CME CREDIT

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THIRD IN A SERIES

Unfractionated and low-molecular-weight heparins in acute coronary syndromes: Current recommendations

ABSTRACT

All patients with acute coronary syndromes and without obvious bleeding or acute cerebrovascular events are candidates for heparin therapy. This article is a review of the pharmacology of unfractionated and low-molecular-weight heparins, trials of heparin therapy in acute coronary syndromes, and recommendations for using these agents.

KEY POINTS

If unfractionated heparin is given, a bolus of 4,000 to 5,000 units followed by an infusion with frequent aPTT monitoring is recommended. The aPTT should be kept within a narrow therapeutic window to enhance effectiveness and reduce bleeding complications.

Low-molecular-weight heparin is given as a weight-adjusted dose and does not require monitoring of its effect.

Important considerations in deciding to use unfractionated or low-molecular-weight heparin are cost, the need for invasive procedures, and estimated length of hospitalization.

WHAT IS THE BEST REGIMEN of antithrombotic drugs to use in acute coronary syndromes? Aspirin or one of the other oral antiplatelet drugs (ticlopidine or clopidogrel) should be the cornerstone of therapy (see Tan and Moliterno[1]). In the pages that follow I present the case for the next brick in the structure: heparin. I also examine some recent evidence that low-molecular-weight heparin may offer advantages over standard, unfractionated heparin.

ROLE OF THROMBIN

Acute coronary syndromes occur when a vulnerable endothelial plaque ruptures, triggering the formation of a thrombus.[2] The process is complex and involves platelets, subendothelial constituents, and soluble coagulation factors.

Thrombin plays a key role in all these intricate interactions. Its activity is enhanced in acute coronary syndromes, as demonstrated by elevated levels of fibrinopeptide A, a by-product of fibrinogen cleavage. Specifically, thrombin:

- Catalyzes the transformation of fibrinogen into fibrin
- Regulates the function of coagulation factors V and VIII
- Stimulates the normal epithelium to release tissue plasminogen activator and plasminogen activator inhibitor-1
- Regulates the tone of arterioles with normal endothelium (via nitric oxide and prostacyclin) and abnormal endothelium (via endothelin)

- Causes platelet aggregation
- Promotes smooth muscle proliferation.

Thus, there is a strong theoretic rationale for altering thrombin function to control thrombosis in acute coronary syndromes.

Thrombin activity is tightly regulated by naturally occurring substances and can be inhibited by endogenous and exogenous compounds. The most important endogenous inhibitor is antithrombin (formerly known as antithrombin III), a serine protease inhibitor produced by the liver. Antithrombin directly inhibits thrombin by binding with it to form a thrombin-antithrombin complex which is quite stable. However, this process is relatively slow.

Exogenous direct thrombin inhibitors include hirudin, hirulog, hirugen, efegatran, argatroban, and PPACK (D-phenylalanyl-L-prolyl-L-arginine chloromethylketone) which inhibit thrombin by binding to it, unlike heparin which inhibits thrombin and coagulation indirectly.

Two types of heparin are available: unfractionated (high-molecular-weight, a mixture of polysaccharides with molecular weights ranging from 3,000 to 50,000 daltons) and low-molecular-weight (a more homogeneous mixture of smaller molecules). The two types have somewhat different mechanisms for inhibiting coagulation.[3]

To reverse heparin, give protamine 1 mg/50–100 U heparin

Unfractionated heparin binds to antithrombin, modifying its shape (FIGURE 1), and thus accelerating the formation of thrombin-antithrombin complexes several thousandfold. Although the thrombin-antithrombin complex is quite stable, the heparin can leave the complex once it is formed and is free to bind to another antithrombin molecule.

Unfractionated heparin also indirectly neutralizes other coagulation factors higher in the coagulation cascade such as factor Xa, via the modified antithrombin molecule.

Low-molecular-weight heparin has little effect on thrombin, because most of its molecules are too short to bridge the thrombin-antithrombin complex. Instead, it exerts its main inhibitory effect on factor Xa, an activator that precedes thrombin in the coagulation cascade.[3]

TRIALS OF UNFRACTIONATED HEPARIN

Unfractionated heparin plus aspirin in unstable angina, non–Q-wave MI

Oler et al[4] performed a meta-analysis of six randomized clinical trials[5–10] that compared the combination of aspirin plus unfractionated heparin vs aspirin alone in patients with unstable angina. According to their calculations, patients receiving both drugs had a 33% lower incidence of death or MI in the hospital, although the trend narrowly failed to reach statistical significance (relative risk 0.67, 95% confidence interval 0.44–1.02; FIGURE 2).

