New Anticoagulants: a Replacement for Coumadin, Heparin?

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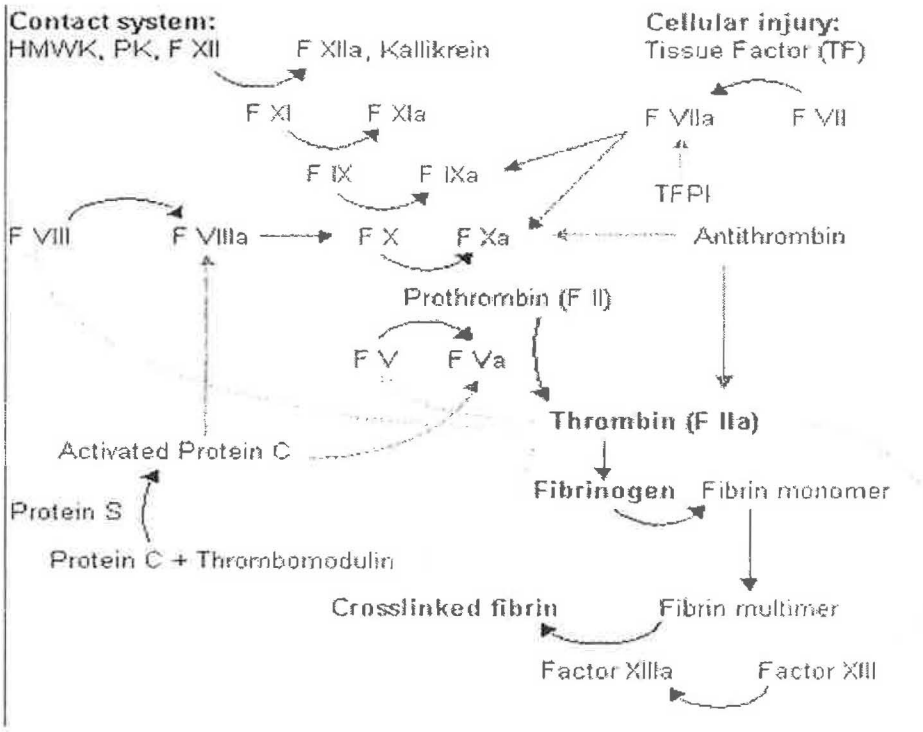
Thrombosis

Arterial and Venous Thrombosis are a major cause of morbidity and mortality [12]. Arterial Thrombosis is mostly due to Platelet aggregates and a small amount of fibrin clot. It leads to Myocardial Infarction (MI), Stroke (CVA), and Peripheral Vascular Disease (PVD). On the other hand, Venous Thrombosis is due to fibrin and leads to Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE). There are unfortunately limitations in the current anticoagulants. Doses often vary, response can be unpredictable, monitoring is often required, doses are frequently adjusted, and it is inconvenient and often costly. Amazingly, despite the plethora of medications and the importance of anticoagulation, we have had no new oral anticoagulant x 55 yrs. Improved understanding of thrombosis and coagulation have led to many new anticoagulants which may lead to more choices in the clinical arena.

Hemostasis is an important balance that maintains the integrity of the circulatory system. [21] Pathologic processes can overwhelm the regulatory mechanisms of hemostasis, thus initiating thrombosis. The endothelium is disrupted or a vessel wall is breached, collagen and tissue factor are exposed, and thrombus formation is initiated. Collagen triggers accumulation and activation of platelets. Tissue factor initiates the generation of thrombin which converts fibrinogen to fibrin and activates platelets. Once formed, thrombin activates cofactors to generate a burst of thrombin and amplify thrombosis.

Thrombin is central to the clotting process [23]. It converts fibrinogen to fibrin, generates more thrombin by activating factors V, VIII, XI, stimulates platelets, and stabilizes clot. On the other hand, natural anticoagulants such as tissue factor (TF) pathway inhibitor, Protein C and S, and antithrombin provide balance to help regulate coagulation and hemostasis

One can divide anticoagulants into rapidly active, acute agents for rapid initial anticoagulation, which may be given parenterally. They minimize the risk of thrombus extension and would be important in severe Venous Thrombombolism (VTE). Examples include Heparin, Low Molecular Weight Heparin (LMWH), and Fondaparinux. On the other hand, oral agents can be given for extended anticoagulation and for long term treatment. These would prevent recurrent VTE and the post-phlebitic syndrome. We've only had one oral long term anticoagulant available-Coumadin. New anticoagulants may help streamline VTE treatment.



INDICATIONS FOR ANTICOAGULANTS

We commonly use anticoagulants, such as Coumadin and Heparin, for numerous indications including DVT and PE Prophylaxis and Treatment, Atrial Fibrillation, Prosthetic Heart Valves, Acute Coronary Syndromes (ACS), Cardiac Thrombus, CVA, and Heparin Induced Thrombocytopenia (HIT) treatment [24]. Their use therefore encompasses most areas of Medicine. The incidence and importance of these diseases also has wide implications for potential new anticoagulants.

