AUSTRALIAN COMMISSION ON SAFETY AND QUALITY IN HEALTH CARE

Clinical Care Standards

Evidence Sources: Venous Thromboembolism Prevention Clinical Care Standard

October 2018

Published by the Australian Commission on Safety and Quality in Health Care
Level 5, 255 Elizabeth Street, Sydney NSW 2000

Phone: (02) 9126 3600
Fax: (02) 9126 3613

Email: mail@safetyandquality.gov.au
Website: www.safetyandquality.gov.au

ISBN: 978-1-925665-57-4

The Commission's preference is that you attribute this publication (and any material sourced from it) using the following citation:

> Australian Commission on Safety and Quality in Health Care. Evidence Sources: Venous Thromboembolism Prevention Clinical Care Standard. Sydney: ACSQHC; 2018

Acknowledgements

The Commission gratefully acknowledges the work of Dr Corinne Mirkazemi in preparing the *Rapid review: Aspirin for the primary prevention of venous thromboembolism following hip and knee replacement surgery* at Appendix 1 to this document.

Disclaimer

The Australian Commission on Safety and Quality in Health Care has produced this Evidence Sources document to support the Venous Thromboembolism Prevention Clinical Care Standard. The clinical care standard supports the delivery of appropriate care for a defined condition and is based on the best evidence available at the time of development. Healthcare professionals are advised to use clinical discretion and consideration of the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian when applying information contained within the clinical care standard. Consumers should use the information in the clinical care standard as a guide to inform discussions with their healthcare professional about the applicability of the clinical care standard to their individual condition.

Please note that there is the potential for minor revisions of this document.
Please check www.safetyandquality.gov.au for any amendments.

The Commission does not accept any legal liability for any injury, loss or damage incurred by the use of, or reliance on, this document.

Contents

Evidence Sources: Venous Thromboembolism Prevention Clinical Care Standard

The quality statements for the Venous Thromboembolism (VTE) Prevention Clinical Care Standard were developed in collaboration with the Venous Thromboembolism Prevention Clinical Care Standard Topic Working Group and are based on best available evidence.

Literature searches are conducted by staff of the Australian Commission on Safety and Quality in Health Care (the Commission) at different stages of the development of a clinical care standard. The initial search for this clinical care standard took place in August 2016. A draft evidence summary was prepared, which was reviewed for completeness by the VTE Clinical Care Standard Topic Working Group. Subsequent searches were conducted as the clinical care standard was developed.

The searches were aimed at identifying and reviewing the evidence base for each potential quality statement. Several steps were involved. The first step was to locate national clinical practice guidelines; if they were relevant, current, based on available evidence, developed using systematic methods and endorsed by relevant organisations, they would be the key sources of evidence. The second step was to locate other Australian guidelines, standards, policies, protocols, and international guidelines and standards. The third step was to identify high-level evidence published after the release of the key clinical practice guidelines.

Australian clinical practice guidelines, standards and policies were identified by searching:

- The clinical practice guideline portal of the National Health and Medical Research Council (NHMRC)
- Websites of professional colleges and organisations
- Websites of state and territory health departments and agencies
- The internet, through search engines.

International clinical practice guidelines were identified by searching:

- Guideline clearing houses such as the Agency for Healthcare Research and Quality (AHRQ), and the Guidelines International Network (GIN)
- Websites of guideline developers, such as the UK's National Institute for Health and Care Excellence (NICE) , the Scottish Intercollegiate Guideline Network (SIGN)
- Medical literature databases (such as Medline and Embase).

Other high-level evidence was identified by searching:

- The Cochrane Collaboration for systematic literature reviews and meta-analyses
- Medical literature databases (such as Medline and Embase) for systematic reviews and meta-analyses.

A summary of evidence sources for each draft quality statement is attached. Pages 6-13 identify a high-level summary of all sources used across quality statements. Pages 14-31 provide more granular information for each quality statement, including page references for sources.

Evidence sources for each quality statement at a glance

Reference	QS1	QS2	QS3	QS4	QS5	QS6	QS7
Australian guidelines							
Cardiology Expert Group. Therapeutic Guidelines: Cardiovascular version 6. Melbourne: Therapeutic Guidelines Limited; 2012. Available from https://www.tg.org.au/	✓	✓	✓		✓		✓
Queensland Health. Venous thromboembolism (VTE) prophylaxis in pregnancy and the puerperium. Queensland Clinical Guidelines; 2014. Available from https://www.health.qld.gov.au/__data/assets/pdf_file/0011/140024/g-vte.pdf	✓	✓	✓	✓	✓	✓	✓
International guidelines							
American Academy of Orthopaedic Surgeons. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. Evidence-based guideline and evidence report. Rosemont, IL: AAOS; 2011. Available from: http://www.orthoguidelines.org/topic?id=1006	✓	✓			✓		
Qaseem A, Chou R, Humphrey LL, Starkey M, Shekelle P. Venous thromboembolism prophylaxis in hospitalised patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2011; 155:625-632. Available from: http://annals.org/aim/article/1033137/venous-thromboembolism-prophylaxis-hospitalized-patients-clinical-practice-guideline-from-american	✓	✓			✓		
Guyatt GH, Elie AA, Crowther M, Gutterman DD, Shunemann HJ. Antithrombotic therapy and prevention of thrombosis 9th edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Chest 2012; 141(2)(Suppl):7S-47S. Available from: http://journal.publications.chestnet.org/issue.aspx?issueid=23443	✓	✓			✓		
Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopaedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: 6 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2_suppl):e278S-e325S. Available from: http://journal.chestnet.org/article/S0012-3692(12)60126-3/pdf	✓	✓					

Reference	QS1	QS2	QS3	QS4	QS5	QS6	QS7
Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in Nonorthopedic Surgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e227S-e77S. Available from: http://journal.chestnet.org/article/S0012-3692(12)60125-1/pdf	✓	✓					
Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al. Prevention of VTE in Nonsurgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e195S-e226S. Available from http://journal.chestnet.org/article/S0012-3692(12)60124-X/pdf	✓	✓					
Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline Update 2014. J Clin Oncol. 2015 20;33(6):654-6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25605844	✓	✓			✓		
European Society of Anaesthesiology. Guidelines on perioperative venous thromboembolism prophylaxis. ESA; 2018. Available from: https://www.esahq.org/about-us/the-esa/esa-news/2017/2017-11-09-guidelines/	✓	✓					
International Angiology. Prevention and treatment of venous thromboembolism: International Consensus Statement. The Journal of Vascular Biology, Medicine, Surgery and Phlebology. April 2013;32(2). Available from: http://europeanvenousforum.org/wp-content/uploads/2015/02/IUA_Guidelines_2013.pdf	✓	✓			✓	✓	✓
National Institute for Health and Care Excellence. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NG 89. London: NICE; 2018; Available from: https://www.nice.org.uk/guidance/ng89	✓	✓	✓		✓	✓	✓
National Institute for Health and Care Excellence. Venous thromboembolism in adults: reducing the risk in hospital. QS3. London: NICE; 2010 (updated 2018); Available from: https://www.nice.org.uk/guidance/qs3	✓	✓	✓		✓	✓	✓
Royal College of Obstetricians and Gyneacologists. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-top Guideline No. 37a. London: RCOG; 2015. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf	✓	✓	✓		✓	✓	✓

Reference	QS1	QS2	QS3	QS4	QS5	QS6	QS7
Scottish Intercollegiate Guidelines Network. Prevention and management of venous thromboembolism. Pub. No. 122 Edinburgh: SIGN; 2010 (updated October 2014). Available from: http://www.sign.ac.uk/assets/sign122.pdf	✓	✓	✓		✓	✓	✓
Additional sources							
Australian Commission on Safety and Quality in Health Care, New South Wales Therapeutic Advisory Group Inc. National Quality Use of Medicines indicators for Australian hospitals. Sydney: ACSQHC; 2014. Available from: http://www.ciap.health.nsw.gov.au/nswtag/pages/indicators.html	✓	✓		✓			
Australian Commission on Safety and Quality in Health Care. National Safety and Quality Health Service Standards. 2nd ed. Sydney 2017: https://www.safetyandquality.gov.au/our-work/assessment-to-the-nsqhs-standards/nsqhs-standards-second-edition/ (accessed February 2018).			✓				
Australian Commission on Safety and Quality in Health Care. Medication Safety. 2018 [cited Jul 2018]; Available from: https://www.safetyandquality.gov.au/our-work/medication-safety/.	✓			✓	✓		
Australian Commission on Safety and Quality in Health Care (2017). Top tips for safe health care. ACSQHC. Available from: https://www.safetyandquality.gov.au/publications/top-tips-for-safer-health-care/							✓
Australian Commission on Safety and Quality in Health Care 2012. Accreditation outcome results and evidence of implementation of the National Safety and Quality Health Service (NSQHS) Standards. ACSQHC: Sydney. Available from: https://safetyandquality.gov.au/wp-content/uploads/2012/03/Accreditation-outcome-results-and-evidence-of-implementation.pdf							✓
Australian Commission on Safety and Quality in Health Care. Health literacy: Taking action to improve safety and quality. Sydney: ACSQHC; 2014 [cited January 2018]; Available from: https://www.safetyandquality.gov.au/publications/health-literacy-taking-action-to-improve-safety-and-quality/.					✓		
Australian Medicines Handbook 2018 (online). Adelaide: Australian Medicines Handbook Pty Ltd; 2018; July; Available from: https://amhonline.amh.net.au/	✓	✓			✓		

Reference	QS1	QS2	QS3	QS4	QS5	QS6	QS7
The Arthroplasty Society of Australia on behalf of the Australian Orthopaedic Association. Guidelines for VTE prophylaxis for hip and knee arthroplasty. AOA; 2016; Available from: https://www.aoa.org.au/docs/default-source/advocacy/asa-guidelines-for-vte-prophylaxis-for-hip-and-knee-arthroplasty-february-2018.pdf?sfvrsn=7555c604_2	✓						
Buckinghamshire Healthcare NHS Trust/Aylesbury Vale and Chiltern Clinical Commissioning Groups. Guideline 295FM.2 Dabigatran, rivaroxaban, apixaban and endoxaban for deep vein thrombosis and pulmonary embolism - amber initiation guide V2. Buckinghamshire Healthcare: NHS Trust; 2014 (updated 2016). Available from: http://www.bucksformulary.nhs.uk/docs/Guideline_295FM.pdf.							✓
Clinical Excellence Commission. Framework for the prevention of venous thromboembolism. Medication Safety and Quality VTE Prevention Centre. Sydney: CEC, 2014. Available from: http://cec.health.nsw.gov.au/__data/assets/pdf_file/0009/259506/framework_prevention_of_vte.pdf	✓	✓	✓	✓	✓	✓	✓
Clinical Excellence Commission. Adult Venous Thromboembolism (VTE) Risk Assessment Tool. [cited January 2017]; Available from: http://cec.health.nsw.gov.au/__data/assets/pdf_file/0009/259515/adult_vte_risk_assessment_tool.pdf	✓						
Clinical Excellence Commission. NSW Maternity Venous Thromboembolism Risk Assessment Tool. [cited July 2017]; Available from: http://cec.health.nsw.gov.au/__data/assets/pdf_file/0006/362166/Maternity-Venous-Thromboembolism-VTE-Risk-Assessment-Tool-NH700088.pdf	✓						
Institute for Safe Medication Practices. ISMP Medication safety self-assessment for antithrombotic therapy. Philadelphia: ISMP; 2017. Available from http://www.ismp.org/selfassessments/Antithrombotic/2017/2017_ISMP_Antithrombotic_Self_Assessment.pdf			✓	✓	✓		✓
The Joint Commission. Discharge instructions/education materials for venous thromboembolism (VTE): a comprehensive approach to medication management compendium of resources. USA [cited July 2017]. Available from: https://www.jointcommission.org/discharge_instructions_for_venous_thromboembolism_vte/.			✓		✓		✓
Maynard G. Preventing hospital-associated venous thromboembolism: a guide for effective quality improvement, 2nd ed. Rockville, MD: Agency for Healthcare Research and Quality; August 2016. ARHQ Publication No. 16-0001-EF. Available from: http://www.ahrq.gov/professionals/quality-patient-safety/patient-safety-resources/resources/vtguide/index.html	✓	✓			✓	✓	

Reference	QS1	QS2	QS3	QS4	QS5	QS6	QS7
National Health and Medical Research Council. Stop the Clot: Reducing the risk of blood clots in your legs and lungs. National Health and Medical Research Council; 2014 [cited June 2017]; Available from: https://www.nhmrc.gov.au/guidelines-publications/cp134a.			✓				
National Institute for Health and Care Excellence. Department of Health VTE risk assessment tool. UK Department of Health; 2018; Available from: https://www.nice.org.uk/guidance/ng89/resources/department-of-health-vte-risk-assessment-tool-pdf-4787149213	✓						
National Institute for Health and Care Excellence. The Royal Collge of Obstetrics and Gynaecologists VTE risk assessment tool. 2018; Available from: https://www.nice.org.uk/guidance/ng89/resources/royal-college-of-obstetricians-and-gynaecologists-risk-assessment-tool-pdf-4787150509	✓						
NSW Ministry of Health. Policy Directive: Prevention of venous thromboembolism. Sydney: NSW Ministry of Health; 2014. Available from: http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2014_032.pdf	✓	✓	✓	✓	✓	✓	✓
NSW Therapeutic Advisory Group. Safe use of heparins and oral anticoagulants for venous thromboembolism prophylaxis in adults. Position statement NSW TAG. 2008 (updated August 2010). Available from: http://www.ciap.health.nsw.gov.au/nswtag/documents/publications/position-statements/heparin-vte-aug-2010.pdf	✓	✓			✓	✓	
NSW Ministry of Health. High-risk medicines management policy. Sydney: NSW Ministry of Health; 2015; Available from: http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2015_029.pdf					✓		
New Zealand Venous Thromboembolism Prevention. National policy framework: VTE prevention in adult hospital patients in NZ. NZVTEP; 2012. Available from https://www.hqsc.govt.nz/assets/Other-Topics/QS-challenge-reports/VTE-Prevention-programme-National-Policy-Framework.pdf	✓	✓	✓	✓	✓	✓	✓
Queensland Government Department of Health. Patient Safety Notice: Anticoagulation management. Patient Safety and Quality Improvement Service, Queensland Government Department of Health; 2017.	✓	✓	✓		✓		✓
Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003;107(23 Suppl 1):I9-16. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12814980	✓						
Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction	✓						

Reference	QS1	QS2	QS3	QS4	QS5	QS6	QS7
Score. J Thromb Haemost. 2010;8(11):2450-7. Available from https://www.ncbi.nlm.nih.gov/pubmed/20738765							
Chapman N, Brighton T, Harris M, Caplan G, Braithwaite J, Chong B. Venous thromboembolism Management in general practice. Aust Fam Physician. 2009;38:36-40. Available from: https://www.racgp.org.au/afp/2009/januaryfebruary/venous-thromboembolism/			✓				
Edmonds MJ, Crichton TJ, Runciman WB, Pradhan M. Evidence-based risk factors for postoperative deep vein thrombosis. ANZ journal of surgery. 2004;74(12):1082-97. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15574153	✓						
Geerts W. Prevention of venous thromboembolism: a key patient safety priority. J Thromb Haemost. 2009;1:1-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19630756					✓		
Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Arch Intern Med. 2002;162(11):1245-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12038942	✓						
Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon W, Melton L, et al. Risk factors for deep vein thrombosis and pulmonary embolism: A population-based case-control study. Arch Internal Med. 2000;160(6):809-15. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10737280	✓						
Heit JA, Melton LJ, III, Lohse CM, Petterson TM, Silverstein MD, Mohr DN, et al. Incidence of Venous Thromboembolism in Hospitalized Patients vs Community Residents. Mayo Clin Proc. 2001;76(11):1102-10. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11702898			✓				
Huang W, Anderson FA, Spencer FA, Gallus A, Goldberg RJ. Risk-assessment models for predicting venous thromboembolism among hospitalized non-surgical patients: a systematic review. J Thromb Thrombolysis. 2013;35(1):67-80. Epub 2012/07/25. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22826096	✓						
Horwitz LI. Self-care after hospital discharge: knowledge is not enough. BMJ Quality & Safety. 2016;26(1):7. Available from: http://qualitysafety.bmj.com/content/26/1/7.info							✓
Kahn SR, Morrison DR, Diendéré G, Piché A, Filion KB, Klil-Drori AJ, et al. Interventions for implementation of thromboprophylaxis in hospitalized medical and surgical patients at risk for venous thromboembolism. Cochrane Database Syst Rev. 2018(4). Available from: http://cochranelibrary-	✓						

Reference	QS1	QS2	QS3	QS4	QS5	QS6	QS7
wiley.com/doi/10.1002/14651858.CD008201.pub3/full							
Kucher N, Koo S, Quiroz R, Cooper JM, Paterno MD, Soukonnikov B, et al. Electronic Alerts to Prevent Venous Thromboembolism among Hospitalized Patients. N Engl J Med. 2005;352(10):969-77. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa041533	✓						
MacLean S, Mulla S, Akl EA, Jankowski M, Vandvik PO, Ebrahim S, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e1S-e23S. Epub 2012/02/15. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22315262					✓		
Maynard G, Jenkins IH, Merli GJ. Venous thromboembolism prevention guidelines for medical inpatients: mind the (implementation) gap. J Hosp Med. 2013;8(10):582-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23983041	✓						
Padron M, Miyares MA, Ferrell KW, Hill AM. Development of an Anticoagulation Stewardship Program at a Large Tertiary Care Academic Institution. Journal of Pharmacy Practice. 2013;28(1):93-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24326411					✓		
Parvizi J, Huang R, Rezapoor M, Bagheri B, Maltenfort MG. Individualized Risk Model for Venous Thromboembolism After Total Joint Arthroplasty. The Journal of Arthroplasty.31(9):180-6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27094244	✓						
Pedersen AB, Sorensen HT, Mehnert F, Overgaard S, Johnsen SP. Risk Factors for Venous Thromboembolism in Patients Undergoing Total Hip Replacement and Receiving Routine Thromboprophylaxis. JBJS. 2010;92(12):2156-64. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20844157 (accessed July 2017).	✓						
Rogers SO, Jr., Kilaru RK, Hosokawa P, Henderson WG, Zinner MJ, Khuri SF. Multivariable predictors of postoperative venous thromboembolic events after general and vascular surgery: results from the patient safety in surgery study. J Am Coll Surg. 2007;204(6):1211-21. Epub 2007/06/05. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17544079	✓						
Spyropoulos AC, Anderson FA, FitzGerald G, Decousus H, Pini M, Chong BH, et al. Predictive and Associative Models to Identify Hospitalized Medical Patients at Risk for VTE. Chest. 2011;140(3):706-14.	✓						

Reference	QS1	QS2	QS3	QS4	QS5	QS6	QS7
Available from: https://www.ncbi.nlm.nih.gov/pubmed/21436241							
Stuck AK, Spirk D, Schaudt J, Kucher N. Risk assessment models for venous thromboembolism in acutely ill medical patients. A systematic review. Thromb Haemost. 2017;117(4):801-8. Epub 2017/02/06. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28150851	✓						
Therapeutic Goods Administration. Department of Health. Apixaban (Eliquis), dabigatran (Pradaxa) and rivaroxaban (Xarelto): Information for health professionals. 2015 [cited Jul 2017]; Available from: https://www.tga.gov.au/alert/apixaban-eliquis-dabigatran-pradaxa-and-rivaroxaban-xarelto-information-health-professionals.					✓		
Therapeutic Goods Administration. Department of Health. Dabigatran (Pradaxa) and risk of bleeding: information for health professionals. 2013 [cited Jul 2017]; Available from: https://www.tga.gov.au/alert/dabigatran-pradaxa-and-risk-bleeding-information-health-professionals.					✓		
The Stroke Foundation. Clinical guidelines for stroke prevention and management. The Stroke Foundation; 2017; Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1538-7836.2010.04044.x.	✓						
T Rocha A, F Paiva E, Lichtenstein A, Milani R, Cavalheiro-Filho C, H Maffei F. Risk-assessment algorithm and recommendations for venous thromboembolism prophylaxis in medical patients. Vascular Health and Risk Management. 2007;3(4):533-53. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17969384	✓						
Tooher R, Middleton P, Pham C, Fitridge R, Rowe S, Babidge W, et al. A Systematic Review of Strategies to Improve Prophylaxis for Venous Thromboembolism in Hospitals. Annals of Surgery. 2005;241(3):397-415. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15729062	✓						
Woller SC, Stevens SM, Jones JP, Lloyd JF, Evans RS, Aston VT, et al. Derivation and validation of a simple model to identify venous thromboembolism risk in medical patients. Am J Med. 2011;124(10):947-54.e2. Epub 2011/10/04. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21962315	✓						

Quality statement 1

Assess and document VTE risk

A patient potentially at risk of VTE (as determined by local hospital/unit policy) receives a timely assessment of VTE risk using a locally endorsed evidence-based tool to determine their need for VTE prevention. The result is documented at the time of the assessment, in a place that is easily accessible to all clinicians involved in the patient's care.

Evidence sources

Australian guidelines

Cardiology Expert Group. Therapeutic Guidelines: Cardiovascular version 6. Melbourne: Therapeutic Guidelines Limited; 2012: p.2. Available from https://www.tg.org.au/ (accessed July 2017).

Queensland Health. Venous thromboembolism (VTE) prophylaxis in pregnancy and the puerperium. Queensland Clinical Guidelines; 2014: pp.9,10. Available from https://www.health.qld.gov.au/__data/assets/pdf_file/0011/140024/g-vte.pdf (accessed July 2017).

International guidelines

American Academy of Orthopaedic Surgeons. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. Evidence-based guideline and evidence report. Rosemont, IL: AAOS; 2011: pp.49-60. Available from: http://www.orthoguidelines.org/topic?id=1006 (accessed July 2017).

Qaseem A, Chou R, Humphrey LL, Starkey M, Shekelle P. Venous thromboembolism prophylaxis in hospitalised patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2011; 155:625-632: p.625. Available from: http://annals.org/aim/article/1033137/venous-thromboembolism-prophylaxis-hospitalized-patients-clinical-practice-guideline-from-american (accessed July 2017).

Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuunemann HJ. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl). Availabel from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278060/ (accessed July 2017).

Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2_suppl): e278S-e325S: pp.e283S-e284S. Available from: http://journal.chestnet.org/article/S0012-3692(12)60126-3/pdf (accessed July 2017).

Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in Nonorthopedic Surgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e227S-e277S. Available from: http://journal.chestnet.org/article/S0012-3692(12)60125-1/pdf (accessed July 2017).

Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al. Prevention of VTE in Nonsurgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest.

2012;141(2 Suppl):e195S-e226S: pp.199S-200S. Available from http://journal.chestnet.org/article/S0012-3692(12)60124-X/pdf (accessed January 2017).

Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline Update 2014. J Clin Oncol. 2015 20;33(6):654-6: p.655. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25605844 (accessed July 2017).

European Society of Anaesthesiology. Guidelines on perioperative venous thromboembolism prophylaxis. ESA; 2018. Available from: https://www.esahq.org/about-us/the-esa/esa-news/2017/2017-11-09-guidelines/ (accessed February 2018).

International Angiology. Prevention and treatment of venous thromboembolism: International Consensus Statement. The Journal of Vascular Biology, Medicine, Surgery and Phlebology. April 2013;32(2): pp.117,136,174. Available from: http://europeanvenousforum.org/wp-content/uploads/2015/02/IUA_Guidelines_2013.pdf (accessed July 2017).

National Institute for Health and Care Excellence. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NG 89. London: NICE; 2018; Available from: https://www.nice.org.uk/guidance/ng89 (accessed March 2018).

National Institute for Health and Care Excellence. Venous thromboembolism in adults: reducing the risk in hospital. QS3. London: NICE; 2010 (updated 2018); p7. Available from: https://www.nice.org.uk/guidance/qs3 (accessed March 2018).

Royal College of Obstetricians and Gynaecologists. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-top Guideline No. 37a. London: RCOG; 2015: pp.2,8. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf (accessed July 2017).

Scottish Intercollegiate Guidelines Network. Prevention and management of venous thromboembolism. Pub. No. 122 Edinburgh: SIGN; 2010 (updated October 2014): pp.4, 7, 9, 33. Available from: http://www.sign.ac.uk/assets/sign122.pdf (accessed July 2017).

Additional sources

Australian Commission on Safety and Quality in Health Care, New South Wales Therapeutic Advisory Group Inc. National Quality Use of Medicines indicators for Australian hospitals. Sydney: ACSQHC; 2014: pp.24-25. Available from: http://www.ciap.health.nsw.gov.au/nswtag/pages/indicators.html (accessed January 2017).

Australian Commission on Safety and Quality in Health Care. Medication Safety. 2018 [cited Jul 2018]; Available from: https://www.safetyandquality.gov.au/our-work/medication-safety/. (accessed July 2018).

Australian Medicines Handbook 2018 (online). Adelaide: Australian Medicines Handbook Pty Ltd; 2018; July; Available from: https://amhonline.amh.net.au/. (accessed July 2018).

The Arthroplasty Society of Australia on behalf of the Australian Orthopaedic Association. Guidelines for VTE prophylaxis for hip and knee arthroplasty. AOA; 2016; Available from: https://www.aoa.org.au/docs/default-source/advocacy/asa-guidelines-for-vte-prophylaxis-for-hip-and-knee-arthroplasty-february-2018.pdf?sfvrsn=7555c604_2 (accessed February 2018).

Clinical Excellence Commission. Framework for the prevention of venous thromboembolism. Medication Safety and Quality VTE Prevention Centre. Sydney: CEC, 2014. Available from: http://cec.health.nsw.gov.au/__data/assets/pdf_file/0009/259506/framework_prevention_of_vte.pdf (accessed July 2017).

