16. Venous Thromboembolism

Eleanor Fitall, M.P.H., and Kendall K. Hall, M.D., M.S.

Introduction

Background

Venous thromboembolism (VTE) is a disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). A DVT occurs when a blood clot forms in a deep vein, usually in the lower leg, thigh, or pelvis. A PE occurs when a clot breaks loose and travels through the bloodstream to the lungs.[1]

It is estimated that 300,000 to 600,000 Americans are affected each year by VTE, making it the third leading vascular diagnosis behind heart attack and stroke, and the leading cause of death due to major orthopedic surgery.[2,3] Common causes for VTE are surgery, cancer, immobilization, or hospitalization.[2,4] The risk of VTE is the highest for patients undergoing major orthopedic surgery, such as total knee arthroplasty (TKA), total hip arthroplasty (THA), or hip fracture surgery (HFS).[3,5,6] Without appropriate prophylaxis, rates of VTE among these patients have been estimated to be as high as 60 percent.[7] Given that major orthopedic surgeries typically occur among older adults, the Centers for Medicare & Medicaid Services (CMS) has made the prevention and treatment of VTE a priority among their quality improvement efforts, such as through programmatic measure inclusion and harm area prioritization in initiatives. Accreditation organizations have followed suit, with the Joint Commission and the National Committee for Quality Assurance including measures for VTE treatment and prevention in their hospital accreditation and certification programs.

Method for Selecting Patient Safety Practice

Agency for Healthcare Research and Quality (AHRQ) subject matter experts requested an update of the previous Making Healthcare Safer reports' coverage of the topic of VTE prophylaxis, with a specific focus on the use of aspirin.

What's New/Different Since the Last Report

The previous Making Healthcare Safer reports reviewed the effectiveness, safety, cost effectiveness, and indicators for VTE prophylaxis, as well as the most effective VTE prophylaxis regimens and interventions to improve adherence to prevention strategy guidelines. Whereas the last report discussed newer pharmacologic agents on the market and approaches to improve clinical decision making and guideline adherence, this review specifically focuses on the use of aspirin for prophylaxis. With the increase of pharmacologic agents on the market, research has focused primarily on the effectiveness of these agents and, to some degree, their safety. This current review provides an update on the state of the evidence specifically for the use of aspirin as a low-cost, widely available generic option.

References for Introduction

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16.1 Patient Safety Practice: Use of Aspirin for VTE Prophylaxis

16.1.1 Practice Description

As VTE, in particular DVT, can be very difficult to diagnose, actively employing prevention techniques is critical to ensuring patient safety. Prevention methods include both mechanical and pharmacologic prophylaxis. Mechanical prophylaxis includes the use of compression devices, such as stockings and foot pumps. Pharmacologic prophylaxis is available via a number of different anticoagulant and antiplatelet drugs, including heparin derivatives, vitamin K antagonists, direct thrombin inhibitors, direct factor Xa inhibitors, and aspirin.

There are two different types of pharmacologic agents available for VTE prophylaxis—anticoagulants and antiplatelets. Aspirin is an antiplatelet, and while there are other antiplatelets used for other cardiovascular conditions, these are not recommended for use in VTE prophylaxis and are therefore not the focus of this review. There is slight variation in existing guidelines regarding the use of aspirin for pharmacologic prophylaxis. The American Society of Hematology (ASH)[1] the American College of Chest Physicians (ACCP),[2] and the American Academy of Orthopedic Surgeons (AAOS)[3] all recommend pharmacologic prophylaxis and/or mechanical prophylaxis for patients undergoing THA, TKA, or HFS. ASH and AAOS further recommend that patients receive both forms of prophylaxis, particularly patients who are at an increased risk for VTE. However, ASH and ACCP provide a list of recommended pharmacologic agents that specifically includes aspirin, whereas AAOS does not make recommendations regarding specific pharmacologic agents. Further, ACCP recommends low molecular weight heparin (LMWH) over other pharmacologic prophylaxis agents, whereas other guidelines have not made such a specific recommendation statement specifying the use of one type of pharmacologic prophylaxis agent over another.

Many hospitals include the use of aspirin in their surgical protocols for patients undergoing major orthopedic surgery. For prescribing surgeons, its use is at their discretion based on guideline recommendations, perceived patient risk, and the need to balance prevention with safety concerns, such as bleeding risk. This balance has become increasingly important as a growing number of studies have found that newer anticoagulant drugs are associated with a higher incidence of bleeding than prophylaxis agents.[4] The review's key findings are located in the box to the right.

Key Findings:

- Use of aspirin following major orthopedic surgery was generally found to be of similar effectiveness as other agents.
- An overwhelming majority of studies concluded that aspirin has a lower bleeding risk rate than other pharmacologic agents, which, combined with its lower cost, makes it an appealing option for VTE prophylaxis, particularly in low-risk patients.
- More prospective randomized controlled trials are needed to directly compare the effectiveness of aspirin with other prophylactic methods across patient risk levels.

16.1.2 Methods

To answer the question, "Is aspirin safe and effective for post-operative VTE prophylaxis in patients undergoing surgery?" two databases (CINAHL® and MEDLINE®) were searched for "Venous Thrombosis/Prevention & Control," "deep vein thrombosis," "pulmonary embolism," and related synonyms, as well as "Aspirin/therapeutic use," "Surgical Procedures, Operative," "Perioperative Care/methods," "Postoperative Complications/prevention & control," and other similar terms. Articles

included were published from 2008 to 2018. The initial search yielded 123 results. Once duplicates were removed and additional relevant articles from selected other sources were added, a total of 63 articles were screened for inclusion and full-text articles were retrieved. Of those, 33 were selected for inclusion in this review. Articles were excluded if the outcomes were not relevant to this review, the article was out of scope (including not quantitative), or study design was insufficiently described. As the results of this literature review were predominantly about major orthopedic surgery, relevance to this review included limiting articles to patients undergoing major orthopedic surgery.

General methods for this report are described in the Methods section of the full report.

For this patient safety practice, a PRISMA flow diagram and evidence table, along with literature-search strategy and search-term details, are included in the report appendixes A through C.

16.1.3 Review of Evidence

A box summarizing key findings related to the use of aspirin for the prevention of VTE in patients undergoing major orthopedic surgery is located in the Practice Description section. This section reviews applicable studies, organized by the scope of the intervention the patient received (aspirin alone, aspirin in combination with another pharmacologic prophylaxis agents, and aspirin in combination with mechanical prophylaxis) before discussing implementation considerations and any potential unintended consequences.

All included studies took place in the hospital setting and addressed patients undergoing total joint arthroplasty (TJA), THA, TKA, or HFS, with one notable exception of a study analyzing VTE outcomes in patients receiving surgery to remove cancerous tissue from a lower limb. Findings in this chapter can be best summarized by the conclusions reached in the six systematic reviews that met our inclusion criteria. Findings from these reviews varied in their determination of the efficacy of aspirin as a VTE prophylaxis and its benefits over other pharmacologic prophylaxis agents with regard to safety outcomes, predominant operative site, and other major bleeding.

One pooled analysis by Brown (2009) reviewed 14 randomized clinical trials to determine whether aspirin decreased the rate of operative site bleeding, without increasing the rate of thromboembolic events in patients undergoing THA, TKA, or HFS. The analysis found that the rates of VTE were not significantly different with aspirin when compared with vitamin K antagonists, LMWH, and pentasaccharides, but that the risk of bleeding was lower with aspirin.[5] Similarly, Mistry et al. (2017) reviewed eight articles published from 2014 to 2017 on the use of aspirin for VTE prophylaxis following TKA or THA. Five of the articles concluded that aspirin was effective, and the systematic review noted that aspirin had a lower rate of complications while also being more cost effective than other available anticoagulants.[6] Finally, a meta-analysis performed by Wang et al. (2017) sought to provide a comprehensive review of pharmacologic prophylaxis agents and reviewed 104 trials, 30 different drugs, and outcomes in 110,643 patients. Researchers found that aspirin, along with factor XI antisense oligonucleotide (FXI-ASO), ardeparin, and apixaban, were the most effective drugs at both preventing all-cause VTE and avoiding unintended bleeding events. While the meta-analysis findings were supportive of the use of aspirin, apixaban was found to have the most favorable outcomes.[4]

