



## 고관절치환술 후의 Rivaroxaban의 국내임상적용

유옥리<sup>1,2</sup> · 나현오<sup>2</sup> · 이정연<sup>1,3\*</sup>

<sup>1</sup>이화여자대학교 임상보건과학대학원, <sup>2</sup>가톨릭대학교 서울성모병원 약제부, <sup>3</sup>이화여자대학교 약학대학

(2014년 1월 12일 접수 · 2014년 3월 18일 수정 · 2014년 3월 19일 승인)

### Rivaroxaban in Patients Undergoing Hip Arthroplasty in Korean Patients: Implications in Clinical Practice

Yu Li Liu<sup>1,2</sup>, Hyen O La<sup>2</sup>, and Sandy Jeong Rhie<sup>1,3\*</sup>

<sup>1</sup>Graduate School of Clinical Health Sciences, Ewha Womans University, Seoul 120-750, Korea

<sup>2</sup>Seoul St. Mary's Hospital, Seoul 137-718, Korea

<sup>3</sup>College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea

(Received January 12, 2014 · Revised March 18, 2014 · Accepted March 19, 2014)

**Objective:** Currently, rivaroxaban is widely used clinically for thromboprophylaxis after surgery. However, there are concerns on effectiveness and safety of rivaroxaban for its proper use. We aimed to evaluate the effectiveness and safety of rivaroxaban in orthopaedic patients after total hip replacement surgery in a large medical centre after the preferred formulary was switched from enoxaparin to rivaroxaban. **Methods:** The study was conducted on the patients who underwent hip arthroplasty surgery at the department of Orthopaedic Surgery at Seoul St. Mary's Hospital, South Korea. Electronic medical records were retrospectively reviewed to identify patients treated with rivaroxaban following total hip replacement between February 2011 and March 2012. Evaluation criteria included indications for use, dose, initiation and duration of therapy, drug interactions, adverse reactions, and status of health care reimbursement. The patients who were on enoxaparin were also reviewed as a reference. **Results:** We identified 57 patients who received rivaroxaban and 50 who received enoxaparin. All patients were prescribed the drugs for Korean Food and Drug Administration-approved indications. No thromboembolic or bleeding events were observed in either group. However, only 5.3% of rivaroxaban-treated patients had an appropriate length of prophylaxis and only 3.5% began rivaroxaban treatment at the recommended time. Surprisingly, 47.4% of rivaroxaban-treated patients received rivaroxaban despite being ineligible for reimbursement benefits. **Conclusion:** Rivaroxaban was generally well tolerated clinically. However, the duration of treatment, the time of initiation and patient eligibility for reimbursement require improvements, emphasising the need for education which indicates the area of pharmacists' involvement.

□ Key words - drug utilization review, drug therapy, rivaroxaban, thromboembolism, anticoagulant

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), has a negative impact on patient mortality and morbidity.<sup>1,2)</sup> The incidence of VTE is high after orthopaedic total hip replacement (THR) surgery and total knee replacement (TKR). Without proper prophylaxis, the rate of DVT can

range from 41–85%, the rate of PE can be as high as 30%, and fatal PE rates can range from 0.1 to 2%.<sup>2,3)</sup> VTE is usually prevented by anticoagulant treatment, including intravenous injections of unfractionated heparin, low molecular weight heparin (LMWH) and fondaparinux. However, the inconvenience of injections limits self-administration of these anticoagulants, especially after discharge from the hospital.<sup>2,4)</sup> Warfarin can be used to prevent VTE after orthopaedic surgery, but it has a narrow therapeutic index, requires close monitoring, and is associated with late onset VTE, which then requires bridging with heparin preparations.<sup>5)</sup>

Correspondence to : Sandy Rhie

Division of Life and Pharmaceutical Sciences  
and College of Pharmacy, Ewha Womans  
University, Seoul 120-750, Korea  
Tel: +82-2-3277-3023, Fax: +82-2-3277-2851  
E-mail: sandy.rhie@ewha.ac.kr

