Comparative study between Aspirin and Oral anticoagulant for VTE Prophylaxis after Knee Arthroplasty

ElSayed Morsi[1], MD; Mohamed ElSawy Habeeb[1], MD; Hany ElSayed AbdelGawad[2], MD and Mohamed Samy Aly Said Ahmed[3], MBBCh

1-Professor of Orthopedics Surgery, Faculty of Medicine, Menoufia University- Egypt.
2- Lecturer of Orthopedic Surgery, Faculty of Medicine, Menoufia University- Egypt.
3- Resident of Orthopedic Surgery, Om Elmasrien Hospital-Cairo, Egypt.

Corresponding Author: Mohamed Samy Aly Said Ahmed.
Address: Elmostashfa Eldawly st., Mansoura, Egypt.
Email: m_samy11@yahoo.com
Mob: 01020065872

The Egyptian Orthopedic Journal; 2020 supplement (2), December, 55: 7-13

ABSTRACT

Background;
Osteoarthritis (OA) is a condition that is particularly prevalent among the elderly. At first, the majority of patients with OA receive nonoperative treatment.
Objective;
This investigation aims to evaluate the efficacy and safety of Aspirin as a prophylactic measure for venous thromboembolism (VTE) in comparison to the direct oral anticoagulant (DOAC) following total knee arthroplasty (TKA).
Patients and Methods;
This is a prospective study that targets a convenient sample which includes (40) patients. The study included all patients admitted to Menoufia University Hospital and Om Elmasrien Hospital to have primary TKA from April 2019 to December 2019. Alternately, the research subjects were allocated to two groups:
Group (1) received Rivaroxaban 10 mg orally once daily for 14 days, commencing on the first postoperative day.
Group (2) commencing on the first postoperative day, the patient was administered 81 mg of oral aspirin daily for 14 days.
Results;
The current study demonstrated that the mean age of the patients in the rivaroxaban group was 60.30 ± 5.85 years, while the mean age of the patients in the aspirin group was 63.20 ± 4.61 years. Females represented 90% of the patients in both groups and 100% of the patients in both groups were non-smokers. The affected side was the left side in 80% of the patients in the rivaroxaban group; meanwhile, it was the right side in 60% of the patients in the aspirin group.
Conclusion;
In the rivaroxaban groups, the incidence of DVT was only 5%. Aspirin is a safe and effective agent for the prevention of VTE, and it was not significantly different from the DOAC rivaroxaban in the prevention of DVT or pulmonary embolism (PE) after TKA.

Keywords;
Aspirin - Oral Anticoagulant - Knee Arthroplasty.

INTRODUCTION

Osteoarthritis (OA) is one of the most prevalent conditions that affect the elderly population. Initially, the majority of patients with OA receive nonoperative treatment. After conservative treatment has been unsuccessful, Total Knee Arthroplasty (TKA) is necessary for severe cases of knee OA. The results of the study indicated that TKA improved pain, mobilization, and quality of life. The number of arthroplasties has been increasing annually over the past few decades. [(1)]

Conversely, patients who endure an arthroplasty are susceptible to venous thromboembolism (VTE), which encompasses pulmonary embolism (PE) and deep vein thrombosis (DVT). VTE may occur in more than 35% of patients who undergo an arthroplasty in the absence of prophylaxis. However, the majority of patients are asymptomatic. Prophylaxis is advised in the context of VTE following arthroplasty due to the relatively high incidence. [(2,3)]

The most effective agents and protocols for reducing VTE in these situations are unknown. Prophylaxis options are delineated in the most recent guidelines from the American Academy of Orthopedic Surgeons and the American College of Chest Physicians. Aspirin (ASA), warfarin, heparin-based medications, and other direct oral anticoagulants (DOAC) are among the options available. However, They do not provide any recommendations regarding the customization of VTE prophylaxis. [(2, 4)] Although there are a multitude of chemical agents available to prevent VTE, their efficacy and the risk of hemorrhage are inconsistent. Consequently, The selection of an

agent is contingent upon a delicate equilibrium between the desire to reduce VTE and the effort to reduce the risk of bleeding, which can have both undesirable and occasionally fatal repercussions. [5] The safety, efficacy, and simplicity of use of the DOAC frequently lead to their prescription for extended prophylaxis. [6,7]

