Methods of Venous Thromboembolic Prophylaxis in Orthopedic Surgeries

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Abstract:

Background: Venous thromboembolic prophylaxis after major orthopaedic surgeries is an essential topic to review and has a lot of controversies and differences regarding which method to emphasize and the duration of each method of prophylaxis to be used in daily practice in orthopaedic surgery. Here we mentioned the review of literature with respect to thromboembolic prophylaxis in orthopaedic surgery including the latest guidelines and we made a meta-analysis of data from many studies regarding the use of different pharmacological agents after major orthopaedic surgeries like total hip replacement (THR), total knee replacement (TKR), hip fracture and knee arthroscopic surgery. **Method:** we searched Medline via PubMed, SCOPUS, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar from 2010 till November 2019. The search retrieved 2089 unique records. We then retained 57 potentially eligible records for full-texts screening. Finally, 29 studies were included. **Results:** the rate of DVT was higher with DTI than with LMWH and lowest with FXaI, while the rate of PE was higher with DTI than FXaI and lowest with LMWH. The rate of major bleeding was higher with LMWH than with FXaI and lowest with DTI, indicating that FXaI has the lead in thromboembolic prophylaxis after THR or TKR with lower risk of bleeding compared to LMWH. **Conclusion:** FXaI was the most effective agent after THR and TKR. In hip fracture surgery and Knee arthroscopy, thromboprophylaxis is needed, but variable results regarding the drug choice warrant more research.

Keywords: Thromboembolic; prophylaxis; orthopedic

Introduction

Venous thromboembolism (VTE) is a common complication during and after hospitalization for medical and surgical patients, including orthopaedic patients. More than half of all hospitalized patients are at risk for VTE, with a higher risk in surgical patients than in medical patients (1).

However, the overall VTE rates are in the range of 13% to 70%, implying a large variability between institutions and countries. Without any prophylaxis, pulmonary embolism (PE) is responsible for 5% to 10% of deaths in hospitalized patients. The incidence of fatal PE in hospitalized patients is 0.1% to 0.8% after elective general surgery, 2% to 3% after elective hip replacement and 4% to 7% after hip fracture surgery. Similarly, deep venous thrombosis (DVT) affects approximately 0.1% of persons per year (2).

The overall incidence of DVT in medical and general surgery hospitalized patients is in the range of 10% to 40%; in comparison, the incidence of DVT ranges up to 40% to 60% in major orthopaedic surgery (3).

The overall average age- and sex-adjusted annual incidence of venous thromboembolism (VTE) is 0.117% (DVT, 0.048%; PE, 0.069%), with higher age-adjusted rates among males than females (0.130 vs 0.110 %, respectively). Both sexes are equally afflicted by a first VTE, men having a higher risk of recurrent thrombosis. DVT is predominantly a disease of the elderly with an incidence that rises markedly with age (4).

Death within one month of diagnosis occurs in approximately 6% of DVT patients and approximately 12% of PE patients. The cumulative ten-year incidence of recurrent VTE reaches 39.9% (35.4% to 44.4%) (2).

The incidence of VTE is low in children. Annual incidences of 0.0007 to 0.0014% children and 0.053% hospital admissions have been reported in Caucasian studies. This low incidence may be due to decreased capacity to generate thrombin, increased capacity of alpha-2-macroglobulin to inhibit thrombin, and enhanced antithrombin potential of vessel walls. The highest incidence in childhood is during the neonatal period, followed by another peak in adolescence. The incidence rate is comparatively higher in adolescent females because of pregnancy and use of oral contraceptive agents (5).

Pregnant women have a much higher risk of VTE than non-pregnant women of similar age and the risk has been shown to be higher after cesarean section than after vaginal delivery (6).

Orthopaedic patients are at higher risk among all patients for DVT and VTE. In the early

2000s, despite the existence of VTE prophylaxis guidelines, the use of VTE prophylaxis was low (7). Currently, the adherence to the different VTE prophylaxis guidelines, especially for orthopaedic patients, is increasing.

We aimed at investigating the recent trends of research in the last ten years. There have been a tremendous advances in venous thromboembolism (VTE) prophylaxis. Guidelines have also been developed and put in action. We aimed at studying the current state of art in VTE prophylaxis after major orthopaedic surgeries.

Materials and methods

We performed this systematic review and meta-analysis in accordance to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement. PRISMA and MOOSE are reporting checklists for authors, editors, and reviewers of meta-analyses of interventional and observational studies. According to International committee of medical journal association (ICJME), reviewers must report their findings according to each of the items listed in those checklists (8).

The present review included studies that fulfilled the following criteria:

1- Studies that included adult patients who underwent one of the following procedures; hip fracture surgery, knee arthroscopy, total knee replacement, and total hip replacement.

2- Studies that assessed the safety and effectiveness of different lines of VTE prophylaxis after major orthopedic procedures.