Rivaroxaban, a direct and selective oral coagulation factor Xa inhibitor, has been investigated as a replacement for traditional anticoagulants.<sup>5,7)</sup> This agent has a bioavailability of about 80–100% and a half-life of about 5–9 h.<sup>8,9)</sup> Rivaroxaban also shows post-THR superiority to enoxaparin, a LMWH, in efficacy and safety in randomized clinical trials.<sup>10,11)</sup> The rivaroxaban dose for VTE prophylaxis is 10 mg/day orally, with regular monitoring is not required for efficacy and safety.<sup>8)</sup> The duration of anticoagulation prophylaxis is based on the type and severity of surgery and individual risk factors for VTE, but the guidelines recommend that rivaroxaban be administered for 35 days after THR and for 14 days after TKR.<sup>3)</sup> Approximately 14% of treated patients in the phase III trials experienced adverse reactions, with 3.3% and 1% experiencing bleeding and anaemia, respectively.<sup>14)</sup> Other common adverse reactions included nausea and an increase in transaminases.<sup>14)</sup>

The department of Orthopaedic Surgery at Seoul St. Mary Hospital, one of the major university hospitals in South Korea with a 1400-bed capacity, switched the preferred formulary of post-THR prophylaxis from enoxaparin to rivaroxaban in September 2011. Although rivaroxaban showed superior post-THR outcomes compared with enoxaparin in major clinical trials,<sup>11)</sup> it can only benefit to patients if it is used appropriately which involves that physicians prescribe it according to evidence. The drug utilization review needs to be followed to assess and correct the appropriateness of drug prescription<sup>1-3)</sup> when it is still new on the market with few post-marketing reports.

The objective of this study was to investigate whether rivaroxaban is being prescribed and administered properly according to the guidelines in practice during this early stage of use in patients who underwent THR.

## METHOD

This single-centre, time-comparative, retrospective electronic medication review involved 107 patients, 50 receiving enoxaparin from February to August 2011

and 57 receiving rivaroxaban from September 2011 to March 2012. The formulary change from enoxaparin to rivaroxaban occurred in September 2011, with no THR patient receiving enoxaparin after the formulary change and therefore no patient overlaps in medication. The study protocol was approved by the institutional review board of Seoul St. Mary Hospital.

We included all patients admitted for THR who received rivaroxaban or enoxaparin to prevent VTE during the study periods. Data collection was managed and evaluated by the American Society of Hospital Pharmacists "Criteria of Drug Use Evaluation, Vol. 1"<sup>15)</sup> Compliance criteria were based on the recommendations of the American College of Chest Physicians (ACCP) and Summary of Product Characteristics (SPC) of rivaroxaban which included use for the prophylaxis of DVT, which may lead to PE, in patients undergoing THR. The dosage for prophylaxis after THR was 10 mg po daily. According to the guidelines, treatment should be initiated within 6–10 h after surgery and when the patient became haemodynamically stable, and should be continued for 35 days.<sup>3,14)</sup> Use in pregnancy (pregnancy category C) and lactation and concomitant medication use with possible drug interactions were investigated, mainly for non-steroidal anti-inflammatory drugs (NSAIDs) and antiplatelet agents. Adverse drug reactions included any bleeding or thrombosis-related to surgery were also examined. The bleeding episode was evaluated by blood transfusion records, any  $>2$  g/dL decrease in haemoglobin concentration, and any gastrointestinal or minor bleeding. Patients were followed up for 3 months after discharge by reviewing the outpatient clinic visit records. Eligibility criteria of the study subjects were assessed for reimbursement for rivaroxaban by the National Health Insurance (NHI) of Korea. These included THR or TKR with body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>, concurrent oestrogen therapy, varicose veins in the legs, aged  $\geq 60$  years, immobility  $\geq 1$  week, congestive heart failure, respiratory failure, malignancy, insertion of central venous catheter, chemotherapy, sepsis and a history of VTE.<sup>16)</sup> Enoxaparin was also evaluated with the same criteria used with rivaroxaban to be used as a reference.

## RESULTS

### Study Subjects

The baseline characteristics of the two groups were similar, including mean age, the ratio of males to females, and body mass index (BMI) (Table 1). The percentages of patients >60 years old who were considered at high risk for VTE were 43.9% in the rivaroxaban and 54% in enoxaparin groups, respectively, as were the percentages with pre-existing comorbid conditions.

