European Journal of Internal Medicine 61 (2019) 29–33

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

# Healthcare resource use in XALIA: A subgroup analysis of a non-interventional study of rivaroxaban versus standard anticoagulation for deep vein thrombosis

Lorenzo G. Mantovani[a,*], Sylvia Haas[b], Reinhold Kreutz[c], Kerstin Folkerts[d], Martin Gebel[d], Danja Monje[e], Jonas Schneider[e], Martin van Eickels[e], Kurtulus Sahin[f], Elizabeth Zell[g], Walter Ageno[h], Alexander G.G. Turpie[i]

[a] Center for Public Health Research, School of Medicine, University of Milano-Bicocca, Via Cadore 48, I-20900 Monza, Italy
[b] Formerly Technical University, Munich, Germany
[c] Institute of Clinical Pharmacology and Toxicology, Charité-Universitätsmedizin Berlin; corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin and Berlin Institute of Health, Berlin, Germany
[d] Bayer AG, Wuppertal, Germany
[e] Bayer AG, Berlin, Germany
[f] ClinStat GmbH, Cologne, Germany
[g] Stat-Epi Associates Inc., Ponte Vedra Beach, Florida, USA
[h] Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy
[i] Department of Medicine, Hamilton Health Sciences, Hamilton, ON, Canada

ARTICLE INFO

*Keywords:*
Anticoagulation
Healthcare resources
Hospitalisation
Hospital length of stay
Rivaroxaban
Venous thromboembolism

ABSTRACT

*Introduction:* The non-interventional XALIA study compared the safety and effectiveness of rivaroxaban with standard anticoagulation for the treatment of venous thromboembolism in routine clinical practice. This substudy assessed the effect of treatment with rivaroxaban on healthcare resource use, hospital length of stay (LOS) and frequency of hospitalisation.

*Methods:* In XALIA, patients aged ≥18 years scheduled to receive ≥3 months of rivaroxaban or standard anticoagulation treatment for deep vein thrombosis (DVT) were eligible. Treatment decisions were at the physician's discretion. Healthcare resource use, including hospital admission for the index DVT and initial LOS, was documented. The main analyses in this substudy were conducted in a 1:1 propensity score-matched set (PMS) of patients, with adjustment for cancer at baseline.

*Results:* In the PMS analysis, 1124 rivaroxaban-treated patients and 1124 standard anticoagulation-treated patients were included. Baseline characteristics were similar between groups (mean age 60.8 years vs. 61.2 years, DVT only rates of 89.7% vs. 90.2% and cancer rates of 8.4% vs. 8.5%, respectively). Of these, 433/1124 (38.5%) rivaroxaban-treated patients and 438/1124 (39.0%) standard anticoagulation-treated patients were hospitalised. Index event LOS in the PMS analysis was a least-squares mean of 2.6 days shorter with rivaroxaban vs. standard anticoagulation (5.4 vs. 8.0 days; geometric means ratio = 0.67 [95% confidence interval 0.61–0.74, $P < 0.001$]).

*Conclusions:* In XALIA, hospital LOS was shorter with rivaroxaban than with standard anticoagulation, consistent with the phase III study results. DVT treatment with rivaroxaban in routine clinical practice may reduce the cost per patient vs. standard anticoagulation.

*Abbreviations:* CrCl, creatinine clearance; DVT, deep vein thrombosis; EMA, European Medicines Agency; LMWH, low molecular weight heparin; LOS, length of stay; LS, least-squares; PE, pulmonary embolism; PMS, propensity score-matched set; SD, standard deviation; VKA, vitamin K antagonist; VTE, venous thromboembolism

* Corresponding author.
*E-mail address:* lorenzo.mantovani@unimib.it (L.G. Mantovani).

https://doi.org/10.1016/j.ejim.2018.10.002
Received 22 June 2018; Received in revised form 25 September 2018; Accepted 8 October 2018
Available online 19 October 2018