Clinical Excellence Commission. Adult Venous Thromboembolism (VTE) Risk Assessment Tool. [cited January 2017]; Available from: http://cec.health.nsw.gov.au/__data/assets/pdf_file/0009/259515/adult_vte_risk_assessment_tool.pdf

Clinical Excellence Commission. NSW Maternity Venous Thromboembolism Risk Assessment Tool. [cited July 2017]; Available from: http://cec.health.nsw.gov.au/__data/assets/pdf_file/0006/362166/Maternity-Venous-Thromboembolism-VTE-Risk-Assessment-Tool-NH700088.pdf

Maynard G. Preventing hospital-associated venous thromboembolism: a guide for effective quality improvement, 2nd ed. Rockville, MD: Agency for Healthcare Research and Quality; August 2016. ARHQ Publication No. 16-0001-EF: Available from: http://www.ahrq.gov/professionals/quality-patient-safety/patient-safety-resources/resources/vtguide/index.html (accessed July 2017).

National Institute for Health and Care Excellence. Department of Health VTE risk assessment tool. UK Department of Health; 2018; Available from: https://www.nice.org.uk/guidance/ng89/resources/department-of-health-vte-risk-assessment-tool-pdf-4787149213 (accessed July 2018).

National Institute for Health and Care Excellence. The Royal College of Obstetrics and Gynaecologists VTE risk assessment tool. 2018; Available from: https://www.nice.org.uk/guidance/ng89/resources/royal-college-of-obstetricians-and-gynaecologists-risk-assessment-tool-pdf-4787150509. (accessed July 2018).

NSW Ministry of Health. Policy Directive: Prevention of venous thromboembolism. Sydney: NSW Ministry of Health; 2014: pp.4-6,10-11,13,14. Available from: http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2014_032.pdf (accessed July 2017).

NSW Therapeutic Advisory Group. Safe use of heparins and oral anticoagulants for venous thromboembolism prophylaxis in adults. Position statement NSW TAG. 2008 (updated August 2010): p.4. Available from: http://www.ciap.health.nsw.gov.au/nswtag/documents/publications/position-statements/heparin-vte-aug-2010.pdf (accessed July 2017).

New Zealand Venous Thromboembolism Prevention. National policy framework: VTE prevention in adult hospital patients in NZ. NZVTEP; 2012. Available from https://www.hqsc.govt.nz/assets/Other-Topics/QS-challenge-reports/VTE-Prevention-programme-National-Policy-Framework.pdf (accessed July 2017).

Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003;107(23 Suppl 1):I9-16. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12814980 (accessed July 2017).

Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost. 2010;8(11):2450-7. Available from https://www.ncbi.nlm.nih.gov/pubmed/20738765 (accessed February 2018).

Edmonds MJ, Crichton TJ, Runciman WB, Pradhan M. Evidence-based risk factors for postoperative deep vein thrombosis. ANZ Journal of Surgery. 2004;74(12):1082-97. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15574153 (accessed July 2017).

Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Arch Intern Med. 2002;162(11):1245-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12038942 (accessed July 2017).

Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon W, Melton L, et al. Risk factors for deep vein thrombosis and pulmonary embolism: A population-based case-control study. Arch Internal Med. 2000;160(6):809-15. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10737280 (accessed July 2017).

Huang W, Anderson FA, Spencer FA, Gallus A, Goldberg RJ. Risk-assessment models for predicting venous thromboembolism among hospitalized non-surgical patients: a systematic review. J Thromb Thrombolysis. 2013;35(1):67-80. Epub 2012/07/25. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22826096 (accessed Februart 2018).

Kahn SR, Morrison DR, Diendéré G, Piché A, Filion KB, Klil-Drori AJ, et al. Interventions for implementation of thromboprophylaxis in hospitalized medical and surgical patients at risk for venous thromboembolism. Cochrane Database Syst Rev. 2018(4). Available from: http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD008201.pub3/full (accessed June 2018).

Kucher N, Koo S, Quiroz R, Cooper JM, Paterno MD, Soukonnikov B, et al. Electronic Alerts to Prevent Venous Thromboembolism among Hospitalized Patients. N Engl J Med. 2005;352(10):969-77. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa041533 (accessed Feburary 2018).

Maynard G, Jenkins IH, Merli GJ. Venous thromboembolism prevention guidelines for medical inpatients: mind the (implementation) gap. J Hosp Med. 2013;8(10):582-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23983041 (accessed July 2017).

Parvizi J, Huang R, Rezapoor M, Bagheri B, Maltenfort MG. Individualized Risk Model for Venous Thromboembolism After Total Joint Arthroplasty. The Journal of Arthroplasty.31(9):180-6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27094244 (accessed July 2017).

Pedersen AB, Sorensen HT, Mehnert F, Overgaard S, Johnsen SP. Risk Factors for Venous Thromboembolism in Patients Undergoing Total Hip Replacement and Receiving Routine Thromboprophylaxis. JBJS. 2010;92(12):2156-64. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20844157 (accessed July 2017).

Queensland Government Department of Health. Patient Safety Notice: Anticoagulation management. Patient Safety and Quality Improvement Service, Queensland Government Department of Health; 2017.

Rogers SO, Jr., Kilaru RK, Hosokawa P, Henderson WG, Zinner MJ, Khuri SF. Multivariable predictors of postoperative venous thromboembolic events after general and vascular surgery: results from the patient safety in surgery study. J Am Coll Surg. 2007;204(6):1211-21. Epub 2007/06/05. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17544079 (accessed February 2018).

Spyropoulos AC, Anderson FA, FitzGerald G, Decousus H, Pini M, Chong BH, et al. Predictive and Associative Models to Identify Hospitalized Medical Patients at Risk for VTE. Chest. 2011;140(3):706-14. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21436241 (accessed February 2018).

Stuck AK, Spirk D, Schaudt J, Kucher N. Risk assessment models for venous thromboembolism in acutely ill medical patients. A systematic review. Thromb Haemost. 2017;117(4):801-8. Epub 2017/02/06. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28150851 (accessed February 2018).

The Stroke Foundation. Clinical guidelines for stroke prevention and management. The Stroke Foundation; 2017; Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1538-7836.2010.04044.x. (accessed February 2018).

T Rocha A, F Paiva E, Lichtenstein A, Milani R, Cavalheiro-Filho C, H Maffei F. Risk-assessment algorithm and recommendations for venous thromboembolism prophylaxis in medical patients. Vascular Health and Risk Management. 2007;3(4):533-53. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17969384 (accessed July 2017).

Tooher R, Middleton P, Pham C, Fitridge R, Rowe S, Babidge W, et al. A Systematic Review of Strategies to Improve Prophylaxis for Venous Thromboembolism in Hospitals. Annals of Surgery. 2005;241(3):397-415. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15729062 (accessed July 2017).

Woller SC, Stevens SM, Jones JP, Lloyd JF, Evans RS, Aston VT, et al. Derivation and validation of a simple model to identify venous thromboembolism risk in medical patients. Am J Med. 2011;124(10):947-54.e2. Epub 2011/10/04. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21962315 (accessed February 2018).

Quality statement 2

Develop a VTE prevention plan, balancing the risk of VTE against bleeding

A patient assessed to be at risk of VTE has a prevention plan developed that balances the risk of thrombosis against the risk and consequences of bleeding (as an adverse effect of VTE prevention medicines). Other contraindications to VTE prevention methods are also considered before offering any to the patient.

Evidence sources

Australian guidelines

Cardiology Expert Group. Therapeutic Guidelines: Cardiovascular version 6. Melbourne: Therapeutic Guidelines Limited; 2012: p.2. Available from https://www.tg.org.au/ (accessed July 2017).

Queensland Health. Venous thromboembolism (VTE) prophylaxis in pregnancy and the puerperium. Queensland Clinical Guidelines; 2014: p.9,10. Available from https://www.health.qld.gov.au/__data/assets/pdf_file/0011/140024/g-vte.pdf (accessed July 2017).

International guidelines

American Academy of Orthopaedic Surgeons. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. Evidence-based guideline and evidence report. Rosemont, IL: AAOS; 2011: pp.461-65. Available from: http://www.orthoguidelines.org/topic?id=1006 (accessed July 2017).

Qaseem A, Chou R, Humphrey LL, Starkey M, Shekelle P. Venous thromboembolism prophylaxis in hospitalised patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2011; 155:625-632: p.625. Available from: http://annals.org/aim/article/1033137/venous-thromboembolism-prophylaxis-hospitalized-patients-clinical-practice-guideline-from-american (accessed July 2017).

Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuunemann HJ. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl). Availabel from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278060/ (accessed July 2017).

Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of vte in orthopedic surgery patients: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2_suppl): e278S-e325S: pp.e283S-e284S. Available from: http://journal.chestnet.org/article/S0012-3692(12)60126-3/pdf (accessed July 2017).

Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in Nonorthopedic Surgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e227S-e277S. Available from: http://journal.chestnet.org/article/S0012-3692(12)60125-1/pdf (accessed July 2017).

Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al. Prevention of VTE in Nonsurgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest.

2012;141(2 Suppl):e195S-e226S: pp.199S-200S. Available from http://journal.chestnet.org/article/S0012-3692(12)60124-X/pdf (accessed January 2017).

Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline Update 2014. J Clin Oncol. 2015 20;33(6):654-6: p.655. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25605844 (accessed July 2017).

European Society of Anaesthesiology. Guidelines on perioperative venous thromboembolism prophylaxis. ESA; 2018. Available from: https://www.esahq.org/about-us/the-esa/esa-news/2017/2017-11-09-guidelines/ (accessed February 2018).

International Angiology. Prevention and treatment of venous thromboembolism: International Consensus Statement. The Journal of Vascular Biology, Medicine, Surgery and Phlebology. April 2013;32(2): pp.247-248 Available from: http://europeanvenousforum.org/wp-content/uploads/2015/02/IUA_Guidelines_2013.pdf (accessed July 2017).

National Institute for Health and Care Excellence. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NG 89. London: NICE; 2018; Available from: https://www.nice.org.uk/guidance/ng89 (accessed March 2018).

National Institute for Health and Care Excellence. Venous thromboembolism in adults: reducing the risk in hospital. QS3. London: NICE; 2010 (updated 2018); p7. Available from: https://www.nice.org.uk/guidance/qs3 (accessed March 2018).

Royal College of Obstetricians and Gynaecologists. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-top Guideline No. 37a. London: RCOG; 2015: pp.36. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf (accessed July 2017).

Scottish Intercollegiate Guidelines Network. Prevention and management of venous thromboembolism. Pub. No. 122 Edinburgh: SIGN; 2010 (updated October 2014): pp.4, 6, 9, 33, 57. Available from: http://www.sign.ac.uk/assets/sign122.pdf (accessed July 2017).

Additional sources

Australian Commission on Safety and Quality in Health Care, New South Wales Therapeutic Advisory Group Inc. National Quality Use of Medicines indicators for Australian hospitals. Sydney: ACSQHC; 2014: pp.24-25. Available from: http://www.ciap.health.nsw.gov.au/nswtag/pages/indicators.html (accessed January 2017).

Australian Medicines Handbook 2018 (online). Adelaide: Australian Medicines Handbook Pty Ltd; 2018; July; Available from: https://amhonline.amh.net.au/. (accessed July 2018).

Clinical Excellence Commission. Framework for the prevention of venous thromboembolism. Medication Safety and Quality VTE Prevention Centre. Sydney: CEC, 2014. Available from: http://cec.health.nsw.gov.au/__data/assets/pdf_file/0009/259506/framework_prevention_of_vte.pdf (accessed July 2017).

Maynard G. Preventing hospital-associated venous thromboembolism: a guide for effective quality improvement, 2nd ed. Rockville, MD: Agency for Healthcare Research and Quality; August 2016. ARHQ Publication No. 16-0001-EF: Chapter 4 pp:23-34. Available from: http://www.ahrq.gov/professionals/quality-patient-safety/patient-safety-resources/resources/vtguide/index.html (accessed July 2017).

NSW Ministry of Health. Policy Directive: Prevention of venous thromboembolism. Sydney: NSW Ministry of Health; 2014: pp.4-6. Available from:

http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2014_032.pdf (accessed July 2017).

NSW Therapeutic Advisory Group. Safe use of heparins and oral anticoagulants for venous thromboembolism prophylaxis in adults. Position statement NSW TAG. 2008 (updated August 2010): p.4, 9. Available from: http://www.ciap.health.nsw.gov.au/nswtag/documents/publications/position-statements/heparin-vte-aug-2010.pdf (accessed July 2017).

New Zealand Venous Thromboembolism Prevention. National policy framework: VTE prevention in adult hospital patients in NZ. NZVTEP; 2012. Available from https://www.hqsc.govt.nz/assets/Other-Topics/QS-challenge-reports/VTE-Prevention-programme-National-Policy-Framework.pdf (accessed July 2017).

Queensland Government Department of Health. Patient Safety Notice: Anticoagulation management. Patient Safety and Quality Improvement Service, Queensland Government Department of Health; 2017.

Quality statement 3

Inform and partner with patients

A patient at risk of VTE receives information and education about VTE and ways to prevent it tailored to their risks and needs, and shares in decisions regarding their VTE prevention plan.

Evidence sources

Australian guidelines

Cardiology Expert Group. Therapeutic Guidelines: Cardiovascular version 6. Melbourne: Therapeutic Guidelines Limited; 2012: p.10. Available from https://www.tg.org.au/ (accessed July 2017).

Queensland Health. Venous thromboembolism (VTE) prophylaxis in pregnancy and the puerperium. Queensland Clinical Guidelines; 2014: p.19. Available from https://www.health.qld.gov.au/__data/assets/pdf_file/0011/140024/g-vte.pdf (accessed July 2017).

International guidelines

National Institute for Health and Care Excellence. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NG 89. London: NICE; 2018; Available from: https://www.nice.org.uk/guidance/ng89 (accessed March 2018).

National Institute for Health and Care Excellence. Venous thromboembolism in adults: reducing the risk in hospital. QS3. London: NICE; 2010 (updated 2018); p.9, 17. Available from: https://www.nice.org.uk/guidance/qs3 (accessed March).

Royal College of Obstetricians and Gynaecologists. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-top Guideline No. 37a. London: RCOG; 2015: pp.2. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf (accessed July 2017).

Scottish Intercollegiate Guidelines Network. Prevention and management of venous thromboembolism. Pub. No. 122 Edinburgh: SIGN; 2010 (updated October 2014): pp. 9, 60. Available from: http://www.sign.ac.uk/assets/sign122.pdf (accessed July 2017).

Additional sources

Australian Commission on Safety and Quality in Health Care. National Safety and Quality Health Service Standards. 2nd ed. Sydney 2017: https://www.safetyandquality.gov.au/our-work/assessment-to-the-nsqhs-standards/nsqhs-standards-second-edition/ (accessed February 2018).

Clinical Excellence Commission. Framework for the prevention of venous thromboembolism. Medication Safety and Quality VTE Prevention Centre. Sydney: CEC, 2014. Available from: http://cec.health.nsw.gov.au/__data/assets/pdf_file/0009/259506/framework_prevention_of_vte.pdf (accessed July 2017).

Institute for Safe Medication Practices. ISMP Medication safety self-assessment for antithrombotic therapy. Philadelphia: ISMP; 2017: p.22 (Points 84-91,93-99,105). Available from

http://www.ismp.org/selfassessments/Antithrombotic/2017/2017_ISMP_Antithrombotic_Self_Assessment.pdf (accessed July 2017).

The Joint Commission. Discharge instructions/education materials for venous thromboembolism (VTE): a comprehensive approach to medication management compendium of resources. USA [cited July 2017]; Available from: https://www.jointcommission.org/discharge_instructions_for_venous_thromboembolism_vte/. (accessed July 2017).

National Health And Medical Research Council. Stop the Clot: Reducing the risk of blood clots in your legs and lungs. National Health and Medical Research Council; 2014 [cited June 2017]; Available from: https://www.nhmrc.gov.au/guidelines-publications/cp134a. (accessed July 2017).

NSW Ministry of Health. Policy Directive: Prevention of venous thromboembolism. Sydney: NSW Ministry of Health; 2014: pp.11, 12. Available from: http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2014_032.pdf (accessed July 2017).

New Zealand Venous Thromboembolism Prevention. National policy framework: VTE prevention in adult hospital patients in NZ. NZVTEP; 2012. Available from https://www.hqsc.govt.nz/assets/Other-Topics/QS-challenge-reports/VTE-Prevention-programme-National-Policy-Framework.pdf (accessed July 2017).

Queensland Government Department of Health. Patient Safety Notice: Anticoagulation management. Patient Safety and Quality Improvement Service, Queensland Government Department of Health; 2017.

Chapman N, Brighton T, Harris M, Caplan G, Braithwaite J, Chong B. Venous thromboembolism Management in general practice. Aust Fam Physician. 2009;38:36-40. Available from: https://www.racgp.org.au/afp/2009/januaryfebruary/venous-thromboembolism/ (accessed July 2017).

Heit JA, Melton LJ, III, Lohse CM, Petterson TM, Silverstein MD, Mohr DN, et al. Incidence of Venous Thromboembolism in Hospitalized Patients vs Community Residents. Mayo Clin Proc. 2001;76(11):1102-10. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11702898 (accessed July 2017).

Quality statement 4

Document and communicate the VTE prevention plan

A patient's VTE prevention plan is documented and communicated to all clinicians involved in their care.

Evidence sources

Australian guidelines

Queensland Health. Venous thromboembolism (VTE) prophylaxis in pregnancy and the puerperium. Queensland Clinical Guidelines; 2014: p.9. Available from https://www.health.qld.gov.au/__data/assets/pdf_file/0011/140024/g-vte.pdf (accessed July 2017).

Additional sources

Australian Commission on Safety and Quality in Health Care, New South Wales Therapeutic Advisory Group Inc. National Quality Use of Medicines indicators for Australian hospitals. Sydney: ACSQHC; 2014: pp.24-25. Available from: http://www.ciap.health.nsw.gov.au/nswtag/pages/indicators.html (accessed January 2017).

Australian Commission on Safety and Quality in Health Care. Medication Safety. 2018 [cited Jul 2018]; Available from: https://www.safetyandquality.gov.au/our-work/medication-safety/. (accessed July 2018).

Clinical Excellence Commission. Framework for the prevention of venous thromboembolism. Medication Safety and Quality VTE Prevention Centre. Sydney: CEC, 2014. Available from: http://cec.health.nsw.gov.au/__data/assets/pdf_file/0009/259506/framework_prevention_of_vte.pdf (accessed July 2017).

Institute for Safe Medication Practices. ISMP Medication safety self-assessment for antithrombotic therapy. Philadelphia: ISMP; 2017: p.13 (point 19). Available from http://www.ismp.org/selfassessments/Antithrombotic/2017/2017_ISMP_Antithrombotic_Self_Assessment.pdf (accessed July 2017).

NSW Ministry of Health. Policy Directive: Prevention of venous thromboembolism. Sydney: NSW Ministry of Health; 2014: pp.6, 10, 11. Available from: http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2014_032.pdf (accessed July 2017).

New Zealand Venous Thromboembolism Prevention. National policy framework: VTE prevention in adult hospital patients in NZ. NZVTEP; 2012: pp.9,10. Available from https://www.hqsc.govt.nz/assets/Other-Topics/QS-challenge-reports/VTE-Prevention-programme-National-Policy-Framework.pdf (accessed July 2017).

Quality statement 5

Use appropriate VTE prevention methods

A patient requiring a VTE prevention plan is offered medicines and/or mechanical methods of VTE prevention according to a current, locally endorsed, evidence-based guideline taking into consideration the patient's clinical condition and their preferences.

Evidence sources

The Commission acknowledges that guidelines differ regarding whether or not aspirin is recommended for the prevention of VTE in patients having orthopaedic surgery of the hip or knee. As such, a rapid review of the evidence has been conducted regarding whether aspirin is superior to other antithrombotic agents for the prevention of VTE in these patients. This review is at Appendix 1.

Australian guidelines

Cardiology Expert Group. Therapeutic Guidelines: Cardiovascular version 6. Melbourne: Therapeutic Guidelines Limited; 2012: p.2-3. Available from https://www.tg.org.au/ (accessed July 2017).

Queensland Health. Venous thromboembolism (VTE) prophylaxis in pregnancy and the puerperium. Queensland Clinical Guidelines; 2014: p.13. Available from https://www.health.qld.gov.au/__data/assets/pdf_file/0011/140024/g-vte.pdf (accessed July 2017).

International guidelines

American Academy of Orthopaedic Surgeons. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. Evidence-based guideline and evidence report. Second edition. Rosemount: AAOS; 2011: pp.y, vii. Available from: http://www.aaos.org/research/guidelines/VTE/VTE_full_guideline.pdf (accessed July 2017).

Qaseem A, Chou R, Humphrey LL, Starkey M, Shekelle P. Venous thromboembolism prophylaxis in hospitalised patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2011; 155:625-632: p.625. Available from: http://annals.org/aim/article/1033137/venous-thromboembolism-prophylaxis-hospitalized-patients-clinical-practice-guideline-from-american (accessed July 2017).

Guyatt GH, Elie AA, Crowther M, Gutterman DD, Shunemann HJ. Antithrombotic therapy and prevention of thrombosis 9th edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Chest 2012; 141(2)(Suppl):7S-47S: pp.13S, 14S. Available from: http://journal.publications.chestnet.org/issue.aspx?issueid=23443 (accessed July 2017).

Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline Update 2014. J Clin Oncol. 2015 20;33(6):654-6: p.655. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25605844 (accessed July 2017).

International Angiology. Prevention and treatment of venous thromboembolism: International Consensus Statement. The Journal of Vascular Biology, Medicine, Surgery and Phlebology. April 2013;32(2): pp.123,137,148,150. Available from: http://europeanvenousforum.org/wp-content/uploads/2015/02/IUA_Guidelines_2013.pdf (accessed July 2017).

National Institute for Health and Care Excellence. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NG 89. London: NICE; 2018; Available from: https://www.nice.org.uk/guidance/ng89 (accessed March 2018).

National Institute for Health and Care Excellence. Venous thromboembolism in adults: reducing the risk in hospital. QS3. London: NICE; 2010 (updated 2018); p.11,15. Available from: https://www.nice.org.uk/guidance/qs3 (accessed March 2018).

Royal College of Obstetricians and Gyneacologists. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-top Guideline No. 37a. London: RCOG; 2015: p.8. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf (accessed July 2017).

Scottish Intercollegiate Guidelines Network. Prevention and management of venous thromboembolism. Pub. No. 122 Edinburgh: SIGN; 2010 (updated October 2014): pp.4,10, 17,21,26,27,31. Available from: http://www.sign.ac.uk/assets/sign122.pdf (accessed July 2017).

Additional sources

Australian Commission on Safety and Quality in Health Care. Medication Safety. 2018 [cited Jul 2018]; Available from: https://www.safetyandquality.gov.au/our-work/medication-safety/. (accessed July 2018).

Australian Commission on Safety and Quality in Health Care. Health literacy: Taking action to improve safety and quality. Sydney: ACSQHC; 2014 [cited January 2018]; Available from: https://www.safetyandquality.gov.au/publications/health-literacy-taking-action-to-improve-safety-and-quality/. (accessed July 2017).

Australian Medicines Handbook 2018 (online). Adelaide: Australian Medicines Handbook Pty Ltd; 2018; July; Available from: https://amhonline.amh.net.au/. (accessed July 2018).

Clinical Excellence Commission. Framework for the prevention of venous thromboembolism. Medication Safety and Quality VTE Prevention Centre. Sydney: CEC, 2014. Available from: http://cec.health.nsw.gov.au/__data/assets/pdf_file/0009/259506/framework_prevention_of_vte.pdf (accessed July 2017).

Institute for Safe Medication Practices. ISMP Medication safety self-assessment for antithrombotic therapy. Philadelphia: ISMP; 2017: p.12 (points 15,16) p.13 - 15 (points 23,27,37,43) p.21 (points 81, 83) p.22-24 (core characteristic #9) p.25 (point 111-112). Available from http://www.ismp.org/selfassessments/Antithrombotic/2017/2017_ISMP_Antithrombotic_Self_Assessment.pdf (accessed July 2017).

Geerts W. Prevention of venous thromboembolism: a key patient safety priority. J Thromb Haemost. 2009;1:1-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19630756. (accessed July 2017).

The Joint Commission. Discharge instructions/education materials for venous thromboembolism (VTE): a comprehensive approach to medication management compendium of resources. USA [cited July 2017]; Available from: https://www.jointcommission.org/discharge_instructions_for_venous_thromboembolism_vte/. (accessed July 2017).

Maynard G. Preventing hospital-associated venous thromboembolism: a guide for effective quality improvement, 2nd ed. Rockville, MD: Agency for Healthcare Research and Quality; August 2016. ARHQ Publication No. 16-0001-EF: p.17,21, 62-3. Available from:

http://www.ahrq.gov/professionals/quality-patient-safety/patient-safety-resources/resources/vtguide/index.html (accessed July 2017).

NSW Ministry of Health. Policy Directive: Prevention of venous thromboembolism. Sydney: NSW Ministry of Health; 2014: pp.6-10. Available from: http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2014_032.pdf (accessed July 2017).

NSW Ministry of Health. High-risk medicines management policy. Sydney: NSW Ministry of Health; 2015; Available from: http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2015_029.pdf.

NSW Therapeutic Advisory Group. Safe use of heparins and oral anticoagulants for venous thromboembolism prophylaxis in adults. Position statement NSW TAG. 2008 (updated August 2010): p.4. Available from: http://www.ciap.health.nsw.gov.au/nswtag/documents/publications/position-statements/heparin-vte-aug-2010.pdf (accessed July 2017).

New Zealand Venous Thromboembolism Prevention. National policy framework: VTE prevention in adult hospital patients in NZ. NZVTEP; 2012. Available from https://www.hqsc.govt.nz/assets/Other-Topics/QS-challenge-reports/VTE-Prevention-programme-National-Policy-Framework.pdf (accessed July 2017).

MacLean S, Mulla S, Akl EA, Jankowski M, Vandvik PO, Ebrahim S, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e1S-e23S. Epub 2012/02/15. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22315262 (accessed February 2018).

Padron M, Miyares MA, Ferrell KW, Hill AM. Development of an Anticoagulation Stewardship Program at a Large Tertiary Care Academic Institution. Journal of Pharmacy Practice. 2013;28(1):93-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24326411 (accessed July 2017).

