

Dabigatran & Rivaroxaban – Rat Poison in Better Packaging?

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Declaration

- I have no conflicts of interest to declare

Deep Vein Thrombosis - Prophylaxis

- Orthopedic Surgery
 - Elective Hip Replacement
 - LMWH, starting 12 h before surgery or 12-24 h after surgery, or 4-6 h after surgery at half usual dose & ↑ to usual dose following day
 - fondaparinux 2.5 mg 6-24 h after surgery
 - adjusted-dose VKA started preop or evening of surgical day (INR target = 2.5; INR range= 2-3)
 - High risk bleeding = mechanical thromboprophylaxis with venous foot pump (VFP) or intermittent pneumatic compression (IPC)
 - Grade 1A

Chest 2008;133:381S-453S

Deep Vein Thrombosis - Prophylaxis

- Total Knee Replacement
 - LMWH, fondaparinux, or adjusted-dose VKA (INR target = 2.5; INR range = 2-3)
- Grade 1A
 - Alternative = IPC
- Grade 1B
 - High risk of bleeding
 - IPC (Grade 1A)
 - VFP (Grade 1B)

Chest 2008;133:381S-453S

Deep Vein Thrombosis - Prophylaxis

- Knee Arthroscopy
 - No risk factors
 - Early mobilization (Grade 2B)
 - Thromboembolic risk factors or following a complicated procedure,
 - LMWH (Grade 1B)
- Hip Fracture Surgery
 - Fondaparinux (Grade 1A)
 - LMWH (Grade 1B)
 - Adjusted dose VKA (INR target = 2.5; INR range = 2-3) [Grade 1B]
 - Low dose UH (Grade 1B)
 - Surgery is delayed, start thromboprophylaxis with LMWH or low dose UH (Grade 1C)
 - High risk of bleeding
 - Mechanical thromboprophylaxis (Grade 1A)

Chest 2008;133:381S-453S

Deep Vein Thrombosis - Prophylaxis

Surgery	Duration of therapy	
	10 days	Up to 35 days
THR	Grade 1A	Grade 1A
TKR	Grade 1A	Grade 2B
HFS	Grade 1A	Grade 1A

Risk factors: previous VTE, current obesity, delayed mobilization, advanced age, & cancer

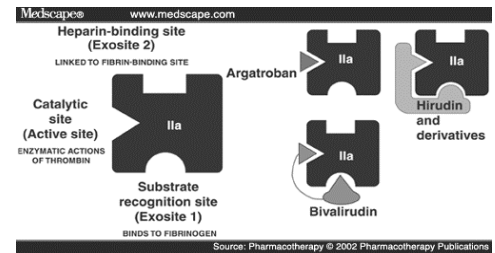
Chest 2008;133:381S-453S

Notice Of Compliance - Dabigatran

- Notice of Compliance
 - June 10, 2008
- Uses
 - Prevention of DVT/PE in pts undergoing elective total hip or total knee replacement
- Dosing
 - 150-220 mg po daily

eCPS 2009; Dabigatran Monograph

Mechanism of Action - Dabigatran



ADME - Dabigatran

- Absorption
 - F = 6.5%
 - Requires acidic environment
 - Peak plasma concentrations = 6 hrs
- Distribution
 - Vd = 0.85 – 1 L/kg
 - ~35% protein bound
- Metabolism
 - Rapidly & completely converted from pro-drug (dabigatran etexilate) to active form (dabigatran)
- Elimination
 - Excreted unchanged in the urine primarily via glomerular filtration

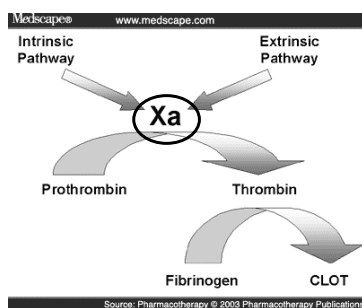
eCPS 2009; Dabigatran Monograph

Notice of Compliance – Rivaroxaban

- Notice of Compliance
 - September 15, 2008
- Uses
 - Prevention of DVT/PE in pts undergoing elective total hip or total knee replacement
- Dosing
 - 10 mg po daily

eCPS 2009; Rivaroxaban Monograph

Mechanism of Action - Rivaroxaban



ADME - Rivaroxaban

- Absorption
 - F = 100%
 - Peak plasma concentrations = 2-4 hrs
- Distribution
 - Vd = 0.7 L/kg
 - ~95% protein bound
- Metabolism
 - CYP 3A4, CYP 2J2, & CYP-independent mechanisms
- Elimination
 - 1/3 excreted unchanged in the urine
 - 1/3 excreted as inactive metabolites in the urine
 - 1/3 excreted as inactive metabolites via fecal route

eCPS 2009; Rivaroxaban Monograph

Orthopedic Literature

Dabigatran

RE-NOVATE

R,DB,P

n = 3494

P	Pts with total hip replacement
I	dabigatran 150 mg po daily (n = 1174) x 28-35 days OR dabigatran 220 mg po daily (n = 1157) x 28-35 days
C	vs. enoxaparin 40 mg SC daily (n = 1162) x 28-35 days
O	total venous thromboembolism (venographic or symptomatic) & death from all causes during treatment