Conversely, Drescher et al. (2014) found in the eight clinical trials included in their review that, while overall the rate of DVT did not differ between aspirin and anticoagulants, aspirin may be associated with a higher risk of DVT following hip fracture repair when compared with anticoagulants, although it may

be associated with lower bleeding risk.[7] Similarly, Wilson et al. (2016) found in their analysis of 13 studies that, while there is evidence from one of their included studies that aspirin has similar rates of VTE following TKA when compared with LMWH, the majority of trials included were at a moderate to severe risk of bias and had insufficient evidence that aspirin was more or less effective than LMWH, warfarin, or dabigatran.[8] Finally, in their review of 14 studies to assess the appropriateness of aspirin as a prophylaxis in high-risk patients undergoing THA, TKA, or HFS, Stewart and Freshour (2013) determined that the evidence is inconsistent as to whether aspirin is effective at preventing VTE and whether there is a decreased risk of bleeding in comparison with other anticoagulants. This may indicate a need for patient risk stratification when determining the appropriateness of aspirin, as discussed later in this chapter.[9]

16.1.3.1 Aspirin as Sole Prophylaxis Treatment

Five studies included in our review discussed aspirin as the sole prophylaxis used in patients at risk for developing VTE following surgery. A number sought to directly compare its effectiveness as a sole approach with other pharmacologic approaches. Goel et al. (2018) found that, in patients undergoing simultaneous bilateral TKA, the risk for PE was significantly lower for patients prescribed aspirin (n=1528) versus warfarin (n=2157) after accounting for baseline VTE risk (p=0.005). Goel et al. also found that the risk for combined VTE, consisting of both PE and DVT, was nearly significantly lower for those on aspirin (p=0.052).[10]

In a more comprehensive analysis of available pharmacologic prophylaxis options, Agaba et al. (2017) conducted a retrospective review of patients undergoing THA using a nationwide private and Medicare insurance database. Patients studied received either aspirin alone or one of five anticoagulants. The analysis found that patients given aspirin alone had a significantly lower rate of both DVT and PE at 30 and 90 days following surgery, with an insignificant bleeding risk. Following a review of the effectiveness and safety side effects of each of the pharmacologic agents included in the study, Agaba et al. concluded that while rivaroxaban and fondaparinux have lower bleeding and thromboembolic events compared with other newer anticoagulants, aspirin also meets these criteria. In addition, aspirin is an easy-to-use, inexpensive option for prophylaxis following THA.[11] In a similar study reviewing TKAs over a 9-year period in a combined Humana and Medicare database, Bala et al. (2017) compared outcomes of patients receiving aspirin (n=1016) matched by age and sex with patients receiving enoxaparin (n=6096), warfarin (n=6096), and factor Xa inhibitors (n=5080). Factor Xa inhibitors were found to have the lowest incidence of DVT and PE (p<0.01) at 90 days, and there was no difference in bleeding-related complications between the agents (p=0.81). However, researchers concluded that aspirin had the lowest incidence of postoperative anemia (p<0.01) and blood transfusion (p<0.01) at 90 days, and provided VTE prophylaxis comparable to Xa inhibitors and more effective than enoxaparin and warfarin.[12]

Mendez et al. (2017) conducted a retrospective review of medical records for patients who underwent lower-limb surgery as a component of their oncology treatment. Patients either received 325 mg of aspirin twice daily (n=103) or were assigned to the non-aspirin group (n=39) (which included LMWH, unfractionated heparin, warfarin, and intermittent pneumatic compression device only). No patient in the aspirin group developed a VTE. Aspirin for VTE prophylaxis in patients undergoing orthopedic oncologic surgery appears to be effective, but more robust study may be necessary.[13]

16.1.3.2 Multimodal Prophylaxis

16.1.3.2.1 Aspirin in Combination With Other Pharmacologic Prophylaxis

Several of the studies reviewed addressed the use of aspirin in combination with other pharmacologic prophylactic agents. Anderson et al. (2013) conducted a randomized controlled trial at 12 tertiary care orthopedic referral centers in Canada. All patients undergoing elective THA surgery were prescribed a 10-day course of LMWH before being randomly assigned to either 28 days of continued LMWH (n=400) or 28 days of aspirin (n=386). Findings indicate that switching patients to aspirin following an initial course of LMWH was not worse (p<0.001) but not better than continued use of LMWH. Additionally, clinically significant bleeding occurred in five patients with a continued course of LMWH (1.3%), versus two (0.5%) who switched to aspirin (p=0.45).[14]

In a similar study, Anderson et al. (2018) conducted a double-blind randomized controlled trial at 15 university-affiliated health centers in Canada. Patients undergoing elective unilateral primary or revision hip or knee arthroplasty received once-daily oral rivaroxaban for the first 5 days following surgery, and then were randomized to either continue the course of rivaroxaban or switch to aspirin for the next 9 days after TKA, or 30 days after THA. Findings indicate that aspirin is not worse (p<0.001) but not better than continued use of rivaroxaban. Additionally, there was not a significant difference in bleeding between the two groups (p=0.43).[15]

Finally, Hamilton et al. (2012) conducted a retrospective review of patients receiving aspirin prophylaxis after primary hip and knee arthroplasties. Patients received a course of enoxaparin during their inpatient stay, followed by a course of aspirin for 28 days following discharge. Patients were compared with a control group that first received enoxaparin for 2 weeks following discharge before receiving a course of aspirin for a further 2 weeks. Researchers concluded that a protocol of only inpatient enoxaparin and then aspirin post discharge was both safe and effective in standard-risk patients.[16]

16.1.3.2.2 Aspirin in Combination With Mechanical Prophylaxis

The majority of articles reviewed (20) included the use of an anticoagulant or antiplatelet in combination with other mechanical prophylaxis methods. Seventeen of the articles reviewed concluded that aspirin was safe and effective when used in combination with mechanical prophylaxis methods. For example, Deirmengian et al. (2016) conducted a retrospective review of patients undergoing TJA. All patients received mechanical prophylaxis and then either warfarin (n=2463) or aspirin (n=534). The study found that the differences between the groups with regard to DVT or PE alone were not statistically significant (p=0.15; p=0.06, respectively). Fisher's exact test showed a significantly higher risk for any symptomatic VTE in patients receiving warfarin (43 events, 1.75%) compared with patients receiving aspirin (3 events, 0.56%; odds ratio [OR]: 3.2; 95% confidence interval [CI], 1.03 to 16.3; p=0.03).[17] Similarly, Raphael et al. (2014) conducted a retrospective analysis of patients undergoing TJA. Patients were treated with compression devices while at the same time receiving either aspirin (n=2,800) or warfarin (n=26,123) prophylaxis. The analysis found that the overall symptomatic PE rate was lower (p<0.001) in patients receiving aspirin (0.14%) than in the patients receiving warfarin (1.07%). The incidence of symptomatic DVT was significantly lower in the aspirin group (0.29%) than in the warfarin group (0.99%) (OR=3.50; 95% CI, 1.75 to 8.19; p<0.001) and the risk of symptomatic DVT remained lower in the aspirin group than in the warfarin group even after propensity score matching was performed.[18]

Only two studies among those reviewed assessed whether the effectiveness of aspirin was improved by the use of mechanical devices, with mixed findings. Daniel et al. (2008) performed a retrospective study comparing the incidence of VTE in patients undergoing THA and hip resurfacing among those who received aspirin for 30 days following surgery (n=258) and those who received aspirin and mechanical prophylaxis for 30 days (n=229). Results indicate a statistically significant difference in DVT prevalence, indicating aspirin in combination with mechanical prophylaxis is more effective than aspirin alone.[19] However, Hamilton et al. (2012), in their retrospective review of patients receiving primary hip and knee arthroplasties, compared patients receiving enoxaparin and mechanical compression prior to a 28-day course of aspirin post discharge, versus enoxaparin alone during the inpatient stay prior to an outpatient 2-week course of enoxaparin followed by a 2-week course of aspirin. There was a trend toward a lower rate of DVT among those who received mechanical compression compared with those who did not, but this difference did not near statistical significance until using a Fisher exact test (p=0.07). Additionally, there was no significant difference between the two groups in the number of patients with the following outcomes: pulmonary embolus, deep infection, superficial infection, readmission, or death.[16]

Three articles did not reach a conclusion as to whether aspirin in conjunction with mechanical prophylaxis was safe and effective for preventing VTE in orthopedic patients. In two studies, this was because either the incidence of VTE in the patient population was so low that it was too difficult to achieve statistical significance in the data analysis[20] or the incidence was so low that there were no DVTs or PEs identified in the patient population.[21] However, in one of the three studies, the authors concluded that antiplatelet agents were not effective in preventing symptomatic VTE in HFS patients after those who received an aspirin or other antiplatelet had a VTE incidence of 4.8 percent, compared with no antiplatelet use with an incidence of 4.3 percent (p=0.718).[22]

