Update on Oral Anticoagulants and Reversal Strategies

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Dabigatran - Pradaxa (direct thrombin inhibitor)

- Thromboembolism (e.g., stroke) prevention in nonvalvular A fib (150 mg BID) For patients with CrCl 15-30 mL/min: 75 mg orally, twice daily (no data with this dose).

- VTE prevention post-hip replacement (220 mg once daily x 28 to 35 days. If started on day of surgery [1 to 4 hrs postop, assuming hemostasis achieved], initial dose is 110 mg).
  - Post-hip/knee replacement: comparable to enoxaparin for prevention of VTE & mortality (combined endpoint); comparable major bleeding
  - Prophylaxis for at least 10 to 14 days after hip or knee replacement, and up to 35 days, especially after hip replacement. Chest 2012;141(Suppl 2):e278S-e325S.

Dabigatran - Pradaxa (direct thrombin inhibitor)

- DVT/PE treatment (following 5 to 10 days' treatment with a parenteral anticoagulant)/prevention of recurrence (150 mg BID). (Start 0 to 2 hours before the next dose of parenteral anticoagulant would have been due, or at the time of discontinuation of heparin drip.)
  - For VTE treatment, continue for at least three months
  - Cost 150 mg x 60 $379.00 GoodRx.com
Rivaroxaban – Xarelto (Xa inhibitor)

- Thromboembolism (e.g., stroke) prevention in nonvalvular A fib (20 mg once daily with evening meal to improve absorption)
  - A fib indication requires renal dosing (15 mg with evening meal for CrCl 15 to 50 mL/min)
  - Cost 10, 15 and 20 mg x 30 $389.00 for all GoodRx.com

Rivaroxaban – Xarelto (Xa inhibitor)

- VTE prevention post-hip or knee replacement (10 mg once daily for 35 days [hip] or 12 days [knee] starting 6 to 10 hrs post-op, assuming hemostasis achieved)
  - Post-hip/knee replacement: prevents 4 more VTEs compared to LMWH and causes 9 more serious bleeds per 1000 patients treated for 14 days. Chest 2012;141(Suppl 2):e278s-e325s.
- DVT/PE treatment/prevention of recurrence (15 mg twice daily for 3 weeks, then 20 mg once daily, with food to improve absorption)

Apixaban – Eliquis (Xa inhibitor)

- Thromboembolism (e.g., stroke) prevention in nonvalvular A fib (5 mg BID; 2.5 mg BID for patients with two or more of the following: age 80 years and older, weight 60 kg or less, serum creatinine 1.5 mg/dL or greater)
  - A fib: for every 1000 patients treated per year, apixaban prevents three more strokes, avoids ten major bleeds, and prevents four deaths compared to warfarin. N Engl J Med 2011;365:981-92
- VTE prevention post-hip or knee replacement (2.5 mg twice daily for 35 days [hip] or 12 days [knee] starting 12 to 24 hrs post-op)
  - Post-hip/knee replacement: at least as effective as enoxaparin for preventing VTE; comparable bleeding.
  - Prophylaxis for at least 10 to 14 days after hip or knee replacement, and up to 35 days, especially after hip replacement (Knee: Lancet 2010;375:807-15. Hip N Engl J Med 2010;363:2487-98)
Apixaban – Eliquis (Xa inhibitor)

- DVT/PE treatment (10 mg BID for seven days, then 5 mg BID)
  - For VTE treatment, continue for at least three months.
  - Benefit of extended use may not outweigh risk in patients with high bleeding risk.
  - DVT/PE prevention of recurrence (2.5 mg BID after at least six months of treatment)
  - Cost 2.5 and 5 mg x 60 $389.00 GoodRx.com

Edoxaban – Savaysa (Xa inhibitor)

- Thromboembolism (e.g., stroke) prevention in nonvalvular A fib in patients with CrCl <95 mL/min (60 mg once daily).
  - A fib: about as effective as warfarin if CrCl <95 mL/min, with lower risk of major bleeding (six fewer bleeds per 1000 patients per year). N Engl J Med 2013;369:2093-104
  - For A fib, does not work as well as warfarin in patients with normal renal function; dose may not be high enough.