3- Studies that compared those interventions with each other or no comparison.

4- Studies that reported any of the following outcomes:

- Postoperative VTE.
- Pulmonary embolism (PE)
- Bleeding
- Major adverse event.
- In-hospital mortality.

5- Studies that were randomized controlled trials (RCTs), comparative studies, or prospective cohort studies.

6- Studies that were published since 2010 to November 2019.

We excluded review articles, non-English studies, theses, dissertations and conference abstracts, and trials with unreliable date for extraction.

An electronic search was conducted from 2010 till November 2019 in the following bibliographic databases: Medline via

PubMed, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science to identify relevant articles. We used different combinations of the following queries: ((("Arthroplasty, Replacement, Hip"[Mesh]) OR "Arthroplasty, Replacement, Knee"[Mesh]) OR "Hip Fractures"[Mesh]) AND "Venous Thromboembolism"[Mesh]. Also we used other keywords like venous thromboembolism after orthopedic surgeries, knee arthroscopy, pharmacological and mechanical prophylaxis and guidelines for DVT prophylaxis.

Results

In the present study, we searched Medline via PubMed, SCOPUS, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar from 2010 till December 2019. The search retrieved 2089 unique records. We then retained 57 potentially eligible records for full-texts screening. Finally, 29 studies were included (Figure 1).

Overall, twelve studies reported the rates of DVT among patients receiving LMWH. The overall effect estimates showed that the rate of DVT was 9.2% (95% CI 6.6– 11.8%). The pooled studies showed significant heterogeneity (p =0.001; I^2 =83%; Figure.2).

Overall, nine studies reported the rates of DVT among patients receiving FXaI. The overall effect estimates showed that the rate of DVT was 3.9% (95% CI 1.9– 6%). The pooled studies showed significant heterogeneity (p =0.001; I^2 =85%; Figure.3).

Nine studies compared LMWH versus FXaI for the rates of DVT. The overall effect estimates favored FXaI over LMWH (RR 0.42, 95% CI [0.19 – 0.96], P = 0.04). The pooled studies showed significant heterogeneity (p =0.001; I^2 =86%; Figure.4).

Nine studies reported the rates of PE among patients receiving LMWH. The overall effect estimates showed that the rate of PE was 0.3% (95% CI 0.1– 0.6%). The pooled studies showed no significant heterogeneity (p =0.84; I^2 =0%; Figure.5).

Six studies reported the rates of PE among patients receiving FXaI. The overall effect estimates showed that the rate of PE was 0.6% (95% CI 0.02– 1%). The pooled studies showed no significant heterogeneity (p =0.97; I^2 =0%; Figure.6).

Six studies compared LMWH versus FXaI for the rates of PE. The overall effect estimates did not favor any of the two drugs (RR 0.43, 95% CI [0.24 – 1.9], P = 0.28). The pooled studies showed no significant heterogeneity (p =0.702; I^2 =0%; Figure.7).

Ten studies reported the rates of major bleeding among patients receiving LMWH. The overall effect estimates showed that the

rate of major bleeding was 1.3% (95% CI 0.6– 1.9%). The pooled studies showed significant heterogeneity (p =0.002; I^2 =66%; Figure.8)

Seven studies reported the rates of major bleeding among patients receiving FXaI. The overall effect estimates showed that the rate of major bleeding was 0.4% (95% CI 0.02– 0.7%). The pooled studies showed no significant heterogeneity (p =0.59; I^2 =0%; Figure.9).

Six studies compared LMWH versus FXaI for the rates of major bleeding. The overall effect estimates favored FXaI over LMWH (RR 0.34, 95% CI [0.17 – 0.73], P = 0.28). The pooled studies showed no significant heterogeneity (p =0.78; I^2 =0%; Figure.10)

Overall, five studies reported the rates of proximal DVT among patients receiving LMWH. The overall effect estimates showed that the rate of proximal DVT was 1.4% (95% CI 0.6– 2.3%). The pooled studies showed no significant heterogeneity (p =0.29; I^2 =18%; Figure.11).

Three studies reported the rates of symptomatic DVT among patients receiving LMWH. The overall effect estimates showed that the rate of symptomatic DVT 1% (95% CI 0.1– 1.8%). The pooled studies showed no significant heterogeneity (p =0.19; I^2 =39%; Figure.12).

Six studies reported the rates of total DVT among patients receiving LMWH. The overall effect estimates showed that the rate of total DVT 11.2% (95% CI 3.5– 18.8%). The pooled studies showed significant heterogeneity (p =0.001; I^2 =93%; Figure.13).

Overall, two studies reported the rates of symptomatic DVT among patients receiving FXaI. The overall effect estimates showed that the rate of symptomatic DVT was 0.5% (95% CI 0.3– 1.4%). The pooled studies showed no significant heterogeneity (p =0.75; I^2 =0%; Figure.14).

