Platelet Activity, Coagulation, and Fibrinolysis During Exercise in Healthy Males

Effects of Thrombin Inhibition by Argatroban and Enoxaparin

Nailin Li, Shu He, Margareta Blombäck, Paul Hjemdahl

Background—Relationships between exercise-induced activation of platelets, blood coagulation, and fibrinolysis, and the importance of thrombin for responses to exercise are not clear.

Methods and Results—Effects of thrombin inhibition on hemostatic parameters were examined in a double-blind crossover study comparing the direct thrombin inhibitor argatroban (350 μg/kg intravenous bolus followed by 25 μg/kg per minute of infusion), the indirect thrombin inhibitor enoxaparin (0.75 mg/kg, intravenous bolus), or placebo (saline) in 21 healthy males. Measurements were made at rest, before and during/after thrombin inhibitor treatment, and immediately after exhaustive exercise. At rest argatroban abolished, and enoxaparin attenuated platelet activation by thrombin, but not by adenosine diphosphate. Argatroban and, even more so, enoxaparin decreased thrombin generation (prothrombin F1+2) and the coagulation potential, and increased the fibrinolytic potential. Exercise increased circulating activated platelets (from 5.5±0.3 to 9.4±0.9×10⁹/L; P<0.001), circulating platelet–platelet microaggregates, the platelet responsiveness to in vitro stimulation, leukocyte activation (leukocyte CD11b expression and plasma elastase), and platelet–leukocyte aggregation (P<0.01 for all). Exercise increased coagulation (F1+2; P<0.01) and fibrinolysis, but did not alter the balance between them; fibrin gel permeability increased (P<0.01), probably because of release of endogenous tissue plasminogen activator from the vessel wall. Neither argatroban nor enoxaparin counteracted exercise-induced platelet or leukocyte activation. Both thrombin inhibitors augmented exercise effects on fibrinolysis.

Conclusions—Strenuous exercise enhances platelet and leukocyte activation independently of thrombin. Exercise augments both coagulation and fibrinolysis, but the balance between them appears to be maintained. At therapeutic dosages argatroban counteracted thrombin-induced platelet activation most efficiently, whereas enoxaparin had somewhat stronger anticoagulant and profibrinolytic effects. (Arterioscler Thromb Vasc Biol. 2007;27:407-413.)

Key Words: coagulation ■ exercise ■ fibrin gel permeability ■ fibrinolysis ■ leukocytes ■ platelets ■ thrombin inhibition

Physical exertion may trigger acute coronary syndromes,1 and strenuous exercise provokes a prothrombotic state with platelet and leukocyte activation and increased platelet–leukocyte conjugation.2-4 Thus, exercise increases circulating activated platelets, platelet–platelet and platelet–leukocyte aggregates, as well as the CD11b expression of circulating leukocytes and leukocyte secretion (elastase) in vivo.5 Exercise also enhances the responsiveness of platelets and leukocytes to agonist stimulation in vitro.2,3 Treatment with aspirin6 or clopidogrel7 does not prevent exercise-induced platelet activation, indicating that neither thromboxane A₂ nor ADP is an important mediator. An interesting possibility is that thrombin is involved in the platelet activation induced by strenuous exercise.

Exercise also enhances blood coagulation and fibrinolysis,6 as evidenced by elevated plasma levels of prothrombin fragment 1+2 (F1+2),3 and tissue plasminogen activator.7 However, the balance between coagulation and fibrinolysis during exercise has not been well defined. This issue may be addressed by measurements of the overall hemostasis potential,8,9 which measures the balance between thrombin-induced fibrin gel formation and plasmin-induced fibrin digestion. Furthermore, as exercise enhances fibrinolysis, it is of considerable interest to investigate how exercise influences the fibrin gel network, being the final outcome of coagulation, using a permeability assay.10

Platelet activation has a pivotal role in arterial thrombosis. Thrombin is the primary activator of platelets at the site of thrombus formation and a major driving force in thrombus growth.11 Thus, thrombin inhibition is important in the treatment of acute coronary syndromes and during percutaneous coronary intervention.12,13 Argatroban is an arginine-
derived, small molecule, thrombin inhibitor that binds selectively to the catalytic site of thrombin. Enoxaparin is a low-molecular-weight heparin that inhibits thrombin via both anti-FXa (80%) and anti-FIIa activity (20%). Both argatroban and enoxaparin have been used in acute coronary syndromes and percutaneous coronary intervention. We compared the effects of direct and indirect thrombin inhibition on indices of platelet activation, blood coagulation, and fibrinolysis at rest and during strenuous exercise in healthy volunteers.