VENOUS THROMBOEMBOLISM (VTE)

VTE is a major cause of significant morbidity, mortality. Prevalence is unclear, but there may be 900,000 VTE/yr in the US and 300,000 deaths from VTE/yr in the US. It can lead to PE, DVT, death, Pulmonary HTN, post-thrombotic syndrome, venous insufficiency, and leg ulcers. It is the leading cause of death in hospitalized patients. Fatal PE may be the #1 preventable cause of inpatient death in the US. PE account for 5-10% of hospital deaths, but often is not suspected, is difficult to diagnose and can be rapidly fatal before diagnosed. [22] Prophylaxis is therefore very important and is highly effective.

The risk for VTE is related to risk factors, so all hospitalized patients should be risk stratified. Prophylaxis should be given for patients >40 yo, with limited mobility, and >1 risk factor for VTE. Heparin, LMWH, and Fondaparinux are all approved for VTE prophylaxis in medical patients.

Despite prophylaxis, the incidence of VTE remains high, especially after orthopedic surgery. The Surgeon General has issued a "Call to Action to Prevent VTE". The Agency for Healthcare Research and Quality (AHRQ) made VTE prophylaxis its highest ranked safety practice. While prophylactic anticoagulation with Heparin, LMWH,

and Coumadin are effective, the risks remain high, particularly after orthopedic fracture and joint replacement, so treatment remains an important clinical challenge.

VTE AFTER THR, TKR-"never events"

The US Centers for Medicare and Medicaid Services (CMS) added VTE after THR and TKR to the list of "never events". CMS will not pay for VTE after THR (Total Hip Replacement), or TKR (Total Knee Replacement). VTE is a common cause of preventable harm and many hospitalized patients fail to receive thromboprophylaxis. While financial incentives might encourage better performance and less VTE, VTE prophylaxis isn't perfect. Even with appropriate prophylaxis, 1-2% will still develop VTE and 1-2% may have bleeding. So, even with appropriate prophylaxis, 1-2% of VTE after THR, TKR will not be reimbursed by Medicare, Medicaid. These numbers are probably underestimates taken from healthy study patients.

In addition, the CMS VTE rule may have unintended deleterious consequences[30]. The rule creates disincentive to provide services for high risk patients (obese, thrombophilia, bleeding disorders, kidney disease, etc), limiting their health care options. The rule creates disincentives to perform THR and TKR and may shift to other areas since they will be less likely to be reimbursed for the THR or TKR. The rule establishes a disincentive to pursue evidence of VTE which may delay its diagnosis. It encourages physicians to possibly be overly aggressive in prophylaxis in patients at high risk for bleeding. In addition, the rule is too limited in scope to reduce all preventable VTE in just focusing on THR and TKR.

On the other hand, Joint Commission recommends that all patients receive risk appropriate VTE prophylaxis within 24 hours of admission or transfer. CMS should reconsider its current rule and focus on the preventable metric of appropriate prophylaxis for all hospitalized patients, instead of penalizing everyone inappropriately. CMS can link VTE with failure to receive appropriate prophylaxis to identify preventable VTE for whom reducing reimbursement may be more justifiable

ATRIAL FIBRILLATION-CHADS2 SCORE

Atrial Fibrillation (AF) is an important cause of stroke and embolism, especially in the elderly. However, very low risks patients may not require risky anticoagulation. To help weigh the risks and benefits of anticoagulation, the CHADS2 score is a clinical prediction rule for estimating the risk of stroke in nonvalvular atrial fibrillation. It can be used to determine the degree of anticoagulation therapy required.

In CHADS2, the C stands for Congestive Heart Failure (CHF), H for Hypertension, A for Age > 75yo, and D for Diabetes. Each of these conditions are 1 point. The S stands for Stroke or TIA and is worth 2 points.

Aspirin is sufficient in low risk AF patients with no other risk factors for stroke (0 points). Coumadin (INR 2-3) is indicated in high risk patients with 2 or more points (unless contraindicated due to bleeding, falls, etc). In patients with only 1 point, either Aspirin or Coumadin could be used.

IDEAL ANTICOAGULANT

I'd like to compare and contrast the old and new oral anticoagulants and consider the "Ideal Anticoagulant". The ideal anticoagulant would be efficacious for multiple indications-DVT/PE, AFib, ACS, Valves. It would inhibit thrombosis, but spare hemostasis, so have a relatively low bleeding risk. It would have simple, oral dosing and stable, predictable anticoagulation. Monitoring would be available, but not required. It should be inexpensive with minimal drug interactions. It would be safe in the elderly and those with co-morbidities, pregnancy, and surgery. The ideal anticoagulant would have a rapid onset to avoid "bridging" as well as a rapid offset for bleeding, procedures. An antidote would be available. So, how do the old and new anticoagulants stand up?

COUMADIN

Coumadin works by inhibiting Vitamin K dependent coagulation factor synthesis (Factor II, VII, IX, X). It was developed as rat poison in 1948 [25]. Despite the plethora of pharmacologic agents available today in general, Coumadin has been the only oral anticoagulant available since 1955. It suffers from a narrow therapeutic window, unpredictable pharmacologic effects, and a variable dose response. These may be due to vitamin K intake, genetic polymorphisms, and drug interactions. Coumadin therefore requires frequent INR monitoring to ensure therapeutic anticoagulation and to avoid the increase risk of thrombosis or bleeding, making it very difficult to manage. It is burdensome for patients and providers and adds to the costs.

