Antithrombosis and Intracranial Hemorrhage

Peter Campbell
December 21, 2007
Reversal of Antithrombotic Agents Outline

- I. OAT-ICH
- II. Reversal of LMWH in ICH
- III. Reversal of Thrombolytics in ICH
- IV. Antiplatelet reversal
Antithrombotic Agents: Mechanism of Action

- Anticoagulants: prevent clot formation and extension
- Thrombolytic agents: dissolve existing thrombi
- Antiplatelet drugs: interfere with platelet activity
Clotting Cascade, a quick review

Intrinsic Pathway:
- XII
-XI
- IX
- VIII
- X
- Xa
- Va
- Xa

24 hr half life
48 hr half life
60 hr half life

Common Pathway:
- Pro-II
- Thrombin IIa

Extrinsic Pathway:
- VII
- Tissue Factor
- 4–6 hr half life

Fibrinogen (I)

Fibrin
Warfarin Mechanism of Action

Antagonism of Vitamin K

Vitamin K

Warfarin

Synthesis of Non Functional Coagulation Factors

VII
IX
X
II
An INR of 3.7 to 4.3 results in an increase in the risk of bleeding.

Adapted from: Hylek EM, Singer DE, Ann Int Med 1994;120:897-902
Risk of Intracranial Hemorrhage in Outpatients on Oral Anticoagulation

TABLE 1. Risk Factors for Intracerebral Hemorrhage During Warfarin Anticoagulation

<table>
<thead>
<tr>
<th>Firmly established&lt;sup&gt;12,25–29&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age (especially older than 75 years)</td>
</tr>
<tr>
<td>Hypertension (especially systolic blood pressure ≥160 mm Hg)</td>
</tr>
<tr>
<td>History of cerebrovascular disease</td>
</tr>
<tr>
<td>Intensity of anticoagulation</td>
</tr>
<tr>
<td>Possible</td>
</tr>
<tr>
<td>Concomitant use of aspirin&lt;sup&gt;30&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
<tr>
<td>Asian or Mexican-American ethnicity</td>
</tr>
<tr>
<td>Tobacco smoking</td>
</tr>
<tr>
<td>Heavy alcohol consumption</td>
</tr>
<tr>
<td>Imaging and genetic markers</td>
</tr>
<tr>
<td>Leukoaraiosis detected by brain CT/MRI&lt;sup&gt;29,32&lt;/sup&gt;</td>
</tr>
<tr>
<td>Microbleeds by T2*-weighted MRI</td>
</tr>
<tr>
<td>APOE ε II or IV genotype&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Stroke. 2005;36:1588-1593*
A Common Etiology of ICH
Acquired Coagulopathy — Anticoagulation

- Warfarin indicated in DVT, PE, AF
- Incidence of anticoagulant-associated ICH rose from 5% to 18% of cases of spontaneous ICH in 1990s
- INR 2.5–4.5 increases risk of ICH 10X
- Associated with longer duration of ICH expansion
- Doubles ICH mortality

Reversing Anticoagulation

ICH in any patient on warfarin (with INR $\geq 1.5$) should be considered life-threatening

Goal → Normalize INR to <1.4 ASAP

- Time until initiation of warfarin reversal is the strongest predictor of 24-h coagulation reversal
- Reversal may not occur in 1 of 6 patients

Oral Anticoagulation Therapy (OAT)-ICH

- Anticoagulation to conventional intensities (international normalized ration [INR] 2.5-4.5) increases the risk of ICH 7- to 10-fold, to an absolute rate of nearly 1.8% per year for many stroke-prone patients.
- Life-threatening intracranial hemorrhage, predominantly intracerebral hemorrhage (ICH), is the most serious complication of oral anticoagulant therapy (OAT), with mortality in excess of 50%.
- Early intervention focuses on rapid correction of coagulopathy in order to prevent continued bleeding.
OAT-ICH and hematoma expansion

- OAT-ICH may occur over a longer time frame than in Spontaneous ICH, because of persistent coagulopathy.
- A prolonged natural course of hematoma expansion in OAT-ICH would provide a longer time window for treatment with hemostatic therapy.
Vitamin K

- Concomitant administration of coagulation factors is required.
- At least 6 hours, and often more than 24 hours, to achieve an effective response to vitamin K administration.
- The effect of vitamin K is more rapid when given intravenously.
Vitamin K – IV or SC?

