Pharmacoeconomic Study on Rivaroxaban vs Conventional Venous Thromboembolism Prophylaxis Following Elective Total Hip or Knee Replacement Surgery in Serbia: Single Centre Study

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SUMMARY

Introduction: Venous thromboembolism (VTE) is often clinically unobservable, showing the first symptoms only after the patient has been discharged from the hospital, owing to which symptoms may not be recognized in time and serious complications may arise after hip or knee replacement surgery. The outcome for a patient who has had a symptomatic episode of VTE may be bad due to a risk of recurrent VTE and the development of post-thrombotic syndrome. The annual incidence of VTE is around 80-180 cases in 100,000, based on population studies. Worldwide, orthopaedists and anaesthesiologists mostly refer to ACCP guidelines from America, or guidance from NICE and Scottish Medicines Consortium in Europe. All the guidelines include rivaroxaban as a therapy of choice for the prevention of VTE following elective arthroplasty as the therapy with rivaroxaban has shown both effectiveness and cost-savings. Many countries have included rivaroxaban as a medicine of first choice in the therapy for the above described indication.

Aim: The objective of this analysis is to demonstrate cost-effectiveness of the new therapy with rivaroxaban versus conventional in VTE prophylaxis for patients undergoing elective hip or knee replacement surgery.

Methodology: This paper is a part of the academic IV phase pharmacoeconomic study using extrapolation datas (RECORD 1, RECORD 2, RECORD 3) done in Serbia as single center experience of Institute for Orthopaedic Surgery “Banjica”, in 2015. Information on drug prices, basic pharmacological characteristics, and on services of health institutions, are taken from the List of Drugs and Pricelist of the Republic Health Insurance Fund, as well as the Thromboembolism Prophylaxis Guide of the Institute “Banjica”. The Incremental cost-effectiveness ratio (ICER) and Cost-utility analysis (CUA) have also been used in relation to the Quality-adjusted life-year (QALY). Furthermore, in the calculation the proposed price of a defined daily dose (DDD) of rivaroxaban was 3.36 EUR.

Results: Total savings obtained annually through the application of rivaroxaban instead of usual prophylaxis (6,900 surgeries) could lead to cost savings of EUR 511,248.35 with the ICER value shows that therapy with rivaroxaban is dominant.

Conclusions: The introduction of rivaroxaban in the therapy will enable patients to receive more conformable oral therapy with the same amount of health insurance resources.
INTRODUCTION

Venous thromboembolism (VTE) comprises both: deep vein thrombosis (DVT) and pulmonary embolism (PE) [1,2]. VTE occurs often with an annual frequency of about 80-180 cases per 100,000 estimated based on population studies [3-5]. One third of patients with symptomatic VTE is presented as PE, and two thirds as DVT [4]. It is estimated that 63% of all VTE cases are a complication related to a recent hospitalisation [6]. Venous thromboembolism has been cited as a cause of death in up to 10% of patients who died in hospital [7,8]. In patients undergoing a prophylactic therapy, the rate is significantly lower.

Low molecular weight heparins (LMWH's) are used to prevent and treat thrombosis. Tests for monitoring LMWH's include anti-factor Xa (anti-FXa), activated partial thromboplastin time (aPTT) and thrombin generation. Anti-FXa is the current gold standard despite LMWH’s varying affinities for FXa and thrombin [9].

While anti-FXa activity assays are reliable determinants of the concentration of LMWH in the blood [Harris] and are established as a gold standard, they do not necessarily correlate well to the actual effect of the drug in vivo: they describe pharmacokinetics rather than pharmacodynamics. Tests of global coagulation such as aPTT and PT-INR are different from anti-FXa activity tests in that they reflect LMWH’s varying affinities for FXa and thrombin [9].

