SURGERY: cardiovascular, cardiopulmonary bypass.

Une posologie élevée d'aprotinine de 5–6 millions KIU diminue le saignement et le besoin de produits sanguins homologues utilisés pour la circulation extracorporelle (CEC). Ces doses élevées visent l'atteinte de concentrations de plasmine et de kallicréine plasmatique efficaces in vitro, mais théoriquement, de plus faibles doses devraient suffire in vivo. De plus, l'aprotinine est une produit coûteux et il est normal qu'on n'utilise que la plus petite dose efficace. C'est dans ce contexte que l'efficacité de l'aprotinine prophylactique 1 million KIU (la dose maximale actuellement approuvée) est évaluée sur une population à haut risque d'hémorragies et de transfusions subséquentes. Quarante-

*et-un patients soumis à une ré-opération ou à une intervention cardiaque complexe sont inclus dans une étude prospective à double aveugle, randomisée et contrôlée avec placebo. Avant l'incision de la peau, un bolus de 200 000 KIU d'aprotinine est administré en 20 min, suivi d'une perfusion de 100 000 KIU· hr⁻¹ répartie sur huit heures. Le groupe contrôle reçoit du soluté physiologique en volume égal. La quantité de sang du champ opératoire, l'importance des pertes par les drains thoraciques, les transfusions de produit sanguins homologues, la concentration de l'hémoglobine et les épreuves de coagulation (temps de saignement inclus) sont comparés. On ne trouve pas de différences entre le groupe aprotinine et le groupe placebo pour tous les paramètres cliniques et de laboratoire. L'inefficacité apparente de l'aprotinine peut s'expliquer par l'utilisation d'une dose insuffisante, par un protocole d'administration différent (v.g. absence de bolus dans l'amorce de CEC), ou par l'incapacité de l'aprotinine à diminuer encore plus le saignement et le besoin de transfusions. De plus le nombre de patients étudiés n'exclut pas la possibilité d'une erreur de type II. Toutefois, sur la base des différences minimes observées, nous concluons que l'aprotinine à faible dose en perfusion n'est pas utile cliniquement pour diminuer les pertes par les drains thoraciques et la quantité de sang transfusée chez une population de patients très susceptible de recevoir des produits de sang homologue.*

Excessive bleeding after cardiopulmonary bypass (CPB) has always been a major concern to cardiac anaesthetists and surgeons. In an effort to reduce morbidity associated with transfusion of blood products (transmitted infectious diseases, transfusion reactions, etc.) and to answer concerns that the demand for blood and blood products may exceed the supply, many strategies have been explored to diminish the need for transfusion both during and after CPB. Pharmacological reduction of bleeding associated with CPB has received much attention recently. It has the advantages of being readily available and easy to administer, of avoiding the use of costly equipment, and it may be used prophylactically rather than therapeutically in some instances. Desmopressin (DDAVP), a vasopressin analogue, epsilon-aminocaproic acid (EACA) and tranexamic acid (TA), two synthetic antifibrinolytics, and aprotinin (Apt), an antifibrinolytic derived from bovine lung, have been used either to diminish or to prevent excessive bleeding associated with cardiac surgery.

Aprotinin has been used since 1964 in cardiac surgery with some clinical success, and varying enthusiasm, at doses not exceeding one million units. The administration of 10–20,000 Kallikrein Inactivator Units (KIU) of Apt to patients presenting increased fibrinolytic activity associated with abnormal bleeding after CPB resulted in rapid remission of bleeding in five patients studied by

Tice *et al.* in 1964.[1] In 1968, Mammen reported a considerable reduction of the activation of the fibrinolytic system during CPB in patients receiving Apt (100,000 KIU in pump prime, infusion of 100,000 KIU per hour of extracorporeal circulation, and 100,000 KIU at the end of CPB).[2] In 1971, Ambrus *et al.* treated patients with a four-hour infusion of Apt (total dose: 400,000 KIU) which was started prior to sternotomy.[3] These patients suffered less blood loss than controls.