Queensland Government Department of Health. Patient Safety Notice: Anticoagulation management. Patient Safety and Quality Improvement Service, Queensland Government Department of Health; 2017.

Therapeutic Goods Administration. Department of Health. Apixaban (Eliquis), dabigatran (Pradaxa) and rivaroxaban (Xarelto): Information for health professionals. 2015 [cited Jul 2017]; Available from: https://www.tga.gov.au/alert/apixaban-eliquis-dabigatran-pradaxa-and-rivaroxaban-xarelto-information-health-professionals. (accessed February 2018)

Therapeutic Goods Administration. Department of Health. Dabigatran (Pradaxa) and risk of bleeding: information for health professionals. 2013 [cited Jul 2017]; Available from: https://www.tga.gov.au/alert/dabigatran-pradaxa-and-risk-bleeding-information-health-professionals. (accessed February 2018)

Bayer Australia Ltd. Xalrelto (rivaroxaban) Product Information. 1 Mar 2016.

Boehringer Ingelheim Pty Limited. Pradaxa (dabigatran etexilate) Product Information. 1 Nov 2015.

Bristol-Myers Squibb Australia Pty Ltd. Eliquis (apixaban) Product Information. 1 Mar 2016.

Quality statement 6

Reassess risk and monitor the patient for VTE-related complications

During hospitalisation, a patient's thrombosis and bleeding risk is reassessed and documented at intervals no longer than every seven days, whenever the patient's clinical condition or goals of care change, and on discharge from hospital. The patient is also monitored for VTE-related complications each time risk is reassessed.

Evidence sources

Australian guidelines

Queensland Health. Venous thromboembolism (VTE) prophylaxis in pregnancy and the puerperium. Queensland Clinical Guidelines; 2014: p.10. Available from https://www.health.qld.gov.au/__data/assets/pdf_file/0011/140024/g-vte.pdf (accessed July 2017).

International guidelines

International Angiology. Prevention and treatment of venous thromboembolism: International Consensus Statement. The Journal of Vascular Biology, Medicine, Surgery and Phlebology. April 2013;32(2): p.136. Available from: http://europeanvenousforum.org/wp-content/uploads/2015/02/IUA_Guidelines_2013.pdf (accessed July 2017).

National Institute for Health and Care Excellence. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NG 89. London: NICE; 2018; Available from: https://www.nice.org.uk/guidance/ng89 (accessed March 2018).

National Institute for Health and Care Excellence. Venous thromboembolism in adults: reducing the risk in hospital. QS3. London: NICE; 2010 (updated 2018); p.13. Available from: https://www.nice.org.uk/guidance/qs3 (accessed March 2018).

Royal College of Obstetricians and Gyneacologists. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-top Guideline No. 37a. London: RCOG; 2015: p.2. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf (accessed July 2017).

Scottish Intercollegiate Guidelines Network. Prevention and management of venous thromboembolism. Pub. No. 122 Edinburgh: SIGN; 2010 (updated October 2014): p.9. Available from: http://www.sign.ac.uk/assets/sign122.pdf (accessed July 2017).

Additional sources

Clinical Excellence Commission. Framework for the prevention of venous thromboembolism. Medication Safety and Quality VTE Prevention Centre. Sydney: CEC, 2014. Available from: http://cec.health.nsw.gov.au/__data/assets/pdf_file/0009/259506/framework_prevention_of_vte.pdf (accessed July 2017).

Maynard G. Preventing hospital-associated venous thromboembolism: a guide for effective quality improvement, 2nd ed. Rockville, MD: Agency for Healthcare Research and Quality; August 2016. ARHQ Publication No. 16-0001-EF: p.46, 58. Available from: http://www.ahrq.gov/professionals/quality-patient-safety/patient-safety-resources/resources/vtguide/index.html (accessed July 2017).

NSW Ministry of Health. Policy Directive: Prevention of venous thromboembolism. Sydney: NSW Ministry of Health; 2014: pp.5,12-13. Available from: http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2014_032.pdf (accessed July 2017).

NSW Therapeutic Advisory Group. Safe use of heparins and oral anticoagulants for venous thromboembolism prophylaxis in adults. Position statement NSW TAG. 2008 (updated August 2010): p.19. Available from: http://www.ciap.health.nsw.gov.au/nswtag/documents/publications/position-statements/heparin-vte-aug-2010.pdf (accessed July 2017).

New Zealand Venous Thromboembolism Prevention. National policy framework: VTE prevention in adult hospital patients in NZ. NZVTEP; 2012: p.17. Available from https://www.hqsc.govt.nz/assets/Other-Topics/QS-challenge-reports/VTE-Prevention-programme-National-Policy-Framework.pdf (accessed July 2017).

Quality statement 7

Transition from hospital and ongoing care

A patient at risk of VTE following hospitalisation receives a written discharge plan or care plan before they leave hospital, which describes their ongoing, individualised care to prevent VTE following discharge. The plan is discussed with the patient before they leave hospital to ensure they understand the recommended care and follow-up that may be required. The plan is also communicated to the patient's general practitioner or ongoing clinical provider within 48 hours of discharge so that ongoing care to prevent VTE can be completed in accordance with the plan.

Evidence sources

Australian guidelines

Cardiology Expert Group. Therapeutic Guidelines: Cardiovascular version 6. Melbourne: Therapeutic Guidelines Limited; 2012: p.2. Available from https://www.tg.org.au/ (accessed July 2017).

Queensland Health. Venous thromboembolism (VTE) prophylaxis in pregnancy and the puerperium. Queensland Clinical Guidelines; 2014: p.19. Available from https://www.health.qld.gov.au/__data/assets/pdf_file/0011/140024/g-vte.pdf (accessed July 2017).

International guidelines

National Institute for Health and Care Excellence. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NG 89. London: NICE; 2018; Available from: https://www.nice.org.uk/guidance/ng89 (accessed March 2018).

National Institute for Health and Care Excellence. Venous thromboembolism in adults: reducing the risk in hospital. QS3. London: NICE; 2010 (updated 2018); p. 19. Available from: https://www.nice.org.uk/guidance/qs3 (accessed March 2018).

Royal College of Obstetricians and Gyneacologists. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-top Guideline No. 37a. London: RCOG; 2015: p.7. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf (accessed July 2017).

Scottish Intercollegiate Guidelines Network. Prevention and management of venous thromboembolism. Pub. No. 122 Edinburgh: SIGN; 2010 (updated October 2014): p.12. Available from: http://www.sign.ac.uk/assets/sign122.pdf (accessed July 2017).

Additional sources

Australian Commission on Safety and Quality in Health Care (2017). Top tips for safe health care. ACSQHC. Available from: https://www.safetyandquality.gov.au/publications/top-tips-for-safer-health-care/ (accessed July 2017).

Australian Commission on Safety and Quality in Health Care 2012. Accreditation outcome results and evidence of implementation of the National Safety and Quality Health Service (NSQHS) Standards. ACSQHC: Sydney. Available from: https://safetyandquality.gov.au/wp-content/uploads/2012/03/Accreditation-outcome-results-and-evidence-of-implementation.pdf (accessed July 2017).

Buckinghamshire Healthcare NHS Trust/Aylesbury Vale and Chiltern Clinical Commissioning Groups. Guideline 295FM.2 Dabigatran, rivaroxaban, apixaban and endoxaban for deep vein thrombosis and pulmonary embolism - amber initiation guide V2. Buckinghamshire Healthcare: NHS Trust; 2014 (updated 2016). Available from: http://www.bucksformulary.nhs.uk/docs/Guideline_295FM.pdf. (accessed July 2017).

Clinical Excellence Commission. Framework for the prevention of venous thromboembolism. Medication Safety and Quality VTE Prevention Centre. Sydney: CEC, 2014. Available from: http://cec.health.nsw.gov.au/__data/assets/pdf_file/0009/259506/framework_prevention_of_vte.pdf (accessed July 2017).

Horwitz LI. Self-care after hospital discharge: knowledge is not enough. BMJ Quality & Safety. 2016;26(1):7. Available from: http://qualitysafety.bmj.com/content/26/1/7.info (accessed July 2017).

Institute for Safe Medication Practices. ISMP Medication safety self-assessment for antithrombotic therapy. Philadelphia: ISMP; 2017: p.22-24 (core characteristic #9). Available from http://www.ismp.org/selfassessments/Antithrombotic/2017/2017_ISMP_Antithrombotic_Self_Assessment.pdf (accessed July 2017).

The Joint Commission. Discharge instructions/education materials for venous thromboembolism (VTE): a comprehensive approach to medication management compendium of resources. USA [cited July 2017]; Available from: https://www.jointcommission.org/discharge_instructions_for_venous_thromboembolism_vte/. (accessed July 2017).

NSW Ministry of Health. Policy Directive: Prevention of venous thromboembolism. Sydney: NSW Ministry of Health; 2014: pp.12-13. Available from: http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2014_032.pdf (accessed July 2017).

New Zealand Venous Thromboembolism Prevention. National policy framework: VTE prevention in adult hospital patients in NZ. NZVTEP; 2012; p.11. Available from https://www.hqsc.govt.nz/assets/Other-Topics/QS-challenge-reports/VTE-Prevention-programme-National-Policy-Framework.pdf (accessed July 2017).

Queensland Government Department of Health. Patient Safety Notice: Anticoagulation management. Patient Safety and Quality Improvement Service, Queensland Government Department of Health; 2017.

Appendix 1

Rapid review: Aspirin for the primary prevention of venous thromboembolism following hip and knee replacement surgery

Summary: rapid review

Background

The Australian Commission on Safety and Quality in Health Care (the Commission) commenced the development of the Venous Thromboembolism (VTE) Prevention Clinical Care Standard in response to safety and quality issues highlighted by states and territories regarding the primary prevention of VTE in hospital.

States and territories have also highlighted the need for national guidance on VTE prevention, given the absence of a national clinical practice guideline on VTE prevention for hospitalised patients.

Specifically, the lack of consensus in guidelines regarding the use of aspirin for primary VTE prevention in hip and knee replacement surgery patients has created uncertainty for clinicians and health services across Australia.

The aim of this rapid review was to identify and appraise the findings of key studies on the use of aspirin for the primary prevention of VTE following hip and knee replacement surgery.

Research question

Is aspirin superior to other antithrombotic agents, for the primary prevention of VTE in patients who have had hip or knee replacement surgery?

What is the quality and breadth of the evidence that supports this view?

Methods

A search of the literature published from 1 January 2009 to 1 July 2017 was performed in the PubMed, Scopus, Open Grey and Cochrane databases. A total of 35 studies were included in the main analysis. The studies were analysed based on three protocols: aspirin only, aspirin as a component of staged prescribing, and aspirin used in 'routine risk' patients following risk stratification. The National Health and Medical Research Council's (NHMRC) Evidence Hierarchy and Scottish Intercollegiate Guidelines Network's (SIGN) critical appraisal tools were used to assess the quality of the included articles and the evidence available for statements in the final results.

Results

The studies included in the main analysis were of varying quality and evidence level, and were often based either on small cohorts, very small event rates, or both, making them inadequately powered to determine superiority between treatment regimens. There was, nevertheless, some evidence to suggest that in patients prescribed multi-modal prophylaxis, aspirin may be considered either as a suitable alternative to other pharmacological agents or as a component of a staged supply thromboprophylaxis regimen that involves initial anticoagulant use postoperatively. These findings are only relevant to hip and knee arthroplasty patients who are not at an increased risk of VTE or bleeding following surgery; this is approximately 50% to 85% of patients undergoing hip and knee arthroplasty. These findings are in general agreement with those reported by Wilson *et al* in their systematic review of papers published between 2004 and 2014.[1]

Background

The true baseline incidence of symptomatic VTE following modern-day hip and knee arthroplasty is difficult to estimate; however, population-based analyses performed overseas suggest that the incidence is between 0.44% and 1.7% between one and six months following surgery.[2-4] The baseline incidence of pulmonary embolism (PE) in this period is estimated to be approximately 0.1% to 0.9%.[2-4] In Australia, recent studies suggest that the incidence of VTE (with various forms of thromboprophylaxis) following hip and knee arthroplasty is approximately 1% to 4.7% during the inpatient period (1.1-3.0% post hip arthroplasty, 2.7-6.5% post knee arthroplasty); this is higher than any other surgical group*.[5-7]

In 2009 the NHMRC released clinical practice guidelines to promote the safe and effective use of mechanical and pharmacological methods for preventing VTE (known as mechanical and pharmacological thromboprophylaxis, respectively) in patients admitted to Australian hospitals, including patients undergoing hip and knee replacements.[8]

Upon completing individualised bleeding and VTE risk assessments for each patient, the NHMRC recommended postoperative extended-duration thromboprophylaxis with an anticoagulant (+/- mechanical prophylaxis if appropriate) for the 'average' arthroplasty patient.[8] The guideline also recommended against mechanical prophylaxis or antiplatelet use as sole thromboprophylaxis. The guideline was rescinded in 2016 as it was considered out of date.

In October 2016, the Arthroplasty Society of Australia (ASA) released the latest edition of their thromboprophylaxis guideline.[9] In this guideline the ASA promotes practices similar to the thromboprophylaxis guideline issued by the American College of Chest Physicians (ACCP) in 2012. This involves stratifying patients according to bleeding and VTE risk, and providing whatever combination of mechanical, antiplatelet and/or anticoagulant prophylaxis is deemed necessary – including sole mechanical and antiplatelet use if appropriate.[10]

The United Kingdom's National Institute for Health and Care Excellence (NICE), like the NHMRC Guideline, recommend against using aspirin as sole prophylaxis following hip and knee replacement. It should be noted that this recommendation is from a guideline released in 2010.[11] Although some recommendations were reviewed in 2015, this one was not. The entire guideline is in the process of being updated, with an expected release date of March 2018. The American Association of Orthopaedic Surgeons recommends the use of pharmacological agents and/or mechanical compressive devices to prevent VTE following surgery in its 2011 guideline; however, the Association does not recommend for or against specific prophylaxis for hip and knee replacement patients.[12]

The Commission is aware from consultation with states and territories that the aforementioned conflicting advice provided in guidelines has resulted in ongoing uncertainty about the use of aspirin for the prevention of VTE post hip and knee replacement surgery. The Commission now poses this research question: is aspirin superior to other antithrombotic agents, for the primary prevention of VTE in patients who have had hip or knee replacement surgery? What is the quality and breadth of the evidence that supports this view?

* All of the DVT in the knee arthroplasty study by Pow *et al* (i.e. the 4.7% VTE incidence in inpatient knee arthroplasty patients) were distal DVTs.

Research method

A search of the PubMed, Scopus, Open Grey and Cochrane databases for relevant search terms (see below) was conducted in March, April, June and July 2017, respectively. A supplementary search of the PubMed, Scopus and Open Grey databases was conducted in July 2017. As the NHMRC thromboprophylaxis guideline reviewed papers published up until January 2009, only papers published after 1 January 2009 were included in this review. Language was restricted to English, and where applicable, the 'human' filter was used. References of included articles and reviews were reviewed for additional relevant papers.

PubMed:

- Aspirin AND Arthroplasty as MeSH terms = 70 records
- Aspirin AND Venous Thromboembolism as MeSH terms = 121 records
- Aspirin AND VTE = 129 records
- Aspirin AND "Joint Replacement" = 14 records
- Supplementary search using above combinations = 11 records.

Scopus: terms searched in *article title, abstract* and *keywords*

- Aspirin AND Arthroplasty = 478 records
- Aspirin AND Venous Thromboembolism = 1,806 records
- Aspirin AND VTE = 493 records
- Aspirin AND Joint Replacement = 37 records
- Supplementary search using above combinations = 18 records.

Open Grey:*

- Venous Thromboembolism = 40 records
- Arthroplasty = 185 records
- Aspirin = 99 records
- Joint Replacement = 81 records.

Cochrane: terms searched in *article title*, *abstract* and *keywords*

- Aspirin AND Arthroplasty = 38 records
- Aspirin AND Venous Thromboembolism = 91 records
- Aspirin AND VTE = 45 records
- Aspirin AND Joint Replacement = 3 records.

* Due to inadequacies with the filtering process in the Open Grey database (i.e. only 49 of 99 records were attributed to a year), all records were reviewed.

Selection criteria

Eligible studies for this review included those in adult humans (18 or more years) in which at least one patient cohort underwent hip or knee arthroplasty surgery with one of the following three pharmacological prophylaxis protocols:

1. **Aspirin as sole pharmacological prophylaxis**
   In this type of protocol, aspirin is provided to everyone in the cohort* and their outcomes are compared to another cohort using anticoagulant prophylaxis.

2. **Aspirin as a component of staged supply prophylaxis**
   In this type of protocol, aspirin is provided as the second component of a staged supply of thromboprophylaxis. In the first stage, the cohort receives an anticoagulant for a predetermined period, such as for two weeks postoperatively or just for the inpatient period. Their outcomes are compared to either another staged supply cohort (with a longer first stage duration) or to anticoagulant prophylaxis.

3. **Aspirin used as part of a risk stratification protocol**
   In this protocol, the participants are divided into different subgroups based on their predicted risk of postoperative VTE: low-risk patients† receive aspirin, and high-risk patients receive an anticoagulant. This data is presented in two ways: as comparisons made between the outcomes of the high- and low-risk groups, or as comparisons between the risk-stratified cohort as a whole and another cohort that receives either staged supply (as in protocol 2) or anticoagulant prophylaxis. The various risk stratification criteria used in these studies are briefly outlined on pages 70-72 of this review.

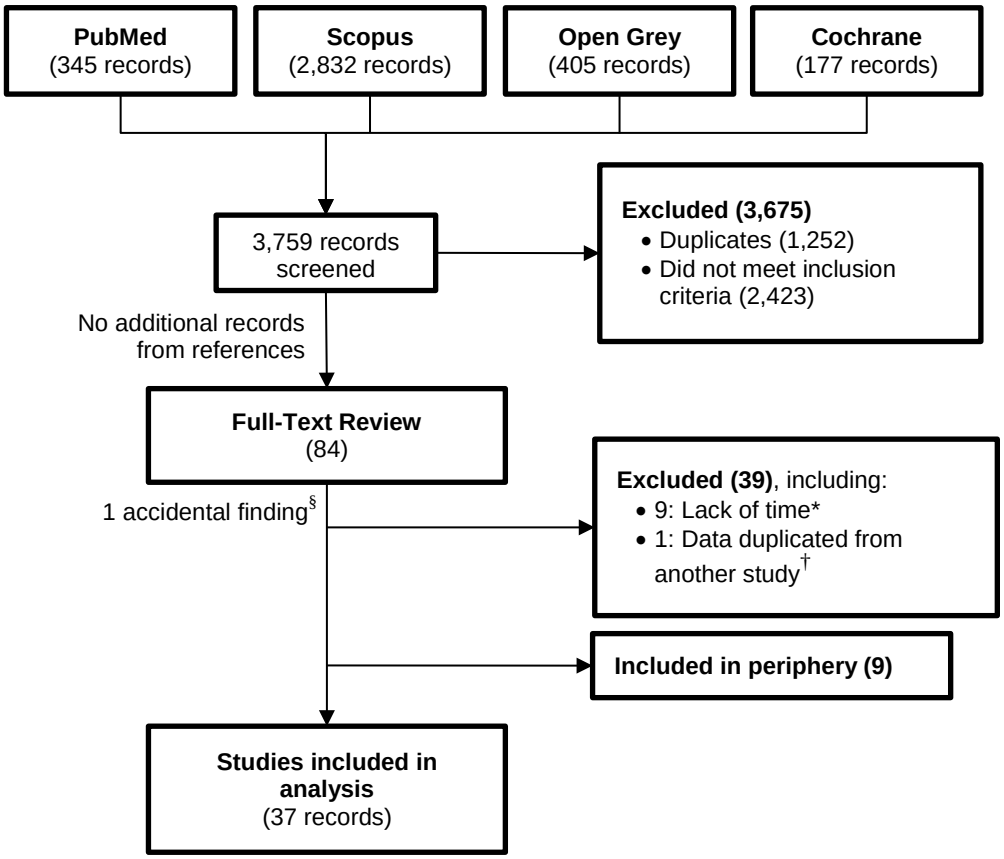
Included studies were required to report efficacy (and safety, preferably) endpoints, such as VTE and bleeding. As outlined above, only studies published after 1 January 2009 were included in this review; this increases the chance of focusing on data reflective of modern-day surgical procedures. Studies of hip fracture and/or trauma patients were excluded due to the associated increased risk of VTE from preoperative immobility and bone trauma. Figure 1 displays the flowchart of study selection.

Data collected from the relevant articles are summarised in tables on pages 45-69. To complement these studies, real-world data from national joint registries are summarised on pages 73-77. This is followed by meta-analyses and systematic reviews (pages 78-80) and finally by a brief review of the evidence used in the NHMRC guideline (pages 81-82).

---

* These studies often exclude patients who would be perceived as ‘high’ risk (such as patients with a history of VTE), as well as patients on long-term anticoagulation for a prior medical condition.
† Also referred to as ‘average’, ‘routine-risk’ and ‘standard-risk’ patients.

Figure 1: Flowchart of study selection.



Quality appraisal

The NHMRC Evidence Hierarchy and SIGN's critical appraisal tools were used to assess the quality of the included articles and the evidence they provided for statements in the final results. The following terms[#] have been used to refer to potential sources of bias in this review:

- **Selection Bias:** the bias introduced by the selection or non-randomised allocation of patients to different treatment cohorts
- **Performance Bias:** the bias introduced when individuals (patients and/or personnel) are not blinded to the treatment allocated to a patient. This may influence the level of attention and ancillary treatment received by an individual (e.g. how often they are mobilised or see a physiotherapist postoperatively). It may also influence the level of attentive surveillance and diagnostic investigation received by an individual. For example, a patient receiving warfarin requires regular international normalised ratio (INR) monitoring; they may consequently have more outcome surveillance during the postoperative period than a person using aspirin, who not only does not require any regular laboratory monitoring, but can purchase their medication without a prescription

---

* Predominantly mortality-related papers and several meta-analyses.[13-21]
† Study by Haynes et al[22]
§ Study by Yhim et al[23]
# Based on the Cochrane website (http://methods.cochrane.org/bias/assessing-risk-bias-included-studies)

- **Detection Bias:** the bias introduced when personnel assessing patients for outcomes (for example, of VTE) are not blinded to patients' treatment
- **Attrition Bias:** the bias introduced when there are differences in the rates of withdrawal from treatment cohorts
- **Reporting Bias:** the bias introduced when there are differences in the outcomes of reported versus unreported study findings. For example, the findings of small studies in particular are more likely to be in favour of an intervention, potentially due to the under-reporting of small studies with non-significant or negative effects. In contrast, large studies are likely to be published, irrespective of their findings. This phenomenon is referred to as the small study bias risk in the review.

Limitations

Review limitations

This review was conducted as a rapid-review and thus bears the limitations typical of a rapid-review: each step was conducted by one reviewer only and the data collection, analysis and synthesis were conducted within a limited timeframe to suit the needs of the working group timeline. By nature of this review topic, the studies are limited in number, of varying quality and evidence level, and are often based either on small cohorts, very small event rates, or both, making them inadequately powered to determine superiority between treatment regimens.

Conclusion limitations

The study results reported in this review typically are representative of specialised teams (some of whom work within institutions devoted to orthopaedic surgery), and thus may not be generalisable. Furthermore, the trial findings are limited in their applicability by their inclusion and exclusion criteria, and are generally representative of patients prescribed multi-modal prophylaxis, which typically includes use of regional anaesthesia, early mobilisation, and mechanical prophylaxis (often intermittent compression devices).

Rapid review results

The below data represent findings from the review of each protocol separately. Of note, none of the studies included below are Level I in the NHMRC Evidence Hierarchy, only three of the fifteen were Level II, and most contain varying levels of selection, performance, detection and attrition bias. It should be noted that the lack of a significant statistical difference between cohort outcomes is not evidence for equivalence or non-inferiority of treatment regimens (unless otherwise stated).

Protocol 1: Aspirin as sole pharmacological prophylaxis

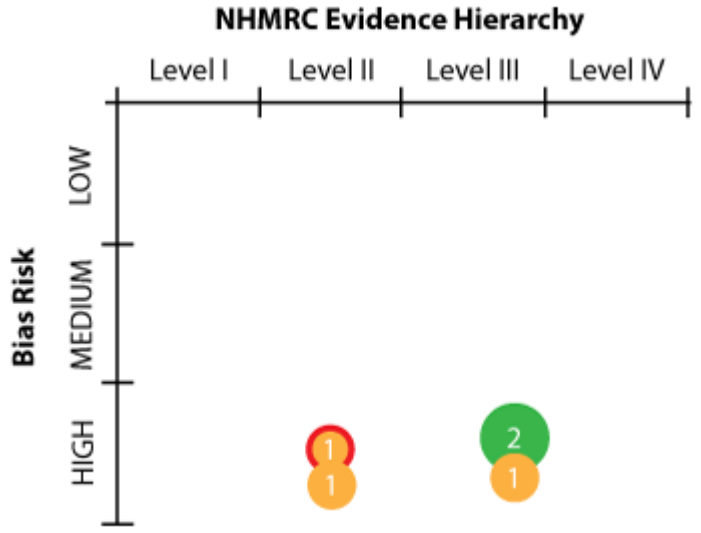


Figure 2: Studies reviewed in Protocol 1, considering the NHMRC Evidence Hierarchy and bias risk.