Acetylsalicylic acid, commonly referred to as aspirin, is a medication that is used to prevent VTE in the aftermath of arthroplasty. Its effectiveness in reducing VTE following arthroplasty has been documented in numerous investigations. [8, 9] At least in North America, there has been a significant change in the use of aspirin as the primary method for VTE prophylaxis following arthroplasty in recent years. In 2016, A survey of over 1200 attendants at the annual meeting of the American Association of Hip and Knee Surgeons revealed that over 80% of them administered aspirin as the primary prophylaxis to their patients who were undergoing arthroplasty of the hip or knee. [10, 11]

The prevalence of aspirin as a prophylactic agent is due to a variety of factors. In addition to its demonstrated efficacy, it is well-tolerated and cost-effective, and it does not necessitate routine bloodwork. [12,13] In addition, This agent is considered "milder" and is not likely to cause hematoma formation, which could require additional surgery and increase the risk of infection..[14] Aspirin is also markedly less likely to be associated with persistent lesion drainage, which has all of its undesirable consequences, in contrast to agents such as low-molecular-weight heparin (LMWH) or other more aggressive agents. [15, 16]

To prevent VTE following TKA, In contrast to the DOAC, We investigated the safety and effectiveness of extended prophylaxis with aspirin.

PATIENTS AND METHODS

Study design

This is a prospective study that targets a convenient sample which includes (40) patients. The study included all patients admitted to Menoufia University Hospital and Om Elmasrien Hospital to have primary TKA from April 2019 to December 2019. The subjects of the investigation were alternately assigned to two groups:

Group (1) Commencing on the first postoperative day, the patient was administered Rivaroxaban 10 mg orally once daily for 14 days.

Group (2) commencing on the first postoperative day, the patient was administered 81 mg of oral aspirin daily for 14 days.

Inclusion criteria:

All Patients who were admitted to the hospital to have primary TKA.

Exclusion criteria:

1. History of previous VTE.
2. Prominent varicose vein.
3. Cardiac patient on a pre-operative regimen of anticoagulant e.g. warfarin.
4. Revision knee arthroplasty.
5. Restricted weight-bearing after TKA.

Methods

Preoperative, operative, and postoperative data were collected for all patients enrolled in this study.

A) Preoperative data: include

1) **History taking** Included in the history were a prior orthopedic operation, substance consumption, medical disease, and venous thromboembolism.
2) **General assessment** includes the presence of lower limb varicose veins, symptoms of vascular insufficiency, body weight, and body mass index.
3) **Laboratory assessment:** International normalizing ratio (INR), complete blood count, serum creatinine, and liver function test.
4) Explanation of details of study and informed consent.

B) Operative data:

The surgical approach, the type of total knee, the volume of blood transfusion, the duration of the procedure, and the patient's position on the operative table were all documented. Additionally, the type of anesthesia (general or spinal) was specified. Routine medications were administered.

C) Post-operative data:

Day (1-14) post-operative:

10mg of rivaroxaban was administered once daily to the rivaroxaban group for 14 days, commencing 12 hours following the surgery.

The Aspirin group was administered 81 mg of aspirin on the evening of the surgery or the following day, and then once daily for 14 days.

Additionally, We could determine the patient's general condition, the quantity of blood loss in the drain, the patient's requirements for blood transfusion, and the results of the post-operative CBC, in addition to the volume of blood transfusion, the wound condition, tenderness, swelling, or pitting edema of the lower limb, ischemic stroke, non-fatal PE, and unexplained

mortality. The drug's side effects, including significant bleeding, minor bleeding, vomiting, and allergy, were documented throughout the therapy. The drain was evacuated every 24 hours and removed after 48 hours.
Patients were monitored for at least three days postoperatively in the hospital for hemorrhage, calf pain or swelling, and bilateral lower limb venous duplex if there was any clinical suspicion of deep venous thrombosis at any time.

Day (15):
Patients were clinically evaluated on the 15th day following surgery before receiving duplex ultrasound. The evaluation was conducted to evaluate the wound condition, tenderness, swelling or pitting edema of the lower limb, significant bleeding, minor bleeding, ischemic stroke, and non-fatal PE.