Recommendations. The Agency for Health Care Policy and Research recommends that, as soon as the diagnosis of intermediate-risk or high-risk unstable angina is made, all patients should receive a bolus of 5,000 units of unfractionated heparin (80 units/kg for patients with lower body weight), followed by 18 units/kg/hour for 2 to 5 days or until revascularization, in addition to aspirin and other anti-ischemic therapy.[11]

If anticoagulation with unfractionated heparin must be reversed urgently, such as for impending surgery or life-threatening bleeding, give protamine 1 mg per 50 to 100 units of intravenous heparin. Monitoring of the activated clotting time facilitates fast and precise reversal.

Unfractionated heparin plus t-PA in acute Q-wave myocardial infarction

Physicians began giving unfractionated heparin as an adjunct to fibrinolytic drugs even before the clear benefit of the combination was established. Several trials in the past 10 years have confirmed the value of this strategy.

The HART (Heparin-Aspirin Reperfusion Trial),[12] published in 1990, randomly assigned 205 patients receiving t-PA for acute Q-wave MI to also receive either unfractionated heparin (a 5,000-unit bolus intravenously followed by 1,000 units/hour to maintain the partial thromboplastin time at 1.5 to 2 times the baseline value) or aspirin (80 mg by mouth daily). One day later, 82% of the infarct-related arteries were patent in the heparin group, compared with 52% of those in the aspirin group ($P < .0001$). The incidence of subsequent reocclusion, bleeding, and rein-

How heparins work

ANTITHROMBIN naturally attaches to thrombin, thereby inactivating thrombin; this occurs slowly under normal circumstances

UNFRACTIONATED HEPARIN accelerates this natural process several thousandfold and then releases itself to promote the binding of more thrombin-antithrombin complexes

LOW-MOLECULAR-WEIGHT HEPARINS bind to antithrombin, but the molecules are too short to also bind thrombin and therefore do not promote the formation of thrombin-antithrombin complexes

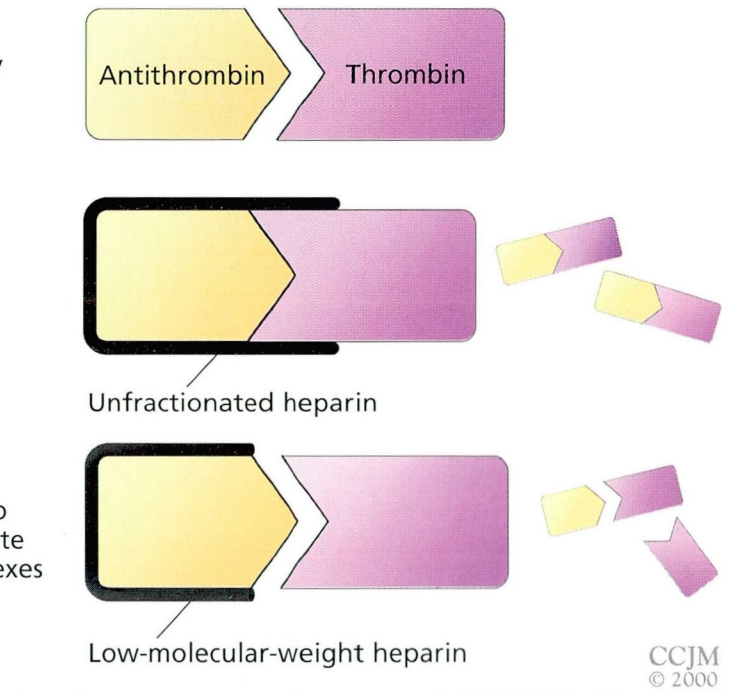

FIGURE 1. Unfractionated heparin has a lower bioavailability than low-molecular-weight heparin and requires frequent monitoring of its anticoagulant effect because it has a heterogeneous and inconstant molecular structure. Both types of heparin inhibit factor Xa (not shown here), but whereas unfractionated heparin inhibits factor Xa and thrombin at a ratio of 1 to 1, low-molecular-weight heparins inhibit factor Xa vs thrombin at ratios of 2:1 to 4:1.

farction was similar in the two groups.

