

Effects of Unfractionated Heparin, Low-Molecular-Weight Heparin, and Heparinoid on Thromboelastographic Assay of Blood Coagulation

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Abstract

Thromboelastography (TEG) has been used increasingly as an intraoperative hemostasis monitoring device. Low-molecular-weight heparins are given increasingly to reduce the development of antibodies against the heparin-platelet factor 4 complex, and heparinoids are given to patients who have developed the antibody. We studied the effect of unfractionated heparin, a low-molecular-weight heparin (enoxaparin sodium [Lovenox]), and a heparinoid (danaparoid sodium [Orgaran]) on blood clotting assayed with TEG (TEG clotting) in vitro and the efficacy of protamine sulfate and heparinase for reversing the effect. Heparin, enoxaparin, and danaparoid all caused a dose-dependent inhibition of TEG clotting of normal blood. Concentrations of enoxaparin and danaparoid that totally inhibited TEG clotting only minimally prolonged the activated partial thromboplastin time. While inhibition of TEG clotting by heparin and enoxaparin was reversed by protamine sulfate and heparinase, inhibition by danaparoid was reversed only by heparinase. Abnormal TEG clotting was observed in patients receiving enoxaparin whose plasma level of the drug was more than 0.1 antiXa U/mL. However, the degree of TEG abnormality did not always coincide with plasma levels of the drug.

The thromboelastograph is a device invented more than half a century ago.¹ It measures the dynamic process of blood coagulation, with defined parameters reflecting integrity of specific hemostatic components.² Thromboelastography (TEG) had not gained popularity in clinical coagulation services until it was used as an intraoperative coagulation monitoring modality during liver transplantation more than 15 years ago.³⁻⁶ Today, many liver transplantation centers use TEG in or near the operating suite to monitor coagulation changes and assist in hemostatic management during liver transplantation. During the last several years, TEG has started to gain acceptance as an intraoperative hemostatic monitoring device in coronary bypass surgery as well.⁷⁻¹² Reduced blood product use has been reported during and after cardiac bypass surgery when TEG was used to assess the hemostatic condition of the patient.^{13,14}

In bypass and heart transplant operations, the patient usually receives unfractionated heparin to prevent clotting in the extracorporeal circuit. Heparin is neutralized with protamine sulfate on completion of the procedure. When unfractionated heparin cannot be used in patients with a history of heparin-induced thrombocytopenia or thrombosis, a heparinoid^{15,16} often is used instead. Low-molecular-weight heparins (LMWHs) are used increasingly in a number of clinical conditions including bypass surgery.¹⁷⁻²⁰ In a single patient undergoing bypass surgery and receiving a heparinoid, abnormal blood clotting assayed with TEG (TEG clotting) was recorded.¹⁰ Nadroparin, an LMWH, has been shown to inhibit TEG clotting of normal blood.²¹ In view of the increasing use of LMWHs and heparinoids as therapeutic agents and the thromboelastograph as a hemostatic monitoring device, we sought to further define the effect of LMWHs and heparinoids on blood coagulation assayed with TEG and the efficacy of

protamine sulfate and heparinase for reversing the anticoagulant effect. The latter study, to our knowledge, has not been described. Furthermore, we performed TEG on patients receiving enoxaparin sodium (Lovenox), also an LMWH, and correlated thromboelastographic abnormalities with plasma levels of the LMWH.

Materials and Methods

Heparin, LMWH, and Heparinoid

Unfractionated sodium heparin, 1,000 U/mL, with a mean molecular weight of 15,000 d, was extracted from porcine intestinal mucosa. Heparin was diluted to 10 U/mL with saline. Enoxaparin sodium (Lovenox) is an LMWH with a mean molecular weight of 4,500 d. According to the product insert, each milligram contains approximately 100 antiXa U. Dilutions were based on 100 anti Xa U/mg. Danaparoid sodium (Orgaran, org 10172), 750 antiXa U in 0.6 mL, is a heparinoid extracted from porcine intestinal mucosa, which is a mixture of about 84% heparan sulfate, 12% dermatan sulfate, and 4% chondroitin sulfate and has a mean molecular weight of 5,500 d.

