Antiplatelets to Anticoagulants: Making Sense of the Coagulation Cocktails

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Anticoagulation is the cornerstone of therapy in patients with ischemic cardiovascular disease. In patients who develop an acute coronary syndrome, following percutaneous coronary interventions, or with an acute ischemic stroke, the rupture or injury of an atherosclerotic arterial plaque serves as a nidus for platelet aggregation and thrombus formation, which, in turn, may cause myocardial infarction, stroke, or death[1,2] Activation and expression of the glycoprotein IIb/IIIa receptor (where fibrinogen binds) on platelets leads platelet aggregation and, thrombus formation.[2] When this receptor is activated, circulating fibrinogen binds to it and cross-links with adjacent platelets to create a platelet-fibrinogen matrix. Since platelets have a pivotal role in the pathogenesis of thrombosis after plaque rupture, antiplatelet agents including aspirin, thienopyridines (clopidogrel-Plavix), and the glycoprotein IIb/IIIa inhibitors, reduce adverse events that are associated with plaque rupture.[3] Fibrinolytic agents are infrequently used in the current era with all of the available catheter and pharmacologic agents available. As a result, patients often present for surgery with underlying hemostatic disorders because of preexisting preoperative anticoagulation or antiplatelet therapy.[4] Patients may also present receiving anticoagulation therapy for reasons that include atrial fibrillation, venous thrombosis prophylaxis, prosthetic valves, or for coronary artery disease. All therapies that prevent clot from forming in pathologic states, also interfere with normal hemostasis, an important mechanism to protect patients from exsanguination.[5,6]

Under normal circumstances, there is a complex and delicate equilibrium between blood cells, platelets, coagulation factors, natural inhibitors of coagulation, and the fibrinolytic system.[7] Surgical patients also develop additional acquired hemostatic alterations that contribute to postoperative bleeding, causes that include activation of the coagulation, fibrinolytic, and inflammatory pathways.[8] Even healthy patients can develop massive hemorrhage and/or tissue injury following trauma, surgery, or in an obstetrical population.[9] Hemostasis is also a far more complex system than intrinsic and extrinsic hemostatic activation as taught in medical school.[10,11] Multiple factors are responsible for stopping bleeding including release of tissue factor, and generation of factor VIIa, platelet activation, and the complex cellular and humoral amplification that follows.[11–14] The increasing use of low-molecular weight heparins (LMWH), heparinoids (Orgaran), pentasaccharide (fondaparinux), oral anticoagulants (warfarin and new oral anti-Xa inhibitors), platelet inhibitors (thienopyridines-clopidogrel or IIb/IIIa receptor antagonists), or direct thrombin inhibitors (r-hirudin, bivalirudin, argatroban), also may potentiate bleeding.[15,16] This review will focus on current pharmacologic therapies surgical patients may receive and therapeutic prohemostatic pharmacologic approaches that are used to treat or prevent bleeding.

ANTICOAGULATION: HEPARIN, DERIVATIVES, AND THROMBIN INHIBITORS

Anticoagulation is based on inhibiting both thrombin activation and platelet activation.[16–19] Thrombin is a potent procoagulant that generates fibrin from soluble fibrinogen, activating factors V and VIII, and activating platelets.[11] Activated platelets adhere to injured vascular endothelia, express IIb/IIIa receptors, aggregate, and further enhance generation of thrombin.[20] Because of the complex humoral amplification system linking both hemostatic and inflammatory responses, there are multiple pathways to produce thrombin and prothrombotic effects.[5] Anticoagulation is based on inhibiting both thrombin activation and platelet activation. Thrombin is a potent procoagulant that generates fibrin from soluble fibrinogen, activating factors V and VIII, and activating platelets. Activated platelets adhere to injured vascular endothelia, express IIb/IIIa receptors, aggregate, and further enhance generation of thrombin. Current and future anticoagulants used to prevent clot formation will be considered.