16.1.3.3 Aspirin Dosing Considerations

Several included studies examined the impact of different aspirin doses on clinical outcomes following surgery. In their retrospective analysis, Faour et al. (2018) analyzed the medical records of patients receiving aspirin twice daily for 4 to 6 weeks following TKA. Patients received low-dose, 81 mg, aspirin (n=1,327) or standard-dose, 325 mg (n=2,903). Analysis concluded that aspirin is safe and effective but that there was a significant difference in the incidence of VTE and DVT between the two groups (p=0.02 and p<0.001, respectively), with those receiving a standard dose experiencing a higher incidence of VTE and DVT (1.5% vs. 0.7% and 1.4% vs. 0.3%). However, there was not a significant difference in the incidence of PE (p=0.13), and a regression analysis showed no correlation between aspirin doses and the incidence of VTE (both DVT and PE) or DVT alone (p=0.94 and 0.20). Further, there is no statistically significant difference in the incidence of gastrointestinal (GI) or wound bleeding (p=0.62). Faour et al. reached similar conclusions when conducting the same retrospective analysis for patients undergoing THA (2018),[23] but Feldstein et al. (2017) noted there may be more GI distress and nausea when patients are prescribed standard-dose aspirin versus low-dose aspirin following TJA.[24]

In their retrospective multi-institutional study, Goel et al. (2018) reviewed the outcomes for patients receiving either aspirin or warfarin following unilateral or bilateral TKA. Patients in the aspirin group received either regular-dose (325 mg) or low-dose aspirin (81 mg), at the surgeons' discretion. The results showed that regardless of the dosing, aspirin was more effective than warfarin and deemed an appropriate agent for VTE prophylaxis for patients in all risk categories.[10]

16.1.3.4 Economic Outcomes

When considering the use of aspirin for VTE prophylaxis in patients undergoing major orthopedic surgery, cost considerations are a factor noted in a number of the articles reviewed. While there were no cost-effectiveness analyses included in the identified articles, Hamilton et al. (2012) noted that limiting enoxaparin to the inpatient setting and prescribing only aspirin post discharge saved on average $400.30 per case in medication costs.[16] Further, Mendez et al. (2017) estimated that, in 2010 wholesale drug prices, 14 days of aspirin therapy is approximately $0.38, versus $730.50 for 14 days of twice-daily LMWH.[13] Similarly, Jiang et al. (2014) also found a cost savings in the use of aspirin when compared with rivaroxaban and LMWH.[25] Other study authors frequently noted that use of aspirin should be considered, particularly among low-risk patients, due to not only its similar efficacy but also its low cost—compared with both direct and indirect costs associated with other pharmacologic agents—as a "widely available generic agent." (Anderson et al., 2018). [11,14,15,17,23,26]

16.1.3.5 Unintended Consequences

16.1.3.5.1 Positive Unintended Consequences

There are a number of potential positive unintended consequences associated with the use of aspirin for VTE prophylaxis. As previously mentioned, generic aspirin is widely available and significantly cheaper than alternative medications. Additionally, administrative costs are lower than with some alternative pharmacologic prophylaxis agents that require intravenous delivery or ongoing laboratory monitoring, such as with warfarin. Ease of administration may in turn have a positive impact on patient quality of life during the treatment period and support medication adherence.

16.1.3.5.2 Negative Unintended Consequences

As with other pharmacologic prophylaxis agents, there is the potential risk that patients prescribed aspirin following major orthopedic surgery will experience operative site or major bleeding. The analysis of the incidence of these events was a priority for many of the articles included in this review. Twenty-three of the studies specifically addressed unintended patient safety outcomes in their analysis and conclusions. Of those, 22 concluded that overall aspirin was safer than other pharmacologic options, or had comparable risk. For example, Jiang et al. (2014) found that patients in the aspirin group had a lower blood loss index than patients who received LMWH or rivaroxaban following TKA (p=0.000), and Deirmengian et al. (2016) found a higher rate of bleeding events in patients prescribed warfarin versus aspirin (p=0.02) following TJA.[17,25] The identified systematic reviews reached similar conclusions, with two of the reviews determining that use of aspirin has a lower bleeding relative risk than other pharmacologic options.[5,6] Other studies found no difference in bleeding risk between aspirin and other therapies. For example, Anderson et al. (2018) found there was no statistical difference in major bleeding and clinically nonmajor bleeding between aspirin and rivaroxaban following THA or TKA (p=0.43).[15] Similarly, Zou et al. (2014) found no significant differences in hidden blood loss between patients receiving aspirin, rivaroxaban, or LMWH, and Huang et al. (2016) found no significant difference in GI complications between patients receiving warfarin or aspirin.[26,27]

16.1.4 Implementation

16.1.4.1 Patient Risk Stratification

An important consideration when establishing the appropriateness and potential efficacy of aspirin following major orthopedic surgery is the patient risk profile. While 24 of the 27 included studies

determined aspirin is safe and as effective, if not more effective, than other prophylaxis methods, a potential confounding or even misleading factor is the risk stratification of patients. In almost 50 percent of studies, some degree of patient risk stratification occurred. For example, Kaye et al. (2015) conducted a randomized prospective study comparing the use of standard-dose aspirin with no form of chemoprophylaxis among patients undergoing arthroscopic knee surgery (n=170). They found that there were no incidences of DVT or PE regardless of treatment status, and a logistical regression found that aspirin was not statistically significant for a decreased risk of complications following arthroscopic knee surgery. However, they conducted this study specifically in low-risk patients and no conclusions can be made for other risk groups.[21] Parvizi et al. (2017) similarly excluded patients at high risk from their prospective data collection protocol.[28] Among retrospective studies, Raphael et al. (2014) specifically removed patients considered at high risk for VTE from their retrospective data analysis and Deirmengian et al. (2016) indicated that treatment was based on the surgeons' discretion, which may imply some risk stratification in treatment determinations as part of normal practice.[17,18]

16.1.4.2 Resources To Assist With Implementation

Resources to help identify patient VTE risk are available from:

- AHRQ
  - Preventing Hospital-Associated Venous Thromboembolism: A Guide for Effective Quality Improvement: https://www.ahrq.gov/professionals/quality-patient-safety/patient-safety-resources/resources/vtguide/vtguide4.html[a]
    - This guide includes a chapter that provides an overview of the major categories and characteristics of VTE risk assessment models to support the development of a VTE prevention protocol within the facility.
- The Center for Outcomes Research at the University of Massachusetts Medical School: https://www.outcomes-umassmed.org/risk_models_improve_vte.aspx [b]
  - The IMPROVE VTE Risk Calculator is a clinical decision tool for VTE risk assessment and prophylaxis that can be accessed via computer, iPhone, and iPad.
- The University of Michigan: https://www.med.umich.edu/clinical/images/VTE-Risk-Assessment.pdf[c]
  - A thrombosis risk factor assessment checklist is available to be printed for manual use. This checklist is for elective general surgery but may be modified for patients undergoing major orthopedic surgery.

[a]Agency for Healthcare Research and Quality. Preventing Hospital-Associated Venous Thromboembolism: Chapter 4 – Choose the Model to Assess VTE and Bleeding Risk. https://www.ahrq.gov/professionals/quality-patient-safety/patient-safety-resources/resources/vtguide/vtguide4.html.
[b]University of Massachusetts Medical School. Center for Outcomes Research: Risk Assessment Models – IMPROVE (VTE). https://www.outcomes-umassmed.org/risk_models_improve_vte.aspx.
[c]University of Michigan. Deep Vein Thrombosis Prophylaxis Orders: Thrombosis Risk Factor Assessment. https://www.med.umich.edu/clinical/images/VTE-Risk-Assessment.pdf.

16.1.5 Gaps and Future Directions

16.1.5.1 Gaps

There are a number of gaps in current literature highlighted by our review. First, only eight of the included studies were prospective and only six included patient randomization to an intervention. As previously mentioned, risk stratification of patients for treatment determination may play an important role in ultimate patient outcomes. So, while the overarching evidence from this review does indicate that aspirin is an effective and safe option for VTE prophylaxis following major orthopedic surgery, there may be limitations to the generalizability of these findings. There is a need for more prospective, randomized controlled trials directly comparing patient outcomes between those prescribed aspirin and those given other available prophylaxis options across risk levels. Second, there is a lack of studies providing direct comparison between aspirin in conjunction with mechanical prophylaxis versus aspirin alone. Given that the use of mechanical prophylaxis is pervasive in the studies identified, it would be useful to determine whether this makes a difference across different levels of patient risk. Finally, while researchers often note that aspirin is cheaper and more cost effective than other prophylaxis options, formal cost-effectiveness analyses are needed for both chemoprophylaxis and mechanical prophylaxis alternatives.