Materials and Methods

Study Design
We performed a randomized, double-blind, placebo-controlled crossover study that was registered at the European Medicines Agency (EudraCT No: 2004-001859-11), and approved by the regional Ethics Committee and the Swedish Medical Products Agency (MPA No: 151-2004/53781).

Twenty-four healthy, physically fit males were enrolled, of whom 21 subjects (30±1 years, body weight 80±2 kg, height 183±1 cm) completed the study, and 3 subjects were withdrawn because of an activated clotting time >400 seconds (HemoTec ACT II; Medtronic AB, Järfälla, Sweden) before the exercise test; this was a safety precaution specified in the protocol. Subjects visited the Phase I laboratory at the Karolinska Clinical Trial Center on 3 occasions separated by ≥2 weeks. They were instructed not to take any platelet inhibiting medication (eg, aspirin) during 2 weeks before each experiment, and to refrain from caffeine, nicotine, and alcohol intake during ≥12 hours before each visit.

Basal (untreated) blood samples were taken after 30 minutes of supine rest. Thereafter, the volunteers received enoxaparin (0.75 mg/kg intravenous injection followed by saline infusion; natriumlorid; Fresenius Kabi), argatroban (350 µg/kg intravenous bolus followed by 25 µg/kg per minute of continuous infusion), or placebo (saline bolus plus infusion). Infusions were administered, and activated clotting time was measured by an independent nurse who kept all other personnel blinded to the actual treatment given. After 45 minutes of infusion, sampling was repeated for studies of responses to drug treatment at rest. The volunteers thereafter rested another 30 minutes, to allow processing of the second set of samples, before performing the exercise test.

Exercise was performed on a computerized cycle ergometer (Siemens-Elema AB, Stockholm, Sweden), with a starting workload of 30 W and a gradual increase of 10 W per minute. Blood pressure and heart rate were monitored intermittently, and fatigue was estimated by the 20-grade Borg scale. The test was terminated on exhaustion. Immediately on termination, the recumbent position was resumed, and blood sampling was repeated. Thereafter, infusions of argatroban or placebo were discontinued.

Sample Handling
Venous blood was collected by venepuncture without stasis, using siliconized vacutainers containing 1/10 volume 129 mmol/L trisdodium citrate (Becton Dickinson, Meylan, France). Plasma was removed after centrifugation (1400g, 4°C, 10 minutes for immunoassays; 2000g, 22°C, 15 minutes for overall hemostasis index and fibrin gel permeability analyses), and stored at −80°C before analyses.

Flow Cytometry
Whole blood flow cytometric assays of platelet P-selectin expression, leucocyte CD11b expression, single platelet and platelet–leucocyte microaggregate counts, and platelet–leucocyte aggregates (PLAs) have been described previously. Platelet P-selectin expression is reported as percentages of P-selectin–positive cells in the platelet population and as absolute counts of P-selectin–positive platelets. Leucocyte CD11b expression is reported as mean fluorescence intensity of the total leucocyte population and of leucocyte subpopulations. PLAs are presented as absolute counts and as percentages of platelet-conjugated leucocytes in the total leucocyte population and, among lymphocytes, monocytes, and neutrophils.

Determination of Fibrin Gel Permeability
The fibrin gels were prepared by adding 45 µL of a modified gel-initiating cocktail consisting of 5 pM rTF, 4 µmol/L PPL, and 20 mmol/L CaCl₂, to 200 µL plasma, followed by incubation overnight at room temperature to mature. Permeability (porosity) of the gel was measured by the volume of a buffer percolated through the gel under different hydrostatic pressures.

