



TITLE: Acetylsalicylic Acid for Venous Thromboembolism Prophylaxis: A Review of Clinical Evidence, Benefits and Harms

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CONTEXT AND POLICY ISSUES:

Thromboembolism occurs when a blood clot dislodges from one site in the circulatory system and blocks another blood vessel.¹ A formation of a blood clot in deep veins is termed deep venous thrombosis (DVT), while a blockage in the lung is termed pulmonary embolism (PE). Most clinically important PEs result from DVT however, emboli can also originate from pelvic veins.¹ Orthopedic procedures for total hip arthroplasty (THA), total knee arthroplasty (TKA) and hip fracture surgery (HFS) place patients at higher risk for VTE due to venous stasis, vascular injury and/or hypercoagulability.^{2,3} The rate of total and proximal DVT in HFS patients is 50% and 27%, respectively.² The rate of fatal PE after HFS ranges from 0.66% to 7.5% and is higher than the rate associated with THA or TKA.² Preventive therapies involving warfarin, low molecular weight heparin, and pentasaccharides reduce the rate of VTE but may increase the risk of major bleeding.⁴ ASA is an attractive alternative because it is inexpensive, easy to administer and does not require monitoring.⁵

Current practice requires consideration of conflicting recommendations to prevent PE and DVT in patients undergoing THA or TKA.⁵ The American College of Chest Physicians (ACCP)⁶ recommends using anticoagulant medications in all patients, while the American Academy of Orthopaedic Surgeons (AAOS) recommend that clinical judgment and patient history be used in deciding VTEP. Thromboprophylaxis may be individually prescribed based on a composite risk estimate.⁴ Patients assessed to be at an elevated risk for PE included those diagnosed with congestive heart failure, atrial fibrillation, recent surgery for malignancy or active chemotherapy, VTE within the previous 5 years, or heritable or acquired thrombophilias.⁴ Acetylsalicylic acid (ASA) is recommended in patients assessed as “standard” risk for PE or “elevated” risk of bleeding because ASA may reduce the risk of postoperative bleeding complications.⁴ In contrast, the ACCP guidelines do not risk-stratify patients but recommend that all patients receive anticoagulants instead of ASA.⁴

A review of the clinical evidence of the benefits and harms of using ASA for VTEP is needed to inform clinical management of THA, TKA and HFS.

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A summary of the evidence on ASA for VTEP was conducted to determine the role of ASA in VTEP.⁷ This report provides a critical appraisal of the clinical evidence on the benefits and harms of using ASA for VTEP based on the existing summary of evidence.

RESEARCH QUESTION:

1. What is the clinical evidence on the benefits and harms of using acetylsalicylic acid for venous thromboembolism prophylaxis?

KEY MESSAGE:

Most of the available evidence from two studies suggested that ASA results in fewer surgical site bleeds and is as effective as VKA, LMWH, or pentasaccharides for preventing VTE after THA, TKA, and HFS.^{3,8} A prospective cohort study suggested that ASA is less efficacious than LMWH in reducing the risk of VTE in standard-risk patients.⁴

METHODS:

Literature Search Strategy

A limited literature search was conducted on key resources including Medline and Embase (via OVID), PubMed, The Cochrane Library (2011, Issue 7), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies containing safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and July 22, 2011.

Selection Criteria and Methods

One reviewer screened citations to identify health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies regarding the use of ASA for VTEP. Potentially relevant articles were ordered based on titles and abstracts, where available. Full-text articles were considered for inclusion based on the selection criteria listed in Table 1.

Table 1: Selection Criteria

Population	Hip or knee arthroplasty and hip fracture patients
Intervention	Acetylsalicylic acid
Comparator	Standard care
Outcomes	Prevention or mitigation of complications Clinical benefits and harms Serious adverse events (including gastric irritation and ulcers)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies

Exclusion Criteria

Articles were excluded if they did not satisfy the selection criteria, provided incomplete study methods and results, were narrative reviews or published prior to 2006.

Critical Appraisal of Individual Studies

Systematic reviews were assessed for quality using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.⁹ The methodological quality of randomized and non-randomized studies was assessed using the Downs and Black instrument.¹⁰ Instead of calculating numeric scores, the strengths and limitations of each study were described.

