

Clinical Scenario:

40 year old male patient arrives for pre-op visit before total knee arthroplasty. He wants to know what type of thromboembolism prophylaxis he will receive post-op, because he is concerned about developing a DVT and PE after surgery. He states that he heard from one friend that rivaroxaban is the safest and most effective venous thromboembolism prophylactic treatment, while another told him that aspirin therapy is a cheaper alternative that is just as good. The patient asks if current literature indicated that rivaroxaban is better for him.

Search Question:

Is venous thromboembolism prophylactic treatment with rivaroxaban safer and more effective than aspirin therapy in patients after total knee arthroplasty (TKA)?

PICO search terms:

P	I	C	O
post-op	rivaroxaban	aspirin	Prevention of VTE
Total knee arthroplasty	Thromboprophylactic rivaroxaban treatment	Aspirin therapy	morbidity/mortality
TKA patients			Serious adverse events
Adults			Major bleeding
Post-operative venous thromboembolism risk			DVT/PE

Search Strategy:

→ If meta-analyses or systematic reviews were not available, I would look for randomized controlled trials. These studies examine the outcomes of two groups, one treated with rivaroxaban and one treated with aspirin and then determine which one had the best outcomes. Of the RCTs, a double blinded study would be the highest level of evidence.

→ If RCTs were not available, I would look for a cohort study that would prospectively or retrospectively study a group of patients post TKA who were treated with either rivaroxaban or aspirin for VTE prophylaxis and compare their relative outcomes in terms of safety/negative effects and efficacy in preventing VTE.

Search tools and strategy used:

Results found:

PubMed:

“Rivaroxaban prophylaxis” → 2,395

Filter: 5 years → 1,176

+ aspirin → 179

Add “TKA” → 12

Google Scholar:

“TKA rivaroxaban” → 1,540

Filter: since 2017 → 826

+”aspirin” → 858

+ meta analysis → 672

+ since 2020 → 276

+ efficacy → 248

+ safety → 200

JAMA:

“rivaroxaban” → 241

Filter: since 2015 → 197

+”aspirin” → 97

+ TKA → 5

Explain how you narrow your choices to the few selected articles:

I narrowed my articles by ruling out the ones that did not relate to my PICO question. For example, some articles compared rivaroxaban to other medications such as Enoxaparin or fondaparinux, so I eliminated those. I also chose articles that looked at the outcome I discussed, such as safety/ adverse effects, efficacy in preventing VTE, and morbidity/mortality. Google Scholar offered the most results, so I used that database to get an overview of the articles available on this topic. Because there were so many articles available there, I was able to narrow my search to articles published since 2020, so I knew I was getting the most current research. I also specifically filtered for safety/efficacy, which eliminated articles that were more focused on mechanism of action or other outcomes.

I then searched more specialized databases such as PubMed and JAMA to narrow down my selection. In doing this, I found that there was actually a lot of current research, so I was able to be more picky regarding the level of evidence that the articles provided. I found three meta-analyses that were relatively recent, as well as an RCT and prospective cohort all within five years. I therefore eliminated articles that were published more than five years ago (before 2016.)

Results found:

Article #1

Citation:

Colleoni, Jose Luiz, et al. "Venous thromboembolism prophylaxis after total knee arthroplasty (TKA): aspirin vs. rivaroxaban." *Revista Brasileira de Ortopedia (English Edition)* 53.1 (2018): 22-27.

Venous thromboembolism prophylaxis after total knee arthroplasty (TKA): aspirin vs. rivaroxaban

Jose Luiz Colleoni, Fernando Noel Ribeiro, Paulo Augusto Castro Mos \*, João Paulo Reis, Henrique Rosa de Oliveira, Beatriz Kawata Miura

Link: <https://www.sciencedirect.com/science/article/pii/S225549711730188X>

Objectives

To compare the efficacy and safety of aspirin and [rivaroxaban](#) in preventing [venous thromboembolism](#) (VTE) after total [knee arthroplasty](#) (TKA).

