VENOUS THROMBOPROPHYLAXIS IN PAEDIATRIC SURGICAL AND TRAUMA PATIENTS - CHW

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Most paediatric patients are at very low risk for venous thromboembolism (VTE).
- Good hydration and early mobilisation after surgery or trauma are important in reducing the risk of VTE.
- Consider pharmacologic prophylaxis with low molecular weight heparin for patients at high risk for VTE, defined within this guideline; also see Enoxaparin (Clexane) – Low Molecular Weight Heparin – CHW.
- Mechanical methods of prophylaxis such as intermittent pneumatic compression are not routinely recommended but may be used at the discretion of the treating consultant.
- Thromboprophylaxis Guideline Summary - see Flowchart on page 3.

CHANGE SUMMARY

- Due for mandatory review.
- Addition of the word "Venous" to the title. No other changes to the document.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st March 2022	**Review Period**: 3 years
Team Leader:	Staff Specialist	**Area/Dept**: Haematology

Date of Publishing: 8 February 2022 4:12 PM Date of Printing: 8 February 2022

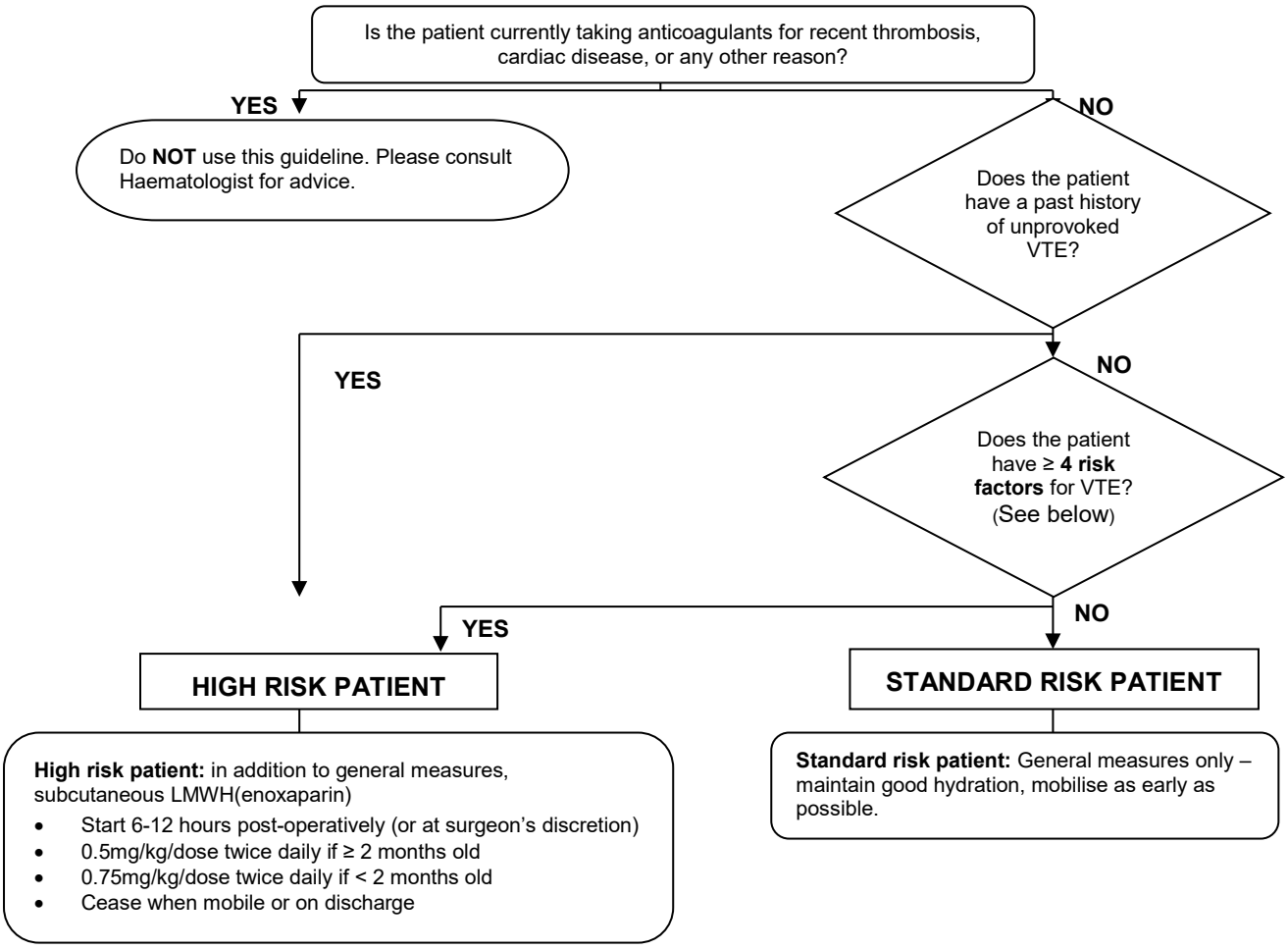
READ ACKNOWLEDGEMENT

- Read Acknowledge Only – Clinical staff involved in the care of surgical and trauma patients at risk of venous thromboembolism

Acronym	
CHW	The Children's Hospital at Westmead
CVAD	Central Venous Access Device
HITTS	Heparin-induced Thrombotic Thrombocytopenia Syndrome
IPC	Intermittent Pneumatic Compression
LMWH	Low Molecular Weight Heparin
PICC	Peripherally Inserted Central Catheter
TEDS	Thromboembolic Deterrent Stockings
UFH	Unfractionated Heparin
VTE	Venous Thromboembolism

This document reflects what is currently regarded as safe practice. However, as in any clinical situation, there may be factors which cannot be covered by a single set of guidelines. This document does not replace the need for the application of clinical judgement to each individual presentation.

Thromboprophylaxis Guidelines Summary



Risk Factors for VTE

- Age less than 3 months **OR** post-pubertal
- Severe injury
- Major surgery – e.g. chest, abdominal, spinal, lower limb orthopaedic, craniotomy