KEY

1 One study where the incidence of VTE was statistically higher in the aspirin group compared to rivaroxaban, but similar compared to enoxaparin[24]

1 One study with no statistical difference in VTE incidence between aspirin and an anticoagulated group (either dalteparin plus rivaroxaban or enoxaparin, dalteparin, and warfarin used individually)[25, 26]

2 Two studies where VTE incidence was statistically lower in the aspirin group compared to the warfarinised group.[27, 28]

The evidence-base for this protocol investigation is subject to a high risk of bias. Furthermore, it should be noted that in one of the two studies comparing aspirin and warfarin, two-thirds of the warfarinised patients were inadequately anticoagulated (and potentially in a pro-coagulant state depending on Protein C and S titres) when they developed a VTE (that is, potentially biasing results *to* aspirin).[27] This is likely to have been similarly the case in the second study, in which 81% of all PEs in the warfarinised cohort occurred within the first three days following surgery; however, it is not possible to confirm this with the available data.[28] This leaves one small study in which the total VTE incidence (including asymptomatic VTE) in the aspirin group was found to be higher than in the rivaroxaban group, but no different compared to the low molecular weight heparin (LMWH) group, and another two similarly inadequately powered studies in which neither

asymptomatic or symptomatic VTE incidence were different in the aspirin group compared to the anticoagulated group(s).[24-26]

Consequently, there is poor evidence that aspirin (combined with early mobilisation and appropriate mechanical prophylaxis) may be as effective as LMWH (and potentially warfarin (INR 1.5-2.0), but not rivaroxaban in preventing VTE (symptomatic and asymptomatic). This was with potentially less bleeding (compared to warfarin and rivaroxaban, but not LMWH), in patients undergoing primary and revision lower-limb arthroplasty who did not have any additional risk factors for postoperative bleeding or VTE. However, well-designed research is necessary to investigate the efficacy and safety of this protocol in larger samples.

Protocol 2: Aspirin as a component of staged supply prophylaxis

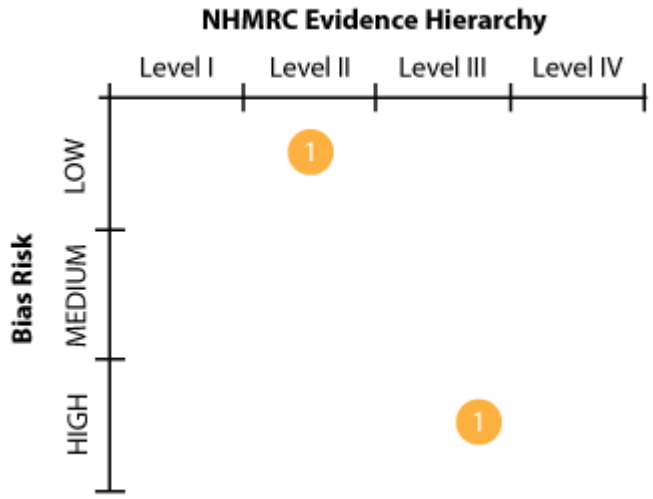


Figure 3: Studies reviewed in Protocol 2, considering the NHMRC Evidence Hierarchy and bias risk.

KEY

1 One study in which the incidence of VTE was not statistically different between staged supply (incorporating LMWH) and either extended LMWH prophylaxis[29] OR extended staged supply prophylaxis (also incorporating LMWH).[30]

There is satisfactory evidence that staged supply with aspirin following initial dalteparin use postoperatively may be as effective as extended-duration dalteparin in preventing symptomatic VTE following hip arthroplasty in patients who are not at an increased risk of bleeding or VTE. Although well-designed and at a low risk of bias, the trial on which this statement is based (EPCAT) was stopped early due to slow enrolment.[29] There is a need for further, well-designed research to confirm the safety and efficacy of this protocol in larger hip arthroplasty populations.

There is poor evidence in knee arthroplasty patients that staged supply with aspirin following initial enoxaparin use may be as effective as extended-duration enoxaparin therapy in preventing symptomatic VTE in patients who are not at an increased risk of bleeding or VTE. There is a need for further, well-designed research to investigate the safety and efficacy of this approach.

The EPCAT team is expected to complete a randomised clinical trial in December 2017 exploring the efficacy of using aspirin following initial treatment with rivaroxaban after hip and knee arthroplasty.[31] It is likely that their findings, when published, will greatly assist in clarifying the safety and efficacy of staged protocols.

Protocol 3: Aspirin as part of a risk stratification protocol

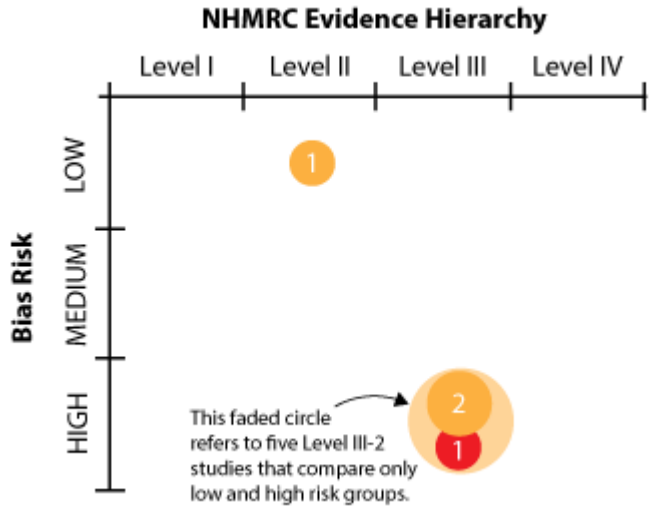


Figure 4: Studies reviewed in Protocol 3, considering the NHMRC Evidence Hierarchy and bias risk

KEY

1 One study where the incidence of VTE was not statistically different between the risk stratified group and control group (extended staged supply incorporating enoxaparin)[32]

1 One study where the incidence of VTE was statistically higher in the risk stratified cohort compared to the control group (extended anticoagulant use, predominantly warfarin)[33]

2 Two studies where the incidence of VTE was not statistically different between the risk stratified group and the control group (extended anticoagulant use with warfarin or enoxaparin predominantly).[34, 35]

There is satisfactory evidence that extended-duration thromboprophylaxis with aspirin to standard-risk patients as part of a risk stratification protocol may be as effective as an extended-staged thromboprophylaxis protocol, incorporating enoxaparin or routine extended anticoagulation, in preventing symptomatic VTE following knee arthroplasty. Further research is required to confirm this in larger populations and in the hip arthroplasty cohort (for whom the evidence is poor, but still suggests VTE incidence with a risk-stratification protocol is not different to routine anticoagulation).

NB: It should be noted that all five Level III studies in this protocol employed warfarin in their high-risk cohort, thereby exposing their results to similar potential biases *to* aspirin as discussed previously in Protocol 1 (page 39).[36-40]

A summary of risk stratification protocols used in each study is on pages 70-72.

Joint registry data

Joint registry data suggest aspirin is similar in efficacy to other antithrombotic agents for the prevention of symptomatic VTE following primary elective hip and knee arthroplasty. These data are useful because some of the trials included in the data tables are too small to reliably detect clinically important differences between two active treatments. However, although some of the data presented are adjusted data (to account for some patient and hospital factors), it is observational retrospective data from patient groups wherein anticoagulants were perhaps more regularly employed for patients deemed to be at high risk of developing VTE, and who may have also received more attentive surveillance. Consequently, it should only be used to support aspirin use in standard VTE risk patients until more stringent data are available. Based on the studies outlined in the Protocol 3 data tables, this appears to be approximately 50% to 85% of patients undergoing hip and knee arthroplasty, varying depending on the risk stratification protocol implemented. The meta-analyses and reviews cautiously suggest aspirin may be effective with the caveat that insufficient evidence prohibits conclusive findings.

Conclusion

To answer the research question as to whether aspirin is superior to other antithrombotic agents, for the primary prevention of VTE in patients who have had hip or knee replacement surgery: there are no data in this review to suggest that aspirin is superior to other antithrombotic agents. There are, however, limited data available to suggest there might be a role for the use of aspirin either as an adjunct to anticoagulant therapy as part of a staged protocol, or as extended therapy in the 'average' lower-limb arthroplasty patient (that is, a patient who is not at increased risk of VTE). In these instances, aspirin *may* provide similar protection against VTE as extended anticoagulant use, whilst potentially reducing bleeding and wound complications and improving patient satisfaction (and compliance) postoperatively. Further high-quality research in large cohorts is required to confirm this. This review has highlighted a paucity of sufficiently powered randomised controlled trials.

A note about the dose of aspirin

One of the reasons why there may be some variation in findings (particularly over the last 30 years and more) is that aspirin has been dosed differently through the years and differently in different continents. The commonly used antiplatelet dose of aspirin is 100mg daily in Australia, but it can range from 75mg to 150mg daily. The studies in this rapid review used doses ranging from 81mg daily to 325mg twice daily.

Borgdorff et al. completed a review of prospective randomised controlled trials in preventing VTE after orthopaedic or general surgery, in which aspirin was investigated either alone or when added to anticoagulants.[41] They identified that the mean weighted relative risks of VTE compared to control (placebo or no prophylaxis) went from 1.12 (95CI 0.73-1.72) for the highest dose of aspirin (2000 mg/day), via 0.89 (95CI 0.74-1.06)* for the medium dose range (600-1300 mg/day) to 0.65 (95CI 0.52-0.81) for the lowest dose range (160-250 mg/day). A contrast between the effect of high and low dose aspirin was also evident when sole aspirin use was compared to sole anticoagulant use postoperatively: high dose (3000 mg/day): 1.89 (95CI 0.69-5.16), moderate dose (650-1300 mg/day): 1.74 (95CI 1.31-2.32), low dose (81-250 mg/day): 1.09 (0.73-1.63)[†]. A possible explanation presented by the authors for the difference in efficacy of different aspirin doses is:

> Aspirin inhibits platelet aggregation by irreversibly blocking COX-1 mediated thromboxane formation in platelets, but may enforce aggregation when it also inhibits COX-2mediated synthesis of platelet inhibiting prostacyclin (PGI2) in endothelial cells. Since platelets are anucleate, without de novo protein synthesis, a low dose of aspirin is sufficient to inhibit COX-1 activity for the rest of platelet life (7–10 days). The nucleated endothelial cells can, however, perform protein resynthesis, and resume PGI2 production soon after ingestion of low dose aspirin, but not when higher doses are used. Since PGI2 potently depresses most forms of

---

* Of note, the number of participants in individual randomised controlled trials (RCTs) using high and medium-dose aspirin ranged from only 35 to 303, with only three (out of 11) having more than 100 participants overall, and only one with more than 100 participants in each arm (large 95% confidence intervals). By contrast, two out of the three low-dose trials included over 2,000 participants in each arm. The clinical significance of this is uncertain; however, there is some evidence that small studies (that is, less than 100 patients per trial arm) may be more likely to report larger treatment benefits compared to larger trials (Nüesch et al. (BMJ 2010; 341); this would suggest that high-dose aspirin might be associated with even less favourable outcomes.

[†] Five out of the seven high and medium-dose trials had fewer than 100 participants in each arm, whereas three out of the five low-dose trials had at least 100 participants in each arm (see previous footnote).

> platelet activation, a reduction of plasma PGI2 by high dose aspirin will enhance platelet aggregability despite COX-1 blockade.[41]

While intriguing, the large confidence intervals in the aforementioned review, particularly with high-dose aspirin, mean that the results should be interpreted with caution. There are two studies that were not included in the review that may also be of interest. The first is a prospective cross-over study of 4,651 primary total joint arthroplasty patients (surgeries performed between 2013 and 2015), which found that 81mg aspirin daily was non-inferior to 325mg twice daily for VTE prophylaxis* and was statistically similar for safety endpoints (gastrointestinal (GI) bleeding and ulceration, acute peri-prosthetic joint infection and 90-day mortality).[42] Secondly, a one-year prospective cohort study of 643 primary unilateral joint arthroplasties conducted by a single surgeon reported an increased risk of side effects (GI upset and nausea) in patients taking 325mg aspirin twice daily compared to 81mg daily.[43] The VTE incidence was too low in the second study (n=1) to draw conclusions about the thromboprophylaxis efficacy of the two dosing regimens.

* VTE incidence: 0.1% (95CI 0-0.3%) vs. 0.3% (95CI 0.1-0.6%), p=0.345.

Data tables

This page outlines how the data are presented in the following data tables. In some instances, abbreviations have been used; refer to pages 83-84 for a list of these abbreviations, along with their meanings. The data tables for each of the protocols outlined on page 36 are presented consecutively.

Study	Design	Findings	Assessment
First author et al[ref] Country Year(s) data collected Operation(s) Year published NHMRC evidence hierarchy Funding information Conflict of Interest information NB: 'no COI = authors declare no conflicts of interest'	**Patients:** how many patients, and how they were divided into relevant cohorts. ***Group A* =** this text outlines what a cohort received for thromboprophylaxis (pharmacological + where different between groups, mechanical also). ***Group B* =** see above. If placebo (tablets and/or injections) were utilised, it is outlined here. **Excluded if:** exclusion criteria are included here; this is especially relevant to the applicability of the study outcomes. **Outcomes:** primary outcome and safety endpoints within X days post-arthroplasty. **Other details:** this section includes anaesthesia data, mobilisation data, and mechanical prophylaxis data (only when identical across treatment groups). Treatment adherence, follow-up data and any other information of interest is also recorded here.	First Table = VTE related endpoints (at X days post-op) **Group A (n=GHI)** | **Group B (n= JKL)** | ***p*** e.g. DVT | (-) = none | | *p* values provided if in study PE | n (%) | | Total VTE | | | | | | Second table = Other postoperative complications (at X days post-op) **Group A (n=GHI)** | **Group B (n= JKL)** | ***p*** e.g. Major bleeding | As above | | | Minor bleeding | | | | Wound infection | | | | Death | | | | Other results that may be of interest are noted here.	**Bias considerations:** aspects worth considering re: bias potential. **Bias Risk:** assessment as unknown / low / moderate / high. **Efficacy Finding:** brief statement on how aspirin relevant protocol fared compared to the other protocol(s) for VTE prevention. **Safety Finding:** brief statement on how aspirin relevant protocol fared compared to the other protocol(s) for safety endpoints. **Other comments:** some other comments on study quality or findings.

Where relevant, observational data are used to supplement clinical trial data. This is included at the end of each protocol section.

Data tables: Protocol 1 – Aspirin as sole pharmacological prophylaxis

Study	Design	Findings	Assessment
Zou et al [24] China d.2011-2013 Primary unilateral total knee arthroplasty (TKA) p.2014 <u>Level II</u> Randomised controlled trial No CoI Funding not reported	**Patients:** Randomised 324 patients into three treatment groups (all 14 days of treatment): **Group A =** rivaroxaban 10mg/day **Group B =** LMWH 40mg/day* **Group C =** aspirin 100mg/day All were operated on by the same surgeon. **Excluded if:** - history of haemorrhagic disease or bleeding tendency (pre-op coagulation test), - a history of VTE, - received >2 litres of infused fluids 24 hour after surgery, - underwent knee arthroplasty (NB: this is as listed in the study, however given the patient population they may have meant 'prior TKA', 'staged TKA' or that the current operation was a revision TKA procedure), - used a combination of drugs that might impact the findings (no further information in study paper). **Outcomes:** total VTE (symptomatic and asymptomatic DVT and symptomatic PE), and wound complications at four weeks post-surgery. **Other details:** continuous epidural anaesthesia, mobilising one day after surgery, ankle pump exercises starting six hours after surgery. Pre-op Doppler U/S performed on both legs in both groups to ensure everyone was DVT-negative. No drop-out/withdrawal data available. Treatment adherence not reported, nor how the analysis was performed (i.e. was it done via an intention-to-treat analysis?). *standard of care.	**Table 1: VTE (at 4 weeks post-op)** **Rivaroxaban (n=102)** / **LMWH (n=112)** / **Aspirin (n=110)** Total DVT (sym† + asym): 3 (2.94%) / 14 (12.50%) / 18 (16.36%) p values: 0.029[a] 0.017[b] 0.831[c] † One LMWH patient (0.9%) and two aspirin patients (1.8%) experienced symptomatic DVT in the calf veins; the rest were asymptomatic VTE picked up on Doppler ultrasound (U/S) conducted either 2 or 4 weeks post-arthroplasty. None had PE or other cardiovascular disease (CVD) complications. **Table 2: Other postoperative complications (at 4 weeks post-op)** **Rivaroxaban (n=102)** / **LMWH (n=112)** / **Aspirin (n=110)** Hidden blood loss in L (SD): 1.7 (1.2-3.0) / 1.2 (0.8-2.3) / 1.3 (0.6-2.4) *p* values: 0.009[§] 0.004[#] 0.327[**] SC ecchymosis (%): 72.6 / 55.4 / 49.1 *p* values: 0.193[§] 0.039[#] 0.427[**] Wound comp (%): 4.9 / 2.7 / 1.8 *p* values: 0.027[§] 0.014[#] 0.209[**] Limb swelling (%): 37.3 / 25.0 / 21.8 *p* values: 0.288[§] 0.119[#] 0.448[**] § Rivaroxaban vs. LMWH # Rivaroxaban vs. aspirin ** LMWH vs. Aspirin	**Bias Considerations:** All patients were scanned for asymptomatic VTE preoperatively and at two and four weeks post-operation. No treatment blinding; similar age, gender and body mass index (BMI) breakdown, but no comparison of patients' medical characteristics; small study bias risk; drop-out/withdrawal/ treatment adherence not reported (attrition bias risk unclear). **Bias Risk:** High **Efficacy Finding:** No significant difference in total VTE incidence between LMWH and aspirin users; rivaroxaban users had significantly less VTE than either aspirin or LMWH users. **Safety Finding:** Rivaroxaban was associated with a significantly increased risk of postoperative bleeding and wound complications. There was no significant difference between aspirin and LMWH. **Other comments:** Findings based on total VTE, majority of which were asymptomatic DVT (i.e. clinical relevance?); small follow-up period likely underestimates incidence of VTE post-operation.

Study	Design	Findings	Assessment
Yi et al [26] China d.2012-2013 Primary unilateral knee arthroplasty (KA) p.2014 <u>Level II</u> Randomised controlled trial Funding information not available CoI not information available	**Patients:** 120 patients (same surgeon) randomised to receive either: ***Group A* =** aspirin 100mg/day from day one to 14 ***Group B* =** dalteparin 5000 units/day on days one to five, then rivaroxaban 10mg/day to day 14. **Excluded if:** hepatic or renal dysfunction, coagulation abnormalities, anaemia, anticoagulant use that presents a contraindication to surgery, a history of digestive tract ulcers, a previous history of VTE, non-steroidal anti-inflammatory drug (NSAID) allergy, diabetes, or preoperative arterial abnormalities are present. **Outcomes:** primary outcome measure was *asymptomatic* DVT (detected via U/S) on days four and five post-operation; in addition, symptomatic VTE to six weeks was also reported. Secondary outcome measure was adverse events and blood loss index in hospital, and general thromboprophylaxis (TP) cost. **Other details:** General and regional anaesthesia used in all patients, and early mobilisation and exercises were implemented from day one post-operation. Intermittent pneumatic compression devices (IPCD) used for up to five days (until discharge); thromboembolic deterrent stockings (TEDs) used for two weeks. No patients withdrew.	**Table 3: VTE** | | **Group A (n=60)** | **Group B (n=60)** | ***p*** | |---|---|---|---| | Asymptomatic DVT* at 5 days post-operation | 10 (16.7%) | 11 (18.3%) | 0.5 | | Symptomatic VTE + death at 6/52 | - | - | - | *One popliteal DVT in each group, the rest were calf DVTs. **Table 4: Other postoperative complications (in hospital)** | | **Group A (n=60)** | **Group B (n=60)** | ***p*** | |---|---|---|---| | Blood loss index (g/L) | 33.4 ± 3.7 | 38.1 ± 3.8 | <0.001 | | Wound effusion | 1 | 2 | 0.559 | | Ecchymosis area | 1.6 ± 1.6 | 3.1 ± 2.0 | <0.001 |	**Bias considerations:** No pre-operative scan. No blinding (potential performance and detection bias). Similar age, gender and BMI breakdown, but no comparison of patients' medical characteristics. Significant small study risk bias. No withdrawals, however treatment adherence not reported. **Bias Risk:** High. **Efficacy Findings:** No significant difference in VTE incidence between groups. **Safety Findings:** Blood loss and area of ecchymosis was significantly greater in the anticoagulated group. **Other comments:** All of the DVT were asymptomatic, and thus of unknown clinical relevance. Furthermore, the study was underpowered to detect statistically significant differences in DVT.

Study	Design	Findings	Assessment
Deirmengian et al [27] USA d.2005-2013 Revision hip arthroplasty (HA) and KA 2016 <u>Level III-3</u> Retrospective cohort (with historical and concurrent cohort) [prospectively collected database] No external funding CoI present but not accessible	**Patients:** 2,997 patients operated on between 2005 and 2013. In 2010 the institution's practice changed from routinely using warfarin to aspirin. The groups are divided based on what patients received, noting that surgeons used both aspirin and warfarin from 2010 onwards based on both surgical and patient risk factors*. **Group A =** received warfarin (INR 1.8-2.0) for 6/52 **Group B =** received aspirin (dose not reported) for 6/52 **Excluded if:** previous history of VTE or received any form of pharmacological prophylaxis other than aspirin or warfarin. **Outcomes:** symptomatic VTE, local hematoma at operation site that required reoperation, bleeding in other organs, surgical site infection (SSI) and mortality within 90 days of surgery. **Other details:** All patients received IPCD throughout their inpatient stay and were mobilised beginning the day of surgery. No mention of anaesthesia. *Figure 1 in the study paper suggests aspirin was not used prior to 2010. †'At the beginning, more patients were investigated for PE with CT angiograph or ventilation-perfusion scan. Therefore, over-diagnosis of PE was possible, and it is important to note that all patients received warfarin during that period. Nevertheless, we did not see a change in the incidence of PE after the change of practice took place.' § 'One possible reason for the higher VTE rate in the warfarin group could be under treatment during the first few days after surgery, when prothrombin time (INR) did not reach the desired threshold.' It may also be due to the transient hypercoagulability caused by depletion of innate anticoagulant proteins C and S upon warfarin initiation.'	**Table 5: VTE (at 90 days post-operation)** | | **Warfarin (n=2,463)** | **Aspirin (n=534)** | **p** | |---|---|---|---| | DVT | 23 (0.9%) | 2 (0.4%) | 0.15 | | PE | 23 (0.9%) | 1 (0.2%) | 0.06 | | VTE | 43 (1.75%)* | 3 (0.56%) | 0.03 | *The mean INR tested at the time of VTE diagnosis was 1.64 (range 1.12 - 3.3; SD 0.47); only 13/36 (36%) had INR ≥1.8 at the time of diagnosis. **Table 6: Other postoperative complications (at 90 days post-operation)** | | **Warfarin (n=2,463)** | **Aspirin (n=534)** | **p** | |---|---|---|---| | Major bleeding | 37 (1.5%) | 2 (0.4%) | 0.02 | | Hematoma evacuation | 27 (1.1%) | 2 (0.4%) | | | GI / urinary bleeding | 10 (0.4%)# | - | | | SSI** | 1.7% | 1.6% | 0.53 | | Mortality | 9 (0.4%) | 1 (0.2%) | 0.93 | #Mean INR at the time of bleeding was 1.7 (range 1.1-2.3; SD: 0.38). **post-hoc analysis demonstrated at least 3,780 and 940 patients would have been needed in the warfarin and aspirin groups respectively to have detected a statistically significant difference in the cohorts.	**Bias considerations:** Retrospective study of cohorts with slightly different demographics and breakdown of KA in each group – biased to aspirin. Warfarin users were more likely to be operated on earlier on in the data period - this is relevant if perioperative procedures changed during the nine-year study period, and if VTE diagnosis changed (it did†). There was no indication as to how many patients were using concurrent aspirin (for long-standing CVD) in warfarin group. Most patients were not adequately anticoagulated when they developed a VTE– likely representative of real-world clinical practice. Performance and attrition bias unknown. **Bias Risk:** High **Efficacy Findings:** There was a significantly lower incidence of VTE in aspirin users. § **Safety Findings:** There was significantly less major bleeding in the aspirin

Warfarin patients were more likely to be sicker (increased Charlson Comorbidity Index (CCI) score <1 59.5% vs. 66.5%, p<0.002 for CCI breakdown overall), older (64.9 vs 63.4, p=0.005), heavier (BMI 30.3 vs 29.0, p=0.004) and have longer surgery time (123 mins vs. 113 mins, p=0.0001). Logistic regression analysis took potential confounders into consideration and identified that warfarin use was associated with a higher risk of any VTE (OR 2.92) compared with aspirin, however this did not reach statistical significance (p=0.074). Increased age and CCI score were statistically associated with an increased risk of VTE (OR 1.04, p=0.0057 and OR 1.2, p=0.04 respectively). CCI was also a significant predictor for major bleeding and mortality (OR 1.3, p=0.006). **Other comments:** Although hospital readmissions within 90 days were reviewed, study did not capture readmissions to other hospitals or out-of-hospital complications – and thus may underestimate/inaccurately describe actual VTE incidence.	group; SSI and mortality were similar. Also see other comments.

