The Journal of Arthroplasty 31 (2016) 2264–2268

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Complications - Other

Primary Joint Arthroplasty Surgery: Is the Risk of Major Bleeding Higher in Elderly Patients? A Retrospective Cohort Study

Jorge I. Quintero, MD [a, b], Laura L. Cárdenas, MD [a, b], Mónica Navas, MD, MSc [a, b], Maria P. Bautista, MD, MSc [a], Guillermo A. Bonilla, MD [a, b, c, *], Adolfo M. Llinás, MD [a, b, c], on behalf of the Clinical Care Program in Joint Replacement Surgery

[a] Department of Orthopedics and Traumatology, Hospital Universitario Fundación Santa Fe de Bogotá. Bogotá, Colombia
[b] School of Medicine, Universidad del Rosario. Bogotá, Colombia
[c] School of Medicine, Universidad de Los Andes. Bogotá, Colombia

ARTICLE INFO

Article history:
Received 16 January 2016
Received in revised form
7 March 2016
Accepted 9 March 2016
Available online 21 March 2016

Keywords:
aged
anticoagulants
arthroplasty
hip
knee
postoperative hemorrhage

ABSTRACT

Background: Increased risk of bleeding after major orthopedic surgery (MOS) has been widely documented in general population. However, this complication has not been studied in elderly patients. The purpose of this study is to determine whether the risk of major bleeding after MOS is higher in elderly patients, compared with those operated at a younger age.
Methods: This retrospective cohort study included total hip and total knee arthroplasty patients operated during 5 consecutive years. The main outcome was the occurrence of major bleeding. Patients with other causes of bleeding were excluded. Relative risks (RRs) and confidence intervals (CIs) were calculated, and a multivariate analysis was performed.
Results: A total of 1048 patients were included, 56% of patients were hip arthroplasties. At the time of surgery, 553 (53%) patients were older than 70 years. Patients aged >70 years showed an increased risk of major bleeding (RR: 2.42 [95% CI: 1.54-3.81]). For hip arthroplasty, the RR of bleeding was 2.61 (95%CI: 1.50-4.53) and 2.25 (95% CI: 1.03-4.94) for knee arthroplasty. After multivariate analysis, age was found to be independently associated with higher risk of major bleeding.
Conclusion: According to European Medicines Agency criteria, patients aged ≥70 years are at a higher risk of major bleeding after MOS, result of a higher frequency of blood transfusions in this group of patients. Standardized protocols for blood transfusion in these patients are still required.

Major orthopedic surgery is associated with a higher risk of postoperative complications compared with other types of procedures [1,2]. Furthermore, patients who are candidates for major orthopedic surgery are frequently of age >65 years [3-5]. With aging, the onset of comorbidities and impairment of hepatic, renal, and cardiac function increases not only the risk of developing venous thromboembolism (VTE) but also the incidence of major bleeding [3,6-8].

In addition, the use of thromboprophylaxis has been associated with an increased risk of major bleeding, intracranial bleeding, and fatal bleeding [2,6,9]. Based on physiological changes, some guidelines recommend the administration of adjusted doses of anticoagulant agents according to age, body mass index (BMI), and renal or hepatic function [10,11]; however, there is still a lack of evidence regarding its use in special populations such as elderly patients.

The effect of age on the risk of bleeding and thrombotic events after major orthopedic surgery has not been clearly identified. In the literature, age is both described to increase this risk independently [2,12,13] or not to be associated at all [7,8]. To our knowledge, there are no studies that assess directly the risk of bleeding after joint arthroplasty surgery in elderly patients, and this information

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to http://dx.doi.org/10.1016/j.arth.2016.03.025.

* Reprint requests: Guillermo A. Bonilla, MD, Department of Orthopedics and Traumatology, Hospital Universitario Fundación Santa Fe de Bogotá, Carrera 7 No. 117-15, Bogotá, 110111186, Colombia.

http://dx.doi.org/10.1016/j.arth.2016.03.025
0883-5403/

could be of cornerstone relevance because an adequate postoperative management of this group of patients is critical to reduce morbidity, mortality, and additional costs [6,10,14].

The aim of this study is to identify the risk of major bleeding after hip or knee arthroplasty surgery in the cohort of patients aged ≥70 years, in comparison with those who are younger at the time of surgery.