Duplex US was performed on all patients on the fifteenth day following the operation.
Duplex ultrasonography is a simplified technique used for quick DVT diagnosis; It is capable of detecting deep vein thrombosis with a high degree of specificity and sensitivity.

One month postoperative:
A clinical reevaluation to identify early postoperative complications.

Three months postoperative:
The presence of tenderness, swelling, or pitting edema in the lower extremity was evaluated three months after the surgery of the patients, in addition to inexplicable mortality, ischemic stroke, major bleeding, minor hemorrhage, and non-fatal PE.

Ethical consideration:
1. The participants and the ethical committee were promptly informed of any unforeseen hazards that arose during the research.
2. An informed consent was obtained from all participants in this research.
3. The privacy of participants and confidentiality of the data were maintained.
4. No photos were taken of the participant.
5. There are no hazards of this research on the environment or the participants.

RESULTS

Demographic data of rivaroxaban and aspirin groups (Table 1):
For the rivaroxaban group; the age of the patients was 60.30± 5.85, 18 (90 %) females and 2 (10 %) males, all were non-smokers, and 16 (80 %) patients with left side and 4 (20 %) patients with right side.
For the aspirin group; the age of the patients was 63.20 ± 4.61, 18 (90 %) females and 2 (10 %) males, all were non-smokers, and 8 (40 %) patients with left side and 12 (60 %) patients with right side. Statistically, there was no significant difference in age between the two categories.

Table (1): Demographic data of rivaroxaban and aspirin groups

Variables	Rivaroxaban group	Aspirin group
Individuals, n	20 (100 %)	20 (100 %)
Age (yr)		
54 – 63	16 (80 %)	12 (60 %)
≥ 63 – 72	4 (20 %)	8 (40 %)
Mean ± SD	60.30 ± 5.85	63.20 ± 4.61
Gender		
Females	18 (90 %)	18 (90 %)
Males	2 (10 %)	2 (10 %)
BMI		
	30.59 ± 4.35	27.80 ± 4.12
Smoking habit		
Non-Smokers	20 (100 %)	20 (100 %)
Smokers	0 (0 %)	0 (0 %)
Side		
Left	16 (80 %)	8 (40 %)
Right	4 (20 %)	12 (60 %)

Comorbidity (Table 2)
In the rivaroxaban group, bronchial asthma was recorded in 2 patients (10 %) and hypertension was recorded in 2 patients (10 %). However, in the Apirin group, hypertension was recorded in 6 patients (30 %), hypothyroidism was recorded in 2 patients (10 %), and ischemic heart disease was recorded in 2 patients (10 %).

Table (2): Comorbidities

Variables	Rivaroxaban group (n = 20)	Aspirin group (n = 20)	Chi-square value	P-value
Bronchial asthma			-	-
Yes	2 (10 %)	0 (0 %)		
No	18 (90 %)	20 (100 %)		
Hypertension			0.234	0.629
Yes	2 (10 %)	6 (30 %)		
No	18 (90 %)	14 (70%)		
Hypothyroidism			-	-
Yes	0 (0 %)	2 (10 %)		
No	20 (100 %)	18 (90%)		
Ischemic heart disease			-	-
Yes	0 (0 %)	2 (10 %)		
No	20 (100 %)	18 (90%)		

Pre-operative laboratory investigation (Table 3):
The table showed hemoglobin concentration, platelets count, and INR in both the Rivaroxaban group and the Aspirin group. There were non-significant differences in hemoglobin concentration, platelets count, and INR between both the Rivaroxaban group and the Aspirin group.

Table (3): Pre-operative laboratory investigations

Variables	Rivaroxaban group (n = 20)	Aspirin group (n = 20)	t-value	P-value
Hemoglobin (gm/dl)	12.27 ± 0.87	12.63 ± 1.24	- 1.067	0.293
Platelets (count X 10^3/microliter)	210.40 ± 45.97	231.50 ± 48.38	- 1.414	0.166
INR	1.05 ± 0.05	1.03 ± 0.03	- 1.047	0.302

Post-operative clinical data (Table 4):

The edema of the lower limb, major bleeding, wound, and GIT bleeding were not significantly different between the Rivaroxaban and Aspirin groups. However, The minor bleeding between the Rivaroxaban and Aspirin groups was significantly different ($P < 0.05$). Five patients in the Rivaroxaban group developed ecchymosis.

