**World Journal of Cardiovascular Diseases, 2014, 4, 586-593**
Published Online November 2014 in SciRes. http://www.scirp.org/journal/wjcd
http://dx.doi.org/10.4236/wjcd.2014.412071

# Thromboprophylaxis for Hip and Knee Arthroplasty: Current Managements and Review of the Literature

**Ismail Hakki Korucu[1*], Faik Turkmen[1], Burkay Kacira[1], Onur Bilge[1], Alper Kilicaslan[2], Serdar Toker[1]**

[1]Orthopaedic and Traumatology Department, Meram School of Medicine, Necmettin Erbakan University, Konya, Turkey
[2]Anesthesiology Department, Meram School of Medicine, Necmettin Erbakan University, Konya, Turkey
Email: [*]drihkorucu@gmail.com

Received 1 September 2014; revised 17 October 2014; accepted 2 November 2014



## Abstract

**Total Hip Arthroplasty (THA) and Total Knee Arthroplasty (TKA) are major surgical procedures which can cause high morbidity and even mortality. Among these complications is venous thrombo embolism (VTE) comprising deep vien thrombosis (DVT) and pulmonary embolism (PE). Therefore, after these operations, thromboprophylaxis is routinely used. However, it has some complications such as bleeding, adverse effect of chemical agents for using prevention of DVT. Antithrombotic prophylaxis includes: low molecular weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low dose unfractionated heparin (LDUH), adjusted dose vitamin K antagonist (VKA), aspirin, or mechanical thromboprophylaxis devices. All over the World, orthopaedic surgeons consider a balance between thromboprophylaxis and bleeding. However, it has been still controversy about optimum prophylaxis for DVT. In this current paper, we aimed to review the literature under light of the current studies.**

## Keywords

**Total Hip Arthroplasty, Total Knee Arthroplasty, Thromboprophylaxis**

## 1. Introduction

As well known by orthopaedic surgeons, Total Hip Arthroplasty (THA) and Total Knee Arthroplasty (TKA) are

[*]Corresponding author.

**How to cite this paper:** Korucu, I.H., Turkmen, F., Kacira, B., Bilge, O., Kilicaslan, A. and Toker, S. (2014) Thromboprophylaxis for Hip and Knee Arthroplasty: Current Managements and Review of the Literature. *World Journal of Cardiovascular Diseases*, **4**, 586-593. http://dx.doi.org/10.4236/wjcd.2014.412071

major surgical procedures which they can cause high morbidity and even mortality. Among these complications is venous thrombo embolism (VTE) comprising deep vien thrombosis (DVT) and pulmonary embolism (PE). While incidence of asymptomatic VTE after these orthopaedic surgeries is about 40% - 60%, symtomatic DVT is 4.3% without any thromboprophylaxis [1]. With appropriate thromboprophylaxis these rates are increase 1% - 3% incidence of symptomatic DVT and 0.2% - 1.1% incidence of PE [1]. For this reason, thromboprophylaxis use has been recommended for all patient undergoing THA and TKA [2]. A number of guidelines including American College of Chest Physicians (ACCP) and American Academy of Orthopaedic Surgeons (AAOS) have recommended thromboprophylaxis.

Although thromboprophylaxis after THA and TKA have been ruotinely used, it has some complications such as bleeding, adverse effect of chemical agents for using prevention of DVT. Bleeding is a main complication including minor bleeding (hemorrhage, wound hematoma, persisting wound drainage, failure of wound healing, risk of infection) and major bleeding (transfusion demand two or more units of blood products, life threatening hemoglobin levels, intra-cranial, intra-abdominal and retroperitoneal bleeding events) [3]-[5]. All over the World, orthopaedic surgeons consider a balance between thromboprophilaxis and bleeding. However, it has been still controversy about optimum prophylaxis for DVT.

Although many guidelines exist for thromboprophylaxis, in orthopaedic thromboprophylaxis, American College of Chest Physicians (ACCP) and American Academy of Orthopaedic Surgeons (AAOS) guidelines are generally used. Therefore, we will briefly mention these guidelines.