More recent studies using larger doses of Apt (up to five million KIU during the surgical procedure) have shown reductions of both blood loss and transfusion of blood products associated with CPB[4–11] and have rekindled interest for this old drug. The rationale for high-dose Apt is to achieve plasma concentrations of more than $250 \, KIU \cdot ml^{-1}$ during CPB, which have been shown to inhibit plasmin completely and are the threshold for complete inhibition of plasma kallikrein *in vitro*.[12] The inhibition of plasmin[4,6] and kallikrein[9] are thought to preserve platelet function during open heart surgery. However, as stated by Fritz and Wunderer, "smaller quantities of aprotinin should suffice under *in vivo* conditions since small amounts only of the proenzymes are activated ordinarily ... "[12] Thus, it is possible that the presently approved doses of Apt of 200,000 KIU as a bolus followed by an infusion of $100,000 \, KIU \cdot hr^{-1}$, not to exceed one million $KIU \cdot 24hr^{-1}$ (product monograph), could be clinically effective.

While high doses of Apt appear to be efficacious in reducing blood loss and transfusion requirements after CPB, this dosage regimen may be difficult to enforce since it promises to carry a substantial cost, at a time when hospital administrators are attempting to reduce expenses and require efficiency studies before approving new therapeutic modalities. High doses of Apt may be efficacious in all patients undergoing surgery under CPB, but the most efficient use of this drug could require restricting its administration to those patients at high risk of bleeding, because less expensive alternatives such as intraoperative autotransfusion and postoperative return of shed mediastinal blood, for example, are available and effective for patients at low risk of bleeding.

This study was conducted to evaluate the effectiveness of low-dose Apt administered prophylactically during cardiac surgical procedures previously identified in our experience as being associated with the greatest use of blood products[13] since (1) the initial clinical studies yielded positive results, (2) such doses of Apt may well be sufficient to inhibit proteolytic enzymes in the clinical situation, (3) the financial burden of this dosage regimen is more acceptable and (4) these are the patients most exposed to blood products and, therefore, most at risk of morbidity secondary to transfusions.

## Methods

This randomized double-blind study was approved by the Ethics Committee of the Montreal Heart Institute. Between April and September 1991, 44 patients scheduled for repeat myocardial revascularization, repeat valve surgery, or a combined procedure (primary or repeat) were randomized by the Department of Pharmacy to receive Apt (Group A) or placebo (Group C). Informed consent was obtained from all patients. Patients previously exposed to Apt (most likely to present an allergic reaction to the drug),[14] or presenting a congenital coagulation disorder, were to be excluded ($n = 0$). Each successive block of four patients was randomized (random allocation of two patients to Group A and two patients to Group C), to insure an equal number of patients in both groups and a similar distribution of patients over time. It was initially calculated that 26 patients in each group would be necessary to obtain a Type I error of 0.05 and a Type II error of 0.20, assuming a 50% reduction in blood loss or transfusion requirements.

After the induction of anaesthesia, but before skin incision, a bolus of 200,000 KIU of Apt was administered in a double-blind fashion over a period of 20 min to patients of Group A, followed by an infusion of 100,000 $KIU \cdot hr^{-1}$ during the entire surgical procedure and in the intensive care unit (ICU), for a total dose of one million KIU. Group C patients received an equal volume of sodium chloride 0.9% throughout surgery and recovery.

All members of the Departments of Anaesthesia and Surgery participated in the study and no attempt was made to standardize the practice of either group. The usual management of anaesthesia and CPB has been described previously[13] but the following modifications to established practice were adopted for the purpose of this study: (1) a membrane oxygenator (Maxima Hollow Fiber Oxygenator, Medtronic Cardiopulmonary Division, Anaheim, CA) was used in all cases, (2) the CPB circuit was primed uniformly with 2,000 ml crystalloid solution and (3) milder hypothermia (32°C) was maintained during aortic cross-clamping. Transfusion of autologous blood products and retransfusion of shed mediastinal blood were not employed.