Table (4) Post-operative clinical assessment in both Rivaroxaban group and Aspirin group

	Rivaroxaban group (n = 20)	Aspirin group (n = 20)	Mann-Whitney	Z-value	P-value
Edema of lower limb			180.00	-0.874	0.382
Minimal	2 (10 %)	4 (20 %)			
Negative	18 (90 %)	16 (80 %)			
Minor bleeding			150.00	-2.360	0.018
Ecchymosis	5 (25 %)	0 (0 %)			
Negative	15 (75 %)	20 (100 %)			
Major bleeding			200.00	0.001	1.000
Positive	0 (0 %)	0 (0 %)			
Negative	20 (100 %)	20 (100 %)			
Wound			200.00	0.001	1.000
Infected	0 (0 %)	0 (0 %)			
Clean	20 (100 %)	20 (100 %)			
GIT bleeding			200.00	0.001	1.000
Positive	0 (0 %)	0 (0 %)			
Negative	20 (100 %)	20 (100 %)			

Post-operative thromboembolism (Table 5):

DVT was observed in only 5% of patients in the rivaroxaban group, and PE was not observed in any of the patients included in the study, as indicated by the table. Nevertheless, The postoperative incidence of pulmonary embolism or DVT did not exhibit any statistically significant differences between the two groups.

Table (5): Post-operative thromboembolism

	Rivaroxaban group (n = 20)	Aspirin group (n=20)	Mann-Whitney	Z-value	P-value
Deep vein thrombosis (DVT)			180.00	-1.433	0.152
Positive	1 (5 %)	0 (0 %)			
Negative	19 (95 %)	20 (100%)			
Pulmonary embolism			200.00	0.001	1.000
Positive	0 (0 %)	0 (0 %)			
Negative	20 (100 %)	20 (100%)			

Table (5) shows post-operative assessment in both the Rivaroxaban group and the Aspirin group. Both the Rivaroxaban and Aspirin groups exhibited non-significant differences in DVT and PE.

Three months Post-operative (Table 6):

There were non-significant differences between both groups as regards the postoperative clinical data, the incidence of DVT, and pulmonary embolism**.**

Table (6): 3 months post-operative

	Rivaroxaban group (n = 20)	Aspirin group (n = 20)	Mann-Whitney	Z-value	P-value
Edema of lower limb			180.00	-1.433	0.152
Minimal	1 (5 %)	0 (0 %)			
Negative	19 (95 %)	20 (100 %)			
Minor bleeding			200.00	0.001	1.000
Ecchymosis	0 (0 %)	0 (0 %)			
Negative	20 (100 %)	20 (100 %)			
Major bleeding			200.00	0.001	1.000
Positive	0 (0 %)	0 (0 %)			
Negative	20 (100 %)	20 (100 %)			
Wound			200.00	0.001	1.000
Infected	0 (0 %)	0 (0 %)			
Clean	20 (100 %)	20 (100 %)			
GIT bleeding			200.00	0.001	1.000
Positive	0 (0 %)	0 (0 %)			
Negative	20 (100 %)	20 (100 %)			
Deep vein thrombosis (DVT)			180.00	-1.433	0.152
Positive	1 (5 %)	0 (0 %)			
Negative	19 (95 %)	20 (100 %)			
Pulmonary embolism			200.00	0.001	1.000
Positive	0 (0 %)	0 (0 %)			
Negative	20 (100 %)	20 (100 %)			

DISCUSSION

Major orthopedic surgery, which primarily involves hip fracture surgery and hip and knee arthroplasty, is associated with significant morbidity and mortality. This is particularly attributed to the high risk of postoperative "VTE" (106) and VTE, DVT, and PE are significant complications that can occur as a result of "TKA" and "THA." [(17)]. DVT has been reported to occur at a rate of 40-60% after THA and 40-85% after TKA in the absence of thromboprophylaxis following a significant orthopedic surgery. The utilization of pharmacological thromboprophylaxis regularly could potentially decrease these rates to 1- 10% [(18)]. Furthermore, After THA, the mortality rate is approximately 15%, and the incidence of PE without prophylaxis ranges from 0.9-28% and 1.5-28%, respectively, and after TKA. [(19)] and the risk remains for a period of 3 to 6 months following the surgery [(20)].

