

Continuing Education for Pharmacists

Oral anticoagulation without protimes: A review of two emerging agents that may come to market.

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Goals:

The goals of this lesson are to provide an overview of two emerging oral anticoagulants and address their potential place in therapy should they be approved by the FDA for the U.S. market. Published clinical trial data will be presented to assess the safety and efficacy of these agents compared to currently available anticoagulants.

Objectives:

At the conclusion of this lesson, successful participants should be able to:

Review elements of the clotting cascade and clotting terminology.

List the most common indications for anticoagulation therapy.

Identify reasons why new oral anticoagulants could be beneficial in clinical practice.

Define the mechanism of action of the two emerging anticoagulants discussed.

Based on presented clinical trial data, be able to describe the benefits and risks associated with each new agent.

INTRODUCTION

Anticoagulants are essential components in the medical management of conditions including the prevention and treatment of thromboembolic disorders such as deep vein thrombosis and pulmonary embolism and in the prevention of cardioembolic events such as stroke from atrial fibrillation. These conditions carry with them significant morbidity and mortality. For patients requiring long-term anticoagulation therapy there is only one oral anticoagulant available on the U.S. market, warfarin, which has many challenges associated with its use. All other available anticoagulants require either intravenous or subcutaneous administration which can be inconvenient or worrisome to patients. New oral anticoagulants are being developed that will hopefully be more efficacious than those currently available while maintaining favorable pharmacokinetic and safety profiles. Due to the inherent risks of interfering with the body's clotting system, no anticoagulant will be without risk. That said, the goal of anticoagulation therapy is to minimize risk and maximize safety while reducing complications of clot formation within the body.

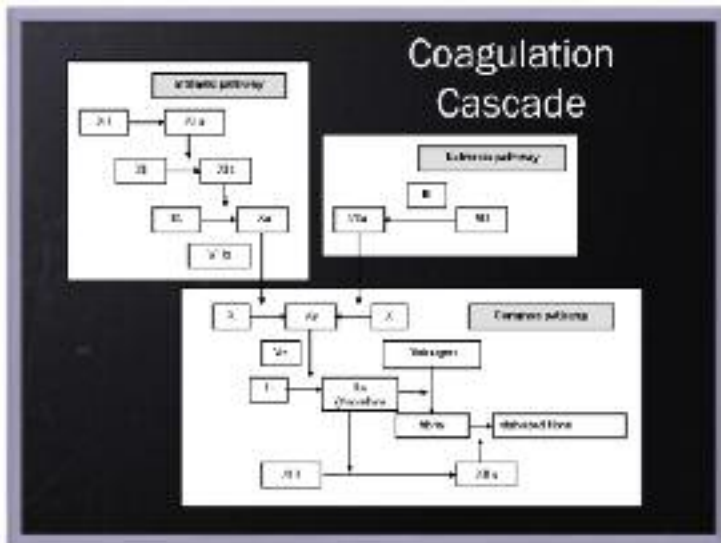
INDICATIONS FOR ANTICOAGULATION THERAPY

Common indications for anticoagulation therapy include prevention of cardioembolic stroke in patients with atrial fibrillation or mechanical heart valve prosthesis, and in the treatment and prevention of venous thromboembolism (VTE) which consists of deep vein thrombosis (DVT) and pulmonary embolism (PE). The vast majority of the patient population undergoing anticoagulation therapy falls into one of these categories. The emerging anticoagulants referred to in this article will be discussed in terms of the risks and benefits of these novel agents as they relate to these disease states.

