Venous Thromboembolism Prevention Guideline: Thromboprophylaxis (CGI)

Site Applicability

All VCH-PHC acute sites. Target population: all patients admitted to hospital for acute care.

Practice Level

Physicians, Pharmacists & Nurse Practitioners - Basic skill

Policy Statement

Physicians must

1) **evaluate** each patient's risk of VTE at the time of hospital admission and transfer from one service or area of care to another;
2) **prescribe** pharmacological or mechanical thromboprophylaxis that is appropriate for the level of risk, and
3) **document** the rationale for any deviation from the recommended practices outlined in the VCH-PHC Venous Thromboembolism Prevention Guideline in the patient's chart.

It is the responsibility of all medical and surgical directors of inpatient units to include VTE assessment and thromboprophylaxis orders in admission/transfer pre-printed order sets as outlined in the VCH-PHC Venous Thromboembolism Prevention Guideline.

Need to Know

Venous thromboembolism is a common and potentially fatal complication in hospitalized patients. Despite overwhelming evidence that thromboprophylaxis reduces the incidence of preventable VTE and leads to cost savings, physician compliance with established, evidence-based guidelines in prescribing appropriate thromboprophylaxis remains suboptimal. The Venous Thromboembolism Prevention Guideline is created to support the Regional Thromboprophylaxis Policy (BD-00-11-40018) for VTE risk assessment and thromboprophylaxis prescription and includes the following information:

1. Scope of the guideline
2. Summary of recommendations
3. Thromboprophylaxis recommendations
4. Background and rationale
5. VTE risk assessment
6. Methods of thromboprophylaxis
7. Efficacy and safety of thromboprophylaxis
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Equipment and Supplies

Anticoagulants (unfractionated heparin, low molecular weight heparin, fondaparinux)

Intermittent pneumatic or sequential compression devices

Graduated compression stockings (GCS), including ThromboEmbolism Deterrent Stockings

Practice Guideline

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1. Scope of the Guideline

This guideline provides supportive documentation for the VCH-PHC Thromboprophylaxis Policy for patients admitted to a hospital for acute care. It outlines the recommended thromboprophylaxis practice based on available published evidence and local practice standards on the prevention of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) in hospitalized patients. The recommendations are based on consultation with content experts and stakeholders and a review of well-recognized evidence-based consensus guidelines, including the American College of Chest Physicians (ACCP) Clinical Practice Guideline on Antithrombotic and Thrombolytic Therapy and the United Kingdom (UK) National Institute for Health and Clinical Excellence (NICE) clinical guidelines.

This document also outlines the approaches to be used for VTE assessment, bleeding assessment, the rationale for the thromboprophylaxis recommendations, and the roles and responsibilities of health care providers. Key references are listed and included in appendices.

Although the evidence-based thromboprophylaxis strategies and options described in this guideline apply to most patients at risk of VTE, individual cases may require a different approach. This guideline is not intended to replace physician clinical judgment, which should be exercised in all cases to optimize the quality and safety of patient care being delivered at all VCH-PHC sites.

For certain groups of patients in very high risk settings for both VTE and bleeding, a multidisciplinary approach with discussion amongst various consultants is necessary to tailor thromboprophylaxis in order to achieve the optimal balance between the competing risks for thrombosis and bleeding. Physicians are also advised to consult consensus guidelines for specific patient populations and seek expertise advice for complex and unusual cases. It is especially important in these cases that patients and family members (when appropriate) be involved with the decision making regarding thromboprophylaxis because of the potential risk of providing or withholding thromboprophylaxis. To ensure transparency, maximize patient safety and facilitate communication, the decision making process should be clearly documented in the patient's chart.

Updated changes to the guideline will be made as needed when new evidence emerges regarding more effective strategies, thromboprophylaxis options or other advances relevant to the optimal assessment of VTE and thromboprophylaxis prescription.