SUMMARY OF EVIDENCE:

Quantity of Research Available

The literature search yielded 245 citations. Upon screening titles and abstracts, 237 citations were excluded and eight potentially relevant articles were retrieved for full-text review. No additional potentially relevant reports were retrieved from grey literature or hand searching. Of the eight potentially relevant reports, two did not contain the population of interest and three were narrative reviews. Three articles reported on the benefits and harms of using ASA for VTEP after THA, TKA, or HFS.^{3,4,8} The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

Study design

One meta-analysis,³ a prospective cohort,⁴ and a retrospective cohort study⁸ were selected for review. All articles were published in the United States and ranged in date from 2009 to 2011.^{3,4,8}

Population

The systematic review reported on THA, TKA, and HFS patients from 14 randomized controlled trials (RCTs) included in the ACCP guideline.⁴ Six hundred and ninety-six consecutively chosen THA and TKA patients, presenting to a hospital joint centre, participated in the prospective cohort.⁴ The retrospective cohort included 93,840 TKA patients from 307 hospitals.⁸ Insufficient detail was provided to determine whether populations across the studies were comparable in terms of their demographic characteristics.

Interventions

Four classes of pharmacologic agents were reported in the meta-analysis. They were ASA, vitamin K antagonists (VKA), low molecular weight heparins (LMWH), and pentasaccharides.³ In the prospective cohort study, 152 standard-risk patients received ASA and 1239 elevated-risk patients received warfarin as per the AAOS guidelines, while 415 patients received warfarin without risk-stratification as per the ACCP guidelines.⁴ The retrospective cohort analyzed clinical

data from 51,923 warfarin recipients, 37,198 patients receiving injectable agents, 4,719 ASA recipients.⁸

Outcomes

The meta-analysis reported pooled rates that compared ASA to pentasaccharides, LMWH and warfarin.³ The prospective and retrospective cohorts both reported DVT, PE, bleeding and death as primary outcomes.^{4,8}

Summary of Critical Appraisal

The meta-analysis had a clearly described research question and inclusion criteria.³ While the review was based on the 14 RCTs included in the 2004 ACCP guideline, no additional literature searches were conducted, so potentially relevant articles may be missing.³ The quality of included studies was not formally assessed and it is unclear whether the study selection and data extraction was performed by at least two independent reviewers.³

Both cohort studies had clearly described research questions, patient characteristics, main outcome measures, findings, and adverse events.^{4,8} Neither study performed sample size calculations.^{4,8} In the prospective cohort, patients were recruited consecutively and likely represented the population as a whole.⁴ Outcomes were assessed by an expert panel who were blinded to the management strategy used as VTEP.⁴ The retrospective cohort database study adjusted for biases using propensity scores.⁸

Summary of Findings

One meta-analysis and two cohort studies provided clinical evidence on the benefits and harms of using ASA as VTEP after THA, TKA, or HFS.^{3,4,8}

Pooled analyses of the 14 RCTs cited in the ACCP guideline showed that VKA recipients had a higher rate of symptomatic DVTs than ASA recipients. While the ACCP guideline stated that there was no evidence on the effectiveness of ASA in the reduction of VTE after orthopaedic surgery, the use of VKA, LMWH, and pentasaccharides increased the risk of surgical site bleeds without reducing clinically relevant symptomatic DVT, PE and fatal PE rates. Table 2 shows the relative risks of VTE and bleeds related to pentasaccharides, LMWH and warfarin compared to ASA.³

Table 2. Comparison of Relative Risks for VTEP by Agent

VTEP Agent	DVT RR (95%CI)	PE RR (95%CI)	Fatal PE RR (95% CI)	Surgical Site Bleeds RR (95% CI)	Non- Surgical Site Bleeds RR (95% CI)
Pentasaccharide versus ASA	0.98 (0.66-1.45)	1.30 (0.83-2.03)	1.40 (0.67-2.93)	4.16 (2.83-6.13)	0.18 0.11-0.30
LMWH versus ASA	1.33 (0.99-1.78)	0.73 (0.49-1.09)	0.59 (0.29-1.22)	6.38 (4.56-8.92)	0.52 (0.41-0.66)
Warfarin versus ASA	2.09 (1.52-2.88)	0.64 (0.38-1.10)	0.20 (0.05-0.87)	4.88 (3.28-7.72)	0.58 (0.42-0.81)

ASA: acetylsalicylic acid, CI: confidence interval; DVT: deep venous thrombosis; LMWH: low molecular weight heparin; PE: pulmonary embolism; RR: relative risk; VTEP: venous thromboembolism prophylaxis.

The prospective cohort study reported that non-stratified warfarin recipients had significantly lower rates of symptomatic PE and VTE compared to standard-risk ASA recipients (0.6% versus 4.6%; $P=0.001$, and 1.1% versus 7.9%; $p<0.0001$, respectively).⁴ The odds of symptomatic PE and DVT for standard-risk ASA recipients was 6.6 times greater versus the risk for non-stratified warfarin recipients (Bonferroni-adjusted $p=0.03$).⁴ While the study contained 256 THA patients and 439 TKA patients, most events (16/18) occurred in TKA patients. No significant difference was noted in the rate of major bleeding or death between groups.