COAGULATION CASCADE

The human body utilizes an elaborate system of proteins & feedback mechanisms to maintain homeostasis in regard to bleeding and clotting. This coagulation system relies on communication of tissues and coagulant proteins (clotting factors) that provide both a means to repair wounds (fibrin clot formation) and degrade clots once the tissues have been fully repaired (fibrinolysis).¹ The clotting and fibrinolytic system is an intricate series of successive protein activation and is called the "coagulation cascade", see Figure 1. The coagulation cascade consists of two primary pathways, the intrinsic and extrinsic pathways, which both lead to the final common pathway and ultimately fibrin clot (thrombus) formation.¹ Inhibition of the activity or production of clotting factors results in disruption of the coagulation cascade and decreased thrombus formation. Current and emerging anticoagulants alter different steps within the clotting cascade either by decreasing the production of clotting factors (e.g. warfarin), through indirect inhibition of clotting factors (e.g. heparin, low-molecular weight heparins, fondaparinux), or through direct inhibition of clotting factors (e.g. direct thrombin inhibitors, direct factor Xa inhibitors).¹ Simply stated, anticoagulants slow the rate of coagulation. Two common misconceptions about anticoagulation therapy are that anticoagulants completely prevent clotting from occurring and that anticoagulant therapy causes bleeding.

Figure 1 – Coagulation Cascade



Adapted from figure 1 in Reference 1.

MECHANISM OF ACTION OF CURRENTLY AVAILABLE ANTICOAGULANTS

Currently the US market has nine FDA approved agents for anticoagulation therapy, each with differing indications and limitations (Tables 1 and 2).

Table 1: FDA approved anticoagulants

Approval Date	Drug Name	Administration	Drug Class
02/1939	Heparin	IV, SQ	Heparin
05/1954	Warfarin (Coumadin [®])	PO	Vitamin K Antagonist
03/1993	Enoxaparin (Lovenox [®])	SQ	Low Molecular Weight Heparin
12/1994	Dalteparin (Fragmin [®])	SQ	Low Molecular Weight Heparin
03/1998	Lepirudin (Refludan [®])	IV	Direct Thrombin inhibitor
05/2000	Argatroban	IV	Direct Thrombin inhibitor
07/2000	Tinzaparin (Innohep [®])	SQ	Low Molecular Weight Heparin
12/2000	Bivalirudin (Angiomax [®])	IV	Direct Thrombin inhibitor
12/2001	Fondaparinux (Arixtra [®])	SQ	Indirect Factor Xa Inhibitor

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IV: intravenous, SQ: subcutaneous, PO: oral

Warfarin depletes vitamin K dependent clotting factors II, VII, IX, and X thereby effectively inhibiting both the intrinsic and extrinsic pathways of coagulation.¹ Since 1954, the vitamin K antagonist (VKA) warfarin has been and remains the only available oral anticoagulant on the U.S. market. Challenges associated with use of warfarin include the need to individualize the dosage due to its unpredictable anticoagulant effect, multiple food & drug interactions, and narrow therapeutic window.¹ Warfarin therapy requires regular monitoring of the patient's international normalized ratio (INR) to maintain safety and efficacy. This monitoring requires trained medical professionals who are diligent with, at minimum, monthly follow-up with patients.

Heparin potentiates the actions of antithrombin III. Antithrombin III inactivates thrombin (factor IIa) and factors IXa, Xa, XIa, and XIIa.¹ The actions of heparin inhibit the propagation of the intrinsic and final common pathways of the coagulation cascade. Drawbacks to the use of unfractionated heparin (UFH) include route of administration (intravenous or subcutaneous) and unpredictable anticoagulant effect due to unspecific binding.¹ The unpredictable anticoagulant effect of UFH requires regular monitoring of the activated partial thromboplastin time (aPTT) and careful dose titration by skilled providers.¹ Additionally, heparin carries the paradoxical risk of thrombosis called heparin-induced thrombocytopenia (HIT).¹

Low-molecular weight heparins (LMWHs) such as enoxaparin, dalteparin, and tinzaparin cause antithrombin III-mediated inhibition of factor Xa and, to a lesser extent, inhibition of thrombin (factor IIa).¹ Limitations to

anticoagulation treatment with LMWHs include the requirement of subcutaneous administration, risk of accumulation of drug with renal impairment, and risk of HIT.¹