### Indications and Dosage

All patients received rivaroxaban or enoxaparin for approved prophylaxis after THR. All study subjects were compliant with the recommended prophylactic doses of rivaroxaban 10 mg/day orally or enoxaparin 40 mg/day subcutaneously daily (Tables 2).

### Initiation of Medication and Duration of Therapy

The mean starting time of rivaroxaban treatment was 4.4 days after the end of surgery, with only two of 57 (3.5%) starting rivaroxaban at the time recommended by the criteria. None of the patients in the enoxaparin group began treatment at the time recommended by the guidelines.

The recommended duration of prophylaxis after major orthopaedic surgery is 35 days with rivaroxaban and 7–10

days with enoxaparin.<sup>2,13)</sup> We found that only three of 57 (5.3%) patients in the rivaroxaban group and only six of 50 (12%) in the enoxaparin group were treated for the recommended duration. Forty-two patients (73.7%) in the rivaroxaban group were treated for less than 35 days, and 43 patients (86%) in the enoxaparin group were treated for ≤3 days (Tables 2).

### Use in Specific Populations

One nursing mother was treated with rivaroxaban for 5 days while in the hospital (Table 2).

### Drug Interactions and Adverse Reactions

Postoperatively, 84.2% of patients in the rivaroxaban group and 76% in the enoxaparin group were taking NSAIDs, but no harmful interactions were observed. No patient experienced any bleeding or thromboembolism relating to rivaroxaban use were reported during the study (Table 2).

### Reimbursement Eligibility

Of the 57 patients treated with rivaroxaban, 30 (52.6%) were eligible for reimbursement by the Korean NHI. Although all patients were eligible for reimbursement for enoxaparin, 27 rivaroxaban-treated patients (47.4%) were not eligible and paid for this drug out-of-pocket.

**Table 1. Demographics of the Patients Receiving Rivaroxaban or Enoxaparin Following Total Hip Arthroplasty.**

	Rivaroxaban n=57	Enoxaparin n=50	P-value*
<b>Age, Average</b>	55.6	61.22	
> 60 years old, n (%)	25 (43.9%)	27 (54%)	0.15
<b>Women, n (%)</b>	32 (56.1%)	26 (52%)	0.67
<b>Long-Term Immobility, n (%)</b>	1 (1.75%)	None	
<b>Median Body Mass Index, kg/m<sup>2</sup></b>	22.7	22.8	0.32
<b>History of Thromboembolism, n (%)</b>	1 (1.75%)	None	
<b>Comorbidities, n, (%)</b>	28 (49.1%)	27 (54%)	0.98
Hypertension	8 (14%)	8 (16%)	
Diabetes mellitus (DM)	4 (7%)	2 (4%)	
Systemic lupus syndrome	2 (3.5%)	1 (2%)	
Rheumatic arthritis	1 (1.8%)	2 (4%)	
Hypertension & DM	3 (5.3%)	7 (14%)	
Renal/hepatic insufficiency	0	0	
Others**	10 (17.5%)	7 (14%)	

\*Student *t* tests and  $\chi^2$  tests were applied for continuous and nominal data as appropriate. *p* < 0.05

\*\*Schizophrenia, acute myeloid leukaemia, urinary tract infection, tuberculosis, thyroid nodule, history of brain tumour, kidney transplantation, thyroid goitre, Parkinson's disease, ischemic cerebral attack, osteoporosis, hypothyroidism, and asthma.

The non-reimbursed patients in the rivaroxaban group paid about US\$211 for prophylaxis, whereas the cost for full duration of enoxaparin prophylaxis was US\$69 (Tables 2).

### Outpatient Follow-up

Follow-up data for at least 3 months after discharge were available by reviewing the record from outpatient clinic visits. Thirty three rivaroxaban-treated and 42 enoxaparin-treated patients were available upon reviewing. None of the patients in either group reported bleeding or VTE (Tables 2).

## DISCUSSION

With rivaroxaban was introduced to the hospital as a

replacement of enoxaparin in patient who underwent THR, drug utilization evaluation was performed. We found that indications for use and prescribed dosages of rivaroxaban and enoxaparin were well compliant with the criteria of each drug.<sup>8)</sup> However, we did observe deviations in the timing of initiation and the duration of therapy.