Subjects

Healthy persons with no known hemostatic abnormality donated blood for the study. Blood samples from 12 patients receiving enoxaparin therapy for at least 2 days also were tested. Eight patients were receiving 30 mg of enoxaparin, and 4 patients were receiving 60 mg administered subcutaneously, twice daily. None of the patients was receiving concomitant warfarin therapy. Blood samples for the study were obtained between 2 and 4 hours after the last injection of enoxaparin. Our institutional review board approved obtaining 1 sample of 20 mL or less, and donors provided individual consent.

Blood Sampling

Blood samples from patients were obtained from a central line or an antecubital vein using the Vacuette (Greiner & Sohne, Kremsmunster, Austria). When the sample was obtained from a central line, the first 10 mL was discarded. The Vacuette contains 3.2% buffered trisodium citrate and evacuates 3.15 mL of blood to each tube. The citrate/blood ratio was 1:9. Two tubes of blood were obtained from each subject. One random tube of blood was used for thromboelastographic testing and the other for other coagulation tests.

Blood samples from healthy persons were obtained using the same Vacuette system. Citrated whole blood was spiked with heparin, enoxaparin, or danaparoid to final concentrations of 0 to 0.5 U (for heparin) or 0 to 0.5 antiXa U (for enoxaparin and danaparoid) per milliliter.

Thromboelastography

TEG was performed on C3000 TEG instruments (Hemoscope, Skokie, IL) according to the manufacturer's instructions. All disposable supplies were purchased from Hemoscope. Briefly, 340 μ L of citrated blood was mixed with 20 μ L of calcium chloride (a 0.2-mol/L concentration) in a plain plastic cup or a cup coated with 2 U of heparinase (the final concentration of heparinase would be 5.6 U/mL). The reaction started immediately after mixing. A second set of TEG was performed in plain plastic cups in which protamine sulfate was included. In the latter cases, 310 μ L of blood was mixed with 30 μ L of 0.01% or 30 μ L of 0.03% protamine sulfate (final concentrations, 8.3 and 25 μ g/mL, respectively), followed by the addition of 20 μ L of calcium chloride.

Interpretation of TEG Assay Results

TEG assay results were quantified according to the time a detectable clot was formed (designated as R for reaction time), the time a defined degree of clot firmness was achieved (k), and the rate of clot formation (α). Another value, the maximal amplitude indicating clot strength, was not, in our opinion, as informative about coagulability as the other 3 values and was not used in the calculations. The units of R and k were not given as minutes and seconds, but as millimeters on TEG graphs. The distance in millimeters between the initiation of a test to the point at which the clot starts to form is the R, or graphically, from a straight line (unclotted blood) to the point at which the line begins to split into 2 symmetrical lines. The k is the distance between the splitting point and the point at which the upper and lower lines are 20 mm apart. Each 2 mm of R on the computer screen equals 1 minute. A TEG clotting curve for a healthy person and the R, k, and α measurements are illustrated in **Figure 1**.

The smaller the R and k values, and the larger the α value, the greater the coagulability of the blood. In our study, a test was terminated when those values appeared on the TEG recordings. When there were no values given owing to blood samples that would not form a clot, the test was terminated at 60 minutes or beyond. In the latter cases, values of 120 for R and k and 0 for α were assigned arbitrarily. With these values, the effects of heparin, enoxaparin, and danaparoid on TEG clotting and the efficacy of heparinase and protamine sulfate for reversing the anticoagulant effect were determined.

Other Coagulation Testing

The tube of patient's blood that was not used in TEG testing was centrifuged at 1,200g for 15 minutes at room temperature. Plasma was aspirated and recentrifuged. After the prothrombin time (PT) and activated partial

thromboplastin time (aPTT) were determined, the remaining plasma was stored at -70 C for the antiXa assay. The PT and aPTT were assayed on an MLA-1000 coagulation instrument (Medical Laboratory Automation Inc, Pleasantville, NY) with a PT reagent from Ortho-Hemoliance (Raritan, NJ) and an aPTT reagent from Dade-Behring (Miami, FL). The antiXa assay was performed on patient plasma samples with antiXa assay kits purchased from Diagnostica Stago (Asnieres-sur-Seine, France). The assay was performed on a CA-6000 coagulation instrument (Sysmex, Kobe, Japan). An aPTT for pooled normal plasma spiked with 0 to 0.5 U of heparin or 0 to 0.5 antiXa U/mL of enoxaparin or danaparoid also was determined.