HEPARIN

Heparin, the most commonly used anticoagulant, is isolated from either porcine intestine or from beef lung where it is stored in the mast cell granules. Heparin is an acidic polysaccharide, with sulfate groups important in its anticoagulant activity. Unfractionated heparin is a heterogeneous mixture of 3000 to 30,000 Dalton fragments.[21] Heparin binds to antithrombin III (antithrombin or AT III) increasing the rate of thrombin-AT III complex formation, but also

inhibits other steps in coagulation, through acceleration of the reactions between antithrombin and thrombin or factor Xa.[21] One of the advantages of heparin anticoagulation is that it can be reversed immediately by removing heparin from AT III with protamine.[22] Unfractionated heparin is also an important cause of heparin induced thrombocytopenia.

LOW-MOLECULAR-WEIGHT HEPARINS (LMWH)

Like unfractionated heparin, low-molecular-weight heparins are glycosaminoglycans.[18] Low-molecular-weight heparins are fragments of unfractionated heparin purified to a mean molecular weight of about 5000.[18] Low-molecular-weight heparins have a longer half-life, and dose-independent clearance; the recovery of antifactor Xa activity approaches 100 percent, compared with about 30% with unfractionated heparin. The plasma half-life of low-molecular-weight heparins is longer than unfractionated heparin, ranging 2–4 hours after IV injection, and 3–6 hours after subcutaneous injection.[18]

SYNTHETIC Xa INHIBITORS (FONDAPARINUX AND DANAPAROID)

Fondaparinux is a synthetic antithrombotic agent with specific antiXa activity. Its pharmacokinetic properties allow for a simple, fixed-dose, once-daily regimen of subcutaneous injection, without the need for monitoring. Danaparoid is also a synthetic agent that, although approved for use in the United States, is not currently available and is used in Europe for treating heparin induced thrombocytopenia (HIT).

ORAL ANTICOAGULANTS

Vitamin K antagonists (VKAs) (e.g., warfarin) are the only oral anticoagulants currently available for clinical use. These agents inhibit II, VII, IX and X, key components of the hemostatic cascade, but also inhibit protein C and S. Warfarin has major limitations, including slow onset and offset, a narrow therapeutic window, and metabolism affected by diet, concomitant drugs, and genetic polymorphisms and requires careful monitoring.[23] Ximelgatran was the first oral anticoagulant, but was not approved in the United States because of organ toxicity. Rivaroxaban and apixiban are new oral anticoagulants in advanced stages of clinical development that are directed against the active site of factor Xa or thrombin, the enzymes responsible for thrombin generation and fibrin formation, respectively.[23] Rivaroxaban and apixiban target factor Xa, whereas dabigatran etexilate inhibits thrombin. Rivaroxaban is a small molecule directed against the active site of factor Xa. After oral administration, it is absorbed in the stomach and small intestine with a bioavailability of 60% to 80%. Peak plasma levels are achieved in 3 hours, and the drug circulates with a half-life of 9 hours.[23] Ximelagatran is an oral anticoagulant that has recently been withdrawn in Europe.

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

Heparin-induced thrombocytopenia (HIT) is a serious, yet treatable, prothrombotic disease that develops in 1% to 3% of heparin-treated patients and dramatically increases their risk of thrombosis.[24] The antibodies that mediate HIT, i.e., heparin-platelet factor 4 antibodies, occur more frequently than the overt disease itself and, even in the absence of thrombocytopenia, are associated with increased thrombotic morbidity and mortality.[24] HIT should be suspected whenever the platelet count drops >50% from baseline after starting heparin (or sooner if there was prior heparin exposure) and/or new thrombosis occurs during, or soon after, heparin treatment, with other causes excluded. When HIT is strongly suspected, with or without complicating thrombosis, heparins should be discontinued and a fast-acting, non heparin alternative anticoagulant such as a direct thrombin inhibitor (argatroban or r-hirudin), or danaparoid should be initiated immediately.[24,25]

Even without inducing thrombocytopenia, heparin-PF4 antibodies are clinically important, increasing morbidity or mortality in various patient populations. In patients with, versus without, heparin-PF4 antibodies, irrespective of platelet count, there are significant increases in the length of hospitalization and in-hospital mortality after cardiac surgery[26] and postoperatively in orthopedic surgery patients. Despite their association with long-term adverse effects, circulating heparin-PF4 antibodies are transient. For cardiac surgery, bivalirudin has emerged as the agent most studied in this setting, for on or off pump surgery.[27,28] However, HIT is a prothrombotic disease that carries significant morbidity and mortality and requires immediate therapy.[24] The agents approved for use in HIT are the direct thrombin inhibitors and danaparoid based on current recommendations.[25]