Overall Hemostasis Potential Analysis
The overall hemostasis potential assay we previously used was modified. Briefly, 50 µL of a fibrin formation-triggering cocktail containing rTF, PPL, and CaCl₂, without or with rt-PA was added to 150 µL aliquots of plasma to initiate analyses of the coagulation profile (Cp) and the fibrinolysis profile (Fp), respectively. The final reagent concentrations were: 2.1 pM rTF, 2.4 µmol/L PPL, 17 mmol/L CaCl₂, and 0 or 135 ng/mL of rt-PA. Fibrin absorbance at 405 nm was assessed using a spectrophotometer (Dynex Technologies, Va.). The obtained raw data were used to calculate the velocities of OD changes without and with exogenous rt-PA. The maximal velocities of OD increases or decreases in OD divided by the required time (minutes) yield Cp or Fp, respectively. The Overall Hemostasis Index (OHI) is the ratio of Cp over Fp.

Immunoassays
Plasma elastase (DPC Biermann GmbH, Bad Nauheim, Germany), soluble P-selectin and sE-selectin (R&D System, Abingdon, UK), and prothrombin F1+2 (Behringwerke AG, Marburg, Germany) were determined by enzyme immunoassays.

Data Presentation and Statistics
Data reported are from the 21 completed study subjects, and are presented as mean±SEM or median and range. Effects of exercise and thrombin inhibition were analyzed by repeated measures ANOVA, Student paired t test, and/or Wilcoxon signed rank test as appropriate using StatView 4.5 and SuperANOVA (Abacus Concepts, Berkeley, Calif). P<0.05 was considered to indicate significance.

Results
Physiological and Hematologic Parameters
Heart rate and systolic blood pressure at rest (63±2 bpm and 125±3 mm Hg, respectively) did not change during placebo infusion, but increased markedly during exercise (to 185±2 bpm and 179±4 mm Hg, respectively). Neither argatroban nor enoxaparin influenced these parameters (data not shown).
Maximal workload (≈265 W) and exercise duration (≈24 minutes) were similar on the 3 occasions.

On the placebo occasion, exercise elevated erythrocyte counts (from 4.7±0.1 to 5.2±0.1×10^12/L), hematocrit (41±1% to 47±1%), and platelet counts (229±9 to 305±11×10^9/L). Exercise almost doubled leukocyte counts (5.3±0.3 to 10.0±0.4×10^9/L), with increments mainly among lymphocytes (1.6±0.1 to 4.1±0.2×10^9/L) and granulocytes (3.4±0.2 to 5.3±0.2×10^9/L). These responses to exercise were not influenced by argatroban or enoxaparin (data not shown).

Platelet Activation

The basal (pretreatment) platelet responsiveness to thrombin or ADP stimulation in vitro was similar on all 3 occasions. Placebo infusion and prolonged rest did not influence the platelet P-selectin expression (2.4±0.1% before and 2.7±0.1% after infusion) or platelet reactivity to agonist stimulation (eg, 63.3±4.9% before and 63.0±5.3% after saline infusion with 0.04 U/mL thrombin). Exercise increased both unstimulated (3.3±0.2%; P<0.01) and stimulated (71.7±4.7% with 0.04 U/mL thrombin; P<0.01) platelet P-selectin expression. Argatroban virtually abolished platelet activation by 0.04 U/mL thrombin both at rest (3.4±0.4%) and after exercise (5.5±1.4%). Enoxaparin treatment shifted the dose–response curve for thrombin with attenuation of platelet activation mainly at low concentrations (from 62.9±5.0% before to 11.9±1.7% after treatment with 0.04 U/mL thrombin); the inhibitory effect of enoxaparin was further diminished after exercise (26.6±4.2% with 0.04 U/mL thrombin). Neither argatroban nor enoxaparin influenced ADP-induced platelet activation.

Exercise markedly elevated the circulating P-selectin positive platelet counts in the absence of in vitro stimulation (from 5.5±0.3 to 9.4±0.9×10^9/L; P<0.001), and markedly increased the numbers of thrombin- and ADP-activated platelets in the blood, caused by exercise-enhanced platelet activity and thrombocytosis (Figure 1A). Argatroban did not counteract the increase of circulating activated platelets by exercise (from 5.8±0.5 to 9.8±1.1×10^9/L), but virtually abolished platelet activation by thrombin also after exercise (Figure 1B). In contrast, enoxaparin only mildly attenuated the enhancement by exercise (Figure 1C).