Four studies reported the rates of major bleeding among patients receiving LMWH. The overall effect estimates showed that the rate of major bleeding was 0.5% (95% CI 0.1– 1%). The pooled studies showed no significant heterogeneity (p =0.57; I^2 =0%; Figure.15).

Overall, four studies reported the rates of symptomatic VTE among patients receiving prophylaxis. The overall effect estimates showed that the rate of symptomatic VTE was 0.7% (95% CI 0.2– 1.1%). The pooled studies showed no significant heterogeneity (p =0.91; I^2 =0%; Figure.16).

Four studies reported the rates of symptomatic and asymptomatic VTE among patients receiving prophylaxis. The overall effect estimates showed that the rate of

symptomatic and asymptomatic VTE was studies showed no significant heterogeneity (p =0.82; I^2 =0%; Figure.17).

Overall, four studies reported the rates of major bleeding among patients receiving prophylaxis. The overall effect estimates showed that the rate of major bleeding was 0.2% (95% CI 0 – 0.4%). The pooled studies showed no significant heterogeneity (p =0.75; I^2 =0%; Figure.18).

0.8% (95% CI 0.2– 1.3%). The pooled

Overall, two studies reported the rates of all bleeding among patients receiving prophylaxis. The overall effect estimates showed that the rate of major bleeding was 6.6% (95% CI 4– 12.9%). The pooled studies showed significant heterogeneity (p =0.001; I^2 =90%; Figure19