Coumadin has numerous food (vitamin K) and drug interactions (Bactrim). Its slow onset requires overlap with Heparin (in the hospital) or LMWH for 5 days. Its slow offset requires stopping and bridging with Heparin or LMWH before procedures. The trend has been to use longer durations for VTE treatment and prophylaxis, thus requiring longer exposures to the hassles of Coumadin.

Although the pill itself is inexpensive, there are added costs of monitoring. Coumadin is contraindicated in pregnancy (category X). There is an inexpensive antidote in vitamin K.

A new advancement is the ability to check for genetic variants Cytochrome P450 2C9 or Vitamin K epoxide reductase to help predict proper the dose, but by the time the test returns it may not be clinically useful[18]. In one study this was not cost effective.

Coumadin is so difficult and dangerous, we have special anticoagulation clinics solely to manage Coumadin. Thus, Coumadin is far from ideal, but it's all we've had.

HEPARIN

Heparin acts as an anticoagulant by binding antithrombin and thus inactivates thrombin indirectly. It has a short half life and is given IV or SQ. Heparin's variable bioavailability and protein binding makes dosing difficult and requires frequent PTT monitoring. Heparin is unable to inactivate bound thrombin which limits its effect on the thrombus where active thrombin triggers further thrombus formation.

Heparin has a rapid onset and offset. It is an inexpensive medicine, but has the added costs of monitoring and hospitalization when given IV. It does have an antidote available in Protamine

A dreaded complication is Heparin Induced Thrombocytopenia (HIT), mediated thru Platelet Factor 4 binding where high risk patients are at risk for further thrombosis

and bleeding and require alternative anticoagulation. In addition, there has been a recent outbreak of Heparin contamination [17].

Low Molecular Weight Heparin (LWMH)

Low Molecular Weight Heparin (LMWH) binds antithrombin and inhibits Thrombin and Factor Xa It represents a significant advance over Heparin. It has a longer half life and can be given SQ once or twice daily with more predictable anticoagulation. There is no protein binding and has a reproducible effect, so it can be given on a weight basis without monitoring. Although it is more expensive, it is more convenient since monitoring is not required.

LMWH has allowed for outpatient treatment and prophylaxis of VTE. It has replaced Unfractionated Heparin as more convenient, as effective and as safe. There is also less HIT. One can monitor Factor Xa levels if needed. LMWH is FDA approved for DVT/PE treatment and prophylaxis and Acute Coronary Syndromes (ACS).

It does suffer from difficult dosing in obesity and renal disease and is a pregnancy category B. There is no antidote.

New Anticoagulants

Given the difficulties with Coumadin, there obviously remains a need for a safe, oral anticoagulant with rapid onset that could be used for both short and long term therapy. Again, there has been no new oral anticoagulant for 55 years!

I'd like to discuss 3 categories of new anticoagulants:

1. Indirect Factor Xa inhibitors (Fondaparinux, Idraparinux)
2. Direct Thrombin inhibitors (Dabigatran)
3. Direct Factor Xa inhibitors (Rivaroxaban, Apixaban)

Indirect Factor Xa inhibitors

Fondaparinux (Arixtra) is an Indirect Factor Xa inhibitor that binds antithrombin thus inhibiting Xa. It is given as a fixed dose, once daily SQ injection without the need for monitoring. It is FDA approved for DVT/ PE prophylaxis and treatment once per day. It is contraindicated with Creatinine Clearance (CrCl) <30. Fondaparinux validates Factor Xa as an effective target.

Idraparinux and SSR 126517 are derivatives of Fondaparinux [1]. They bind antithrombin with 100% bioavailability, have an 80 hr half life, and a predictable anticoagulant response. So, they can be given SQ, once weekly, with no monitoring required. They are excreted via the kidneys and are contraindicated CrCl < 30. Idraparinux production was halted due to a concern of excess bleeding. Unlike the other new anticoagulants, there is an antidote for SSR 126517.

If a new Indirect Factor Xa inhibitor is proven effective and safe and becomes available, it could easily streamline care. It would be easy to extend VTE prophylaxis and treatment with a once weekly injection. They could also provide anticoagulation coverage awaiting a therapeutic INR on Coumadin.

DIRECT THROMBIN AND DIRECT XA INHIBITORS

Since Thrombin is the final enzyme in the clotting cascade, it's an ideal target for anticoagulation. Thrombin inhibitors block the **activity** of thrombin, while Factor Xa inhibitors block thrombin **generation**. Either way, both direct thrombin inhibitors and direct Xa inhibitors reduce thrombin activity, fibrin formation, and inhibit coagulation. Limiting thrombin is important, because thrombin catalyzes the conversion of fibrinogen to fibrin, acts as a platelet agonist, and amplifies its own generation by feedback activation [12].