- Coexisting disease – cancer (including leukaemia), severe infection, inflammatory disease, congenital heart disease, nephrotic disease, diabetes
- Obesity
- Prolonged immobilisation
- Central venous catheter
- Previous **line-related** proximal VTE
- Oestrogenic state – oral contraceptive pill, pregnancy, miscarriage/termination in last 3 months
- Inherited or acquired thrombophilia (see text for specific conditions)

Administration of Enoxaparin

DO NOT administer for **12 hours prior to** insertion or removal of epidural or spinal catheter

DO NOT administer for **2 hours after** insertion or removal of epidural or spinal catheter

TABLE OF CONTENTS

1 Purpose

To outline the epidemiology of venous thromboembolism (VTE).

To describe the available methods of thromboprophylaxis and their evidence base.

To recommend general measures suitable for all paediatric surgical or trauma patients to minimise risk of VTE.

To identify high risk paediatric surgical or trauma patients who may benefit from specific interventions to reduce their risk of VTE.

2 Principles

- VTE, including deep venous thrombosis and pulmonary embolism, is uncommon in children (in contrast to adults).
- VTE is a potentially preventable disease which, when it does occur, is associated with significant morbidity and mortality, even in children.
- Surgery and trauma are well described risk factors for VTE.
- **Simple, non-invasive general measures should be provided to all post-operative/trauma children in order to minimise the risk of VTE.**
- **Identify the small group of children who may be at increased risk of VTE, and provide effective interventions to ameliorate this risk.**

3 Recommendations

Note: The below recommendations have been drawn from the discussion in Sections 4 & 5.

3.1 Definition of Risk Groups

Most children are at **low risk** of VTE. These patients are referred to as "standard risk" for the purposes of this guideline.

"High risk" patients are considered to be those that have **4 or more risk factors** as outlined below **OR** a past history of non-line related/unprovoked VTE. All patients not fulfilling these criteria are standard risk.