### 1.1. ACCP Thromboprophylaxis Guideline 9th Edition

The ACCP has published reguler guidelines for the prevention of VTE since 1986. The ninth ACCP provides evidence-based guidelines in 2012 for VTE prevention in patients who have undergone THA and TKA. İt has based on the use of prophylaxis to reduce the patient important outcomes of fatal and symptomatic DVT, whis is balanced against the hazard of an increase in symtomatic bleeding [1] [6]. ACCP have recommended in patients who have undergone THA or TKA that use of one of the following for a minimum of 10 to 14 days rather than no anti-thrombotic prophylaxis: low molecular weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low dose unfractionated heparin (LDUH), adjusted dose vitamin K antagonist (VKA), aspirin, or an intermittent pneumatic compression device (IPCD). Also ACCP recommend extending thrombo-prophylaxis in out patient period for up to 35 days from the day of surgery and using dual prophylaxis with an antithrombotic agent and an IPCD during hospital stay [1] [6].

For patients who have increased bleeding risk, the ACCP recommends an intermittent pneumatic compression device or no prophylaxis.

Among recommended drugs by ACCP which needs parenteral application or labratory monitorization, in patients undergoing major orthopaedic surgery and who decline ora re uncooperative with injection or an IPCD, ACCP recommends using Apixaban or Debigatran [1].

### 1.2. AAOS Thromboprophylaxis Guideline 2011

The American Academy of Orthopaedic Surgeons has developed its own guideline recommendations that were updated most recently in September 2011 [7]. This evidance based guideline recommends that all patients be assesed preoperatively for risk of VTE and bleeding so AAOS does not recommend specific agents or duration for prophylaxis as ACCP's recommends. The AAOS guideline have not accepted the use of venographically detected asymptomatic DVT as a valid outcome when assesing the efficacy of thromboprophylaxis in clinical studies and instead consider fatal PE as only clinically relevant outcome [7] [8]. Patints undergoing THA or TKA who have also had a previous VTE are recommended to receive both pharmacologic prophylaxis and mechanical compressive devices, whereas those who have a known bleeding disorder and active liver disease are recommended to solely use mechanical compressive devices for preventing VTE [8] [9].

## 2. Thromboprophylactic Agents

VTE prophylaxis after major orthopaedic surgeries such as THA and TKA are available in chemical and/or mechanical forms. Chemical agent has been rapidly developed in recent years. These chemical agents included in guidelines were low molecular weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban,

low dose unfractionated heparin (LDUH), adjusted dose vitamin K antagonist (VKA), aspirin. These drugs are all approved in United States and some other countries. In this current paper we will briefly describe above mentioned agents with studies has been publised in the availeble literature.

### 2.1. Application of Low Molecular Weight Heparin (LMWH)

LMWH is generated from unfractionated heparin via physical, chemical, enzymatic depolarization. Its commonly used forms are enoxaparine, dalteparin and tinzaparin. For prevention of VTE after major orthopaedic surgery only enoxaparin and dalteparin are used [6] [10].

LMWHs are applied subcutaneously, with enoxaparin prescribed either as a 30 mg dose given twice a day (North American regimen) or as a 40 mg dose given once a day (European standart). According to ACCP guidelines prophylaxis should started 12 hours before surgery and 12 - 24 h after surgery and using of LMWH should continiue minimum 10 - 14 days postoperativelly [1].

LMWHs have rapid antithrombotic effect and do not necessitate any daily laboratory monitoring. Several prospective comparative randomize control trials have been performed to assess the effectiveness of LMWH after THA and TKA surgeries. In studies compared UFH and warfarin, LMWH have shown superior efficiency to preventing DVT [11] [12]. In a meta-analysis performed by Westrich *et al.*, in terms of rates of DVT, LMWH beter than warfarin and aspirin [13]. The other meta-analysis performed by Brookhental *et al*., they showed that LMWH protected significantly beter than warfarin from both proximal and distal DVT [14]. Rates of symtomatic PE, fatal embolism, major hemorrhage or total mortality were similar between two groups.

Including compared enoxaparin with the novel oral anticoagulants (NOAC) (rivaroxaban, dabigatran, apixaban) a meta-analysis study performed by Outes *et al*., demonstrated that NOAC are higher in efficacy, but also have higher risk of bleeding [15]. On the other hand, in the same study there was no significant difference between LMWH and NOAC after balancing efficacy and safety (symtomativ DVT or PE with clinically relevant bleeding events).