Materials and Methods

A retrospective cohort study including consecutive patients who underwent primary total hip or total knee joint arthroplasty by 12 different surgeons, between January 2009 and July 2013, was performed. All patients diagnosed with degenerative joint disease were included. Patients who received simultaneous bilateral arthroplasty and patients with chronic use of anticoagulant therapy, congenital or acquired coagulation disorders, active cancer, requiring a second surgical intervention during hospitalization, and incomplete medical records were excluded. All patients were followed until hospital discharge.

All patients were screened for medical risks and contraindications for surgery before the procedure. This assessment included the measurement of preoperative hemoglobin levels. All hip arthroplasties were performed through a mini-incision posterolateral approach and knee arthroplasties through either a midvastus or a medial parapatellar approach with the use of a tourniquet. The perioperative protocol of care did not include the use of tranexamic acid. After surgery, pharmacologic prophylaxis for VTE was prescribed according to institutional guidelines (Table 1). Surgeons were able to select the pharmacologic agent among those listed in the guideline. Postoperative hemoglobin was measured at 6 hours after skin closure. Because a standardized protocol for blood transfusion was not included in this study, the requirement of blood transfusion for each patient was defined with the following criteria: (1) hemoglobin levels <9.0 g/dL, (2) presence of symptoms related to anemia, or (3) physicians' clinical perception of higher risk of cardiovascular events due to anemia.

Main outcomes were major bleeding and VTE. Major bleeding was defined according to European Medicines Agency (Table 2). These criteria are used to assess clinical safety of antithrombotic medication when performing clinical trials. However, the use of a validated classification system for major bleeding allows the standardization of these outcomes [11]. Thromboembolic disease was defined as the presence of symptomatic deep vein thrombosis (DVT) confirmed by Doppler ultrasound, pulmonary embolism (PE) confirmed by computed tomography angiography or ventilation/perfusion scan, or death caused by thromboembolism.

Statistical Analysis

Sample size was calculated considering a 1:1 ratio between patients from the 2 cohorts (<70 years and >70 years), an alpha error of 5%, a power of 80%, and a minimum detectable relative risk (RR) of 1.8 (95% confidence interval, 2 queues). Assuming an expected frequency of patients with major bleeding of 8% in the study group and a 5% of losses, a minimum of 400 patients in each group was defined.

A case-control analysis was carried out to identify the highest odds ratio (OR) for major bleeding at different groups of age (60, 65, 70, and 75), to determine the threshold to split the sample into 2 cohorts. After this analysis, it was found that the OR for major bleeding increased with age; however, from the age of ≥75, there was no longer statistically significance. Accordingly, the limit age to divide the 2 groups of study was set at 70 years. A homogeneity test was performed to confirm that groups were comparable.

The frequencies of major bleeding events by groups of age are reported. The RR and 95% confidence interval for major bleeding within the 2 cohorts and by type of surgery were calculated, and the chi-square test was used to assess statistical significant differences between groups. Significance was established at a P value <.05. A logistic multivariate regression analysis was performed to evaluate the association of other variables including comorbidities such as diabetes, hypertension, autoimmune diseases, and obesity, as well as of other variables regarding the postoperative care.

Table 1
Recommendations for Thromboprophylaxis From the Institutional Guidelines for the Management of Thromboprophylaxis in Orthopedic Surgery.

Hip and Knee Arthroplasty
1. Thromboprophylaxis with both mechanical and pharmacological methods is indicated.
2. During the surgical procedure, use antiembolism stockings and intermittent pneumatic compression devices on the contralateral limb.
3. During hospitalization, use:
a. Enoxaparin, dabigatran, rivaroxaban, apixaban, or fondaparinux.
b. Antiembolism stockings and intermittent pneumatic compression devices on both limbs, until the patient has restriction of movement.
4. Continue prophylaxis for 35 days after surgery.

Table 2
European Medicines Agency Criteria for Major Bleeding.