3.1.1 Risk Factors for VTE

- Age: less than 3 months or post-pubertal.
- Severe injury – including severe chest, abdominal/pelvic or head injuries, spinal injuries, and lower limb fractures requiring open reduction and/or internal/external fixation.
- Major surgery – including chest, abdominal/pelvic, spinal, lower limb orthopaedic, craniotomy.

- Certain coexisting disease, including
  - Cancer, including haematological malignancy
  - Infection, particularly if severely unwell
  - Inflammatory disease, eg inflammatory bowel disease, rheumatological disease, Kawasaki disease
  - Congenital heart disease
  - Nephrotic syndrome
  - Diabetes
- Obesity.
- Prolonged immobilisation.
- Presence of a central venous catheter.
- Previous line-related proximal VTE – i.e., thrombosis at the site of a central venous catheter or PICC line.
- "Oestrogenic states" – use of the oral contraceptive pill, pregnancy, miscarriage or termination in the last 3 months.
- Thrombophilia
  - Inherited - protein C deficiency, protein S deficiency, antithrombin deficiency, factor V Leiden gene mutation, prothrombin gene mutation, raised plasma factor VIII, raised plasma homocysteine.
  - Acquired - antiphospholipid syndrome.

3.2 Thromboprophylaxis for Standard risk patients

Good hydration and mobilisation as early as possible should be employed in all patients, both standard risk and high risk.

Given the very low risk of VTE in paediatric patients, pharmacological thromboprophylaxis is **not** generally recommended for standard risk patients at The Children's Hospital at Westmead (CHW).

3.3 Thromboprophylaxis for High risk patients

Pharmacologic prophylaxis should be considered for high risk patients, in addition to maintenance of good hydration and early mobilisation. At CHW, the recommended pharmacologic thromboprophylaxis is:

- Age 2 months or more: subcutaneous enoxaparin 0.5 mg/kg/dose twice daily
- Age less than 2 months: subcutaneous enoxaparin 0.75 mg/kg/dose twice daily
- Consult the Haematologist on-call for dosage adjustment if there is co-existing renal impairment

Commencing 6-12 hours post-operatively once bleeding risk was considered low or at the surgeon's discretion and continuing until discharge. However, variation in the timing and duration may be appropriate in individual cases.

SAFETY OF NEURAXIAL ANAESTHESIA IN PATIENTS RECEIVING HEPARINS

Do **NOT** administer enoxaparin or any LMWH for at least 12 hours prior to insertion or removal of an epidural or spinal catheter.

Do **NOT** administer enoxaparin or any LMWH for at least 2 hours after insertion or removal of an epidural or spinal catheter.

3.4 Role of Mechanical Thromboprophylaxis

Mechanical thromboprophylaxis is not routinely recommended at CHW as it has not been demonstrated to be effective in children. There may, however, be indications for use in individual cases.

Given the lack of data demonstrating efficacy even in adults, TED stockings and graduated compression stockings are not generally recommended for patients at CHW. It may be appropriate to use them in certain individual cases at the discretion of the treating surgeon.

Intermittent pneumatic compression devices (IPC's) are not recommended for most patients at CHW. However, their use may be appropriate in certain individual cases, particularly in older children who may have contraindications to anticoagulation. They may also be employed in addition to pharmacologic thromboprophylaxis in certain cases. Again, this use is at the discretion of the treating surgeon.

4 Epidemiology of Venous Thromboembolism

The estimated incidence of VTE in hospital patients was 961 per 100 000 person-years for adults, compared with only 5.3 per 100 000 person-years for children. These rates are 50-100 times higher than those of VTE occurring in the general community (7 and 0.07-0.14 per 100 000 person-years for adults and children, respectively)[1].

Documented risk factors for VTE in children include the following[2]:

- Central venous access devices (CVAD)
- Age (neonates or post-pubertal)
- Surgery
- Trauma
- Acute infection or inflammatory states, including local infection
- Cancer and/or chemotherapy
- Thrombophilia (see below)
- Abortion/other oestrogenic states

However, as many as 90% of children with VTE have more than one risk factor[3].