Time Course of Reversal of Anticoagulant Effect of Warfarin by Intravenous and Subcutaneous Phytonadione

Gana Raj, MD; Raninder Kumar, MD; W. Paul McKinney, MD

Mean international normalized ratio (INR) at baseline and 8 and 24 hours after administration of phytonadione in the intravenous (IV) and subcutaneous (SC) groups. P = .70 for difference at baseline; P = .006 at 8 hours; and P = .009 at 24 hours. Mean decrease in INR from baseline for the IV and SC groups is 3.4 and 0.4 (P = .02) at 8 hours and 4.9 and 3.4 (P = .18) at 24 hours.
Vitamin K

- Grade 1C: IV vitamin K supplemented with PCC or rfVIIa is recommended in cases of "life-threatening" bleeding.
- Grade 1A: In patients with mild to moderately elevated INRs without major bleeding vitamin K is to be given orally rather than subcutaneously.
- About SC vitamin K: The response to vitamin K1 administered SC is less predictable compared to oral vitamin K1 and is sometimes delayed.

2.1.4.4. In patients with serious bleeding and elevated INRs, we recommend holding warfarin therapy and giving vitamin K1 (10 mg) by slow IV infusion supplemented with fresh plasma, prothrombin complex concentrate, or recombinant factor VIIa, depending on the urgency of the situation. Vitamin K1 administration can be repeated every 12 h (all Grade 1C).

2.1.4.5. In patients with life-threatening bleeding and elevated INRs, we recommend holding warfarin therapy and administering prothrombin complex concentrate or recombinant factor VIIa supplemented with vitamin K1, 10 mg by slow IV infusion. Repeat this, if necessary, depending on the INR (Grade 1C).
Vitamin K cons

The incidence of anaphylaxis following intravenous phytonadione (vitamin K₁): a 5-year retrospective review
Douglas L. Rieger-Johnson, MD* and Gerald W. Volcheck, MD†

- The incidence of anaphylaxis was 3 per 10,000 doses.
- The incidence of anaphylaxis after IV phytonadione is comparable or slightly less than other drugs known to cause anaphylaxis (IV contrast and penicillins).
- The factor responsible for the anaphylaxis is not phytonadione but the solubilizing vehicle, polyethoxylated castor oil, PEO-CO.
- Literature review: 14 reported cases of anaphylaxis after IV phytonadione in 12 reports from 1966 to 2002.
Reversal with FFP

- FFP contains all coagulation factors in a non-concentrated form
- Standard of an FFP unit is based on its factor VIII content; the actual levels of vitamin K–dependent coagulation factors are not specified and vary considerably
- FFP volumes required to reduce the INR below 1.4 may vary considerably: for example, between 800 and 3500 mL
FFP Cons

- Increased time frame required for INR normalization.
- The large volume required and a rapid transfusion rate can lead to circulatory overload
- Transfusion-related acute lung injury
- Blood-borne infection
- Citrate toxicity
- Allergic reactions
Prothrombin Complex Concentrates

- Contains VII, IX, X, and prothrombin as well as proteins C, S, and Z in a concentrated form.
- Can be given without waiting for compatibility testing and thawing.
- Given via 10min – 1 hour infusion
- Trials with small numbers of patients suggest that PCC corrects a prolonged INR more rapidly than FFP.
The main concerns with PCC-use focus on the potential to induce thrombosis and disseminated intravascular coagulation.

Whether current PCCs are associated with thrombosis has never been substantiated.

Most of the available data suggest that use of PCC in warfarin-associated ICH is relatively safe.