Moreover, THA was associated with a higher incidence of VTE in a comparison cohort than in the general population up to one year after surgery [(21)]. Furthermore, VTE was identified as the most common cause of emergency readmission following lower limb arthroplasty [(22)].

After surgery, the hypercoagulable state may persist for up to 12 weeks and typically begins on the operating table [(23)]**.** The aggregate mortality rate from fatal PE will unquestionably be reduced by reducing the rate of VTE through the use of mechanical and pharmacological prophylaxis [(24)]. The American College of Chest Physicians guidelines suggest that pharmacological thromboprophylaxis be administered for a minimum of 10 days following TKA and a maximum of 35 days following THA [(17)]**.** In comparison to placebo or untreated controls, extended-duration prophylaxis significantly reduced the frequency of post-discharge symptomatic VTE after THA or TKA, as demonstrated by a meta-analysis of data from randomized trials [(25)]. The perioperative administration of anticoagulant prophylaxis has been shown to reduce the rates of mortality and complications associated with VTE following these procedures. Furthermore, it was recognized that the extent of prophylaxis beyond hospital discharge, particularly after THA, provided an additional benefit **(26)**.

Due to their safety, efficacy, and ease of use, DOAC are frequently prescribed for extended prophylaxis [(27)]. In the interim, aspirin is a generic, cost-effective, and broadly accessible antiplatelet medication. In addition, Aspirin has shown promise in preventing VTE after surgery, according to clinical trials and meta-analyses; however, there is a dearth of comparisons with DOACs [(28)].

This study compared the DOAC after TKA to aspirin to see which was more effective and safe for use as a VTE prophylaxis.

The average age of the patients in the rivaroxaban group was 60.30 ± 5.85 years, whereas in the aspirin group, it was 63.20 ± 4.61 years, according to the current study. Females represented 90% of the patients in both groups and 100% of the patients in both groups were non-smokers. In the rivaroxaban group, the affected side was the left side in 80% of the patients, while in the aspirin group, it was the right side in 60% of the patients. The age range of patients included in this study is consistent with the information published by **Kuperman et al.** [(29)] in 2016, The preponderance of patients who undergo TKA are elderly, and they maintained that TKA is a common and effective treatment for end-stage OA of the knee. Additionally, concerning the greater proportion of women, This discovery is consistent with the findings of **Lavernia** [(30)]) as he stated that the percentage of patients undergoing TKA is disproportionately female in comparison to males and that in the majority of regions, The proportion of female patients who undergo TKA is greater.

In this investigation, there was no significant difference in the percentages of ischemic heart disease, hypothyroidism, hypertension, and bronchial asthma between the two groups, according to the co-morbidities that were considered. **(Table 2)**. This equilibrium in the baseline characteristics functions as the basis for comparing the study groups, as it reduces bias [(31)].

The present study revealed that both groups were comparable as regards the results of pre-operative laboratory investigations with no statistically significant differences between both groups as regards hemoglobin level, platelet count, or INR level. Again, to compare the research groups, it is necessary to ensure that their baseline characteristics are balanced. This will help to minimize bias [(31)].

Postoperative lower leg edema, severe bleeding, wound infection, and GIT bleeding were not significantly different between the two groups, according to the current study. When comparing the two groups for the incidence of mild bleeding after surgery, there was a statistically significant difference (p=0.018). The aspirin group did not experience minor bleeding in 100% of patients, while 25% of the rivaroxaban group experienced minor bleeding in the form of ecchymosis. Nearly similar findings were published by **Anderson et al.** [(32)] To evaluate the efficacy of aspirin and DOAC in the prevention of VTE (proximal DVT or PE) following total hip or TKA beyond hospital discharge, a comparable study was conducted on 3424 patients, 1804 of whom were undergoing total hip arthroplasty and 1620 of whom were undergoing TKA. However, In terms of major or clinically pertinent non-major hemorrhage complications, their analysis revealed no statistically significant distinctions between the two sets of data. These findings are also comparable to those published by **Huang et al.** [(33)] They studied 390 patients to determine whether aspirin or rivaroxaban was more effective in preventing VTE after hip fracture surgery, and which was safer, after enoxaparin therapy. When comparing the two groups' rates of major bleeding events and clinically relevant non-major bleeding, they found no statistically significant differences. And most recently, similar findings were also published by **Xu et al.** [(34)] who analyzed five studies with a combined total of 2,257 aspirin-