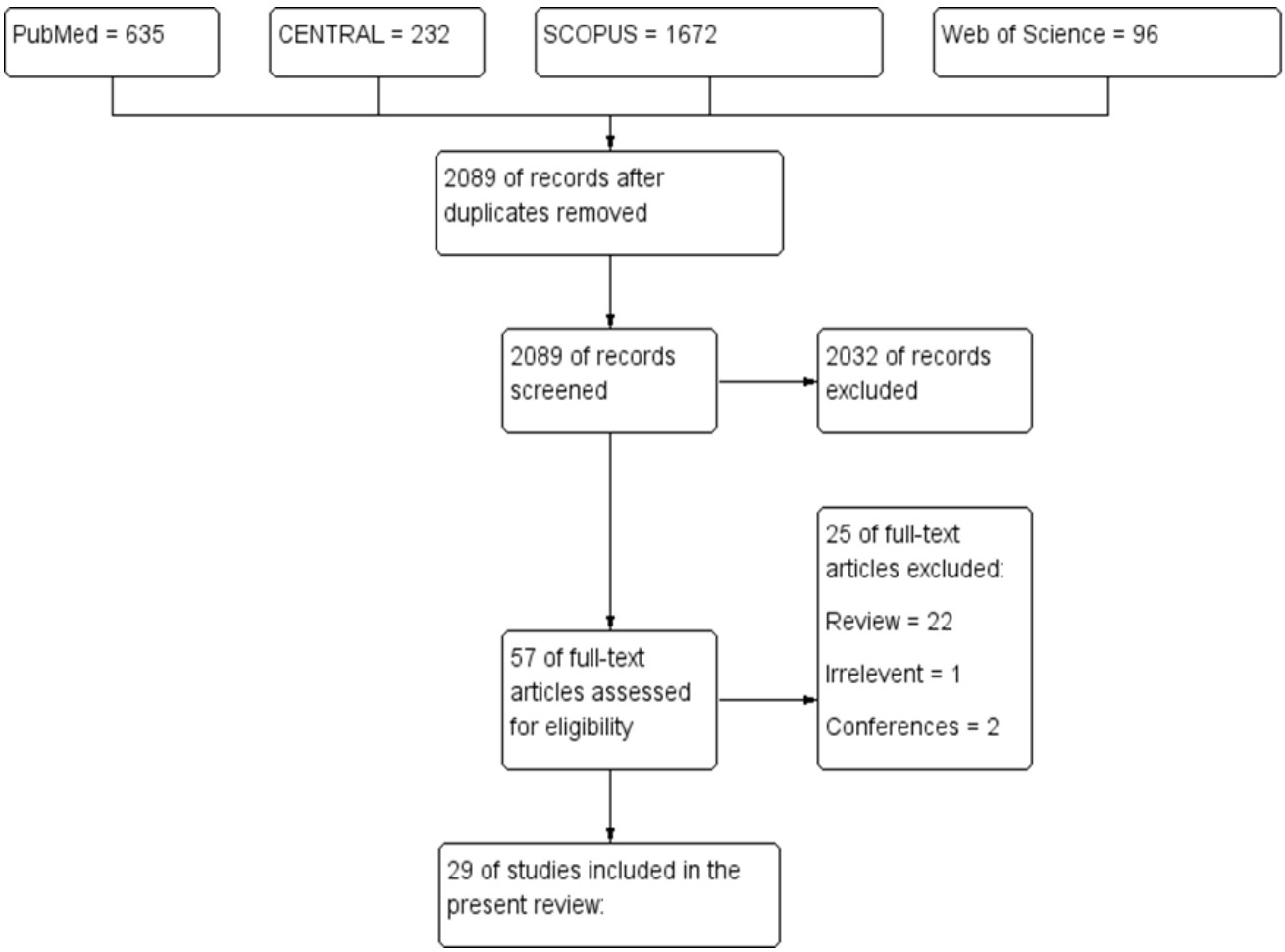

Figure 1: PRISMA flow-chart

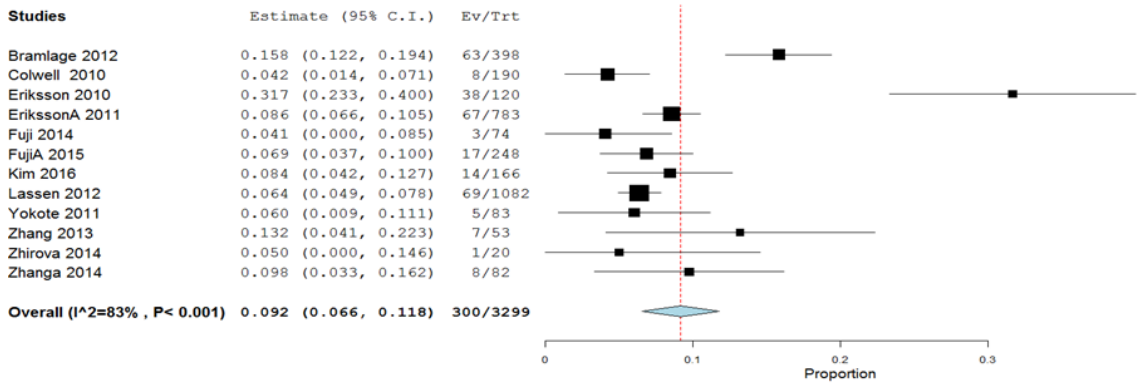

Figure 2: Forest Plot of rates of DVT among patients receiving LMWH after THR

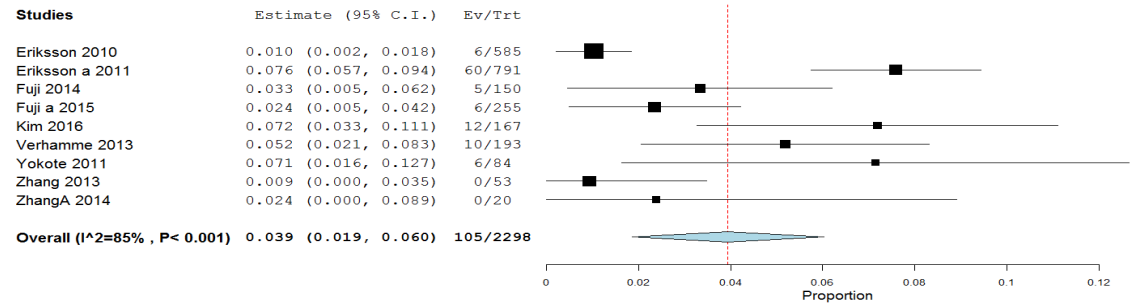

Figure 3: Forest Plot of rates of DVT among patients receiving FXaI after THR

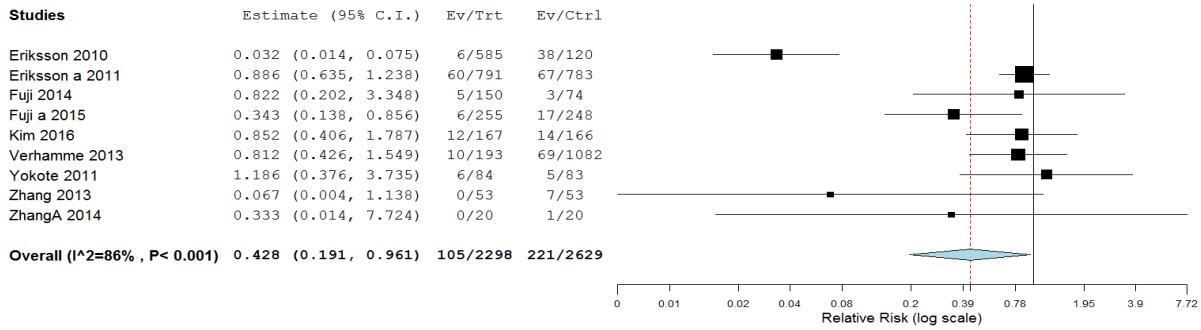

Figure 4: Forest Plot of rates of DVT for LMWH versus FXaI after THR

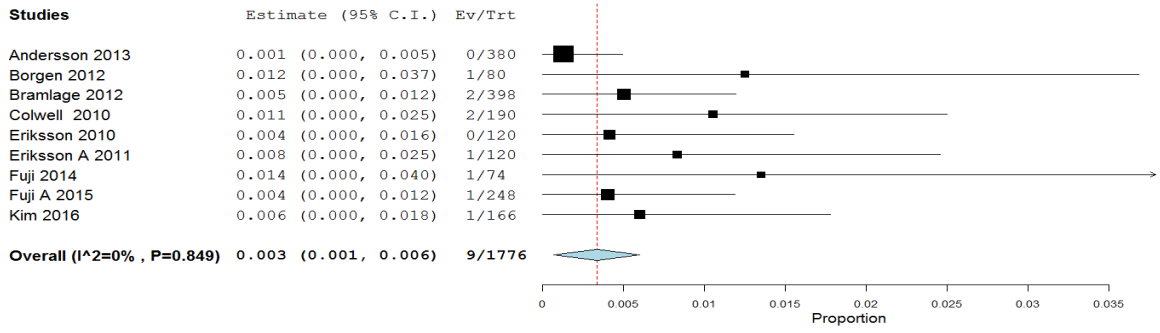