Edoxaban – Savaysa (Xa inhibitor)

- DVT/PE treatment (following 5 to 10 days’ treatment with a parenteral anticoagulant) (60 mg once daily; 30 mg once daily if body weight <60 kg).
  - For VTE treatment, continue for at least three months.
  - Cost 15, 30 and 60 mg x 30 $325.00 GoodRx.com
Warfarin - Coumadin

- Prevention/treatment of thromboembolism due to A fib or prosthetic heart valve
  - A fib: prevents stroke (NNT = 32 vs placebo for one year to prevent one stroke). Chest 2008;133(Suppl 6):546S-592S

- Secondary prevention post-MI
  - Post-MI: reduces reinfarction, stroke, and mortality (INR 2.8 to 4.8); 29 warfarin (INR 2 to 2.5) plus aspirin (75 mg once daily) superior to aspirin alone or warfarin (INR 2.8 to 4.2) alone (combined endpoint). N Engl J Med 2002;347:969-74.

- Prevention/treatment of venous thrombosis/PE

- Post hip/knee replacement:
  - prevents 3 fewer major clots compared to LMWH and causes two more fatal bleeds per 1000 patients treated for 14 days. Chest 2012;141(Suppl 2):e278S-e325S
  - Cost $15.00 generic x 30 GoodRx.com

**CHADS2 -> CHA2DS2-VASc**

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2014 AHA/ACC/HRS Atrial Fibrillation Guideline

Summary of Recommendations for Prevention of Thromboembolism/Stroke in Patients With AF

- Antithrombotic therapy selection based on risk of thromboembolism as assessed with the CHA2DS2-VASc score
- With prior stroke, TIA, or CHA2DS2-VASc score ≥2, oral anticoagulants recommended. Options include:
  - Warfarin (IA)
  - Dabigatran, rivaroxaban, or apixaban (IB)

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• Journal of the American College of Cardiology (2014), doi: 10.1016/j.jacc.2014.03.021
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2014 AHA/ACC/HRS Atrial Fibrillation Guideline

- Little benefit with aspirin: This quote says a lot. "No studies, with the exception of the [Stroke Prevention in Atrial Fibrillation-1] SPAF-1 trial, show benefit for aspirin alone in preventing stroke among patients with AF."
  - urged to question the common practice of using aspirin in low-risk patients. "aspirin has not been studied in a low-risk AF population"
- AF ablation has been moved to first-line status for both paroxysmal and persistent AF patients. This welcome change aligns these guidelines with those from Europe
  - AF ablation should not be performed in patients who cannot be treated with anticoagulants, and AF ablation should not be done with the sole intent of avoiding anticoagulation.

Am Acad Neurology Evidence-based guideline update: Prevention of stroke in nonvalvular atrial fibrillation

- These guidelines have been endorsed by the World Stroke Organization
- For patients with NVAF, which therapies that include antithrombotic medication, as compared with no therapy or with another therapy, reduce stroke risk and severity with the least risk of hemorrhage?
  - In patients who have NVAF but no risk factors, the absolute risk of major bleeding (3%/year) is larger than the absolute reduction in stroke from anticoagulation (1.3%/year).