group patients and 2,337 rivaroxaban-group patients in a meta-analysis. The objective of the meta-analysis was to compare the efficacy of aspirin and rivaroxaban in the prevention of VTE following TKA and THA. When comparing the aspirin and rivaroxaban groups, they did not find any significant differences in the incidence of serious bleeding, overall bleeding, or wound complications.

In terms of the incidence of postoperative thromboembolism, the current investigation demonstrated that none of the patients included in the study experienced PE, and the rivaroxaban group experienced DVT in only 5% of patients. However, The postoperative incidence of PE or DVT did not exhibit any statistically significant differences between the two groups. Similar findings were published by **Anderson et al. [(32)]** given that they did not observe any significant variations in the rates of thromboembolic events between the two groups. Similarly, **Huang et al. [(33)]** In terms of the incidence of PE, Neither group showed any statistically significant variations from the other. Recently, Similar results were released by **Xu et al. [(34)]** upon comparing rivaroxaban with aspirin, they found no differences concerning VTE, its components, DVT, or PE.

CONCLUSION

The rivaroxaban groups had a much lower risk of DVT, with a rate of only 5%. Aspirin is a safe and effective medication for the prophylaxis of VTE, and the oral anticoagulant rivaroxaban was not significantly different from it in preventing DVT or PE following TKA.