Figure 5: Forest Plot of rates of PE among patients receiving LMWH after THR

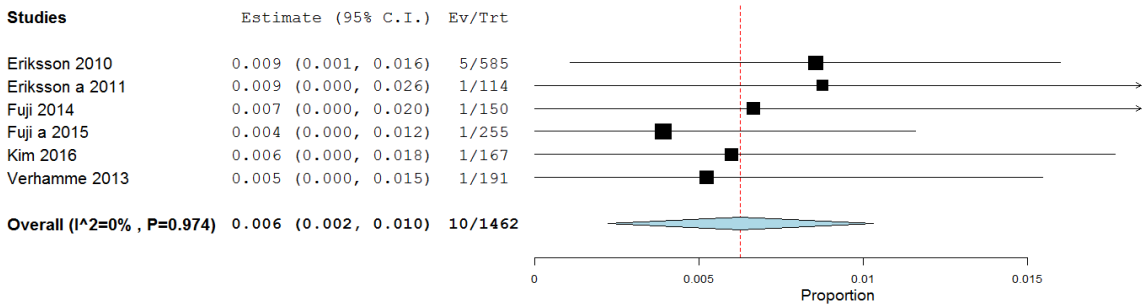

Figure 6: Forest Plot of rates of PE among patients receiving FXaI after THR

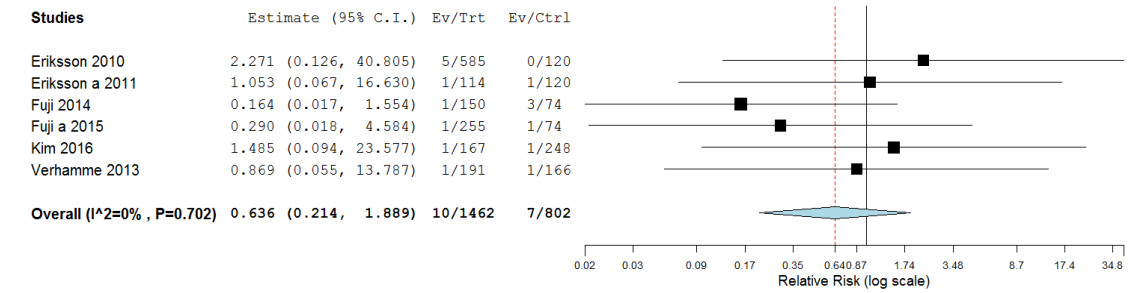

Figure 7: Forest Plot of rates of PE for LMWH versus FXaI after THR

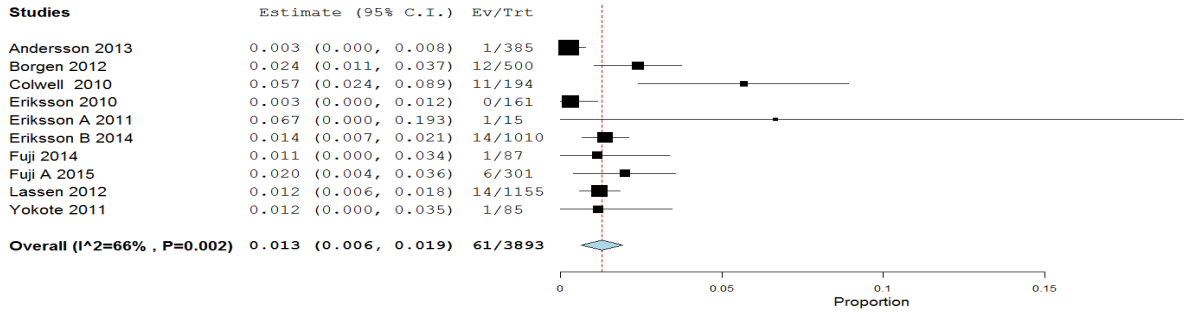

Figure 8: Forest Plot of rates of major bleeding among patients receiving LMWH after THR