The timing of initiation and the duration of prophylactic therapy are reflected on individuals' VTE risks and the types of orthopaedic surgery. It is commonly recommended that the first dose of rivaroxaban be administered within 6–10 h or when the patient becoming haemodynamically stable after THR surgery and be continued for 35 days.<sup>2)</sup> By contrast, enoxaparin for thromboprophylaxis should be administered either 12 h before surgery (in Europe) or 12 h after surgery (in North America).<sup>8,13,14)</sup> Although North American recommendation is more con-

**Table 2. Evaluation of Rivaroxaban Usage: Criteria and Compliance.**

Evaluation Criteria	Rivaroxaban		Enoxaparin	
	n	%	n	%
<b>Indication of Use</b>	57	100%	50	100%
<b>Therapy Initiated on Time*</b>	2	3.5%		None
<b>Duration of Therapy</b>				
Rivaroxaban				
35 days	3	5.3%		NA
<35 days (Unmet criteria)	42	73.7%		NA
>35 days (Unmet criteria)	12	21%		NA
Enoxaparin				
7-10 days		NA	6	12%
5-7 days (Unmet criteria)		NA	1	2%
≤3 days (Unmet criteria)		NA	43	86%
<b>Dose 10 mg once daily</b>	57	100%		
<b>Use During Lactation</b>	56	98.2%	50	100%
<b>Concomitant Use of Drugs with Known Interactions**</b>				NA
NSAIDs*** (ex diclofenac, ibuprofen, celecoxib, meloxicam, piroxicam, ketoprofen.)	48	84.2%	38	76%
Systemic glucocorticosteroids	NA	NA	48	96%
Potassium sparing diuretics	NA	NA	50	100%
Angiotensin receptor inhibitors	NA	NA	49	98%
<b>Reimbursement Eligibility#</b>	30	52.6%	50	100%
<b>Adverse Reactions</b>				
Bleeding or venous thromboembolism in 3 months of discharge	None		None	

\* Rivaroxaban: Initiated within 6-10 h after surgery and haemodynamically stable. Enoxaparin: Administered either 12 h before surgery (in Europe) or 12 h after surgery (in North America)

\*\* At least one dose during administration of rivaroxaban was considered concomitant use

\*\*\* Non-steroidal anti-inflammatory drugs (NSAIDs)

#THR or TKR, body mass index (BMI) ≥30 kg/m<sup>2</sup>, concurrent oestrogen therapy, varicose veins in the legs, aged ≥60 years, immobility ≥1 week, congestive heart failure, respiratory failure, malignancy, insertion of central venous catheter, chemotherapy, sepsis and a history of VTE

servative than European's in the effort of avoiding potential major bleed in preoperative preparations and restrictions in anaesthetic procedure, the timing of the first dose of anticoagulant is to administer as early as possible after surgery with haemodynamic stability warranted.<sup>3)</sup> Low rate of compliance in the categories in the study indicates that the need for education for providers and other healthcare professionals in perioperative use of rivaroxaban in the orthopaedic patient population.

Extended prophylaxis for THR has been found to reduce the incidence of symptomatic and asymptomatic VTE more effectively than shorter-term prophylaxis.<sup>17)</sup> New diagnosis of DVTs has been reported to form after the discontinuation of short-term prophylaxis.<sup>18)</sup> Several meta-analyses have suggested that extended thromboprophylaxis after THR reduces the incidence of symptomatic VTE events, without increasing the risks of major bleeding.<sup>19-21)</sup> Indeed, the guideline from the ACCP recommends extended thromboprophylaxis after THR as a grade 1A recommendation.<sup>3)</sup> The National Institute of Health and Clinical Excellence (NICE) guidelines in 2007 and 2009 also recommend that enoxaparin or fondaparinux be administered for 4 weeks.<sup>14)</sup> It mentions that rivaroxaban, a newer anticoagulant, 10 mg orally to be administered within 6–10 h after surgery when an absence of bleeding is confirmed. Furthermore, they recommend that rivaroxaban, regardless the presence of mechanical prophylaxis, be continued for 35 days in patients at high risk of VTE. This includes patients who are aged  $\geq 60$  years and have a history of VTE, long-term immobility, congestive heart failure, obesity, myocardial infarction or stroke.<sup>14,22)</sup> In our study subjects, there were about a half of the patients with  $>60$  years old, a history of VTE, and/or immobility which considered as high risk. However, only two subjects started rivaroxaban in recommended time frame and only three patients continued rivaroxaban for 35 days. Six patients (10.5%) in the rivaroxaban group and 41 (82%) in the enoxaparin group were on compression stockings, the pharmacological prophylaxis is still preferred in addition to mechanical prophylaxis due to the VTE risk after THA surgery.<sup>3,29)</sup>