While a strict protocol for the administration of homologous blood products (HBP) was not enforced, the current indications for HBPs were reviewed by our haematologist (D.R.) at a meeting attended by anaesthetists, surgeons, residents and fellows involved in the care of the patients, before the initiation of the study. Our usual practice is to maintain a haemoglobin concentration of $70 \text{ g} \cdot \text{L}^{-1}$ during CPB and haemoglobin concentrations as low as $80 \text{ g} \cdot \text{L}^{-1}$ are tolerated after CPB as long as haemodynamic stability is maintained. Human albumin

(not plasma) is used when volume expansion alone is desired. Persistent bleeding and coagulopathy are treated with fresh frozen plasma (FFP), cryoprecipitate, and/or platelets as required according to the results of coagulation testing.

Clinical data compared between patients of Groups A and C included basic demographic data, nature of the surgical intervention, duration of CPB and of operation, preoperative use of anticoagulants and/or acetylsalicylic acid (ASA), dosage of heparin and of protamine administered during the operation, postoperative administration and dosage of protamine and/or DDAVP. Dryness of the operative field was evaluated by the surgeon on a one to four scale, prior to initiation of CPB and again at the end of the procedure, prior to chest closure. Score of one, two and three indicated minimal, moderate and heavy bleeding respectively. A score of four indicated profuse bleeding suggestive of a coagulopathy. Blood loss during the operation was evaluated by the attending anaesthetist. The volume of mediastinal blood shed after the operation was measured hourly by the ICU nurses. Transfusions of packed red blood cells (PRBC), platelets, FFP, or cryoprecipitate during the operation and/or in the ICU were recorded.

Laboratory data collected for each patient included the activated coagulation time (ACT) before and after the administration of Apt or placebo, after the administration of heparin, and upon arrival in the ICU. The haemoglobin concentration, platelet count, routine coagulation profile, and template bleeding time (measured in minutes; prolonged bleeding time reported as $>15$ min) were measured prior to induction of anaesthesia and upon arrival in the ICU. Haemoglobin concentrations at the time of discharge from the hospital were compared.

Results are given as the mean and the standard deviation (SD) of the mean. Continuous variables were analysed by one-way analysis of variance and Fisher's protected least significant difference (PLSD) test. Chi-square analysis was used for categorical data. Statistical significance was established when $P < 0.05$.

## Results

Interim analysis of the results revealed no treatment effect and, consequently, the study was stopped before obtaining the planned number of patients (see discussion: limitations of the study). A total of 44 patients was studied.

Three patients in Group C were excluded: one patient died in the operating room and another upon arrival in the ICU (neither was a result of haemorrhagic complications). The third patient was excluded when the surgeon proceeded to a single valve replacement instead of the planned combined procedure. Groups A and C were comparable with respect to sex, age, size and weight of

TABLE I   Comparison of perioperative characteristics of patients receiving aprotinin (Group A) or placebo (Group C)

| | Group A | Group C | P |
|---|---|---|---|
| Sex (M/F) | 16/6 | 12/7 | NS |
| Age (yr) | 62 ± 9 | 58 ± 11 | NS |
| Size (cm) | 165 ± 9 | 166 ± 9 | NS |
| Weight (kg) | 70 ± 12 | 76 ± 19 | NS |
| CABG/valve | 12/9 | 11/7 | NS |
| Combined procedure/total | 1/22 | 1/19 | NS |
| Pre-op coumadin/total | 5/22 | 3/19 | NS |
| Pre-op heparin/total | 14/22 | 10/19 | NS |
| Pre-op ASA/total | 4/22 | 6/19 | NS |
| Duration of CPB (min) | 122 ± 40 | 115 ± 49 | NS |
| Duration of surgery (min) | 240 ± 65 | 250 ± 66 | NS |

All results mean ± SD; NS: no significant difference between groups.