Methods

Thirty-two patients with [osteoarthritis](#) of the knee and knee arthroplasty indication were selected. The operated patients were randomized into two groups (A and B). Group A received 300 mg of [acetylsalicylic acid](#) (aspirin) and Group B received 10 mg of rivaroxaban daily for 14 days. Follow-up was performed weekly for four weeks and evaluated the presence of signs and symptoms of DVT, the healing of the [surgical wound](#), and possible local complications such as [hematoma](#), and superficial or deep infection that required surgical approach.

Results

It was verified that there were no differences between groups (rivaroxaban and aspirin) regarding gender, age, and ( $p > 0.05$ ). After using the general linear model (GLM) test, it was found that there was a decrease in Hb and Ht levels, preoperatively and at one, three, seven, and 14 days (Hb:  $p = 1.334 \times 10^{-30}$ ; Ht:  $p = 1.362 \times 10^{-28}$ ). However, they did not differ as to the type of medication (Hb:  $p = 0.152$ ; Ht:  $p = 0.661$ ). There were no identifiable differences in local complications, systemic complications, [deep vein thrombosis](#) (DVT), [readmission](#) to hospital, [reoperation](#), or death ( $p > 0.05$ ) between groups (rivaroxaban and aspirin).

Conclusions

Both aspirin and rivaroxaban can be considered useful among drugs available VTE the prevention after TKA.

Article #2

Citation: Xu, Joshua, et al. "A comparison of aspirin against rivaroxaban for venous thromboembolism prophylaxis after hip or knee arthroplasty: A meta-analysis." *Journal of Orthopaedic Surgery* 28.1 (2020): 2309499019896024.

A comparison of aspirin against rivaroxaban for venous thromboembolism prophylaxis after hip or knee arthroplasty: A meta-analysis

Joshua Xu, [Aran Kanagaratnam](#), [Jacob Y Cao](#), [Gurpreet S Chaggar](#), [Warwick Bruce](#)

LINK: <https://journals.sagepub.com/doi/full/10.1177/2309499019896024>

**Abstract:**

**Purpose:**

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) patients are at an elevated risk of post-operative venous thromboembolism (VTE). Newer thromboprophylactic agents such as rivaroxaban are increasingly used and effective in preventing thromboembolic events but may worsen bleeding risk. Recent studies have suggested that the more cost-effective aspirin may also be effective in preventing VTE. This systematic review and meta-analysis aimed to compare the efficacy of aspirin against rivaroxaban for the prevention of VTE following TKA and THA.

**Methods:**

Electronic searches were performed using five databases from their date of inception to August 2018. Relevant studies were identified, with data extracted and meta-analyzed from the studies.

**Results:**

Five studies were included, which consisted of 2257 in the aspirin group and 2337 in the rivaroxaban group. There were no differences between aspirin and rivaroxaban for either VTE ( $p = 0.48$ ) or its components deep vein thrombosis ( $p = 0.44$ ) and pulmonary embolism ( $p = 0.98$ ). Also, there were no differences between groups for either major bleeding ( $p = 0.17$ ), any bleeding ( $p = 0.62$ ), readmissions ( $p = 0.37$ ) or wound complications ( $p = 0.17$ ).

**Conclusion:**

Aspirin was not significantly different to rivaroxaban for prevention of VTE or adverse events after TKA or THA. However, this study was limited by the significant heterogeneity of the included studies. More large randomized studies are needed to add to this body of evidence.

**Article #3**

**Citation:**

Efficacy and safety of aspirin and rivaroxaban for venous thromboembolism prophylaxis after total hip or knee arthroplasty A protocol for meta-analysis

Le, Guoping, et al. "Efficacy and safety of aspirin and rivaroxaban for venous thromboembolism prophylaxis after total hip or knee arthroplasty: A protocol for meta-analysis." *Medicine* 99.49 (2020).

[Guoping Le](#), MD,<sup>a</sup> [Chengzhi Yang](#), MD,<sup>b</sup> [Ming Zhang](#), MS,<sup>b</sup> [Licheng Xi](#), MS,<sup>b</sup> [Hanwen Luo](#), MD,<sup>b</sup> [Jingli Tang](#), MD,<sup>b</sup> and [Jinmin Zhao](#), MD<sup>a,\*</sup>

LINK: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7717737/>

#### Abstract:

##### Background:

The purpose of this meta-analysis is to compare the efficacy and safety of aspirin and rivaroxaban in the prevention of venous thromboembolism (VTE) following either total knee arthroplasty or total hip arthroplasty.

