New oral anticoagulants: A review of current indications

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Objectives

- To review indications for anticoagulation
- To discuss the new oral anticoagulants
- To review the evidence for new anticoagulants in stroke prevention in atrial fibrillation and treatment of DVT/PE
- To discuss the management of bleeding
Disclosures

- Pharmaceutical Company Affiliations
  - None

- Grants/Research Support
  - None

- Speakers Bureau/Advisory Boards
  - Boehringer-Ingelheim
  - Bayer Inc
  - Leo Pharma

- Consulting Fees
  - None
Overview

- Anticoagulants are widely used
- Vitamin K antagonists used to be the only oral option
- Times are changing…
Prescriptions

The Business of Health Care

August 31, 2010, 11:41 AM

The Race to Replace Warfarin

By NATASHA BINGER

Updated: For investors who have been asking themselves whether medium-size pharmaceutical companies can survive in an industry that has seen recent mega-mergers, the answer seems to be yes. At least for Bristol-Myers Squibb.

The company's experimental anticoagulant drug apixaban worked better than aspirin in preventing stroke and systemic blood clots for patients who have a history of heart attacks or strokes. The company is seeking U.S. approval for apixaban, which could be marketed as a daily pill for patients at higher risk of vascular problems.

Approval of new drug heralds 'momentous' advance in stroke prevention

By SHARON KIRKET, POSTMEDIA NEWS

OCTOBER 28, 2010

More on this story

Pradaxa (dabigatran) factsheet

Gallery: Sneaky sources of salt

Diabetes costs to cripple health budgets, study warns

Non-stick cookware may boost cholesterol

Pradaxa bests warfarin for atrial fibrillation stroke risk

By E.J. Mundell, HealthDay

The drug Pradaxa has been approved by the U.S. Food and Drug Administration to help prevent stroke in people with a type of abnormal heart rhythm called atrial fibrillation.

The drug may prove a new option for patients who now use standard blood thinners such as warfarin to control the heart condition.

More than 2 million Americans have atrial fibrillation, which occurs when the hearts two upper chambers beat quickly and not in sync, the FDA said Wednesday in a news release.

Pradaxa (dabigatran) is an anti-coagulating drug that inhibits an enzyme involved in blood clotting. Clinical studies of the drug...
Overview

- Big advantage:
  - *No lab monitoring*

- Big disadvantage:
  - *No lab monitoring*

- Unpredictability of coagulation tests
  - But very predictable action
- No reversal agents
  - But ?less bleeding
- Variety of different agents with different characteristics
Background

- What are anticoagulants?
  - Substances that prevent blood from clotting
    - “Blood thinners”

- How do they do this?
  - Interfering with coagulation mechanisms
Hemostasis

- Complex process which causes bleeding to stop:
  - Formation of blood clot formation at the site of vessel injury
  - Carefully regulated system
    - Involves platelets and coagulation factors
  - Lack of coagulation factors $\rightarrow$ bleeding
  - Overactive coagulation cascade $\rightarrow$ thrombosis
Coagulation system

Bleeding

Clotting
Coagulation system

Bleeding

Clotting

Thrombosis
Indications for anticoagulation

- Atrial fibrillation
- DVT/PE
- Mechanical heart valves
  - No evidence for new anticoagulants as of yet
Atrial fibrillation

- Most common cardiac rhythm disorder
- Affects >10% in those > 80 years old

Incidence of atrial fibrillation in 4000 male air crew recruits

Atrial fibrillation

- Independent risk factor for ischemic stroke
  - Rate of stroke in those not on antithrombotic therapy is ~4.5%/year

- Aspirin
  - Meta-analysis of 6 RCT’s comparing ASA to placebo in atrial fibrillation
    - ASA reduced the incidence of stroke or TIA by 22%

- Warfarin
  - Various studies have compared warfarin to placebo in atrial fibrillation
    - Warfarin reduced the incidence of stroke by 68%
    - 3x as effective as ASA

1. Wolf, Stroke, 1991
Venous thromboembolism

Deep venous thrombosis

Pulmonary embolism
Venous thromboembolism

- Deep venous thrombosis
  - Blood clot in the proximal veins of the leg
  - Less commonly in the arms
  - Symptoms include:
    - Pain
    - Swelling
    - Redness
    - Warmth
    - *Above affecting one limb*
Venous thromboembolism