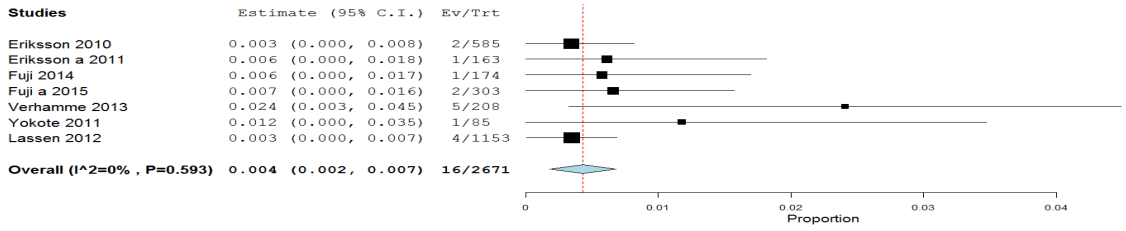

Figure 9: Forest Plot of rates of major bleeding among patients receiving FXaI after THR

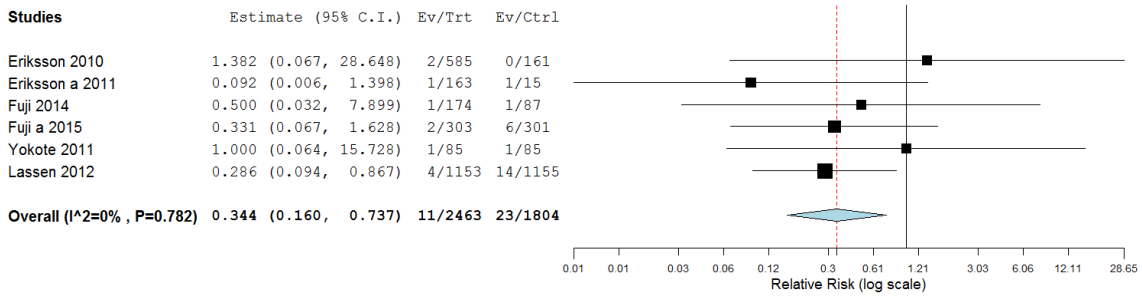

Figure 10: Forest Plot of rates of major bleeding for LMWH versus FXaI after THR

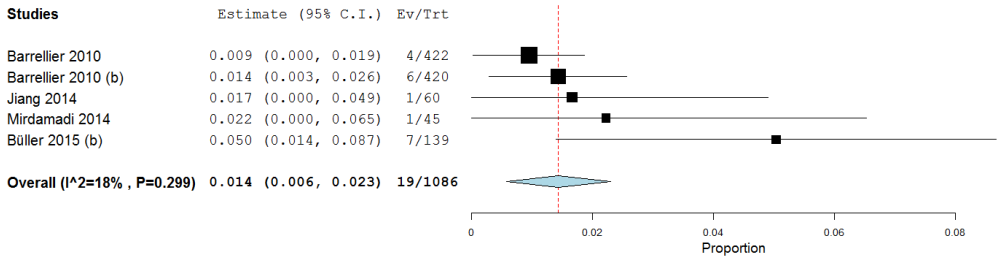

Figure 11: Forest Plot of rates of proximal DVT among patients receiving LMWH after TKR

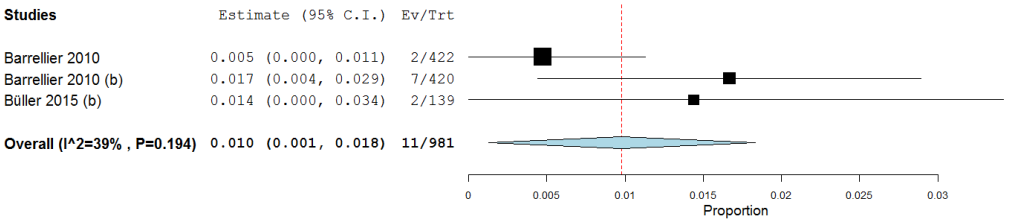

Figure 12: Forest Plot of rates of symptomatic DVT among patients receiving LMWH after TKR