##### Methods:

A comprehensive literature search of several electronic databases (PubMed, Embase, and Web of Science) was conducted to identify relevant studies. Outcomes of interest included VTE rate, deep vein thrombosis (DVT) rate, pulmonary embolism rate, major bleeding events, mortality rate, blood transfusion, and wound complication. Risk ratio (RR) with 95% confidence intervals (95% CIs) were calculated using a fixed-effects model or random-effects model.

##### Results:

A total of 8 studies with 97,677 patients met the inclusion criteria and were included in this meta-analysis. Compared with rivaroxaban, aspirin had a significantly higher incidence of DVT (RR=1.48, 95%CI: 1.27, 1.72; P<.001), and decreased risk of blood transfusion (RR=0.94, 95%CI: 0.93, 0.94; P<.001). However, there were no significant differences between the 2 drugs in terms of total VTE rate (RR=1.39%, 95%CI: 0.94, 2.05; P=.101), pulmonary embolism rate (RR=1.64, 95%CI: 0.92, 2.92; P=.094), mortality rate (RR=1.13, 95%CI: 0.15, 8.27; P=.907), major bleeding (RR=1.00, 95%CI: 0.44, 2.27; P=.995), and wound complication rate (RR=0.37, 95%CI: 0.07, 1.87; P=.229).

##### Conclusion:

Our results suggested that aspirin and rivaroxaban offered similar effect in the prevention of VTE after total knee arthroplasty or total hip arthroplasty. However, rivaroxaban seemed to have better effect than aspirin in reducing the risk of DVT, and aspirin was safer than rivaroxaban in decreasing the blood transfusion rate.

#### Article #4

##### Citation:

Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty  
Anderson, David R., et al. "Aspirin or rivaroxaban for VTE prophylaxis after hip or knee arthroplasty." *New England Journal of Medicine* 378.8 (2018): 699-707.

David R. Anderson, M.D., Michael Dunbar, M.D., John Murnaghan, M.D., Susan R. Kahn, M.D., Peter Gross, M.D., Michael Forsythe, M.D

LINK: <https://www.nejm.org/doi/full/10.1056/nejmoa1712746>

Abstract:

BACKGROUND

Clinical trials and meta-analyses have suggested that aspirin may be effective for the prevention of venous thromboembolism (proximal deep-vein thrombosis or pulmonary embolism) after total hip or total knee arthroplasty, but comparisons with direct oral anticoagulants are lacking for prophylaxis beyond hospital discharge.

METHODS

We performed a multicenter, double-blind, randomized, controlled trial involving patients who were undergoing total hip or knee arthroplasty. All the patients received once-daily oral rivaroxaban (10 mg) until postoperative day 5 and then were randomly assigned to continue rivaroxaban or switch to aspirin (81 mg daily) for an additional 9 days after total knee arthroplasty or for 30 days after total hip arthroplasty. Patients were followed for 90 days for symptomatic venous thromboembolism (the primary effectiveness outcome) and bleeding complications, including major or clinically relevant nonmajor bleeding (the primary safety outcome).

RESULTS

A total of 3424 patients (1804 undergoing total hip arthroplasty and 1620 undergoing total knee arthroplasty) were enrolled in the trial. Venous thromboembolism occurred in 11 of 1707 patients (0.64%) in the aspirin group and in 12 of 1717 patients (0.70%) in the rivaroxaban group (difference, 0.06 percentage points; 95% confidence interval [CI], -0.55 to 0.66;  $P < 0.001$  for noninferiority and  $P = 0.84$  for superiority). Major bleeding complications occurred in 8 patients (0.47%) in the aspirin group and in 5 (0.29%) in the rivaroxaban group (difference, 0.18 percentage points; 95% CI, -0.65 to 0.29;  $P = 0.42$ ). Clinically important bleeding occurred in 22 patients (1.29%) in the aspirin group and in 17 (0.99%) in the rivaroxaban group (difference, 0.30 percentage points; 95% CI, -1.07 to 0.47;  $P = 0.43$ ).