## 1. Introduction

The traditional approach to venous thromboembolism (VTE) treatment has been initial administration of a parenteral agent (e.g. heparin or fondaparinux), overlapping with and followed by a vitamin K antagonist (VKA) such as warfarin. The former is often administered in hospital (although some patients self-administer injections of low molecular weight heparin [LMWH] outside the hospital setting), whereas the latter can be administered post-discharge. The proportion of patients presenting with deep vein thrombosis (DVT) and/or pulmonary embolism (PE) who are admitted to hospital varies between 50% and 90% and mainly depends on the type of event and on concomitant diseases [1–4]. Patients with PE are admitted to hospital more frequently than those with DVT, as are patients with concomitant conditions (e.g. cancer). Despite this, outpatient treatment of most venous thromboembolic events is feasible, even for haemodynamically stable PE. Healthcare systems also need to address resource burdens associated with the duration of hospital stays. LMWH has been shown to reduce hospital length of stay (LOS) vs. unfractionated heparin, but delays in discharge are still a common occurrence, mainly because of hospital practice and physician judgment [5]. Premature discharge may also increase the risk of re-hospitalisation in some patients with VTE [6,7].

The phase III EINSTEIN DVT and EINSTEIN PE studies showed that the non-VKA oral anticoagulant rivaroxaban significantly reduced median LOS compared with standard anticoagulation (LMWH [enoxaparin]/VKA treatment) [8]. A post hoc subanalysis of North American patients also showed that rivaroxaban reduced the median LOS by 1 day compared with enoxaparin/VKA treatment; contributing to a total treatment cost reduction of US$3419 per patient [9]. These findings were supported by the Japanese EINSTEIN DVT and EINSTEIN PE studies, in which rivaroxaban was associated with a median LOS of 10 days vs. 15 days for standard anticoagulation [10].

The non-interventional XALIA study assessed the safety and effectiveness of rivaroxaban vs. standard anticoagulation for the treatment of DVT in routine clinical practice (patients with concomitant PE were also eligible after the approval of rivaroxaban in the PE indication during the study) [11]. The results of the propensity score analysis in XALIA were consistent with those of the EINSTEIN DVT and EINSTEIN PE studies, with rivaroxaban-treated patients experiencing similar rates of major bleeding, recurrent VTE and all-cause mortality compared with patients in the standard anticoagulation group. This substudy of XALIA assessed the effect of rivaroxaban treatment on LOS, frequency of re-hospitalisation and healthcare resource use.

## 2. Methods

The methods have been published previously in the XALIA primary publication, including the full study protocol (available as a supplementary appendix of the XALIA primary publication), which was developed by the study sponsor in collaboration with regulators at the European Medicines Agency (EMA) [11]. These are described briefly below, along with the methodology for the analysis of patient satisfaction with treatment.

### 2.1. Patients

Patients from 19 European countries (Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Moldova, the Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, Switzerland, Ukraine and the United Kingdom), Canada and Israel were enrolled. The study sponsor sought approval from an independent Ethics Committee or Institutional Review Board in all countries where such procedures were in place.

### 2.2. Treatments

Patients were administered either rivaroxaban or standard anticoagulation; type, dose and duration of treatment were at the attending physician's discretion. Patients receiving rivaroxaban immediately, or who initially received heparin or fondaparinux for up to 48 h before enrolment, were included in the rivaroxaban cohort. Patients who initially received heparin and/or fondaparinux for > 2–14 days with or without a VKA for 1–14 days before switching to rivaroxaban were designated as ‘early switchers’. These patients were excluded from the main safety analysis and reported separately [12].

### 2.3. Healthcare resource utilisation

Healthcare resource utilisation included the number of healthcare professional visits (either at home or in the clinic), readmission to hospital for recurrent VTE or in-hospital bleeding, and the initial LOS after the index venous thromboembolic event.