PLATELET INHIBITORS

In patients with myocardial ischemia and or atherosclerotic vascular disease, inhibiting platelet activation is the cornerstone of therapy.[29] Platelet inhibitors/antiplatelet agents should also be considered as anticoagulants, and potentially place the patient at risk for bleeding. The antiplatelet agents differ in their modes of action, potency, onsets of action, and indications. Aspirin irreversibly inhibits platelet cyclooxygenase and thromboxane A2, a platelet activator. Aspirin is a relatively weak antiplatelet agent.[30] Nonsteroidal anti-inflammatory drugs also reversibly inhibit cyclooxygenase. Aspirin, however, irreversibly alters the cyclooxygenase so that platelet pool is destroyed until effective replacement occurs from the bone marrow, however resistance can occur.[31] More potent antiplatelet agents include clopidogrel (Plavix) and IIb/IIIa receptor antagonists (abiximab, tirofiban, eptifibatide). Clopidogrel is more potent than aspirin, and inhibits platelets by selectively and irreversibly binding to the

P2Y12 receptor to inhibit the adenosine diphosphate-dependent pathway of glycoprotein IIb/IIIa-receptor activation although resistance can occur.[30,32,33] Clopidogrel is the major agent used with the least knowledge available about how to manage these patients or monitor its effects.

Antiplatelet therapy with aspirin and clopidogrel is standard care following revascularization by percutaneous coronary intervention with stent insertion. This so-called dual therapy is recommended for up to 4 weeks after intervention for bare-metal stents and for 6–12 months after intervention for drug-eluting stents.[29]

Vincenzi noted a 45% complication rate and a mortality of 20% reported in patients undergoing noncardiac surgery after coronary artery stenting.[34] Discontinuation of antiplatelet drugs appeared to be of major influence on outcome. They prospectively evaluated 103 patients receiving stents within 1 year before noncardiac surgery. Antiplatelet drug therapy was not, or only briefly, interrupted. Heparin was administered to all patients. Of 103 patients, 44.7% suffered complications after surgery; 4.9% of the patients died. All but two (bleeding only) adverse events were of cardiac nature. Most complications occurred early after surgery. The risk of suffering an event was 2.11-fold greater in patients with recent stents (<35 days before surgery) compared with percutaneous cardiac intervention more than 90 days before surgery.[34] The clopidogrel package insert suggests if a patient is to undergo elective surgery and an antiplatelet effect is not desired, it should be stopped 5 days before surgery. However, if patients bleed, therapy or monitoring its effects has not been established. Further, the risk compared to the benefit of stopping clopidogrel, need to be weighted against the risk of stent thrombosis, and the need for surgical intervention as well.

PROCOAGULANT AGENTS

Anesthesiologists are frequently called on to correct coagulopathy in patients who are actively bleeding despite transfusion and other therapies. Further, many patients may also have received any one or combination of the anticoagulant agents just are reviewed. Therefore, clinicians must understand some of the potential procoagulant therapies available to reverse bleeding or anticoagulation therapy.[35] These agents include antifibrinolytics, protamine, desmopressin, fibrinogen, purified protein concentrates, recombinant factor VIIa [rFVIIa]), and topical hemostatic agents, and each will be considered separately.

APROTININ

Aprotinin is a broad-spectrum serine protease inhibitor that inhibits factor XII, kallikrein, plasmin, and PAR1 receptors.[36] In cardiac surgery, multiple randomized, placebo-controlled trials on aprotinin safety and efficacy have demonstrated that aprotinin therapy reduces bleeding (i.e., mediastinal and chest tube drainage) and decreases the need for allogeneic transfusion, and the proportion of patients needing transfusion of allogeneic blood.[37,38] Sedrakyan reported data from 35 CABG trials (n = 3879) confirming that aprotinin reduces transfusion requirements (relative risk 0.61) relative to placebo, with a 39% risk reduction, and was not associated with increased or decreased mortality (relative risk 0.96), myocardial infarction (relative risk 0.85), or renal failure (relative risk 1.01) risk, but it was associated with a reduced risk of stroke (relative risk 0.53). Aprotinin's mechanism of action is complex and may also involve reduction of the inflammatory response.[39] Aprotinin has also been studied in clinical trials in vascular, liver transplantation,[40] and orthopedic surgery.[41]