One study reported 3 of 11 (2 with prosthetic heart valves) ischemic strokes in patients treated with PCC for OAT-ICH, but did not report dosages nor composition or PCC used.
rFVIIa

- rFVIIa is FDA approved for the treatment of bleeding in patients with hemophilia.
- 4 small trials with a total of 28 patients on OAT reveals an INR <1.5 minutes after a single dose of rFVIIa.
- Given via bolus infusion
rVIIa Mechanism

**FIGURE 1.** Schematic representation of normal hemostasis. Tissue factor (TF) and factor VII on fibroblasts or monocytes activate cell-based and circulating coagulation factors IX, X, and V to generate thrombin (FIIa) from prothrombin (FII). Thrombin causes degranulation and activation of platelets and circulating coagulation factors (Fig. 2). Reproduced with permission from: Hoffman M, Monroe DM, Roberts HR: Activated Factor VII activates Factors IX and X on the surface of activated platelets: thoughts on the mechanism of action of high-dose activated Factor VII. *Blood Coagul Fibrinol 9* (Suppl 1): S61–S65, 1998.
• Sørensen et al reported 6 patients who had been on OAT and were treated with rFVIIa for central nervous system bleeding. The doses used ranged from 10 to 40 μg/kg and the pretreatment INRs, which ranged from 1.7 to 6.6, were normalized to 1.5 within 10 minutes after rFVIIa administration.
Recombinant factor VIIa

Cons

- Arterial thrombosis (ischemic stroke and myocardial infarction) occurred in 5% of those assigned to rFVIIa vs none assigned to placebo.

The NEW ENGLAND JOURNAL of MEDICINE

 ORIGINAL ARTICLE

Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage

Stephan A. Mayer, M.D., Nikolai C. Brun, M.D., Ph.D., Kamilla Begtrup, M.Sc., Joseph Broderick, M.D., Stephen Davis, M.D., Michael N. Diringer, M.D., Brett E. Skolnick, Ph.D., and Thorsten Steiner, M.D., for the Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators*
By the way... Recombinant factor VIIa Phase III trial for SICH...

- Phase III blinded, randomized trial showed rVIIa decreased hematoma volume, but
  - Death and disability were unchanged at 90 days
- Novo Nordisk pulled application for FDA approval for SICH
PCC vs rVIIa

- No studies have compared rFVIIa infusion with PCC in OAT-ICH.
- Those who advocate rFVIIa for reversal of warfarin induced coagulation defects note that its short half-life makes induction of a thrombogenic state less likely compared with infusion of a PCC.
Timeline of coagulopathy correction in OAT-ICH

- OAT-ICH, the natural course of hematoma expansion is probably more prolonged, perhaps up to 24 or 48 hours, raising the possibility that patients presenting as late as 24 hours (or even later) may benefit from effective hemostatic treatment.
Timeline for various interventions to correct INR

- Vitamin K and fresh frozen plasma (FFP) are standard therapies to reverse warfarin anticoagulation, but neither agent is ideal for emergency anticoagulation reversal.

### TABLE 3. Reversing Anticoagulation in Warfarin-Associated Intracerebral Hemorrhage*

<table>
<thead>
<tr>
<th>Management option</th>
<th>Time to anticoagulation reversal</th>
<th>Comments and cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuing warfarin therapy</td>
<td>5-14 d</td>
<td>Replacement of factors IX and X takes longer than 24 hours, risk of anaphylaxis with intravenous injection, warfarin resistance in higher doses up to 1 wk</td>
</tr>
<tr>
<td>Vitamin K†</td>
<td>6-24 h to correct the INR</td>
<td>Volume (2-4 L to normalize INR) can be prohibitive</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>3-6 h for infusion, typically</td>
<td>Limited availability, cost, variable cofactor content based on manufacturer, potentially prothrombotic</td>
</tr>
<tr>
<td></td>
<td>12-32 h for reversal</td>
<td></td>
</tr>
<tr>
<td>Prothrombin complex concentrate</td>
<td>15 min after 10-min to 1-h</td>
<td>Short half-life, cost, potentially prothrombotic, uncertain safety</td>
</tr>
<tr>
<td></td>
<td>infusion</td>
<td></td>
</tr>
<tr>
<td>Factor VIIa concentrate</td>
<td>15 min after bolus infusion</td>
<td></td>
</tr>
</tbody>
</table>

*INR = international normalized ratio.
†A total of 10 mg intravenously by slow infusion throughout 10 minutes.
Guidelines for OAT-ICH