Results

Dose-Dependent Inhibition of TEG Clotting In Vitro

Heparin, enoxaparin, and danaparoid all caused a dose-dependent inhibition of TEG clotting of normal blood (Table 1). However, there were marked variations in TEG clotting of individual samples, as indicated by the large SDs. A graphic display of dose-dependent inhibition by these 3 compounds is shown in Figure 2. On a per antiXa unit basis, the inhibition of TEG clotting by danaparoid was comparable to if not more than that by enoxaparin. The concentrations of enoxaparin and danaparoid that significantly

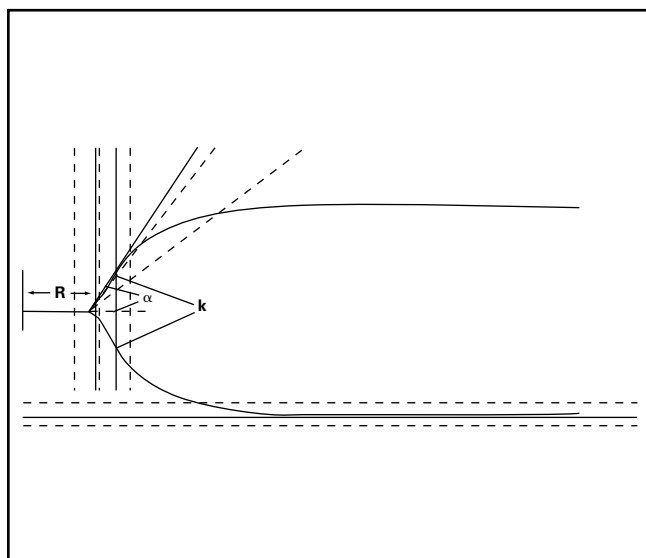


Figure 1 A normal thromboelastograph showing the R, k, and alpha. R is the distance (in millimeters) between the initiation of clotting and the point at which the straight line is split into 2 symmetrical lines; k, the distance in (millimeters) between the point the line is split and the point at which the 2 symmetrical lines are 20 mm apart; alpha, the angle (in degrees) of the split lines.

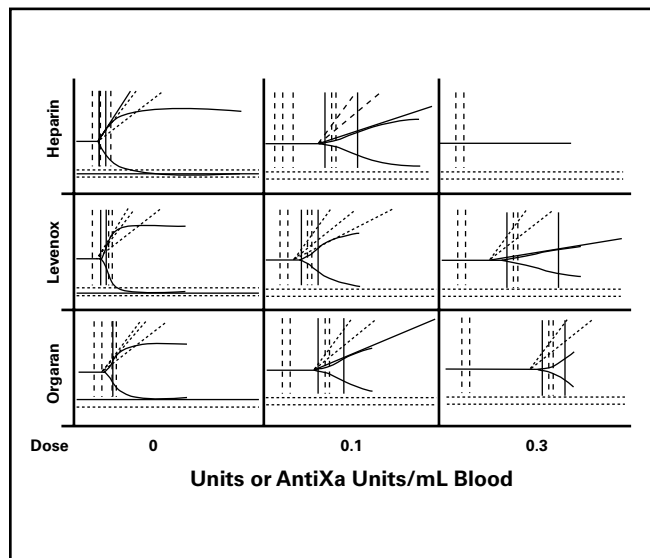


Figure 2 Dose-dependent inhibition of thromboelastographic clotting of normal blood by heparin, enoxaparin sodium (Lovenox), and danaparoid sodium (Orgaran).

Table 1 Dose-Dependent Inhibition of Thromboelastographic Clotting of Normal Blood by Heparin, Enoxaparin Sodium (Lovenox), and Danaparoid Sodium (Orgaran) for 6 Samples*