The indirect factor Xa inhibitor, fondaparinux, exerts its anticoagulant effects through antithrombin III mediated selective inhibition of factor Xa.¹ Limitations to fondaparinux include requirement of subcutaneous administration and the risk of drug accumulation with renal impairment.¹

Table 2: Limitations of current anticoagulants

Anticoagulant	Limitations	Consequences
UFH	Parenteral mode of administration Unpredictable anticoagulant effect due to unspecific binding Risk of HIT	Inconvenient for long-term use Regular monitoring of aPTT required Monitoring of platelet count required
LMWH	Parenteral mode of administration Risk of HIT Accumulation can occur with renal impairment	Inconvenient & expensive for long-term use Monitoring of platelet count required Risk of adverse events (e.g. bleeding)
Warfarin	Unpredictable anticoagulant effect Narrow therapeutic window Slow onset & offset of action Food & drug interactions	Regular monitoring & dose adjustments required to ensure patients stay within target INR (usually 2-3) Bridge therapy may be required peri-procedurally Risk of adverse events (e.g. bleeding)
Fondaparinux	Parenteral mode of administration Accumulation can occur with renal impairment	Inconvenient & expensive for long-term use Risk of adverse events (e.g. bleeding)

Adapted from table 1 in Reference 1.

EMERGING ANTICOAGULANT AGENTS

As discussed, there are many limitations and undesirable attributes to the currently available anticoagulants on the U.S. market today. A novel oral anticoagulant that could provide equivalent or superior efficacy and similar or enhanced safety would be a beneficial addition to current therapy options. An agent that does not require regular measurement of clotting times (e.g. INR, aPTT) would also be preferable. Table 3 lists desired attributes for newly developed anticoagulants.

Dabigatran and rivaroxaban are two oral anticoagulants that are being developed for the treatment of various clotting disturbances. According to ClinicalTrials.gov there are currently 19 trials involving dabigatran and 25 trials involving rivaroxaban in various stages of completion.² These agents are being studied for the prevention of cardioembolic stroke due to atrial fibrillation, in the treatment and prevention of venous thromboembolism, and in the medical management of acute coronary syndrome. Even though these agents have not been approved by the FDA and are therefore not available in the U.S. at this time, there are several published clinical trials that offer insight into the possible risks and benefits of their use.

Table 3: Desired attributes for newly developed anticoagulants

Desired Attribute	Advantage of Attribute
Directly targets a specific clotting factor	Predictable coagulant response
Oral administration	Patient convenience / minimize risks associated with parenteral administration
Standardized dosing regimens	No dose titration required
Low risk of bleeding	Enhanced safety
Available antidote	Ability to reverse agent if patient was bleeding or over-anticoagulated
No measurement of clotting time required	Patient / provider convenience Decreased cost of therapy
Minimal drug & food interactions	Avoidance of adverse drug events
No organ toxicity (e.g. hepatic, renal)	Patient safety