Study	Design	Findings	Assessment
Raphael et al [28] USA d.2000-2012 Total joint arthroplasty (TJA) p.2014 Level III-3 Retrospective cohort (with historical and concurrent cohort) [prospectively collected database] Funding not reported No CoI	**Patients:** 28,923 patients. In 2010 the institution's practice changed from routinely using warfarin to aspirin or warfarin depending on a patient's VTE risk factors. The groups are divided based on what patients received. **Group A =** received warfarin (INR 1.5-1.8) for 6/52 **Group B =** received aspirin 325mg BD for 6/52. **Excluded if:** previous history of VTE or received any form of pharmacological prophylaxis other than aspirin or warfarin. **Outcomes:** 90-day incidence of symptomatic PE and DVT, wound complications (hematoma formation, acute infection (within 30 days postoperatively), prolonged wound drainage), and mortality. **Other details:** Spinal anaesthesia for all, no mention of mechanical prophylaxis or early mobilisation. [*] 81% of all PEs in the warfarin cohort occurred within the first 3 days. As with Deirmengian et al, one possible reason for the higher VTE rate in the warfarin group could be under treatment during the first few days after surgery, when prothrombin time (INR) may not have reached the desired threshold. It may also be due to the transient hypercoagulability caused by depletion of innate anticoagulants protein C and S upon warfarin initiation.	This data is from the 3:1 propensity score-matched patients[†] **Table 7: VTE (at 90 days post-operation)** | | **Warfarin (n=5,670)** | **Aspirin (n=1,890)** | **p** | | --- | --- | --- | --- | | PE | 38 (0.67%) | 2 (0.11%) | <0.001 | | DVT | 51 (0.90%) | 2 (0.11%) | <0.001 | **Table 8: Other postoperative complications (at 90 days post-operation)** | | **Warfarin (n=5,670)** | **Aspirin (n=1,890)** | **p** | | --- | --- | --- | --- | | Acute infection | 30 (0.53%) | 4 (0.21%) | 0.08 | | Haematoma/bleeding | 5 (0.09%) | - | 0.3 | | Wound drainage | 8 (0.14%) | - | 0.2 | | 90 day mortality | - | - | 1.0 | [†] Although smaller, statistically significant gaps persisted in the age, CCI, length of stay (LOS) and BMI variables between these matched cohorts, biased to aspirin. Multi-variate analyses showed CCI and BMI to be associated with increased risk of VTE. IT also showed anticoagulation to be an important factor for PE and DVT (OR 7.14, p=0.006 and OR 2.48, p=0.012 respectively) but not bleeding, wound complications or mortality.	**Bias considerations:** Retrospective study with cohorts with slightly different demographics that were accounted for as much as possible in the propensity score-matching, but still persisted (biased to aspirin); slightly less KA in aspirin group (36.8% vs 47.0%, potential bias to aspirin). Warfarin users were more likely to be operated on earlier on in the data period - this is relevant if surgical procedures changed during the 13-year study period. Acknowledged some people may have had supra or subtherapeutic INR but no therapeutic time in range (TTR) data reported. There was no indication as to how many patients were using concurrent aspirin (for long-standing CVD) in warfarin group. Performance and attrition bias unknown. **Bias Risk:** High. **Efficacy Findings:** There was a significantly lower incidence of VTE in aspirin users.[*] **Safety Findings:** The rate of bleeding was similar

Unmatched data:

Table 9: VTE (at 90 days post-operation)

	Warfarin (n=26,123)	**Aspirin (n=2,800)**	**p**
PE	280 (1.07%)	4 (0.14%)	<0.001
DVT	259 (0.99%)	8 (0.29%)	<0.001

Table 10: Other postoperative complications (at 90 days post-operation)

	Warfarin (n=26,123)	**Aspirin (n=2,800)**	**p**
Acute infection	198 (0.76%)	11 (0.39%)	0.03
Haematoma/bleeding	33 (0.13%)	-	0.07
Wound drainage	198 (0.76%)*	1 (0.04%)	<0.001
90 day mortality	85 (0.30%)*	1 (0.04%)	0.003

* These percentages are different to those reported in the original article (which appear to be wrong for warfarin for wound drainage n=198/26123, 0.57% and 90 day mortality n=85/26,123 0.03%).

Other comments: Did not capture readmissions to other hospitals or out-of-hospital complications – and thus may underestimate/inaccurately describe actual VTE incidence in cohorts.

between cohorts, but there was a trend to increased risk of infection in the warfarin cohort.

Also see other comments.

Study	Design	Findings	Assessment
Holden et al [25] USA d.2011-2013 HA or KA p.2015 <u>Level III-3</u> Retrospective cohort (with historical and concurrent cohort) [retrospectively collected database] External funding not reported No CoI	**Patients:** 1,486 patients (53% KA), divided by what they received. In January 2013 the institution added aspirin to the options for prophylaxis, and use subsequently increased from 14% to >75%. **Group A =** aspirin *† **Group B =** enoxaparin (18%) / dalteparin (54%) / warfarin (INR 1.7-2.3, (25%)) / unspecified (2%)^ **Excluded if:** long-term therapeutic anticoagulant use, or if the prophylaxis regimen could not be determined. **Outcomes:** symptomatic VTE (within hospital or any readmissions within 35 days of discharge). **Other details:** "There was no differences in the use of nonpharmacologic prophylaxis (>95% in each group)". Patients were generally mobilised as early as possible after surgery. *Dose not specified, but the majority (8/9) of VTE in aspirin users were using 325mg twice daily (bd). †Duration not specified. No overall or long-term adherence data collected, however all inpatient doses of treatment were administered for patients who developed a VTE.	**Table 11: VTE (at 35 days post-operation)** | | **All anticoag. (n=827)** | **Aspirin (n=552)** | **Enoxaparin (n=153)** | | VTE§ | 11 (1.33%) | 9 (1.63%) | 1 (0.65%) | NB: 'all anticoagulants' includes enoxaparin users, however they have also been separated out as part of the analysis. § p not significant for any comparisons. Does not specify what the risk factors were: 'Demographic information were similar between groups. …No difference was found between a random sample of 100 patients treated with aspirin and 100 treated with anticoagulants in baseline VTE risk.' **Other comments:** Authors note study was under-powered to detect statistically significant differences in VTE. Furthermore, study didn't capture readmissions to other hospitals or out-of-hospital complications – and thus may underestimate/ inaccurately describe actual VTE incidence in cohorts.	**Bias considerations:** Retrospective study reliant on admission/readmission data for VTE incidence or adjustment in analyses i.e. likely to have under-reported VTE incidence generally, with potential bias against warfarin due to the increased attentive surveillance required with warfarin treatment. No anaesthesia data or treatment adherence/TTR data (attrition bias unknown). **Bias Risk:** High **Efficacy Findings:** No difference in VTE incidence between groups, and no change in VTE incidence when the institution's aspirin utilisation increased 5-fold. **Safety Findings:** None available. Also see other comments.

Observational data

Bozic et al. (d.2003-2005, p. 2014, USA)[44]: A retrospective analysis of 93,840 primary KA patients across 307 hospitals who received either aspirin, warfarin or prophylactic doses of an injectable anticoagulant postoperatively reported that warfarin users had a higher adjusted risk of proximal DVT or PE events compared to aspirin users (OR 1.34 (95%CI 1.05-1.70, p<0.01)). There was a statistically significant unadjusted difference in bleeding risk between aspirin and anticoagulant users; this was not significant after adjustment for patient factors, site characteristics, propensity score etc. There were no differences in unadjusted / adjusted odds ratio for surgical site infection or mortality between the aspirin and anticoagulant users. 'Aspirin, when used with other clinical care protocols, may be effective for certain TKA patients.'

Chu et al. (d.2009-2012, p.2017, USA)[45]: A retrospective analysis of 399,696 elective KA and HA patients at 323 and 327 hospitals respectively who received either aspirin (only 8% of patients), an anticoagulant (80%) or aspirin plus an anticoagulant (12%), reported that patients who underwent KA and received aspirin only had a lower risk of postoperative VTE (adjusted OR of 0.34 (95CI 0.24-0.48)) compared to patients who received an anticoagulant or an anticoagulant and aspirin. For HA patients, VTE risk was not statistically different between the aspirin only and anticoagulant-based prophylaxis.

Data tables: Protocol 2 – Aspirin as a component of staged supply prophylaxis

Study	Design	Findings	Assessment

Anderson et al [29]

Canada

d.2007-2010

Elective unilateral HA

p.2013

Level II Randomised controlled trial

Funded by Canadian Institutes of Health Research and Pfizer Pharmaceuticals Canada. In-kind support provided by Bayer HealthCare.

Several authors paid personally / received grants by Pfizer or other pharmaceutical / medical entities. See COI form for more information.

Patients: 785 patients (multi-centre) received dalteparin 5000 units for 10 days and then were randomised into two groups:

***Group A* =** dalteparin 5000 units for another 28 days

***Group B* =** aspirin 81mg for another 28 days

Patients also received placebo tablets / injections and everyone was blinded to allocation of the study medication.

Excluded if: history of hip fracture in prior 3/12, metastatic cancer, life expectancy < 6/12, bleeding that precluded use of anticoagulant prophylaxis (investigator's judgement), active peptic ulcer disease or gastritis that precluded aspirin use (per investigator's judgement), aspirin allergy, heparin induced thrombocytopaenia (HIT) or heparin allergy, creatinine clearance (CrCl)<30mL/min/1.73m^2, platelet count < 100x10^9 cells/L, need for long-term anticoagulation due to a pre-existing comorbid condition or VTE developing after surgery but before randomisation, and unwillingness/inability to give informed consent. Long-term aspirin users were also initially excluded, but then were randomly assigned to the two groups, provided their dose was less than 100 mg daily.

Outcomes: Primary outcome measure was incidence of symptomatic proximal DVT or PE within 90 days post-randomisation. Secondary outcome measure was death, major bleeding, clinically important non-major bleeding, myocardial infarction, stroke and wound infection. Primary safety endpoint was bleeding (major if overt and either fatal, symptomatic into a critical area / organ, or caused ≥ 20g/L Hb loss or transfusion of 2 units or more

Table 12: VTE (at 90 days post-randomisation)

	Dalt-Dalt (n=398)	Dalt-Aspirin (n= 380)	*p*
Proximal DVT	2 (0.5%)	1 (0.3%)	-
Non-fatal PE	3 (0.8%)	-	-
Fatal PE	-	-	-
Total	5 (1.3%)*	1 (0.3%)	0.22

*does not include 1 distal DVT in dalteparin-dalteparin group which was not considered an outcome event by the nature of its location.

Table 13: Other post-operation complications (at 90 days post-randomisation)

	Dalt-Dalt (n=400)	Dalt-Asp (n= 385)	*p*
Major bleeding	1 (0.3%)	-	1.00
Clinically significant non-major bleeding	4 (1.0%)	2 (0.5%)	0.68
Minor bleeding	18 (4.5%)	8 (2.1%)	0.16
Wound infection	10 (2.5%)	12 (3.1%)	0.67
Myocardial infarction	1 (0.3%)	-	1.00
Death	1 (0.3%)*	-	1.00
Stroke	-	-	1.00
Thrombocytopenia	1 (0.3%)	-	1.00

Bias Considerations:

No comparison across different study centres (operational procedure left to discretion of surgeon; no mention of whether mechanical TP/ mobilisation practices differed); no scan to exclude pre-op VTE; early termination meant study did not meet pre-study targets (1,100 per group). Relatively large noninferiority margin (2%) but findings well within the margin. Drop-out was low (~1%).

Bias Risk: Low.

Efficacy Finding: Aspirin following dalteparin found to be non-inferior to continuing dalteparin, ((0.3% vs 1.3% (1% difference, CI -0.5 to 2.5 % points) *p*<0.001) but not superior (*p*=0.22), for the prevention of VTE.

Safety Finding: No statistically significant differences observed in secondary outcomes (wound infections, arterial vascular events or death) or safety endpoint.

Other comments: This is one of the better designed trials in this review.

of whole blood or red blood cell (RBC)). Minor bleeding was overt bleeding that did not fall into one of the aforementioned categories.

Other details: Approximately two thirds received regional anaesthesia (RA) in each group, and one third received general anaesthesia (GA). Mobilisation and mechanical thromboprophylaxis details unavailable.

Study aimed for 1,100 patients per group, but stopped early due to slow recruitment (when rivaroxaban entered the market).

Treatment adherence self-reported at > 90% (poorer adherence in LMWH group (details not available)); analysis was performed as an intention-to-treat analysis.

*died by suicide.

No patients on long-term aspirin (n=39) had a VTE or major bleeding event – only one clinically significant non-major bleed occurred in this group.

Although the two groups had some differences in demographics related to VTE risk factors (e.g. prior history of VTE, active cancer in past 5 years) and bleeding (e.g. prior history of major bleeding) that favoured aspirin, they were not statistically significant. Furthermore, in a letter to the editor (in response to Granziera et al), the authors state that none of the patients with these VTE or bleeding risk factors developed a VTE or bleed (respectively) postoperatively.[46, 47]

Study	Design	Findings	Assessment
Hamilton et al [30] USA d.2009-2010 Primary HA and KA p.2012 Level III-3 Retrospective cohort study No external funding CoI online but not accessible	**Patients:** 1,000 arthroplasty cases, divided into two groups depending on who their operating surgeon was. ***Group A* =** operated on by 2 surgeons (study group). Patients received enoxaparin during inpatient stay (30mg bd for knees and 40mg daily for hips; renally impaired patients received enoxaparin 30mg daily irrespective of surgery). Upon discharge, they received 325mg aspirin bd for 28 days. Average LOS was 3.75 days (average anticoagulant prophylaxis was 2.75 days). ***Group B* =** operated on by a third surgeon (control). Patients received enoxaparin for 2 weeks, followed by aspirin 325mg bd for 2 weeks. **Excluded if:** - a history of VTE - current treatment with warfarin - undergoing simultaneous bilateral (B/L) procedures, - current diagnosis of malignancy, - a history of bleeding disorder or major bleeding episodes (intracranial bleed or GI bleed requiring transfusion). **Outcomes:** Follow-up was at six weeks and six months. 3-month data were collected for complications. Endpoints of interest: symptomatic VTE (DVT, PE), postoperative transfusion requirements, infection (superficial and deep) and readmission within three months. **Other details:** All performed under general anaesthesia, mechanical calf compression devices were used on all patients and physical therapy began the day of surgery or one day postoperatively for afternoon operations.	**Table 14: VTE (at 3 months post-operation)** | | **Study group (n=500)** | **Control (n= 500)** | ***p*** | |---|---|---|---| | DVT | 1 (0.2%) | 7 (1.4%) | 0.07 | | PE | 2 (0.4%) | 2 (0.4%) | 1.00 | **Table 15: Other post-operative complications (at 3 months post-operation)** | | **Study group (n=500)** | **Control (n= 500)** | ***p*** | |---|---|---|---| | Bleeding | 9 (1.8%) | 14 (2.8%) | 0.4 | | Deep infection | 1 (0.2%) | 4 (0.8%) | 0.37 | | Superficial infection | 14 (2.8%) | 23 (4.6%) | 0.18 | | Average units of RBC transfused per person | 0.39 | 0.57 | 0.001 | | Death | - | - | 1.00 | **Other comments:** Did not capture readmissions to other hospitals or out-of-hospital complications – and thus may underestimate/inaccurately describe actual VTE incidence in cohorts.	**Bias considerations:** There was no blinding and patients were allocated to treatment groups based on who their operating surgeon was (selection and performance bias risk). No scan to exclude pre-operative VTE. There were slight demographic differences (no ranges / standard deviation (SD) reported, unknown clinical relevance, no statistical test to check significance) and more KA (51% vs 44%) in the study group (potential bias against study group), however lower mean American Society of Anaesthesiologists (ASA) scores in the study group (potential bias to study group). Concurrent treatment with pre-operative aspirin was not taken into account as a possible confounder. No assessment of treatment adherence. **Bias Risk:** High. **Efficacy Finding:** No significant difference in overall VTE (though positive trend in study group for DVT) between treatment regimens. **Safety Finding:** No significant difference in bleeding and infection rates. Significantly increased need for RBC transfusion in patients who received longer course of anticoagulant. Also see other comments.

Observational data

Asopa et al. (d.2002-2012, p.2015, Australia)[48]: A staged supply study (enoxaparin 20mg daily in inpatient period (high-risk patients: 20mg BD) and then aspirin 300mg daily until 6 weeks post-operation) in all HA and KA patients operated on at a private hospital (n=9,035) reported a six-week VTE incidence of 2.55% (total (incl. asymp.) PE: 1.28%, incl. 0.03% fatal PE). All-cause mortality was 0.07%. The slightly higher VTE incidence (2.55% at six weeks vs. 1.2% at 3 months (Hamilton et al.[30])) may in part be because of differences in mechanical prophylaxis (TEDS vs. compression devices), in enoxaparin dosing (20mg vs 40 to 60mg per day in standard risk patients), and because the total VTE incidence included asymptomatic PE (all patients with confirmed symptomatic DVT were assessed for PE).

Data tables: Protocol 3 – Aspirin part of a risk-stratification protocol

The risk stratification protocols for the below studies are summarised on pages 70-72.

Study	Design	Findings	Assessment
Kulshrestha et al [32] India d.2008-2011 Elective unilateral or staged bilateral KA p.2013 <u>Level II</u> Randomised controlled trial No external funding No CoI	Patients: 673 patients (900 operations, incl. 227 staged bilateral KA*) were randomised into two groups (same surgeon): *Group A* = Control group. Enoxaparin (half dose 8 hours after surgery, then 20 or 40 mg daily based on renal function) for two weeks followed by two weeks of aspirin 325mg bd. *Group B* = Study group. Patients risk stratified by a DVT score – patients with scores ≤ 2 were considered standard risk and received aspirin 325mg bd for four weeks; patients with scores >2 received the above protocol (enoxaparin for 2/52 followed by aspirin for 2/52). Two fifths of patients (43%) considered standard-risk. All patients received placebo tablets / injections and patients and staff were blinded to both medication and patients' risk score. The two cohorts were similar age, BMI and gender breakup, but functional comorbidity scale was slightly higher in the control group (1.71 vs 1.56 p=0.06, *r*=0.15) and there were slightly more people in their moderate / high-risk category for DVT (score>2) (63% vs 57%, p=0.06) (i.e. biased to study group). Excluded if: using an anticoagulant long-term prior to surgery or had a contraindication to NSAIDs. Outcomes: Patient follow-up was at six weeks, three months, six months and one year (none lost). Primary outcome was symptomatic DVT and wound complications. Other details: Spinal anaesthesia; mobilised on same day of operation with regular ankle exercises as soon as regional anaesthesia wore off; intermittent calf stimulator for everyone for the first seven days. *evenly distributed between groups.	Results were analysed both based on cohort (Tables 16 and 18) and based on thromboprophylaxis (Tables 17 and 19). **Table 16: VTE (at one year)** **Control (n=450)** / **Risk stratified (n=450)** / **p** Symptomatic DVT: 8 (1.8%) / 11 (2.4%) / 0.487 Non-fatal PE: 1 (0.2%) / 2 (0.4%) / - Fatal PE: 1 (0.2%) / 1 (0.2%) / - **Table 17** / **Aspirin only (n=194)** / **Staged prophylaxis (n=706)** / **p** Symptomatic DVT: 4 (2.1%) / 15 (2.1%) / 0.957	**Bias considerations:** Placebo-controlled, double-blinded RCT. Objective risk assessment tool reduced inter and intra-observer variability (NB: only one operating surgeon but likely varying junior staff); cohorts generally similar, with trend to higher DVT and FCI scores in control group (bias potential *to* aspirin). Follow-up was 100% but treatment adherence not reported. No pre-operative VTE check. Concurrent treatment with pre-op aspirin was not reported as a possible confounder. **Bias Risk:** Low. **Efficacy Finding:** Symptomatic DVT rates not significantly different between both protocols. **Safety Finding:** Significantly higher incidence of wound complications in anticoagulated patients. **Other comments:** The 'staged supply' in this instance includes 2/52 of anticoagulation – which is what was recommended in the NHMRC Guideline following KA. Also see more comments.

Table 18: Other post-operative complications (at one year)

Table 18	Control (n=450)	Risk stratified (n=450)	p
Wound complications	38 (8.4%)	20 (4.4%)	0.014
Superficial wound infection (SWI)	6 (1.3%)	2 (0.4%)	-
Deep wound infection (DWI)	4 (0.9%)	1 (0.2%)	

Table 19	Aspirin only (n=194)	Staged prophylaxis (n=706)	p
Wound complications	2 (1.0%)	56 (7.9%)	0.0005

More comments: VTE incidence is higher in this study than the two staged supply studies in Protocol 2, however unlike those studies it only studied KA patients, who generally have a higher incidence of VTE than HA patients. Furthermore, it followed patients up for one year (vs approx. three months), and reported VTE incidence from day 0 post surgery (unlike Anderson et al[29]).

Study	Design	Findings	Assessment
Inter-mountain Joint Replacement Centre Writing Committee [33] USA d.2008-2009 Elective THA and TKA (including bilateral) or revision p.2012 Level III-2 Non-randomised experimental trial Funding not detailed. CoI online, but not accessible.	**Patients:** 696 consecutive patients were divided into two groups based on who their operating surgeon was: **Group A =** Control group (operated on by multiple surgeons) received ACCP based protocol (enoxaparin 30mg bd (2%) or warfarin (98%)). Warfarin duration varied based on target INR (INR 2.5 for 4 weeks, or 1.8-2.5 for 4 to 6 weeks). Enoxaparin duration averaged at 18 days (range 8 to 30 days). **Group B =** Study group (one surgeon's patients) received thromboprophylaxis based on a risk stratification protocol: aspirin 600mg PR post-op, then 325mg bd for 1/12 (if considered at standard risk of PE/elevated risk of bleeding) or warfarin (INR 1.8-2.5) for four weeks if considered at elevated risk of VTE. Approximately half (54%) considered standard risk. Aspirin reduced to 81mg daily if GI symptoms developed. All warfarin patients started treatment the night before surgery. **Excluded if:** trauma or fracture patient, or patient undergoing hemiarthroplasty. **Outcomes:** Primary outcomes were efficacy (symptomatic PE, DVT and total VTE) and safety (major bleeding and death) at 90 days (with follow-up questionnaires, telephone calls, social security database and death certificate review). **Other details:** 89% received spinal anaesthesia, 10.5% received general (rest = epidural). Physical therapists mobilised patients on same day of operation. All patients had foot or calf compression in the operating room and continued in the post-anaesthesia care unit. Standardised dosing nomogram used for warfarin dosing, but TTR not reported (averages at ~67% for their institution).	The study did not analyse the two cohorts separately in the statistical analysis but instead compared standard risk patients to the control group. NB: Similar breakdown of HA and KA patients in all cohorts. **Table 20: VTE (at 90 days post-operation)** **Control (n=415)** / **Risk stratified (n=281)**: Standard (n=152), Elevated (n=129) / **p (standard risk vs. control)** DVT*: 3 (0.7%) / 7 (4.6%) / 1 (0.8%) / 0.03 PE: 3 (0.7%) / 7 (4.6%) / - / 0.03 VTE: 5 (1.2%) / 12 (7.9%) / 1 (0.8%) / 0.001 Post-hoc analysis of TKA patients identified significantly more PE (5.5% vs 1.2% 95CI 1.8-12.4%, p=0.03), DVT (7.7% vs 1.2% 95CI 3.1-15.2%; p=0.004) and total VTE (11% vs 1.9% 95CI 5.4-19.3%, p<0.001) in the standard risk patients compared with the comparator group. No difference was observed in THA patients, however the number of events (2) was too low to draw conclusions. *It is not reported how many of these were proximal vs. distal DVTs. In a study of in-hospital VTE incidence in an Australian hospital, of the 4.5% DVT incidence, most (89%) were distal DVTs.[7] **Table 21: Other post-op complications (at 90 days post-op)** **Control (n=415)** / **Risk stratified (n=281)**: Standard (n=152), Elevated (n=129) / **p (standard risk vs. control)** Major Bleeding: 1 (0.2%) / 1 (0.7%) / - / 0.464 Death: 6 (1.5%) / - / 1 (0.8%) / 0.350	**Bias Considerations** Non-randomised, and unclear if care differed between surgeons (and hence groups). Treatment only blinded to physicians detecting VTE on scans. The outcomes were analysed by treatment – and the stratified groups were (as expected) statistically different to each other and the control group (biased to aspirin). The target INRs and therapy duration varied and it's not certain if TTR was similar to the institution's average. Follow-up rate was >99%, but treatment adherence rate was not reported. No pre-operative DVT check. The authors did include an analysis to exclude diagnostic suspicion bias. Concurrent treatment with pre-op aspirin was not taken into account as a possible confounder. VTE risk assessment didn't incorporate subtleties contained in Kulshrestha et al [32] (page 58). **Bias Risk:** High **Efficacy Finding:** The authors did not compare the two cohorts directly, however based on their data, the VTE comparison is 1.2% control, 4.6% risk stratified group (p=0.01) i.e. against risk stratifying. **Safety Finding:** Aspirin patients had similar bleeding incidence compared to control patients.

Study	Design	Findings	Assessment
Gesell et al [35] USA d.2005-2010 Elective primary TKA (includes bilateral) p.2013 <u>Level III-2</u> Retrospective cohort study Funding not detailed CoI online, but not accessible.	**Patients:** 2,017 patients assigned to two groups depending on who their operating surgeon was (consecutive patients for each surgeon).* Both groups received thromboprophylaxis for 6 weeks. **Group A** = A risk-stratified group from two surgeons' lists. Patients received aspirin 325mg bd if they were considered at low risk for VTE, or warfarin (INR=2) if they were considered at high risk of VTE/had an alert against aspirin/were on long-term warfarin for a cardiac condition (only 16 received enoxaparin cover until INR was therapeutic (deemed at very high risk of VTE)). Two patients also had a vena cava filter inserted preoperatively and received LMWH and warfarin postoperatively. Almost two thirds were considered low-risk (67.6%). **Group B =** Control group (one surgeon). Patients received warfarin without enoxaparin cover unless they were deemed at very high-risk of VTE (4.4%). INR target was 2. **Excluded if:** None. **Outcomes:** Not specifically stated, but all patients were followed for three months; authors compared incidence of symptomatic VTE, PE, bleeding, general and wound complications, readmission and mortality data between the two groups. **Other details:** Epidural anaesthesia, mobilised first day postoperatively, IPCD through hospital stay and encouraged to perform ankle exercises. 100% follow-up; no treatment adherence data. *study group had patients that were slightly older and heavier (3 years and BMI difference of 2.4 points, p<0.0001 for both) than the control group (i.e. bias *against* the study group), but cohorts were similar when comparing VTE and arthritic history.	**Table 22: VTE (at 3 months post-operation)** | | Study (n=1,016) | Control (n=1,001) | *p* | |---|---|---|---| | VTE | 25 (2.5%) | 22 (2.6%) | 0.7 | | Distal DVT | 9 (0.9%) | 11 (1.1%) | - | | Proximal DVT | 7 (0.7%) | 4 (0.4%) | - | | PE | 11 (1.1%) | 9 (0.9%) | 0.68 | **Table 23: Other post-op complications (at 3 months post-operation)** | | Study (n=1,016) | Control (n=1,001) | *p* | |---|---|---|---| | Wound complications[§] | 4 (0.4%) | 13 (1.3%) | 0.03 | | Major bleeding | - | 3 | 0.12 | | Mortality | 1 (0.1%)[†] | 1 (0.1%) | 0.5 | [†]death in study group was an obese lady (115 kg) who requested and received aspirin post-op; she died months months after the second side of a staged bilateral TKA performed two months apart. Cause of death unknown, however based on the stratification protocol, she should have been prescribed warfarin post-operation. [§] study group wound complications resolved with conservative management, whereas ~40% of control group wound complications required irrigation and debridement of the knee. In-hospital complications and readmission rates were similar between the two groups.	**Bias Considerations:** This study was retrospective and compared the outcomes of different surgeons' patients, creating potential allocation and performance bias (although surgeons were reported to have had 'similar surgical technique'). There were slight demographic differences with uncertain clinical relevance, however the data were potentially biased *against* the study group. There was no pre-op VTE check and concurrent treatment with pre-op aspirin was not included as a possible confounder. No assessment of treatment adherence, and TTR data not reported. **Bias Risk:** High **Efficacy Findings:** VTE incidence was similar in both groups. **Safety Findings:** The incidence of wound complications was significantly higher in the control group, however other complications (including readmissions) were similar.