Units or AntiXa U/mL	Reaction Time			k			alpha (angle)		
	Heparin	Enoxaparin	Danaparoid	Heparin	Enoxaparin	Danaparoid	Heparin	Enoxaparin	Danaparoid
0	28.5 ± 8.4	27.5 ± 5.4	29.3 ± 9.6	8.7 ± 3.9	7.6 ± 3.2	8.0 ± 3.1	45.8 ± 12.7	47.3 ± 9.8	47.1 ± 12.2
0.1	88.9 ± 41.1	45.8 ± 17.4	58.5 ± 10.6	91.6 ± 44.1	21.0 ± 8.8	24.9 ± 8.4	5.9 ± 5.7	27.9 ± 15.3	21.8 ± 12.2
0.2	>120	91.3 ± 28.9	79.2 ± 33.3	>120	21.2 ± 13.2	58.4 ± 48.1	0	5.7 ± 7.7	15.0 ± 16.7
0.3	>120	96.0 ± 27.6	104.0 ± 23.6	>120	77.0 ± 47.6	76.7 ± 47.6	0	6.0 ± 7.0	7.1 ± 7.8
0.5	>120	103.4 ± 14.2	115.0 ± 13.0	>120	>120	>120	0	4.1 ± 3.6	1.8 ± 3.2

* Data are given as mean ± SD. Reaction time is the time a detectable clot was formed; k, the time a defined degree of clot firmness was achieved; and alpha, the rate of clot formation. The units for reaction time and k are millimeters on thromboelastography graphs.

to completely inhibited TEG clotting only mildly prolonged the aPTT of pooled normal plasma **Table 2**.

Reversal of Inhibition by Protamine Sulfate and Heparinase

The reversal of the inhibitory effect of 0.2 and 0.5 U/mL of heparin, and 0.2 and 0.5 antiXa U/mL of enoxaparin and danaparoid, is shown in **Table 3**. Doses of 0.2 and 0.5 U/mL of heparin prevented blood clotting as measured by TEG. Both doses of protamine sulfate and heparinase almost completely reversed the inhibition. Heparinase seemed somewhat more effective than protamine sulfate, but the higher dose of protamine sulfate was not more effective than the lower dose.

Heparinase was more effective than protamine sulfate for reversing the inhibition of TEG clotting by enoxaparin. Protamine sulfate largely reversed the inhibition, however. The inhibition by danaparoid was not affected by either dose of protamine sulfate. Heparinase, on the other hand, substantially corrected the inhibition. An illustration of the reversal

by protamine sulfate and heparinase of the inhibition on TEG reaction time (R) by 0.5 U/mL of heparin and 0.5 antiXa U/mL of enoxaparin and danaparoid is shown in **Figure 3**.

TEG of normal blood assayed in the presence of heparinase (referred to by some as heparinase-modified TEG) had shorter R and k values and greater alpha values than that assayed in the absence of the enzyme. However, paired *t* tests of R, k, and alpha obtained from samples assayed in the plain and heparinase cups yielded statistically nonsignificant *P* values of .274, .116, and .124, respectively.

Patient Studies

Abnormal TEG parameters of R, k, and/or alpha were obtained for patients whose plasma levels of enoxaparin were more than 0.1 antiXa U/mL. In general, the higher the antiXa levels, the greater the TEG changes. However, this was not always the case with all 3 TEG parameters. The PT and aPTT results for most patients were within the reference ranges, despite marked abnormality of TEG clotting. In 1 case, the aPTT was less than 3 seconds beyond the upper limit of the reference range at which TEG showed total absence of clotting. Addition of protamine sulfate to blood in vitro or assaying the sample in the heparinase-containing cup normalized TEG results for these patients (data not shown).

Table 2
Activated Partial Thromboplastin Time (aPTT) for Normal Pooled Plasma Spiked With Heparin, Enoxaparin Sodium (Lovenox), or Danaparoid Sodium (Orgaran)

U/mL or AntiXa U/mL	aPTT (s)		
	Heparin	Enoxaparin	Danaparoid
0	28.0	29.4	29.0
0.1	30.4	30.7	32.0
0.2	39.8	32.6	34.1
0.3	51.1	35.1	36.7
0.4	66.8	37.2	38.5
0.5	80.1	39.4	40.1

Discussion

The present study established a dose-dependent inhibition of TEG clotting by unfractionated heparin, enoxaparin, and danaparoid of normal blood and determined the efficacy of protamine sulfate and heparinase for reversing the inhibitory effect. The purpose of the study was not to

Table 3
Reversal of Effects of Heparin, Enoxaparin Sodium (Lovenox), and Danaparoid Sodium (Orgaran) on Thromboelastographic Clotting of Normal Blood by Protamine Sulfate and Heparinase for 6 Samples*