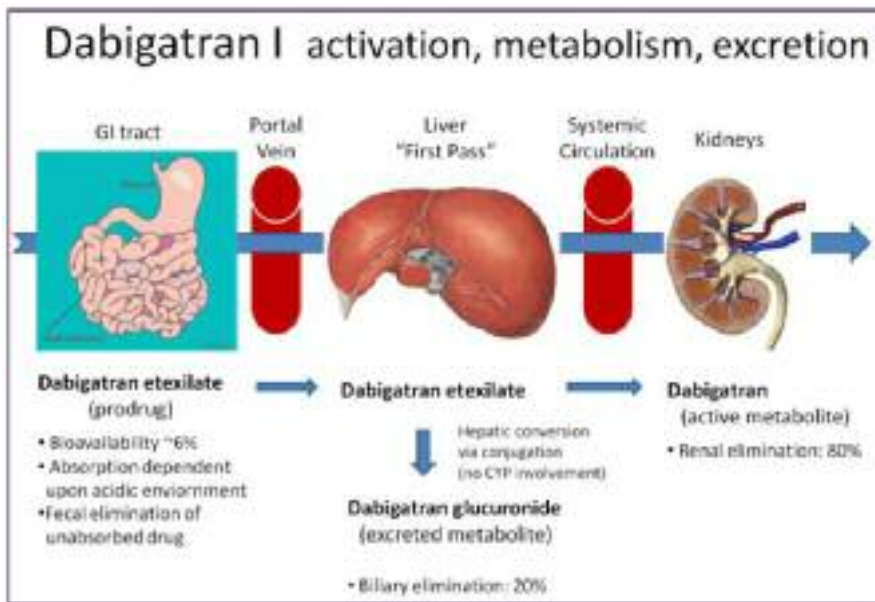
DABIGATRAN

Dabigatran is an oral direct thrombin inhibitor.³ It was approved for use in Europe and Canada in 2008 for venous thromboembolism (VTE) prophylaxis in elective total hip and total knee replacement (THR/TKR) under the brand names of Pradax[®] and Pradaxa[®], respectively.⁴ Dabigatran binds specifically to thrombin and has little effect on other clotting factors.⁴ By binding to the active site of thrombin, dabigatran inhibits the conversion of fibrinogen to fibrin,

thereby blocking the final step of the coagulation cascade and thus fibrin clot formation.

Dabigatran has a unique pharmacokinetic profile (see Figure 1). Dabigatran etexilate is given orally and is converted into its active metabolite, dabigatran, after absorption from the gastrointestinal tract. The bioavailability of dabigatran is very poor and absorption is dependent upon an acidic environment.³ To overcome this, the manufacturer designed a capsule containing pellets with a tartaric acid core and coated with dabigatran etexilate.⁵ This creates an acidic microenvironment that improves dissolution and absorption of the drug independent of gastric pH.⁵ The prodrug dabigatran etexilate is hepatically converted into two active metabolites, dabigatran glucuronide which is excreted through the biliary system, and dabigatran which is renally eliminated.⁵ Because of the extensive renal elimination of dabigatran, it is contraindicated in patients with severe renal impairment.⁴ The onset of effect for dabigatran is within 1 hour of dosing and the anticoagulant effect parallels plasma concentrations.⁴ As a result of the quick onset of effect, anticoagulant therapy with dabigatran would not require bridge therapy with heparins or fondaparinux when immediate anticoagulation is critical.

Figure 2: Pharmacokinetic profile for dabigatran



Adapted from text in Reference 4.

The RE-LY trial was a non-inferiority trial comparing warfarin and dabigatran for stroke prevention in patients with atrial fibrillation (AF).⁶ Adjusted dose warfarin with a goal INR of 2-3 was compared to two different dosages of dabigatran, 110mg bid and 150mg bid (Table 4). There were over 18,000 patients enrolled in this study. Median follow up time for this trial was 2 years. For the primary outcome of stroke or systemic embolism dabigatran showed non-inferiority (or equivalence) to warfarin for both dosages and superiority with the higher dosage of 150mg bid. The rate of stroke or systemic embolism per year was 1.69% for warfarin, 1.53% for dabigatran 110mg, and 1.11% for dabigatran 150mg. Major bleeding was no different between warfarin (3.36%/yr) and the 150mg dose dabigatran (3.11%/yr) but was significantly less for the 110mg dose of dabigatran (2.71%/yr). Although there was no difference in major bleeding between dabigatran and warfarin at the 150mg dosage, there was a significant increase in GI bleeding with this dosage of dabigatran compared to warfarin, 1.51%/yr and 1.02%/yr respectively. Furthermore there was an increased rate of drug discontinuation with dabigatran (14.5%/yr for 110mg dose, 15.5%/yr for 150mg dose) over warfarin (10.2%/yr), mainly due to an increase in dyspepsia. The authors postulate that the increase in dyspepsia and potentially the increased risk of GI bleeding can be attributed to the required acidic microenvironment utilized in the capsule to aid in drug absorption.⁶ There was an increased rate of myocardial infarction (MI) with both dosages of dabigatran (0.72%/yr for 110mg dose, 0.74%/yr for 150mg dose) compared to warfarin (0.53%/yr) with the difference in rate of MI with the 150mg dosage being statistically significant. The investigators suggest that this may be due to the protective nature of warfarin against MI and not as a result of dabigatran causing MI.⁶ Overall this study found a decrease in death from any cause with the use of dabigatran versus warfarin with a more pronounced effect with the higher dosage of dabigatran. It is important to note that patients with severe renal or hepatic dysfunction were excluded from this trial, so more data are needed to determine the effect of dabigatran on this subset of patients. Currently there is an ongoing trial, named RELY-ABLE, which has an estimated completion date of July 2011 that is a long term extension of the RE-LY trial to evaluate long-term safety of this agent.⁷ In conclusion, the results of the RE-LY trial support the use of