Exercise increased the circulating platelet microaggregate counts (from 2.2±0.1 to 3.3±0.2×10^9/L; P<0.01), with similar responses after argatroban (2.2±0.1 to 3.3±0.2×10^9/L) or enoxaparin treatment (2.5±0.2 to 3.4±0.2×10^9/L). Exercise also elevated plasma soluble P-selectin (Table 1). Argatroban and enoxaparin tended to reduce soluble P-selectin at rest, but neither treatment counteracted the response to exercise (Table 1).

Leukocyte Activation

Neither argatroban nor enoxaparin influenced leukocyte CD11b expression without (reflecting circulating leukocyte activity) or with fMLP stimulation in vitro (reflecting leukocyte reactivity) (Figure 2A). Exercise increased the unstimulated CD11b expression of all leukocyte subpopulations analyzed, ie, neutrophils (Figure 2B), lymphocytes and monocytes (data not shown), and enhanced neutrophil CD11b expression with fMLP stimulation (Figure 2B). The fMLP-stimulated total leukocyte CD11b expression was, however, slightly reduced after exercise (Figure 2A), because of a markedly increased proportion of lymphocytes, which respond poorly to fMLP. Plasma elastase, a marker of neutrophil and monocyte activation in vivo, was similarly doubled after exercise with all treatments (Table 1).

PLA Formation

Exercise increased the percentages of circulating platelet-conjugated leukocytes, eg, platelet-neutrophil aggregates increased from 1.5±0.1% to 2.2±0.2% (P<0.05) on the placebo occasion. Agonist stimulation in vitro markedly increased platelet-leukocyte conjugation, as PLAs increased from 2.1±0.1% to 24.6±2.9% with thrombin (0.04 U/mL) and to 13.8±1.5% with ADP (1 μmol/L), respectively, at rest. These responses were augmented by exercise (to 29.8±2.9% and 19.7±1.9%, respectively; P<0.01 for both). Neither argatroban nor enoxaparin counteracted the circulating PLA responses to exercise. Argatroban abolished, and enoxaparin markedly inhibited, thrombin-induced PLA formation; both drugs slightly, but significantly, attenuated...
ADP-induced PLA formation after exercise (percentage data not shown). Because exercise induced leukocytosis and thrombocytosis, PLA formation in vivo and in vitro are also presented as PLA counts in the blood. Figure 3 shows that exercise elevated circulating PLAs similarly on all 3 occasions, and that thrombin- and ADP-induced PLA formation were markedly enhanced after exercise with placebo treatment. Argatroban abolished, whereas enoxaparin markedly reduced thrombin-induced PLA formation. Both drugs attenuated the enhancement of ADP-stimulated PLA formation by exercise (P<0.05 for both; Figure 3), suggesting a contribution by thrombin to this enhancement. Similar data were found for platelet–neutrophil, platelet–lymphocyte, and platelet–monocyte aggregates (not shown).

Balance Between Blood Coagulation and Fibrinolysis
Exercise enhanced the generation of thrombin in vivo, as assessed by plasma F1+2 (Table 1). Argatroban and enoxaparin decreased F1+2 levels slightly at rest, but did not significantly attenuate the increment caused by exercise (Table 1).

The Cp, the Fp, and the OHI changed little with continued rest, and were not significantly altered by exercise during placebo infusion (Figure 4). Argatroban and, especially, enoxaparin treatment markedly decreased Cp (Figure 4A) and OHI (Figure 4C), and elevated Fp (Figure 4B) at rest. Enoxaparin actually prevented plasma clotting in 9 of the 21 Fp measurements. During argatroban infusion, exercise caused only minor changes of Cp and Fp, whereas the marked changes in Cp and Fp seen at rest after enoxaparin treatment were less pronounced after exercise (Figure 4A and 4B). The OHI was similarly reduced by both thrombin inhibitors also after exercise (Figure 4C).

Fibrin Gel Formation and Gel Permeability
Placebo infusion did not influence fibrin gel permeability. After exercise, fibrin gel permeability was increased in 16 of the 21 subjects; fibrin gels from the remaining 5 subjects were initially formed but lysed during the overnight incubation that is needed to form a stable fibrin gel (Table 2).