- There are currently no standardized guidelines for reversal of the anticoagulant effect in patients with OAT-ICH.
- British Committee for Standards in Haematology recommend 5 mg of intravenous or oral vitamin K, and 50 U/kg of PCC or 15 mL/kg of FFP.
- The American Thoracic Society recommends 10 mg of intravenous vitamin K and PCC, without specifying the dose of PCC.
Since no real guidelines exist; some expert recommendations

**Treatment of Warfarin-Associated Intracerebral Hemorrhage: Literature Review and Expert Opinion**

Maria L. Aguilar, MD; Robert G. Hart, MD; Carlos S. Kase, MD; William D. Freeman, MD; Maj Barbara J. Hoeben, PharmD, USAF; Rosa C. Garcia, RPh; Jack E. Ansell, MD; Stephan A. Mayer, MD; Bo Norrving, MD, PhD, FESC; Jonathan Rosand, MD, MSc; Thorsten Steiner, MD; Eelco F. M. Wijdicks, MD; Takenori Yamaguchi, MD; and Masahiro Yasaka, MD

<table>
<thead>
<tr>
<th>Question</th>
<th>Expert 1</th>
<th>Expert 2</th>
<th>Expert 3†</th>
<th>Expert 4†</th>
<th>Expert 5†</th>
<th>Expert 6</th>
<th>Expert 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How can anticoagulation best be reversed (INR=2.5)?</td>
<td>rFVIIa and vitamin K</td>
<td>rFVIIa if deteriorating; FFP and vitamin K otherwise</td>
<td>rFVIIa, FFP, and vitamin K</td>
<td>FFP or PCCs and vitamin K</td>
<td>PCCs and vitamin K</td>
<td>PCCs and vitamin K</td>
<td>PCCs and vitamin K</td>
</tr>
<tr>
<td>2. When should anticoagulation with prosthetic cardiac valve be restarted?</td>
<td>&gt;7 d in most patients‡</td>
<td>&gt;7 d if computed tomogram stable</td>
<td>5-10 d</td>
<td>Low-dose heparin as early as 48 h</td>
<td>10-14 d§</td>
<td>1-3 d</td>
<td>7 d</td>
</tr>
<tr>
<td>3. Should warfarin therapy be restarted for atrial fibrillation?</td>
<td>With reluctance</td>
<td>If prior ischemic stroke</td>
<td>Probably never</td>
<td>If ICH is deep (ie, nonlobar)</td>
<td>If ICH is deep (ie, nonlobar)</td>
<td>If ICH is deep (ie, nonlobar)</td>
<td>In secondary prevention‡</td>
</tr>
</tbody>
</table>
Monitoring Hemostasis in OAT-ICH

- PT-INR is routinely used for regulating OAT as well as monitoring the reversal of its anticoagulant effect.
- Test is sensitive to decreased levels of factor VII and factor X, and prothrombin, but not to decreased levels of factor IX.
- Makris et al found that administration of 800 mL FFP decreased the mean INR from 6.73 to 2.38, whereas the mean factor IX levels were essentially unchanged (from 26.45 IU/dL to 27.36 IU/dL).
- The use of the INR for monitoring patients treated with rFVIIa is also problematic.
- Pharmacological doses of rFVIIa will always lower the INR regardless of the levels of other coagulation factors.
Table 7—Annualized Risk of Thrombotic Complications in the Absence of Anticoagulant Therapy for Selected Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Annualized Thrombosis Risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lone atrial fibrillation</td>
<td>1</td>
</tr>
<tr>
<td>Average risk atrial fibrillation</td>
<td>5</td>
</tr>
<tr>
<td>High-risk atrial fibrillation</td>
<td>12</td>
</tr>
<tr>
<td>Dual-leaflet (St. Jude) aortic valve prosthesis</td>
<td>10–12</td>
</tr>
<tr>
<td>Single-leaflet (Bjork-Shiley) aortic valve prosthesis</td>
<td>23</td>
</tr>
<tr>
<td>Dual-leaflet (St. Jude) mitral valve prosthesis</td>
<td>22</td>
</tr>
<tr>
<td>Multiple St. Jude prostheses</td>
<td>91</td>
</tr>
</tbody>
</table>
Restarting Anticoagulation After ICH
ACC/AHA 2006 Guideline

• Discontinue anticoagulants and antiplatelets for at least 1–2 weeks

• If required, resume oral anticoagulation after 3–4 weeks (rigorous monitoring, INR in lower range); if anticoagulation is needed sooner after ICH, IV heparin (with PTT 1.5 to 2.0 times normal) or LMWH may be better acute therapy than oral warfarin.