Although trauma is a known risk factor for VTE, the majority of children with trauma do not experience VTE. The incidence of VTE in paediatric trauma patients was described according to age in a level 1 US trauma centre[4]:

- Less than 13 years old – zero
- 13 to 17 years old – 0.2%
- Over 17 years old – 0.5%

Risk factors for VTE in the paediatric trauma population include[5]:

- Severity of injury
- Major vascular surgery
- CVAD
- Craniotomy
- Age greater than 10 years

In the above review, an injury severity score (ISS) of 25 or greater was associated with a 21 fold increased risk of VTE on multivariate analysis. The relative risks of VTE were 16 for major vascular surgery, and 5 for CVAD, craniotomy or age over 10 years. In addition, it was noted that the types of injury particularly associated with VTE were severe spinal injury, severe head injury, severe thoracic injury, and lower limb fracture requiring open reduction/internal fixation.

"Thrombophilia" refers to the state of having certain inherited or acquired prothrombotic factors or conditions. These include, but are not limited to, the following:

- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- Antiphospholipid syndrome (this is NOT the same as simply having positive tests for either anticardiolipin antibodies or the lupus anticoagulant; certain clinical criteria must coexist)
- Factor V Leiden gene mutation
- Prothrombin gene mutation
- Raised plasma factor VIII levels
- Raised plasma homocysteine levels

Whilst it is becoming apparent that these factors increase the risk of VTE in both children and adults, particularly when multiple factors coexist, it is far from clear as to how significant this risk is in any one given individual. Few universally recognised recommendations exist as to when and under what circumstances these individuals should receive pharmacologic thromboprophylaxis. Therefore, thrombophilia should be considered in the overall context of a given patient's clinical features and other risk factors, but should **never be regarded** as an automatic indication for pharmacologic thromboprophylaxis or anticoagulation.

Finally, it is important to remember that perhaps the most important single risk factor for VTE is a personal past history of VTE (particularly, if unprovoked). Recurrent VTE is as high as 30% in adults[6] and between 6-23% in children[7].

5 Methods Used For Thromboprophylaxis

5.1 Hydration and early mobilisation

A change in blood composition is one of the elements of Virchow's triad which may predispose to thrombosis. Dehydration may increase blood viscosity. Therefore, it is rational to maintain good hydration status in all patients.

Immobility is a described risk factor for VTE, and mobilisation of post-surgical or trauma patients as early as possible is generally recommended as a way of modifying this risk factor.

5.2 Thromboembolic deterrent stockings (TEDS) or graduated compression stockings

These are often recommended as an adjunctive measure for thromboprophylaxis in adults. However, there is no good evidence that they are effective in adults[8]. No good data exist for children. In addition, whilst these stockings are generally safe, complications such as pressure ulcers and peripheral neuropathy have been reported in adults with poorly fitting stockings[9, 10].

5.3 Intermittent pneumatic compression devices

These have been shown to reduce the risk of post-operative VTE in high risk adult patients, although it was less effective than prophylaxis with heparin[11]. The advantage of these devices is that they have almost no side effects, making them attractive in patients with contraindications to heparins and/or at high risk of bleeding. IPC's may also be used in conjunction with heparin prophylaxis but data of its use in children are sparse.

IPC's may be commenced pre-operatively, intra-operatively, or post-operatively. There is at present no firm evidence that timing of commencement influences risk of VTE. It is more important to continue the IPC's until the patient is fully ambulatory[12]. If IPC's are started post-operatively, they should be instituted soon after surgery, as there is a hypothetical risk of them dislodging preformed thrombus in a patient who has had a prolonged period without thromboprophylaxis.

5.4 Pharmacologic – heparins and warfarin

Heparins – both unfractionated heparin (UFH) and low molecular weight heparins (LMWH) such as enoxaparin ("Clexane") – are well documented to decrease the risk of post-operative VTE in adults[13-16]. UFH and LMWH both indirectly inhibit thrombin formation via potentiation of the action of antithrombin, increasing its activity several thousand fold. UFH is typically administered subcutaneously 2-3 times a day, whilst LMWH is generally given once daily in adults. With prophylactic usage of UFH or LMWH, monitoring can be performed but does not need to be done routinely.