| TABLE 1. Effects of Drug/Placebo Infusion and Exercise on Parameters Assessed in Plasma |
|-----------------------------------------------|----------------|----------------|
|                                               | Placebo       | Argatroban     |
|                                               | 103.8±8.0     | 104.7±7.6      |
| Pretreatment sP-selectin, ng/mL               | 39.9±1.9      | 40.3±2.5       |
| sE-selectin, ng/mL                           | 28.5±1.7      | 28.8±1.7       |
| Elastase, ng/mL                              | 23.8±1.3      | 23.0±1.5       |
| F1+2, nM                                     | 104.0±7.8     | 99.3±7.6*†     |
| Posttreatment sP-selectin, ng/mL              | 38.9±1.7      | 37.5±1.5†      |
| sE-selectin, ng/mL                           | 28.6±1.6      | 28.6±1.6       |
| Elastase, ng/mL                              | 24.1±1.5      | 23.9±1.2       |
| F1+2, nM                                     | 121.5±9.2‡    | 111.6±8.8‡†    |
| Postexercise sP-selectin, ng/mL               | 47.2±3.1‡     | 43.7±2.5‡      |
| sE-selectin, ng/mL                           | 31.5±1.8‡     | 30.6±1.6‡      |
| Elastase, ng/mL                              | 51.7±3.6‡     | 46.9±3.1‡      |

*P<0.01 compared to pretreatment; †P<0.05 compared to placebo treatment; §P<0.01 compared to posttreatment; ¶P<0.05<P<0.10, compared to pretreatment.

Mean±SEM; n=21.

Figure 2. Effects of thrombin inhibition on leukocyte CD11b expression. Blood samples were obtained before (white columns) and after (black columns) infusion of placebo, argatroban, or enoxaparin and immediately after exercise (stippled columns). Leukocyte CD11b expression of unstimulated (Unsti.) and 0.1 µmol/L fMLP-stimulated samples was measured by whole blood flow cytometry. CD11b mean fluorescence intensities (MFIs) of total leukocytes (A) and neutrophils (B) are plotted. Mean±SEM, n=21. *P<0.05 compared with corresponding sample before infusion/exercise; †P<0.05 compared with corresponding unstimulated samples.
Argatroban and, even more so, enoxaparin enhanced fibrin gel permeability markedly at rest. The effect of thrombin inhibition was further augmented by exercise (10 and 11 samples, respectively, did not form stable fibrin gels; \( P < 0.05 \) compared with placebo) (Table 2). Thus, both thrombin inhibitors markedly increased the permeability.

**Endothelial Activation**

Exercise slightly but significantly elevated plasma soluble E-selectin, a marker of endothelial cell activation; this response was not influenced by thrombin inhibition (Table 1).

**Discussion**

The present study shows that direct thrombin inhibition by argatroban abolishes, and indirect thrombin inhibition by enoxaparin attenuates thrombin-induced platelet activation at therapeutic dosages.\(^{19,20}\) Both thrombin inhibitors markedly reduced the coagulation profile and enhanced the fibrinolytic profile and fibrin gel permeability in samples taken at rest. Strenuous exercise induced platelet and leukocyte activation in vivo, augmented the responsiveness of platelets and leukocytes to agonist stimulation in vitro, and increased platelet-leukocyte aggregation. Thrombin inhibition did not counteract exercise-induced platelet activation in vivo or the enhancement of ADP-induced platelet activation following exercise. Exercise also enhanced both blood coagulation and fibrinolysis, but the balance between these 2 opposing mechanisms appears to be maintained during stress.

Argatroban demonstrated potent inhibition of thrombin-induced platelet activation, without influencing responses to ADP. Argatroban also had potent anticoagulant effects, as evidenced by marked increases in fibrin gel permeability and decreases in the Cp. Increased fibrin gel permeability implies impaired fibrinogen clotting, leading to a loose fibrin gel structure with increased susceptibility to fibrinolysis. Enoxaparin exerts its antithrombotic effect through both anti-FXa and anti-FIIa (thrombin) activity, with an activity ratio of 4:1.\(^{15}\) This resulted in some selectivity for anti-coagulant effects in the present study. Thus, enoxaparin reduced the Cp and increased the Fp and fibrin gel permeability more markedly than argatroban, but was less effective than argatroban in inhibiting thrombin-induced platelet activation. The effects of enoxaparin on responses to exercise were probably underestimated because we chose a dosage regimen without continuous infusion,\(^{19}\) and the plasma levels of enoxaparin may have decreased importantly at the postexercise sampling.\(^{21}\) Similarly, additional administration of enoxaparin may be appropriate during prolonged coronary interventions when enoxaparin is given as an intravenous bolus.