### 2.2. Application of Warfarin

Since 1954 in United states, widely using warfarin is a vitamin K antagonist and inhibits vitamin K dependent cloting factors. Althoug it is used orally, it has some restriction such as bleeding risk, potantial drug interaction and requirement for constant monitoring (INR) [16]. Due to orally administration, it provides more compliance compared with parenteral antithrombotic agents. AAOS recommends warfarin using such that INR $\leq 2$ during 2 - 6 weeks after TKA and THA surgeries. Several studies have compared the efficacy of warfarin to LMWH for thromboprophylaxis after THA and TKA. All these trials demonstrated that warfarin is an effective and safe anticoagulant. However, warfarin is inferior to LMWH at preventing VTE [12] [17].

Although warfarin orally administrated, there are some limitation in clinical practice such as narrow therapeutic window, exhibit a variable and unpredictable dose response and assosiated with several food and drug interaction.

### 2.3. Application of Aspirin

For last decades, aspirin has been widely using as antitrombotic agent after major orthopaedic surgery. Its pharmacological effects on platelet aggregation via inhibiting thromboxan A2 and thus decreasing thrombus formation [18]. The ACCP guideline recommends aspirin as a chemoprophylactic agent, rather than no prophylaxis at all [1]. Although aspirin has referred in to ACCP guideline, it's usage do not consider to sole agent of thromboprophylaxis [1] [19].

### 2.4. Application of Fondaparinux as a Indirect Factor Xa Inhibitor

As a synthetic pentasaccaride, fondaparinux indirectly inhibits factor Xa through binds to anti-thrombin and prevents thrombus formation [20]. This drug approved by Food and Drug Administration (FDA) and it has taken place in the market since 2002. Inspite of using LMWH after TKA highly DVT rates, fondaparinux was using as 2.5 mg once daily subcutaneous injection. A recent study conducted by Ralay *et al*., fondaparinux can use orally administration via nanoparticles coated gastroresistant capsules [21]. However, there are no study in the literature about orally administreted fondaparinux.

In literature, a study performed by Bauer *et al*., in which they performed a double-blind, randomized control trial comparing fondaparinux 2.5 mg once daily to enoxaparin 30 mg given twice a day in patients who underwent major elective orthopaedic surgery. They found that despite of fondaparinux decrease DVT compared to LMWH, it had significantly higer rates of bleeding [22]. A meta-analysis completed by Turpie *et al*. above mentioned findings was corraborated [23].

## 2.5. Application of Direct Factor Xa Inhibitors

This group includes rivaroxaban, apixaban, endoxaban and betrixaban as orally administreted anti thrombotic agents. After THA and TKA, rivaroxaban and apixaban are roccomended by ACCP guideline [1]. Therefore, we will briefly refer to rivaroxaban and apixaban.

### 2.5.1. Rivaroxaban

Rivaroxaban is an first orally bioavailable, direct and selective factor Xa inhibitor. It has been approved by FDA. Following ingestion it reaches plasma peak level after 2 - 4 h. Its half life is 5 - 9 h. Approximately two-thirds of rivaroxaban is metabolised through renal and faecal route. The remain one-third is excreted unchanged in urine [24] [25]. In mild or severe renal impairment, it is not require dose adjusment, but in hepatic disease with coagulopathy and bleeding risk its using is contraindicate. Due to it is metabolised via CYP3A4 and P-gp, it is not recommended in patients who have been treated with azole antifungals or systemic HIV protease inhibitors [26].

Rivaroxaban was studied in four Phase III trials called RECORD (Regulation of Coagulation in Orthopaedic Surgery to prevent deep venous thrombosis and pulmonary embolism) for prevention of VTE. Among these studies, two after THA (RECORD 1 and 2) and the others after TKA (RECORD 3 and 4). In RECORD 1 - 3 investigators used 40 mg enoxaparin once daily and in RECORD 4 they used enoxaparin 30 mg twice daily as comparator, it was started 12 h before surgery and restarted 6 - 8 h after wound closure. All in four trials dose of rivaroxaban was 10 mg once daily started 6 - 8 h after wound closure. All in these trials, rivaroxaban was highly effective compared with enoxaparin. Althhough the number of bleeding events were higher in rivaroxaban treatment group, incidence of advers events and bleeding rates were similar with enoxaparin [27]-[30].