Study	Design	Findings	Assessment
Nam et al [40] USA d.2010-2014 Elective unilateral primary or revision TKA or THA, unicompartm-ental knee arthroplasty (UKA) or surface replacement arthroplasty p.2016 <u>Level III-2</u> Non-randomised experimental trial Funding from Medical Compression Systems. CoI online, but not accessible	**Patients:** 3,143 joint arthroplasties were divided into two groups based on VTE risk*. **Group A =** Routine risk patients received a mobile compression device (MCD) for 10 days[†] with aspirin 325 mg bd for 6 weeks (70.7% were considered routine-risk in this study). **Group B =** High-risk patients received a (MCD) for their inpatient period with warfarin for 4 weeks postoperatively (target INR 1.8 to 2.2). TEDS for 6/52. **Excluded if:** they had a DVT detected on preoperative U/S, were being treated for a recent DVT, had a history of PE, were on chronic warfarin therapy, or scheduled for multiple surgeries within three months. Patients determined to be high risk for wound complications (e.g. due to poor nutritional status, based on discretion of treating surgeon), with a history of wound healing complications, on immunosuppressive medications for inflammatory arthritis or a solid organ transplant, or on renal dialysis were also excluded. **Outcomes:** Primary outcome was symptomatic DVT or PE at six weeks and six months. Safety outcome was rate of major bleeding (six weeks) and wound problems (two weeks). Patient deaths due to VTE and all causes were also recorded. **Other details:** As part of the study protocol, all patients received mechanical prophylaxis (see above group details). Anaesthesia not reported. All patients were mobilised early. Ultrasound conducted to exclude patients with pre-operative DVT, but only performed on people who had a history of DVT (positive patients were excluded, and negative patients were deemed high-risk). *NB: Protocol changed over the study period. In the initial period, 57.1% were categorised as standard-risk; following the protocol change, this increased to 83.1% (overall = 70.6%). [†] Goal was to wear them for 23 hours a day; approximately 84.5% wore the MCDs for >18 hours daily.	**Table 24: VTE (all data[§])** | | Routine (n=2,222) | High-risk (n=921) | *p* | |---|---|---|---| | VTE at 6 weeks | 13/1996 (0.7%) | 4/785 (0.5%) | 0.67 | | VTE at 6 months | 13/2057 (0.6%) | 9/848 (1.1%) | 0.23 | | DVT at 6 Months | 8 (0.4%) | 7 (0.8%) | | | PE at 6 Months | 5 (0.2%) | 2 (0.2%) | | **Table 25: Other post-operative complications (all data[§])** | | Routine (n=2,222) | High-risk (n=921) | *p* | |---|---|---|---| | Major bleeding at 6 weeks | 7/1991 (0.4%) | 16/787 (2.0%) | <0.001 | | Wound prob. at 2 weeks | 5/2088 (0.2%) | 11/835 (1.3%) | <0.001 | | Days of drainage[#] 0-3 4-7 >7 | N=2084 86.6% 9.4% 4.0% | N=831 80.1% 11.9% 7.9% | <0.001 | | Death – VTE | 0 | 0 | - | | Death – all causes | 1 (0.4%) | 1 (0.7%) | >0.9 | [§] All data are presented even though VTE risk assessment changed during the study. This is because the VTE incidence before and after the change was 'virtually identical'. NB: Study table 9 in the original paper shows there was a statistically significant increase in the 6-month VTE incidence in the high-risk group after the protocol change (from 0.5% to 2.4%, p=0.04),	**Bias considerations:** No blinding and six surgeons with ability to exclude patients at their discretion based on their potential for wound complications. Average TTR not reported, and the mechanical prophylaxis use differed between the two groups (cannot control for its effect). Pre-operative DVT screen only performed on patients with a history of VTE. No assessment of treatment adherence or performance bias (particularly in relation to outcome surveillance). Patients likely to be completely different between cohorts, but age, gender and operation details (revision vs. primary, right vs. left) were the only comparisons reported (as expected, biased *to* aspirin cohort). Unclear if surgery distribution (i.e. of KA patients) varied between cohorts. **Bias Risk:** High (incl. study design). **Efficacy Findings:** VTE incidence not different between cohorts, however this must be interpreted in light of cohort differences (i.e. one could argue VTE incidence may have been lowered in the routine cohort if they had been prescribed an anticoagulant).

		however this may in part be due to the increased concentration of high-risk patients in the group when the protocol was changed. [#]There was a statistically significant decline in the number of patients who required ≥4 days drainage in both low (from 18.1% to 10.5%) and high (from 22.2% to 14.8%) risk groups after the risk stratification protocol changed.	**Safety Findings:** Significantly less bleeding and wound complications in the aspirin group. **Other Comments:** Patients in the aspirin group had superior satisfaction scores when surveyed at two and six weeks vs. patients in the warfarin group.

Study	Design	Findings	*Assessment*
Odeh et al [34] USA d.2013-2014 Primary, revision or bilateral total hip or knee arthroplasty p.2016 Level III-2 Retrospective cohort study with historical comparison [Electronic medical records] Funding not detailed. CoI online, but not accessible	**Patients:** 2,611 consecutive patients were divided into two groups depending on when they were operated on at a single institution. **Group A =** operated on between October 2013 and March 2014; received enoxaparin 40mg daily for 2 to 4 weeks* ('gold standard') or rivaroxaban 10mg daily for 14 days or warfarin with target INR 2-3 (duration unclear). **Group B =** operated on after May 2014 (through to October 2014) after a transition month (April 2014). All patients were risk stratified. Standard risk patients received aspirin 325mg bd for 28 days and were discharged with a sequential pneumatic compression device (SPCD) to be used for 20 hours a day for 28 days†. High-risk patients received an anticoagulant (as above, except enoxaparin changed to 30mg bd for two to four weeks *§). Almost two-thirds (59.9%) were considered standard-risk in this cohort. **Excluded if:** None. **Outcomes:** Patients were followed up at around two to four weeks and then again at six to ten weeks post-operation depending on surgeon preference. Outcomes not very clear (time-wise), however patients were reviewed for symptomatic DVT and PE, infection, SWI, DWI, bleeding complications and 30-day readmission rates. **Other details:** Everyone took 325mg aspirin the night before surgery, and received SPCD on the non-operative limb during the operation. Ongoing SPCD used in group B standard risk patients only. Anaesthesia not reported. Patients received postoperative physio, but unclear when they mobilised. SPCD compliance unknown, however patients received follow-up calls to encourage compliance post-discharge. * Unclear if duration was based on operation (i.e. two weeks for KA, four weeks for HA) or surgeon / patient preference. † The text is not clear here. It states standard risk patients were "placed on the aspirin and/or SPCDs protocol", but then suggests all standard risk patients received both. §In the text, authors state that 40mg bd of enoxaparin was prescribed, however in figure 1 of the study paper, it is listed as 30mg bd.	**Table 26: VTE (time-line unclear)** | | **Control (N=1,203)** | **Risk stratified (N=1,408)** | | **p** | | | | Standard (n=843) | Elevated (n=565) | p | | | Total VTE | 19 (1.6%) | 10 (1.2%) | 11 (1.9%) | 0.249 | 0.855 | | DVT | 6 (0.5%) | 1 (0.1%) | 1 (0.2%) | | | | PE | 13 (1.1%) | 9 (1.1%) | 10 (1.7%) | | | **Table 27: Other post-operative complications (time-line unclear)** | | **Control (N=1,203)** | **Risk stratified (N=1,408)** | | **P** | | | | Standard (n=843) | Elevated (n=565) | | | Adverse events | 48 (4.0%) | 27 (3.2%) | 24 (4.3%) | 0.624 | | 30 day readmission | 30 (2.5%) | 17 (2.0%) | 14 (2.5%) | 0.622 | **Safety Findings:** There is a trend to reduced adverse events in the standard risk patients (those who received aspirin) but this did not reach statistical significance.	**Bias considerations:** Retrospective study with historic control, however the time difference is very small, and the authors state that there was no other difference in treatment variables between the two periods. Cohorts were similar in age, gender and BMI, but no cohort analysis of medical characteristics was reported; surgery distribution also not reported. Mechanical prophylaxis use differed between the two groups (cannot control for its effect). Multiple surgeons' patients were reviewed, and authors noted there were variations in procedures and implants, however cohorts were not assigned based on surgeon. Unclear what proportion of patients were prescribed warfarin, no TTR data and no assessment of treatment adherence or performance bias (particularly in relation to outcome surveillance). Unclear how follow-up timeline/treatment durations varied between cohorts. **Bias Risk:** High. **Efficacy Findings:** No difference in VTE incidence in the two protocols (1.6% vs. 1.5%). (p=0.563), potentially due to the study being under-powered. Also see safety findings.

Study	Design	Findings	Assessment
Vulcano et al [36] USA d.2005-2011 Elective primary HA and KA (TKA and UKA) p.2012 Level III-2 Retrospective Cohort Study Funded by an individual and the Simon Foundation No CoI	**Patients** 1,568 patients (one surgeon) were retrospectively reviewed. All patients were stratified into three risk groups in hospital – standard, high risk, very high risk. They received six weeks of thromboprophylaxis, varying based on their group.* **Group A =** standard risk = aspirin 325mg bd **Group B =** high risk = warfarin† **Group C =** very high risk = warfarin† with LMWH 40mg until INR therapeutic, or vena cava filter and warfarin,† and LMWH postoperatively. Over two thirds were considered standard-risk (73.5%) in this study. **Excluded if:** None. **Outcomes:** 90-day symptomatic complications. **Other details:** Epidural anaesthesia (99%), IPCD in recovery (duration unclear), mobilised on day one postoperatively and encouraged to perform ankle exercises. No patients lost to follow-up. *Some patients received different treatment to what was assigned to their group; this occurred both ways with some Group A patients receiving warfarin, and some Group B patients receiving aspirin. †Target INR = 2 NB: Some of these patients were also reported in the study by Gesell et al (see page 61).	**Table 28: VTE (at 90 days post-operation), by group** | | Standard (n=1,152) | High risk (n=389) | Very high risk (n=27) | | VTE | 13 (1.1%) | 6 (1.5%) | - | **Table 29: VTE (at 90 days post-operation), by agent (excludes group C)** | | Aspirin (n=1,115) | Warfarin (n=426) | | Total VTE | 1.2% | 1.4% | | PE | 0.36% | 0.9% | | Proximal DVT | 0.45% | 0.47% | | Distal DVT | 0.36% | 0.47% | **Table 30: Other 90-day post-operative complications, by group** | | Standard (n=1,152) | High risk (n=389) | Very high risk (n=27) | | Minor bleeding | - | 4 (1%) | - | | Major bleeding | 3 (0.3%) | 3 (0.8%)§ | - | | SWI | 3 (0.3%) | 11 (2.8%) | - | | DWI | - | 1 (0.3%) | - | § one patient underwent bilateral TKA.	**Some considerations:** Surgeon blinded to treatment at time of the review, however no further blinding (e.g. of patients or other staff) reported. TTR data not reported and no assessment of treatment adherence or performance bias (particularly in relation to outcome surveillance) reported. Preoperative conditions and demographics not compared between treatment groups (only operation groups), but presumably different. IPCD use not clear. Standardised protocol for surgery and implant. The distribution of TKA patients increased from Group A to C (36%, 54%, and 63%) potentially biasing to standard risk patients. **Bias risk:** High (incl. study design). **Efficacy Findings:** VTE incidence appears similar between aspirin and warfarin groups, however statistical comparison not reported. Furthermore, this result must be interpreted in light of cohort differences (i.e. one could argue VTE incidence may have been lowered in the aspirin group if they had been prescribed an anticoagulant). **Safety Findings:** Less bleeding and wound complications in the aspirin group compared to the warfarin group, and in the

standard vs high risk group (no statistical comparison reported).

Table 31: Other 90-day complications, by agent (excludes group C)

	Aspirin (n=1,115)	Warfarin (n=426)
Minor bleeding	-	0.9%
Major bleeding	0.3%	0.7%
Wound complications	0.45%	3.5%
SWI	0.27%	2.6%
DWI	-	0.2%
Wound drainage	0.18%	0.7%

Study	Design	Findings	Assessment
Nam et al [38] USA d.2011-2014 Simultanous bilateral TKA p.2015 <u>Level III-2</u> Retrospective Cohort Study Funding details not reported CoI online, but not accessible.	**Patients:** 96 patients (192 TKAs) were retrospectively reviewed; they had received thromboprophylaxis based on a risk stratification protocol instigated in hospital: ***Group A* =** standard risk = 47 patients received aspirin (325mg bd for 6/52) + MCD for 10 days. ***Group B* =** high risk = 49 received warfarin (target INR either 2 or 2.5 at surgeon's discretion, for 4/52) + MCD for inpatient period. Just under half of all patients were considered standard-risk in this study (49.0%). **Excluded if:** undergoing staged bilateral TKA, or with current diagnosis of DVT, PE or chronic VTE on ultrasound. **Outcomes:** Primary outcome measure was incidence of symptomatic VTE. Follow-up was at two weeks and then again at four to six weeks postoperatively. Any postoperative wound or medical complications and readmissions within three months of surgery were also evaluated. **Other details:** Most patients received spinal anaesthesia (>78%), and were mobilised on day 0. Mobile compression devices were part of both protocols, but varied in duration of use.	No VTE in aspirin group, and only one proximal DVT in the warfarin group. Although the numbers are small, it is worth noting that this study was conducted in response to a study by Levy et al. which compared thrombosis incidence in unilateral (287 knees) vs simultaneous bilateral TKA (110 knees) using MCDs only as prophylaxis.[49] Levy et al. reported a 3-month symptomatic VTE incidence of 3.1% (0 PE) in the unilateral TKA group and 10.9% (3.6% PE) in the simultaneous bilateral group i.e. significantly higher than in this study. Patient groups in the present study were similar in ASA score but slightly younger (4.4 years, p=0.03) and more likely to be male in aspirin group (55% vs 43%, p=0.09).	**Some considerations:** Small numbers mean small incidence of outcomes to compare and the study is at significant risk of small trial bias risk (total population <100); no blinding of thromboprophylaxis, no information about TTR, no adherence information and mechanical prophylaxis differed between the two groups (cannot control for its effect). Unclear if follow-up timeline varied significantly between cohorts. **Bias risk:** High (incl. study design). **Efficacy:** The results of the present study, viewed in light of the findings by Levy et al. (though both limited by small numbers), suggest that risk-stratified pharmacological prophylaxis + MCD is more effective at preventing VTE than MCD alone following bilateral TKA, however this warrants further investigation. **Safety:** Cannot evaluate.

Study	Design	Findings	Assessment
Nam et al [39] USA d.2010-2014 Primary and revision (unilateral) THA, or surface replacement arthroplasty p.2015 <u>Level III-2</u> Non-randomised experimental trial Funding received from Medical Compression Systems CoI online but not accessible.	**Patients:** 1,859 hip arthroplasty patients were prospectively divided by their VTE risk into two groups*: **Group A =** standard (routine) risk patients = received MCD for 10 days with aspirin 325 mg bd for six weeks **Group B =** MCD for inpatient stay with warfarin for four weeks postoperatively (target INR 1.8 to 2.2). High-risk patients also got thigh high compression stockings for both legs for 6/52. **Excluded if:** they had a DVT detected on preoperative U/S, were being treated for a recent DVT, history of PE, were on chronic warfarin therapy, or scheduled for multiple surgeries within three months. Patients determined to be high risk for wound complications (e.g. poor nutritional status, deconditioned status based on discretion of treating surgeon, multiple previous incisions around the hip, previous radiation therapy around the hip) were also excluded. **Outcomes:** Primary outcome was symptomatic DVT and PE incidence. Patients reviewed at two weeks postoperatively, at the four to six week mark, and then again at the six month mark for complications. **Other details:** Everyone received MCD in contralateral limb prior to the operating room, and operative extremity postop in the operating room. Authors aimed for MCDs to be used for 23 hours/day (compliance unknown). Mobilised on day 0. Anaesthesia not reported. *NB: Protocol changed over the study period. In the initial period, 64.4% were categorised as routine-risk; following the protocol change, this increased to 85.1% (overall = 75.4%).	**Table 32: VTE** | | **Routine (n=1,402)** | **High risk (n=457)** | **p** | | VTE at 6 weeks | 7/1,284 (0.5%) | 2/389 (0.5%) | 1.00 | | DVT | 5 (0.4%) | - | 0.21 | | PE | 2(0.2%) | 2 (0.5%) | - | | VTE at 6 months | 8/1,215 (0.7%) | 5/398 (1.3%) | 0.25 | **Table 33: Other post-operative complications** | | **Routine (n=1,402)** | **High risk (n=457)** | **p** | | Major bleeding at 6 weeks | 7/1,282 (0.5%) | 8/391 (2.0%) | 0.006 | | Wound problems at 2 weeks | 2/1,324 (0.2%) | 5/419 (1.2%) | 0.01 | | Days of drainage 0-3 4-7 >7 | n=1,325 84.1% 11.2% 4.7% | n=416 74.8% 14.2% 11.1% | <0.001 | | Readmission within 6 months | 121/1,215 (10.0%) | 56/398 (14.1%) | 0.02 | All data are presented even though VTE risk assessment changed during the study. This is because patients' VTE incidence before and after the change was 'identical'. NB: Unlike Nam et al [40] tables were not provided in the original article for the reader to compare event rates pre and post protocol change.	**Some considerations:** Preoperative U/S was completed, however there was no blinding of thromboprophylaxis; there was also no information about TTR and no assessment of treatment adherence or performance bias (particularly in relation to outcome surveillance). Mechanical prophylaxis differed between the two groups (cannot control for its effect). Patients likely to be completely different in demographics and co-morbidities between cohorts, but age, gender and operation details were the only comparisons reported (as expected, biased to aspirin cohort). **Bias risk:** High (incl. study design) **Efficacy:** VTE incidence was similar between cohorts. **Safety:** Incidence of wound problems and major bleeding was significantly lower in the routine group. **Other Comments:** Patients in the aspirin (routine) group had superior satisfaction scores when surveyed at two and four to six weeks vs. patients in the warfarin group. This may have impacted on compliance and potentially outcomes.

Study	Design	Findings	Assessment
Huang et al [37] USA d.2000-2014 Primary or revision TJA p.2016 <u>Level III-2</u> Retrospective cohort study [prospectively collected database] Funding details not reported COI online, not accessible.	**Patients:** 30,270 patients received either warfarin or aspirin post TJA. They were retrospectively divided into two groups based on a risk stratification protocol (low and high risk for VTE). **Group A** = 22,751 low-risk (18% aspirin, 82% warfarin)* **Group B** = 7,519 high-risk (10.5% aspirin, 89.5% warfarin) Determination of thromboprophylaxis was dependent on surgeon preference, however warfarin INR target was 1.8-2.0, for four weeks, and aspirin was dosed at either 81mg or 325mg bd for four weeks. **Excluded if**: received heparin or heparin based products, or a direct oral anticoagulant (DOAC) pre- or post-operatively. **Outcomes**: 90-day incidence of symptomatic VTE, acute periprosthetic joint infection (PJI), GI complications and mortality within 90 days. **Other details**: All patients received mechanical compression devices during their hospital stay and physical therapy began on the day of surgery, or next. No information regarding anaesthesia. *Three-quarters of patients were considered low-risk (75.1%).	**Table 34: VTE (at 90 days post-operation)** | | **Low-risk** | | | **High-risk** | | | | | Aspirin | Warfarin | ***p*** | Aspirin | Warfarin | ***p*** | | VTE | 0.2% | 1.8% | † | 0.6% | 3.2% | † | | DVT | 0.1% | 0.8% | † | 0.5% | 1.7% | § | | PE | 0.1% | 1.2% | † | 0.1% | 1.8% | † | **Table 35: Other post-op complications (at 90 days post-operation)** | | **Low-risk** | | | **High-risk** | | | | | Aspirin | Warfarin | ***p*** | Aspirin | Warfarin | ***p*** | | PJI | 0.2% | 1.1% | † | 0.1% | 1.7% | † | | GI# | 0.2% | 0.2% | - | - | 0.6% | | | Death | 0.1% | 0.2% | - | 0.1% | 1.1% | † | † $p<0.001$ § $p<0.05$ #GI complication (ulcer/bleed) Age, BMI, CCI were all higher in the warfarin groups cf. aspirin groups. In the multivariate analysis, warfarin was an independent risk factor for VTE in the higher risk VTE patients (OR 5.1 (95CI 2.1-12.5 p<0.001)). Other independent risk factors for VTE in this group: - Older age (OR 1.05 (95CI 1.04-1.06)) - Higher BMI (OR 1.04 (95CI 1.02-1.05)) - Anaemia (OR 1.4 (95CI 1.0-1.9) - Chronic obstructive pulmonary disease (COPD) (1.5 (95CI 1.1-2.0) - Hypercoagulable state/history of VTE (OR 3.0 (95CI 1.8-5.0)) - A history of MI (OR 1.6 (95CI 1.1-2.5). Warfarin was also a risk factor for acute PJI in the high-risk group (OR 13.7 (95CI 1.9-98.5) p<0.001), along with older age, higher BMI, hypercoagulable state and history of myocardial infarction.	**Bias considerations:** Retrospective study with selection bias potential (to aspirin). A different VTE diagnostic tool was used from 2007 onwards - could there have also been changes in surgical procedure over the 15 years that influenced outcomes? No TTR data reported, nor was potential performance bias addressed (particularly in relation to outcome surveillance). There was no indication as to how many patients were using concurrent aspirin (for long-standing CVD) in warfarin group (and presumably vice versa). Different aspirin doses used. **Bias Risk**: High. **Efficacy Findings:** VTE incidence was significantly lower in aspirin groups, even in higher risk patients. **Safety Findings**: Aspirin users were significantly less likely to develop prosthetic joint infection cf. warfarin users, even in the high-risk group. They also had a significantly lower mortality rate in the high-risk group. **Other Comments:** Sub-analyses identified that the incidence of postoperative VTE in people with a history of VTE was 7.3% in warfarin users and 3.8% in aspirin users.

Protocol 3: Risk-stratification protocols

Kulshrestha et al [32]
Considered high risk if DVT score > 2 points. DVT scoring below.

3 points for each of the following:
- Age >75 years*
- History of DVT or PE
- Family history of thrombosis
- Family history of blood clotting disorders.

2 points for each of the following:
- Age 60-74 years
- Cancer (current or previous)
- Recent (within 6 weeks) major surgery lasting >45 mins
- Recent (within 6 weeks) confinement to bed for more than 72 hours
- Plaster immobilisation of lower limb in the past six weeks
- Central venous access.

1 point for each of the following:
- Age 41-60 years
- Varicose veins
- Major surgery within the past month
- History of inflammatory bowel disease (IBD)
- Legs are currently swollen
- Overweight or obese
- History of recent MI
- Congestive heart failure
- Serious infection (e.g. pneumonia)
- COPD
- Insulin dependent diabetes mellitus (IDDM)
- Currently on bed rest or restricted mobility
- Hormone replacement therapy (HRT)
- Pregnant / had a baby in the past month
- Smoker.

*Age not clearly categorised into the different point groups.

Nam et al [40]
High risk if:
- Age ≥ 70 years
- History of DVT with negative preoperative ultrasound examination
- Active cancer
- Hypercoagulable states (protein C, protein S, factor V Leiden etc.)
- Multiple medical comorbidities (two of the following three conditions: heart disease, lung disease, diabetes)
- Morbid obesity (BMI ≥ 40 kg/m^2)
- Family history (parent or sibling) of DVT or PE
- Immobility (i.e. limited weight bearing) – surgeon's discretion.

At the two-year mark, a mid-term analysis identified that patients in the high-risk cohort had a similar incidence of VTE as the routine-risk patients, but a greater incidence of major

bleeding, wound problems and incisional drainage. Subsequently, some risk factors were removed from the inclusion criteria for the high-risk cohort (age ≥ 70, multiple medical comorbidities, and BMI ≥ 40 kg/m^2).

Intermountain Group [33]
High risk if:

- Heart failure
- Atrial fibrillation (AF)
- Recent surgery for malignancy or active chemotherapy
- VTE within the previous 5 years
- Heritable or acquired thrombophilia.

Patients not considered high risk if:

- Had a history of VTE over 5 years ago
- Inactive malignancy
- Currently used HRT
- Chronic tobacco use
- Blood diseases including sickle cell anaemia, polycythaemia vera or thrombocytopenia.

Gesell et al [35]
Low risk if no personal or family history of VTE, or predisposing factors for VTE (as listed below).

High risk if obese, have active or recent malignancy, personal history of VTE, familial history of spontaneous VTE, or known hypercoagulable disorder.

In addition, patients who were expected to mobilise slowly after surgery either due to a poor preoperative functional status (e.g. wheelchair bound), comorbidities or morbid obesity were also assigned to the high-risk group.