In a subsequent analysis,[13] the HART investigators found that the mean activated partial thromboplastin time (aPTT) was higher in patients with a patent artery than in those with a closed artery (81 vs 54 seconds, $P < .01$), lending credence to the concept that unfractionated heparin promotes and maintains coronary artery patency after t-PA therapy.

The GUSTO-1 (Global Use of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries) trial[14–16] provided supporting evidence for this concept in a much larger cohort. The study compared four strategies in treating acute MI:

- Streptokinase plus subcutaneous unfractionated heparin
- Streptokinase plus intravenous unfractionated heparin
- t-PA plus intravenous unfractionated heparin
- Streptokinase, t-PA, and intravenous unfractionated heparin.

The lowest mortality rate occurred in the group receiving t-PA plus intravenous heparin.[14] Furthermore, a subsequent analysis[15] of a subset of the 30,000 patients who received intravenous heparin revealed something surprising: regardless of treatment group, the lowest 30-day mortality rate was in those with an aPTT at 12 hours of 50 to 70 seconds. Furthermore, those with an aPTT in this range also had the lowest incidence of bleeding (FIGURE 3).

Unfractionated heparin plus streptokinase in acute Q-wave MI

The use of unfractionated heparin as an adjunct to streptokinase is less well established than its use with t-PA.

Neither the **GISSI-2 trial** (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)[17] nor the **ISIS-3 trial** (International Study of Infarct

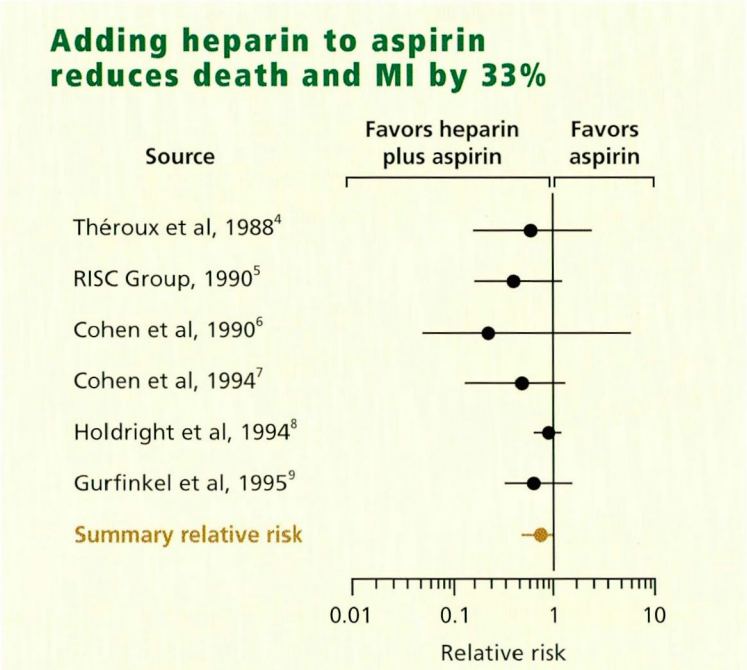

FIGURE 2. Meta-analysis by Oler et al showing the benefit of adding unfractionated heparin to aspirin in reducing the incidence of myocardial infarction and death in patients with unstable angina. Together, the six studies showed a risk reduction of 33%.

SOURCE: OLER A, WHOOLEY MA, OLER J, GRADY D. ADDING HEPARIN TO ASPIRIN REDUCES THE INCIDENCE OF MYOCARDIAL INFARCTION AND DEATH IN PATIENTS WITH UNSTABLE ANGINA. A META-ANALYSIS. JAMA 1996; 276:811–815.

Survival)[18] showed any difference in mortality between patients treated with streptokinase plus subcutaneous unfractionated heparin vs streptokinase plus placebo.

The GUSTO-1 trial[14] did not show any difference in mortality when patients receiving streptokinase also received unfractionated heparin intravenously rather than subcutaneously. However, more patients who received heparin intravenously had patent arteries on angiographic evaluation.[16]

Recommendations. All patients receiving t-PA or recombinant plasminogen activator, and probably most patients receiving streptokinase, should receive a bolus of unfractionated heparin of 60 units/kg (maximum 4,000 units) as soon as possible, followed by an infusion not exceeding 12 units/kg/hour. The aPTT should be adjusted 12 hours after starting fibrinolysis at 50 to 70 seconds and maintained at this level for at least 24 hours.