TABLE II   Management of anticoagulation in the perioperative period

| | Group A | Group C | P |
|---|---|---|---|
| Pre-Apt ACT (sec) | 126 ± 17 | 128 ± 23 | NS |
| Post-Apt ACT (sec) | 126 ± 11 | 126 ± 21 | NS |
| Intra-op heparin (mg) | 286 ± 52 | 296 ± 84 | NS |
| Post-heparin ACT (sec) | 504 ± 146* | 531 ± 201* | NS |
| Intra-op protamine (mg) | 302 ± 52 | 324 ± 69 | NS |
| Post-protamine ACT (sec) | 132 ± 24 | 141 ± 24 | NS |
| Post-op protamine (yes/no) | 11/11 | 12/7 | NS |
| DDAVP (yes/no) | 7/15 | 9/10 | NS |

All results mean ± SD; NS: no significant difference between groups.
*$P = 0.0001$ compared to pre-Apt, post-Apt and post-protamine ACT within each group.

TABLE III   Comparison of blood losses

| | Group A | Group C | P |
|---|---|---|---|
| Surgeon's evaluation | | | |
| - before CPB (1/2/3/4) | 17/5/0/0 | 11/7/1/0 | NS |
| - post-CPB (1/2/3/4) | 7/11/1/2 | 6/11/1/0 | NS |
| Anaesthetist's evaluation (ml) | 882 ± 501 | 642 ± 252 | NS |
| Post-op chest drainage (ml) | 565 ± 589 | 631 ± 423 | NS |
| Surgical re-exploration (yes/no) | 1/21 | 0/19 | NS |

All results mean ± SD; NS: no significant difference between groups; scores of 1 to 4 indicate minimal to profuse bleeding.

TABLE IV   Haematologic parameters

| | Group A | Group C | P |
|---|---|---|---|
| Haemoglobin concentration (g · L$^{-1}$) | | | |
| - control | 137 ± 18 | 137 ± 13 | NS |
| - arrival in ICU | 98 ± 16 | 92 ± 14 | NS |
| - discharge | 105 ± 13 | 104 ± 13 | NS |
| Platelets ($10^9$/L) | | | |
| - control | 213 ± 56 | 236 ± 77 | NS |
| - arrival in ICU | 114 ± 46 | 117 ± 40 | NS |
| - discharge | 267 ± 125 | 262 ± 98 | NS |
| Normal prothrombin time (PT; < 12 sec) | | | |
| - control | 19/22 | 16/16 | NS |
| - arrival in ICU | 2/22 | 2/19 | NS |
| Normal partial thromboplastin time (PTT; <33 sec) | | | |
| - control | 18/22 | 11/17 | NS |
| - arrival in ICU | 1/22 | 2/19 | NS |
| Fibrinogen concentration (g · L$^{-1}$) | | | |
| - control | 3.83 ± 1.2 | 3.92 ± 1.12 | NS |
| - arrival in ICU | 1.96 ± 0.43 | 2.39 ± 0.86 | 0.051 |
| Bleeding time (≤9.5 min) | | | |
| - control | 15/22 | 16/19 | NS |
| - arrival in ICU | 2/22 | 1/19 | NS |

All results mean ± SD; NS: no significant difference between groups.

patients. Also, the surgical procedures performed, duration of CPB and of surgery, and preoperative use of anticoagulants were similar in both groups (Table I).

Patients of Groups A and C received the same doses of heparin and protamine intraoperatively. The ACT was not prolonged by the administration of Apt. The number of patients receiving DDAVP and protamine in the ICU was not different between groups (Table II).

The surgeon's evaluation of bleeding before and after CPB was not different between groups. Also, the anaesthetist's evaluation of the volume of blood lost during the operation was not different between both groups. After the operation, the volume of blood lost into the chest drains was similar in both groups. Of the 41 patients studied, one patient in Group A required re-exploration of the mediastinum for excessive bleeding (Table III). No surgically correctable site of bleeding was found at reoperation.

The haemoglobin concentration was not different between groups preoperatively, upon arrival in the ICU, and at the time of discharge from the hospital. Platelet counts were normal preoperatively and at the time of discharge. Upon arrival in the ICU, the number of platelets was decreased similarly in Groups A and C (Table IV). Prothrombin time, partial thromboplastin time, and fibrinogen levels were abnormal in a majority of patients of both groups on arrival in the ICU (Table IV). Plasma concentration of fibrinogen was lower in Apt treated patients at arrival in ICU ($P = 0.051$).