The risk for VTE in major orthopaedic surgeries among the highest for all surgical specialities. Anticoagulant therapy in orthopaedic surgery patients is usually administered in two stadium: - in the first, with quick anticoagulation the risk of thrombus extension is minimised as well as the risk of fatal PE, and - in the second, prolonged stadium, with long term anticoagulation. On this way recurrence of VTE is prevented and thus long term complications from the disease are reduced such development of post-thrombotic syndrom and chronic hypoxic pulmonary hypertension [12]. It is estimated that approximate risk for the combined symptomatic VTE untreated baseline risk for the first 35 days is 4.3% for all three major orthopedic surgeries (hip and knee replacement, hip fracture). LMWH has become the thromboprophylaxis agent against which newer drugs are compared. For hip and knee replacement LMWHs consistently reduces asymptomatic DVT by 50% combined risk ratio (RR), 0.50; 95% CI, 0.43-0.59). A lot of guidelines include rivaroxaban as as the therapy of choice for prevention of VTE after elective arthroplasty since the therapy with rivaroxaban has provided, apart from efficacy, cost–effectiveness [13-15]. The guidelines recommend the continuation of use of rivaroxaban upon the patient's discharge from hospital treatment for additional 35 days for the hip replacement and 14 days for the knee replacement. Rivaroxaban is an oral, direct and specific factor Xa inhibitor [16,17]. It inhibits the free and fibrin-bound factor Xa, inhibits the creation of thrombins and does not influence directly aggregation of thrombocytes and thus the primary hemostasis. During the application of rivaroxaban there is no need for the PV (INR) monitoring and its once daily dose of 10mg makes it very simple and practical for application in all adult patients [16,17].

In XAMOS, an international, IV phase-noninterventional, observational, open-label, real-world study designed to assess the safety and effectiveness of oral rivaroxaban compared with any other VTE prophylaxis (referred to as SOC) in clinical practice in patients after major orthopaedic surgery (including fracture surgery in those countries in which rivaroxaban is approved for this indication), the incidence of symptomatic thromboembolic events was significantly lower in the rivaroxaban group (0.9%) compared with

Keywords: venous thromboembolism prophylaxis, low molecular weight heparins, rivaroxaban, hip, knee replacement surgery
The SOC group (1.4%; odds ratio, 0.65; 95% confidence interval, 0.49–0.87) [18].

The RECORD 1 (n = 4541) [19] and RECORD 2 (n = 2509) [20] programme trials were multicentre, prospective, double-blind, parallel-group design RCTs comparing rivaroxaban with enoxaparin for the prevention of VTE after total hip replacement surgery. In RECORD 1, rivaroxaban was administered at a dosage of 10 mg once daily for 35 days starting on the day of surgery. Enoxaparin was administered at a dosage of 40 mg starting 1 day before surgery and for 35 days thereafter. For this study, the manufacturer reported a statistically significant difference in the incidence of the composite primary endpoint between rivaroxaban and enoxaparin based on a ‘modified’ intention to treat (MITT) analysis. The primary endpoint occurred in 1.1% of the rivaroxaban group compared with 3.7% of the enoxaparin group; relative risk reduction (RRR) was 70% (95% CI 49 to 82, p < 0.001) [20].

In Serbia, the anticoagulant therapy with unfractionated heparin (UFH), low molecular weight heparin (LMWH) and warfarin are standard of care treatment for VTE after orthopedic surgery Institute for Orthopaedic Surgery “Banjica”, Belgrade, Serbia doctors use Thromboembolism Prophylaxis Guide prepared and adopted in Institute [21].

THE AIM

The aim of this study is to demonstrate cost-effectiveness of the new therapy with rivaroxaban versus conventional in VTE prophylaxis for patients undergoing elective hip or knee replacement surgery.

METHODS

This paper is a part of the academic IV phase pharmacoeconomic study using extrapolation datas, done in Serbia as single center experience of Institute for Orthopaedic Surgery “Banjica”. With at least 4600 expected elective hip replacement and 2300 expected elective knee replacement surgeries per year in Serbia, patients who are under the same age and sex are comparable with the patients included in studies RECORD 1 and RECORD 2 [19,20].

Information on drug prices, basic pharmacological characteristics, and on services of health institutions, are taken from the List of Drugs and Pricelist of the Republic Health Insurance Fund [22], as well as the Thromboembolism Prophylaxis Guide of the Institute “Banjica” [21]. The Incremental cost-effectiveness ratio (ICER) and Cost–utility analysis (CUA) have also been used in relation to the Quality-adjusted life-year (QALY).