- Pulmonary embolism
  - Blood clot (from DVT) breaks off
  - Travels to lung
  - Can lead to infarct
  - Symptoms:
    - Chest pain
    - Shortness of breath
    - Lightheadedness (low BP)
    - Syncope
    - Hemoptyasis
  - Can be life threatening
Venous thromboembolism

- Not uncommon
  - Longitudinal investigation of thromboembolism etiology (LITE) study\(^1\)
  - >21,000 participants
  - Cohort study
  - *Incidence of 1\(^{st}\) time VTE = 1.92 per 1000 person years*

- Major cause of morbidity and mortality

- *Most common preventable cause of in-hospital death*

\(^1\)Cushman, Am J Med, 2004
\(^2\)Dismuke, JAMA, 1986
Pulmonary embolism

- Untreated PE
  - Mortality rate of ~30%\(^1\)
  - Most die within hours of diagnosis

- Treated PE
  - Prospective NEJM study looked at 399 patients with newly diagnosed PE
  - 94% received conventional treatment (warfarin)
  - Only 2.5% (10 patients) died of PE

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*Treatment with anticoagulants is life-saving!*

\(^1\)Dalen, *Prog Cardiovasc Dis*, 1975

\(^2\)Carson, *NEJM*, 1992
Warfarin

- Oral vitamin K antagonist
- Been in use since the 1950’s
- Effect measured by the INR
- Can be reversed:
  - Vitamin K
  - Fresh frozen plasma
  - Activated prothrombin complex concentrates
Difficulties with warfarin use

- Requires monitoring
- Numerous drug and diet interactions
- Narrow therapeutic range
- Difficult to control – takes time to get in or out of the system

Role for new anticoagulants?
Qualities of an ideal anticoagulant:

- An ideal anticoagulant:
  - No monitoring
  - Fewer interactions
  - Oral
  - Reversible
  - Equally efficacious
  - Equally safe
New anticoagulants

- Many new targets being explored
  - Eg. thrombin, factor Xa, tissue factor, protein C, factor V and VIII

- New agents developed
  - Direct thrombin inhibitors
  - Factor Xa inhibitors

- Increasing data on:
  - Dabigatran – oral direct thrombin inhibitor
  - Rivaroxaban – oral factor Xa inhibitor
  - Apixaban – oral factor Xa inhibitor
New anticoagulants

![Diagram of the coagulation cascade with new anticoagulants highlighted.](Leung, The Hematologist, 2011)
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*
Dabigatran for atrial fibrillation

- RELY trial
  - 18,113 atrial fibrillation patients
  - Randomized to dabigatran (110 mg or 150 mg BID) vs warfarin
  - Followed for two years
Dabigatran for atrial fibrillation

- RELY trial

- Principal outcome (stroke or systemic embolism)
  - 1.69% per year with warfarin
  - 1.53% with dabigatran 110 mg
  - 1.11% with dabigatran 150 mg

- Bleeding
  - 3.36% with warfarin
  - 2.71% with dabigatran 110 mg
  - 3.11% with dabigatran 150 mg

- Consider higher dose if <80 and low risk of bleeding
Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.
Dabigatran for atrial fibrillation

- RELY trial
  - Similar bleeding between 150 mg dose and warfarin
  - Note trend towards increased MI rates with dabigatran 150 mg BID
  - Also increased dyspepsia and upper GI bleeds
  - Consider higher dose if <80 and low risk of bleeding
Dabigatran

- Approved by Health Canada for atrial fibrillation
- Covered by MSI for those not able to take warfarin
- Not approved for VTE treatment
- Costs $3.20 per day
Factor Xa inhibitors

- Lack of direct thrombin inhibition = less bleeding?
Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D.,
and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*
Rivaroxaban

- Studied in ROCKET-AF trial
  - Rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation

- Phase III, non-inferiority, double-blind study of rivaroxaban 20 mg OD vs. warfarin in patients with non-valvular atrial fibrillation and 2 other stroke risk factors

- 14,264 patients
  - Mean CHADS2 score = 3.5
ROCKET-AF

- Primary efficacy outcome: stroke or systemic thromboembolism
  - 2.2% with warfarin
  - 1.7% with rivaroxaban