16.1.5.2 Future Directions

In addition to addressing the gaps noted above, a further area that may help better determine the efficacy of aspirin in different patient populations is research into best methods or approaches for diagnosing VTE, in particular DVT. Additionally, as noted in Stewart and Freshour (2013), individual studies may define “bleeding” differently, posing a challenge when making comparisons across multiple bodies of research. Therefore, a standardized definition may be helpful for researchers and providers alike.[9]

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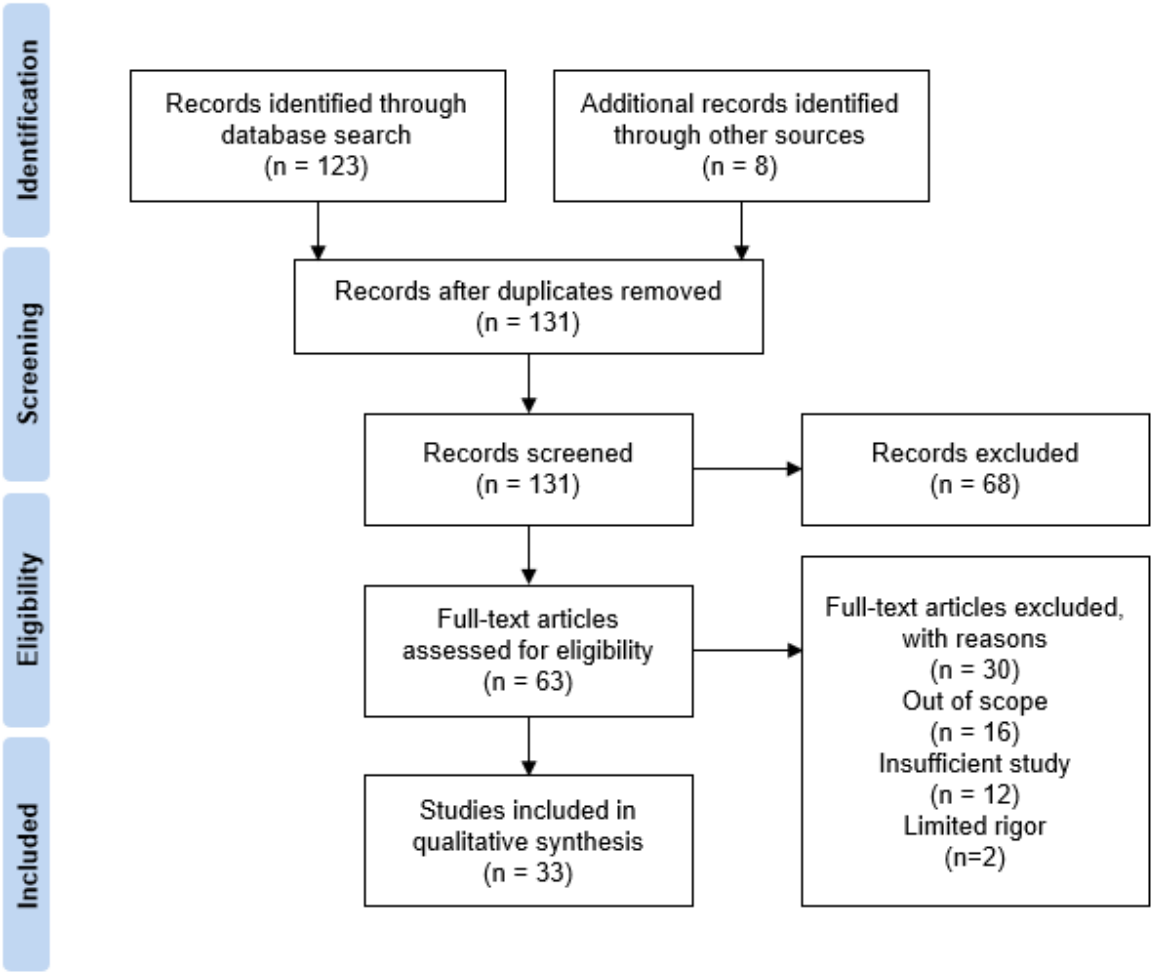
Conclusion and Comment

The Patient Safety Practice reviewed in this chapter aims to reduce VTE by providing an effective, safe, and low-cost approach to pharmacologic prophylaxis in patients undergoing major orthopedic surgery. This review of the evidence generally finds that use of aspirin following these surgical procedures—either as the sole prophylaxis agent in combination with other pharmacologic agents or in conjunction with mechanical prophylaxis—is equivalent to other agents or has a better safety profile. Many studies were retrospective and/or included patient risk stratification either in the treatment allocation or in the exclusion of data for analysis. This indicates a need for prospective randomized controlled trials directly comparing the impact of different prophylaxis methods across patient risk categories. However, this review provides greater insight into the effectiveness of aspirin for preventing VTE in patients following major orthopedic surgery.

Appendix A. Venous Thromboembolism PRISMA Diagram

Figure A.1: Venous Thromboembolism Prophylaxis: Study Selection for Review



PRISMA criteria described in Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7): e1000097. doi:10.1371/journal.pmed1000097.

Appendix B. Venous Thromboembolism Evidence Tables

Table B.1: Venous Thromboembolism Prophylaxis—Systematic Reviews and Meta-Analyses

Note: Full references are available in the Section 16.1 reference list.

Author, Year	Description of Patient Safety Practice	Settings and Population	Summary of Findings	Implementation Themes/Findings
Brown, 2009[5]	Use of pharmacologic agents for venous thromboembolism (VTE) prophylaxis after total hip arthroplasty (THA), total knee arthroplasty (TKA), or hip fracture.	Patients undergoing THA, TKA, hip fracture surgery (HFS).	The VTE rates with aspirin were not significantly different than the rates for vitamin K antagonists, low molecular weight herarin (LMWH), and pentasaccharides. The operative site bleeding relative risks of vitamin K antagonists, LMWH, and pentasaccharides versus aspirin, are 4.9, 6.4, and 4.2, respectively. A pooled analysis of randomized controlled trial (RCTs) supports the use of aspirin for VTE prophylaxis after major orthopedic surgery.	This quantitative systematic review found no significant difference in clinically relevant VTE outcomes, except that vitamin K antagonists have a higher rate of symptomatic deep vein thrombosis (DVTs) compared with aspirin.
Drescher et al., 2014[7]	Treatment with anticoagulation or antiplatelet agents following major lower extremity orthopedic surgery.	Patients undergoing major lower extremity orthopedic surgery.	Eight clinical trials were included in analysis. Overall rates of DVT did not differ statistically between aspirin and anticoagulants (relative risk [RR]: 1.15 [95% confidence interval (CI), 0.68 to 1.96]). However, by type of surgery, there was a nonsignificant trend favoring anticoagulation following hip fracture repair but not knee or hip arthroplasty (hip fracture RR: 1.60 [95% CI,: 0.80 to 3.20], 2 trials; arthroplasty relative risk (RR): 1.00 [95% CI, 0.49 to 2.05], 5 trials). The risk of bleeding was lower with aspirin than anticoagulants following hip fracture repair (RR: 0.32 [95% CI, 0.13 to 0.77], 2 trials), with a nonsignificant trend favoring aspirin after arthroplasty (RR: 0.63 [95% CI, 0.33 to 1.21], 5 trials). Rates of pulmonary embolism were too low to provide reliable estimates.	Aspirin may be associated with a higher risk of DVT in hip fracture repair, but not lower extremity arthroplasty. Across procedures, aspirin may be associated with a lower risk of bleeding.