### 2.4. Propensity score matched design and statistical analysis

The main analyses in this substudy were conducted on the propensity score-matched set (PMS) of patients; further analyses were also conducted for the PMS by selected patient subgroups and with adjustment for the presence of cancer at baseline. Propensity score matching was used to account for known potential factors influencing prognosis, treatment decision, outcomes and resource consumption. The generation of the propensity score design in XALIA is described in the supplementary appendix of the XALIA primary publication [11] and was based on the 34 priority-one covariates, 68 priority-two covariates and 23 priority-three covariates, which were used for the derivation of the propensity scores. The priority order was prespecified by the Steering Committee. The 1:1 matching of propensity scores was done using the greedy algorithm with no outcome data available [13]. Hospital LOS was calculated from investigator records of admission and discharge dates; non-hospitalised patients were assigned a value of 0 for this parameter. An analysis of variance was used to analyse the effect of treatment on (logarithmised) initial length of hospitalisation in a model adjusted for cancer at baseline. The p-value for initial LOS was calculated with the van Elteren test stratified by cancer at baseline. All statistical comparisons were done using SAS (Cary, North Carolina, USA) version 9.4.

## 3. Results

### 3.1. Patients

In total, 4768 patients were included in the XALIA safety analysis; 2619 (54.9%) of these patients received rivaroxaban and 2149 (45.1%) received standard anticoagulation. The PMS consisted of a total of 2248 patients in a 1:1 ratio between rivaroxaban and standard anticoagulation treatment groups. The baseline demographics and clinical characteristics of patients in the PMS analysis are shown in Table 1; these were similar between treatment groups. Mean age was approximately 61 years in both groups, and 90% of patients in each cohort had DVT without concomitant PE. Rates of cancer at baseline were also similar; 8.4% in the rivaroxaban group and 8.5% in the standard anticoagulation group.

### 3.2. Hospitalised patients

In the safety analysis set, 727/2619 (27.8%) of the rivaroxaban-treated patients were hospitalised for the index event, as were 1011/2149 (47.0%) of those administered standard anticoagulation. In the PMS analysis, 433/1124 (38.5%) rivaroxaban-treated patients and 438/1124 (39.0%) standard anticoagulation-

**Table 1**
Baseline demographics and clinical characteristics of hospitalised patients in the XALIA study (PMS).

| Characteristic[a] | Rivaroxaban (n = 1124) | Standard anticoagulation (n = 1124) |
|---|---|---|
| Age, years, mean (SD) | 60.8 (16.2) | 61.2 (17.2) |
| Age category | | |
| < 60 years | 490 (43.6) | 501 (44.6) |
| ≥60 years | 634 (56.4) | 623 (55.4) |
| Male sex | 508 (45.2) | 523 (46.5) |
| Weight | | |
| < 50 kg | 13 (1.2) | 20 (1.8) |
| 50–70 kg | 226 (19.4) | 226 (18.8) |
| > 70– < 90 kg | 375 (33.4) | 363 (32.3) |
| ≥90 kg | 279 (24.8) | 284 (25.3) |
| Missing | 231 (20.6) | 231 (20.6) |
| First available CrCl | | |
| < 30 mL/min | 8 (0.7) | 22 (2.0) |
| 30– < 50 mL/min | 56 (5.0) | 60 (5.3) |
| 50– < 80 mL/min | 222 (19.8) | 184 (16.4) |
| ≥80 mL/min | 455 (40.5) | 437 (38.9) |
| Missing | 383 (34.1) | 421 (37.5) |
| Index diagnosis | | |
| DVT only | 1008 (89.7) | 1014 (90.2) |
| DVT with PE | 116 (10.3) | 110 (9.8) |
| Hospitalisation for index VTE | | |
| Yes | 433 (38.5) | 438 (39.0) |
| No | 691 (61.5) | 686 (61.0) |
| Type of VTE | | |
| Provoked | 368 (32.7) | 390 (34.7) |
| Unprovoked | 756 (67.3) | 734 (65.3) |
| Previous VTE | 270 (24.0) | 264 (23.5) |
| Active cancer at baseline | 94 (8.4) | 95 (8.5) |
| Known thrombophilic condition | 67 (6.0) | 69 (6.1) |
| Previous major bleeding episode | 23 (2.0) | 24 (2.1) |

CrCl, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism; PMS, propensity score-matched set; SD, standard deviation; VTE, venous thromboembolism.
[a] All values are n (%) unless stated otherwise.

treated patients were hospitalised (Table 1).