Bleeding event that meets at least one of the following criteria:
Fatal bleeding
Critical bleeding
Intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intra-articular, or intramuscular with compartment syndrome.
Clinically overt bleeding associated with a decrease in the hemoglobin level of >2 g/dL
Clinically overt bleeding leading to transfusion of ≥2 units of whole blood or packed cells
Clinically overt bleeding leading to surgical intervention

Results

A total of 1062 patients were identified. Of these, 14 were excluded: 5 patients had history of active cancer, 1 patient had simultaneous bilateral arthroplasty, 4 patients did not receive pharmacologic prophylaxis according to institutional guidelines, and 4 patients had incomplete medical records (Fig. 1).

Among 1048 patients included in the analysis, 553 (53%) were older than 70 years, 582 (55.4%) were hip arthroplasties, average BMI was 26.76 kg/m^2 (standard deviation: 4.30), and mean preoperative hemoglobin was 14.48 g/dL (standard deviation: 1.51). In the group of patients aged <70 years, creatinine clearance levels were higher than in older patients; however, this difference was not statistically significant ($P = .3$). In both groups, preoperative and postoperative hemoglobin levels were similar (Table 3). Overall prevalence of thromboembolic events was 0.86%: 1 case of DVT and 3 cases of PE were identified in the cohort of patients aged <70 years and 3 cases of DVT and 3 cases of PE were identified in the cohort of patients aged ≥70 years. None of these cases were fatal. Three patients in the ≥70-year-old cohort died in the postoperative period because of cardiovascular complications.

Ninety patients (8.58%) met at least one criterion for major bleeding. The most frequent event that defined major bleeding in this cohort of patients was blood transfusion. Twenty-four patients younger than 70 years (4.85%) and 65 patients older than 70 years (11.75%) required transfusion in the postoperative period ($P < .005$). Within the ≥70-year-old cohort, 3 cases of surgical site bleeding and 2 cases of gastrointestinal bleeding were reported (Table 4). The latter cases occurred after the first 12 hours after the surgical

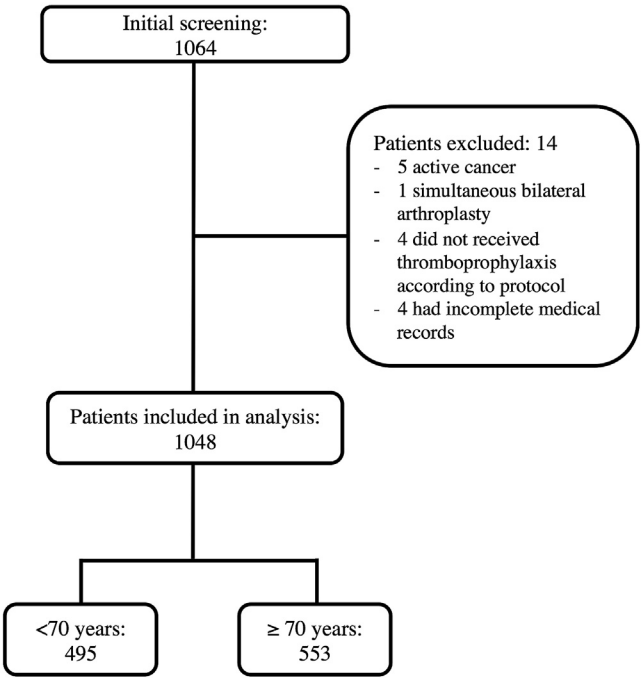

Fig. 1. Diagram of patient selection.

procedure, one of them related to esophageal varices. Similarly, 320 (64.65%) patients <70 years old and 352 (63.65%) patients ≥70 years old presented a decrease of hemoglobin of ≥2 g/dL, at 6 hours after surgery. However, this decrease does not define major bleeding unless it is associated with clinically overt bleeding.

RR of major bleeding in patients ≥70 years was 2.42 (95% CI: 1.54-3.81; Fig. 2). In the analysis performed by type of surgery, 66.7% of major bleeding events among the <70-year-cohort and 63.6% from the ≥70-year-old cohort were patients who underwent hip arthroplasty surgery, and for knee arthroplasty surgery, major bleeding events were present in 36.4% and 33.3%, respectively (Table 5). RR after hip arthroplasty was 2.61 (95% CI: 1.50-4.53) and 2.25 (95% CI: 1.03-4.94) after knee arthroplasty (Fig. 2).