• Higher risk of recurrent ICH if anticoagulation resumed in lobar ICHs, microbleeds, and suspected CAA.

Conclusions from OAT-ICH

• Current management of OAT-ICH is varied and not based on evidence from randomized controlled trials.

• Use IV Vitamin K, SC is the least effective route of administration.

• Consider PCC or rFVIIa with respect to risk of thrombosis.
Reversal of patients treated with therapeutic doses of LMWH

- The reversal of LMWH has not been well-defined.
- The package insert for tinzaparin (Innohep®), enoxaparin (Lovenox®), and dalteparin (Fragmin®) all recommend reversal of LMWH anti-coagulant effects with protamine sulfate.
- Protamine reverses the prolonged aPTT caused by enoxaparin and dalteparin in animal studies, but fails to reverse the anti-Xa effect.
LMWH and reversal with protamine

- Reduced sulphate charge density is the primary reason that LMWH are not completely neutralized by protamine sulphate.

Mechanisms responsible for the failure of protamine to inactivate low-molecular-weight heparin

Fig 1. Titration of antifactor Xa activity with protamine. Unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) were assayed for the ability to catalyse inhibition of factor Xa by antithrombin in the presence of various amounts of protamine sulphate (prepared from either the salmon or the herring). Results were compared with standard curves from plasmas containing known amounts of either UFH or LMWH reference heparins in order to determine the units of activity per ml of plasma. The antifactor Xa activity remaining was calculated as a percentage of the activity observed for the heparins when no protamine sulphate was added.
Reversal of patients treated with LMWH

- Two commercially available varieties of LMWH, tinzaparin (Innohep®) and dalteparin (Fragmin®) have higher degrees of sulfonation compared with enoxaparin (Lovenox®).
- These appear to be more susceptible to protamine reversal.

<table>
<thead>
<tr>
<th>Heparin</th>
<th>% Anti-factor Xa Activity Neutralized by Protamine</th>
<th>Total sulphate (% SO4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>54.2</td>
<td>32.3 ± 0.2</td>
</tr>
<tr>
<td>Fraxiparine</td>
<td>57.7</td>
<td>34.7 ± 0.7</td>
</tr>
<tr>
<td>Clivarain</td>
<td>51.4</td>
<td>34.8 ± 0.2</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>74.0</td>
<td>36.8 ± 0.1</td>
</tr>
<tr>
<td>Tinzaparint</td>
<td>85.7</td>
<td>39.0 ± 0.1</td>
</tr>
<tr>
<td>SSLMWH</td>
<td>100</td>
<td>41.9 ± 1.1</td>
</tr>
</tbody>
</table>
Reversal of ICH in the setting of thrombolytics

- Thrombolytic therapy with plasminogen activators is a highly effective modality for achieving both vascular reperfusion and clinical benefit in patients with arterial occlusions.

- Patients treated for ischemic stroke are especially prone to symptomatic or lethal ICH, with an occurrence of 6.4-16% receiving IV tPA or streptokinase.

- Very little clinical data exists regarding the reversal of these drugs, since the half-life ranges from 5-20 minutes depending on the drug.
ICH S/P Thrombolytic

- One study suggested treatment with antifibrinolytic (ε-aminocaproic acid) and fibrinogen if thrombolytic agent is thought to be present at time of evaluation.

- Otherwise, symptomatic treatment focused around ICP and blood pressure management/surgical evacuation as indicated.
Antiplatelets

Platelet/Fibrin Clot
Events Leading to Thrombus Formation

- Adhesion
- Activation
- Aggregation
Platelet Inhibitors

- ASA
- Clopidogrel (Plavix), Ticlid
- Aspirin/Dipyridamole (Aggrenox)
- ReoPro (abciximab)
Platelet Activation Pathways

- Collagen
- Thrombin
- Epinephrine
- ADP

- Arachidonic acid
- TxA2

GP IIb/IIIa
Effect of Antiplatelets on ICH overall outcomes

- In the Stroke Literature...
- Aspirin doubled the 3-month mortality of ICH patients compared with nonusers

*Stroke. 2006;37:129-133*
Effect of Antiplatelets on ICH overall outcomes

- In the trauma literature...
- Patients on ASA or plavix have an overall mortality rate of 23%, approximately a threefold increase over the rate for a matched control group.