Neurology® 2014;82:716–724
Selection of a Specific Oral Anticoagulant

To reduce the risk of stroke or subsequent stroke in patients with NVAF judged to require oral anticoagulants, clinicians should choose one of the following options:

- Warfarin, target international normalized ratio (INR) 2.0–3.0
- Dabigatran 150 mg twice daily (if creatinine clearance [CrCl] > 30 mL/min)
- Rivaroxaban 15 mg/day (if CrCl 30–49 mL/min) or 20 mg/day
- Apixaban 5 mg twice daily (if serum creatinine < 1.5 mg/dL) or 2.5 mg twice daily (if serum creatinine > 1.5 and < 2.5 mg/dL, and body weight < 60 kg or age at least 80 years [or both])

Level B

Gi bleeding risk

- Clinicians might offer apixaban to patients with NVAF and GI bleeding risk who require anticoagulant medication. Level C

INR monitoring

- Clinicians should offer dabigatran, rivaroxaban, or apixaban to patients unwilling or unable to submit to frequent periodic testing of INR levels.

Neurology® 2014;82:716–724
Am Acad Neurology Evidence-based guideline update:
Prevention of stroke in nonvalvular atrial fibrillation

Patients unsuitable for warfarin

• Clinicians should offer apixaban to patients unsuitable for being treated, or unwilling to be treated, with warfarin. Level B

• Where apixaban is unavailable, clinicians might offer dabigatran or rivaroxaban. Level C

• Where oral anticoagulants are unavailable, clinicians might offer a combination of aspirin and clopidogrel. Level C

Neurology® 2014;82:716–724

Antithrombotic Therapy for VTE Disease

Choice of Long-Term (First 3 Months) and Extended (No Scheduled Stop Date)
Anticoagulant

• 1. In patients with proximal DVT or pulmonary embolism (PE), we recommend long-term (3 months) anticoagulant therapy over no such therapy (Grade 1B).
  – CHEST 2016; 149(2):315-352

Antithrombotic Therapy for VTE Disease

• *2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B). (NOTE: order of listing for meds is based upon the chronology of publication of the phase 3 trials in VTE not order of preference)
  – * indicates either a new or changed recommendation since 9th Ed
  – CHEST 2016; 149(2):315-352
3. In patients with DVT of the leg or PE and cancer (“cancer-associated thrombosis”), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C).

4. In patients with DVT of the leg or PE who receive extended therapy, we suggest that there is no need to change the choice of anticoagulant after the first 3 months (Grade 2C).

5. In patients with a proximal DVT of the leg or PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (e.g., 6, 12, or 24 months) Grade 1B), or (iii) extended therapy (no scheduled stop date) (Grade 1B).
6. In patients with a proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B) and (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B), and recommend treatment for 3 months over extended therapy if there is a high risk of bleeding (Grade 1B).

CHEST 2016; 149(2):315-352

7. In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor, we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C), we recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B), and we recommend treatment with anticoagulation for 3 months over extended therapy (no scheduled stop date) (Grade 1B).

CHEST 2016; 149(2):315-352

8. In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B), and we recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B).

CHEST 2016; 149(2):315-352
9. In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).

– CHEST 2016; 149(2):315-352

10. In patients with a second unprovoked VTE and who have a (i) low bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months (Grade 1B); (ii) moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B); or (iii) high bleeding risk, we suggest 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 2B).

– CHEST 2016; 149(2):315-352

11. In patients with DVT of the leg or PE and active cancer (“cancer-associated thrombosis”) and who (i) do not have a high bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B), or (ii) have a high bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B).

– CHEST 2016; 149(2):315-352
Aspirin for Extended Treatment of VTE

• *12. In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE (Grade 2B).
  – Because aspirin is expected to be much less effective at preventing recurrent VTE than anticoagulants, we do not consider aspirin a reasonable alternative to anticoagulant therapy in patients who want extended therapy.
  – CHEST 2016; 149(2):315-352

Whether and How to Anticoagulate Isolated Distal DVT

• 13. In patients with acute isolated distal DVT of the leg and (i) without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over anticoagulation (Grade 2C) or (ii) with severe symptoms or risk factors for extension, we suggest anticoagulation over serial imaging of the deep veins (Grade 2C).
  – CHEST 2016; 149(2):315-352

• 14. In patients with acute isolated distal DVT of the leg who are managed with anticoagulation, we recommend using the same anticoagulation as for patients with acute proximal DVT (Grade 1B).
  – CHEST 2016; 149(2):315-352
15. In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we (i) recommend no anticoagulation if the thrombus does not extend (Grade 1B), (ii) suggest anticoagulation if the thrombus extends but remains confined to the distal veins (Grade 2C), and (iii) recommend anticoagulation if the thrombus extends into the proximal veins (Grade 1B).