In the five countries with the largest numbers of patients enrolled in the study, the hospitalisation rates were: France 45.0% (494/1097); Germany 23.5% (221/941), Spain 49.1% (408/831), the Netherlands 6.9% (17/246) and the Czech Republic 37.3% (76/204).

### 3.3. Healthcare professional visits

In the PMS analysis, rivaroxaban-treated patients had fewer healthcare professional visits compared with patients administered standard anticoagulation (777 vs. 1080 visits, respectively). For outpatient hospital visits, the mean number of visits for patients in the standard anticoagulation group was twice as many as for patients receiving rivaroxaban (mean number of visits: 3.9 vs. 2.0). Patients treated with rivaroxaban also had fewer mean visits to a general practitioner, a specialist or a nurse than patients treated with standard anticoagulation. The results are shown in Table 2.

### 3.4. Hospital readmission

The proportion of hospital readmissions was similar between the treatment groups, with 19/1124 (2%) patients in the rivaroxaban group and 23/1124 (2%) patients in the standard anticoagulation group readmitted for recurrent VTE or treated for in-hospital bleeding events.

**Table 2**
Healthcare professional visits by treatment group and treatment setting (PMS).

| Type of visit[a] | Rivaroxaban (n = 1124) | Standard anticoagulation (n = 1124) |
|---|---|---|
| Overall, n | 777 | 1080 |
| Outpatient hospital consultation | 186 (2.0 ± 2.27) | 177 (3.9 ± 4.59) |
| General practitioner | 263 (4.2 ± 5.52) | 377 (7.5 ± 8.11) |
| Specialist | 233 (2.0 ± 2.23) | 282 (3.1 ± 3.54) |
| Nurse | 95 (7.9 ± 17.0) | 244 (21.6 ± 55.7) |

PMS, propensity score-matched set.
[a] All values are the number of patients who made a visit (mean number of visits per person ± standard deviation) unless stated otherwise.

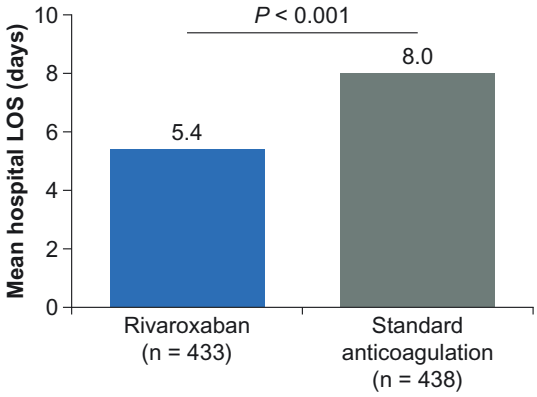


**Fig. 1.** LS mean LOS by treatment group for index event (adjusted for cancer at baseline) (PMS). LOS, length of stay; LS, least-squares; PMS, propensity score-matched set.

### 3.5. Length of stay

For the index event, LOS (with adjustment for cancer at baseline) in the PMS was 2.6 days shorter with rivaroxaban than with standard anticoagulation (least-squares [LS] means of 5.4 days vs. 8.0 days, respectively; geometric means ratio of 0.67 [95% confidence interval 0.61–0.74, P < 0.001]) (Fig. 1). The LS mean for LOS in the PMS for a readmission to hospital was numerically shorter in the rivaroxaban group (8.2 days vs. 9.8 days in the standard anticoagulation group).

For the five countries in XALIA with the largest enrolment numbers, mean LOS for the index event was 11.6 days in France, 16.9 days in Germany, 6.8 days in Spain, 5.0 days in the Netherlands and 7.3 days in the Czech Republic.