This regimen should be adjusted if the patient is also receiving a platelet IIb/IIIa receptor inhibitor (see below). Concomitant aspirin therapy should prevent rebound thrombosis after heparin is stopped. Additional complicating features such as recurrent ischemia, atrial fibrillation, or severe left ventricular dysfunction may mandate longer therapy with heparin.

Patients not receiving reperfusion therapy are likely to benefit from unfractionated heparin for 24 to 48 hours, although definitive data are not available. For those undergoing direct mechanical revascularization, anticoagulation with heparin is standard during the procedure, and some practitioners continue it for 24 to 48 hours after the sheath is removed.

Trials of unfractionated heparin with IIb/IIIa receptor antagonists

Recently, a new class of antiplatelet drugs, the platelet glycoprotein IIb/IIIa receptor antagonists, has been combined with unfractionated heparin in treating acute coronary syndromes. The combination allows one to give lower doses of fibrinolytics,[19] while increasing the patency rate.

In unstable angina or non–Q-wave MI, four large randomized clinical trials tested the triple regimen of aspirin, unfractionated heparin, and a IIb/IIIa antagonist vs the classic combination of aspirin and heparin, and found that triple therapy substantially reduced the incidence of death or MI at 30 days.[19]

TRIALS OF LMW HEPARIN

The effect of low-molecular-weight heparin in acute Q-wave MI has not yet been evaluated. In contrast, its utility in unstable angina and non–Q-wave MI has been extensively studied.

Compared with placebo. In the Fragmin During Instability in Coronary Artery Disease (FRISC) study,[20] 1,506 patients received aspirin and then were randomly assigned to receive placebo or dalteparin, a low-molecular-weight heparin preparation. At 6 days, 1.8% of patients receiving aspirin plus dalteparin had died or had an MI, compared with 4.8% of those receiving aspirin and placebo. At 150 days, the incidence of death, MI, or revascularization was 24.1% in the dalteparin group vs

28.7% in the placebo group, a statistically significant 16% reduction in relative risk.

Combined with IIb/IIIa antagonists. The use of low-molecular-weight heparin with or without IIb/IIIa antagonists is currently being tested in clinical trials of patients with acute coronary syndromes or who are undergoing percutaneous revascularization. The findings are likely to alter the current standards of anticoagulant therapy.

IS LMW HEPARIN BETTER THAN UNFRACTIONATED HEPARIN?

Low-molecular-weight heparin has both advantages and disadvantages compared with unfractionated heparin in treating acute coronary syndromes.

Possibly better efficacy

Several studies found low-molecular-weight heparin at least as effective as unfractionated heparin, and possibly more so. The difference in efficacy may be due to a combination of relative and absolute inhibition of factors Xa and IIa (thrombin), chemical structure (type of salt) and release of endothelial procoagulant and anticoagulant substances.

The FRIC study (Fragmin in the Treatment of Unstable Coronary Disease)[21] randomized 1,482 patients to receive dalteparin or unfractionated heparin in conjunction with aspirin. The rate of death or MI was similar in the two groups at 6 days (3.6% vs 3.9%) and at 45 days, as was the incidence of major bleeding.

The ESSENCE study (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events)[22] randomized 3,171 patients to receive unfractionated heparin or enoxaparin (another low-molecular-weight heparin preparation) 1 mg/kg twice a day. All patients received aspirin. By 30 days, 23.3% of the unfractionated heparin group and 19.8% of the low-molecular-weight heparin group had died or had an MI or recurrent angina (P = .017). There were more minor bleeding events in the low-molecular-weight heparin group.

The TIMI 11B study (Thrombolysis in Myocardial Infarction)[23] included 3,910 patients who received aspirin and were randomized to receive unfractionated heparin or enoxaparin 1 mg/kg twice a day. By 14 days, the incidence of death, MI, or urgent revascularization was reduced from 16.7% in the unfractionated heparin group to 14.2% in the low-molecular-weight heparin group (P = .03), without a significant difference in major bleeding episodes.