CHEST 2016; 149(2):315-352

*29. In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily (at least 1 month) (Grade 2C).

CHEST 2016; 149(2):315-352

*30. In patients who have recurrent VTE on longterm LMWH (and are believed to be compliant), we suggest increasing the dose of LMWH by about one-quarter to one-third (Grade 2C).

CHEST 2016; 149(2):315-352
Warfarin Bleeding

• Serious bleeding – Patients with serious or life-threatening bleeding and a prolonged INR (eg, >2) should have warfarin withheld and should receive vitamin K (10 mg) by slow intravenous infusion, along with a rapid reversal agent. We suggest a 4-factor prothrombin complex concentrate (PCC) rather than Fresh Frozen Plasma (FFP) (Grade 2B). Vitamin K administration can be repeated every 12 hours for persistently elevated INR.

Warfarin Bleeding

• Surgery – Patients who require emergent (eg, same day) surgery and warfarin reversal should have warfarin held and should receive vitamin K and a rapid reversal agent as done for serious bleeding. We suggest a 4-factor PCC rather than FFP (Grade 2B).

• Individuals who can wait 24 hours and require warfarin reversal may be managed by holding warfarin and giving vitamin K without the use of a PCC.

Warfarin Bleeding

• INR >9 without bleeding – warfarin therapy should be held and 2.5 to 5 mg of vitamin K administered orally. Nonbleeding patients should not be given PCC or FFP solely to correct a supratherapeutic INR, as these products have associated risks. The INR is monitored daily or every other day, and warfarin is resumed at a lower dose once the INR is in the therapeutic range.

• INR 5 to 9 without bleeding – without bleeding, warfarin is held temporarily (eg, one or two doses) with or without administration of a small dose of oral vitamin K (eg, 1 to 2.5 mg). Warfarin generally is resumed at a lower dose once the INR is in the therapeutic range.

• INR <5 without bleeding – one or more doses of warfarin may be omitted and/or the dose is reduced slightly. If the INR elevation is minimal and/or expected to be transient, no dose reduction may be necessary. Additional therapies such as vitamin K are not indicated in this setting.
FDA Grants “Breakthrough” Status to Idarucizumab Antidote for Dabigatran

- June 26, 2014 the FDA has granted Breakthrough Therapy Designation to Idarucizumab by BI, a fully humanized antibody fragment or Fab being studied as a specific antidote for dabigatran – Pradaxa
  - Data from a phase I study presented at the American Heart Association Scientific Sessions in 2013 showed that idarucizumab was able to achieve immediate, complete and sustained reversal of dabigatran-induced anticoagulation in healthy humans.
  - A global phase III study, RE-VERSE AD™, is underway in patients taking dabigatran who have uncontrolled bleeding or require emergency surgery or procedures (NCT02104947).

Idarucizumab - Praxbind® by BI

- FDA approved 10-16-2015 Idarucizumab (Praxbind) is a humanized monoclonal antibody fragment (Fab) indicated in patients treated with dabigatran (Pradaxa®) when reversal of the anticoagulant effects of dabigatran is needed:
  - For emergency surgery/urgent procedures
  - In life-threatening or uncontrolled bleeding
  - Administered as a 5 Gram IV infusion or IV bolus, provided as two separate vials each containing 2.5 g/50 mL idarucizumab