In addition, clot bound thrombin is an important thrombogenic stimulus. Direct inhibitors inactivate both free and fibrin bound thrombin. These new direct inhibitors avoid problems of the old anticoagulants like Heparin-protein binding, antithrombin (AT) deficiency, and inability to inactivate clot bound thrombin. They don't suffer from protein binding so they have a more predictable response. They don't bind Platelet Factor 4, so they avoid and can treat Heparin Induced Thrombocytopenia (HIT). By reducing thrombin mediated activation of platelets, they may also have antiplatelet effect

Direct Thrombin Inhibitors (DTI)

We already have 3 available, FDA approved, parenteral Direct Thrombin Inhibitors (DTI).

1. Lepirudin is FDA approved for HIT
2. Argratroban is FDA approved for HIT
3. Bivalirudin is FDA approved for Percutaneous Coronary Intervention (PCI)

They validate Thrombin as an effective target. I'd like to discuss a new oral DTI.

DABIGATRAN

Dabigatran is a DTI that binds directly to the active thrombin site with high affinity and specificity, potentially reducing side effects. It is given in a fixed, oral, once or twice daily dose. It has a rapid onset and rapid offset, reaching peak concentration in 2 hrs. It has predictable, consistent anticoagulation effect without the need for monitoring. Unfortunately it has low bioavailability and requires acid for absorption. It is excreted thru both the kidneys and the biliary system. It has no Cytochrome P 450 metabolism interactions so has a low potential for drug interactions [1].

3 phase III trials of Dabigatran in Orthopedic VTE prophylaxis have been published.

1. RE-NOVATE studied Dabigatran vs Enoxaparin 40mg SQ qd after Total Hip Replacement (THR) and showed similar efficacy and bleeding for VTE prophylaxis after THR [14].

2. RE-MODEL showed Dabigatran was as effective as Enoxaparin 40mg SQ qd for VTE prophylaxis after Total Knee Replacement (TKR) with no difference in bleeding or Liver Function Tests (LFT's) abnormailities [13].

3. RE-MOBILIZE however showed Dabigatran was less effective than Enoxaparin 30 mg BID SQ for VTE prophylaxis after TKR [15].

Note the first 2 studies which showed noninferiority of Dabigatran used a lower dose of Enoxaparin that is approved in Europe for Orthopedic VTE prophylaxis, but not in the US. It was not proven as effective against the higher, US Enoxaparin dose.

There are multiple ongoing studies for treatment and prevention of VTE as well as Atrial Fib (RE-VOUTION, RE-LY, RE-COVER, RE-MEDY).

Dabigatran has been approved in Canada and Europe.

XIMELAGATRAN

Ximelagatran was an oral direct thrombin inhibitor that didn't make it to market [1]. It exhibited efficacy and safety for initial and extended VTE treatment as well as Atrial Fib and CAD [9,10]. It validated thrombin as a target. It showed that fixed dosing without monitoring with an oral agent was achievable.

However, Ximelagatran was withdrawn for hepatic toxicity. The unanswered question remains-was this unique to Ximelagatran or a class effect? But it obviously raises a flag for caution for these new anticoagulants.

DIRECT FACTOR XA INHIBITORS

Factor Xa is a promising target as the convergence for internal and external coagulation. Factor Xa catalyzes the conversion of Prothrombin to Thrombin. One Factor Xa generates >1,000 Thrombin. Inhibition of Factor Xa prevents the burst of Thrombin and the activation of coagulation and platelets. 2 new oral direct Factor Xa inhibitors are Rivaroxaban and Apixaban. They offer once daily, oral dosing without the need for monitoring so could provide a replacement for Coumadin.

RIVAROXABAN

Rivaroxaban is an oral direct Factor Xa inhibitor that doesn't require antithrombin like indirect inhibitors. Indirect inhibitors (Fondaparinux, LMWH, and Heparin) require antithrombin and are limited to affect free Factor Xa only. Direct inhibitors affect both circulating and bound Factor Xa, and thus offer a potential advantage vs indirect inhibitors [1].

Rivaroxaban is well absorbed with 80% bioavailability and a half life of 9 hrs. It has a predictable anticoagulation effect, so no monitoring is required. It's given in a fixed, once daily dosing. It inhibits factor Xa for 24 hrs without an effect on thrombin, antithrombin, PT, or PTT. It has a rapid onset of 2-4 hrs (possibly obviating the need for acute IV treatment) and a rapid offset. It's excreted via the kidney and intestines. Caution is suggested with renal insufficiency. It is metabolized by Cytochrome P 450 3A4 (Ketoconazole). There is no dose adjustment for age or obesity. It has unknown safety in pregnancy. It is unclear if one can monitor Xa inhibition. There is no antidote and the cost is unknown.

Its once daily oral dose without monitoring makes it ideal for long term treatment. It has been approved in Canada and Europe (Xarelto).

There have been 4 phase III trials of Rivaroxaban-RECORD 1-4.

RECORD 1

Regulation of Coagulation in Orthopedic Surgery to Reduce Risk of DVT and PE 1 (RECORD 1) was published in NEJM in 6/08 [2]. Extended VTE prophylaxis for 5 weeks (vs 10 days) is now recommended (1a recommendation) after THR to prevent DVT, but options are limited. This study compared Rivaroxaban vs Enoxaparin for extended VTE prophylaxis after THR. It included 4541 patients in a randomized, double blind comparison of Rivaroxaban 10mg PO qd vs Enoxaparin 40mg SQ qd, plus placebo tab/inject, x 35 days. (Enoxaparin 30mg SQ BID is approved in the US for Orthopedic VTE prophylaxis, while Enoxaparin 40mg SQ qd is approved for Orthopedic VTE prophylaxis in Europe or for medical VTE prophylaxis in the US.)