According to the multivariate analysis, age was an independent risk factor for major bleeding and other variables such as gender, BMI, and creatinine clearance were not statistically significant.

Table 3
Demographic and Clinical Characteristics of Patients Included in the Study.

Variable	N (%)		*P* Value
	<70 y	≥70 y	
Number of patients	495 (47)	553 (53)	
Age (y), mean	60	77	
Gender			
Male	136 (27.8)	141 (25.5)	.46
Female	359 (72.3)	412 (74.5)	
BMI (kg/m^2), mean	27.17	26.37	.01
Type of surgery			
Hip arthroplasty	290 (58.6)	292 (52.8)	.11
Knee arthroplasty	205 (41.4)	261(47.2)	.32
Creatinine clearance (mL/min), mean	90.1	65	.02
Hemoglobin (g/dl), mean			
Preoperative	14.58	14.39	.06
Postoperative	11.71	11.54	.15
Prophylactic agent			
Dabigatran	24 (5)	36 (7)	
Fondaparinux	36 (7)	29 (5)	
LMWH	110 (22)	184 (33)	
Rivaroxaban	325 (66)	304 (55)	

BMI, body mass index; LMWH, low-molecular-weight heparin.

Table 4
Number of Cases of Major Bleeding According to European Medicines Agency Criteria.

Criteria for Major Bleeding[a]	N (%)	
	<70 y	≥70 y
Total no. of patients who presented major bleeding	24 (4.85)	66 (11.9)
Fatal bleeding	0	0
Critical bleeding	0	0
Gastrointestinal bleeding	0	2 (0.36)[b]
Clinically evident bleeding		
Surgical site bleeding requiring reoperation[c]	1 (0.20)	2 (0.36)
Transfusion >2 RBC units	24 (4.85)	65 (11.75)

RBC, red blood cell.
[a] Patients can present with >1 criterion.
[b] Only 1 patient required blood transfusion of ≥2 RBC units.
[c] All patients required blood transfusion of ≥2 RBC units.

Similarly, hypertension (OR: 1.1; 95% CI: 0.01-5), diabetes mellitus (OR: 1.5; 95% CI: −0.6 to 3.0), and other autoimmune diseases (OR: 0.8; 95% CI: 0.3-7) were not associated with the outcome. The risk of major bleeding was also independent of the type of pharmacologic agent selected for VTE prophylaxis. However, the frequency of blood transfusion in the group of patients aged >70 years was significantly higher when rivaroxaban or enoxaparin was used (Table 6).

Discussion

As life expectancy increases, the demand for joint arthroplasty surgery in elderly patients is also growing [5,15,16]. Although elderly patients are considered at higher risk for bleeding and VTE [2,3,6], most studies assessing the risk of bleeding or VTE after major orthopedic surgery did not include an independent analysis or special considerations for this population [9,17-23]. Therefore, recommendations for the management of these patients are only based on the assumption of a physiological impairment of renal and hepatic function that occurs with age but not on objective evidence of the increased risk of bleeding in this group of patients [4,24-26].

In this study, an association between the occurrence of major bleeding events after major orthopedic surgery and age older than 70 years was found. The increased risk of bleeding within this group of patients was statistically significant, not only in the overall analysis but also in the analysis by type of surgery (Fig. 2). This difference between cohorts was found to be independent of renal function, preoperative hemoglobin, and type of the anticoagulant. Our results are comparable with those reported by Ahmed et al [13], in which the rate of blood transfusion increased with age and preoperative hemoglobin, age, and weight were found to be

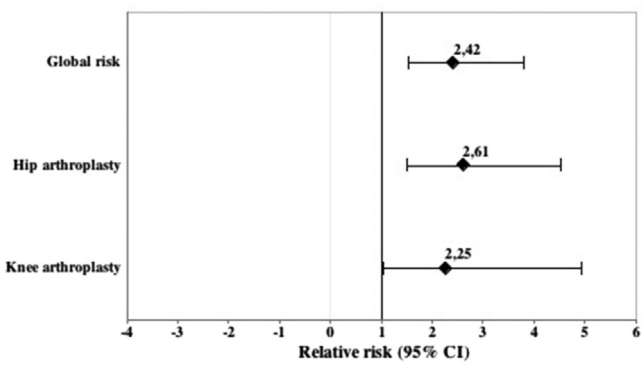

Fig. 2. Graph of relative risk for major bleeding after major orthopedic surgery in patients aged >70 years.