The recommended dose of rivaroxaban is 10 mg orally once daily starting 6 - 10 h after surgery. For patients undergoing THA , treatment duration of 35 days is recommended; for TKA this duration is 12 days [26].

### 2.5.2. Apixaban

Also apixaban is an oral highly selective, reversible and directly acting factor Xa inhibitor. This drug has not been approved by FDA. Following ingestion, more than 50% of apixaban has had bioavailability and it has arrived peak plasma concentration in 30 minutes to 2 hours, with a terminal half life of approximately 12 h. Totally it has been metabolised both liver and renal. Approximately 30% of the drug has been metabolised through renal and the remained amount faecal route [31]. Therefore, apixaban is not recommended in patients with a creatin clearance (CrCl) less than 15 ml/min, patient on dialysis or with severe hepatic impairment. Due to apixaban is also metabolised via both CYP3A4 and P-glycoprotein (P-gp), it is not recommended in patients receiving concomitant systematic treatment with strong inhibitors of these enzymes [31].

In three large phase III studies, Apixaban was compared with enoxaparin. ADVANCE 1 and 2 have been studied in patients with TKA, ADVANCE 3 in patients with THA. All in these three trials, dose of apixaban was 2.5 mg twicw daily starting 12 - 24 hours after surgery. While in ADVANCE 1, dosage of enoxaparin was 30 mg twice daily starting 12 - 24 hours after surgery, in ADVANCE 2 and 3 dosage of enoxaparin was 40 mg once daily 12 hours starting after surgery. At the end of these trials, apixaban was superior to enoxaparin in terms of reducing total VTE and all cause death. It had similar bleeding rates with enoxaparin. Thus, apixaban is approved by European Union as 2.5 mg orally twice/day and its initial dose taken 12 - 24 hours after surgery [32].

## 2.6. Application of Direct Thrombin Inhibitors

As competitive and reversible direct thrombin inhibitor dabigatran etexilate is a prodrug form. Following its orally taken, it is rapidly converted to dabigatran by esterases in the blood and liver [33]. Approximately 80% of this drug is excreted unchanged via the kidneys and remained amount of the drug via the biliary system after

conjugation. In case of renal and hepatic failure the drug is not recommended. In patients with CrCL less than 30 ml/min and elevated liver enzymes raised to more than twice the upper limit of normal, it is conraindicated. Although dabigatran is not metabolised by CYP enzymes, it should be used caution in patients who are treated with strong P-gp inhibitor drugs [34] [35].

Dabigatran was studied in four phase III trials to prevention of VTE. In RE-NOVATE and RE-NOVATE 2 are after THA and RE-MODEL, RE-MOBILIZE are after TKA. While in RE-NOVATE and RE-MODEL dabigatran was compared with enoxaparin 40 mg once daily, in RE-MOBILIZE dabigatran was compared with enoxaparin 30 mg twice daily. Dosage of dabigatran was 220 mg and 150 mg once daily in RE-NOVATE, RE-MODEL and RE-MOBILIZE. In RE-NOVATE 2 dosage of dabigatran was 220 mg once daily. All these trials demonstrated that dabigatran had no inferiority and in terms of bleeding outcomes were similar between enoxaparin and dabigatran group [36]-[39]. The results of these trials have been based for approval of dabigatran by european and Canadian regulators in 2008. They recommend the dosage of dabigatran as 220 mg once daily taken in two 110 mg capsules. Patient with moderate renal impairment (CrCL 30 - 50 ml/min) and over 75 years of age recommended dosage of the drug 150 mg once daily in two 75 mg capsules [33].

## 3. Mechanical Prophylaxis

Various type of external compression devices are available to provide DVT prophylaxis such as graduated compression stocking (GCS), intermittent pneumatic compression devices (IPCD) [40]. The primary advantages of these devices are the lack of a side effect bleeding.