REFERENCES

1. **Kurtz S, Mowat F, Ong K, et al.** Prevalence of primary and revision total hip and knee arthroplasty in the United States from 1990 through 2002. J Bone Joint Surg [Am] 2005; 87-A: 1487–1497.
2. **Falck-Ytter Y, Francis CW, Johanson NA, et al.** Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141(2): 278S–325S.
3. **Markel DC, York S, Liston MJ, et al.** Venous thromboembolism: management by American Association of Hip and Knee Surgeons. J Arthroplasty 2010; 25: 3–9.
4. **Jacobs JJ, Mont MA, Bozic KJ, et al.** American Academy of Orthopaedic Surgeons clinical practice guideline on: preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. J Bone Joint Surg Am 2012; 94(8): 746.
5. **Lanas Á, Carrera-Lasfuentes P, Arguedas Y, et al.** Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants. Clin Gastroenterol Hepatol 2015; 13: 906–912.
6. **Garcia D, Libby E, Crowther MA.** The new oral anticoagulants. Blood 2010; 115: 15-20.
7. **Turpie AGG, Lassen MR, Davidson BL, et al.** Rivaroxaban versus enoxaparin for thrombo-prophylaxis after total knee arthroplasty (RECORD4): a randomized trial. Lancet 2009; 373: 1673-1680.
8. **Faour M, David P, Alison K, Nicolas S.** Low-Dose Aspirin Is Safe and Effective for Venous Thromboembolism Prophylaxis Following Total Knee Arthroplasty. J Arthroplasty 2018; 33: S131– S135.
9. **Anderson DR, Murnaghan J, Kahn SR, et al.** Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty. N Engl J Med 2018; 378: 699-707
10. **Azboy I, Barrack R, Thomas AM, et al.** Aspirin and the prevention of venous thromboembolism following total joint arthroplasty: commonly asked questions. The bone & joint journal. 2017 Nov; 99(11): 1420-30.
11. **Wilson DG, Poole WE, Chauhan SK, et al.** A systematic review of aspirin for thromboprophylaxis in modern elective total hip and knee arthroplasty. Bone Joint J 2016; 98-B: 1056–1061.
12. **Lotke PA, Lonner JH.** The benefit of aspirin chemoprophylaxis for thromboembolism after total knee arthroplasty. Clin Orthop Relat Res 2006; 452: 175–180.
13. **Bozic KJ, Vail TP, Pekow PS.** Does aspirin have a role in venous thromboembolism prophylaxis in total knee arthroplasty patients? J Arthroplasty 2010; 25: 1053–1060.
14. **Huang R, Buckley PS, Scott B, et al.** Administration of aspirin as a prophylaxis agent against venous thromboembolism results in lower incidence of periprosthetic joint infection. J Arthroplasty, 2015; 30(9): 39–41.
15. **Bloch BV, Patel V, Best AJ.** Thrombo-prophylaxis with dabigatran leads to an increased incidence of wound leakage and an increased length of stay after total joint replacement. Bone Joint J 2014; 96-B: 122–126.
16. **Zou Y, Tian S, Wang Y, Sun K.** Administering aspirin, rivaroxaban and low-molecular-weight heparin to prevent deep venous thrombosis after total knee arthroplasty. Blood Coagul Fibrinolysis 2014; 25: 660–664.
17. **Geerts WH, Bergqvist D, Pineo GF, et al.** Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2008; 133(6): 381S–453S.
18. **Baser O.** Prevalence and economic burden of venous thromboembolism after total hip arthroplasty or total knee arthroplasty. American Journal of Managed Care. 2011; 17(1): S6-8.
19. **Januel JM, Chen G, Ruffieux C, et al.** IMECCHI Group. Symptomatic in-hospital deep vein thrombosis and pulmonary embolism following hip and knee arthroplasty among patients receiving recommended prophylaxis: A systematic review. JAMA.; 307(3): 294–303.
20. **Eichinger S and Kyrle PA.** Prevention of deep vein thrombosis in orthopedic surgery. Eur J Med Res. 2004; 9(3): 112–8.
21. **Pedersen AB, Johnsen SP and Sørensen HT.** Increased one-year risk of symptomatic venous thromboembolism following total hip replacement: A nationwide cohort study. J Bone Joint Surg Br. 2012; 94(120: 1598–603
22. **Samama CM, Ravaud P, Parent F, Barré J, et al.** Epidemiology of venous thromboembolism after lower limb arthroplasty: The FOTO study. J Thromb Haemost. 2007; 5(12): 2360–7.
23. **Fisher WD.** New oral anticoagulants and outpatient prophylaxis of venous thromboembolism. Am J Manag Care. 2011; 17(1): S15–S21.
24. **Cusick LA and Beverland DE.** The incidence of fatal pulmonary embolism after primary hip and knee replacement in a consecutive series of 4253 patients. J Bone Joint Surg Br. 2009; 91(5): 645–8.
25. **Eikelboom JW, Quinlan DJ and Douketis JD.** Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: A meta-analysis of the randomized trials. Lancet. 2001; 358(9275): 9–15.
26. **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.
27. **Garcia D, Libby E and Crowther MA.** The new oral anticoagulants. Blood. 2010; 115(1): 15-20.
28. **Anderson DR, Dunbar MJ, Bohm ER, et al.** Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: A randomized trial. Ann Intern Med. 2013; 158(11): 800-6.
29. **Kuperman EF, Schweizer M, Joy P, et al.** The effects of advanced age on primary total knee arthroplasty: A meta-analysis and systematic review. BMC Geriatr. 2016; 16: 41.

30. **Lavernia CJ.** Higher incidence of total knee arthroplasty in women than in men. Orthopedics. 2008; 31(5): 460-1.
31. **Sedgwick P**. Randomised controlled trials: Balance in baseline characteristics. BMJ. 2014; 349(3): g5721.
32. **Anderson DR, Dunbar MJ, Murnaghan J, et al.** Aspirin or rivaroxaban for VTE prophylaxis after hip or knee arthroplasty. N Engl J Med. 2018; 378(8): 699-707.
33. **Huang Q, Xing SX, Zeng Y, et al.** Comparison of the efficacy and safety of aspirin and rivaroxaban following enoxaparin treatment for prevention of venous thromboembolism after hip fracture surgery. Orthop Surg. 2019; 11(5): 886–94.
34. **Xu J, Kanagaratnam A, Cao JY, et al.** A comparison of aspirin against rivaroxaban for venous thromboembolism prophylaxis after hip or knee arthroplasty: A meta-analysis. Journal of Orthopedic Surgery. 2020; 28(1): 1-8.