In the long-term phase of the trial, patients were re-randomized to receive placebo or enoxaparin for 42 days. At the end of

GUSTO-1 trial:
Ideal aPTT is 50–70 seconds

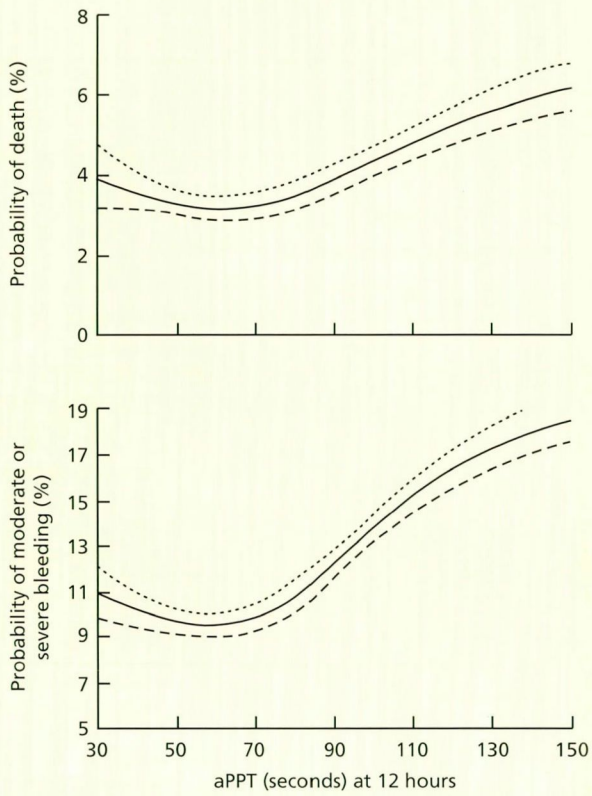

FIGURE 3. Probability of death (**top**) and moderate or severe bleeding (**bottom**) at 30 days after an acute MI according to the activated partial thromboplastin time (aPTT) at 12 hours after enrollment in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO-1) trial. Patients were receiving unfractionated heparin in addition to thrombolytic therapy. Dotted lines are the 95% confidence intervals.

SOURCE: GRANGER CB, HIRSH J, CALIFF RM, ET AL. ACTIVATED PARTIAL THROMBOPLASTIN TIME AND OUTCOME AFTER THROMBOLYTIC THERAPY FOR ACUTE MYOCARDIAL INFARCTION: RESULTS FROM THE GUSTO-1 TRIAL. CIRCULATION 1996; 93:870–878.

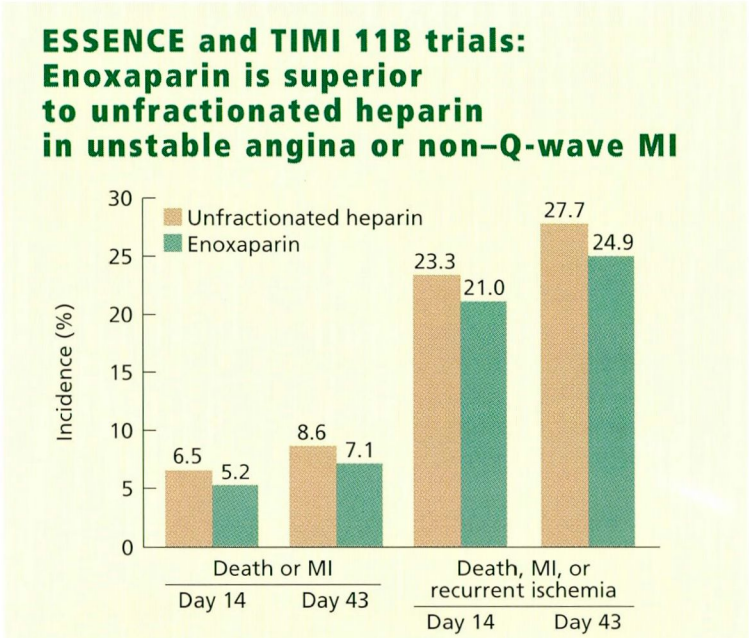

FIGURE 4. Meta-analysis by Antman et al of the ESSENCE and TIMI 11B trials, which compared enoxaparin with unfractionated heparin for patients with unstable angina or non-Q-wave myocardial infarction. All comparisons were statistically significant ($P \leq .03$).