RECORD-2 was a randomized trial comparing 35 days

of rivaroxaban 10 mg/day and 15 days of enoxaparin 40 mg/day followed by oral placebo for 20 days as prophylaxis in the setting of THR.<sup>10)</sup> Rivaroxaban was found to be significantly superior to enoxaparin in the incidence of the primary efficacy outcome of a composite of DVT, non-fatal PE, and all-cause mortality up to day 30–42 and the secondary endpoints as well. This result actually added to the evidence that an extended duration of thromboprophylaxis after THA is more effective than short-term therapy. Noting that extended thromboprophylaxis after THA is already recommended in the current guidelines with LMWHs, fondaparinux or vitamin K antagonists, but there were concerns that such treatment is underused after hospital discharge to complete the recommend treatment course. Unfortunately, the similar occurrence was observed in our study. With fixed oral dosing and no monitoring, rivaroxaban would be thought an easier option to carry out compared to warfarin or LMWHs, but it may be too early to be reflected in the current practice yet. Interestingly, four patients in the rivaroxaban group were found to be treated for longer than recommended, which no proven benefit with the elongation of treatment period, whereas bleeding risk is increased.

Nevertheless the prevalence of VTE is known to be lower in Asian compared to other ethnicities; the incidence of VTE is increasing in recent years.<sup>25,26)</sup> Misconception of low VTE rates in Asia region would make people believe that the low dose or short duration of prophylaxis could be sufficient to prevent VTE after surgery in Koreans.<sup>25,26)</sup> A recent evaluation of VTE prevalence following mechanical prophylaxis in Korean patients after orthopaedic surgery found that VTE had an incidence of 1.99%.<sup>23,25)</sup> Some studies in Korean patients undergoing hip surgery showed that VTE rates without prophylaxis were between 10% and 16%.<sup>28,29,31)</sup>

Firstly, shorter duration of treatments in practice, such as observed in this study, is likely due to a lack of education given to hospital providers and the absence of a well-organized hospital protocols and policies in place. Another reason for hesitation to use rivaroxaban with a full prophylactic course may be unknown direct reversal agent which can be an issue when prescribed as a discharge

medication. Proactive use of prophylactic anticoagulants should be established as long as patients are haemodynamically stable without active bleeding concerns.

The Rocket AF trial showed that the concomitant use of  $\leq 100$  mg/day aspirin was an independent risk factor for major bleeding with rivaroxaban.<sup>33)</sup> This supports the notion that NSAIDs are associated with bleeding risk when used with rivaroxaban. However, we did not observe bleeding episodes resulting from interactions between NSAIDs and rivaroxaban in our study. This is likely because of the relatively short follow-up period and the small number of included subjects. It should still be emphasized, however, that any signs or symptoms of blood loss be monitored in rivaroxaban-treated patients receiving concomitant NSAIDs or other platelet aggregation inhibitors.

A cost-effectiveness associated with rivaroxaban compared to enoxaparin favoured rivaroxaban for the prevention of VTE by a decision-analytic model based on the results from RECORD trials.<sup>31,32)</sup> Yet, another study analysed a lack of adequate financial incentives to German hospitals to use rivaroxaban.<sup>32)</sup> Our study wasn't designed to look at the cost saving effectiveness from rivaroxaban in the hospital, but we decided to investigate if any presence of drug cost burden to THR patients. Reimbursement for pharmaceuticals after THR in Korea is governed by the National Health Institute (NHI). While enoxaparin, warfarin and INR monitoring visits are all have no restrictions to get paid for THR related medication cost, rivaroxaban still is not fully eligible to get reimbursed under Korean NHI plan. The hospital protocols and policies, and education programs regarding optimal choices for postoperative anticoagulants, safe and effective use and reimbursement information are expected to solve the current problems in a certain extent.