CONCLUSIONS

Among patients who received 5 days of rivaroxaban prophylaxis after total hip or total knee arthroplasty, extended prophylaxis with aspirin was not significantly different from rivaroxaban in the prevention of symptomatic venous thromboembolism.

Article #5

Citation:

Hu, Bangsheng, et al. "Rivaroxaban versus aspirin in prevention of venous thromboembolism following total joint arthroplasty or hip fracture surgery: a meta-analysis." *Journal of orthopaedic surgery and research* 16.1 (2021): 1-7.  
Rivaroxaban versus aspirin in prevention of venous thromboembolism following total joint arthroplasty or hip fracture surgery: a meta-analysis

[Bangsheng Hu](#), [Lianxiang Jiang](#), [Haixia Tang](#), [Meizhu Hu](#), [Jun Yu](#) & [Zeping Dai](#)

LINK: <https://josr-online.biomedcentral.com/articles/10.1186/s13018-021-02274-z>

**Abstract:**

**Objective**

To evaluate the efficacy and safety of rivaroxaban versus aspirin in prevention of venous thromboembolism (VTE) following total hip (THA) or knee arthroplasty (TKA) or hip fracture surgery.

**Methods**

Major databases were systematically searched for all relevant studies published in English up to October 2020. The meta-analysis was conducted using RevMan 5.3 software.

**Results**

In total, 7 studies were retrieved which contained 5133 patients. Among these patients, 2605 patients (50.8%) received rivaroxaban, whereas 2528 patients (49.2%) received aspirin. There was no statistical difference between aspirin and rivaroxaban for reducing VTE (RR = 0.75, 95% CI 0.50–1.11, I<sup>2</sup> = 36%, p = 0.15), major bleeding (RR = 0.94, 95% CI 0.45–2.37, I<sup>2</sup> = 21%, p = 0.95), and all-cause mortality (RR = 0.88, 95% CI 0.12–6.44, I<sup>2</sup> = 0%, p = 0.90) between the two groups. Compared with aspirin, rivaroxaban significantly increased nonmajor bleeding (RR = 1.29, 95% CI 1.05–1.58, I<sup>2</sup> = 0%, p = 0.02).

**Conclusion**

There was no significant difference between aspirin and rivaroxaban in prevention of venous thromboembolism following total joint arthroplasty or hip fracture surgery. Aspirin may be an effective, safe, convenient, and cheap alternative for prevention of VTE. Further large randomized studies are required to confirm these findings.

Author (Date)	Level of Evidence	Sample/ Setting	Outcomes studied	Key Findings	Limitations and Biases
Jose Luiz Colleo ni, Fernando Noel Ribeiro, Paulo Augusto Castro Mos *, João Paulo Reis, Henrique Rosa	Prospective Cohort	Thirty-two patients with osteoarthritis of the knee and indication of TKA for primary osteoarthritis were selected. Group A consisted of one man (7.1%) and 13 women (92.9%), while group B consisted of four men (22.2%) and 14 women (77.8%). The	local and systemic complications infection, dehiscence, DVT, reoperation, rehospitalization, and mortality.	no differences were identified between the groups (rivaroxaban and aspirin) regarding local complications, systemic complications, DVT, rehospitalization, reoperation, and death (p > 0.05) The similar incidence of local and systemic complications between aspirin and rivaroxaban found in the present series of patients may contribute to the consensus that aspirin is a safe drug for use in	The study does have the limitation of having a limited number of patients included and a follow up time <30 days ( VTE can be observed in up to 90 days postoperatively if no antithrombotic therapy is used)