- Major bleeding rates
  - 3.4% with warfarin
  - 3.6% with rivaroxaban
    - Less intracranial bleeding
    - Slightly more GI bleeding

- Approved by Health Canada for atrial fibrillation
**Figure 1.** Summary of recommendations for antithrombotic agent use based on Congestive Heart Failure, Hypertension, Age > 75, Diabetes Mellitus, and Prior Stroke or Transient Ischemic Attack (CHADS$_2$) score. Additional risk factors of age > 65, vascular disease, and female sex are integrated to increase granularity at low CHA2DS2-VASc score (CHA2DS2-VASc = 0). ASA, acetylsalicylic acid (aspirin); OAC, oral anticoagulant.
Original Article

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*
Rivaroxaban

- **EINSTEIN study**
  - NEJM study (Dec 2010)
  - Complicated – 2 studies in one
    - Noninferiority study
  - One study compared rivaroxaban to warfarin for acute DVT
    - 1700 patients
    - 15 mg po BID x 3 weeks, then 20 mg OD
    - No LMWH bridging in rivaroxaban arm
Rivaroxaban

- Similar outcomes in both arms for bleeding/thrombosis
  - Rate of recurrent VTE with warfarin 3.0%
  - Rate of recurrent VTE with rivaroxaban 2.1% (non-inferiority)

- Conclusion: Rivaroxaban as safe and effective as warfarin for DVT

- Now approved for DVT in Canada
Rivaroxaban

- Approved for atrial fibrillation
- Approved for DVT only as of now
  - No bridging with LMWH needed
  - 15 mg po BID x 3 weeks, then 20 mg po OD
- ~$2.84 per day
Bleeding

- ~2% of patients/year on long term anticoagulants will end up with a major bleed requiring medical attention

- Holding anticoagulants is the first step, but often other steps are needed

- Depends on anticoagulant
object. Repeat until vomit fluid is clear. DO NOT induce vomiting or give anything by mouth to an unconscious person. For all cases of human ingestion, immediately notify a physician or poison control centre. Take container, label or product name and P.C.P. Registration Number with you when seeking medical attention. If pet or livestock poisoning is suspected, immediately contact a veterinarian.

TOXICOLOGICAL INFORMATION: Vitamin K₁ in the form of intramuscular or subcutaneous injections, or by oral ingestion are suggested remedial treatments for anticoagulant poisoning. The severity of the case measured by establishing prolonged prothrombin times (P.T.) will determine appropriate therapy. Monitoring P.T. will indicate the necessity of repeated treatments.

STORAGE: Store in a cool, dry place away from other chemicals and food or feed. Store product not in use, in original container, in a secure location inaccessible to children and non-target animals. DISPOSAL: Do not reuse empty container. Dispose of empty container by placing in household garbage. Dispose of dead rodents in garbage or by burying.

NOTICE TO USER: This pest control product is to be used only in accordance with the directions on the label. It is an offence under the Pest Control Products Act to use this product in a way that is inconsistent with the directions on the label. The user assumes the risk to persons or property that arises from any such use of this product.

For additional product information or in case of emergency, spills or fire call toll-free 1-800-268-2804
Bleeding

- Warfarin
  - Give vitamin K 5-10 mg if acute bleed
  - Fresh frozen plasma
  - Octaplex
    - Prothrombin complex concentrate
    - Works within 1 hour
    - More effective than plasma at reversing INR
    - Small volume
    - 40 ml usually enough for most patients
    - $$$$$
Reversal of new anticoagulants

- Warfarin had several predictable options for reversal:
  - Vitamin K
  - Fresh frozen plasma
  - Activated prothrombin complex concentrates

- No reversal agents for new anticoagulants
Bleeding

- Dabigatran, rivaroxaban and other new agents
  - No known antidotes
  - Half-lives roughly 7-17 hours
  - Blood product support
  - Fresh frozen plasma
  - Consider dialysis with dabigatran…
Reversal of new anticoagulants

Suggested approach:

- Transfuse as necessary
  - Packed red blood cells
  - Platelets if less than 50

- Consider use of other blood products
  - ?Fresh frozen plasma
  - ?Activated prothrombin complex concentrates
  - ?Activated factor VIIa – should it even be offered?