Author, Year	Description of Patient Safety Practice	Settings and Population	Summary of Findings	Implementation Themes/Findings
Mistry et al., 2017[6]	Aspirin for VTE prophylaxis after lower limb arthroplasty.	Patients undergoing lower limb arthroplasty surgery.	Eight articles were found. Five articles concluded that aspirin was an effective prophylactic. The collation of results on the DVT rate involved 43,012 patients who were prescribed aspirin, of whom 283 (0.66%) suffered from symptomatic DVTs. Aspirin was noted for its good side effect profile and cost effectiveness. It was noted that anticoagulants had a higher rate of complications, including bleeding and wound-oozing.	Aspirin is an effective and safe prophylactic against DVT following major elective lower limb arthroplasty surgery.
Stewart et al., 2013[9]	Aspirin administered solely or in combination with mechanical compression devices in patients undergoing THA, TKA, or HFS.	Patients undergoing high-risk orthopedic surgery.	Trials evaluating aspirin have not consistently shown benefit in the reduction of VTE after TKA, THA, and HFS. Nor have they definitively demonstrated a decreased risk of bleeding for aspirin compared with other anticoagulants. Suggests that LMWH and warfarin have consistently demonstrated benefit with limited bleeding risk.	RCTs, meta-analyses, and retrospective reviews do not consistently conclude that aspirin is safe and effective for preventing VTE.
Wang et al., 2017[4]	Treatment with anticoagulation or antiplatelet agents following THA or TKA.	Primarily patients with knee or hip replacement or arthroplasty, but 13 trials included patients with major joint surgery.	Factor XI antisense oligonucleotide (FXI-ASO), ardeparin, aspirin, and apixaban were ideal for preventing all-cause VTE and reducing all bleeding events, while betrixaban, dalteparin, warfarin, and eribaxaban were ideal for preventing major VTE and reducing major/clinically relevant nonmajor bleeding events.	While the meta-analysis is supportive of the use of aspirin, apixaban was found to have the most favorable outcomes.
Wilson et al., 2016[8]	Treatment with anticoagulation or antiplatelet agents following THA or TKA.	Patients undergoing THA or TKA.	Thirteen studies were included in analysis. There was limited evidence (one RCT study) that there was no difference between aspirin and LMWH following TKA. In all other instances there was insufficient evidence to draw conclusion regarding whether aspirin is more or less effective than anticoagulation agents. However, there appears to be better safety outcomes in the use of aspirin.	Aspirin may be suitable for VTE prophylaxis, but evidence is limited with potential for bias.

Table B.2: Venous Thromboembolism Prophylaxis—Single Studies

Note: Full references are available in the Section 16.1 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Agaba et al., 2017[11]	Use of pharmacologic prophylactic agents following total hip arthroplasty (THA), including aspirin, enoxaparin, warfarin, and factor Xa inhibitors	Retrospective review of data collected from January 2007 to April 2016 within a nationwide private and Medicare insurance healthcare database. A total of 25,966 patients who underwent THA and received a single medication for venous thromboembolism (VTE) prophylaxis during the early postoperative period, including 551 receiving aspirin alone, 6,791 receiving enoxaparin alone, 12,008 receiving warfarin alone, 337 receiving apixaban alone, 876 receiving fondaparinux alone, and 5403 receiving rivaroxaban alone.	Nationwide	Warfarin was associated with a higher risk for deep vein thrombosis (DVT) and had the highest risk for 30-day and 90-day complications. Despite 3 times increased 30-day risk for bleeding, apixaban was effective in preventing VTE during the high-risk 3-month period. Enoxaparin had the lowest risk for pulmonary embolism (PE) and DVT, while rivaroxaban had the lowest risk for prosthetic joint infection hematoma, incision and discharge hemorrhage, and transfusion.	Aspirin had the highest risk for incision and drainage (I&D).	Aspirin has a relatively low bleeding and thromboembolic complication profile and is an inexpensive, easy-to-administer option for VTE prophylaxis following total joint arthroplasty (TJA).	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Anderson et al., 2013[14]	After an initial 10-day course of low molecular weight heparin (LMWH) following elective THA, patients were randomly assigned to an additional 28 days of LMWH or aspirin.	Multicenter randomized controlled trial included 778 patients receiving elective unilateral THA between 2007 and 2010; 400 received LMWH and 386 received aspirin.	12 tertiary care orthopedic referral centers in Canada	Five of 398 patients (1.3%) randomly assigned to LMWH and 1 of 380 (0.3%) randomly assigned to aspirin had VTE. Aspirin was noninferior (p<0.001) but not superior (p=0.22) to LMWH. The absolute between-group difference in a composite of all VTE and clinically significant bleeding events was 1.7 percentage points (confidence interval [CI], 0.3 to 3.8 percentage points; p=0.091) in favor of aspirin.	Clinically significant bleeding occurred in five patients (1.3%) receiving LMWH and two (0.5%) receiving aspirin.	Given its low cost and convenience to access and administer, aspirin may be considered a reasonable alternative for extended thromboprophylaxis after THA.	Included in Wang et al., 2017[4]
Anderson et al., 2018[15]	All 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 (TKA) or for 30 days after THA.	Double-blind randomized controlled trial; 3,427 patients undergoing elective unilateral primary or revision hip or knee arthroplasty underwent randomization; 1,707 received aspirin and 1,717 received rivaroxaban.	15 university-affiliated health centers in Canada	In the comparison with rivaroxaban, aspirin was found to be noninferior (p<0.001) but not superior (p=0.84) for the prevention of postoperative proximal DVT or PE.	A combination of major bleeding and clinically relevant nonmajor bleeding occurred in 22 patients (1.29%) in the aspirin group and in 17 (0.99%) in the rivaroxaban group (95% CI, −1.07 to 0.47; p=0.43).	Aspirin is not significantly different than rivaroxaban in the prevention of VTE following THA or TKA.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Azboy et al., 2017[29]	Treatment with VTE prophylaxis following hip preservation surgery (HPS). Patients received warfarin, aspirin 325 mg twice daily, or aspirin 81 mg twice daily for 4 weeks postoperatively, beginning on the day of surgery along with compression mechanical prophylaxis for the length of the hospital stay.	Retrospective study of prospective data 2003 to 2016; 683 patients undergoing HPS, 448 receiving aspirin 325 mg, 238 receiving aspirin 81 mg, 44 receiving warfarin.	Single site, performed by single surgeon	There was no difference between aspirin 325 mg and aspirin 81 mg in regard to the VTE rate after HPS (p=0.653). Also, there was no difference between aspirin 325 mg and warfarin in regard to VTE rate after HPS (0.911). No difference in VTE rate was observed between aspirin 325 mg and aspirin 81 mg after femoroacetabular osteoplasty (p=0.667). Furthermore, no difference in VTE rate was observed between aspirin 325 mg and aspirin 81 mg after periacetablular osteotomy (p=0.516).	Not provided	No significant difference in symptomatic VTE rates following HPS in patients receiving warfarin, aspirin 325 mg, or aspirin 81 mg.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Bala et al., 2017[12]	Use of one of four thromboprophylactic agents (aspirin, warfarin, enoxaparin, factor Xa inhibitors) during primary TKA.	Retrospective study of prospective data from 2007 to 2016; 1,016 patients undergoing primary TKA who received aspirin age- and sex-matched with 6,096 patients taking enoxaparin, 6.096 patients taking warfarin, and 5,080 patients taking factor Xa inhibitors.	Nationwide	There was a difference in the incidence of DVT at 90 days ($p<0.01$). Factor Xa inhibitors (2.9%) had the lowest incidence of DVT, followed by aspirin (3.0%), enoxaparin (3.5%), and warfarin (4.8%). There was a difference in the incidence of PE at 90 days ($p<0.01$). Factor Xa inhibitors (0.9%) had the lowest incidence of PE, followed by enoxaparin (1.1%), aspirin (1.2%), and warfarin (1.6%).	There were no differences in bleeding-related complications ($p=0.81$) between the groups.	Aspirin provided comparable VTE prophylaxis compared with factor Xa inhibitors and improved VTE prophylaxis compared with enoxaparin and warfarin, with the lowest risk of bleeding.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Bayley et al., 2016[30]	Use of one of three thromboprophylactic agents for patients undergoing THA: warfarin, LMWH, or aspirin in combination with calf compression, foot pumps, anti-embolism stockings, and early mobilization.	Retrospective study of prospective data from 2000 to 2012; 7,983 patients undergoing THAs. Warfarin used in 1,571 patients, LMWH used in 1,838 patients, and aspirin used in 4,574 patients.	Single hospital, UK	A total of six (0.08%) deaths were attributable to PE, three occurring within 42 days of surgery and three within 90 days. All three of the early PEs were in the LMWH group. Of those occurring later, two were in the LMWH group and one in the warfarin group.	The 90-day mortality for the three groups was six patients, 0.38% (95% CI, 0.18 to 0.83); 20 patients, 1.09% (95% CI, 0.71 to 1.67); and 20 patients, 0.43% (95% CI, 0.28 to 0.67), respectively. The difference between LMWH and aspirin reaches statistical significance ($p<0.05$, 95% CIs do not overlap).	PE is rare after elective primary THA. No such events occurred in those treated with aspirin.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Bozic et al., 2010[31]	Use of either aspirin or another guideline-approved prophylactic agent following TKA. Other agents may include warfarin, LMWH, or synthetic pentasaccharides. Aspirin may be the sole prophylaxis method or in combination with mechanical prophylaxis.	Retrospective analysis of data collected in Perspective, a Premier proprietary database of patients undergoing TKA between October 2003 and September 2005; 51,923 patients received warfarin, 37,198 received injectable agents, and 4,719 received aspirin.	307 hospitals	Unadjusted odds ratios (ORs) for DVT or PE were significantly higher in the warfarin group (1.69 times higher odds, 95% CI, 1.39 to 2.05), and the LMWH/ fondaparinux group (1.34 times higher odds, 95% CI, 1.10 to 1.63) when compared with aspirin. The adjusted analysis indicated that the magnitude of the differences in risk of VTE between the aspirin and warfarin groups decreased, and for the LMWH group was no longer significant.	No differences were observed between the groups with regard to bleeding risk.	Aspirin may be effective for VTE prophylaxis in certain TKA patients.	Reference article
Chu et al., 2017[32]	Patients undergoing TKA or THA received either (1) aspirin only; (2) anticoagulants only; or (3) aspirin and anticoagulants. Anticoagulants included warfarin, injectable heparin sodium, LMWH heparin, fondaparinux, or direct oral anticoagulation.	Retrospective cohort analysis of data collected in Perspective, a Premier proprietary database of patients undergoing TKA or THA from 2009 to 2012; 231,780 underwent TKA and 110,621 underwent THA.	Hospitals participating in Premier consortium	Compared with anticoagulants, aspirin was not associated with a higher risk for postoperative VTE either after TKA (adjusted OR and 95% CI 0.34 [0.24–0.48]) or THA (OR 0.82 [0.45–1.51]). For both TKA and THA, the lowest bleeding risk was found in patients who received aspirin only.	Not provided	Aspirin resulted in similar rates of postoperative VTE as anticoagulants.	Reference article