## 4. Discussion

Real-world studies, such as XALIA, provide important clinical data because of their high external validity (e.g. vs. phase III trials), meaning that the results are more generalisable to a broad patient population than those from a randomised controlled trial. In this XALIA subanalysis, for the XALIA safety analysis set there were more hospitalisations among patients in the standard anticoagulation group than in the rivaroxaban group. This was expected because patients with a higher number of, or more severe, concomitant conditions are at higher risk of admission, and they were more frequently allocated to standard anticoagulation (e.g. the standard anticoagulation group contained a higher proportion of patients with cancer at baseline [19% vs. 6%]). Consequently, the admission rate of the standard anticoagulation group was around 50%, which was consistent with previous evidence for patients with DVT [1]. However, in the PMS, which accounted for imbalances in baseline characteristics, a similar proportion of patients was hospitalised from each treatment cohort.

The results from the PMS analysis demonstrated that patients treated with rivaroxaban generally required fewer healthcare professional visits, particularly in the outpatient setting, compared with patients treated with standard anticoagulation. In addition, with adjustment for cancer at baseline, LOS for the initial event was shorter with rivaroxaban (LS mean of 5.4 days vs. 8.0 days). Although hospital readmission rates were similar between treatment groups, rivaroxaban was associated with a shorter LOS (LS mean of 8.2 days vs. 9.8 days) after a recurrent venous thromboembolic event or hospital-treated bleeding episode. No quantification, in monetary terms, was conducted of the additional days of hospitalisation observed for patients who received standard anticoagulation, because the monetary quantification depends on the perspective of the analysis (e.g. purchaser vs. provider of care) and on the specific healthcare system. Healthcare consumption is, therefore, reported in physical units, thus allowing the reader to quantify the difference into monetary terms according to the local/national healthcare system-specific costs, charges and tariffs that are appropriate to them.

The results from XALIA were consistent with findings from subanalyses of the EINSTEIN DVT and EINSTEIN PE clinical trials [8,9], and demonstrated that reductions in LOS can be achieved with rivaroxaban in routine clinical practice.

In addition to the impact on morbidity and mortality, VTE and VTE-related hospitalisation are a significant economic burden on healthcare systems [14]. Episodes of PE generally cost more than DVT because of increased hospital facility, hospital professional and outpatient costs [14]. Cost estimates of hospitalisation for VTE vary by country; for example, a study estimating costs per hospitalisation for PE estimated the cost to be over $8700 in the US (where healthcare costs are generally highest globally) and over €3400 in Italy and Belgium [15]. Another report estimated that hospitalisation costs from PE in Spain were almost €4400 per patient [16]. Within the English National Health Service, the unit cost for DVT treatment and PE treatment ranges from £381–£1000 and £798–£3245, respectively, depending on the complexity of the care (based on the National Schedule of Reference costs for 2016–2017) [17]. Cancer-associated thrombosis is particularly costly (because of factors such as increased rates of complications and hospital LOS compared with patients without cancer), with an average LOS of 11 days and costs of over US$20,000 per patient [18]. Previous studies have suggested that hospital costs for VTE are highest at Day 1 post event and are stable from Day 3 onwards [19]. Any reduction in LOS for VTE treatment is, therefore, likely to yield significant cost savings. Although much of the cost associated with VTE stems from management of the acute event, there are also significant costs associated with its long-term effects. A previous analysis of the EINSTEIN DVT and EINSTEIN PE phase III studies suggested that treatment with rivaroxaban is likely to be cost-effective vs. standard anticoagulation, regardless of therapy duration [20]. It would, therefore, be of interest to determine whether this is also the case in routine clinical practice with rivaroxaban.

There were some limitations in this study. LOS can be impacted by factors other than the choice of treatment regimen. Local reimbursement practices based around minimum and maximum stay durations may impact the decision whether to keep a patient in hospital or discharge them, and lengthy diagnostic procedures could also extend the duration of hospital stay. Background hospital admission rates also had the potential to influence the results because these vary between localities; for example, in Canada, treatment centres tend not to hospitalise patients with DVT. Selection bias may have influenced the overall admission rates, because inclusion of inpatients in a study is generally easier than inclusion of outpatients as a result of the relative ease of acquiring informed consent from patients in the former group during the admission process. Confirmation of cost savings will require separate analysis, in part because of the aforementioned possibility of selection bias influencing admission rates, and also if the bulk of the costs are incurred early in the hospitalisation process then a reduction in LOS may not offer as large a cost saving as predicted. Treatment allocation bias and a subsequent imbalance of patients between treatment groups was minimised with the propensity score-matched design. However, although the propensity score-matched design could balance baseline covariates between the treatment groups, the effect of unmeasured characteristics and confounders (e.g. possible reporting bias) cannot be assessed.