There was an impressive 70% Relative Risk Reduction (RRR) in DVT, PE, or death at 36 days, with 1.1% in Rivaroxaban vs 3.7% in Enoxaparin, for an Absolute Risk Reduction (ARR) of 2.6%, p<.001. Rivaroxaban reduced DVT, but there was no change in PE or mortality. There was no difference in major bleeding (.3% Rivaroxaban vs.1% Enoxaparin, p=.18) or Liver Function Tests (LFT's). So, Rivaraxaban was more effective than Enoxaparin at VTE prophylaxis after THR with similar safety profiles.

RECORD 2

RECORD 2 Was published in Lancet in 7/08 [3]. The risk of VTE is high after THR and persists after discharge. Despite evidence that extended prophylaxis x 5 weeks (vs 10 days) reduces VTE after THR, its use is < 50% (requires injections, monitoring). RECORD 2 compared Rivaroxaban for extended prophylaxis vs short term prophylaxis with Enoxaparin. It had 2509 elective THR patients in a randomized, double blind, multi-center trial of Rivaroxaban 10mg PO qd x 35 days vs Enoxaparin 40mg SQ qd x 10-14 days (with placebo injection/pill).

DVT, PE, or death occurred in Rivaroxaban 2.0% vs Enoxaparin 9.3%, for an ARR 7.3%, p<.0001, and Number Needed to Treat (NNT) of 14. DVT occurred in Rivaroxaban 1.6% vs Enoxaparin 8.2 %, ARR 6.5%, p<.0001. There were trends in reducing PE, death, but they were not statistically significant. On treatment bleeding occurred in Rivaroxaban 6.6% vs Enoxaparin 5.5%, p=.25.

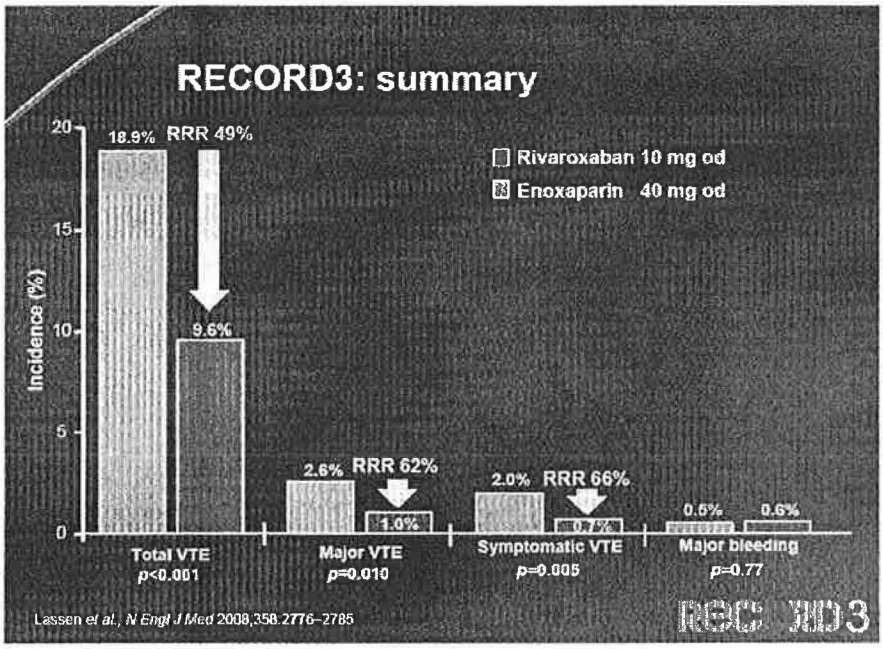
Extended prophylaxis Rivaroxaban was more effective than short term Enoxaparin for DVT prevention after THR. It was not an equal comparison of 35 vs 10-14 days, but possibly a "real world" comparison-would an easy, daily, oral medication be prescribed, taken more than current alternatives, and thus lower risks.

RECORD 3

RECORD 3 was published in NEJM in 6/08 [4]. VTE is a major complication after TKR, but anticoagulants are underutilized and other options would be preferred. Rivaroxaban was compared vs Enoxaparin in preventing DVT after TKR. 2531 patients undergoing elective TKR were randomized in a double blind trial of Rivaroxaban 10mg PO qd vs Enoxaparin 40mg SQ qd x 10-14 days, then followed x 7 weeks.

DVT, PE, or death occurred in Rivaroxaban 9.6% vs Enoxaparin 18.9%, for a RRR 49%, ARR 9.2%, p<.001. PE occurred in Rivaroxaban 0 vs Enoxaparin.3%, p=.05. There was no difference major bleeding or adverse events.

Rivaroxaban, an oral direct factor Xa inhibitor, given in a fixed, once-daily dose without coagulation monitoring, was superior Enoxaparin for VTE prophylaxis after TKR, with similar bleeding rates.