Idarucizumab - Praxbind®

- Idarucizumab is a humanized monoclonal antibody fragment (Fab) derived from an IgG1 isotype molecule, whose target is the direct thrombin inhibitor dabigatran. Using recombinant expression technology, idarucizumab is produced in a well characterized recombinant (mammalian) CHO cell line and is purified using standard technology.
- Idarucizumab is a specific reversal agent for dabigatran. It is a humanized monoclonal antibody fragment (Fab) that binds to dabigatran and its acylglucuronide metabolites with higher affinity than the binding affinity of dabigatran to thrombin, neutralizing their anticoagulant effect.
Idarucizumab - Praxbind®

• This indication is approved under accelerated approval based on a reduction in unbound dabigatran and normalization of coagulation parameters in healthy volunteers. Continued approval for this indication may be contingent upon the results of an ongoing cohort case series study.
  – an ongoing single cohort case series trial with dabigatran-treated patients who have life-threatening or uncontrolled bleeding, or who require emergency surgery or urgent procedure (RE-VERSE AD).

Idarucizumab - Praxbind®

• An interim analysis of the ongoing RE-VERSE-AD trial included data for 123 patients: 66 patients with serious bleeding (Group A) and 57 requiring an urgent procedure (Group B). Approximately half of the patients in each group were male. The median age was 77 years and the median creatinine clearance was 55 mL/min.
  • Among the 90 patients with available data, the median maximum reversal of the pharmacodynamic anticoagulant effect of dabigatran as measured by ECT or dTT in the first 4 hours after administration of 5 g idarucizumab was 100%, with most patients (>89%) achieving complete reversal.
    – Reversal of the pharmacodynamics effects was evident immediately after administration.
    – Results for Groups A and B were similar.
  – In a limited number of patients, between 12 and 24 hours after administration of 5 g idarucizumab, elevated coagulation parameters (e.g., aPTT or ECT) have been observed.

Idarucizumab - Praxbind®

• Based upon additional data from RE-VERSE-AD presented 2-19-2016 at the International Stroke Conf in LA there were 18 patients (11 men and 7 women, avg age 79) who suffered an intracranial bleed while taking dabigatran who were given idarucizumab two 2.5 Gm bolus infusions no more than 15 min apart. The primary endpoint was maximum reversal of the anticoagulant effect of dabigatran and it was achieved in 100% of the 18 patients with a brain bleed and was not associated with any tendency for increased clotting.
Idarucizumab - Praxbind®

WARNINGS AND PRECAUTIONS

• Thromboembolic Risk: Patients being treated with dabigatran therapy have underlying disease states that predispose them to thromboembolic events. Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. To reduce this risk, resumption of anticoagulant therapy should be considered as soon as medically appropriate.

• Re-elevation of Coagulation Parameters: In a limited number of patients in the clinical program, between 12 and 24 hours after administration of 5 g idarucizumab, elevated coagulation parameters (e.g., activated partial thromboplastin time (aPTT) or ecarin clotting time (ECT)) have been observed.

• If reappearance of clinically relevant bleeding together with elevated coagulation parameters is observed after administration of 5 g PRAXBIND, administration of an additional 5 g dose of PRAXBIND may be considered. Similarly, patients who require a second emergency surgery/urgent procedure and have elevated coagulation parameters may receive an additional 5 g dose of PRAXBIND.

WARNINGS AND PRECAUTIONS (Continued)

• Hypersensitivity Reactions: There is insufficient clinical experience with PRAXBIND in patients to evaluate risk of hypersensitivity to idarucizumab. In clinical studies adverse events possibly indicative of hypersensitivity reactions where a possible relationship could not be excluded were reported. If an anaphylactic reaction or other serious allergic reaction occurs, immediately discontinue administration of PRAXBIND and institute appropriate treatment.

• Risks of Serious Adverse Reactions in Patients with Hereditary Fructose Intolerance due to Sorbitol Excipient: In patients with the condition of hereditary fructose intolerance who have received parenteral administration of sorbitol, serious adverse reactions, including fatal reactions, have been reported. Reactions have included hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, acute liver failure with breakdown of excretory and synthetic function.