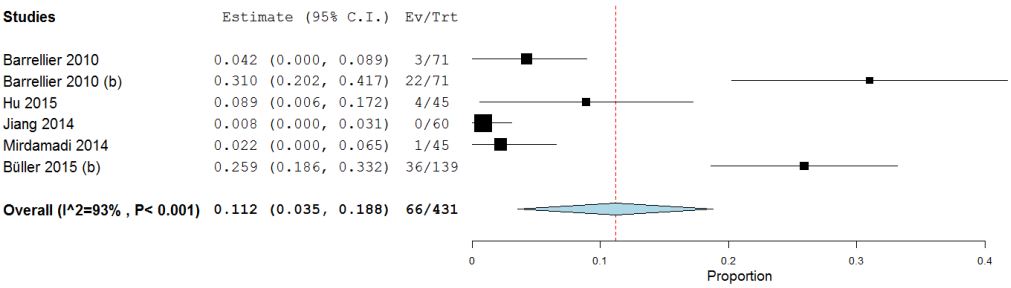

Figure 13: Forest Plot of rates of total DVT among patients receiving LMWH after TKR

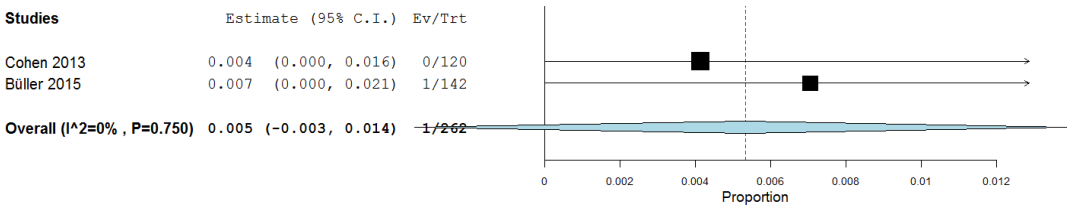

Figure 24: Forest Plot of rates of symptomatic DVT among patients receiving FXaI after TKR

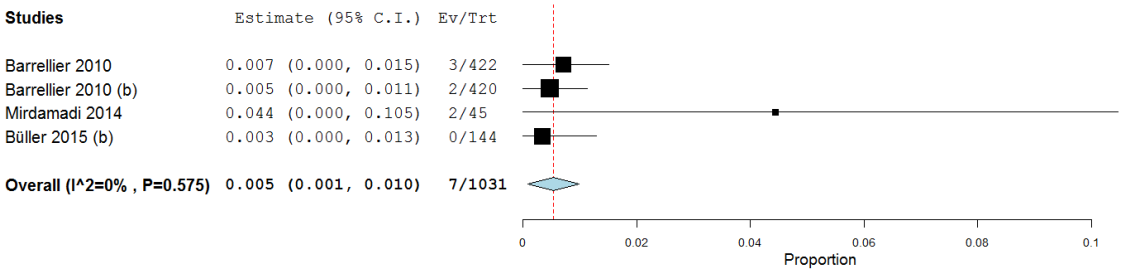

Figure 15: Forest Plot of rates of major bleeding among patients receiving LMWH after TKR

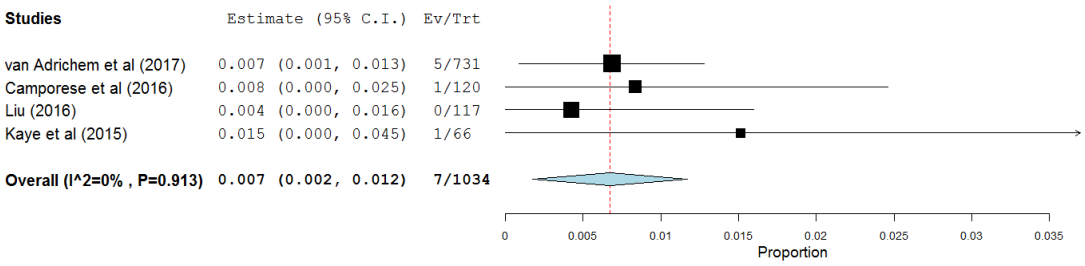

Figure 16: Forest Plot of rates of symptomatic VTE among patients receiving prophylaxis after arthroscopic knee surgery

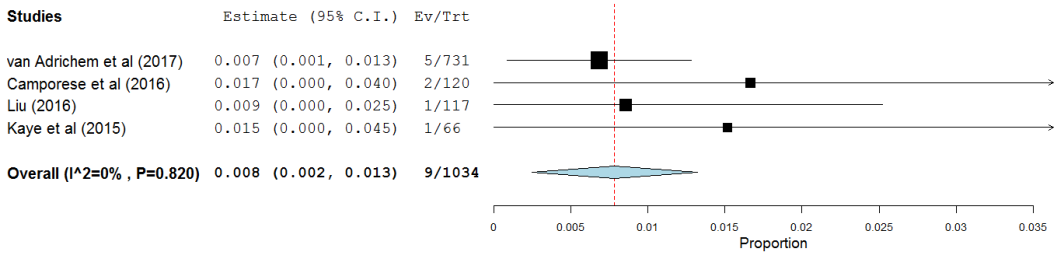

Figure 17: Forest Plot of rates of symptomatic and asymptomatic VTE after arthroscopic knee surgery