Over the past 2 years, two articles were published from observational databases that questioned the safety of aprotinin.[42,43] In response to these articles, and to an additional observational study called the i3 Drug Safety study, the United State's Food and Drug Administration (FDA) conducted two meetings to review the risk/benefit profile of Trasylol® (aprotinin injection) to reduce bleeding in coronary artery bypass graft (CABG) surgery, information that can be found at the FDA web site www.FDA.gov. On October 19, 2007, FDA was notified of a Data Safety Monitoring Board's (DSMB) recommendation to stop patient enrollment in an independent Canadian study, the aprotinin treatment group arm of the Blood conservation using antifibrinolytics: A randomized trial in a cardiac surgery population (BART) study. The preliminary findings suggest that, compared to the antifibrinolytic drugs, ε-aminocaproic acid and tranexamic acid, aprotinin increases the risk of death (http://www.fda.gov/cder/drug/early_comm/aprotinin.htm). The BART study was designed to test the hypothesis that aprotinin was superior to ε-aminocaproic acid and tranexamic acid in decreasing the occurrence of massive bleeding associated with cardiac surgery. The study had planned to enroll approximately 3,000 adult Canadian patients who were to undergo various types of cardiac surgery that placed them at high risk for bleeding. Information from the interim analyses performed by the DSMB is limited, but FDA has been informed of the following: the 30-day mortality in the aprotinin group nearly had reached conventional statistical significance at the interim analysis, when compared to either ε-aminocaproic acid or tranexamic acid; a trend toward increased mortality in the aprotinin group had been observed throughout the study; the use of aprotinin was associated with less serious bleeding than either of the comparator drugs; however, more deaths due to hemorrhage had been observed among patients receiving aprotinin; the DSMB concluded that continued enrollment of patients into the aprotinin group was unlikely to significantly change the study findings.

The FDA noted that "additional data collection and analyses must be performed to more thoroughly assess the findings from the BART study." On November 5, 2007, the FDA announced that, at the agency's request, Bayer Pharmaceuticals Corporation had agreed to a marketing suspension of aprotinin (Trasylol) a drug used to control bleeding during heart surgery, pending detailed review of preliminary results from a Canadian study that suggested an increased risk for death ((http://www.fda.gov/bbs/topics/NEWS/2007/NEW01738.html). They noted the "FDA requested the suspension in the interest of patient safety based on the serious nature of the outcomes suggested in the preliminary data. FDA has not yet received full study data but expects to act quickly with Bayer, the study's researchers at the Ottawa Health Research Institute, and other regulatory agencies to undertake a thorough analysis of data to better understand the risks and benefits of Trasylol. There are not many treatment options for patients at risk for excessive bleeding during cardiac surgery. Thus, FDA is working with Bayer to phase Trasylol out of the marketplace in a way that does not cause shortages of other drugs used for this purpose. Until FDA can review the data from the terminated study it is not possible to determine and identify a population of patients undergoing cardiac surgery for which the benefits of Trasylol outweigh the risks. Understanding that individual doctors may identify specific cases where benefit outweighs risk, FDA is committed to exploring ways for those doctors to have continued, limited access to Trasylol."

ANTIFIBRINOLYTIC AGENTS: EPSILON-AMINOCAPROIC ACID (EACA) AND TRANEXAMIC ACID (TXA)