dabigatran for stroke prevention in patients with atrial fibrillation.

Table 4: Results of RE-LY trial

	Warfarin (adjusted dose) N = 6015	Dabigatran (110mg bid) N = 6015	Dabigatran (150mg bid) N = 6076
Stroke or systemic embolism	1.69 %/yr	1.53 %/yr (p < 0.001) non-inferior	1.11 %/yr (p < 0.001) superior
Ischemic stroke	1.2 %/yr	1.34 %/yr	0.92 %/yr p = 0.003
Myocardial infarction	0.53 %/yr	0.72 %/yr	0.74 %/yr p = 0.048
Major bleeding	3.36 %/yr	2.71 %/yr p = 0.003	3.11 %/yr
GI bleeding	1.02 %/yr	1.12 %/yr	1.51 %/yr p < 0.001
Death from any cause	4.13 %/yr	3.75 %/yr	3.64 %/yr p = 0.051

Adapted from tables and text in Reference 6.

Dabigatran has also been studied for the use of VTE prophylaxis in total hip and total knee replacement (THR/TKR). The RE-NOVATE, RE-MODEL, and RE-MOBILIZE trials evaluated enoxaparin versus dabigatran at doses of 150mg or 220mg once daily (Table 5).⁸ It is helpful to be familiar with the two different dosage regimens for enoxaparin that were used in these trials. In Europe enoxaparin is used for VTE prophylaxis for THR/TKR at a dosage of 40mg SQ once daily started 12 hours prior to surgery.⁹ In the U.S., enoxaparin is used for VTE prophylaxis for TKR at an approved dosage of 30mg SQ twice daily starting 12 – 24 hours after surgery.⁹ Both dosage regimens are approved for VTE prophylaxis in THR in the U.S. When evaluating the outcomes of these trials, it is important to keep in mind the regimen that is used for enoxaparin for this indication in the U.S. as this will most closely mirror the true effects in the U.S. patient population. It is also important to be familiar with duration of anticoagulation therapy used for prophylaxis in these trials. The CHEST 2008 Guidelines recommend at least 10 days but up to 35 days of anticoagulation therapy for VTE prophylaxis in THR and at least 10 days of prophylaxis for TKR.¹ The first two trials, RE-NOVATE and RE-MODEL, provided prophylaxis for 6 – 10 days, meaning that not all patients met the 10 day minimum recommended by CHEST.⁸ Together, these trials enrolled over 8,000 patients.⁷ In the RE-NOVATE trial, enoxaparin 40mg daily was compared to dabigatran 150mg or 220mg once daily for VTE prophylaxis in THR. Dabigatran was shown to be non-inferior (equal) to enoxaparin for this indication. The primary outcome of VTE and all-cause mortality occurred in 6.7% of patients in the enoxaparin group, 8.6% in the dabigatran 150mg group, and 6.0% in the dabigatran 220mg group. In the RE-MODEL trial, enoxaparin 40mg daily was compared to dabigatran for VTE prophylaxis in TKR. Dabigatran was also shown to be non-inferior (equal) to enoxaparin for this indication. The primary outcome of VTE and all-cause mortality occurred in 37.7% of patients in the enoxaparin group, 40.5% in the dabigatran 150mg group, and 36.4% in the dabigatran 220mg group. The results and data gained from these two trials aided in the approval of this medication in Europe and Canada. In the RE-MOBILIZE trial, U.S. enoxaparin dosing of 30mg twice daily was compared to dabigatran for VTE prophylaxis in TKR. For the primary endpoint of VTE and all-cause mortality, both dosages of dabigatran were found to be inferior to enoxaparin (dabigatran 150mg 33.7%, dabigatran 220mg 31.1%, and warfarin 25.3%). Major bleeding was not significantly different among any dosage regimen for enoxaparin or dabigatran across all three studies. In conclusion, dabigatran may be useful in the prophylaxis of VTE in THR/TKR with more data being needed comparing the U.S. enoxaparin dosage regimen with dabigatran and appropriate lengths of treatment. No difference in bleeding rates, hepatic enzyme elevation, or acute coronary syndrome between enoxaparin and dabigatran was found in any of these three trials.