Units or AntiXa U/mL	Reaction Time				k				alpha			
	Control	PS 8.3	PS 25	Heparinase	Control	PS 8.3	PS 25	Heparinase	Control	PS 8.3	PS 25	Heparinase
Heparin												
0.2	>120	37.3 ± 8.5	35.3 ± 7.5	31.8 ± 5.5	>120	11.0 ± 3.2	13.3 ± 8.5	10.7 ± 4.2	0	35.4 ± 7.7	35.7 ± 13.2	42.3 ± 9.9
0.5	>120	36.8 ± 6.0	41.1 ± 12.9	31.2 ± 6.0	>120	12.2 ± 2.6	16.9 ± 11.6	9.8 ± 3.6	0	33.5 ± 6.4	32.8 ± 17.7	41.2 ± 11.5
Enoxaparin												
0.2	91.3 ± 28.9	45.5 ± 10.2	46.4 ± 18.1	40.4 ± 11.6	86.7 ± 43.6	21.2 ± 13.2	26.1 ± 18.2	12.7 ± 5.5	5.7 ± 7.7	29.5 ± 16.8	23.2 ± 12.6	22.6 ± 10.9
0.5	103.4 ± 14.2	47.3 ± 16.9	43.6 ± 16.1	32.3 ± 7.9	>120	34.5 ± 42.5	37.3 ± 41.4	9.2 ± 4.4	4.1 ± 3.6	28.7 ± 6.5	23.6 ± 6.6	39.3 ± 18.3
Danaparoid												
0.2	73.7 ± 29.4	88.4 ± 32.1	81.6 ± 36.8	39.8 ± 9.2	58.7 ± 48.4	76.0 ± 48.4	75.0 ± 49.7	11.6 ± 5.0	13.8 ± 11.6	11.0 ± 13.6	8.4 ± 8.6	36.3 ± 10.9
0.5	117.9 ± 4.0	>120	>120	45.3 ± 11.8	>120	>120	>120	16.8 ± 8.8	0.8 ± 1.3	0	0	30.1 ± 14.8

*Protamine sulfate (PS) was given in dosages of 8.3 or 25 µg/mL; for heparinase, 5.6 U/mL was used. Data are given as mean ± SD. Reaction time is the time a detectable clot was formed; k, the time a defined degree of clot firmness was achieved; and alpha, the rate of clot formation. The units for reaction time and k are millimeters on thromboelastography graphs.

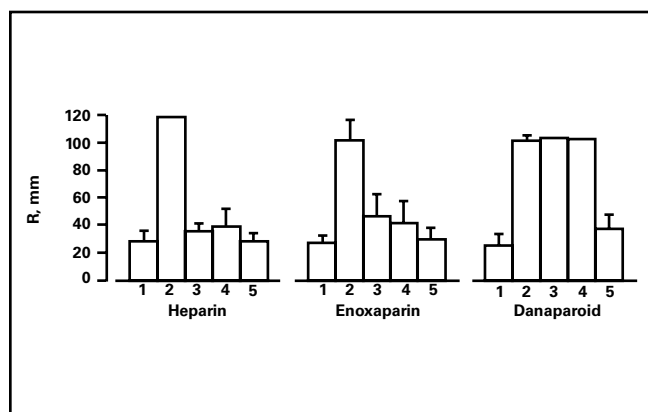


Figure 3 Effect of heparin, 0.5 U/mL, and enoxaparin sodium (Lovenox) and danaparoid sodium (Orgaran), 0.5 antiXa U/mL each, on thromboelastographic reaction time (R) of normal blood and reversal of the effect by protamine sulfate and heparinase. Column 1, control; column 2, samples containing heparin, enoxaparin, or danaparoid; columns 3 and 4, heparinized samples containing protamine sulfate, 8.3 and 25 µg/mL, respectively; column 5, heparinized samples containing heparinase, 5.6 U/mL.

compare the effects of these 3 compounds on TEG clotting in a quantitative sense. An international unit of heparin possesses different antithrombotic activity as an antiXa unit of LMWH or heparinoid; for this reason, comparison based on units would be meaningless. Although the antiXa activity of heparin can be defined, the low anti-IIa activity of LMWH and danaparoid cannot be matched to that of heparin. We have shown that concentrations of enoxaparin and danaparoid that only mildly prolonged the aPTT could markedly or completely inhibit TEG clotting.