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Daniel et al., 2008[19]	All patients received an oral antiplatelet agent, starting on the day of operation and continuing for 30 days after discharge. Half also received mechanical devices (cohort B).	Retrospective study of THA and hip resurfacing surgeries occurring in 2006; 487 procedures—258 procedures with no mechanical compression and 229 with mechanical compression.	UK	No symptomatic calf or above-knee DVT or PE occurred. In 25 patients in cohort A (10.2%) and in 10 patients in cohort B (4.6%) asymptomatic calf DVTs were detected ultrasonographically. This difference was statistically significant (p=0.03).	Not provided	Aspirin followed by mechanical compression supports a low incidence of VTE without subjecting patients to the higher risk of bleeding associated with anticoagulant use.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Deirmengian et al., 2015[17]	In all patients, aspirin or warfarin treatment was initiated on the day of surgery for patients undergoing TJA and continued for 6 weeks postoperatively. In addition to chemoprophylaxis, intermittent pneumatic compression devices were applied immediately after the surgery and used throughout the hospital stay. In addition, patients were mobilized with physical therapy beginning the day of surgery.	Retrospective review of institutional arthroplasty database of patients undergoing TJA between 2005 and 2013 and treated with intermittent pneumatic compression devices; 534 patients received aspirin, 2,463 patients received warfarin.	Medical institution in Philadelphia, PA	The differences between the groups with regard to DVT or PE alone were not statistically significant (p=0.15; p=0.06, respectively). Fisher's exact test showed a significantly higher risk for any symptomatic VTE in patients receiving warfarin (43 events, 1.75%) compared with patients receiving aspirin (3 events, 0.56%; OR: 3.2; 95% CI, 1.03 to 16.3; p=0.03). Twenty-nine patients (1.0%) were reoperated on for evacuation of hematoma: 2 patients (0.4%) in the aspirin group and 27 patients (1.1%) in the warfarin group. Ten patients (0.3%) had bleeding events: five with upper gastrointestinal (GI) bleeding, two with lower GI bleeding, and three with genitourinary bleeding. All bleeding events were in the warfarin group.	Not provided	Aspirin associated with lower rate of complications and may be more effective than warfarin.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Faour et al., 2018[33]	Patients received aspirin twice daily for 4 to 6 weeks after THA surgery and were grouped into two cohorts: a low-dose (81 mg) aspirin group and a standard-dose (325 mg) aspirin group. All patients also received pneumatic compression stockings.	Retrospective analysis of existing database of patients who underwent THA between September 2012 and December 2016; 1,033 patients received low-dose aspirin, 2,903 patients received standard-dose aspirin.	Not provided	The 90-day incidence of symptomatic VTE was 1.0% in the 325 mg group and 0.6% in the 81 mg group (p=0.35). Symptomatic DVT incidence was 0.8% in the 325 mg group and 0.5% in the 81 mg group (p=0.49), and the incidence of symptomatic PE was 0.3% in the 325 mg group and 0.2% in the 81 mg group (p=0.45). After accounting for confounders, regression analyses showed no difference between aspirin doses and the 90-day incidence of symptomatic VTE (OR, 0.90; 95% CI, 0.29 to 2.85; p=0.85) or symptomatic DVT (OR, 0.96; 95% CI, 0.26 to 3.59; p=0.95).	Bleeding was observed in 0.8% of the 325 mg group and 0.5% of the 81 mg group (p=0.75), and 90-day mortality was not different (0.1%) between the groups (p=0.75).	Low-dose aspirin appears to be a reasonable option for VTE prophylaxis in otherwise healthy patients undergoing elective THA.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Faour et al., 2018[23]	All included TKA patients received either 81 mg aspirin twice daily or 325 mg aspirin twice daily on the evening of or the next day after the procedure for 4 to 6 weeks depending on the surgeons' preference. In addition, all patients received pneumatic compression stockings after the procedure as standard of care. Physical therapy was initiated either on the day of surgery or on postoperative day 1 and continued daily throughout the hospital stay.	Retrospective cohort study of patients undergoing elective primary TKA between 2012 and 2016; 4,339 patients receiving 325 mg aspirin and 1,327 receiving 81 mg aspirin.	Not provided	There was a significant difference (p=0.02) in the incidence of VTE between groups: 0.7% in the 81 mg aspirin group compared to 1.5% in the 325 mg aspirin group. The incidence of symptomatic DVT in the 325 mg aspirin group was 1.4% compared with 0.3% in the 81 mg aspirin group (p<0.001). As for PE, the overall incidence in the study population was 0.2% (12/ 5,666 patients). The incidence of PE in the 325-mg aspirin group was 0.2% compared with 0.4% in the 81-mg aspirin group (p=0.13). Regression model showed no correlation between aspirin dose and VTE incidence (OR=1.03; 95% CI, 0.45 to 2.36; p=0.94) or DVT (OR = 0.50; 95% CI, 0.16 to 1.55; p=0.20).	Not provided	Low-dose aspirin was not inferior to high-dose aspirin for the prevention of VTE after TKA. Low-dose aspirin can be considered a safe and effective agent in the prevention of VTE after TKA.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Feldstein et al., 2017[24]	Patients undergoing TJA received standard-dose aspirin (325 mg) or low-dose aspirin (81 mg) twice daily.	One-year prospective cohort study for patients undergoing primary unilateral TJA; 643 patients were included, 282 received 325 mg and 361 received 81 mg.	All surgeries were performed by a single surgeon	Only one patient in the acetylsalicylic acid (ASA) 81 mg group (0.3%) developed a DVT.	The overall rate of GI side effects (GI upset and nausea) was 1.9%, but ASA 325 mg had a higher rate 9/282 (3.2%) than ASA 81 mg 3/361 (0.8%), p=0.04. Overall GI bleeding was 0.9%, with 2/282 (0.7%) in the ASA 325 mg group vs. 4/361 (1.1%) in the ASA 81 mg group, p=0.70.	There is a higher rate of GI distress and nausea among patients taking standard-dose aspirin compared with low dose.	Reference article