The retrospective cohort study reported that TKA patients receiving ASA had lower odds of VTE than warfarin recipients [adjusted OR: 1.36 (95% CI 1.02, 1.82), $p<0.01$] but similar odds as injectable VTEP recipients [adjusted OR: 1.03 (95% CI 0.76, 1.39), NS].⁸ No differences were noted in the risk of bleeding, infection or mortality.⁸

A summary of the clinical evidence on the benefits and harms of VTEP agents is provided in Table 3.

Table 3. Summary of Clinical Evidence on Benefits and Harms of VTEP Agents

Intervention	Evidence	Results
ASA, VKA, LMWH, pentasaccharide VTEP for THA, TKA, or HFS	Meta-analysis (n=14 RCTs)	<ul style="list-style-type: none"> VTE rates with ASA were not significantly different than rates for VKA, LMWH and pentasaccharides. RR of surgical site bleeds was higher in VKA, LMWH and pentasaccharide recipients compared to ASA recipients.
Standard risk ASA, elevated risk warfarin, non-stratified warfarin VTEP for TKA	Prospective cohort	<ul style="list-style-type: none"> Non-stratified warfarin recipients had lower rates of PE and VTE compared to standard-risk ASA recipients. No significant differences in rate of major bleeds or death between groups.
ASA, warfarin, injectable VTEP for THA and TKA	Retrospective cohort	<ul style="list-style-type: none"> ASA recipients had lower odds of VTE than warfarin recipients but similar odds as injectable VTEP recipients. No difference in risk of bleeding, infection or death between groups.

ASA: acetylsalicylic acid; HFS: hip fracture surgery; LMWH: low molecular weight heparin; RCT: randomized controlled trials; RR: relative risk; THA: total hip arthroplasty; TKA: total knee arthroplasty; VKA: vitamin K antagonists; VTEP: venous thromboembolism prophylaxis;

Limitations

The quantity of the clinical evidence on the benefits and harms of using ASA as orthopedic surgery is limited to one meta-analysis and two cohort studies.^{3,4,8} While all three studies reported on VTEP for TKA,^{3,4,8} HFS patients were included in the systematic review only³ and THA was reported in two studies.^{3,8} The systematic review was based on 14 RCTs included in the ACCP guideline published in 2004.³ Without systematically searching the literature for recently published evidence, it is possible that some studies may have been missed and there is a risk of bias in how studies were selected.³ The quality of the RCTs included in the review was not considered in the interpretation of the results.³

Both cohort studies had clearly described research questions, patient characteristics, main outcome measures, findings, and adverse events.^{4,8} A sample size calculation was not performed in either study.^{4,8} The internal validity of the cohort studies was compromised by the fact that patients and surgeons were probably not blinded as treatment assignment was based on risk stratification.^{4,8} In the prospective cohort, patients were recruited consecutively and likely represent the population as a whole.⁴ Outcomes were assessed by an expert panel blind to the management strategy used as VTEP.⁴ The retrospective cohort database study adjusted for biases using propensity scores.⁸ Overall, the results of the included studies are generalizable to the target patient population.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

While ASA is inexpensive, easy to administer and does not require monitoring, guidelines differ on whether ASA should be used as VTEP for THA, TKA and HFS. According to a quantitative review and a prospective cohort study, patients, who received VTEP with ASA, had comparable³ or lower⁴ rates of VTE and similar⁴ or lesser risk³ of surgical site bleeds than those who received VKA, LMWH, or pentasaccharides. In contrast, a smaller retrospective study showed that standard-risk patients taking ASA prophylaxis had higher VTE rates but similar bleed rates as non-stratified warfarin recipients.⁸ While ASA may be a suitable choice for VTEP in some orthopedic patients, evidence for use is limited to one meta-analysis and a prospective cohort study.^{3,4}