GCSs are widely used for prvention and treatment of DVT in nontrauma patients [41]. This device acts via diminishing the diameter of distended veins and increasing venous blood flow. Although Sachdeva *et al*. demostrated that GCSs are effective in decraesing the risk of DVT in hospitalized patients [42], in contrast to a study in the literature performed by Lapidus *et al*. pointed out that there is no different between continuing and discontinuing the use of postoperative GCSs [43].

IPCD is the other mechanical prophylaxis device. Main disadvantage of this device is compliance that the device need to be removed during washing and ambulation. Also after hospital discharge the device require an external power source. However this problem has been solved by technical improvement as new portable and battery powered devices. The comperative study performed by colwell *et al*. demonstrated that IPCD was effective as much as effect of enoxaparin. In this multicenter randomized conrolled study also demontrated that IPCD had lower bleeding rate as per enoxaparin as expected [44]. ACCP guidelines recommend that at least 18 hours per day use of IPCD with combined use with chemoprophylaxis. In patient with high risk of bleeding or contraindicated anticoagulants IPCD is recommneded alone [1]. AAOS also recommend IPCD in patient with hemophilia or active liver desease or as with chemoprophylaxis in paitent with previous VTE [6].

## 4. Conclusion

Total knee arthroplasty and total hip arthroplasty are commonly performed by orthopaedic surgeon. These surgeries are open to complication especially deep vein thrombosis, venous thromboembolism and pulmonary embolism. To avoid these complications orthopaedic surgeons should consider to use anti thrombotic agents and devices. Under light of the ACCP and AAOS guidelines, the treatment and prophylaxy are succesfully applied. In selected treatment, patient compliance is crucial to prevent VTE especially after hospital discharge. Not require monitoring and self administrating drugs are recently favour. These new oral anticoagulant drugs are closer to the ideal antithrombotic drug. However, long term well conducted trials are required to make desicion safety and efficacy of the new drugs.

## References

[1] FalckYtter, Y., Francis, C.W., Johanson, N.A., *et al.* (2012) 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*, **141**, e279S-e325S.

[2] Geerts, W.H., Bergqvist, D., Pineo, G.F., *et al.* (2008) Prevention of Venous Thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th edn. *Chest*, **133**, 381S-453S.

[3] Burnett, R.S., Clohisy, J.C., Wright, R.W., McDonald, D.J., Shively, R.A., Givens, S.A. and Barrack, R.L. (2007) Failure of the American College of Chest Physicians-1A Protocol for Lovenox in Clinical Outcomes for Throm-

boembolic Prophylaxis. *The Journal of Arthroplasty*, **22**, 317-324. http://dx.doi.org/10.1016/j.arth.2007.01.007

[4] Walsh, M., Preston, C., Bong, M., Patel, V. and Di Cesare, P.E. (2007) Relative Risk Factors for Requirement of Blood Transfusion after Total Hip Arthroplasty. *The Journal of Arthroplasty*, **22**, 1162-1167. http://dx.doi.org/10.1016/j.arth.2006.10.014

[5] Schulman, S., Angerås, U., Bergqvist, D., Eriksson, B., Lassen, M.R. and Fisher, W. (2010) Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of Major Bleeding in Clinical İnvestigations of Antihemostatic Medicinal Products in Surgical Patients. *Journal of Thrombosis and Haemostasis*, **8**, 202-204. http://dx.doi.org/10.1111/j.1538-7836.2009.03678.x

[6] Geerts, W.H., Pineo, G.F., Heit, J.A., *et al*. (2004) Prevention of Venous Thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*, **126**, 338S-400S. http://dx.doi.org/10.1378/chest.126.3_suppl.338S

[7] Jacobs, J.J., Mont, M.A., Bozic, K.J., Della Valle, C.J., Goodman, S.B., Lewis, C.G., *et al*. (2012) American Academy of Orthopaedic Surgeons Clinical Practice Guideline on: Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty. *Journal of Bone and Joint Surgery*, **94**, 746-747. http://dx.doi.org/10.2106/JBJS.9408.ebo746