Side effects are minimal, but do include pain at the injection site, local reactions, risk of bleeding, and, extremely rarely in children, heparin-induced thrombotic thrombocytopenia syndrome (HITTS)[17]. Lastly, these agents have a financial cost, particularly LMWH.

Fondaparinux is a synthetic analogue of the antithrombin-binding pentasaccharide region of heparin. It is used for thromboprophylaxis of adults undergoing major orthopaedic surgery, and may have greater efficacy than enoxaparin in this regard[18]. Mature data in children are not available.

Warfarin is an orally administered anticoagulant whose mechanism of action is the inhibition of vitamin K dependent clotting factors. It is effective in the prevention of VTE in adults but it is generally not used in post-surgical or trauma thromboprophylaxis.

5.4.1 Timing and Duration of Pharmacologic Thromboprophylaxis

There is no good data to guide the timing of first dose or duration of thromboprophylaxis in children. The following is a summary of what is known in adults.

The timing of the first dose of peri-operative thromboprophylaxis has undergone a number of changes over the last fifty years. Unfractionated heparin given 2 hours pre-operatively was shown to be safe and effective in the 1970's; however, this schedule resulted in increased post-operative bleeding when used with LMWH. This resulted in a shift in practice by adult orthopaedic surgeons to administer prophylactic LMWH 12 hours either pre or post-operatively.[22]

More recent studies in adults undergoing orthopaedic surgery have shown that LMWH administered 12 hours or more either before or after surgery was less effective than if it was administered 4 – 6 hours post-operatively. Furthermore, an increased bleeding risk was only observed if LMWH was administered within 2 hours of surgery, and that pre-operative administration provided no benefit compared to administration 4 – 6 hours post-operatively[23,24].

The duration of thromboprophylaxis in adult surgical patients has traditionally been until discharge. However, clinical studies in high risk adult surgical patients, particularly those undergoing hip surgery, have shown that extended post-discharge thromboprophylaxis of up to 4 – 6 weeks significantly reduces the incidence of VTE (including both venographically detected and symptomatic deep venous thrombosis)[25, 26].

6 References

1. Gerotziafas GT. Risk factors for venous thromboembolism in children. International Angiology. 2004; 23(3):195-205.
2. Stein PD, Kayali F, Olson RE. Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey. J Pediatr. 2004; 145:563-565.
3. Jackson PC, Morgan JN. Perioperative thromboprophylaxis in children: development of a guideline for management. Pediatric Anesthesia 2008; 18:478-487.
4. Azu MC McCormack JE, Scriven RJ, Brebbia JS, Shapiro MJ, Lee TK. Venous thromboembolic events in pediatric trauma patients: is prophylaxis necessary? J Trauma. 2005; 59:1345-1349.
5. Vavilala MS, Nathens AB, Jurkovich GJ, Mckenzie E, Rivara FP. Risk factors for venous thromboembolism in pediatric trauma. J Trauma. 2002; 52:922-927.
6. Nowak-Gottl U, Junker R, Kreuz W, von Eckardstein A, Kosch A, Nohe N, Schobess R, Ehrenforth S for the Childhood Thrombophilia Study Group. Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors. Blood 2001; 97(4): 858-862.
7. Goldenberg NA. Thrombophilia states and markers of coagulation activation in the prediction of pediatric venous thromboembolic outcomes: a comparative analysis with respect to adult evidence. Hematology (American Society of Hematology Education Program Book). 2008: 236-244.
8. Amaragiri SV, Lees TA. Elastic compression stockings for prevention of deep vein thrombosis. Cochrane Database Syst Rev 2000; (3): CD001484.