RECORD 4

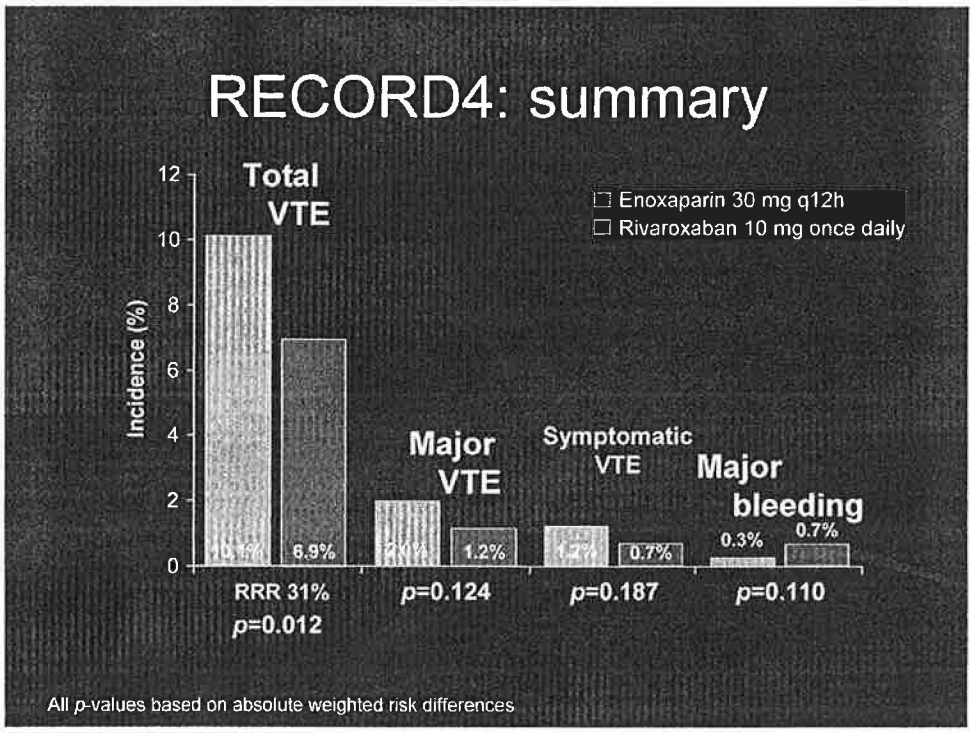
RECORD 4 has not been published, but was presented 6/08 [5]. It looked at prevention of VTE s/p TKR, but with a higher dose of Enoxaparin. 3,148 elective TKR patients were randomized to Rivaroxaban 10mg PO qd vs Enoxaparin 30mg SQ BID x 10-14 days, then followed x 40 days.

DVT, PE, death occurred in Rivaroxaban 6.9% vs Enoxaparin 10.1%, ARR 3.2%, p=.012. There was no difference in bleeding or LFT's

Rivaroxaban in a fixed, unmonitored, once daily, oral dose was still superior against higher dose Enoxaparin for VTE prophylaxis s/p TKR.

"With superior efficacy, no compromise in bleeding, and convenient oral daily dosing, Rivaroxaban seems an obvious choice for simplified VTE thromboprophylaxis."[20]

On 3/20/09 the FDA advisory panel recommended approval of Rivaroxaban (15-2 vote) for short term VTE prophylaxis after THR, TKR. The FDA will vote in 5/09 for possible approval of Rivaroxaban.



ONGOING STUDIES

There are multiple ongoing studies with Rivaroxaban looking at other indications for anticoagulation.

ATLAS ACS TIMI 46

ATLAS ACS TIMI 46 is a phase II dose finding study of secondary prevention in ACS. Death and recurrent MI remain high despite dual platelet therapy s/p ACS. 3,500 post ACS patients were treated with Rivaroxaban 5-20 mg vs Placebo to reduce CV events with recent ACS on top of ASA or on top of ASA and Plavix. It was presented at AHA in 11/08 [6].

There was a trend towards improved efficacy with Rivaroxaban, but there was a dose dependent increase in bleeding (1.2% vs .2%). Death, MI, CVA, Revascularization occurred in Rivaroxaban 5.6% vs Placebo 7.0%, P=.1. There was no difference in LFT's. They plan a phase 3 trial with 16,000 patients x 33 months.

ROCKET-ATRIAL FIBRILLATION

ROCKET-AF will look into Stroke Prevention in Atrial Fibrillation [7]. 14,000 patients with non-valvular Atrial Fibrillation will be randomized in a double blind study comparing Rivaroxaban with dose adjusted Coumadin for Prevention of CVA, Embolism in Atrial Fibrillation.

MAGELLAN

MAGELLAN will study the prevention of DVT in hospitalized medically ill patients[7]. 8,000 patients hospitalized for medical illness with decreased mobility (CHF, CA, CVA) will be studied comparing Rivaroxaban x 1 month vs Lovenox 40mg SQ qd x 10 days for VTE prophylaxis.

EINSTEIN-DVT/PE

EINSTEIN-DVT/PE will enroll 6,200 patients with DVT or PE to compare Rivaroxaban vs Enoxaparin/ Vit K antagonist for DVT or PE Treatment for 3, 6, or 12 months to prevent recurrent VTE [7]. EINSTEIN-Extension will compare Rivaroxaban vs Placebo for VTE prevention after 6 or 12 months treatment.