## 5. Conclusions

This subanalysis of the XALIA study confirmed that admission rates were influenced by the type of event and patients' concomitant conditions, although LOS was influenced by therapeutic regimen. In routine clinical practice, rivaroxaban treatment was associated with shorter hospital LOS than standard anticoagulation, which was consistent with findings of phase III EINSTEIN DVT and EINSTEIN PE clinical trials. Coupled with the reduced rates of healthcare professional visits observed in the rivaroxaban group, the findings suggested that use of rivaroxaban for the treatment of VTE in routine clinical practice may reduce the cost per patient compared with standard anticoagulation. This should be confirmed by further studies.

## Ethics approval and consent to participate

The study/sponsor sought approval from an independent Ethics Committee or Institutional Review Board in all countries where such procedures were in place.

## Data availability statement

Please contact author for data requests.

## Funding

This work was supported by Bayer AG and Janssen Research & Development, LLC.

## Conflicts of interest

L.G. Mantovani has received consultancy fees from Bayer and Daiichi Sankyo, and research support from Boehringer Ingelheim, Janssen-Cilag Ltd. and Pfizer Inc. W. Ageno has received speaker's honoraria from, and participated in scientific advisory boards for, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer and Daiichi Sankyo, and has received research support from Bayer. S. Haas has received consultancy fees from Aspen Pharmacare, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer Inc. and Sanofi SA. R. Kreutz has received consultancy fees from Bayer, Berlin-Chemie Menarini, Daiichi Sankyo, Lundbeck Ltd. and Servier Laboratories Ltd., and speaker's honoraria from Bayer, AstraZeneca, Berlin-Chemie Menarini, Daiichi Sankyo, Lundbeck Ltd. and Servier Laboratories Ltd. K. Folkerts, M. Gebel, D. Monje, J. Schneider and M. van Eickels are employees of Bayer AG. K. Sahin has received consultancy fees from Bayer. E. Zell has received consultancy fees from Bayer. A.G.G. Turpie has received speaker's honoraria and consultancy fees from, and participated in scientific advisory boards for, Bayer and Janssen Research & Development, LLC.

## Acknowledgments

The information contained in this article is presented on behalf of the XALIA Investigators. We thank Robert Gillies (medical writer) of Chameleon Communications International, UK, who provided editorial assistance funded by Bayer AG and Janssen Scientific Affairs, LLC.

## Authors' contributions

The study concept, design and implementation was developed by Lorenzo G. Mantovani, Sylvia Haas, Reinhold Kreutz, Kerstin Folkerts, Martin Gebel, Danja Monje, Jonas Schneider, Martin van Eickels, Walter geno and Alexander G. G. Turpie. Statistical analyses were conducted by Martin Gebel and Kurtulus Sahin. Elizabeth Zell was responsible for the propensity score design. Manuscript development was done by Lorenzo G. Mantovani, Sylvia Haas, Reinhold Kreutz, Kerstin Folkerts, Martin Gebel, Danja Monje, Jonas Schneider, Martin van Eickels, Kurtulus Sahin, Elizabeth Zell, Walter Ageno and Alexander G. G. Turpie. All authors read and approved the final manuscript.

## References


[1] Singer AJ, Thode HC, Peacock WF. Admission rates for emergency department patients with venous thromboembolism and estimation of the proportion of low risk pulmonary embolism patients: A US perspective. Clin Exp Emerg Med 2016;3:126–31.

[2] The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499–510.

[3] The EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287–97.