The two synthetic antifibrinolytic agents currently available include the lysine analogs EACA and TXA that competitively inhibits activation of plasminogen to reduce conversion of plasminogen to plasmin, an enzyme that degrades fibrin clots, fibrinogen, and other plasma proteins, including the procoagulant factors V and VIII. Tranexamic acid also directly inhibits plasmin, but higher doses are required than are needed to reduce plasmin formation.[35,44] The lysine analogs have variable effects on reducing bleeding, especially EACA, and published safety data on these agents are limited. Most of the efficacy data for these agents are reported with TXA, and represent small studies or from meta-analyses of pooled previously published data. we reported a study of 100 patients undergoing CABG surgery, and noted that EACA significantly reduced chest tube drainage by 30% compared to the placebo group (EACA, 650^4 261 mL; placebo, 940 $\pm$ 627 mL; $P = 0.003$); however, it did not reduce the need for allogeneic blood transfusion.[45] Although meta-analyses of patients undergoing cardiac surgery suggests that lysine analogs decrease transfusion requirements and the rate of surgical reexploration from 4.7 to 1.9% (RR, 0.44; 95% CI; 0.22–0.90), these are not consistent finding.[46] In the Cochrane database, 18 trials of TXA (1,342 patients show a reduction in the RBC transfusion rate by a relative 34% (RR, 0.66; 95% CI; 0.54–0.81).[47] while there were only 4 trials of EACA (208 patients that do not demonstrate a reduction in transfusions (RR, 0.48; 95% CI; 0.19–1.19).[47]

PROTAMINE

Protamine is the only available therapeutic approach to reverse unfractionated heparin. Protamine is a polypeptide composed of approximately 70% arginine residues, and thus has a high pKa to reverse the acidic molecule heparin by forming a simple acid-base interaction.[48] Protamine and does not reverse low-molecular-weight heparin. Following administration, protamine rapid reverses heparin as noted by return of activated clotting times, but also with marked elevations plasma concentrations of prothrombin fragment 1.2, thrombin-antithrombin III complex, and fibrin monomer.[49] Protamine can cause adverse reactions including anaphylaxis, acute pulmonary vasoconstriction and right ventricular failure, and hypotension.[48] Patients with diabetes are at an increased risk for adverse reactions due to the presence of neutral protamine Hagedorn (NPH), which contains insulin and protamine, causing increased protamine sensitization.[48,50,51] Individuals reported at risk for protamine reactions include patients with vasectomy, multiple drug allergies, and prior protamine exposure.[52]

DESMOPRESSIN

Desmopressin (DDAVP) is the V2 analog of arginine vasopressin that stimulates the release of ultra large von Willebrand factor (vWF) multimers from endothelial cells.[4,53–55] vWF mediates platelet adherence to vascular subendothelium by functioning as a protein bridge between glycoprotein Ib receptors on platelets and subendothelial vascular basement membrane proteins. DDAVP shortens the bleeding time of patients with mild forms of hemophilia A or von Willebrand disease.[53,54] Surgical patients who might benefit from use of DDAVP are not clear. DDAVP is administered IV at a dose of 0.3 mg/kg, and should be given over 15–30 minutes to avoid hypotension.[56,57,58] Most studies have not confirmed the initial reported efficacy during complex cardiac surgery.[56,58–61] Mannucci noted there have been 18 trials of desmopressin in 1295 patients undergoing cardiac surgery that show a small effect on perioperative blood loss (median decrease, 115 mL).[4,62]

RECOMBINANT COAGULATION PRODUCTS

Recombinant coagulation products are used to manage bleeding in patients with hemophilia, von Willebrand's disease (vWD), or acquired inhibitors to antihemophilic factor (e.g., AHF concentrates, factor IX concentrates,

factor VIIa concentrate, factor IX complexes, anti-inhibitor coagulant complexes).[44,63] Recombinant activated factor VIIa (rFVIIa; NovoSeven®, Novo Nordisk) is approved for hemophilia patients with inhibitors to treat bleeding. Currently, rFVIIa is increasingly used off label as a universal prohemostatic agent in complex clinical situations for life threatening hemorrhage.[64]

Recombinant factor VIIa produces a prohemostatic effect by forming a complex with tissue factor (TF) that is expressed at the site of injury, and locally initiates hemostatic activation.[12] TF is a membrane-bound glycoprotein that is expressed on subendothelial cells after tissue injury and loss of endothelial protective mechanisms.[65] Circulating FVIIa accounts for nearly 1% of circulating FVII, and is inactive until bound with TF.[12] When rFVIIa is administered, it binds to TF that activates factor X to factor Xa, leading to the generation of thrombin (FIIa) and resulting fibrin formation and platelet activation.[13] Giving rFVIIa to patients with multiple hemostatic abnormalities may result in added thrombin generation both on the surface of activated platelets but also at the local site of injury.[66] Multiple publications report rFVIIa in surgical patients and cardiac surgical patients including a recent reported analysis of the clinical studies.[64,67,68] Other publications have reported the cessation of bleeding following major trauma with refractory hemorrhage and coagulopathy. The therapeutic dose of rFVIIa in non hemophilia patients are not established.[69] Additional studies are needed to further evaluate dosing, safety and efficacy in perioperative use of rFVIIa. However, guidelines as reported by Goodnough[69] and Despotis[70] for off label use in patients with life threatening hemorrhages.