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Gesell et al., 2013[34]	Patients undergoing TKA received multimodal thromboprophylaxis. Aspirin was used in 67% of patients and Coumadin in 33% (high-risk patients, or those who were on Coumadin before surgery). This study group was compared with 1,001 consecutive patients who received multimodal thromboprophylaxis and routine Coumadin chemoprophylaxis. Patients also received pneumatic compression devices, flexion and extension exercises of the ankles, and early mobilization.	A retrospective study comparing two patient cohorts undergoing primary TKA procedures; 1,016 patients undergoing 1,118 procedures.	All surgeries in study group performed by same two surgeons; all surgeries in control group performed by one surgeon.	There was no difference in the rate of symptomatic PE or VTE between the groups. In the study group, 25 patients developed VTE. In the control group, 22 patients developed VTE. There were no major bleeding complications due to thromboprophylaxis in the study group. In the control group, one patient required re-admission for hemarthrosis and two patients required readmission for upper GI bleed while on Coumadin (p=0.12). There was a higher incidence of wound complications in the control group (p=0.03).	There was one death in each group (0.1%).	Multimodal thromboprophylaxis with a preference for the use of aspirin in low-risk patients is safe and efficacious in elective TKA surgery. However, risk stratification is necessary to identify patients at increased risk of VTE and to diminish the exposure of patients to anticoagulation, thus reducing the risk of bleeding and wound-related complications.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Goel et al., 2018[10]	Patients undergoing TKA were divided into four groups based on VTE prophylaxis, as determined by institutional electronic databases, and whether they had undergone simultaneous bilateral total knee arthroplasty (SBTKA) or unilateral total knee arthroplasty (UTKA): (1) unilateral aspirin, (2) bilateral aspirin, (3) unilateral warfarin, (4) bilateral warfarin.	A retrospective, multi-institutional study of patients undergoing SBTKA or UTKA between 2000 and 2017; 18,951 patients, 3,685 who underwent SBTKA and 15,266 who underwent UTKA.	Two large academic institutions	The adjusted incidence of PE following SBTKA was 1.0% (95% CI, 0.86 to 1.2) with aspirin and 2.2% (95% CI, 2.0 to 2.4) with warfarin. Similarly, the adjusted incidence of VTE following SBTKA was 1.6% (95% CI, 1.1 to 2.3) with aspirin and 2.5% (95% CI, 1.9 to 3.3) with warfarin. The risks of PE and VTE were reduced by 66% (OR 0.44, 95% CI, 0.25 to 0.78) and 38% (OR 0.62, 95% CI, 0.38 to 1.0), respectively, using aspirin.	Not provided	Aspirin is more effective than warfarin for the prevention of VTE following SBTKA, and serves as the more appropriate agent for VTE prophylaxis for patients in all risk categories.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Griffiths et al., 2012[20]	Between 2003 and 2006 (inclusive), patients undergoing foot and ankle surgery were given aspirin 75 mg once daily starting on the first postoperative day. In patients undergoing surgery to the forefoot, this was continued for 2 weeks; in those undergoing midfoot or hindfoot surgery, it was continued for 6 weeks or until they were out of plaster. Between 2007 and 2010, no form of chemical thromboprophylaxis was used. All patients had pneumatic compression foot pumps placed on the non-operated limb in theater and antiembolism compression stockings on the ward.	Retrospective analysis of patients undergoing foot and ankle surgery; of 2.654 patients, 1,078 received aspirin postoperatively and 1,576 received no form of chemical thromboprophylaxis.	UK	There was no statistical difference in the rate of thromboembolic events between the two groups (p=0.985). However, the overall rate of thromboembolic events was very small; the incidence of a DVT and PE was 0.27% and 0.15% respectively. There was no statistical difference in the rate of PE or DVT between those who received aspirin and those who did not (p=0.9 and p=0.615).	Not provided	The reported risks of routine chemical thromboprophylaxis appear to outweigh any potential benefits, and the use of aspirin does not appear to confer significant protection against symptomatic VTE. An alternative form of thromboprophylaxis should be considered in high-risk patients such as those who are obese, continue with the combined oral contraceptive pill, or have a previous history of VTE or a pro-coagulant condition.	None

Hamilton et al., 2012[16]	Mechanical calf compression devices were used in all patients. Physical therapy was begun the day of surgery or on postoperative day 1 for afternoon operations. Enoxaparin was begun on postoperative day 1 and renally dosed. For a creatinine of less than 1.5, enoxaparin dosing was 30 mg twice daily for knee arthroplasty and 40 mg once daily for hip arthroplasty. For a creatinine of greater than 1.5, enoxaparin dosing was 30 mg daily for both hip and knee arthroplasty. Upon discharge from the hospital, patients were prescribed enteric-coated aspirin 325 mg twice daily for 28 days. A control group of 500 hip and knee cases received enoxaparin for a total of 2 weeks postoperatively and then aspirin 325 mg twice daily for an additional 2 weeks. Anesthesia, therapy, enoxaparin therapy guidelines, and general	A retrospective review; 500 primary hip and knee arthroplasties between January 2009 and February 2019 in 472 patients.	Single site where all hip and knee arthroplasty surgeries were performed by two surgeons.	There was a trend for a lower rate of DVT in the study group compared with the control group, but this difference did not reach statistical significance using a Fisher exact test (p=0.07). There was a significant difference in the average number of packed RBCs transfused between the study (0.39 units/patient) and control (0.57 units/patient) groups, but there was no significant difference between the number of patients receiving 3 or more units. There was no significant difference between the two groups in the number of patients with the following outcomes: pulmonary embolus, deep infection, superficial infection, readmission, or death.	Not provided	A protocol of inpatient enoxaparin and outpatient aspirin proved safe and effective in standard-risk patients after hip and knee arthroplasty. When combined with mechanical compression devices and early mobilization, a low rate of symptomatic thromboembolic disease was noted. There were significant cost savings with a low complication rate and no deaths.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
	postoperative protocol were otherwise similar between the two groups.						
Huang et al., 2016[27]	Following TJA, patients either received aspirin of warfarin in combination with mechanical prophylaxis.	Retrospective analysis of an institutional database of patients undergoing TJA; 30,270 patients were included.	Medical institution in Philadelphia, PA	The incidences of VTE and mortality were higher in patients receiving warfarin compared with aspirin. In multivariate analysis, warfarin was an independent risk factor for VTE and mortality in the higher risk VTE patients ($p<0.001$).	There was no significant difference in GI complications between groups.	Aspirin may be safer than and as effective as warfarin for VTE prophylaxis, even among higher risk patients.	Reference article
Jameson et al, 2011[35]	Following THA, patient received either LMWH or aspirin in combination with mechanical prophylaxis.	Retrospective review of the National Registry combined with Hospital Episode Statistics data for patients undergoing THA; 22,942 included patients received aspirin and 85,642 received LMWH.	UK	Without adjustment, there were no significant differences between the two treatments. The rate of PE was 0.68% in both groups, and 90-day mortality was 0.65% with aspirin and 0.61% with LMWH (OR 0.93; 95% CI, 0.77 to 1.11).	Risk adjustment increased the difference in mortality (OR 0.84; 95% CI, 0.69 to 1.01) and was increased further still with propensity score matching to 0.65% with aspirin and 0.51% with LMWH (OR 0.77; 95% CI, 0.61 to 0.98).	Aspirin is not inferior to LMWH. However, there may be a slightly increased risk of mortality.	Reference article

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Ji et al., 2011[22]	Compared the incidence of symptomatic VTE in hip fracture surgery patients taking low-dose aspirin or other antiplatelet to prevent thrombosis with non-users. Patients received thigh-length antiembolic stockings, and use of the ankle pump was encouraged in bed during the inpatient stay.	Retrospective review of medical records of patients undergoing hip fracture surgery for femoral neck and interochanteric fractures from May 2003 to April 2010; 245 antiplatelet users compared with 579 non-users.	Single institution, Korea	The incidence of symptomatic VTE was 4.8% (12/ 250) in antiplatelet users and 4.3% (26/608) in non-users (p=0.718). Symptomatic VTE after hip fracture surgery (HFS) was not reduced in Korean patients who received antiplatelet agent including aspirin in this study.	Not provided	Results indicate that thromboprophylaxis after HFS is not necessary in Korean patients.	None
Jiang et al., 2014[25]	Patients undergoing TKA were randomly allocated to either receive aspirin or receive LMWH. Both groups also received mechanical prophylaxis.	Prospective randomized study conducted between January 2012 and May 2013; 120 patients underwent randomization.	Single site	DVT was detected in 10 of 60 patients receiving aspirin (16.7%, 95% CI, 7.3% to 26.1%) compared with 11 of 60 receiving LMWH (18.3%, 95% CI, 8.5% to 27.8%). The difference was not significant (p=0.500). Patients receiving aspirin had a lower blood loss index compared to those patients receiving LMWH. This finding was significant.	Not provided	Aspirin combined with mechanical prophylaxis is not inferior to LMWH combined with mechanical prophylaxis in preventing VTE following TKA.	Reference article