Table 5: Results of RE-NOVATE, RE-MODEL, & RE-MOBILIZE

	Enoxaparin E-40mg daily E-30mg bid	Dabigatran (150mg daily)	Dabigatran (220mg daily)
Primary efficacy outcome: VTE (DVT/PE) and all-cause mortality			
RE-NOVATE (THR) E- (Prophylaxis 6 – 10 days)	6.7%	8.6% (p<0.0001) non-inferior	6.0% (p<0.0001) non-inferior
RE-MODEL (TKR) E- (Prophylaxis 6 – 10 days)	37.7%	40.5% (p=0.017) non-inferior	36.4% (p=0.0003) non-inferior
RE-MOBILIZE (TKR) C- (Prophylaxis 12 – 15 days)	25.3%	33.7% (p<0.001) inferior	31.1% (p=0.02) inferior
Primary safety outcome: major bleeding			
RE-NOVATE (THR)	1.6%	1.3%	2.0%
RE-MODEL (TKR)	1.3%	1.3%	1.5%
RE-MOBILIZE (TKR)	1.4%	0.6%	0.6%

Adapted from text in Reference 8.

RIVAROXABAN

Rivaroxaban is a direct factor Xa inhibitor.³ It was also approved for use in Europe and Canada in 2008 for VTE prophylaxis in elective THR and TKR, under the brand name Xarelto®.⁴ Rivaroxaban is different than fondaparinux in that rivaroxaban is a direct inhibitor of factor Xa and does not require antithrombin III to exert its effects. Therefore, rivaroxaban can be referred to as an antithrombin III independent inhibitor of factor Xa. Rivaroxaban inhibits both free and unbound factor Xa and by doing so prevents the conversion of prothrombin to thrombin and preventing thrombus formation.¹

Rivaroxaban is given orally and is 80% bioavailable.³ It is hepatically metabolized by the cytochrome P450 enzymes CYP3A4 and CYP2J2, which means that drugs that inhibit these enzymes may cause plasma drug levels to rise.³ Two-thirds of rivaroxaban is excreted via the kidneys, therefore it can be expected that either dosage adjustments or contraindications for use in impaired renal function will be warranted.⁴ Peak plasma concentrations are achieved within 3 hours and the half-life is 9 hours.⁴ As a result of its quick onset of effect, anticoagulant therapy with rivaroxaban would not require bridge therapy with heparins or fondaparinux when immediate anticoagulation is critical.