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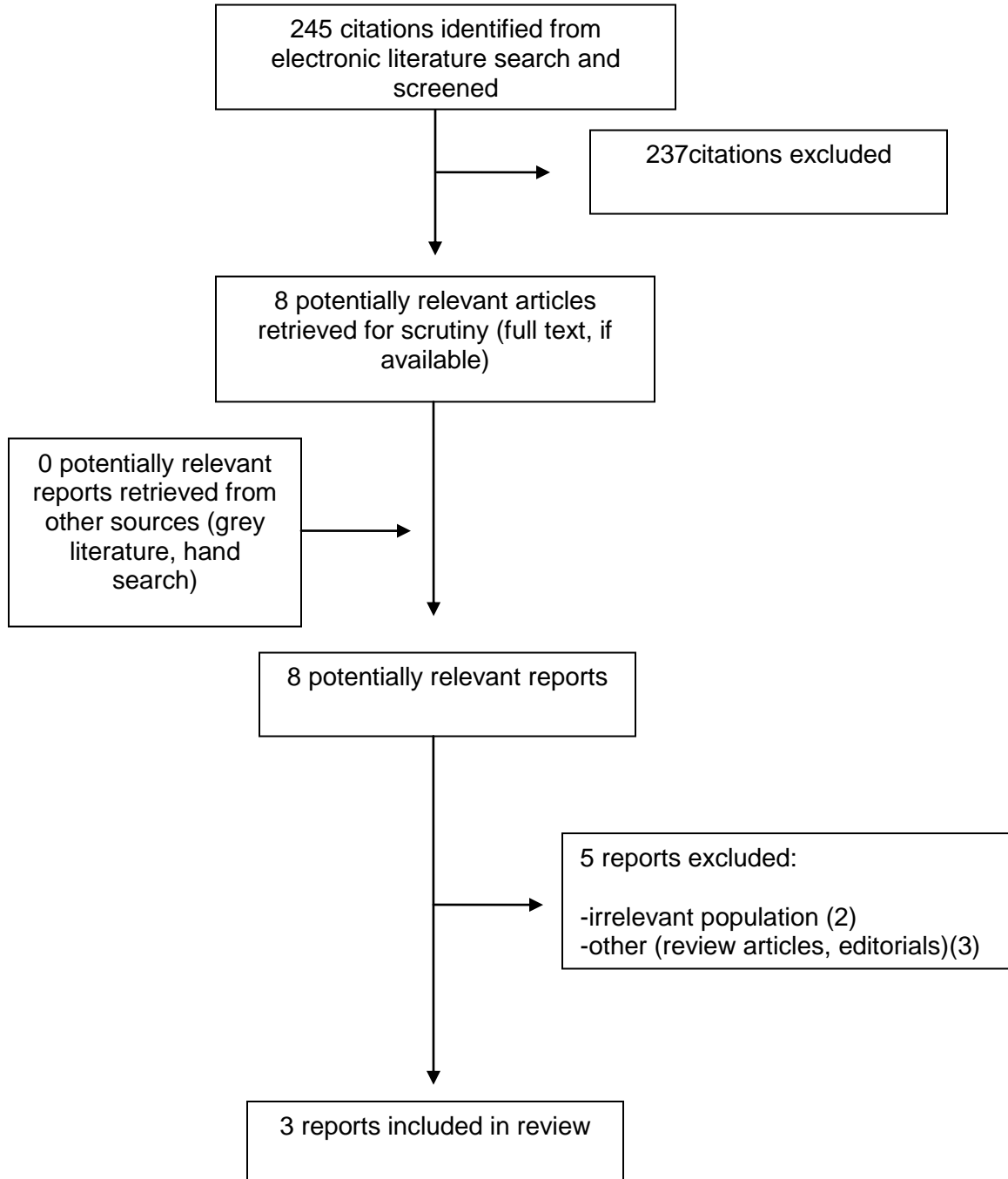
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APPENDICES:

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Study Characteristics

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Brown et al. 2009 ³ United States	Quantitative systematic review	14 RCTs from ACCP guideline involving THA, TKA and HFS patients	VTEP with ASA, VKA, LMWH, or pentasaccharides	ASA (n=8726 patients) Warfarin (n=4518 patients) LMWH (n=9269 patients) Pentasaccharide (n=3616 patients) Placebo (n=8718 patients)	DVT, PE, fatal PE, surgical site bleeding
Intermountain Joint Replacement Centre Writing Committee 2011 ⁴ United States	Prospective cohort	Consecutive THA and TKA patients (n=696)	VTEP with ASA or warfarin	ASA (n=152 standard-risk patients) Warfarin (n=129 elevated-risk patients; 415 non-stratified patients)	DVT, PE, major bleeding, death
Bozic et al. 2010 ⁸ United States	Retrospective cohort	TKA (n=93,840; 307 hospitals)	VTEP with ASA, warfarin, or injectable agent	ASA (n=4719) Warfarin (n=51,923) Injectable VTEP (n=37,190)	DVT, PE, surgical site bleeding, death

ACCP: American College of Chest Physicians; ASA: acetylsalicylic acid; DVT: deep venous thrombosis; HFS: hip fracture surgery; LMWH: low molecular weight heparin; PE: pulmonary embolism; THA: total hip arthroscopy; TKA: total knee arthroscopy; VTEP: venous thromboembolism prophylaxis.