[8] American Academy of Orthopaedic Surgeons (AAOS) (2007) American Academy of Orthopaedic Surgeons Clinical Guideline on Prevention of Symptomatic Pulmonary Embolism in Patients Undergoing Total Hip or Knee Arthroplasty. AAOS, Rosemont. www.aaos.org/Research/guidelines/PE_guideline.pdf

[9] American Academy of Orthopedic Surgeons (2011) Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty: Evidence-Based Guidelines and Evidence Report. www.aaos.org/research/guidelines/VTE/VTE_full_guideline.pdf

[10] Merli, G.J. and Groce, J.B. (2010) Pharmacological and Clinical Differences between Low-Molecular-Weight-Heparins. Implications for Prescribing Practice and Therapeutic İnterchange. *Physical Therapy*, **35**, 95-105.

[11] Leclerc, J.R., Geerts, W.H., Desjardins, L., *et al.* (1996) Prevention of Venous Thromboembolism after Knee Arthroplasty. A Randomized, Doubleblind Trial Comparing Enoxaparin with Warfarin. *Annals of Internal Medicine*, **124**, 619-626. http://dx.doi.org/10.7326/0003-4819-124-7-199604010-00001

[12] Fitzgerald Jr., R.H., Spiro, T.E., Trowbridge, A.A., *et al.* (2001) Prevention of Venous Thromboembolic Disease Following Primary Total Knee Arthroplasty. A Randomized, Multicenter, Open-Label, Parallel-Group Comparison of Enoxaparin and Warfarin. *The Journal of Bone and Joint Surgery. American Volume*, **83-A**, 900-906.

[13] Westrich, G.H., Haas, S.B., Mosca, P. and Peterson, M. (2000) Meta-Analysis of Thromboembolic Prophylaxis after Total Knee Arthroplasty. *The Journal of Bone and Joint Surgery. British Volume*, **82**, 795-800. http://dx.doi.org/10.1302/0301-620X.82B6.9869

[14] Brookenthal, K.R., Freedman, K.B., Lotke, P.A., *et al.* (2001) A Meta-Analysis of Thromboembolic Prophylaxis in Total Knee Arthroplasty. *The Journal of Arthroplasty*, **16**, 293-300. http://dx.doi.org/10.1054/arth.2001.21499

[15] Outes, G.A., Fernandez, A.I.T., Gea, L.S. and Castrillon, E.V. (2012) Dabigatran, Rivaroxaban, or Apixaban vs Enoxaparin for Thromboprophylaxis after Total Hip or Knee Replacement: Systematic Review, Meta-Analysis, and İndirect Treatment Comparison. *BMJ*, **344**, e3675. http://dx.doi.org/10.1136/bmj.e3675

[16] Kirley, K., Qato, D.M., Kornfield, R., Stafford, R.S. and Alexander, G.C. (2012) National Trends in Oral Anticoagulants Use in the United States, 2007-2011. *Circulation*: *Cardiovascular Quality and Outcomes*, **5**, 615-621. http://dx.doi.org/10.1161/CIRCOUTCOMES.112.967299

[17] Hull, R., Raskob, G., Pineo, G., *et al.* (1993) A Comparison of Subcutaneous Low-Molecular-Weight Heparin with Warfarin Sodium for Prophylaxis against Deep-Vein Thrombosis after Hip or Knee Implantation. *The New England Journal of Medicine*, **329**, 1370-1376. http://dx.doi.org/10.1056/NEJM199311043291902

[18] Geerts, W.H., Heit, J.A., Clagett, G.P., *et al.* (2001) Prevention of Venous Thromboembolism. *Chest*, **119**, 132S-175S. http://dx.doi.org/10.1378/chest.119.1_suppl.132S

[19] Lotke, P.A. and Lonner, J.H. (2006) The Benefit of Aspirin Chemoprophylaxis for Thromboembolism after Total Knee Arthroplasty. *Clinical Orthopaedics and Related Research*, **452**, 175-180. http://dx.doi.org/10.1097/01.blo.0000238822.78895.95

[20] Fuji, T., Fujita, S. and Ochi, T. (2008) Fondaparinux Prevents Venous Thromboembolism after Joint Replacement Surgery in Japanese Patients. *International Orthopaedics*, **32**, 443-451. http://dx.doi.org/10.1007/s00264-007-0360-7