The RECORD trials are Phase III clinical trials conducted comparing enoxaparin to rivaroxaban for VTE prophylaxis in total hip and knee replacement.³ The RECORD 1 trial enrolled over 4,500 patients and showed rivaroxaban as having superior efficacy over enoxaparin at the dosage of 40mg SQ once daily for the prevention of VTE in THR, 3.7% vs. 1.1% respectively.¹⁰ There was no difference in rate of major bleeding between the two groups. The trials RECORD 3 and RECORD 4 compared enoxaparin to rivaroxaban for the prevention of VTE in total knee replacement.^{9,11} RECORD 3 used the European enoxaparin dosing of 40mg SQ once daily and RECORD 4 used the US enoxaparin dosing of 30mg SQ twice daily. Both the RECORD 3 and RECORD 4 trials showed a statistically significant decrease (superiority) in risk of VTE and all-cause mortality with rivaroxaban versus enoxaparin with no difference in major bleeding.^{9,11} There are concerns that rivaroxaban may cause drug-induced liver injury and clinically relevant non-major bleeding.¹² Rivaroxaban was submitted for approval to the FDA for the indication of VTE prophylaxis in total hip and knee replacement based on the findings of these trials. The FDA advisory panel preliminarily approved rivaroxaban in March 2009, however in May 2009 the FDA sought further information regarding safety data.¹² At this time, approval of rivaroxaban is still pending FDA review.

Table 6: Results of REORD 1, RECORD 3, & RECORD 4 trials

	Enoxaparin 10-40mg daily C-30mg bid	Rivaroxaban (10mg daily)	Duration of therapy
Primary efficacy outcome: VTE (DVT/PE) and all-cause mortality			
RECORD 1 (THR) \bar{P}	3.7 %	1.1 % (p < 0.001) superior	31 - 39 days
RECORD 3 (TKR) \bar{P}	18.9 %	9.6 % (p < 0.001) superior	10 - 14 days
RECORD 4 (TKR) \bar{C}	10.1 %	6.9 % (p = 0.0118) superior	10 - 14 days
Primary safety outcome: major bleeding			
RECORD 1 (THR) \bar{P}	0.1 %	0.3 %	
RECORD 3 (TKR) \bar{P}	0.5 %	0.6 %	
RECORD 4 (TKR) \bar{C}	0.3 %	0.7 %	

Adapted from tables and text in Reference 3.

CONCLUSIONS

In summary, anticoagulation therapy is an integral part of care for the treatment and prevention of venous thromboembolism and in the prevention of stroke in patients with mechanical heart valve prosthesis or in those with atrial fibrillation. Warfarin, the mainstay of long-term oral anticoagulation therapy, requires close monitoring but has been shown to be very effective when used with care. Other currently available anticoagulants are limited by their need for parenteral administration. There is an enormous amount of data that remains to be gathered, published, and evaluated regarding these two emerging agents, dabigatran and rivaroxaban. Early evidence indicates potential promise for the use of these agents in prevention of cardioembolic stroke in atrial fibrillation and/or VTE prophylaxis in total hip and knee replacement surgeries. In addition to efficacy, long-term safety must be established before either of these agents might be (safely) approved for use in the U.S. market.

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Continuing Education for Pharmacists

Quiz and Evaluation

Oral anticoagulation without protimes: A review of two emerging agents that may come to market.