In Serbia, LMWH’s are most often used in orthopaedic surgery and has been included into the calculation. Difference in price per day of the therapy with low molecular weight heparin is relatively small, so we believe that our applied model may be approximated to an application of other low molecular weight heparins in the prevention of VTE in elective hip and knee surgeries.

In the statistical data processing, for the purpose of authenticity and applicability in „everyday practice” the most used therapeutic scheme has been used, including the frequency of INR controls and the usual number of days of hospital stay.

Pharmacoeconomic model is divided into three modules:
- prophylaxis period,
- extrapolation period,
- late complications period.

Prophylaxis period

Even though in the approved indications for the application of rivaroxaban the proposed dosage scheme is 6-8 hours after the surgical intervention (Xarelto®, Bayer) [17], during the preparation of the pharmacoeconomic study and with the purpose of making it applicable on the territory of Serbia, we have used recommendations provided in the expert opinion which represents an integral part of the documentation of the Application to include the medicine in the Reimbursement List (Official Gazette of the Republic of Serbia) [22]: LMWH administered a day before and 2 days after the surgery, from day 3, including warfarin and continuation of the therapy with the same up to 14 days from the knee surgery, i.e. up to 35 days from the hip surgery. Application of warfarin, determining the dose as well as monitoring of INR are, in line with the approved protocols, followed by regular controls of INR and number of thrombocytes.

Risk of VTE during the prophylaxis period has been estimated based on data from
RECORD 1 and RECORD 3 pivotal phase III studies, for patients undergoing elective hip replacement surgery (RECORD 1) [19] or knee replacement surgery (RECORD 3) [23].

With rivaroxaban there is no need for INR monitoring, and according to internal hospital protocols, the introduction of rivaroxaban could reduce the number of days of hospital stay:
1. elective knee replacement surgery --> reduction of in hospital days from 14 to 10 (total of 4 days)
2. elective hip replacement surgery --> reduction of in hospital days from 21 to 14 (total of 7 days).

**Post-prophylaxis period (extrapolation period)**
In order to assess the probability to develop a symptomatic venous thromboembolism after a non-treated asymptomatic VTE (observed in a period of 90 days after the termination of prophylaxis). It has been used the publication Quinlan et al. (2004),–Mid-term complications.

**Late complications period**
In order to assess recurrence of VTE, observed over a monitoring period of 5 years, data has been used from Prandoni et al. (1997) [13].

Furthermore, Quality adjusted life years (QALYs, quality of life during the monitoring period) has been estimated based on a statistical model which included the probability of occurrence of venous thromboembolism, pulmonary embolism, postthrombotic syndrome, recurrent VTE.

In favour of proper classification of costs of treatment, are shown in the tables all costs following procedures burdening certain therapeutic protocols. Also, in the absence of implementation of the Diagnosis-related group (DRG), shows the cost of the medical staff who work in the department.

**RESULTS**
The data listed in the tables were obtained by extrapolation method data from the register: Additional days of hospitalisation, Costs of treatment of DVT/PE during the prophylaxis application [18], Costs of treatment of recurrent VTE, during the period of 1 year [11].

The use of rivaroxaban may reduce the costs of the Republic Health Insurance Fund by 71.49 EUR per patient on an annual level, with simultaneous improvement of the quality of life. Needlessness of INR monitoring and determining the number of thrombocytes, lower number of days of hospitalisation (7 days), lower costs of treatment of DVT/PE during the prophylaxis application and of recurrent VTE,makes application of rivaroxaban more cost-effective than standard prophylaxis in one year period.

The use of rivaroxaban may reduce the costs of the Republic Health Insurance Fund by 75.84 EUR per patient at a five year level, with simultaneous improvement of the quality of life. Needlessness of INR monitoring and determining the number of thrombocytes, lower number of days of hospitalisation (7 days), lower costs of treatment of DVT/PE during the prophylaxis application and of recurrent VTE, makes application of rivaroxaban more cost-effective than standard prophylaxis in five years period.