[21] Ralay-Ranaivo, B., Desmaële, D., Bianchini, E.P., Lepeltier, E., Bourgaux, C., Borgel, D., Pouget, T., Tranchant, J.F., Couvreur, P. and Gref, R. (2014) Novel Self Assembling Nanoparticles for the Oral Administration of Fondaparinux: Synthesis, Characterization and *in Vivo* Evaluation. *Journal of Controlled Release*, **194**C, 323-331

[22] Bauer, K.A., Eriksson, B.I., Lassen, M.R. and Turpie, A.G. (2001) Fondaparinux Compared with Enoxaparin for the Prevention of Venous Thromboembolism after Elective Major Knee Surgery. *The New England Journal of Medicine*,

**345**, 1305-1310. http://dx.doi.org/10.1056/NEJMoa011099

[23] Turpie, A.G., Bauer, K.A., Eriksson, B.I. and Lassen, M.R., PENTATHALON 2000 Study Steering Committee (2002) Postoperative Fondaparinux vs Postoperative Enoxaparin for Prevention of Venous Thromboembolism after Elective Hip-Replacement Surgery: A Randomized Double-Blind Trial. *The Lancet*, **359**, 1721-1726. http://dx.doi.org/10.1016/S0140-6736(02)08648-8

[24] Eriksson, B.I., Quinlan, D.J. and Weitz, J.I. (2009) Comparative Pharmacodynamics and Pharmacokinetics of Oral Direct Thrombin and Factor Xa Inhibitors in Development. *Clinical Pharmacokinetics*, **48**, 1-22. http://dx.doi.org/10.2165/0003088-200948010-00001

[25] Kubitza, D., Becka, M., Voith, B., *et al*. (2005) Safety, Pharmacodynamics, and Pharmacokinetics of Single Doses of BAY 59-7939 an Oral, Direct Factor Xa Inhibitor. *Clinical Pharmacology Therapeutics*, **78**, 412-421. http://dx.doi.org/10.1016/j.clpt.2005.06.011

[26] Xarelto (Rivaroxaban) Summary of Product Characteristics. Bayer Schering Pharma. Accessed 26 February 2012. http://www.xarelto.com/html/downloads/Xarelto-prescribing_information-Nov-(2012).pdf

[27] Eriksson, B.I., Borris, L.C., Friedman, R.J., *et al*. (2008) Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Hip Arthroplasty. *The New England Journal of Medicine*, **358**, 2765-2775. http://dx.doi.org/10.1056/NEJMoa0800374

[28] Kakkar, A.K., Brenner, B., Dahl, O.E., *et al*. (2008) Extended Duration Rivaroxaban versus Short-Term Enoxaparin for the Prevention of Venous Thromboembolism after Total Hip Arthroplasty: A Double-Blind, Randomised Controlled Trial. *The Lancet*, **372**, 31-39. http://dx.doi.org/10.1016/S0140-6736(08)60880-6

[29] Lassen, M.R., Ageno, W., Borris, L.C., *et al*. (2008) Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Total Knee Arthroplasty. *The New England Journal of Medicine*, **358**, 2776-2786. http://dx.doi.org/10.1056/NEJMoa076016

[30] Turpie, A.G., Lassen, M.R., Davidson, B.L., *et al*. (2009) Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Total Knee Arthroplasty (RECORD4): A Randomised Trial. *The Lancet*, **373**, 1673-1680. http://dx.doi.org/10.1016/S0140-6736(09)60734-0

[31] Raghavan, N., Frost, C.E., Yu, Z., *et al*. (2009) Apixaban Metabolism and Pharmacokinetics after Oral Administration to Humans. *Drug Metabolism and Disposition*, **37**, 74-81. http://dx.doi.org/10.1124/dmd.108.023143

[32] Pfizer, Inc. Eliquis (Apixaban) (2011) Summary of Product Characteristics. Middlesex, UK. Accessed 1 October 2012. www.ema.europaeu/docs/en_GB/document_library/EPAR_Product_Information/human/002148/WC500107728.pdf

[33] Bristol-Myers Squibb and Pfizer EEIG (2012) Eliquis® (apixaban tablets) Summary of Product Characteristics. accessed 10 April 2013. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf

[34] Boehringer Ingelheim Pharmaceuticals (2011) Pradaxa (dabigatran) Summary of Product Characteristics. Ridgefield, CT.