de Oliveira, Beatriz Kawata Miura (2018)		mean age of patients in group A was $71.21 \pm 6.35$ years, vs. $67.11 \pm 7.65$ years in group B.		VTE prophylaxis in patients undergoing TKA.	
Joshua Xu, <a href="#">Aran Kanagaratnam</a> , <a href="#">Jacob Y Cao</a> , <a href="#">Gurpreet S Chaggar</a> , <a href="#">Warwick Bruce</a> (2020)	Meta-analysis	<p>A total of five studies were selected for quantitative analysis.<sup>10–14</sup> These studies included a total of 4594 patients, with 2257 in the aspirin group and 2337 in the rivaroxaban group. From these patients, 2159 were total hip arthroplasty (THA) and 2435 were total knee arthroplasty (TKA).</p> <p>four studies were randomized controlled trials using prospectively collected data and one study was a retrospective observational study.</p> <p>There were no significant differences between the aspirin and rivaroxaban groups with regards to age (<math>p = 0.25</math>), number of females (<math>p =</math></p>	DVT/PE, VTE, major bleeding, readmission, length of hospital stay, wound complications following TKA (and THA)	<p>The mean length of hospital stay in the aspirin group ranged from 2.0 to 3.5 days, compared to the rivaroxaban group which ranged from 3.4 to 3.6 days. There were no significant differences between the groups for any of the operative characteristics.</p> <p>DVT was reported in four studies. No significant difference in DVT rate was found when comparing the rivaroxaban to the aspirin group (RR: 0.67, 95% CI: 0.28–1.76, <math>I^2 = 58\%</math>, <math>p = 0.44</math>)</p> <p>PE was reported in two studies. No significant difference in PE rate was found when comparing the rivaroxaban to the aspirin group (RR: 0.99, 95% CI: 0.38–2.59, <math>I^2 = 0\%</math>, <math>p = 0.98</math>).</p> <p>Any VTE was reported in four studies, with similar VTE rates when comparing the rivaroxaban to the aspirin group (RR: 0.73, 95% CI: 0.31–1.75, <math>I^2 = 60\%</math>, <math>p = 0.48</math>).</p> <p>No significant difference in major bleeding was found when comparing the rivaroxaban to the aspirin group (RR: 0.39,</p>	<p>The primary limitation of this analysis is that the majority of patients came from two studies. There was significant heterogeneity in the outcome which could have stemmed from difference in study protocols. While the dosage of rivaroxaban was the same in all studies, aspirin dosage varied from 81 mg daily to 325 mg bi-daily. The duration of prophylaxis varied between 9 and 35 days, though this was kept consistent between subgroups within the original studies.</p> <p>This meta-analysis also does not address the efficacy of these chemoprophylaxis regimens in high-risk populations, for example, people with cancer or previous VTE.</p>



		0.72) and BMI (p = 0.82)		95% CI: 0.10–1.52, I <sup>2</sup> = 34%, p = 0.17) No significant difference in readmission rate was found when comparing the rivaroxaban to the aspirin group (RR: 0.80, 95% CI: 0.50–1.30, I <sup>2</sup> = 0%, p = 0.37)	
<a href="#">Guopin Le</a> , MD,a <a href="#">Cheng zhi Yang</a> , MD,b <a href="#">Ming Zhang</a> , MS,b <a href="#">Licheng Xi</a> , MS,b <a href="#">Hanwen Luo</a> , MD,b <a href="#">Jingli Tang</a> , MD,b and <a href="#">Jinmin Zhao</a> , MDa, (2020)	Meta-analysis	8 studies met the inclusion criteria, and were included in this meta-analysis The included studies were published between 2014 and 2019. Of these studies, 4 were cohort studies, 3 were RCTs, and 1 was a case-control study. They were carried out in China, Brazil, Korea, Thailand, and Canada. The duration of follow-up ranged from 4 weeks to 3 months.	Outcomes studied include DVT, PE, VTE, wound complications, need for blood transfusions, and major bleeding	rivaroxaban was more effective than aspirin in reducing the incidence of DVT; whereas, they were similarly effective for preventing VTE and PE. Blood transfusion rate was significantly lower in aspirin group compared with rivaroxaban group. There were no significant differences between the 2 groups in terms of major bleeding and wound complication.	the sample size varied greatly among the included studies, which ranged from 32 to 97,878. Studies with small sample size were more likely to produce an overestimated treatment effect as compared with larger trials. Second, the follow-up time in some of the included studies was less than 90 days, which would influence the effect evaluation of anticoagulants since VTE can be developed in 90 days postoperatively when no antithrombotic therapy is used.
David R. Anderson, M.D., Michael Dunbar, M.D., John Murnaghan, M.D.,	Double blind randomized controlled trial	This trial was conducted at 15 university-affiliated health centers in Canada. 3427 patients underwent randomization. A total of 1804 patients underwent total hip arthroplasty, and 1620	symptomatic proximal DVT, PE, death, and major bleeding.	This RCT found that the inexpensive, widely available generic agent aspirin was not significantly different from the more expensive, direct oral anticoagulant rivaroxaban for the prevention of symptomatic, clinically important venous thromboembolism,	Patients were frequently recruited into the RCT postoperatively, so the trial population was not treated with the same standard protocol until after the TKA. Most bleeding events that were related to surgical site bleeding happened early after the patients were enrolled in the study, it