The use of rivaroxaban may reduce the costs of the Republic Health Insurance Fund by 79.30 EUR per patient during the

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>Current prophylaxis</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>117.66</td>
<td>19.28</td>
<td>98.38</td>
</tr>
<tr>
<td>0.00</td>
<td>79.22</td>
<td>-79.22</td>
</tr>
<tr>
<td>0.00</td>
<td>82.58</td>
<td>-82.58</td>
</tr>
<tr>
<td>11.45</td>
<td>17.88</td>
<td>-6.43</td>
</tr>
<tr>
<td>0.60</td>
<td>2.24</td>
<td>-1.64</td>
</tr>
<tr>
<td>129.71</td>
<td>201.20</td>
<td>-71.49</td>
</tr>
<tr>
<td>0.7969</td>
<td>0.7963</td>
<td>0.0005</td>
</tr>
<tr>
<td>0.0049</td>
<td>0.0120</td>
<td>-0.0072</td>
</tr>
</tbody>
</table>

Table 1. Elective hip replacement surgery/costs per patient in EUR/First year
first year period, with simultaneous improvement of the quality of life. Needlesness of INR monitoring and determining the number of thrombocytes, lower number of days of hospitalisation (4 days), lower costs of treatment of DVT/PE during the prophylaxis application and of recurrent VTE, makes application of rivaroxaban more cost-effective than standard prophylaxis in one year period.

The use of rivaroxaban may reduce the costs of the Republic Health Insurance Fund by 93.50 EUR per patient during five years period, with simultaneous improvement of the quality of life. Needlesness of INR monitoring and determining the number of thrombocytes, lower number of days of hospitalisation (4 days), lower costs of treatment of DVT/PE during the prophylaxis application and of recurrent VTE, makes application of rivaroxaban more cost-effective than standard prophylaxis in one year period.
hospitalisation (4 days), lower costs of treatment of DVT/PE during the prophylaxis application and of recurrent VTE, makes application of rivaroxaban more cost-effective than standard prophylaxis in five years period.

### Medical staff expenses

With the present method of financing health care in the Republic of Serbia, the Republic Health Insurance Fund transfers funds in its financial plan to health care institutions for salary payments to medical and non-medical staff. In order to calculate the actual, economic costs of hospitalisation, costs of labour of the medical staff engaged in taking care of patients with a hip or knee replaced should be added to the cost of a hospital day.

This is very important due to changes of the payment system according to the Diagnostically related groups (DRG) which is expected to be implemented in the Republic Health Insurance Fund in the coming period.

A daily cost of income for the medical staff at the department per patient is modelled according to the Institute for Orthopaedic Surgery “Banjica”.

Considering the reduction of in-hospital days after elective knee replacement surgery from 14 to 10 (4 days total) and the reduction of in-hospital after elective hip replacement surgery from 21 to 14 (7 days total), additional saving of 75.50 i.e. 132.00 EUR per patient which, at the total annual level, represents savings of 173,588.50 EUR for patients with knee replacement and 607,559.70 EUR for patients with hip replacement, could lead to total saving for the Republic Health Insurance Fund of 781,148.20 EUR annually.

Incremental cost effectiveness ratio (ICER)

ICER = C XR - C SP / E XR - E SP = ΔC/ΔE

Hip replacement surgery

C XR-costs for patients treated with rivaroxaban for the period of 1 year
C SP-costs for patients treated with current prophylaxis for the period of 1 year
E XR-QALY years of life for patients treated with rivaroxaban
E SP-QALY years of life for patients treated with current prophylaxis

ICER = 129.70 - 201.20 / 7,969 – 7,963
ICER = -71.50 / 0.006 = -11,916.70 EUR/QALY

Knee replacement surgery

C XR-costs for patients treated with rivaroxaban for the period of 1 year
C SP-costs for patients treated with current prophylaxis for the period of 1 year
E XR-QALY years of life for patients treated with rivaroxaban
E SP-QALY years of life for patients treated with current prophylaxis

ICER = 62.97 - 142.30 / 7,985 – 7,971
ICER = -79.33 / 0.014 = -5,666.40 EUR/QALY

Considering that in both cases C XR < C SP and E XR > E SP, we come to a conclusion that rivaroxaban is dominant, i.e. less costly and more effective than current prophylaxis. The incremental cost-effectiveness ratio has shown that costs of therapy with rivaroxaban