[4] Douketis JD. Treatment of deep vein thrombosis: what factors determine appropriate treatment? Can Fam Physician 2005;51:217–23.

[5] The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. N Engl J Med 1997;337:657–62.

[6] Aujesky D, Mor MK, Geng M, Stone RA, Fine MJ, Ibrahim SA. Predictors of early hospital readmission after acute pulmonary embolism. Arch Intern Med 2009;169:287–93.

[7] Stein PD, Hull RD, Matta F, Yaekoub AY. Early discharge of patients with venous thromboembolism: Implications regarding therapy. Clin Appl Thromb Hemost 2010;16:141–5.

[8] van Bellen B, Bamber L, Correa de Carvalho F, Prins M, Wang M, Lensing AWA. Reduction in the length of stay with rivaroxaban as a single-drug regimen for the treatment of deep vein thrombosis and pulmonary embolism. Curr Med Res Opin 2014;30:829–37.

[9] Bookhart BK, Haskell L, Bamber L, Wang M, Schein J, Mody SH. Length of stay and economic consequences with rivaroxaban vs enoxaparin/vitamin K antagonist in patients with DVT and PE: Findings from the north American EINSTEIN clinical trial program. J Med Econ 2014;17:691–5.

[10] Matsuo H, Prins M, Lensing AW, Fujinuma EW, Miyamoto Y, Kajikawa M. Shortened length of hospital stay with rivaroxaban in patients with symptomatic venous thromboembolism in Japan: The J-EINSTEIN pulmonary embolism and deep vein thrombosis program. Curr Med Res Opin 2015;31:1057–61.

[11] Ageno W, Mantovani LG, Haas S, Kreutz R, Monje D, Schneider J, et al. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. Lancet Haematol 2016;3:e12–21.

[12] Coleman CI, Bunz TJ, Turpie AGG. Effectiveness and safety of rivaroxaban versus warfarin for treatment and prevention of recurrence of venous thromboembolism. Thromb Haemost 2017;117:1841–7.

[13] Parsons LS. Performing a 1:N Case-Control Match on Propensity Score. SAS Users Group International. Montreal, Canada, 9–12 May Poster 165–29 http://www2.sas.com/proceedings/sugi29/165-29.pdf; 2004 (Accessed 18 April 2018).

[14] Spyropoulos A, Lin J. Direct medical costs of venous thromboembolism and subsequent hospital readmission rates: an administrative claims analysis from 30 managed care organizations. J Manag Care Pharm 2007;13:475–86.

[15] Fernandez MM, Hogue S, Preblick R, Kwong WJ. Review of the cost of venous thromboembolism. Clinicoecon Outcome Res 2015;7:451–62.

[16] de Miguel-Diez J, Jimenez-Garcia R, Jimenez D, Monreal M, Guijarro R, Otero R, et al. Trends in hospital admissions for pulmonary embolism in Spain from 2002 to 2011. Eur Respir J 2014;44:942–50.

[17] Improvement NHS. National Schedule of Reference Costs 2016–2017. [Document #NSRC01.] Available from: https://improvement.nhs.uk/documents/1973/2_-_National_schedule_of_reference_costs_-_the_main_schedule.xlsx; 2017, Accessed date: 25 May 2018 (Accessed 25 May 2018).

[18] Elting LS, Escalante CP, Cooksley C, Avritscher EB, Kurtin D, Hamblin L, et al. Outcomes and cost of deep venous thrombosis among patients with cancer. Arch Intern Med 2004;164:1653–61.

[19] Dasta JF, Pilon D, Mody SH, Lopatto J, Laliberte F, Germain G, et al. Daily hospitalization costs in patients with deep vein thrombosis or pulmonary embolism treated with anticoagulant therapy. Thromb Res 2015;135:303–10.

[20] Bamber L, Muston D, McLeod E, Guillermin A, Lowin J, Patel R. Cost-effectiveness analysis of treatment of venous thromboembolism with rivaroxaban compared with combined low molecular weight heparin/vitamin K antagonist. Thromb J 2015;13:20.