  – The recommended dose of PRAXBIND contains 4 g sorbitol as an excipient. When prescribing PRAXBIND to patients with hereditary fructose intolerance consider the combined daily metabolic load of sorbitol/fructose from all sources, including PRAXBIND and other drugs containing sorbitol.

Idarucizumab - Praxbind®

• How supplied: Carton containing two 2.5 g/50 mL vials. Cost: ~$3500.00

• Storage: Refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not shake.

  – Prior to use, the unopened vial may be kept at room temperature 25°C (77°F) for up to 48 hours, if stored in the original package in order to protect from light, or up to 6 hours when exposed to light.

  – Once solution has been removed from the vial, administration should begin promptly or within 1 hour.

  – An existing IV line must be flushed with sterile 0.9% Sodium Chloride Injection, USP solution prior to infusion.
Anti Xa Reversal Agent

- Feb 26, 2015 the FDA announced that they had granted Portola Pharmaceuticals Breakthrough Therapy status and -tagged andexanet alfa an Orphan Drug for reversing the anticoagulant effect of direct or indirect Factor Xa inhibitors in patients experiencing a serious uncontrolled bleeding event or who require urgent or emergency surgery. There are no currently approved antidotes for these patients.

Andexanet alfa

- Andexanet alfa, currently in Phase 3 development, is a modified human Factor Xa molecule that acts as a decoy to target and sequester, with high specificity, Factor Xa inhibitors in the blood. Once bound, the Factor Xa inhibitors are unable to inhibit Factor Xa and normal hemostatic processes are restored.

Andexanet alfa

- ANNEXA 4 a multicenter, prospective, open-label, single-group study, evaluated 67 patients who had acute major bleeding within 18 hours after the administration of a factor Xa inhibitor. The patients all received a bolus of andexanet followed by a 2-hour infusion of the drug. Patients were evaluated for changes in measures of anti-factor Xa activity and were assessed for clinical hemostatic efficacy during a 12-hour period. All the patients were subsequently followed for 30 days.
  - The mean age of the patients was 77 years; most of the patients had substantial cardiovascular disease. Bleeding was predominantly gastrointestinal or intracranial.

  - NEJM on-line 8-30-2016 DOI: 10.1056/NEJMoa1607887
Andexanet alfa

- Patients who had taken apixaban or rivaroxaban more than 7 hours before the administration of andexanet, the bolus dose was 400 mg and the infusion dose was 480 mg.

- For patients who had taken enoxaparin, edoxaban, or rivaroxaban 7 hours or less before the administration of the bolus dose or at an unknown time, the bolus dose was 800 mg and the infusion dose was 960 mg.
  - Doses were selected because their use was associated with a rapid reversal of anti–factor Xa activity of 80% or more in previous studies.

  - NEJM on-line 8-30-2016 DOI: 10.1056/NEJMo1607887

Andexanet alfa

Results: The mean (±SD) time from emergency department presentation to the administration of the andexanet bolus was 4.8±1.8 hours. After the bolus administration, the median anti–factor Xa activity decreased by 89% (95% CI 58 to 94) from baseline among patients receiving rivaroxaban and by 93% (95% CI, 87 to 94) among patients receiving apixaban.
  - These levels remained similar during the 2-hour infusion. Four hours after the end of the infusion, there was a relative decrease from baseline of 39% in the measure of anti–factor Xa activity among patients receiving rivaroxaban and of 30% among those receiving apixaban. Twelve hours after the andexanet infusion, clinical hemostasis was adjudicated as excellent or good in 37 of 47 patients in the efficacy analysis (79%; 95% CI, 64 to 89).
  - Thrombotic events occurred in 12 of 67 patients (18%) during the 30-day follow-up.

  - NEJM on-line 8-30-2016 DOI: 10.1056/NEJMo1607887