Opportunities for New Anticoagulants

The new once weekly SQ Indirect Factor Xa Inhibitors-if proven effective and safe, could streamline care. They could make it easy to extend VTE prophylaxis and treatment or provide anticoagulation coverage awaiting therapeutic Coumadin INR's.

The new oral direct inhibitors of Thrombin and Factor Xa, with their rapid onset, have the potential for initial VTE treatment, thus avoiding Heparin and LMWH. The fixed oral dose without monitoring could have a large advantage and convenience for extended, long term VTE treatment. Their convenience might even help expand the indications and length of extended anticoagulation.

Other targets in development

Future targets for anticoagulation in development include Factor XII, Tissue factor, Factor VII, Factor IX, Factor V, and VIII, and Thrombomodulin. The ideal anticoagulant would inhibit thrombosis, but spare hemostasis. Interestingly, mice deficient in Factor XII do not form occlusive thrombus and don't have hemostatic defect.

Factor V, VIII could be attractive targets since they are cofactors, not active enzymes. They have a potential bleeding advantage by dampening clotting without completely blocking thrombin. Recombinant Activated Protein C (Drotrecogin alfa-Xigris), inactivates V, VII, and is approved for severe sepsis acts as a potential example.

Problems, Limitations, Drawbacks

Since the mechanism for Ximelagatran's liver toxicity has not been identified, it is difficult to predict if other DTI's will have similar problem [1]. So far, the lack of a toxicity signal in numerous studies is encouraging, but more patient exposure, longer duration, and post marketing surveillance are needed.

Although monitoring is not routinely required with the new anticoagulants, there may be instances when it's helpful-recurrent thrombosis, bleeding, questionable compliance, obesity, renal/liver disease, concomitant medications that affect coagulation or drug metabolism. How could we monitor new anticoagulants if needed? Routine tests

are not helpful. How will dose adjustments be made if target drug levels and therapeutic ranges are unknown? Although we may be able to use Factor Xa levels to monitor Xa inhibitors, it is not standardized or well studied. In the absence of routine monitoring, we won't be able to assess compliance as easily, especially for "treatment failures".

Since the major complication of all anticoagulants is bleeding, it would be desirable to have an antidote to reverse the anticoagulant effect for major bleeding, urgent surgery or procedure, or major trauma. However, none of the new anticoagulants has a specific antidote. Dialysis may clear direct Xa and thrombin inhibitors, and recombinant factor VIIa could be helpful, but they have not been studied. However, the new oral agents have a short half life, there is no antidote for widely used LMWH, and antidotes are rarely used.

Since the new anticoagulants haven't been FDA approved, their costs are unknown but will obviously be an important factor. But they may be expensive which will obviously impact their use. It will depend if equal or superior in efficacy and safety-may be willing to pay more for higher efficacy, safety. Will payers embrace the higher costs vs inexpensive Coumadin, Heparin? Importantly, what will be the total costs comparisons with/without appropriate monitoring vs drug costs alone? If very expensive, may reserve new anticoagulants for Coumadin failures or those without access to monitoring. Competition may help lower costs. In addition, how do we measure and put a price on convenience?

In contrast to the new agents, we have experience with the older medications, including their use with surgery and procedures. What abut special patients who are frequently excluded from the clinical trials such as those with high risk, hypercoaguable states, Cancer, Anti-Phospholipid Antibody, Pregnancy, and multiple co-morbidities? However, given the limitations of anticoagulants in pregnancy, a new safe, effective agent would be a great advance.

Although Factor Xa and Thrombin are both good targets, the efficacy and safety of both inhibitors may be similar. Which is more effective, safer? If we get new agents for both, it's unlikely to have head to head data comparing the new agents soon to help decide which to use.

Although trials used DVT, PE, or death as primary outcome, it was driven by reduction in asymptomatic DVT diagnosed by venogram-is this an important clinical outcome?

Finally, imbalances in treatment duration and Enoxaparin dose favored Rivaroxaban in RECORD 1-3, but not RECORD 4.

New Anticoagulants

Many new anticoagulants are being studied with numerous ongoing trials-these may lead to new choices and possible replacements for Coumadin, Heparin, and LMWH. New anticoagulants, like Rivaroxaban, have the potential to change how we treat DVT, PE, Atrial Fib, ACS, and Prosthetic Valves. But these potential options may bring about difficult decisions. If approved by the FDA for 1 indication, should we use a new anticoagulant for other indications? Will we use just for limited patients who don't do well with Coumadin, Heparin? Will we just use for evidence based specific individualized indications? Or will we use for broad indications for anticoagulation?

Pt's may voice a preference for simpler oral anticoagulation without monitoring and adjusting. How will we monitor, reverse, and pay for? How do we measure convenience? If successful, what do we do with Anticoagulation clinics and resources?

Thrombosis is a common final pathway to disease and death in MI, CVA, VTE, and Cancer. Hopefully a new agent will inhibit thrombosis but not compromise

hemostasis. Hopefully these new agents will take advantage of the opportunity for advancement in the prevention and treatment thrombotic diseases.

