

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

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

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## 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 vein 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. Anti-thrombotic 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

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## 1. Introduction

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

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**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 vein thrombosis (DVT) and pulmonary embolism (PE). While incidence of asymptomatic VTE after these orthopaedic surgeries is about 40% - 60%, symptomatic 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 routinely 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 thromboprophylaxis 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 regular 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. It has based on the use of prophylaxis to reduce the patient important outcomes of fatal and symptomatic DVT, which is balanced against the hazard of an increase in symptomatic 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 laboratory monitorization, in patients undergoing major orthopaedic surgery and who decline oral or uncooperative with injection or an IPCD, ACCP recommends using Apixaban or Dabigatran [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 evidence based guideline recommends that all patients be assessed 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 assessing the efficacy of thromboprophylaxis in clinical studies and instead consider fatal PE as only clinically relevant outcome [7] [8]. Patients 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 published in the available literature.

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

LMWH is generated from unfractionated heparin via physical, chemical, enzymatic depolymerization. Its commonly used forms are enoxaparin, 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 standard). According to ACCP guidelines prophylaxis should started 12 hours before surgery and 12 - 24 h after surgery and using of LMWH should continue minimum 10 - 14 days postoperatively [1].

LMWHs have rapid antithrombotic effect and do not necessitate any daily laboratory monitoring. Several prospective comparative randomized 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 better than warfarin and aspirin [13]. The other meta-analysis performed by Brookenthal *et al.*, they showed that LMWH protected significantly better than warfarin from both proximal and distal DVT [14]. Rates of symptomatic 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 (symptomatic 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 clotting factors. Although it is used orally, it has some restriction such as bleeding risk, potential 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 administered, there are some limitation in clinical practice such as narrow therapeutic window, exhibit a variable and unpredictable dose response and associated with several food and drug interaction.

### 2.3. Application of Aspirin

For last decades, aspirin has been widely using as antithrombotic agent after major orthopaedic surgery. Its pharmacological effects on platelet aggregation via inhibiting thromboxan A<sub>2</sub> 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, its 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 pentasaccharide, 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. In spite 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 administered 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 higher rates of bleeding [22]. A meta-analysis completed by Turpie *et al.* above mentioned findings was corroborated [23].

## 2.5. Application of Direct Factor Xa Inhibitors

This group includes rivaroxaban, apixaban, endoxaban and betrixaban as orally administered anti thrombotic agents. After THA and TKA, rivaroxaban and apixaban are recommended 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 adjustment, 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 withazole 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. Although the number of bleeding events were higher in rivaroxaban treatment group, incidence of adverse 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 twice 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 contraindicated. 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 prevention 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.* demonstrated that GCSs are effective in decreasing 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 comparative study performed by Colwell *et al.* demonstrated that IPCD was effective as much as effect of enoxaparin. In this multicenter randomized controlled study also demonstrated 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 recommended alone [1]. AAOS also recommend IPCD in patient with hemophilia or active liver disease or as with chemoprophylaxis in patient 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 successfully 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 decision safety and efficacy of the new drugs.

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