Fig. 3. Patient outcomes. Nsg Home, discharge to nursing home; Rehab, inpatient rehabilitation unit; ECF, subacute or long-term extended care facility. No significant differences were found on χ² analysis between type of discharge. *Death was significant with a 23% mortality rate in the study group and 8.9% in the control group; p = 0.016.

Effects of Antiplatelet Agents on Outcomes for Elderly Patients With Traumatic Intracranial Hemorrhage

Christina Ohrn, MD, Alfred Mina, MD, Greg Howell, MD, Holly Bair, RN, and Phillip Bendick, PhD

The Journal of TRAUMA® Injury, Infection, and Critical Care
Reversal of Antiplatelets

- The classic modality for treatment of platelet associated coagulopathy is platelet transfusion.
- True reversal of this coagulopathy by platelet transfusion has never been demonstrated.
Reversal of Antiplatelets-DDAVP

- Desmopressin has hemostatic effects by increasing the plasma levels of coagulation factor VIII and von Willebrand factor.
- Desmopressin significantly accelerated thrombus formation in aspirin-treated animals (rat model).
- Overall platelet function was significantly increased by desmopressin.

Effects of desmopressin on thrombogenesis in aspirin-induced platelet dysfunction

*British Journal of Haematology, 2002, 117, 658–663*

Frank W. Peter,1 Claudia Benkovic,1 Thomas Muehlberger,1 Peter M. Vogt,1 Heinz H. Homann, Cornelius Kuhnen,2 Albrecht Wiebalck3 and Hans U. Steinau1 1Department of Plastic Surgery, 2Institute of Pathology, and 3Department of Anaesthesiology, Bergmannsheil University Hospital, Bochum, Germany

![Fig 4. Overall platelet function. The parameter was altered by aspirin and by desmopressin. Significant differences (*) of the aspirin group versus all the other groups.](image-url)
Reversal of Antiplatelets- DDAVP

- Known elimination half-life is 4-5 hours
- Desmopressin's effect on platelet function only lasts for about 3 hours
- Placebo bleeding time was 730 s
- Aspirin bleeding time was significantly longer, 972 s (P < 0.0166)
- Sixty minutes after desmopressin,
  - the bleeding time had shortened significantly; in the placebo period to 475 s (P < 0.0051)
  - In the aspirin period to 537 s (P < 0.0093).
- In the aspirin period the bleeding time was still shortened after 4 h as compared with baseline (P < 0.0249), but after 6 h it was no longer significantly different (P > 0.2845)

Effect kinetics of desmopressin-induced platelet retention in healthy volunteers treated with aspirin or placebo

S. LETHAGEN,* L. OLOFSSON,† K. FRICK,* E. BERNTORP* and S. BJÖRKMAN†
*Department for Coagulation Disorders, University of Lund and †Hospital Pharmacy, University Hospital, S-205 02 Malmö, Sweden

Fig. 3. Bleeding times in all 10 subjects before and after infusion of desmopressin at 0 h, after previous treatment with placebo and aspirin, respectively. Individual curves (dashed) and the median curves (continuous) are shown for placebo and aspirin treatments, respectively.

Haemophila (2000), 6, 15–20
Oral antiplatelet drugs

- **Aspirin**
  - Irreversible inhibitor of cyclooxygenase (COX) which prevents formation of the platelet-aggregating substance thromboxane A$_2$.