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Number of surgeries</th>
<th>Savings at an annual level (EUR)</th>
<th>Savings at a five years’ level (EUR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip replacement</td>
<td>4600</td>
<td>328,845.58</td>
<td>348,879.48</td>
</tr>
<tr>
<td>Knee replacement</td>
<td>2300</td>
<td>182,402.78</td>
<td>214,995.38</td>
</tr>
<tr>
<td>Total</td>
<td>6900</td>
<td>511,248.35</td>
<td>563,874.85</td>
</tr>
</tbody>
</table>

Table 5. Overview of savings in health insurance

<table>
<thead>
<tr>
<th>Average gross salary</th>
<th>990.23</th>
<th>424.38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Price of working hour (180/month)</td>
<td>5.50</td>
<td>2.36</td>
</tr>
<tr>
<td>No. of working hours a day</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Daily price of the medical staff</td>
<td>132.10</td>
<td>56.58</td>
</tr>
<tr>
<td>No. of patients per medical staff</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Price of labour of medical staff per patient</td>
<td>13.21</td>
<td>5.66</td>
</tr>
</tbody>
</table>

Table 6. Medical staff expenses per patient (in EUR)
are significantly lower than with the current prophylaxis with simultaneous improvement in the quality of life for patients treated with rivaroxaban.

COST- UTILITY ANALYSIS (CUA)

From the table 7 it can be seen that the strategy for introduction of rivaroxaban in the therapy is highly cost-effective as it could result in savings of 12,358.90 EUR per QALY during a one year period.

From the table 8 it can be seen that the strategy for introduction of rivaroxaban in the therapy is highly cost-effective considering it could result in savings of 5,998.30 EUR per QALY during a one year period.

INDIRECT COSTS

It can be assumed that a certain percentage of patients belong to the working population, so the VTE complications surely lead to extension of sick leaves paid by the funds (the

Republic Health Insurance Fund), as well as to previous and subsequent loss in productivity which is not to be dismissed from the socio-economic aspect, both of the patient as of the society as a whole.

NON-MATERIAL (INTANGIBLE) COSTS

Other expenses which accompany VTE complications may not be precisely and exactly defined in monetary units but are not insignificant and put great pressure on the insurers and the insured of the Republic Health Insurance Fund and may be classified in the following sub-groups:
- Somatic factors: pain, disability, low mobility, sleep disorders;
- Mental factors: reaction, concentration, memory;
- Psychic factors: fear, depression, anxiety and apathy;
- Social factors: conflict, addiction.

DISCUSSION

Venous thromboembolism is often clinically unobserved and it shows its first symptoms after the patient is discharged from the hospital which may lead to symptoms not being recognised on time and to serious complications after the knee or the hip surgeries.

With at least 4600 expected elective hip replacement surgeries per year in Serbia and observed during the first year period, application of rivaroxaban would save the Republic Institute for Health Insurance 328,845.60 EUR. Savings achieved at a five year level (long-term complications) would reach 348,879.50 EUR.

Estimated at least 2300 expected elective knee replacement surgeries at annual level and observed during the first year period, application of rivaroxaban would save the Republic Institute for Health Insurance 182,402.80 EUR. Savings achieved at a five year level (later complications) would reach 214,995.40 EUR.

The introduction of rivaroxaban in the therapy will enable patients to receive more conformable oral therapy, with significant savings. This will be obtained owing to a decrease in the number of inpatient days in hospitals, as well as owing to the fact that regular control examinations of INR and number of blood platelets will not be necessary, which otherwise may amount to 511,248.40 EUR an-
nually for the said indication plus additional 781,148.10 EUR upon DRG implementation.

Indirect and non-material (Intangible) costs such as sick leaves paid by the health insurance funds, loss in productivity, pain, disability, low mobility, sleep disorders, reaction, concentration, memory, fear, depression, anxiety and apathy, conflicts, addiction, also affect both the cost of further treatments, and the quality of life of patients and their families.

CONCLUSION

Venous thromboembolism is often clinically unobservable, showing the first symptoms only after the patient has been discharged from the hospital, owing to which symptoms may not be recognized in time and serious complications may arise after hip or knee replacement surgery.

With rivaroxaban there is no need for INR monitoring, and according to internal hospital protocols, the introduction of rivaroxaban could reduce the number of days of hospital stay With at least 4600 expected elective hip replacement surgeries per year in Serbia and observed during the first year period, application of rivaroxaban would save the Republic Health Insurance Fund 511,248.40 EUR. Savings achieved at a five-year level (long-term complications) would reach 563,874.90 EUR.