Controlled clinical trials report the incidence of thrombotic complications among patients who received rFVIIa was relatively low and similar to that among patients who received placebo.[67] However, most case reports administering rFVIIa as rescue therapy include patients who have impaired coagulation, have received multiple transfusions, and are at a high risk for adverse events. The complex role that transfusion therapy has in producing adverse outcomes is increasingly being noted in the literature[71,72] A report using the FDA MED Watch database noted thromboembolic events in patients with diseases other than hemophilia in whom rFVIIa was used off-label basis, and included 54% of the events as arterial thrombosis (e.g., stroke or acute myocardial infarction).[73] Venous thromboembolism (mostly, venous thrombosis or pulmonary embolism) occurred in 56% of patients. In 72% of the 50 reported deaths, thromboembolism was considered the probable cause. It is not clear to what extent the clinical conditions requiring the use of rFVIIa may have contributed to the risk of thrombosis.[4] Other major issues regarding rFVIIa include costs and dosing. Currently, randomized clinical trials are underway to study this agent in various surgical patients. This drug has also seen widespread use in battlefield conditions in Iraq.

REVERSAL OF VITAMIN K ANTAGONISTS ASSOCIATED COAGULOPATHY

Prohemostatic agents are often required to urgently reverse the anticoagulant effect of warfarin in the perioperative setting. Treatments available for reversal include vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), and rFVIIa. Warfarin reversal is becoming a major indication for FFP in some hospitals[74] PCCs were originally developed for repleting factor IX in hemophilia B, and contain standardized amount of FIX along with various amounts of other vitamin K dependent factors (prothrombin, FVII, FX, protein C and S). PCCs are recommended in guidelines as primary treatment for reversal in patients with life-threatening bleeding and an elevated international normalized ratio (INR), and rFVIIa may be considered as an alternative[75] Compared with FFP, evidence suggests PCCs offer quicker INR correction and improved bleeding control; they also have a lower infusion volume and are more readily available without cross matching.[76–78] Although there are historical concerns regarding potential thrombotic risk with PCCs, present-day PCCs are much improved.[78] Clinical data suggest that rFVIIa may provide similar benefits over FFP as PCCs; however, preclinical comparisons suggest that PCCs are more effective in correcting coagulopathy.[78] PCC are being investigated as a therapeutic option in this setting.

TOPICAL HEMOSTATIC AGENTS

Topical hemostatic agents are used extensively by orthopedic, neuro, cardiac, and vascular surgeons to promote hemostasis locally at the site of surgery and vascular. These agents can be classified based on their mechanism of action and include physical or mechanical agents, caustic agents, biologic physical agents, and physiologic agents. Gelatin sponges or Gelfoam® are comprised of purified pork skin gelatin that increases contact activation to help create topical clot. Oxidized regenerated cellulose is also known as Surgicel or Oxycel that works like Gelfoam. Microfibrillar collagen is Avitene®, and is collagen, which is derived from bovine skin. Collagen sponges, these come in a wide variety of different commercial forms, and are derived from bovine Achilles tendon or bovine skin. One of the widely used agents is topical thrombin. Floseal™ is bovine thrombin plus cross-linked gelatin granules mixed together. The problem with bovine thrombin is that antibodies form to this molecule and its contaminant proteins may contribute to hypersensitivity and coagulopathy due to antibody formation.[79] As a result, there are now purified human thrombin (purified from multiple donors) and just recently approved by the FDA a recombinant thrombin for RECOTHROM™ (http://www.zymogenetics.com/products/documents/RECOTHROM_Prescribing_Info.pdf).