- **Clopidogrel**
  - Blocks platelet aggregation by inhibition of ADP receptor on the platelet membrane.
Aspirin and other NSAIDS

- Acetylsalicylic acid (ASA) irreversibly blocks the platelet COX system, preventing formation of thromboxane A2 and inhibiting platelet aggregation for the life of the affected platelet (approximately 10 days).
- Transfusion of five random donor platelet units or their equivalent is recommended to provide sufficient unaltered platelets to support clot formation.
- DDAVP may have a beneficial short-term effect.
ADP Inhibitors

- Clopidogrel (Plavix) and Ticlopidine (Ticlid) alter platelet aggregation via irreversible noncompetitive inhibition of the ADP surface binding site and reduction of ADP release from activated platelets.
- Because of this differing mechanism of action, they are additive to the antiplatelet effects of ASA and are often concurrently prescribed.
- Platelet transfusion is recommended.
- DDAVP may have a beneficial short-term effect.
Aprotonin Decreases Postoperative Bleeding and Number of Transfusions in Patients on Clopidogrel Undergoing Coronary Artery Bypass Graft Surgery
A Double-Blind, Placebo-Controlled, Randomized Clinical Trial

Jan van der Linden, MD, PhD; Gabriella Lindvall, MD; Ulrik Sartipy, MD

Background—Clopidogrel, an irreversible platelet inhibitor, is used to treat patients with unstable angina. These patients often present for coronary artery bypass graft surgery (CABG) and are at increased risk for perioperative bleeding. The current investigation evaluates the impact of aprotonin on bleeding and transfusion requirements in clopidogrel-treated patients undergoing CABG.

Methods and Results—Seventy-five consecutive patients with unstable angina, administered clopidogrel <5 days before CABG, were randomized. Using a double-blind design, patients received full-dose aprotonin (n = 37) or saline (n = 38). Elapsed times between the last dose of clopidogrel and start of the operation were similar between the 2 groups [apronitin, 58±28 hour (mean± SD); control, 54±27 hour; P=0.86], as were age (apronitin, 66.4±10 years; control, 68.3±10 years; P=0.51), number of distal anastomoses (apronitin, 3.6±1.0; control, 3.7±1.0; P=0.79), operative times (apronitin, 192±48 minutes; control, 200±53 minutes; P=0.55), and lowest intraoperative hemoglobin level (apronitin, 87±14 g/L; control, 88±14 g/L; P=0.60). Postoperative bleeding was 760±350 mL in aprotinin-treated patients versus 1200±570 mL (P<0.001) in control. During the hospital stay, patients in the aprotinin group received 1.2±1.5 and 0.1±0.4 U of erythrocytes and platelets, respectively, versus 2.8±3.2 (P=0.02) and 0.9±1.4 (P=0.002) units in the control. In the aprotinin group, 53% of patients received transfusions, whereas 79% of controls were exposed to blood products (P=0.02).

Conclusions—Intraoperative aprotinin decreases postoperative bleeding and the number of transfusions in patients undergoing CABG and treated with clopidogrel <5 days before surgery. (Circulation. 2005;112[suppl 1]:I-276–I-280.)
Apoprotinin

- Preserves of platelet adhesiveness via kallikrein/kinin inhibition.
- Has been studied in numerous cardiac and orthopedic populations.
- Risk of renal failure likely restricts its use to high-risk CABG patients only.
Parenteral antiplatelet drugs

- Glycoprotein IIb/IIIa Inhibitors
  - Abciximab (Reopro®), eptifibatide (Integrilin®), tirofiban (Aggrastat®)
  - Prevent fibrinogen binding to Gly IIb/IIIa receptor and block platelet aggregation producing profound platelet inhibition.
  - Most commonly used in conjunction with percutaneous coronary interventions (PCI).
  - Treatment usually combines a loading bolus followed by an infusion.
Glycoprotein (GP) IIb/IIIa Inhibitor Reversal

- Bleeding is the most frequent adverse event.
- Withholding the medication allows a return of normal platelet function, but requires approximately 48 hours for abciximab and 4 to 8 hours for the others.
- After infusion, platelet administration may be more effective little drug is freely circulating to attach to new platelets.
- There are currently no recommendations on how to treat such patients.
Glycoprotein (GP) IIb/IIIa Inhibitor Reversal

• Because these agents leave the GP receptor unharmed, platelet transfusion increases the proportion of unaffected platelets and is the primary intervention.
Glycoprotein (GP) IIb/IIIa Inhibitor Reversal

- Some evidence that DDAVP may serve as the best means of reversal in an emergency situation.
- Combined use of Platelet transfusion and DDAVP additively enhances recovery of normal PLT function after eptifibatide infusion compared to DDAVP alone.
Geaux Tigers!