1. Anticoagulation therapy:
 - a. completely prevents clot formation
 - b. makes patients bleed
 - c. results in coagulation
 - d. slows the rate of coagulation
2. The only oral anticoagulant available on the U.S. market today is:
 - a. enoxaparin
 - b. dabigatran
 - c. warfarin
 - d. fondaparinux
3. Venous thromboembolism (VTE) includes both:
 - a. deep vein thrombosis (DVT) and pulmonary embolism (PE)
 - b. deep vein thrombosis (DVT) and ischemic stroke
 - c. ischemic stroke and pulmonary embolism (PE)
 - d. atherosclerotic plaque and pulmonary embolism (PE)
4. Indications for anticoagulation therapy include:
 - a. treatment of venous thromboembolism (VTE)
 - b. prevention of VTE in orthopedic surgery
 - c. prevention of stroke in atrial fibrillation
 - d. all of the above
5. Desirable attributes for newly developed anticoagulants include all of the following EXCEPT:
 - a. Oral administration
 - b. Targets multiple clotting factors
 - c. Low risk of bleeding
 - d. Available antidote
6. Dabigatran's mechanism of action is a:
 - a. Direct thrombin inhibitor
 - b. Antithrombin III dependent inhibitor of thrombin
 - c. Direct Factor Xa inhibitor
 - d. Antithrombin III dependent inhibitor of factor Xa
7. All of the following are true EXCEPT:
 - a. Clinical trials have found dabigatran to have equivalent efficacy compared to enoxaparin (40 mg once daily) for VTE prophylaxis in total hip replacement and total knee replacement.
 - b. Clinical trials have found dabigatran to have equivalent efficacy compared to enoxaparin (30mg twice daily) for VTE prophylaxis in total hip replacement.
 - c. Dabigatran is approved for VTE prophylaxis in total hip and total knee replacement in Europe and Canada.
 - d. The RE-LY trial found that dabigatran was non-inferior (equivalent) to warfarin for the prevention of cardioembolic stroke in atrial fibrillation.
8. Rivaroxaban's mechanism of action is a:
 - a. Direct thrombin inhibitor
 - b. Antithrombin III dependent inhibitor of thrombin
 - c. Direct Factor Xa inhibitor
 - d. Antithrombin III dependent inhibitor of factor Xa
9. The RECORD trials found that rivaroxaban has _____ efficacy for the prevention of venous thromboembolism in total knee and total hip replacement as compared to enoxaparin.
 - a. Inferior
 - b. Equivalent
 - c. Superior
 - d. Indeterminant
10. The FDA advisory panel requested further safety data prior to the approval of rivaroxaban likely to assess what concerns:
 - a. Hepatotoxicity and dyspepsia
 - b. Hepatotoxicity and increased bleeding risk
 - c. Pulmonary toxicity and increased bleeding risk
 - d. Pulmonary toxicity and dyspepsia

Journal CPE Answer Sheet

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Oral anticoagulation without protimes: A review of two emerging agents that may come to market.

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ACPE#: 0142-0000-10-105-H01-P

Contact Hours: 1.0 (0.1 CEU)

Release Date: 05/01/2010

Expiration Date: 05/01/2013

1. Select one correct answer per question and circle the appropriate letter below using blue or black ink (no red ink or pencil.)

2. Members submit \$4.00, Non-members must include \$10.00 to cover the cost of grading and issuing statements of credit/ Please send check or money order only. Note: GPhA members will receive priority in processing CE.

Statements of credit for GPhA members will be emailed or mailed within four weeks of receipt of the course quiz.

- | | |
|------------|-------------|
| 1. A B C D | 6. A B C D |
| 2. A B C D | 7. A B C D |
| 3. A B C D | 8. A B C D |
| 4. A B C D | 9. A B C D |
| 5. A B C D | 10. A B C D |

Activity Evaluation: must be completed for credit

Please rate the following items on a scale from 1 (poor) to 5 (excellent) as to how well the activity:

- | | | | | | |
|--|-------|---|---|---|---|
| 1. Met my educational needs: | 1 | 2 | 3 | 4 | 5 |
| 2. Relates to pharmacy practice: | 1 | 2 | 3 | 4 | 5 |
| 3. Achieves the stated learning objectives: | 1 | 2 | 3 | 4 | 5 |
| 4. Faculty presented the information: | 1 | 2 | 3 | 4 | 5 |
| 5. Teaching methods conveyed information: | 1 | 2 | 3 | 4 | 5 |
| 6. Post-test aided in assessing my grasp of the information: | 1 | 2 | 3 | 4 | 5 |
| 7. Avoided any bias or commercial bias: | 1 | 2 | 3 | 4 | 5 |
| 8. How long did it take to complete this activity? | _____ | | | | |

A passing grade of 70% is required for each examination. A person who fails the exam may resubmit the quiz only once at no additional charge.

Please check here if you are indicating a change of address Phone #: _____

Name: _____

License Number(s) and State(s): _____ Email Address: _____

Address: _____

City: _____ State: _____ Zip: _____

Remove this page from the Journal and mail this completed quiz and evaluation to: GPhA, 50 Lenox Pointe NE, Atlanta, GA 30324.