Table 5
Cases of Major Bleeding by Type of Surgery.

Type of Surgery	Major Bleeding, N (%)	
	<70 y	≥70 y
Hip arthroplasty	16 (66.7)	42 (63.6)
Knee arthroplasty	8 (33.3)	24 (36.4)

independent predictors of blood transfusion requirement. Similarly, Pola et al [12] reported a higher rate of blood transfusion in patients aged >75 years (8 out of 20 patients) compared with those aged <75 years (16 out of 65) but did not find a statistically significant difference with younger patients because of the small sample size ($P = .1$). In addition, this study demonstrated a higher frequency of blood transfusions after hip arthroplasty surgery compared with knees, presumably due to the fact that all knees were operated with the use of a tourniquet (Table 6).

The main outcome of this study was defined according to all 4 European Medicines Agency criteria [11]; however, the vast majority of our cases were classified as major bleeding only by the requirement of blood transfusion of ≥2 units. Although preoperative and postoperative hemoglobin levels did not differ significantly between groups, older patients were transfused more frequently than younger patients. This observation might be attributed to a lack of a standardized protocol for blood transfusion, or that physicians could be more likely to prescribe transfusions to older patients or the fact that these patients are more susceptible to develop physiological changes with blood loss. Although age, weight, and preoperative hemoglobin have been demonstrated to be risk factors for blood transfusion [8,12,13], identification of blood transfusion criteria needs to be established because this intervention represents increased morbidity and costs [8,12].

The proportion of usage of different VTE prophylactic agents was similar in both cohorts as seen in Table 5. The results of the multivariate analysis indicate that the use of different types of medications was not associated with major bleeding; therefore, the results of this study were independent of this factor. Although we reported the prevalence of VTE, the assessment of the risk of developing this complication between the 2 groups is beyond the scope of this study. Although the hemoglobin levels were assessed 6 hours after surgery, when VTE prophylaxis had not been started, patients were monitored for blood transfusion until discharge.

The inability to determine indications for transfusion in this cohort of patients could be the most important limitation of this study. In addition, this study is confined to evaluate the in-hospital postoperative period, and this fact could represent another limitation. However, to date, there is no agreement in the literature regarding the risk of bleeding after discharge even with the use of extended regimes of thromboprophylaxis [27-29]. Conversely, we identified that our main strengths were the sample size and the study design (cohort) and the consistency of the results regardless of the type of analysis. According to these strengths, we were able to homogenize the sample, isolate age as an independent variable, and find significant differences between groups.

Table 6
Frequency of Blood Transfusion and Hemoglobin Decrease by Type of Anticoagulant Used.

Type of Prophylaxis	<70 y		≥70 y		*P* Value
	N	Blood Transfusion, n (%)	N	Blood Transfusion, n (%)	
Rivaroxaban	325	10 (3.1)	303	26 (8.6)	.003
Fondaparinux	36	4 (11.1)	29	6 (20.7)	.287
Enoxaparin	110	9 (8.2)	184	30 (16.3)	.047
Dabigatran	24	1 (4.2)	36	2 (5.6)	.809

Whether the risk of bleeding in patients aged >70 years is due to an increased susceptibility to the administration of anticoagulants, to a decreased tolerance to blood loss, or to physiological impairment of renal function that occurs with age [4,25,30], the exact mechanism of this phenomena remains to be established.

Conclusion

The outcomes reported in this study confirm that patients aged >70 years undergoing major orthopedic surgery are at higher risk of major bleeding, mainly conditioned by an increased rate of postoperative blood transfusion. Despite some limitations, the strength of these results should encourage physicians to implement strategies to balance the risk in this special population.