THE FUTURE

The potential for bleeding in surgical patients represents an ongoing problem for clinicians. The increasing use of anticoagulation agents creates a need for multiple pharmacologic approaches. The growing use of clopidogrel and newer anticoagulants including the oral Xa inhibitors will continue to pose new paradigms and potential problems in managing surgical patients. Newer therapies including recombinant therapies provide clinicians with the ability to administer key coagulation proteins to treat hemorrhage when standard therapies are ineffective.

Suggested web sites: Bleedingweb.com, HeparinInducedThrombocytopenia.com

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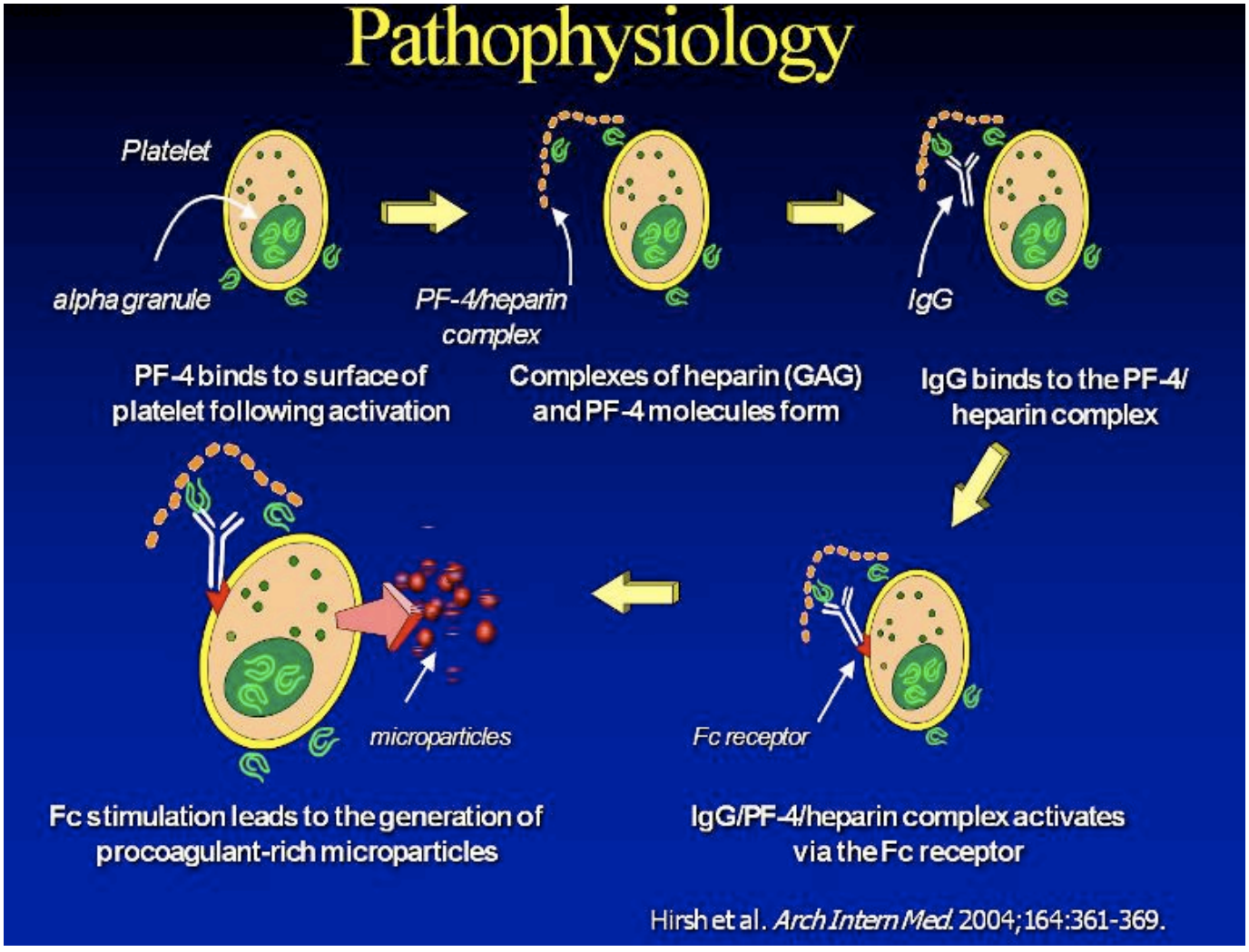

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