<p>Susan R. Kahn, M.D., Peter Gross, M.D., Michael Forsythe, M.D (2018)</p>		<p>underwent total knee arthroplasty. The mean age of the patients was 62.8 years, and 47.8% were men. More than 90% of the patients underwent primary arthroplasty procedures, and the average length of the hospital stay after surgery was 3.5 days in the two groups.</p>		<p>including events of proximal deep-vein thrombosis or pulmonary embolism, after total hip or total knee arthroplasty among patients who had received an initial 5-day postoperative course of rivaroxaban. The patients in the two trial groups had low and very similar rates of symptomatic thromboembolic complications during the 90-day follow-up period after randomization</p>	<p>was harder to determine if the cause of bleeding was the initial 5 days of rivaroxaban or the trial medication. This factor could potentially result in an overestimation of the rate of aspirin-related bleeding. A true comparison of the overall rates of bleeding associated with aspirin versus rivaroxaban after joint arthroplasty would require a head-to-head randomized, controlled trial of the two medications, with both therapies started during the immediate postoperative period. patients often underwent randomization at the time of hospital discharge before postoperative day 5. Because of this timing, some of the trial events occurred before postoperative day 6, when the trial medication was started. According to the intention-to-treat analysis, these events were included in the primary analysis. Despite these limitations, the findings are clinically important. The trial was large and adequately powered to show the noninferiority of aspirin as compared with rivaroxaban</p>
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<p><a href="#">Bangs</a> <a href="#">heng</a> <a href="#">Hu,</a> <a href="#">Lianxia</a> <a href="#">ng</a> <a href="#">Jiang,</a> <a href="#">Haixia</a> <a href="#">Tang,</a> <a href="#">Meizhu</a> <a href="#">Hu,</a> <a href="#">Jun Yu</a> &amp; <a href="#">Zeping</a> <a href="#">Dai</a> (2021)</p>	<p>Meta Analy sis</p>	<p>7 studies were included in this meta-analysis with a total of 5133 patients 2605 patients in the rivaroxaban group and 2528 patients in the aspirin group. 5 were RCTs, 2 were retrospective cohort</p>	<p>VTE, major bleeding, nonmajor bleeding, mortality</p>	<p>The meta-analysis showed that there was no statistically significant difference in the incidence of postoperative VTE between the two groups (RR = 0.75, 95% CI 0.50–1.11, I2 = 36%, p = 0.15) there were no significant differences in major bleeding between the rivaroxaban and aspirin groups (RR = 0.94, 95% CI 0.45–2.37, I2 = 21%, p = 0.94) there was no significant difference in the all-cause mortality between the two groups (RR = 0.88, 95% CI 0.12–6.44, I2 = 0, p = 0.90)</p>	<p>Although this study adopts a comprehensive retrieval strategy, it is still possible to miss some gray literature. The sample size varied greatly among the included studies, which ranged from 32 to 3424. Compared with larger trials, studies with small sample size were more likely to produce an overestimated treatment effect. Only one study has described the use of blind methods, which may have a mixed bias. There are also many influencing factors for the mortality of patients. Some confounding factors cannot be completely avoided in this study. This study did not specifically analyze the basic diseases and medical history of the study patients. Aspirin has been shown to increase the risk of stomach bleeding. Therefore, aspirin should be used with caution in a patient with a history of stomach ulcers.</p>
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Conclusion(s):

Article #1:

Colleoni et al found no differences between the groups (rivaroxaban and aspirin) regarding local complications, systemic complications, DVT, rehospitalization, reoperation, and death ( $p > 0.05$ ). This study did have the limitation of a small sample size, which affects the degree of statistical significance. The follow up time was less than 30 days post op, which makes it difficult to judge these results in comparison with studies that followed patients for at least ninety days.