Postoperatively, prolonged bleeding times were reported in 17 patients, precluding analysis of variance. Thus, bleeding times were recorded as normal (≤9.5 min) or abnormal (>9.5 min). In the ICU, the bleeding time was normal in two patients of Group A, and in one patient of Group C (Table IV).

TABLE V    Units of homologous blood products transfused

|  | Group A | Group C | P |
|---|---|---|---|
| Packed red blood cells | 3.0 ± 2.8 | 2.6 ± 2.3 | NS |
| Fresh frozen plasma | 1.6 ± 2.6 | 0.4 ± 0.8 | NS |
| Platelets | 2.6 ± 5.2 | 1.2 ± 2.9 | NS |
| Cryoprecipitates | 1.9 ± 4.3 | 0.8 ± 2.5 | NS |
| Total | 9.1 ± 13.5 | 5.0 ± 6.3 | NS |

All results mean ± SD; NS: no significant difference between groups.

TABLE VI    Percentage of patients transfused

|  | Group A | Group C | P |
|---|---|---|---|
| Packed red blood cells | 77 | 84 | NS |
| Fresh frozen plasma | 36 | 21 | NS |
| Platelets | 23 | 16 | NS |
| Cryoprecipitates | 18 | 11 | NS |
| All blood products | 77 | 84 | NS |

All results mean ± SD; NS: no significant difference between groups.

The number of units of PRBC, FFP, platelets ad cryoprecipitates transfused in Groups A and C were not different (Table V). The number of patients without transfusion of any homologous blood product was also similar in both groups (Table VI).

## Discussion

The administration of low-dose Apt did not result in a clinically significant reduction of postoperative bleeding or of the need for HBP in patients undergoing surgical procedures associated with the greatest use of blood products. Three reasons may explain the apparent inefficacy of Apt in this study.

First, the dose administered may have been too small. The currently recommended high-dose regimen consists of a two-million KIU loading dose given in 20 min after induction of anaesthesia, followed by a continuous infusion of 500,000 KIU per hour until the patient returns to the ICU, and a dose of two million KIU added to the oxygenator priming volume.[15] Thus, most patients will receive a total of approximately six million KIU. Royston suggests that "the higher the dose, the more beneficial are the effects of aprotinin," but this conclusion is based on the comparison of studies from different centres.[15] On the contrary, much smaller doses have proved efficacious in older[2,3] and also in more recent[7,16,17] studies. Two million KIU added to the priming fluid of the CPB circuit appear to be as efficacious as the full-dose regimen.[7,16] The infusion of 500,000 KIU after induction, and hourly until the end of CPB, also reduced blood loss and the number of patients transfused.[17] Thus, while doses as low as two million KIU are efficacious, reducing the dosage any further may not be warranted in the present surgical context.

Secondly, the mode of administration differs from the two million KIU in the oxygenator prime reported by most authors. A bolus of 200,000 KIU followed by an infusion of 100,000 KIU · hr⁻¹ was administered to prevent the fibrinolysis that seems to occur during the period preceding CPB. This was based on our previous finding that postoperative chest drainage is similar in patients

undergoing all types of cardiac surgery, while transfusions are increased in patients undergoing reoperations and complex surgical procedures, suggesting that blood loss is increased intraoperatively, rather than postoperatively.[13] Reoperations are associated with a longer and more difficult dissection and, possibly, with a more intense fibrinolytic activity during that period. However, the mode of administration chosen for the present study should have decreased blood loss and total transfusion requirements if this hypothesis had held true, assuming the dose of Apt was sufficient. Moreover, low-dose Apt was not effective in preventing the decrease in fibrinogen concentration after cardiac surgery.