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Kaye et al., 2015[21]	Arthroscopic knee surgery patients were randomly allocated to the aspirin or no aspirin group by using sealed envelopes; the operating surgeon sequentially opened the envelope after each surgical procedure. Patients allocated to the aspirin group took 325 mg aspirin tablet daily for 14 days starting on the first postoperative day. Patients allocated to the nonpharmacologic group (control group) did not take any nonsteroidal anti-inflammatory drugs for the first 14 days postoperatively. All patients participating in the study had bilateral, whole leg, compression venous duplex ultrasonography 10 to 14 days postoperatively.	Prospective randomized, single-blind controlled study of patients undergoing arthroscopic knee surgery between June 2011 and June 2013; 170 patients.	East Asian institute	No DVTs or PEs were identified in either group.	29 patients (17%) experienced a complication. While no significant complications were found, minor complications existed, including pain and swelling, residual join line tenderness, incidental finding of a Baker's cyst, arthrofibrosis, instability after a fall, and a limp. Following a logistic regression, aspirin was not statistically significant for a decreased risk of complication following arthroscopic knee surgery.	As no cases of VTE were identified in the patient population, the use of aspirin in a low-risk population undergoing arthroscopic knee surgery is not warranted.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Mendez et al., 2017[3]	Compared patients undergoing surgery for a primary malignant soft-tissue or bone tumor, or metastatic carcinoma who received 325 mg of aspirin twice daily following the operation with patients receiving nonaspirin prophylaxis.	Retrospective review of medical records of patients who had been surgically treated for a primary malignant soft-tissue or bone tumor, or metastatic carcinoma, from 2012 to 2015; 130 patients with 142 surgical procedures. Aspirin given after 103 procedures, non-aspirin prophylaxis after the remaining surgeries.	Surgeries performed by one of two orthopedic oncologists at a single institution	There were six DVTs and one PE after 7 (4.9%) of the 142 surgical procedures. A VTE developed in 3 (2.9%) of the 103 cases with aspirin prophylaxis and 4 (10.3%) of the 39 cases in the non-aspirin group. In the non-aspirin cohort, a DVT developed in 1 (7.1%) of the 14 cases treated with only an intermittent pneumatic compression device, 1 (8.3%) of the 12 treated with LMWH, and 1 (16.7%) of the 6 treated with unfractionated heparin. A PE developed in 1 (20.0%) of the 5 cases in which warfarin had been used.	Not provided	Aspirin for VTE prophylaxis in patients undergoing orthopedic oncologic surgery was positive, especially for patients with soft-tissue sarcoma, who had no documented VTEs.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Parvizi et al., 2017[28]	Six adult-reconstruction surgeons agreed to enroll TJA patients into the study. Three surgeons prescribed 325 mg aspirin twice a day to their patients for a defined period of time (the 325 -mg aspirin group) and then switched to 81 mg aspirin twice a day (the 81 mg aspirin group) for the remainder of the study. The other three surgeons would do the same but in a reverse order. Treatment was in combination with compression devices and early mobilization.	Prospective crossover study from July 1, 2013, through June 30, 2015, of patients receiving joint arthroplasty; 4,651 patients.	Medical institution in Philadelphia, PA	The incidence of venous thromboembolism of 0.1% (95% CI, 0% to 0.3%) in the 81 mg aspirin group was not significantly different (p=0.345) from 0.3% (95% CI, 0.1% to 0.6%) in the 325 mg aspirin group.	The incidence of GI bleeding or ulceration of 0.3% (95% CI, 0% to 0.5%) in the 81 mg aspirin group was slightly, but not significantly (p=0.66), lower than the 0.4% (95% CI, 0.2% to 0.6%) in the 325 mg aspirin group.	Low-dose aspirin is not inferior to high-dose aspirin for VTE prophylaxis following TJA.	None

Raphael et al., 2014[18]	Patients undergoing TJA received either aspirin (325 mg twice daily) or warfarin prophylaxis. All patients received treatment in combination with compression devices.	Retrospective analysis of a prospective database of patients undergoing TJA between January 2000 and June 2012; 28,923 patients, 2,800 receiving aspirin and 26,123 receiving warfarin.	Medical institution in Philadelphia, PA	The overall symptomatic PE rate was lower (p<0.001) in patients receiving aspirin (0.14%) than in patients receiving warfarin (1.07%). The incidence of symptomatic DVT was significantly lower in the aspirin group (0.29%) than in the warfarin group (0.99%) (OR=3.50; 95% CI, 1.75 to 8.19; p<0.001). The risk of symptomatic DVT remained lower in the aspirin group than in the warfarin group even after propensity score matching was performed. With 3:1 matching, the symptomatic DVT rate was lower in the aspirin group (0.11%) than in the warfarin group (0.91%) (OR=8.57; 95% CI, 2.25 to 72.58; p<0.001). In the unmatched patients, the incidences of wound-related complications and 90-day mortality were significantly higher in the warfarin group than in the aspirin group. However, after propensity score	Not provided	Aspirin offers effective prophylaxis and is appropriate for use.	Included in Mistry, 2017

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
				matching, the incidences were not significantly different between groups, except for wound drainage, which was lower in the aspirin group than in the warfarin group after 5:1 matching (p=0.016). Unmatched and matched analyses both showed the mean length of hospital stay to be significantly shorter for patients receiving aspirin.			
Jiang et al., 2014[36]	Postoperative administration of aspirin (group A) versus postoperative administration of LMWH and rivaroxaban sequentially (group B) in patients undergoing TKA. All patients also received mechanical prophylaxis.	Prospective randomized comparative study of patients undergoing primary unilateral TKA for degenerative arthritis from January 2012 to May 2013; 120 patients—60 in Group A and 60 in Group B.	Beijing Jishuitan Hospital	DVT was detected in 10 of 60 patients in the aspirin group (16.7%, 95% CI, 7.3% to 26.1%) compared with 11 of 60 in the LMWH and rivaroxaban group (18.3%, 95% CI, 8.5% to 27.8%; p=0.500). Patients in the aspirin group had the lower blood loss index as compared with patients in the LMWH and rivaroxaban group (p=0.000).	Not provided	The results of this study suggest that aspirin is not inferior in preventing VTE following TKA when compared with sequential LMWH and rivaroxaban.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Comments
Zou et al., 2014[26]	Three groups of TKA patients each received a different postoperative anticoagulant/ antiplatelet treatment. Group A was given rivaroxaban, Group B was given LMWH sodium, and Group C was given aspirin.	Prospective randomized controlled trial of patients with osteoarthritis undergoing primary unilateral TKA from July 2011 to July 2013; 324 patients randomized into three groups: Group A=102 patients, Group B=112 patients, Group C=110 patients.	China	The incidence of DVT was lower in Group A compared with the other two groups (3 [2.94%] vs. 14 [12.50%], p=0.029; 3 [2.94%] vs. 18 [16.36], p=0.017). Hidden blood loss (1.71 [1.19–2.97] vs. 1.18 [0.77–2.31], p=0.009; 1.71 [1.19–2.97] vs. 1.30 [0.61–2.43], p=0.004) and wound complications (5 [4.90] vs. 3 [2.67], p=0.027; 5 [4.90] vs. 2 [1.82], p=0.014) were more common in Group A than in the other groups. There were no significant differences between Group B and Group C in the incidence of DVT (14 [12.50%] vs. 18 [16.36%], p=0.831), hidden blood loss (1.18 [0.77–2.31] vs. 1.30 [0.61–2.43], p=0.327), or wound complications (3 [2.67] vs. 2 [1.82], p=0.209).	Not provided	No significant difference in post-TKA DVT prophylaxis was found between aspirin and LMWH.	None

Appendix C. Venous Thromboembolism Search Terms

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial	Post-Surgical VTE Prophylaxis using Aspirin	((((MH "Aspirin/Therapeutic Use*") OR (AB Aspirin)) AND ((MH "Venous Thrombosis/Prevention & Control" OR "Pulmonary Embolism/Prevention & Control*") OR (AB "Deep Vein Thrombosis" OR "Pulmonary Embolism" OR PE OR DVT)) AND ((MH "Operative, Surgery" OR "Perioperative Care/Methods*" OR "Postoperative Complications/Prevention & Control*") OR (AB Surgery OR "Surgical Procedure*" OR "Postoperative Complicati on*" OR "Perioperative Care Metho ds" OR Operation))) NOT ((MH "Cardiovascular Diseases" OR Heart) OR (AB "Cardiovascular Disease*" OR Heart OR Cardiac)))	((((MH "Aspirin/Therapeutic use*") OR (AB Aspirin)) AND ((MH "Venous Thrombosis/Prevention & Control" OR "Pulmonary Embolism/Prevention & Control*") OR (AB "Deep Vein Thrombosis" OR "Pulmonary Embolism" OR PE OR DVT)) AND ((MH "Surgical Procedures, Operative" OR "Perioperative Care/Methods*" OR "Postoperative Complications/Prevention & Control*") OR (AB Surgery OR "Surgical Procedure*" OR "Postoperative Complicati on*" OR "Perioperative Care Metho ds" OR Operation))) NOT ((MH "Cardiovascular Diseases" OR Heart) OR (AB "Cardiovascular Disease*" OR Heart OR Cardiac)))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Review • Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial • Research Review • Systematic Review			

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