One patient was a nursing mother who was administered rivaroxaban for 5 days, but there was no report of any adverse reactions. It is not known if rivaroxaban is excreted in human milk, thus a decision should be made whether to discontinue nursing or discontinue/change the drug.<sup>8)</sup>

One of interesting finding was the unmet criteria of peri-

operative initiation timing and duration in both enoxaparin and rivaroxaban.

This study had several limitations, including a small sample size, a retrospective design, and being conducted at a single centre. However, as this study was performed at a 1400-bed major university hospital, the result from other practice setting may not differ considerably. The study might be too early to in the transition period of the formulary change. It warrants revisiting the evaluation of rivaroxaban use later. Understanding the efficacy, safety and reimbursement eligibility is important for physicians, nurses and other healthcare providers. The expanded indications for other uses of rivaroxaban emphasize the importance of these results in designing proper policies and procedures for its future use in hospital settings.

## CONCLUSION

This study evaluated the use of rivaroxaban in patients undergoing THR. We observed delays in perioperative initiation and a shorter-than-recommended thromboprophylactic treatment. Further improvements regarding guideline compliance and hospital policies are required for the safe and effective use of rivaroxaban.

## ACKNOWLEDGEMENT

Manuscript processing was supported by the Ewha Womans University Converged Design Business Group.

## REFERENCES

1. Hyers TM. Management of venous thromboembolism: past, present, and future. *Arch Intern Med* 2003; 163(7): 759-68.
2. Kearon C, Akl EA, Comerota AJ, *et al.* Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Chest Physicians Evidence-Based Clinical Thrombosis (9<sup>th</sup> ed.). American College of Practice Guidelines. *Chest* 2012; 141: e419S-e494S.
3. Falck-Ytter Y, Francis CW, Johanson NA, *et al.* Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis (9<sup>th</sup> ed.). American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl): e278S-325S.

4. Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor Xa inhibitors in development. *Clin Pharmacokinet* 2009; 48(1): 1-22.
5. Eriksson BI, Quinlan DJ. Oral anticoagulants in development; focus on thromboprophylaxis in patients undergoing orthopaedic surgery. *Drugs* 2006; 66(11): 1411-29.
6. Perzborn E, Strassburger J, Wilmen A, *et al.* In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939: an oral, direct factor Xa inhibitor. *J Thromb Haemost* 2005; 3(3): 514-21.
7. Depasse F, Busson J, Mnich J, *et al.* Effect of BAY 59-7939—a novel, oral direct factor Xa inhibitor—on clot-bound factor Xa activity in vitro [Abstract]. *J Thromb Haemost* 2005; 3 Suppl 1: P1104.
8. Bayer Schering Pharma. Xarelto® (rivaroxaban 10 mg tablets): EU summary of product characteristics. Available on the internet: <http://www.xarelto.com/en/information-on-xarelto/vte-prevention-in-orthopaedic-surgery>. [Last accessed June 2, 2013].
9. Weinz C, Schwarz T, Kubitzka D, *et al.* Metabolism and excretion of rivaroxaban, an oral, direct factor Xa inhibitor, in rats, dogs, and humans. *Drug Metab Dispos* 2009; 37(5): 1056-64.
10. Kakkar AK, Brenner B, Dahl OE, *et al.* RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008; 372(9632): 31-9.
11. Eriksson BI, Borris LC, Friedman RJ, *et al.* RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008; 358(26): 2765-75.
12. Grégoire JP, Moisan J, Potvin L, *et al.* Effect of drug utilization reviews on the quality of in-hospital prescribing: a quasi-experimental study. *BMC Health Services Research* 2006; 6: 33.
13. Garcia DA, Baglin TP, Weitz JI, *et al.* Parenteral Anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis (9<sup>th</sup> ed.). American College of Chest Physicians Evidence-Based Clinical Practice Guidelines *Chest* 2012; 141: e24S-e43S.
14. National Institute for Health and Care Excellence (NICE) Guideline. Final appraisal determination-Rivaroxaban for prevention of venous thromboembolism after total hip or knee replacement in adults. Issue date: February 2009 Available on the internet: <http://www.nice.org.uk/nicemedia/pdf/RivaroxabanFAD.pdf>. [Last accessed July 12, 2013].
15. Phillips MS, Gayman JE, Todd MW, *et al.* ASHP guidelines on medication-use evaluation. *Am J Health Syst Pharm* 1996; 53: 1953-5.
16. Health Insurance Reviews & Assessment Service. Healthcare Benefits Management. Available on the internet: <http://www.hira.or.kr>. [Last accessed June 14, 2013].
17. Bergqvist D, Benoni G, Björgell O, *et al.* Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *N Engl J Med* 1996; 335(10): 696-700.
18. Planes A, Vochelle N, Darmon JY, *et al.* Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. *Lancet* 1996; 348(9022): 224-8.
19. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet* 2001; 358(9275): 9-15.
20. Hull RD, Pineo GF, Stein PD, *et al.* Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med* 2001; 135(10): 858-69.
21. O'Donnell M, Linkins LA, Kearon C, *et al.* Reduction of out-of-hospital symptomatic venous thromboembolism by extended thromboprophylaxis with low-molecular-weight heparin following elective hip arthroplasty: a systematic review. *Arch Intern Med* 2003; 163(11): 1362-6.
22. Sanofi Korea. Product information. Clexane Injection®. Updated on April 22 2011. Available on the internet: [http://products.sanofi.co.kr/KR\\_Clexane\\_inj.pdf](http://products.sanofi.co.kr/KR_Clexane_inj.pdf). [Last accessed May 22, 2013].
23. Dahl OE. Orthopaedic surgery as a model for drug development in thrombosis. *Drugs* 2004; 64 Suppl 1: 17-25.
24. Agnelli G, Taliani MR, Verso M. Building effective prophylaxis of deep vein thrombosis in the outpatient setting. *Blood Coagul Fibrinolysis* 1999; 10 Suppl 2: S29-35.
25. Xing KH, Morrison G, Lim W, *et al.* Has the incidence of deep vein thrombosis in patients undergoing total hip/knee arthroplasty changed over time? A systematic review of randomized controlled trials. *Thromb Res* 2008; 123(1): 24-34.
26. Fujita S, Hirota S, Oda T, *et al.* Deep venous thrombosis after total of knee arthroplasty in patients in Japan. *Clin Orthop Relat Res* 2000; (300): 168-74.
27. Won MH, Lee GW, Lee TJ, *et al.* Prevalence and risk factors of thromboembolism after joint arthroplasty without chemical thromboprophylaxis in an Asian population. *J Arthroplasty* 2011; 26(7): 1106-11.
28. Kim YH, Suh JS. Low incidence of deep-vein thrombosis after cementless total hip replacement. *J Bone Joint Surg Am* 1988; 70(6): 878-82.
29. Yoo MC, Kang CS, Kim YH, *et al.* A prospective randomized study on the use nadroparin calcium in the

- prophylaxis of thromboembolism in Korean patients undergoing elective total hip replacement. *Int Orthop* 1997; 21(6): 399-402.
30. Zindel S, Stock S, Müller D, *et al.* A multi-perspective cost-effectiveness analysis comparing rivaroxaban with enoxaparin sodium for thromboprophylaxis after total hip and knee replacement in the German healthcare setting. *BMC Health Serv Res* 2012; 12: 192-205.
  31. Duran A, Sengupta N, Diamantopoulos A, *et al.* Cost effectiveness of rivaroxaban versus enoxaparin for prevention of post-surgical venous thromboembolism from a U.S. payer's perspective. *Pharmacoeconomics* 2012; 30(2): 87-101.
  32. McDonald H, Diamantopoulos A, Wells P, *et al.* Cost-effectiveness of rivaroxaban in the prevention of venous thromboembolism: A Canadian analysis using the Ontario Ministry of Health Perspective. *J Med Econ* 2012; 15(5): 817-28.
  33. Patel MR, Mahaffey KW, Garg J, *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365: 883-91.