9. Ong JC, Chan FC, McCann J. Pressure ulcers of the popliteal fossa caused by thromboembolic deterrent stockings (TEDS). Ir J Med Sci. 2009 Jul 25 [Epub ahead of print]. Accessed 16 September 2009.
10. O'Brien CM, Eltigani T. Common peroneal nerve palsy as a possible sequelae of poorly fitting below-knee thromboembolic deterrent stockings (TEDS). Ann Plat Surg. 2006; 57(3): 356-357.
11. Kakkos SK, Caprini JA, Geroulakos G, Nicolaides AN, Stansby GP, Reddy DJ. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism in high-risk patients. Cochrane Database Syst Rev. 2008 Oct 8; (4):CD005258.
12. Urbankova J, Quiroz R, Kucher N et al. Intermittent pneumatic compression and deep venous thrombosis prevention: a meta-analysis in post-operative patients. Thromb Haemost. 2005; 94:1181-1185.
13. Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. Ann Surg. 1988; 208(2): 227-240.
14. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic and urologic surgery. N Engl J Med. 1988; 318(18): 1162-1173.
15. Bergqvist D. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses. Br J Surg. 1998; 85:872.
16. Kakkar VV, Cohen AT, Edmonson RA, Phillips MJ, Cooper DI, Das SK, Maher KT, Sanderson RM, Ward VP, Kakkar S. Low molecular weight heparin versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. The Thromboprophylaxis Collaborative Group. Lancet. 1993; 341(8840): 259 – 265.
17. Leonardi MJ, McGory ML, Ko CY. The rate of bleeding complications after pharmacologic deep venous thrombosis prophylaxis: a systematic review of 33 randomized controlled trials. Arch Surg. 2006; 141(8): 790-797.
18. Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of four randomized double blind studies. Arch Intern Med. 2002; 162(16): 1833 – 1840.
19. Francis CW, Pellegrini VD Jr, Totterman S, Boyd AD Jr, Marder VJ, Liebert KM, Stulberg BN, Ayers DC, Rosenberg A, Kessler C, Johanson NA. Prevention of deep vein thrombosis after total hip arthroplasty. Comparison of warfarin and dalteparin. J Bone Joint Surg Am. 1997; 79(9): 1365-1372.
20. Colwell CW Jr, Collis DK, Paulson R, McCutchen JW, Bigler GT, Lutz S, Hardwick ME. Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty. Evaluation during hospitalization and three months after discharge. J Bone Joint Surg Am. 1999; 81(7): 932-940.
21. SamamaCM, Vray M, Barre J, Fiessinger JN, Rosencher N, Lecompte T, Potron G, Basile J, Hull R, Desmichels D. Extended venous thromboembolism prophylaxis after total hip replacement: a comparison of low molecular weight heparin with oral anticoagulant. Arch Intern Med. 2002; 162(19): 2191-2196.
22. Raskob GE, Hirsh J. Controversies in timing of the first dose of anticoagulant prophylaxis against venous thromboembolism after major orthopedic surgery. Chest. 2003; 124 (6 Suppl): 379S-385S.
23. Hull RD; Pineo GF; Francis C; Bergqvist D; Fellenius C; Soderberg K; Holmqvist A; Mant M; Dear R; Baylis B; Mah A; Brant R. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients: a double-blind, randomized comparison. The North American Fragmin Trial Investigators. Arch Intern Med. 2000; 160(14):2199-207.
24. Hull RD; Pineo GF; Stein PD; Mah AF; MacIsaac SM; Dahl OE; Ghali WA; Butcher MS; Brant RF; Bergqvist D; Hamulyak K; Francis CW; Marder VJ; Raskob GE. Timing of initial administration of low-molecular-weight heparin prophylaxis against deep vein thrombosis in patients following elective hip arthroplasty: a systematic review. Arch Intern Med . 2001;161(16):1952-60.
25. Eikelboom JW; Quinlan DJ; Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. Lancet. 2001; 358(9275):9-15.
26. Hull RD; Pineo GF; Stein PD; Mah AF; MacIsaac SM; Dahl OE; Butcher M; Brant RF; Ghali WA; Bergqvist D; Raskob GE. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. Ann Intern Med. 2001; 135(10):858-69.