So, some may want to bid farewell to conventional anticoagulants. "Gone are the days of nonselective anticoagulants with unfavorable pharmacokinetics, archaic and vulnerable manufacturing processes, and unpredictable off target effects." Many will welcome a new oral, effective, safe anticoagulant.

Others may not be so quick to change. "However, we should not throw the baby out the bath water-the old vitamin K antagonist and heparins have been safe and effective for decades and manufacturing accidents have been extremely rare. "

"As availability of oral, selective, direct anticoagulants expands, selection of the right drug at the right dose for the right patient will require clinical acumen, in-depth knowledge of each drug's pharmacokinetics and specific mechanism of action, as well as familiarity with the coagulation-assessment tools and the pathobiology of the disease. In some settings, a vitamin K antagonist may indeed be the preferred anticoagulant." [31]

Providers, PMH, UTSW, Medicare, Insurances, and Health Care Systems will need to weigh efficacy, safety, cost effectiveness, and convenience. Hopefully these new anticoagulants will highlight the importance of treating DVT, PE, Atrial Fib, ACS, and Prosthetic Valves and improve the efficacy, safety, and convenience. New agents against thrombin and factor Xa have the potential to replace Coumadin and Heparin for the treatment and prophylaxis of thromboembolic disease with improved convenience, safety, and efficacy.

BIBLIOGRAPHY

1. Gross PL.New Anticoagulants for Treatment of Venous Thromboembolism. Arterioscler Throm Vasc Biol.2008;28:380-386

2. Erikson BI. Rivaroxaban vs Enoxaparin for Thromboprohylaxis after Hip Arthroplasty, (RECORD 1). NEJM 2008; 358:2765-75

3. Kakkar AK. Extended Duration Rivaroxaban vs short term Enoxaparin for Prevention of VTE after THR (RECORD 2). Lancet 2008;372:31-39

4. Lassen MR. Rivaroxaban vs Enoxaparin for Thromboprophylaxis after TKA (RECORD 3). NEJM 2008;358:2776-86

5. Heartwire for WebMD 6/08-results of RECORD 4

6. Heartwire from WebMD 11/08-results of ATLAS ACS TIMI 46

7. Rivaroxaban (Xarelto), Bayer website-ROCKET-AF, MAGELLAN, EINSTEIN, ATLAS ACS studies

8. Caprini JA. The Future of Medical Therapy for VTE. Am J Med 2008;121:S10-19

9. Fiessinger JN. Ximelagatran vs LMWH and Warfarin for DVT. JAMA 2005; 293:681-689

10. Schulman S. Secondary Prevention VTE with Ximelagatran. NEJM 2003; 349:1713-1721

11. Leung L. New Anticoagulants. www.uptodate.com

12. Weitz J. New Antithrombotic Drugs. Chest 2008; 133, S

13. Eriksson BI. Oral Dabigatran vs Enoxaparin after TKR, RE-MODEL. J Thromb Haemost 2007; 5: 2178-85

14. Erikson BI. Dabigatran vs Enoaparin afer THR. RE-NOVATE. Lancet 2007; 370:949-56

15. Ginsberg J. Dabigatran vs Enoxaparin after TKR. RE-MOBILIZE. J of Arthroplasty 2009;24:1-9

16. Caprini JA. Dabigatran for major orthopedic surgery (abstract). J Thromb Haemost 2007;5: Supp 2

17. Blossom D. Outbreak of Adverse Reactions with Contaminated Heparin. NEJM 2008;359:2674-84

18. Schwarz U. Genetic Determinants of Response to Warfarin. NEJM 2008;358:999-1008

19. Warwick D. Insufficient duration of VTE prophyaxis after THR or TKR. J Bone joint Surg Br 2007;89:799-807

20. Eikelboom J. Selective Factor Xa inhibition for Thromboprophylaxis. Lancet 2008; 372:6-8

21. Furie B. Mechanisms of Thrombus Formation. NEJM 2008;359:938-49

22. Francis C. Prophylaxis for Thromboembolism in Hopitalized Medical Patients. NEJM 2007;356:1438-44

23. Nisio M. Direct Thrombin Inhibitors. NEJM 2005;353:1028-40

24. Schulman S. Care of Patients Receiving Long Term Anticoagulants. NEJM 2003;349:675-83

25. Shapiro S. Treating Thrombosis in the 21st Century. NEJM 2003;349:1762-64

26. Surgeon General's Call to Action to Prevent VTE, US Dept HHS

27. Antithrombotic and Thrombolytic Therapy: ACCP Evidence Based Clinical Guidelines. Chest 2008;133:S

28. Eckman MH, Rosand J, Greenberg SM, et al. Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. *Ann Intern Med* 2009; 150:73-83.

29. The International Warfarin Pharmacogenetics Consortium. Estimation of the warfarin dose with clinical and pharmacogenetic data. *NEngl JMed* 2009; 360:753-764.

30. Streiff M, CMS Ruling on VTE after THR, TKR. JAMA 2009;301:1063-1065

31. Rivaroxaban for Thromboprophylaxis. NEJM 2008; 359:2174-76

32. O'Brien C. Cost and Effectiveness of Ximelagatran. JAMA 2005; 293:699-706