Thirdly, meticulous surgical haemostasis decreased blood loss to a point where the efficacy of prophylactic aprotinin may be difficult to demonstrate. This is true for most studies published on the efficacy of prophylactic high-dose Apt, as reviewed recently.[18] It is interesting to note that postoperative blood losses in the control group compare favourably with those of Apt-treated patients elsewhere, even though these were high-risk patients. For example, in Munich, patients receiving high-dose Apt bled 738 ± 411 ml postoperatively,[9] a figure similar to the 631 ± 423 ml in Group C. Similarly, a lack of efficacy of prophylactic high-dose aprotinin in elective aortocoronary bypass grafting was reported by Boldt *et al.*[19] Blood losses until the first postoperative day in their patients treated by haemofiltration alone during bypass (390 ± 230 ml) were not different from those in whom high-dose Apt plus haemofiltration were used (260 ± 160 ml).[18] Thus, the higher the bleeding, the more beneficial the effects of Apt appear to be.

Other factors such as the use of membrane oxygenators and the routine attempt to discontinue ASA at least one week before the operation may have contributed to the low postoperative bleeding observed. Platelet number and function are better preserved with membrane oxygenators than with bubble oxygenators.[20] Furthermore, in at least one study, it has been shown that a specific membrane oxygenator was less harmful to platelets, and could negate the effect of two million KIU of Apt administered in the priming fluid of the CPB circuit.[21]

*Limitations of the study*

This study was designed to evaluate the clinical effectiveness of low-dose Apt (effectiveness studies try to show how an intervention works in the real world).[22] Individual anaesthetists or surgeons have little influence on the total number of HBP transfused to a patient in this institution.[13] Consequently, the use of HBP was not strictly controlled, but an effort was made to review the indications of currently utilized HBP with the clinicians involved in the care of those patients. Despite relatively well controlled postoperative blood losses, a high percentage of patients received a considerable number of HBP. The present study could not determine whether an optimal transfusion practice could have reduced transfusion of HBP any further, or if transfusion of FFP, platelets and cryoprecipitate was necessary to prevent bleeding in the ICU. In effect, our surgeons prefer to correct abnormalities of the postoperative coagulogram rapidly to prevent later bleeding.

The other important limitation of this type of study is the number of patients studied, especially when the results are not conclusive. Initially, based on the assumption that low-dose Apt infusion would result in a 50% reduction in blood loss or transfusion requirements, a sample of 26 patients per group was calculated to be sufficient to produce statistically meaningful results. However, based on the postoperative blood losses presented in Table III, 393 patients would have been necessary in each group to obtain a Type I error of 0.05 and a Type II error of 0.20 with the observed average reduction of blood losses of 66 ml and an average SD of blood losses of 506 ml (power analysis, StatChoice©, PSG Publishing Company Inc.). The reduction in postoperative blood losses was small and judged to be clinically insignificant, and was a first reason for not pursuing the study.

The second reason for interrupting the study was based on the finding that blood transfusion requirements were not reduced by low-dose aprotinin infusion. In fact, it appears that, contrary to all previously published evidence, the aprotinin-treated group tended to receive more HBP than the control group. Based on the results presented in Table V, at least 64 patients per group would have been required to obtain a Type I error of 0.05 and a Type II error of 0.20 with the observed average difference of 4.1 units of HBP transfused and an average SD of the number of units transfused of 9.9 units (power analysis, StatChoice©, PSG Publishing Company Inc.). Clearly, the dose and mode of administration of Apt investigated in the present study was not effective and, had we studied a larger number of patients, low-dose Apt infusion possibly could have been counter-productive. However, in the light of the existing literature, this possibility is remote.

Finally, the proportion of patients transfused tended to be smaller in the Apt-treated group. Based on the observed difference of the percentage of patients transfused (Table VI), 393 patients would have been required in each group to obtain statistically meaningful results (power analysis, StatChoice©, PSG Publishing Company Inc.). While the number of patients included in the study does not rule out the possibility that low-dose Apt did reduce bleeding and the proportion of patients transfused (Type II error), the benefits of this dose of Apt and mode of administration are not, in our opinion, clinically important.

In summary, the clinical usefulness of low-dose aprotinin, administered as a bolus (200,000 KIU) followed by a continuous infusion ($100,000 \text{ KIU} \cdot \text{hr}^{-1}$) to patients undergoing cardiac procedures associated with the greatest use of HBP, could not be demonstrated in our institution.

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