Vulcano et al [36]
High risk if history of obesity, malignancy, VTE, active or recent cancer, known hypercoagulable disorder, debilitated patients who were expected to mobilise slowly after surgery, and those undergoing bilateral TKA.

Patients with a history of non-life-threatening VTE (proximal DVT or PE) were considered a very high-risk group (received warfarin and LMWH until the INR was therapeutic).

Patients with a recent history of a life-threatening PE (within 12 months), multiple PE, or multiple proximal DVTs were considered very high risk of VTE (received vena cava filter (either permanently or placed temporarily preoperatively (and removed after three months)) with warfarin and LMWH (presumably until INR therapeutic)).

Nam et al [38]
Stratified into the warfarin group if:

- Prior chronic anticoagulant use
- Prior VTE event
- Family history of VTE
- Cardiac history requiring blood thinners (AF, stents, cardiac valve).

Patients unable to tolerate aspirin and those with a history of gastrointestinal disorders (including ulcers) were also given warfarin instead of aspirin.

Nam et al [39]

High risk if:

- Age ≥ 70 years
- History of DVT with negative preoperative ultrasound examination
- Active cancer
- Hypercoagulable states (protein C or protein S deficiency, Factor V Leiden etc.)
- Multiple medical comorbidities (2 of the following 3 conditions: heart disease, lung disease, diabetes)
- Morbid obesity (BMI ≥ 40 kg/m^2)
- Family history of DVT or PE
- Prolonged immobility (i.e. limited weight bearing) – surgeon's discretion.

At the two-year mark, mid-term analysis identified that patients in the high-risk cohort had a similar VTE incidence as the routine-risk patients; some risk factors were subsequently removed from the inclusion criteria for the high-risk cohort (age ≥ 70, multiple medical comorbidities, and BMI ≥ 40 kg/m^2).

Huang et al [37]

High risk if:

- History of hypercoagulable disorder
- History of VTE
- Active malignancy
- COPD
- Pulmonary hypertension
- Stroke
- A combination of lesser risk factors:
  - Older age
  - Anaemia
  - CHF
  - Peripheral vascular disease
  - History of MI.

Odeh *et al* [34]

High risk if one of the below:

- History of prior DVT or PE
- Active cancer,
- BMI ≥ 40 kg/m^2
- Current smoker.

Registry and Database data

Study	Patients	Findings
Khatod et al [50] USA (national level) d.2001-2008 Primary HA p.2011 Prospectively collected Investigator blinded when reviewing adverse events. No external funding No CoI.	15,732 patients without a history of VTE, known to be using only one form of pharmacological prophylaxis. Excluded patients using >1 chemical prophylaxis and patients using NSAID prophylaxis (not aspirin). Follow-up was 90 days postoperatively. No protocol specified: MP alone = 9.7% Aspirin ± MP = 5.9% LMWH ± MP = 45.8% Warfarin ± MP = 38.5%	Overall PE = 0.41% (95CI 0.32-0.51%) Fatal PE = 0.01% (95CI 0.01-0.02%) Mortality = 0.51% (95CI 0.4-1.01%) Regression models did not show any association between the type of prophylaxis used or the choice of anaesthesia and increased odds of pulmonary embolism when adjusting for age*, sex, and ASA score. *3% (95CI 1-5%) increase in PE risk with each increase in year (p=0.007).
Jameson et al [51] England and Wales d. 2003-2008 Primary HA p.2011 Prospectively collected Database funded by levy raised on sale of hip and knee replacement implants No CoI.	108,584 patients who received either aspirin or LMWH post arthroplasty. Patients using more than one prophylaxis were excluded. Follow-up was 90 days. No protocol specified: Aspirin ± MP = 21.1% LMWH ± MP = 78.9%	Aspirin patients were more likely to have a posterior approach and to receive mechanical prophylaxis (82% vs 72%); otherwise the groups were similar. There was no significant difference in VTE incidence or mortality data (below), even when adjusted based on the multivariate risk model. Overall PE = 0.68% (same for both groups) Overall DVT = 0.95% (0.99% aspirin, 0.94% LMWH) Overall Death = 0.62% (0.65% aspirin, 0.61% LMWH)* Major haemorrhage (CVA or GI) = 0.77% aspirin, 0.72% LMWH. *with propensity score matching, the difference increased (0.65% aspirin and only 0.5% LMWH (OR 0.77 95CI 0.61-0.98) and became statistically significant p=0.04).
Bayley et al [52] United Kingdom d.2000-2012 Primary HA p.2016 No external funding No CoI.	7,983 patients from a prospectively collected audit database to ascertain how common fatal PE is in different patient groups. Follow-up to 90 days. Protocol: all patients not assessed to be at risk of VTE were given either aspirin 75mg daily, warfarin (target INR 1.5) or LMWH 40 mg daily, for six weeks post-surgery. Those assessed at high risk received warfarin. Patients also received regional anaesthesia where possible, calf compression peri-operatively, foot pumps until mobile, TEDs for six weeks, and were mobilised within 24 hours of surgery.	Overall mortality was 0.43% and 0.58% at 42 and 90 days postoperatively respectively. Divided by their prophylaxis, the 90-day mortality rates were: -Warfarin = 0.38% -LMWH = 1.09% -Aspirin = 0.43% Higher mortality with LMWH (p<0.05), aspirin was non-inferior to warfarin. None of the six fatal PE occurred in the aspirin group. These data are not adjusted for any risk factors, and can only be used to suggest that aspirin may be an appropriate part of a multi-modal regimen for patients not deemed to be at an increased risk of VTE.

Study	Patients	Findings
	Aspirin = 57.3% LMWH = 23.0% Warfarin = 19.7%	
Jameson et al [53] England and Wales d.2003-2008 Primary KA p.2012 Prospectively collected Database funded by levy raised on sale of hip and knee replacement implants No CoI.	156,798 patients who received either aspirin or LMWH post-arthroplasty. Patients using more than one prophylaxis were excluded. Follow-up was 90 days. No protocol specified: Aspirin ± MP = 23.1% LMWH ± MP = 76.9%	Aspirin patients were more likely to receive mechanical prophylaxis (84% vs 80%) and undergo treatment in a public hospital, but less likely to receive regional anaesthesia; otherwise the groups were similar. After risk adjustment, the LMWH group was less likely to return to theatre within 30 days (OR 0.73, 95CI 0.58-0.94 p=0.01), but the VTE incidence was statistically similar between the groups. Overall PE = 0.45% (0.49% aspirin, 0.45% LMWH) Overall DVT = 0.64% (0.66% aspirin, 0.63% LMWH) Overall Death = 0.43% (0.39% aspirin, 0.45% LMWH) Major haemorrhage (CVA or GI) = 0.38% (0.37% aspirin, 0.39% LMWH).
Khatod et al [54] USA (California) d.2001-2008 primary KA p.2012 Prospectively collected Investigator blinded when reviewing adverse events. No external funding source CoI statement online but not accessible.	30,020 patients with no history of DVT or PE. Follow-up was 90 days (PE and mortality rates only). No protocol specified: MP alone = 10.2% Anti-inflammatory agents = 0.3% Aspirin ± MP = 12.6% LMWH ± MP = 35.5% Warfarin ± MP = 32.1% >1 pharmacological prophylaxis (PTP) = 3.0% Unknown = 6.3%	Overall PE rate = 0.45% (95CI 0.37-0.53) Overall mortality = 0.3% (95CI 0.23-0.63) If all unknown deaths were attributed to PE, then fatal PE rate = 0.13% (worst case scenario) (95CI 0.48-0.65). Overall PE was significantly more likely to occur in patients using mechanical prophylaxis only, compared to warfarin (0.72% vs 0.38%, p=0.039). There was no other statistically significant difference in event incidence between prophylaxis groups, including fatal PE or death. Age varied significantly (p<0.0001) across prophylaxis groups (aspirin 67.2 years (lowest mean) vs. warfarin 68.3 years (highest mean). GA use was lowest in aspirin and highest in warfarin users (24.1% vs. 34.7%, p<0.001). Age was a significant risk factor for PE (odds increased 2% for each additional year (95CI 0-4%). ASA score ≥3 raised PE odds by 67% (95CI 15-143%) cf. ASA score of 1-2. GA was a significant risk factor cf. non-GA, increasing the odds of an event by 67% (95CI 14-144 p=0.009). When controlled for age, ASA score and anaesthesia, warfarin was the only prophylaxis protective against PE compared to mechanical prophylaxis alone, reducing the odds of PE by 54% (95 14-74% p=0.01).

Study	Patients	Findings
Cafri et al [55] USA (N. and S. California, Hawaii, and Northwest) d.2006-2013 primary KA p.2017 Funding unknown CoI statement online but not accessible.	30,499 patients who did not change pharmacological prophylaxis mid-treatment. Follow-up was 90 days (majority symptomatic VTE but included some incidental ones too). No protocol specified: Aspirin 324/325mg daily = 16.8% Enoxaparin 30mg bd or 40md daily = 43.7% Fondaparinux 2.5 mg daily = 10.6% Warfarin (INR target varied from 1.5-3) = 29.0%	Overall PE rate = 0.58% Overall DVT = 0.57% Overall VTE = 1.04% Overall mortality = 0.21% Although the rates of PE were slightly higher in aspirin users (0.73% cf. fondaparinux 0.41%, enoxaparin 0.62% and warfarin 0.50% respectively), the rates of DVT, PE and VTEs were statistically comparable across prophylaxis groups. 'When specifically testing for noninferiority, enoxaparin was found to be as safe as aspirin with respect to bleeding and fondaparinux as safe as aspirin for risk of wound complications.' 'After weighing based on propensity score, there was a lack of evidence indicating the superiority of any agent relative to aspirin.'
Bala et al [56] USA d.2007-2016 Primary KA p.2017 Funding unknown No CoI.	1,016 primary TKA patients (with no prior history of VTE or recent (within one year) preoperative antiplatelet/anticoagulant use) who received aspirin postoperatively were age and gender matched to 6,096 patients using enoxaparin, 6,096 using warfarin, and 5,090 using a factor Xa inhibitor. Total study size = 18,288. Follow-up was 90 days (efficacy and safety outcomes).	Factor Xa inhibitors had the lowest incidence of DVT and PE (2.9% and 0.9%), followed (in order of PE incidence) by enoxaparin (3.5% and 1.1%), aspirin (3.0%, 1.2%) and warfarin (4.8% and 1.6%). Aspirin had the lowest incidence of postoperative anaemia and transfusion, but there were no differences in bleeding-related complications compared to other agents. Mean CCI was identical for aspirin, enoxaparin, and warfarin groups, but slightly higher for the factor Xa group.
Cusick et al [57] Northern Ireland d.2002-2007 Primary KA and HA p.2009 Prospectively collected No funding information No CoI	2,050 TKA and 2,203 THA consecutive patients treated under one surgeon. Follow-up was at 90 days. Most (95.4%) received 150mg aspirin for 6 weeks; 1.1% accidentally prescribed LMWH by anaesthetist but were changed to aspirin, 3% received nothing and 0.3% received warfarin because of a history of PE. Spinal anaesthesia for all and early mobilisation. Follow-up was to one year post surgery.	Within 90 days: Overall proximal DVT = 0.33% Overall nonfatal PE = 0.66% Overall fatal PE = 0.07% Overall mortality = 0.31%
Colwell et al [58] USA d.2011 Primary KA and HA p.2014	1,551 KA and 1,509 HA patients across 10 sites* in the US, who used a mobile compression device for a minimum of 10 days with or without aspirin (discretion of the surgeon, range of doses employed). Excluded if history	Overall PE rate = 0.16% Overall proximal DVT = 0.1% Overall DVT (proximal and distal) = 0.75% Overall VTE = 0.92% This study was not powered to establish any conclusions with respect to use or non-use of aspirin with MCDs.

Study	Patients	Findings
Prospectively collected Funded by Medical Compression Systems Some CoI online, but not accessible.	of VTE, coagulation disorder, a solid malignant tumour, scheduled for a revision surgery, or had a major surgery within the last three months. Follow-up was at three months. *Anaesthesia protocols differed from site to site.	Compared to the VTE incidence associated with pharmacological prophylaxis (warfarin, rivaroxaban enoxaparin and dabigatran) in other trials, mechanical prophylaxis with or without aspirin was found to be non-inferior (1% margin) for all KA and HA groups, except one: in KA patients, the MCD ± aspirin fell short of the non-inferiority margin by 0.06% compared to rivaroxaban.
Ogonda et al [59] England and Wales d.2002-2014 Primary KA and HA p.2016 Prospectively collected No funding information No CoI.	5,941 HA, 5,028 TKA and 490 UKA patients (single surgeon) who received aspirin 150mg daily for six weeks as standard prophylaxis (with IPCD from 2012 onwards). Patients deemed to be at high risk were prescribed warfarin with LMWH bridge until 2010, and LMWH for 28 days from 2010 onwards.* Follow-up was three months post KA, six weeks post HA, and all mortality and wound complications data was to 90 days post-op. Data from Feb 2012 to June 2013: MP alone = 0.1% Aspirin = 90.4% LMWH = 5.0% Warfarin + LMWH until INR Tx = 3.2% No chemical prophylaxis = 13%	Overall proximal DVT = 0.32% (0.35% HA, 0.30% KA, 0.20% UKA) Overall PE = 0.99% (0.57% HA, 1.47% KA, 1.22% UKA) Wound complications = 0.40% post HA, 0.53% post KA/UKA Overall Mortality = 0.39%
Nielen et al [60] United Kingdom d.2008-2012 Primary KA and HA p.2016 Database collated from computerised records of GPs* Followed patients until the end of valid data collection (transfer out of practice or 1/11/12) NHS funded database No CoI. *This GP based database would not have captured any prescriptions issued in hospital that did not	3,261 KA and 4,016 HA, [†] compared VTE, GI bleeding and mortality rates among patients who received either LMWH, a DOAC or aspirin within the 35 days after surgery. Excluded patients with history of pregnancy in year preceding surgery. No protocol specified: Similar in HA and KA: Aspirin =54.7% LMWH = 35.2% DOAC = 10.0% [†] NB: These numbers do not match the breakdown in Figure 1 of the original article (N=7,101); presumably the missing 176 patients were not prescribed chemoprophylaxis, however it is not possible to confirm this from the available	Compared to aspirin users, KA and HA patients on LMWH users had higher risk of (HR (95CI)): - VTE (17.2 (95CI 6.9–43.0) and 39.5 (95CI 18.0–87.0), respectively) [§] - GI bleeding (20.9 (95CI 1.9–232.3) and 2.0 (95CI 0.2–17.2) respectively) - All-cause mortality (4.3 (95CI 1.7–12.4) and 4.0 (95CI 2.4–6.7), respectively) DOAC use was associated with an increased risk of GI bleeding (HR = 9.4 (95CI 1.1-82.0)) and VTE (4.4 (95CI 0.6-35.5)) in patients undergoing HA. [§]May be distorted due to timing of prescription and VTE rate registration i.e. some LMWH prescriptions may have been issued for VTE treatment.

Study	Patients	Findings
require repeat prescription by the GP.	data.	
Yhim et al [23] Korea d.2009-2013 KA and HA (incl. bilateral) p.2017 Data collected from two population insurance databases Funded by Seoul National University Bundang Hospital No CoI.	261,260 KA and 45,652 HA, compared VTE rates within 90 days of surgery. Excluded patients on VKA or low-dose unfractionated heparin (UFH). No protocol specified: Aspirin = 9.2% Fondaparinux = 2.8% LMWH = 22.4%** Rivaroxaban = 22.7% No chemical prophylaxis = 42.9% Overall, half of all patients who were prescribed chemical prophylaxis received <10 days*: Aspirin = 52.6% Fondaparinux = 26.9% LMWH = 22.9% Rivaroxaban = 76.9%	<table><tr><th rowspan="2">OR compared to no prophylaxis</th><th colspan="2">Total VTE (95CI)</th></tr><tr><th>HA</th><th>KA</th></tr><tr><td>Aspirin</td><td>1.38 (1.23-1.54)</td><td>1.39 (1.07-1.80)</td></tr><tr><td>Fondaparinux</td><td>1.21 (0.99-1.48)</td><td>0.70 (0.37-1.32)</td></tr><tr><td>LMWH†</td><td>2.52 (2.34-2.72)</td><td>1.85 (1.59-2.15)</td></tr><tr><td>Rivaroxaban</td><td>0.72 (0.65-0.79)</td><td>1.40 (1.11-1.76)</td></tr></table> VTE incidence was generally higher in patients using chemoprophylaxis compared to those who were not. It was identified however that patients who received prophylaxis were older and were more likely to receive GA; these were both identified as independent risk factors for developing VTE. The incidence of RBC transfusion was similar in Aspirin users compared to those not prescribed anything; all anticoagulant users had a greater odds ratio of RBC transfusion, as well as amount transfused. *Multivariate analysis identified that patients prescribed ≥10 days of prophylaxis were less likely to develop VTE (OR 0.79, 95CI 0.74-0.85). † The criteria used to determine if LMWH use was for VTE prophylaxis or treatment was not based on dose. Instead, prophylaxis use of LMWH was defined as initiation within 3 days of surgery, with no increase in dose / change of agent through the treatment period. Consequently, any patients who developed a VTE within the first 3 days that were subsequently treated using LMWH could potentially have been erroneously classified as having developed a VTE on LMWH.

Meta-analyses

Study	Findings
Kapoor et al [61] d.1990-2016 p. 2017 Network-analysis of RCTs to indirectly compare different thromboprophylaxis options (LMWH, NOAC, vitamin K antagonist (VKA), aspirin and mechanical TP) in patients undergoing TKA and THA. Ninety-four trials identified with 12 different prophylactic strategies. Unsure how many relate to aspirin as supporting data online are not accessible. ACCEPTABLE QUALITY The review - Did not include grey data / unpublished data - Did not list excluded studies - Did not address the potential for publication bias.	'We found that direct oral Xa inhibitors prevented the most DVTs, including a 4-fold decrease in symptomatic DVTs compared with [daily] LMWH. Major haemorrhage was not significantly worse with direct oral Xa inhibitors compared with [daily] LMWH. Other comparators did not have a more favourable profile than [daily] LMWH. Small numbers prohibit firm conclusions about aspirin... We believe there is sufficient evidence based on the analysis we performed to narrow the choice of prophylaxis options. Direct oral Xa inhibitors have the best profile in terms of efficacy at preventing VTE and avoidance of haemorrhage…. Although we cannot discount aspirin, given the limited number of studies we found, there does not seem to be a compelling reason for professional societies to continue to suggest it as a prophylaxis option for the average patient undergoing THR and TKR. Aspirin could be used in very-low-risk populations, although we are unfamiliar with a robust algorithm to identify sufficiently low-risk patients.' **OR (95CI) compared to daily LMWH** **Total DVT** **Major haemorrhage** **Symptomatic DVT** **Non-fatal PE** Aspirin: 0.80 (0.34-1.86); 1.08 (0.47-2.42); 2.04 (0.56-7.38); 3.97 (0.31-68.64) Direct oral Xa inhibitors: 0.45 (0.35-0.57); 1.21 (0.79-1.90); 0.25 (0.13-0.47); 0.50 (0.16-1.41) Dynamic mechanical TP: 1.17 (0.76-1.78); 0.15 (0.03-0.56); 1.08 (0.11-12.11); 0.62 (0.04-8.36) Placebo: 2.86 (2.18-3.76); 1.10 (0.54-2.16); 2.64 (1.23-5.58); 4.13 (1.33-16.40) Authors limited VTE outcomes to ~11 days because some of the studies did scans around that time point for asymptomatic VTE. VTE incidence peaks within approximately two to three weeks post-surgery. Given the small number of studies / patients, especially in the aspirin trial, a longer period of study may have been useful to maximise outcome data.
Drescher et al [62] Search performed in 2013 p.2014 Meta-analysis of head to head RCTs of aspirin vs. any anticoagulant following MOS (including HFS), where follow-up was at least 7 days and reported at least 1 pre-specified outcome. IPCD allowed, so long as used in both arms of the study. Six trials with moderate risk of bias identified with HA and KA patients only i.e. not hip fracture surgery (HFS) patients (n=1,026). HIGH QUALITY The authors did not list excluded studies, but ticked all other boxes.	**Efficacy:** The rate of total proximal DVT (symptomatic and asymptomatic) was similar in aspirin and anticoagulant users (9.3% vs. 9.7%, RR:1.00 95CI (0.49-2.05), 5 trials). **Bleeding:** Bleeding rates were similar (3.9% vs. 7.8% RR:0.63 (95CI 0.33-1.21, 5 trials). Major bleeding rates were similar in the aspirin and anticoagulant groups (2.1% vs 0.6%, RR 2.86, 95CI 0.65-12.6, 3 trials). **Limitations:** • Pooled sample size is small and four/six studies had less than 100 patients per arm (i.e. small-trial bias risk) • Screening for asymptomatic DVT was done in all studies (not relevant for clinical practice and would have inflated DVT incidence #s) • A wide variety of aspirin doses (250 to 1,200 mg daily) were used in the studies (more likely to affect bleeding risk vs. DVT incidence) and duration varied from 7 to 21 days post-arthroplasty • All but one study (2006) was conducted in the twentieth century (1982-1996), so findings may not reflect current practice.

Reviews

Study	Findings
Wilson et al [1] d.2004-2014 p.2016 Systematic review of studies to assess efficacy and safety of aspirin post hip and knee arthroplasty. 5 Level I, 8 Level III studies. <u>ACCEPTABLE to HIGH QUALITY</u> - Excluded studies are not listed - Grey / unpublished data not included - Publication bias not assessed	**Efficacy and Safety Findings:** Evidence from one good RCT that there is no difference in VTE in patients using aspirin or LMWH following TKA. Insufficient evidence from trials with moderate to severe bias risk to suggest aspirin is more or less effective than LMWH, warfarin, or dabigatran for prevention of VTE following TKA or THA. There is evidence, with moderate risk of bias of increased incidence of wound complications after THA/TKA when dabigatran is used for VTE prophylaxis. Rivaroxaban may reduce the rate of asymptomatic DVT in TKA, but insufficient evidence exists to suggest superiority over aspirin in symptomatic DVT. It may, furthermore, be associated with increased blood loss and wound complications. Significant heterogeneity in thromboprophylactic regimes and assessment made direct comparisons difficult. …In conclusion, the evidence for aspirin is incomplete, but there is reason to consider it a suitable alternative to other chemoprophylactic agents [in THA and TKA]. Its action may well be enhanced with concomitant use of mechanical prophylaxis. A more pragmatic approach to developing thromboprophylactic guidance and to improving the body of evidence for aspirin in the future is needed, as the large numbers required for suitably powered RCTs examining rare outcomes are prohibitive. **Limitations:** - Lack of Level 1 evidence with suitable power - Significant inter-study heterogeneity e.g. wide variety of dosage regimes, different endpoints used, as well as different methods of VTE detection, postoperative recovery protocols varied (as did mechanical prophylaxis) - Together this meant there was a moderate to severe risk of bias in the majority of the studies.
Cohen et al [63] Review of guidelines (and related evidence) on the use of aspirin for primary and secondary prevention in VTE and other cardiovascular disorders The review is a useful critique of studies commonly used in guideline formulation. Of note, its author is a medical consultant that has received consultancy fees from many pharmaceutical companies.	Not a systematic review In relation to prevention of VTE post elective orthopaedic surgery, the authors review the Pulmonary Embolism Prevention (PEP) study and Antiplatelet Trialists Collaboration (APT) meta-analysis data, and end with comments on the study by Anderson et al.[29] ***Findings*** 'For primary VTE prophylaxis in orthopaedic surgery patients, recommendations for aspirin are based on data from studies with methodological limitations. The ultimate purpose of guidelines is, thus, undermined, and the confusion for physicians is compounded by differences in interpretation of evidence across guidelines, resulting in different recommendations.'
Karthikeyan et al [64] Review of meta-analyses of randomised trials and individual RCTs enrolling at least 200 patients that evaluated aspirin for the prevention of VTE. p.2009	Not a systematic review Article reviews aspirin for VTE prevention in different settings (including during long-haul flights and for the prevention of stroke). The authors conclude: 'In summary, there is insufficient data to comment on the efficacy of ASA compared with warfarin or UFH. LMWHs appear to be better than ASA for preventing VTE.' Regarding aspirin specifically following major orthopaedic surgery, the authors include a discussion on the type of study that needs to be designed to end the disagreements on the appropriateness of aspirin as a sole prophylactic agent in patients undergoing major orthopaedic surgery in their concluding paragraph.
Kakkos et al [65] Review comparing IPCDs + pharmacological prophylaxis with either modality alone in high-risk patients (incl. non-	Comparison of IPCD and aspirin vs. IPCD and other pharmacological prophylaxis (TKA, THA, HFS): - Similar frequency of PE in the IPC* plus aspirin control (2/268, 0.75%) and IPC plus pharmacological prophylaxis treatment groups (0/337, 0%) (OR 0.33, 95CI 0.03-3.19); participants = 605; studies =3). - Similar frequency in DVT [incl. asymptomatic VTE] in the IPC plus

orthopaedic). d. to May 2016 p. 2016	aspirin control (32/268, 11.9%) and IPC plus pharmacological prophylaxis treatment groups (30/337, 8.9%) (OR 0.83, 95CI 0.48 to 1.42; participants 605; studies = 3). * IPC = IPCD

Brief NHMRC guideline evidence appraisal

This section includes a very brief appraisal of the evidence used to support the recommendations made in the NHMRC Thromboprophylaxis Guideline in 2009 against aspirin in hip and knee replacement patients.[8]

Hip replacement patients

Aspirin is not recommended as the sole pharmacological agent for thromboprophylaxis following hip replacement surgery.

Evidence: In two RCTs, there were no significant differences in the rates of proximal DVT, distal DVT, PE and the rates of adverse events between groups given aspirin or no treatment.[66]

- NHMRC Thromboprophylaxis Guideline 2009

PEP trial[66]: 4,088 patients were randomly assigned either aspirin or placebo post elective hip or knee arthroplasty (double blinded) in New Zealand (1992-1996). Aspirin dose was 160mg daily for 5 weeks, commenced on admission (pre-operatively). Follow-up for non-fatal events (symptomatic VTE, MI, stroke, bleeding) was only during the hospital stay whereas fatal follow-up was for 35 days postoperatively (>99% follow-up rate achieved).
The use of other thromboprophylaxis or non-study aspirin did not preclude patients from the trial: 5% of patients received non-study aspirin, 27% received other NSAIDs, 2% received unfractionated heparin and 35% received LMWH.