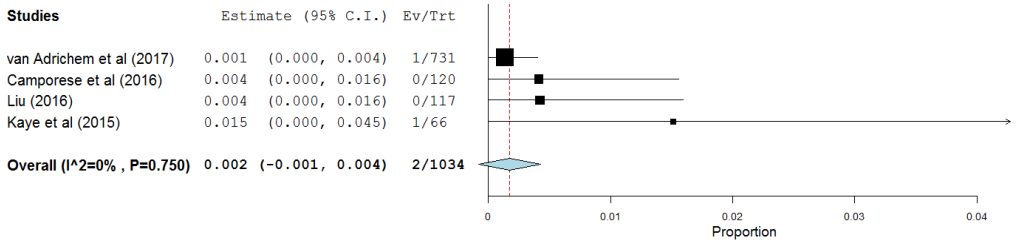

Figure 18: Forest Plot of rates of major bleeding events among patients after arthroscopic knee surgery

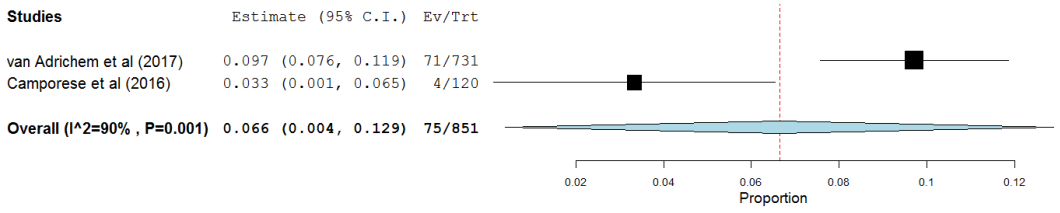

Figure 19: Forest Plot of rates of all bleeding after arthroscopic knee surgery

Discussion

RCTs comparing LMWH with placebo in patients who receive THR or TKR are decreasing recently which is expected as there has been an established evidence on the need for VTE thromboprophylaxis. However, the efficacy and safety of different agent became the center of the research. An old systematic review (9), assessed the use of LMWH compared with placebo in the prevention of thrombosis in an out-patient setting in patients undergoing hip arthroplasty. Compared to placebo, LMWH was associated with decreased rates of DVT,

proximal venous thrombosis, and symptomatic venous thrombosis.

Similarly Tasker et al (10), assessed the clinical outcomes of LMWH compared with placebo in patients who had THA. The results of their meta-analysis showed similarity in the risk of pulmonary embolism, all-cause mortality or major bleeding. However, compared with placebo, LMWH reduced incidence of non-fatal PEs but at the expense of hematoma formation.

And as stated in our review's results regarding the superiority of FXaI over LMWH in thromboembolic prophylaxis after THR and TKR with more bleeding complications occurring with LMWH, yet our review did not compare between different agents of FXaIs, previous meta-analyses found that the factor Xa inhibitors rivaroxaban and apixaban had a better anticoagulant effect compared with enoxaparin. They also found that enoxaparin had a higher incidence of major bleeding compared with some, but not all, of the factor Xa inhibitors. For example, Gomez-Outes et al (11) found that compared with enoxaparin, the risk of clinically relevant bleeding was higher with rivaroxaban, similar with dabigatran, and lower with apixaban in patients having THR or TKR. The authors concluded that the higher efficacy with factor Xa inhibitors was generally associated with a higher bleeding tendency compared with enoxaparin.

Also in agreement to our review, oral FXaI were more effective than LMWH in venous thromboembolic prophylaxis with lower risk of bleeding after THR and TKR. A meta-analysis conducted by Feng et al (12), they analyzed RCTs which compared the efficacy of oral direct factor Xa inhibitor with that of LMWH specially enoxaparin for elective TKR or THR. The direct factor Xa inhibitor included rivaroxaban, apixaban, edoxaban, and several developing drugs. The study concluded that oral FXaIs are more effective to prevent thromboembolic events after THR or TKR. Rivaroxaban, apixaban and edoxaban showed a better anticoagulant effect as compared with enoxaparin. The study also found that rivaroxaban was associated with a higher bleeding incidence than enoxaparin, while apixaban and edoxaban were not associated with significantly higher bleeding risks.

Conclusion

As per our systematic review and meta-analysis comparing between different groups of anticoagulants in thromboembolic prophylaxis following THR, TKR, hip fracture and knee arthroscopic surgeries, FXaI was the most effective agent after THR and TKR. In hip fracture surgery and Knee arthroscopy, thromboprophylaxis is needed,

but variable results regarding the drug choice warrant more research.

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