[35] Stangier, J., Rathgen, K., Staehle, H., *et al*. (2007) The Pharmacokinetics, Pharmacodynamics and Tolerability of Dabigatran Etexilate, a New Oral Direct Thrombin İnhibitor, in Healthy Male Subjects. *British Journal of Clinical Pharmacology*, **64**, 292-303. http://dx.doi.org/10.1111/j.1365-2125.2007.02899.x

[36] Di Nisio, M., Middeldorp, S. and Buller, H.R. (2005) Direct Thrombin İnhibitors. *The New England Journal of Medicine*, **353**, 1028-1040. http://dx.doi.org/10.1056/NEJMra044440

[37] Eriksson, B.I., Dahl, O.E., Rosencher, N., *et al*. (2007) Dabigatran Etexilate versus Enoxaparin for Prevention of Venous Thromboembolism after Total Hip Replacement: A Randomized, Double-Blind, Noninferiority Trial. *The Lancet*, **370**, 949-956. http://dx.doi.org/10.1016/S0140-6736(07)61445-7

[38] Ginsberg, J.S., Davidson, B.L., *et al*., RE-MOBILIZE Writing Committee (2009) The Oral Thrombin Inhibitor Dabigatran Etexilate vs the North American Enoxaparin Regimen for the Prevention of Venous Thromboembolism after Knee Arthroplasty Surgery. *The Journal of Arthroplasty*, **2**, 1-9.

[39] Eriksson, B.I., Dahl, O.E., Rosencher, N., *et al*. (2007) Oral Dabigatran Etexilate versus Subcutaneous Enoxaparin for the Prevention of Venous Thromboembolism after Total Knee Replacement: The RE-MODEL Randomized Trial. *Journal of Thrombosis and Haemostasis*, **5**, 2178-2185. http://dx.doi.org/10.1111/j.1538-7836.2007.02748.x

[40] Hak, D.J. (2001) Prevention of Venous Thromboembolism in Trauma and Long Bone Fractures. *Current Opinion in Pulmonary Medicine*, **7**, 338-343. http://dx.doi.org/10.1097/00063198-200109000-00015

[41] Morris, R.J. and Woodcock, J.P. (2010) Intermittent Pneumatic Compression or Graduated Compression Stockings for Deep Vein Thrombosis Prophylaxis? A Systematic Review of Direct Clinical Comparisons. *Annals of Surgery*, **251**, 393-396. http://dx.doi.org/10.1097/SLA.0b013e3181b5d61c

[42] Sachdeva, A., Dalton, M., Amaragiri, S.V. and Lees, T. (2010) Elastic Compression Stockings for Prevention of Deep

Vein Thrombosis. *Cochrane Database of Systematic Reviews*, **7**, Article ID: CD001484. http://dx.doi.org/10.1002/14651858.CD001484.pub2

[43] Lapidus, L.J., Ponzer, S., Pettersson, H. and de Bri, E. (2013) Symptomatic Venous Thromboembolism and Mortality in Orthopaedic Surgery—An Observational Study of 45,968 Consecutive Procedures. *BMC Musculoskeletal Disorders*, **14**, 177. http://dx.doi.org/10.1186/1471-2474-14-177

[44] Colwell Jr., C.W., Froimson, M.I., Mont, M.A., *et al*. (2010) Thrombosis Prevention after Total Hip Arthroplasty: A Prospective, Randomized Trial Comparing a Mobile Compression Device with Low-Molecular-Weight Heparin. *Journal of Bone and Joint Surgery*. *American Volume*, **92-A**, 527-535.

Scientific Research Publishing (SCIRP) is one of the largest Open Access journal publishers. It is currently publishing more than 200 open access, online, peer-reviewed journals covering a wide range of academic disciplines. SCIRP serves the worldwide academic communities and contributes to the progress and application of science with its publication.

Other selected journals from SCIRP are listed as below. Submit your manuscript to us via either submit@scirp.org or Online Submission Portal.