The introduction of rivaroxaban in the therapy enabled patients to receive more conformable oral therapy.

This analysis demonstrated cost-effectiveness of the new therapy with rivaroxaban versus conventional in VTE prophylaxis for patients undergoing elective hip or knee replacement surgery.

The authors suggest support for the IV phase of the investigator initiated academic clinical trials with the intention of gaining security and personal experiences of doctors who use rivaroxaban in clinical practice.

CONFLICT OF INTEREST

The clinical study reported has not been sponsored by any drug producers.

REFERENCES

14 Eikelboom JW, Karthikeyan G, Fagel N, Hirsh J.


Farmakoekonomiska studija o rivaroksabanu nasuprot konvencionalne profilakse venske tromboembolije u elektivnoj hirurgiji totalne zamene kuka i kolena u Srbiji: unicentrična studija

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KRATAK SADRŽAJ

Uvod: Venska tromboembolija (VTE) je često klinički neprimetna, pokazujući svoje prve simptome tek kada je pacijent otpušten iz bolnice, zbog čega se simptomi ne mogu prepoznati na vreme, pa ozbiljne komplikacije mogu nastati posle hirurške zamene kuka ili kolena. Ishod za pacijenta koji je imao simptomatsku epizodu VTE može biti loš zbog rizika od rekurentne VTE i razvoja post-trombotičkog sindroma. Godišnja incidencna VTE iznosi oko 80-180 slučajeva na 100.000, na osnovu populacionih studija. Širom sveta, ortopedi i anesteziolozi najviše se pozivaju na smernice ACCP vodiča iz Amerike, ili vodiča NICE i Scottish Medicines Consortium-a iz Evrope. Svi vodiči uključuju rivaroksaban kao terapiju izbora za prevenciju VTE u elektivnoj artroplastiji zato što se terapija rivaroksabanom pokazala efikasnijom i štedljivijom. Mnoge zemlje su uključile rivaroksaban kao lek prvog izbora u terapiji za gore opisanu indikaciju.

Cilj: Cilj ove analize je da predstavi isplativost nove terapije rivaroksabanom u odnosu na konvencijalnu VTE profilaksu za pacijente koji se podvrgavaju elektivnoj hirurškoj zameni kuka ili kolena.

Metodologija: Ovaj rad je deo akademske IV faze farmakoekonomiske studije korišćenjem ekstrapolacije podataka (RECORD1 RECORD2, RECORD3) rađene 2015 u Srbiji kao uni-centrična studija “Instituta za ortopedsku hirurgiju “Banjica”. Informacija o cenama lekova, osnovnim farmakološkim karakteristikama i uslugama zdravstvenih ustanova preuzete su iz Liste lekova i Cenovnika usluga Republike Srbije za zdravstveno osiguranje, kao i Vodiča za prevenciju tromboembolije Instituta “Banjica”. Inkrementalni odnos isplativosti (ICER) i analiza odnosa troškova i koristi (CUA) takođe su korišćeni u odnosu na godine života prilagođene prema kvalitetu QALY).

Rezultati: Ukupna ušteda ostvarena na godišnjem nivou kroz primenu rivaroksabana umesto uobičajene profilakse (6,900 operacija) mogla bi da dovede do uštede troškova od EUR 511,248.35 sa ICER vrednošću koja pokazuje da je terapija rivaroksabanom dominantna.

Zaključak: Uvođenje rivaroksabana u terapiju omogućuje pacijentima da primaju mnogo konforniju oralnu terapiju uz iste iznose utrošaka sredstava zdravstvenog osiguranja, dok na strane strane donosi značajne uštede mlanjenjem broja bolničkih dana kao i zbog nepotrebnosti kontrole INR i broja trombocita, koji, s druge strane, mogu dostići iznos od EUR 511,248.35 godišnje za pomenutu indikaciju.

Ključne reči: prevencija venske tromboembolije, nisko molekularni heparini, rivaroksaban, hirurgija zamene kuka, kolena

Received: February 15, 2017
Accepted: March 20, 2017