The reversal of the inhibitory effect of heparin, enoxaparin, and danaparoid by protamine sulfate and heparinase yielded some interesting results. Inhibition of TEG clotting by heparin was largely, but not completely, reversed by 8.3 µg/mL of protamine sulfate. A 3-fold increase in protamine sulfate concentration was not more effective. Heparinase was somewhat more effective than protamine sulfate for reversing the inhibitory effect of heparin. Similar findings were obtained with protamine sulfate and heparinase for reversing the inhibitory effect of enoxaparin. From a laboratory monitoring viewpoint, the same information can be obtained by the use of protamine sulfate as by the use of heparinase in patients whose blood contains heparin or LMWH, a conclusion reached earlier by Spiess et al.²²

The heparinoid danaparoid has been shown to inhibit TEG clotting in a single patient receiving the drug during cardiac bypass surgery.¹⁰ The dose used in that case was considerably higher than the dose used in the present study. We showed substantial inhibition with 0.1 antiXa U/mL of danaparoid on TEG clotting of normal blood. We also found

a complete inability of protamine sulfate to reverse the inhibitory effect of danaparoid. Heparinase, on the other hand, substantially reversed the effect.

The mechanism of antithrombotic activity of danaparoid is not fully understood. About 84% of the mixture in danaparoid is heparan sulfate; the remainder is dermatan sulfate (about 12%) and chondroitin sulfate (about 4%). Heparan sulfate differs from heparin in that it contains fewer N-sulfate glycosamine residues and, thus, is less negatively charged. And, the core protein of heparan sulfate is more complex than that of heparin. However, the mechanism of anticoagulation by heparin and heparan sulfate is thought to be the same, namely, binding to antithrombin III to potentiate its natural anticoagulant activity. Electronegativity on the heparin molecule is essential for the binding. Neutralization of negative charges on heparin by the highly positively charged protamine sulfate nullifies the antithrombotic activity of heparin. Since the inhibition of TEG clotting by danaparoid is not reversed by protamine sulfate, the negative charges on heparan sulfate molecules obviously are not involved in their augmentation of the activities of antithrombin III. A far-fetched alternative explanation would be that protamine sulfate neutralizes negative charges of a certain density, not those below that level of density. Because of their low density on heparan sulfate, the negative charges are not neutralized by protamine sulfate, remaining available to complex with antithrombin III. Danaparoid also contains about 12% of dermatan sulfate. Dermatan sulfate also is negatively charged, exerting its anticoagulant effect by potentiating the activity of heparin cofactor II.²³ Heparin cofactor II inhibits thrombin but not factor Xa.²⁴ To our knowledge, chondroitin sulfate does not possess antithrombotic activity. The fact that heparinase had largely reversed the inhibition of danaparoid on TEG clotting suggests a limited role of dermatan sulfate in the inhibition. Because of the similarity between heparin and heparan sulfate, it should not be surprising that heparinase also could hydrolyze the heparan sulfate to reverse its inhibitory effect on TEG clotting. From a practical viewpoint, an abnormal TEG clotting suspected to result from the presence of danaparoid can be confirmed only by the use of "heparinase-modified" TEG, not by inclusion of protamine sulfate in TEG testing.

Patients receiving therapeutic doses of enoxaparin rarely have an aPTT value that exceeds the upper limit of the normal control. In the present study, we have shown that when the antiXa level of enoxaparin was more than 0.1 U/mL, a hypocoagulable TEG clotting pattern was observed. Most patients receiving LMWH therapy do not require laboratory monitoring. However, monitoring is recommended for pediatric patients and patients with kidney disease. AntiXa is the assay for monitoring LMWH

therapy. Unfortunately, the antiXa assay is not available universally, especially on a stat basis.

In addition to determining TEG clotting for patients receiving LMWH, a second objective of our study was to explore the potential usefulness of TEG to quantitatively reflect the degree of LMWH anticoagulation. Based on inconsistent findings for the 3 TEG parameters for plasma levels of antiXa activity, TEG does not seem to be an appropriate modality for monitoring enoxaparin therapy.

TEG has been used in conditions other than transplantation and bypass operations. These conditions range from assessment of coagulation status in trauma patients to prediction of neonatal sepsis and to monitoring of the effects of abciximab.²⁵⁻³² A reevaluation of potentials and limitations of the method and a study of the effects of medication with direct effects on the hemostatic system should be undertaken.

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