APPENDIX 3: Summary of Critical Appraisal

First Author, Publication Year Country	Strengths	Limitations
Brown et al. 2009 ³ United States	<ul style="list-style-type: none"> • Research question and inclusion criteria were established before conducting the review. 	<ul style="list-style-type: none"> • No literature search was performed, only the 14 RCTs included in the ACCP guidelines were included leading to potential bias. • Quality of included studies was not formally assessed. • Unclear duplicate study selection and data extraction was performed.
Intermountain Joint Replacement Centre Writing Committee 2011 ⁴ United States	<ul style="list-style-type: none"> • The objective, patient characteristic, main outcome measures, findings and variability were clearly described. • All important adverse events were reported. • Patients were recruited consecutively and were likely representative of the population as a whole. • Outcomes assessed by expert panel blind to management strategy used as VTEP. 	<ul style="list-style-type: none"> • It is unlikely that patients were blind to treatment. • No sample size calculation.
Bozic et al. 2010 ⁸ United States	<ul style="list-style-type: none"> • The objective, patient characteristics, interventions, main findings and variability were well described. • All important adverse events were reported. • Analysis used propensity scores for assignment to injectable VTEP versus other VTEP assignment to warfarin versus other VTEP and assignment to ASA versus VTEP. • It is unclear how patients were selected. 	<ul style="list-style-type: none"> • No sample size calculation.

ASA: acetylsalicylic acid; DVT: deep venous thrombosis; LMWH: low molecular weight heparin; NS: not significant; OR: odds ratio; PE: pulmonary embolism; RCT: randomized controlled trial; VKA: vitamin K antagonist; VTE: venous thromboembolism; VTEP: venous thromboembolism prophylaxis

APPENDIX 4: Summary of Findings

First Author, Publication Year Country	Main Study Findings	Authors' Conclusions
Brown et al. 2009 ³ United States	<p>VTE rates with ASA were not significantly different than the rates for VKA, LMWH, and pentasaccharides.³</p> <p>Relative risks of surgical site bleeding for VKA, LMWH, and pentasaccharides versus ASA were 4.9, 6.4, and 4.2, respectively.³</p>	<p>A pooled analysis of RCTs supports the use of ASA for VTEP after major orthopedic surgery.³</p>
Intermountain Joint Replacement Centre Writing Committee 2011 ⁴ United States	<p>The rate of symptomatic PE and VTE among standard-risk patients receiving ASA was greater than patients receiving warfarin (4.6% versus 0.7% and 7.9% versus 1.2%, respectively.⁴</p> <p>TKA Standard risk ASA versus warfarin OR: 4.97 p=0.03 for PE OR: 7.12, p=0.004 for DVT OR: 6.28, p<0.001 for VTE</p> <p>THA Standard risk ASA versus warfarin OR NR for PE, DVT or VTE</p>	<p>Patients with total joint arthroplasty at standard risk for PE receiving ASA had a higher rate of symptomatic PE and DVT than those receiving anticoagulation.⁴</p>
Bozic et al. 2010 ⁸ United States	<p>ASA: 2.3% had DVT or PE LMWH: 3.1% had DVT or PE Warfarin: 4.0% had DVT or PE (p=0.0037 for ASA versus LMWH; p<0.001 for ASA versus warfarin)</p> <p>ASA recipients had lower odds of VTE than warfarin [adjusted OR: 1.36 (95% CI 1.02, 1.82), p<0.01] but similar odds as injectable VTEP recipients [adjusted OR: 1.03 (95% CI 0.76, 1.39), NS].⁸</p> <p>No differences in risk of bleeding, infection or mortality were found.⁸</p>	<p>ASA, when used with other clinical care protocols, may be effective VTEP for certain TKA patients. "Given the observational retrospective design, our conclusions should be considered hypothesis generating rather than conclusive evidence of the comparative safety and efficacy of ASA for VTEP after TKA."(page 1059)⁸</p>

ASA: acetylsalicylic acid; CI: confidence interval; DVT: deep venous thrombosis; LMWH: low molecular weight heparin; NR: not reported; NS: not significant; OR: odds ratio; PE: pulmonary embolism; RCT: randomized controlled trial; TKA: total knee arthroplasty; VKA: vitamin K antagonist; VTEP: venous thromboembolism prophylaxis