Despite these limitations, the similar incidence of local and systemic complications between aspirin and rivaroxaban found in the present series of patients may contribute to the consensus that aspirin is a safe drug for use in VTE prophylaxis in patients undergoing TKA.

#### Article #2:

Xu et al concluded that there were no differences between aspirin and rivaroxaban for either VTE or its components DVT and PE. Similarly, there were no differences between groups for either major bleeding or any bleeding or for readmissions or wound complications. These results suggest that aspirin may be an appropriate choice of chemoprophylaxis agent after TKA and THA, given its lower cost and similar prophylactic and adverse event profiles.

This meta analysis did have the limitation of having a majority of the patients included come from only two studies. There was also significant heterogeneity between the studies, which may be a result of the different study protocols used. One study included started patients in the test group on aspirin directly after surgery, while the other administered five days of rivaroxaban before randomization. The aspirin dosage also varied between studies, from 81 mg daily to 325 mg BID. This study also does not address high risk populations, such as those with cancer or previous VTE. These are all factors which would be important for future research to standardize and look into more closely.

#### Article #3

Le, Guoping, et al. found that rivaroxaban was more effective than aspirin in reducing the incidence of DVT; whereas, they were similarly effective for preventing VTE and PE. Blood transfusion rate was significantly lower in aspirin group compared with rivaroxaban group. There were no significant differences between the 2 groups in terms of major bleeding and wound complication.

The limitations of this study included large differences in sample size between the studies included (a range from 32 to 97,878) which may cause studies with a smaller sample size to be overrepresented in the results. There was also a difference in follow up time between the studies, with some following the patients for less than 90 days post-op.

#### Article #4:

Anderson, David R., et al. determined that among patients who received 5 days of rivaroxaban prophylaxis after total hip or total knee arthroplasty, extended prophylaxis with aspirin was not significantly different from rivaroxaban in the prevention of symptomatic venous thromboembolism.

This article began the trial after all the patients had already received 5 days of rivaroxaban, which makes it difficult to determine if instances of bleeding were due to the trial medication (aspirin) or the initial rivaroxaban, or a result of the combination of both.

#### Article #5:

Hu, Bangsheng, et al. found no significant difference in the efficacy and safety of aspirin in prevention of VTE when compared with rivaroxaban. Aspirin may be an effective, safe, convenient, and cheap alternative for prevention of VTE following total joint arthroplasty or hip fracture surgery.

This study had the limitation of great variability between the studies included, which can cause the smaller studies to have an overestimated treatment effect. The study also did not analyze the patients' specific medical history as a potential cause for adverse reactions to the treatment. For example, a patient with a history of gastric ulcer may be more prone to a GI bleed when given Aspirin. This may have had an effect on the overall results of the trial.

#### Clinical Bottom Line:

The clinical bottom line is that rivaroxaban has not been proven to be safer or more effective than aspirin when used for venous thromboembolism prophylaxis in patients after total knee arthroplasty (TKA). This finding is clinically important because aspirin is a cheaper and more widely available alternative for patients. Because it has been studied to be just as good as rivaroxaban at preventing VTE after TKA it may become a welcome alternative for patients, such as the one in the clinical scenario above.

#### Weight of Evidence:

Article 5: I chose this article to rank highest because it is a recent (2021) meta-analysis that directly answers the PICO question. 7 studies were included in this meta-analysis with a total of 5133 patients. 2605 patients in the rivaroxaban group and 2528 patients in the aspirin group. The large sample size gives weight to the results. In addition, 5 of the studies were RCTs, 2 were retrospective cohorts. The articles included were published in high-level journals, five of which were published in recent 3 years. This makes the results relevant to clinical practice today.