Elective hip arthroplasty patients' data.

	Aspirin (n=2,047)	**Placebo (n=2,041)**	***p****
DVT	15 (0.7%)	19 (0.9%)	0.599
Non-fatal PE	8 (0.4%)	8 (0.4%)	1.000
Total inpatient VTE	22 (1.1%)	24 (1.3%)	0.656
Fatal PE (to 35 days post op)	1 (0.05%)	2 (0.1%)	0.998
All-cause mortality (to 35 days post op) *	17 (0.8%)	22 (1.1%)	0.514

*not included in the original paper.

Although there was good follow-up (>99%), and a similar number of patients completed their treatment (~85%) in both treatment groups, there are several significant flaws with the design / reporting:

- The two treatment groups were similar in age and gender breakdown, but what about other medical conditions? The study was not designed to compare the efficacy of different prophylaxis regimens to prevent VTE. Its primary aim was to identify what effect aspirin has on the incidence of vascular deaths, non-fatal vascular events and major bleeding complications.[67] Consequently, the study team did not collect or analyse VTE risk factors or investigate the influence of concomitant mechanical and pharmacological prophylaxis (or aspirin with other pharmacological agents (including the over one third of patients who received non-study thromboprophylaxis)) use on efficacy.

- Non-fatal follow-up was limited to inpatient duration, but there is no indication how long patients were in hospital for in either treatment group i.e. did follow-up duration vary between groups? (NB: average length of stay in 1991-1994 was 7.9 days, and 3.5 days in 2000s (American data).[68] New Zealand (NZ) data suggest it is now around four to five days for the two procedures.[69])
- It is not clear if results were comparable across the 22 NZ sites.

Monreal et al[70]: compared VTE outcomes in hip fracture and elective hip replacement patients provided unfractionated heparin twice daily for 10 days, who were sub-divided into three groups depending on whether they received concomitant aspirin, triflusal or a placebo in addition to their heparin. Damaged bone marrow activates the clotting cascade, and a direct positive correlation has been reported between the period of surgery delay after hip fracture trauma and VTE risk.[71-73] Furthermore, data suggest that postoperative VTE is more common following hip fracture surgery compared to hip arthroplasty surgery (cumulative 3-month VTE rates of 4.2% vs. 1.5%).[74]One could argue that the study should not have been included in the analysis because it a) didn't separate out the surgical groups, but just as importantly b) was an analysis of whether antiplatelet agents provide an additional benefit to 10 days of unfractionated heparin post-surgery. Of interest, the study reported that preoperative platelet count was a good predictor of postoperative PE (but not DVT) – this may warrant further investigation.

Knee Replacement Patients

Aspirin is not recommended as the sole pharmacological agent for thromboprophylaxis following knee replacement surgery.

Evidence: In two RCTs, intermittent pneumatic compression (IPC) was more effective at reducing DVT than low-dose aspirin (results for high dose aspirin not relevant as this dosage would not be used in surgical patients).[75, 76]

- NHMRC Thromboprophylaxis Guideline 2009

McKenna et al[75]: compared high (1.3g TDS = 3.9g daily) dose aspirin with low (325mg TDS = 975mg daily) dose aspirin, placebo tablets and IPCD. They reported that the high-dose aspirin and IPCD were both effective at reducing asymptomatic DVT compared to low dose aspirin and placebo (8%, 10%, 78% and 75% DVT incidence respectively). Although it was technically blinded and placebo-controlled, patients (and staff) would easily have known who was in the IPCD group vs. oral medication/placebo group. Secondly, the number of patients was low (43 in the final analysis), and thirdly, it is based on asymptomatic clots from surgeries conducted in the 1970s at the earliest (data published in 1980) in patients using doses of aspirin that are significantly higher than would be used in Australia for VTE prophylaxis (3.9g daily). It is then arguable that for these reasons it is not applicable to include its finding re: high-dose aspirin in an analysis of the efficacy of aspirin in preventing VTE in patients undergoing knee arthroplasty in the twenty-first century.

Westrich et al[76]: studied DVT in aspirin (n=136, 325mg bd (4/52)) vs. enoxaparin (n=139, 30mg bd followed by 40mg daily after discharge (for 3/52)) in patients already receiving a calf compression device and spinal anaesthesia. They screened all patients for VTE between days three and five postoperatively, and at the four to six week mark following surgery. The rates of DVT were comparable (14.1% vs 17.8%, p=0.27), suggesting similar efficacy. Of note they did not take into account patients' VTE risk factors when comparing groups, and the enoxaparin was initiated ~48 hours after surgery (potentially delaying the efficacy), whereas aspirin was commenced on the day of surgery. Furthermore, they studied asymptomatic VTE, did not have a control group, and no one was blinded as to patients' treatment groups.

Abbreviations

Abbreviation	Meaning
2/52	two weeks
3/12	3 months
3/52	three weeks
4/52	four weeks
6/52	six weeks
95CI	95% confidence interval
ACCP	American College of Chest Physicians
AF	atrial fibrillation
ASA	Arthroplasty Society of Australia
ASA score	American Society of Anaesthesiologists score
BD or bd	twice daily
B/L	Bilateral
BMI	body mass index
CCI	Charlson Comorbidity Index
CoI	conflicts of interest
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
CVA	cerebrovascular accident
CVD	cardiovascular disease
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
DWI	deep wound infection
GA	general anaesthesia
GI	gastrointestinal
HA	hip arthroplasty
Hb	haemoglobin
HFS	hip fracture surgery
HIT	heparin induced thrombocytopaenia
HRT	hormone replacement therapy
HR	hazard ratio
IBD	Inflammatory bowel disease
IDDM	insulin dependent diabetes mellitus
INR	international normalised ratio
IPC(D)	intermittent pneumatic compression (device)
KA	knee arthroplasty

LMWH	low molecular weight heparin
LOS	length of stay
MCD	mobile compression device
mg	milligram
MOS	major orthopaedic surgery
MP	mechanical prophylaxis
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAID	nonsteroidal anti-inflammatory drug
NZ	New Zealand
OR	odds ratio
PE	pulmonary embolism
PJI	periprosthetic joint infection
PR	per rectum
PTP	pharmacological thromboprophylaxis
RA	regional anaesthesia
RBC	red blood cell
RR	relative risk
SD	standard deviation
SIGN UK	Scottish Intercollegiate Guidelines Network, United Kingdom
SPCD	sequential pneumatic compression device
SSI	surgical site infection
SWI	superficial wound infection
TDS	three times a day
TEDS	thromboembolic deterrent stockings
THA	total hip arthroplasty
TJA	total joint arthroplasty
TKA	total knee arthroplasty
TP	thromboprophylaxis
TTR	therapeutic time in range
UFH	unfractionated heparin
UK	United Kingdom
UKA	unicompartmental knee arthroplasty
U/S	ultrasound
USA	United States of America
VKA	vitamin-K antagonist
VTE	venous thromboembolism

References

1. Wilson DG, Poole WE, Chauhan SK, Rogers BA. Systematic review of aspirin for thromboprophylaxis in modern elective total hip and knee arthroplasty. The Bone and Joint Journal. 2016;98-B(8):1056-61.

2. Yassin M, Mitchell C, Diab M, Senior C. The necessity of pharmacological prophylaxis against venous thromboembolism in major joint arthroplasty. International orthopaedics. 2014;38(5):1073-5.

3. Wu PK, Chen CF, Chung LH, Liu CL, Chen WM. Population-based epidemiology of postoperative venous thromboembolism in Taiwanese patients receiving hip or knee arthroplasty without pharmacological thromboprophylaxis. Thrombosis research. 2014;133(5):719-24.

4. Lee S, Hwang J-I, Kim Y, Yoon PW, Ahn J, Yoo JJ. Venous Thromboembolism Following Hip and Knee Replacement Arthroplasty in Korea: A Nationwide Study Based on Claims Registry. Journal of Korean medical science. 2016;31(1):80-8.

5. Assareh H, Chen J, Ou L, Hollis SJ, Hillman K, Flabouris A. Rate of venous thromboembolism among surgical patients in Australian hospitals: a multicentre retrospective cohort study. BMJ open. 2014;4(10):e005502.

6. Assareh H, Chen J, Ou L, Hillman K, Flabouris A. Incidences and variations of hospital acquired venous thromboembolism in Australian hospitals: a population-based study. BMC Health Services Research. 2016;16:511.

7. Pow RE, Vale PR. Thromboprophylaxis in patients undergoing total hip and knee arthroplasty: A review of current practices in an Australian teaching hospital. Internal medicine journal. 2015;45(3):293-9.

8. National Health and Medical Research Council. Clinical Practice Guideline for the Prevention of Venous Thromboembolism (Deep Vein Thrombosis and Pulmonary Embolism) in Patients Admitted to Australian Hospitals. Canberra, Australian Capital Territory, Australia 2009.

9. Arthroplasty Society of Australia. Arthroplasty Society of Australia Guidelines for VTE Prophylaxis for Hip and Knee Arthroplasty. 2016.

10. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e278S-325S.

11. National Institute for Health and Care Excellence. Venous thromboembolism: reducing the risk for patients in hospital (updated June 2015). 2010.

12. Jacobs JJ, Mont MA, Bozic KJ, Della Valle CJ, Goodman SB, Lewis CG, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on: Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. Journal of Bone and Joint Surgery - Series A. 2012;94(8):746-7.

13. Gonzalez Della Valle A, Lee YY, Saboeiro G, Konin GP, Endo Y, Robador N, et al. One-Year All-Cause Mortality of Patients Diagnosed as Having In-Hospital Pulmonary Embolism

After Modern Elective Joint Arthroplasty Is Low And Unaffected By Radiologic Severity. Journal of Arthroplasty. 2016;31(2):473-9.

14. Poultsides LA, Gonzalez Della Valle A, Memtsoudis SG, Ma Y, Roberts T, Sharrock N, et al. Meta-analysis of cause of death following total joint replacement using different thromboprophylaxis regimens. Journal of Bone and Joint Surgery - Series B. 2012;94 B(1):113-21.

15. Hunt LP, Ben-Shlomo Y, Clark EM, Dieppe P, Judge A, MacGregor AJ, et al. 90-day mortality after 409 096 total hip replacements for osteoarthritis, from the National Joint Registry for England and Wales: A retrospective analysis. The Lancet. 2013;382(9898):1097-104.

16. Hunt LP, Ben-Shlomo Y, Clark EM, Dieppe P, Judge A, Macgregor AJ, et al. 45-day mortality after 467779 knee replacements for osteoarthritis from the National Joint Registry for England and Wales: An observational study. The Lancet. 2014;384(9952):1429-36.

17. Issa K, Mont MA. Total hip replacement: Mortality and risks. The Lancet. 2013;382(9898):1074-6.

18. Parvizi J, Rasouli MR. Mortality after hip replacement. The Lancet. 2013;382(9910):2065.

19. Sobieraj DM, Coleman CI, Tongbram V, Chen W, Colby J, Lee S, et al. Comparative effectiveness of combined pharmacologic and mechanical thromboprophylaxis versus either method alone in major orthopedic surgery: A systematic review and meta-analysis. Pharmacotherapy. 2013;33(3):275-83.

20. Pedersen AB, Sorensen HT, Mehnert F, Johnsen SP, Overgaard S. Effectiveness and safety of different duration of thromboprophylaxis in 16,865 hip replacement patients - A real-word, prospective observational study. Thrombosis research. 2015;135(2):322-8.

21. Sobieraj DM, Coleman CI, Pasupuleti V, Deshpande A, Kaw R, Hernandez AV. Comparative efficacy and safety of anticoagulants and aspirin for extended treatment of venous thromboembolism: A network meta-analysis. Thrombosis research. 2015;135(5):888-96.

22. Haynes J, Barrack RL, Nam D. Mobile pump deep vein thrombosis prophylaxis: just say no to drugs. Bone and Joint Journal. 2017;99-b(1 Supple A):8-13.

23. Yhim H-Y, Lee J, Lee JY, Lee J-O, Bang S-M. Pharmacological thromboprophylaxis and its impact on venous thromboembolism following total knee and hip arthroplasty in Korea: A nationwide population-based study. PloS one. 2017;12(5):e0178214.

24. Zou Y, Tian S, Wang Y, Sun K. Administering aspirin, rivaroxaban and low-molecular-weight heparin to prevent deep venous thrombosis after total knee arthroplasty. Blood Coagulation and Fibrinolysis. 2014;25(7):660-4.

25. Holden DN, Maceira E. Thromboembolism prophylaxis failure rates after hip and knee arthroplasty: Comparison of aspirin and anticoagulants. Current Orthopaedic Practice. 2015;26(3):277-80.

26. Yi J, Hui D, Jian L, Yixin Z. Aspirin combined with mechanical measures to prevent venous thromboembolism after total knee arthroplasty: a randomized controlled trial. Chinese medical journal. 2014;127(12):2201-5.

27. Deirmengian GK, Heller S, Smith EB, Maltenfort M, Chen AF, Parvizi J. Aspirin Can Be Used as Prophylaxis for Prevention of Venous Thromboembolism After Revision Hip and Knee Arthroplasty. Journal of Arthroplasty. 2016;31(10):2237-40.

28. Raphael IJ, Tischler EH, Huang R, Rothman RH, Hozack WJ, Parvizi J. Aspirin: An alternative for pulmonary embolism prophylaxis after arthroplasty? Clinical orthopaedics and related research. 2014;472(2):482-8.

29. Anderson DR, Dunbar MJ, Bohm ER, Belzile E, Kahn SR, Zukor D, et al. Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: A randomized trial. Annals of internal medicine. 2013;158(11):800-6.

30. Hamilton SC, Whang WW, Anderson BJ, Bradbury TL, Erens GA, Roberson JR. Inpatient Enoxaparin and Outpatient Aspirin Chemoprophylaxis Regimen After Primary Hip and Knee Arthroplasty: A Preliminary Study. Journal of Arthroplasty. 2012;27(9):1594-8.

31. Anderson D. Extended Venous Thromboembolism Prophylaxis Comparing Rivaroxaban to Aspirin Following Total Hip and Knee Arthroplasty (EPCAT II): ClinicalTrials.gov; 2017 [cited 2017 July 4th]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT01720108.

32. Kulshrestha V, Kumar S. DVT prophylaxis after TKA: Routine anticoagulation vs risk screening approach - a randomized study. Journal of Arthroplasty. 2013;28(10):1868-73.

33. A prospective comparison of warfarin to aspirin for thromboprophylaxis in total hip and total knee arthroplasty. Journal of Arthroplasty. 2012;27(1):1-9.e2.

34. Odeh K, Doran J, Yu S, Bolz N, Bosco J, Iorio R. Risk-Stratified Venous Thromboembolism Prophylaxis After Total Joint Arthroplasty: Aspirin and Sequential Pneumatic Compression Devices vs Aggressive Chemoprophylaxis. Journal of Arthroplasty. 2016;31(9):78-82.

35. Gesell MW, González Della Valle A, Bartolomé García S, Memtsoudis SG, Ma Y, Haas SB, et al. Safety and Efficacy of Multimodal Thromboprophylaxis Following Total Knee Arthroplasty. A Comparative Study of Preferential Aspirin vs. Routine Coumadin Chemoprophylaxis. Journal of Arthroplasty. 2013;28(4):575-9.

36. Vulcano E, Gesell M, Esposito A, Ma Y, Memtsoudis SG, Gonzalez Della Valle A. Aspirin for elective hip and knee arthroplasty: A multimodal thromboprophylaxis protocol. International orthopaedics. 2012;36(10):1995-2002.

37. Huang RC, Parvizi J, Hozack WJ, Chen AF, Austin MS. Aspirin Is as Effective as and Safer Than Warfarin for Patients at Higher Risk of Venous Thromboembolism Undergoing Total Joint Arthroplasty. Journal of Arthroplasty. 2016;31(9):83-6.

38. Nam D, Nunley RM, Johnson SR, Keeney JA, Barrack RL. Mobile Compression Devices and Aspirin for VTE Prophylaxis Following Simultaneous Bilateral Total Knee Arthroplasty. Journal of Arthroplasty. 2015;30(3):447-50.

39. Nam D, Nunley RM, Johnson SR, Keeney JA, Clohisy JC, Barrack RL. Thromboembolism Prophylaxis in Hip Arthroplasty: Routine and High Risk Patients. Journal of Arthroplasty. 2015;30(12):2299-303.

40. Nam D, Nunley RM, Johnson SR, Keeney JA, Clohisy JC, Barrack RL. The Effectiveness of a Risk Stratification Protocol for Thromboembolism Prophylaxis After Hip and Knee Arthroplasty. Journal of Arthroplasty. 2016;31(6):1299-306.

41. Borgdorff P, Tangelder GJ. Arguments favoring low versus high dose aspirin in the prophylaxis of venous thromboembolism. Thrombosis research. 2016;139:121-4.

42. Parvizi J, Huang R, Restrepo C, Chen AF, Austin MS, Hozack WJ, et al. Low-dose aspirin is effective chemoprophylaxis against clinically important venous thromboembolism following total joint arthroplasty a preliminary analysis. Journal of Bone and Joint Surgery - Series A. 2017;99(2):91-8.

43. Feldstein MJ, Low SL, Chen AF, Woodward LA, Hozack WJ. A Comparison of Two Dosing Regimens of ASA Following Total Hip and Knee Arthroplasties. Journal of Arthroplasty. 2017.

44. Bozic KJ, Vail TP, Pekow PS, Maselli JH, Lindenauer PK, Auerbach AD. Does aspirin have a role in venous thromboembolism prophylaxis in total knee arthroplasty patients? Journal of Arthroplasty. 2010;25(7):1053-60.

45. Chu JN, Maselli J, Auerbach AD, Fang MC. The risk of venous thromboembolism with aspirin compared to anticoagulants after hip and knee arthroplasty. Thrombosis research. 2017;155:65-71.

46. Anderson DR, Dunbar MJ, Kahn SR. Re: Aspirin versus low-molecular-weight heparin after total hip arthroplasty. Annals of internal medicine. 2013;159(7):502-3.

47. Granziera S, Cohen AT. Aspirin versus low-molecular-weight heparin after total hip arthroplasty. Annals of internal medicine. 2013;159(7):502-3.

48. Asopa V, Cobain W, Martin D, Keene G, Bauze A. Staged venous thromboemolic events prophylaxis with low-molecular-weight heparin followed by aspirin is safe and effective after arthroplasty. ANZ journal of surgery. 2015;85(9):652-7.

49. Levy YD, Hardwick ME, Copp SN, Rosen AS, Colwell CW, Jr. Thrombosis incidence in unilateral vs. simultaneous bilateral total knee arthroplasty with compression device prophylaxis. Journal of Arthroplasty. 2013;28(3):474-8.

50. Khatod M, Inacio MCS, Bini SA, Paxton EW. Prophylaxis against pulmonary embolism in patients undergoing total hip arthroplasty. Journal of Bone and Joint Surgery - Series A. 2011;93(19):1767-72.

51. Jameson SS, Charman SC, Gregg PJ, Reed MR, Van Der Meulen JH. The effect of aspirin and low-molecular-weight heparin on venous thromboembolism after hip replacement: A non-randomised comparison from information in the National Joint Registry. Journal of Bone and Joint Surgery - Series B. 2011;93 B(11):1465-70.

52. Bayley E, Brown S, Bhamber NS, Howard PW. Fatal pulmonary embolism following elective total hip arthroplasty: a 12-year study. The Bone and Joint Journal. 2016;98-b(5):585-8.

53. Jameson SS, Baker PN, Charman SC, Deehan DJ, Reed MR, Gregg PJ, et al. The effect of aspirin and low-molecular-weight heparin on venous thromboembolism after knee replacement: A non-randomised comparison using National Joint Registry data. Journal of Bone and Joint Surgery - Series B. 2012;94 B(7):914-8.

54. Khatod M, Inacio MC, Bini SA, Paxton EW. Pulmonary embolism prophylaxis in more than 30,000 total knee arthroplasty patients: is there a best choice? Journal of Arthroplasty. 2012;27(2):167-72.

55. Cafri G, Paxton EW, Chen Y, Cheetham CT, Gould MK, Sluggett J, et al. Comparative Effectiveness and Safety of Drug Prophylaxis for Prevention of Venous Thromboembolism After Total Knee Arthroplasty. Journal of Arthroplasty. 2017.

56. Bala A, Huddleston JI, 3rd, Goodman SB, Maloney WJ, Amanatullah DF. Venous Thromboembolism Prophylaxis After TKA: Aspirin, Warfarin, Enoxaparin, or Factor Xa Inhibitors? Clinical orthopaedics and related research. 2017.

57. Cusick LA, Beverland DE. The incidence of fatal pulmonary embolism after primary hip and knee replacement in a consecutive series of 4253 patients. Journal of Bone and Joint Surgery - Series B. 2009;91(5):645-8.

58. Colwell JC, Froimson M, Anseth S, Giori N, Hamilton W, Barrack R, et al. A mobile compression device for thrombosis prevention in hip and knee arthroplasty. Journal of Bone and Joint Surgery - Series A [Internet]. 2014; 96(3):[177-83 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/399/CN-00985399/frame.html.

59. Ogonda L, Hill J, Doran E, Dennison J, Stevenson M, Beverland D. Aspirin for thromboprophylaxis after primary lower limb arthroplasty: early thromboembolic events and 90 day mortality in 11,459 patients. The Bone and Joint Journal. 2016;98-b(3):341-8.

60. Nielen JTH, Dagnelie PC, Emans PJ, Veldhorst-Janssen N, Lalmohamed A, van Staa TP, et al. Safety and efficacy of new oral anticoagulants and low-molecular-weight heparins compared with aspirin in patients undergoing total knee and hip replacements. Pharmacoepidemiology and drug safety. 2016;25(11):1245-52.

61. Kapoor A, Ellis A, Shaffer N, Gurwitz J, Chandramohan A, Saulino J, et al. Comparative effectiveness of venous thromboembolism prophylaxis options for the patient undergoing total hip and knee replacement: a network meta-analysis. Journal of Thrombosis and Haemostasis. 2017;15(2):284-94.

62. Drescher FS, Sirovich BE, Lee A, Morrison DH, Chiang WH, Larson RJ. Aspirin versus anticoagulation for prevention of venous thromboembolism major lower extremity orthopedic surgery: A systematic review and meta-analysis. Journal of hospital medicine. 2014;9(9):579-85.

63. Cohen AT, Imfeld S, Markham J, Granziera S. The use of aspirin for primary and secondary prevention in venous thromboembolism and other cardiovascular disorders. Thrombosis research. 2015;135(2):217-25.

64. Karthikeyan G, Eikelboom JW, Turpie AG, Hirsh J. Does acetyl salicylic acid (ASA) have a role in the prevention of venous thromboembolism? British journal of haematology. 2009;146(2):142-9.

65. Kakkos SK, Caprini JA, Geroulakos G, Nicolaides AN, Stansby G, Reddy DJ, et al. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism. Cochrane Database of Systematic Reviews [Internet]. 2016; (9). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005258.pub3/abstract.

66. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet (London, England). 2000;355(9212):1295-302.

67. Cohen A, Quinlan D. PEP trial. Pulmonary Embolism Prevention. Lancet (London, England). 2000;356(9225):247; author reply 50-1.

68. Cram P, Lu X, Kates SL, Singh JA, Li Y, Wolf BR. Total knee arthroplasty volume, utilization, and outcomes among Medicare beneficiaries, 1991–2010. JAMA. 2012;308(12):1227-36.

69. Stowers MD, Manuopangai L, Hill AG, Gray JR, Coleman B, Munro JT. Enhanced Recovery After Surgery in elective hip and knee arthroplasty reduces length of hospital stay. ANZ journal of surgery. 2016;86(6):475-9.

70. Monreal M, Lafoz E, Roca J, Granero X, Soler J, Salazar X, et al. Platelet count, antiplatelet therapy and pulmonary embolism--a prospective study in patients with hip surgery. Thrombosis and haemostasis. 1995;73(3):380-5.

71. Jacoby RC, Owings JT, Holmes J, Battistella FD, Gosselin RC, Paglieroni TG. Platelet activation and function after trauma. The Journal of trauma. 2001;51(4):639-47.

72. Singh Mangat K, Mehra A, Yunas I, Porter K. Venous thromboprophylaxis in trauma: a review. Trauma. 2006;8(4):233-47.

73. Zahn HR, Skinner JA, Porteous MJ. The preoperative prevalence of deep vein thrombosis in patients with femoral neck fractures and delayed operation. Injury. 1999;30(9):605-7.

74. Dixon J, Ahn E, Zhou L, Lim R, Simpson D, Merriman EG. Venous thromboembolism rates in patients undergoing major hip and knee joint surgery at Waitemata District Health Board: A retrospective audit. Internal medicine journal. 2015;45(4):416-22.

75. McKenna R, Galante J, Bachmann F, Wallace DL, Kaushal PS, Meredith P. Prevention of venous thromboembolism after total knee replacement by high-dose aspirin or intermittent calf and thigh compression. British medical journal. 1980;280(6213):514-7.

76. Westrich GH, Bottner F, Windsor RE, Laskin RS, Haas SB, Sculco TP. VenaFlow plus Lovenox vs VenaFlow plus aspirin for thromboembolic disease prophylaxis in total knee arthroplasty. Journal of Arthroplasty. 2006;21(6 Suppl 2):139-43.

AUSTRALIAN COMMISSION
ON SAFETY AND QUALITY IN HEALTH CARE

Level 5, 255 Elizabeth Street, Sydney NSW 2000
GPO Box 5480, Sydney NSW 2001

Phone: (02) 9126 3600
Fax: (02) 9126 3613

Email: mail@safetyandquality.gov.au
Website: www.safetyandquality.gov.au