SOURCE: ADAPTED FROM ANTMAN EM, COHEN M, RADLEY D, MCCABE CH, PREMMEREUR J, BRAUNWALD E. ENOXAPARIN FOR UNSTABLE ANGINA/NON-Q WAVE MYOCARDIAL INFARCTION: META-ANALYSIS OF TIMI 11B AND ESSENCE [ABSTRACT]. J AM COLL CARDIOL 1999; 33:351A.

this time, the incidence of death or revascularization was 19.6% in the placebo group vs 17.3% in the enoxaparin group ($P = .049$), with an insignificant increase in minor hemorrhage with enoxaparin. Thus, the early benefit was maintained, but not enhanced. There was no statistical difference in the incidence of any of the individual endpoints or in the rate of death or MI between the two groups.

A meta-analysis of the two studies[24] concluded that compared with unfractionated heparin, enoxaparin reduces the incidence of death or MI by 18% to 23% for at least 6 weeks, without a significant risk of major bleeding (FIGURE 4).

Other advantages of LMW heparin

Better bioavailability. The large molecules of unfractionated heparin are highly negatively charged and thus bind extensively to plasma and vascular matrix proteins, endothelial cells, macrophages, and platelets. These interactions result in a multitude of effects (TABLE 1). However, at low doses, this extensive binding makes unfractionated heparin somewhat unpredictable in its effects on clotting. In particular, unfractionated heparin has a high affinity for platelet factor 4, which thus competes with antithrombin for binding to heparin molecules, reducing heparin's anticoagulant effect. In contrast, low-molecular-weight heparin has excellent bioavailability due to low affinity for other proteins and cells.

Easier to use. Low-molecular-weight heparin has a longer half-life and better absorption after subcutaneous injection than does unfractionated heparin and therefore can be given twice a day subcutaneously. In contrast, unfractionated heparin is best given by continuous intravenous infusion.

Fewer side effects. Low-molecular-weight heparin causes a lower incidence of bleeding complications and fewer platelet-associated side effects such as thrombocytopenia, and is useful as alternative therapy in cases of thrombocytopenia induced by unfractionated heparin.

Less monitoring. Whereas unfractionated heparin requires frequent dosage changes based on the aPTT and prothrombin time (PT), low-molecular-weight heparin is given as a weight-adjusted dose and does not require monitoring. (However, in the rare instances in which monitoring might be needed, the aPTT or activated clotting time cannot be used. We recommend using an anti-Xa chromogenic assay.)

Disadvantages of LMW heparin

Low-molecular-weight heparin has two main disadvantages:

Cost. The cost differential is approximately $150 per day. However, lower rates of adverse events, ease of administration without monitoring, and the potential for early hospital discharge reduce the nominal cost difference.

Inability to monitor the level of anticoagulation. Low-molecular-weight heparin has little effect on the aPTT and activated clotting time (ACT), which can be a problem particularly during invasive procedures.

How to choose

It is very likely that low-molecular-weight heparin will assume a key role in the treatment of patients with acute coronary syn-

dromes. The choice between unfractionated heparin and low-molecular-weight heparin relates to cost and planned invasive procedures. In many catheterization laboratories, patients undergo angioplasty without additional unfractionated heparin if the last dose of low-molecular-weight heparin was within 6 hours of the procedure.

Another factor is the estimated length of hospitalization. Prolonged need for heparin in the hospital would favor low-molecular-weight heparin, which would not entail intravenous administration or monitoring.

Current recommendations are to give an intravenous bolus of 30 mg enoxaparin, followed by twice-a-day subcutaneous injections of 1 mg/kg, without need for aPTT monitoring. Low-molecular-weight heparin reversal can be accomplished with protamine (1 mg/1 mg of enoxaparin) or infusion of fresh frozen plasma.

TABLE 1

Unfractionated heparin interactions and effects

Coagulation cascade
- Inactivates factors IIa (thrombin), IXa, Xa, XIa, XIIa
- Inhibits plasmin-mediated thrombin activation

Endothelial surface
- Restores electronegativity
- Stimulates release of endothelium-derived growth factor
- Stimulates angiogenesis
- Inhibits smooth muscle cell proliferation and platelet-derived growth factor effect

Platelets
- Inhibits thrombin-mediated aggregation
- Inhibits action of von Willebrand factor

Inflammation
- Inhibits leukocyte enzyme release
- Prevents neutrophil chemotaxis
- Attenuates degradation of fibrous cap
- Stimulates release of lipoprotein lipase

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