As expected, strenuous exercise increased P-selectin-positive platelets, platelet–platelet microaggregates, and soluble P-selectin levels in the circulation, indicating platelet activation in vivo. The stress test also augmented thrombin- and ADP-stimulated platelet activation, indicating enhanced platelet reactivity after exercise. Argatroban abolished, whereas enoxaparin attenuated the platelet responsiveness to thrombin stimulation. However, neither drug affected the
enhancement by exercise of platelet activation in vivo. We have previously found that thromboxane synthesis inhibition by aspirin\(^3\) or ADP receptor blockade by clopidogrel\(^5\) failed to counteract exercise-induced platelet activation, suggesting that neither thromboxane A\(_2\) nor ADP mediates the response to exercise. The present data clearly indicate that thrombin is not an important mediator of exercise-induced platelet activation either. Noradrenaline and adrenaline are likely mediators in exercise-induced platelet activation, because the plasma levels of both catecholamines are elevated \(\sim 10\)-fold in the present stress model\(^3\) and they are known to enhance platelet activity in vivo and in vitro at these levels.\(^{22,23}\) However, the hypothesis of catecholamine-induced platelet activation has not been tested in experiments involving \(\alpha\)-adrenoceptor blockade during exercise. Exercise also causes thrombocytosis, and another possible explanation is that platelets that are newly released into the circulation are enhanced, and fibrin gel permeability was increased after exercise with placebo treatment. Increased fibrin gel permeability and impaired fibrin clot formation indicate increased fibrinolysis after exercise, which may contribute to the beneficial effects of exercise training on the risk for myocardial infarction. It should be noted that the measurements of both Cp and Fp are simultaneously influenced by coagulation and fibrinolysis. Under these experimental conditions, exercise-induced release of endogenous t-PA will counteract increases in C\(_p\) and the addition of exogenous t-PA to the samples will influence the measurements of Fp. As noted, the effects of thrombin inhibition were more clear-cut than the physiological changes induced by exercise. Unchanged OHI values after exercise during placebo infusion suggest that the balance between coagulation and fibrinolysis was maintained during exercise without thrombin inhibition. In the global analysis of thrombotic risks associated with strenuous exercise, the prothrombotic effect of exercise on platelet and leukocyte activation should also be taken into account.

Exercise caused leukocytosis and enhanced leukocyte activation, as evidenced by elevated leukocyte CD11b expression and plasma elastase levels. These responses were not influenced by thrombin inhibition. Exercise also increased platelet–leukocyte conjugation without agonist stimulation (ie, circulating PLAs) and PLA formation induced by agonist stimulation in vitro. Thrombin inhibition by argatroban or enoxaparin did not influence PLA formation in vivo either at rest or during exercise, but attenuated thrombin-induced PLA formation in vitro due to inhibition of thrombin-stimulated platelet activation. Interestingly, there was slight attenuation of ADP-induced PLA formation in vitro with both thrombin inhibitors, suggesting that thrombin formed during ADP-induced platelet activation contributed to the response. Increased platelet conjugation to leukocytes during exercise may increase their prothrombotic\(^{25}\) and proatherogenic\(^{26}\) potential.

The present study had some limitations. It included healthy males only to avoid possible influences of the hormone cycle in females. Studies in women and in patients with coronary artery disease would also be of interest. We did not assess the expression of platelet thrombin receptors (eg, PAR-1), which might influence exercise and treatment effects, and we did not perform a full evaluation of coagulation and fibrinolysis with measurements of individual components. The dosages of the thrombin inhibitors were chosen from clinical studies,\(^{19,20}\) and dose–response studies with continuous infusion of the 2 drugs would further clarify their exact potencies regarding the presently evaluated effects.

In conclusion, thrombin inhibition by therapeutic dosages of argatroban or enoxaparin inhibits both blood coagulation and thrombin-induced platelet activation, and enhances fibrinolysis. Strenuous exercise enhances platelet and leukocyte activity, and increases platelet–leukocyte aggregation. Exercise also enhances blood coagulation and fibrinolysis, but the balance between these opposing forces may be maintained. Neither argatroban nor enoxaparin counteracted exercise-induced platelet activation, indicating that thrombin does not contribute to stress-induced platelet activation.

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Disclosures
None.

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