References

1. Taylor JM, Gropper MA. Critical care challenges in orthopedic surgery patients. Crit Care Med 2006;34:S191.
2. Oberweis BS, Nukala S, Rosenberg A, et al. Thrombotic and bleeding complications after orthopedic surgery. Am Heart J 2013;165:427.
3. López-Jiménez L, Montero M, González-Fajardo JA, et al. Venous thromboembolism in very elderly patients: findings from a prospective registry (RIETE). Haematologica 2006;91:1046.
4. Bauersachs RM. Use of anticoagulants in elderly patients. Thromb Res 2012;129:107.
5. Waddell J, Johnson K, Hein W, et al. Orthopedic practice in total hip arthroplasty and total knee arthroplasty: results from the Global Orthopaedic Registry (GLORY). Am J Orthop 2010;39:5.
6. Schulman S, Beyth RJ, Kearon C, et al. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133:257.
7. Pineo GF, Gallus AS, Raskob GE, et al. Apixaban after hip or knee arthroplasty versus enoxaparin: efficacy and safety in key clinical subgroups. J Thromb Haemost 2013;11:444.
8. Guerin S, Collins C, Kapoor H, et al. Blood transfusion requirement prediction in patients undergoing primary total hip and knee arthroplasty. Transfus Med 2007;17:37.
9. Cao YB, Zhang JD, Shen H, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total hip or knee arthroplasty: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol 2010;66:1099.
10. Falck-Ytter Y, Francis C, Johanson N, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141:e278S.
11. European Medicines Agency. Committee for Medical Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products for prevention of venous thromboembolism (VTE) in patients undergoing high VTE-risk surgery. vol. May. 2013.
12. Pola E, Papaleo P, Santoliquido A, et al. Clinical factors associated with an increased risk of perioperative blood transfusion in nonanemic patients undergoing total hip arthroplasty. J Bone Joint Surg Am 2004;86-A:57.
13. Ahmed I, Chan JKK, Jenkins P, et al. Estimating the transfusion risk following total knee arthroplasty. Orthopedics 2012;35:e1465.
14. Wattanakit K, Cushman M, Stehman-Breen C, et al. Chronic kidney disease increases risk for venous thromboembolism. J Am Soc Nephrol 2008;19:135.
15. Bozic K, Chiu V, Slover J. Health state utility in patients with osteoarthritis of the hip and total hip arthroplasty. J Arthroplast 2011;26:129.
16. Bozic KJ, Maselli J, Pekow PS, et al. The influence of procedure volumes and standardization of care on quality and efficiency in total joint replacement surgery. J Bone Joint Surg Am 2010;92:2643.
17. Nieto J, Garrido-Espada N, Gujiarro-Merino R, et al. Dabigatran, rivaroxaban and apixaban versus enoxaparin for thromboprophylaxis after total knee or hip arthroplasty: pool-analysis of phase III randomized clinical trials. Thromb Res 2012;130:183.
18. Gómez-Outes A, Terleira-Fernández A, Suárez-Gea M, et al. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and. BMJ Br Med 2012;3675:1.
19. Lassen MR, Raskob GE, Gallus A, et al. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet 2010;375:807.
20. Lassen M, Gallus A, Raskob GE, et al. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Engl J Med 2010;363:2487.
21. Kakkar A, Brenner B, Dahl O, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboebolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet 2008;372:31.
22. Turpie AGG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet 2009;373:1673.

23. Lassen M, Ageno W, Borris L, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008;358:2776.
24. Siguret V, Gouin-Thibault I, Gaussem P, et al. Optimizing the use of anticoagulants (heparins and oral anticoagulants) in the elderly. Drugs Aging 2013;30:687.
25. Colwell CW, Hardwick ME. Thromboprophylaxis in elderly patients undergoing major orthopaedic surgery. Drugs Aging 2008;25:551.
26. Samama MM. Use of low-molecular-weight heparins and new anticoagulants in elderly patients with renal impairment. Drugs Aging 2011;28:177.
27. Warwick D, Friedman RJ, Agnelli G, et al. Insufficient duration of venous thromboembolism prophylaxis after total hip or knee replacement when compared with the time course of thromboembolic events: findings from the Global Orthopaedic Registry. J Bone Joint Surg Br 2007;89:799.
28. 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;135:858.
29. 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 (London, England) 2001;358:9.
30. Shorr A, Eriksson B, Jaffer A, et al. Impact of stage 3B chronic kidney disease on thrombosis and bleeding outcomes after orthopedic surgery in patients treated with desirudin or enoxaparin: insights from a randomized trial. J Thromb Haemost 2012;10:1515.