- No good evidence!
Assessment of Bleeding Patient Receiving Dabigatran or Rivaroxaban

There is limited clinical data related to reversal of dabigatran and rivaroxaban. With no proven antidote available at the current time, the recommendations below may change as new evidence becomes available.

- **Patient on dabigatran/rivaroxaban presents with bleeding**

  - Initiate appropriate resuscitation measures if required
  - **Blood work**: CBC, creatinine, INR, aPTT, TT
  - Hold or discontinue dabigatran/rivaroxaban (Document time of the last dose)
  - Consider holding or reducing other medications known to increase a patient's bleeding risk (NSAIDs, ASA, Clopidogrel (Plavix®), Prasugrel (Effient®), Ticagrelor (Brilinta®), Ginkgo Biloba, Ginseng, Omega-3 Fatty Acids) or known to interact by increasing the dabigatran plasma levels (Amiodarone, Verapamil, Ketoconazole, Rifampin).

- **Mild Bleeding**
  - Local hemostatic measures
  - Keep hydrated

- **Moderate - Severe Bleeding**
  - MILD BLEEDING directive AND:
    - Manage bleeding (compression, surgery)
    - Fluid replacement → Maintain good urine output
    - Transfuse RBCs, FFP and platelets as needed

- **Life - Threatening Bleeding**
  - MODERATE - SEVERE BLEEDING directive AND:
    - Activate the Massive Transfusion Protocol
    - Consider tranexamic acid (1g IV followed by 1g infusion over 8 hours)
    - Consult with Transfusion Medicine Specialist

The anticoagulant effect of dabigatran or rivaroxaban will not be reversed by the administration of vitamin K or plasma infusion.¹ DO NOT TRANSFUSE PLASMA to reverse an elevated aPTT or INR.

There is insufficient evidence to recommend the use of Prothrombin Complex Concentrates (octaplex® or Beriplex®P/N), FEIBA or rFVIIa (NiaStase®) for the reversal of these medications.⁴
Perioperative management of anticoagulation

- Warfarin confers increased risk of bleeding
- Needs to be stopped for many procedures or surgeries
- Given long half life, warfarin needs to be stopped 5 days before surgery
Perioperative management of new oral anticoagulants

- No data

- However, stopping dabigatran or rivaroxaban 48 hours before surgery seems reasonable
  - Based on half life less than 17 hours
  - As long as CrCl >30 ml/min
  - Monographs do suggest minimum of 24 hours

- Not evidence based as of yet
  - In practice, appears to be safe
  - Ongoing studies based on creatinine clearance
## Pre-operative Management of Dabigatran

<table>
<thead>
<tr>
<th>Renal function (CrCl)</th>
<th>Estimated half-life (hrs)</th>
<th>Stop dabigatran before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50 mL/min (mild dysfunction or normal)</td>
<td><strong>14-17</strong></td>
<td>higher-risk for bleeding</td>
</tr>
<tr>
<td>30 to &lt;50 mL/min (moderate dysfunction)</td>
<td><strong>18-24</strong></td>
<td>4 days</td>
</tr>
<tr>
<td>&lt;30 mL/min (severe dysfunction)</td>
<td>&gt;24</td>
<td>&gt;5 days</td>
</tr>
</tbody>
</table>

# Post-operative Management of Dabigatran

<table>
<thead>
<tr>
<th>Surgery Type</th>
<th>Suggested Approach</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major (or high bleed risk) surgery</td>
<td>resume 150 mg BID 48-72 hrs post-op</td>
<td>substitute 75 or 150 mg dose once-daily for 2-3 days</td>
</tr>
<tr>
<td>Minor (or low bleed risk) surgery</td>
<td>resume 150 mg BID 24 hrs post-op</td>
<td>resume 24-48 hrs post-op</td>
</tr>
</tbody>
</table>

Douketis JD. *Curr Pharm Des* 2010;16:3436
Summary

- New anticoagulants are increasingly being used
- Stroke prevention in atrial fibrillation
  - Dabigatran and rivaroxaban approved
  - Apixaban indication likely coming
- Venous thromboembolism
  - Rivaroxaban approved for DVT, and PE indication likely coming
- No reversal agents as of yet, so supportive care only for bleeding complications
  - However, trend towards lower bleeding rates with new agents
Thank you!

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