Non-inferiority margin = 7.7%

Lancet 2007; 370: 949-56

RE-NOVATE

- Primary endpoint
 - Dabigatran 150 mg: 8.6%
 - Dabigatran 220 mg: 6.0%
 - Enoxaparin: 6.7%
- No difference in bleeding rates
- Author's Conclusions
 - Dabigatran was as effective as enoxaparin in reducing the risk of venous thromboembolism after total hip replacement surgery, with a similar safety profile

Lancet 2007; 370: 949-56

RE-MODEL

R,DB,P

n = 2076

P	Pts with total knee replacement
I	dabigatran 150 mg po daily (n = 708) x 6-10 days OR dabigatran 220 mg po daily (n = 694) x 6-10 days
C	vs. enoxaparin 40 mg SC daily (n = 699) x 6-10 days
O	total venous thromboembolism (venographic or symptomatic) & mortality during treatment

Non-inferiority margin = 9.2%

J Thromb Haemost 2007; 5:2178-85

RE-MODEL

- Primary endpoint
 - Dabigatran 150 mg: 40.5%
 - Dabigatran 220 mg: 36.4%
 - Enoxaparin: 37.7%
- No difference in bleeding rates
- Author's Conclusions
 - Dabigatran was at least as effective as enoxaparin & had a similar safety profile for prevention of VTE after total knee replacement surgery

J Thromb Haemost 2007; 5:2178-85

RE-MOBILIZE

R,DB,P

n = 2615

P	Pts with total knee replacement
I	dabigatran 150 mg po daily x 12-15 days OR dabigatran 220 mg po daily x 12-15 days
C	vs. enoxaparin 30 mg SC BID x 12-15 days
O	total venous thromboembolism (venographic or symptomatic) & mortality during treatment

Non-inferiority trial

J Thromb Haemost 2007; 5(Suppl 2):O-W-050

RE-MOBILIZE

- Primary endpoint
 - Dabigatran 150 mg: 33.7%
 - Dabigatran 220 mg: 31.1%
 - Enoxaparin: 25.3%
- No difference in bleeding rates
- Dabigatran was *inferior* to enoxaparin

J Thromb Haemost 2007; 5(Suppl 2):O-W-050

Orthopedic Literature

Rivaroxaban

RECORD 1

R,DB,P

n = 4541

P	Pts with total hip arthroplasty
I	rivaroxaban 10 mg po daily (n = 1595) x 31-39 days
C	vs. enoxaparin 40 mg sc daily (n = 1558) x 31-39 days
O	total venous thromboembolism (venographic or symptomatic) & mortality

Lancet 2008; 372: 31–39

RECORD 1

- Primary endpoint
 - Rivaroxaban: 1.1%
 - Enoxaparin: 3.7%
- No difference in major bleeds
- Author's Conclusion
 - Rivaroxaban was significantly more effective than enoxaparin for extended VTE prophylaxis following THA, with similar bleeding rates

RECORD 2

R,DB,P

n = 2509

P	Pts with total hip arthroplasty
I	rivaroxaban 10 mg po daily (n = 1252) x 31-39 days
C	vs. enoxaparin 40 mg sc daily (n = 1257) x 10-14 days
O	total venous thromboembolism (venographic or symptomatic) & mortality

Lancet 2008; 372: 31–39

RECORD 2

- Primary endpoint
 - Rivaroxaban: 2%
 - Enoxaparin: 9.3%
- No difference in major bleeds
- Author's Conclusion
 - Extended thromboprophylaxis with rivaroxaban was significantly more effective than short-term enoxaparin for the prevention of venous thromboembolism, in patients undergoing total hip arthroplasty

RECORD 3

R,DB,P

n = 2531

P	Pts with total knee arthroplasty
I	rivaroxaban 10 mg po daily (n = 1254) x 10-14 days
C	vs. enoxaparin 40 mg sc daily (n = 1277) x 10-14 days
O	total venous thromboembolism (venographic or symptomatic) & mortality

Lancet 2008; 372: 31-39

RECORD 3

- Primary endpoint
 - Rivaroxaban: 9.6%
 - Enoxaparin: 18.9%
- No difference in major bleeds
- Author's Conclusion
 - Extended thromboprophylaxis with rivaroxaban was significantly more effective than enoxaparin for venous thromboembolism prophylaxis, in patients undergoing total knee arthroplasty

Summary & Conclusions

- Dabigatran
 - Total Hip Replacement
 - May have a role with extended treatment, but has not been compared to appropriate doses of enoxaparin
 - Continue to use LMWH
 - May be an option in patients not willing to take injections &/or undergo INR monitoring
 - Total Knee Replacement
 - No role vs. enoxaparin at this time
 - Last alternative AFTER other therapeutic options

Summary & Conclusions

- Rivaroxaban
 - Total Hip Replacement
 - May have a role with extended treatment, but has not been compared to appropriate doses of enoxaparin
 - Continue to use LMWH
 - An option in patients not willing to take injections &/or undergo INR monitoring
 - Total Knee Replacement
 - May have a role, but has not been compared to appropriate doses of enoxaparin
 - Option in patients not willing to take injections &/or undergo INR monitoring

Ongoing & Future Studies

- Dabigatran
 - Recurrent symptomatic VTE, acute symptomatic VTE, elective percutaneous coronary intervention, atrial fibrillation, acute coronary syndromes
- Rivaroxaban
 - Acute coronary syndromes, atrial fibrillation, prevention of recurrent symptomatic VTE, acute symptomatic DVT/PE, VTE prophylaxis in medical patients

www.clinicaltrials.gov