Article 2: This study carries the second to most weight because it was a meta-analysis that was published in 2020 and has a fairly large sample size (4594 patients). Additionally, four of the five studies included in this meta-analysis are RCTs, and all five are fairly recent, which makes their results more clinically relevant.

Article 3: this article is ranked third because it is a recent (2020) meta-analysis that directly answers the PICO question. This meta-analysis included 8 studies with 97,677 patients. Although it has more studies included than Article 2, the article did note the limitation that the follow-up time in some of the studies included were less than 90 days. Because VTE can occur up to 90 days without proper anticoagulation, it would have been good for the study to follow the patients for the full 90 days. The study itself suggested in the conclusion that future studies should include a longer follow-up period.

Article 4: This article is ranked fourth because it is a recent (2018) double blind RCT that directly answers the PICO question. It is important to note that this trial began after all the patients received 5 days of rivaroxaban post-op. Only then were they divided into the Aspirin and rivaroxaban groups. This may skew the results slightly, although the article noted that the findings were still statistically significant even with that initial difference. This was a large-scale trial so it was adequately powered to show that aspirin was not inferior compared to

rivaroxaban. In addition, all of the patients were followed for 90 days to ensure that no clinically important events were missed.

Article 1: This article carries the least weight because it is a prospective cohort. While it is recent (2018) I included other articles that are from 2020 and even 2021. It is still useful to study because it answers the PICO question by comparing rivaroxaban and aspirin for VTE prophylaxis and uses studies studying endpoints such as local and systemic complications, DVT, reoperation and mortality. The study does have the limitation of having a limited number of patients included and a follow up time <30 days.

Magnitude of any effects: All of the articles noted above generally came to the same conclusion that rivaroxaban has not been proven to be safer or more effective than aspirin when used for venous thromboembolism prophylaxis in patients after total knee arthroplasty (TKA). Providers may have previously been wary of using Aspirin, however the magnitude of five articles published within the last five years that all indicate that rivaroxaban is not any safer than Aspirin for the general population following TKA should certainly be factored into their decision when choosing post-op anticoagulation.

Clinical Significance: The clinical bottom line that I have derived from these articles is that patients post TKA can be given Aspirin or Rivaroxaban for anticoagulation, because both have similar efficacy and risk profiles. Aspirin is the cheaper and more widely available option, so this finding may be most significant for those who are concerned about cost or availability of medications. While the articles included did not specifically state the cost of each of the drugs, I looked into it further and found an article that the monthly unit cost for rivaroxaban was estimated to be \$359.61 for a 30 pill package of 10 or 20 mg pills. The price of aspirin for a 90 pill package of 81 mg tablets was \$3.67. With this extreme price difference, having studies that show the cheaper option may be as safe and effective as the more expensive one is certainly beneficial for reducing healthcare costs. These results are currently not applicable to those in high-risk groups for either bleeding or clotting disorders, as those populations would need to be studied separately to determine their specific results.

Other considerations:

Some key points to consider are that a few of the articles noted that the studies included only followed the patients for less than thirty days post-op, even though VTE can still occur up to ninety days post-op (when no antithrombotic therapy is used.) Additionally, article #4 only studied aspirin use after an initial rivaroxaban 5 day treatment, which certainly makes a difference when determining clinical practice guidelines. For treatment options in specific populations, article #2 noted that their meta-analysis does not address the efficacy of rivaroxaban versus aspirin VTE prophylaxis in high-risk populations, such as people with cancer or previous VTE, so that will also need further study before recommendations can be made for clinical intervention in this population. Lastly, article #3 noted that rivaroxaban was more effective for reducing DVT, while aspirin was safer in terms of the blood transfusion rate which clinicians need to consider when weighing the relative risk versus benefit of these two options. Overall however, the research for this PICO generally indicated that rivaroxaban was not

significantly safer or more effective than aspirin, providing evidence for post-op VTE prophylaxis with aspirin therapy while taking into consideration the specific harm versus benefit nuances noted above.