2. Summary of Recommendations

2.1. Risk Assessment and Thromboprophylaxis for VTE

Table 1. Risk Assessment of Hospitalized Patients	
Patient Risk Groups (satisfaction of any one or more of the listed criteria)	**Thromboprophylaxis Recommended**
Adult Patients with Low Risk of VTE: • No reduction in mobility compared to usual state • Day surgery[1] and no risk factors for VTE (Table 2) • Surgical procedure with a total anesthetic and surgical time of less than 60 minutes with no risk factors for VTE (Table 2)	**early ambulation**
Adult Patients with Moderate or High Risk of VTE:[2,3] • Any medical or surgical patient having had or are expected to have significantly reduced mobility for 3 days or more • Medical patients with ongoing reduced mobility (compared to their usual state) AND have one or more risk factors for VTE (Table 2) • Surgical procedure with a total anesthetic and surgical time 60 minutes or longer • Acute surgical admission with an inflammatory or intra-abdominal condition • Surgical patients with one or more risk factors for VTE (Table 2)	**LMWH (consider UFH in renal failure)**[4-7]
Pediatric Patients with an increased risk of VTE: • Use of central venous catheters • Malignancy • Congenital heart disease • Renal disease • L-asparaginase • Immobility • Multiple trauma • Inherited thrombophilia	**Consult Pediatric Hematologist**[8]

Obstetrical Patients with an increased risk of VTE:
• Having one or more risk factors for VTE (Table 2)
• Pregnancy-related risk factor:
  • Ovarian hyperstimulation
  • Hyperemesis gravidarum
  • Multiple pregnancy
  • Preeclampsia
  • Emergency caesarean section
	Consider LMWH (UFH in renal failure)[4-6]

1. Day surgery includes patients admitted and discharged within 24 hours for an elective surgical or invasive procedure.
2. Anticoagulant thromboprophylaxis is the method of first choice in medical and surgical patients without contraindications. In medical patients, there is no evidence for using mechanical thromboprophylaxis except in those with an acute stroke and immobility. In surgical patients, there is weak evidence for using mechanical thromboprophylaxis alone and weaker evidence for combining anticoagulant and mechanical prophylaxis to improve efficacy.
3. Prophylaxis should continue during hospitalization. Extended duration for up to 30 days after surgery is recommended in those having hip replacement, hip fracture surgery, abdominal or pelvic surgery for cancer, and those with multiple risk factors.
4. LMWH and UFH should not be given in patients with heparin-induced thrombocytopenia (HIT). Consider consulting Hematology regarding use of alternative agents.
5. If eGFR is 10 – 30 mL/min and duration of prophylaxis exceeds 10 days, can consider using UFH 5000 units BID instead of LMWH. If eGFR <10 mL/min or dialysis dependent, use UFH 5000 units BID.
6. If patient's BMI >40 kg/m^2, consider increasing dose of LMWH or UFH.
7. UFH 5000 units BID should be used if patient is awaiting urgent surgery and is eligible for neuraxial blockade. Refer to Peri-operative Pain Service or Anesthesia regarding timing of epidural catheter insertion and removal.
8. Pediatric Thrombosis service at BCCH: page pediatric hematologist on call at 604-875-2161 for immediate help or 604-875-2316 for non-urgent consultation.

Table 2. Risk Factors for VTE	

• Age 60 years or over
• Active cancer or cancer treatment
• Previous VTE
• Critical care admission
• Obesity (BMI > 30 kg/m^2)
• Known thrombophilia
• First degree relative with VTE
• Varicose veins with phlebitis
• Estrogen-containing contraception
• Hormone replacement therapy
	• One or more significant medical conditions:
	  • Sepsis or severe acute infection
	  • Heart disease
	  • Respiratory pathology
	  • Inflammatory condition
	  • Rheumatological disease
	  • Nephrotic syndrome
	  • Antiphospholipid syndrome
	  • Acute stroke

2.2 Contraindications for Anticoagulant Thromboprophylaxis

Patients should not receive anticoagulant thromboprophylaxis if they have one or more of the following risk factors for bleeding:

Table 3. Contraindications for Anticoagulant Prophylaxis
• Active bleeding of clinical significance requiring intervention • High risk of serious bleeding that might be life-threatening • High risk of bleeding into a critical site (e.g., intracranial, intraspinal, pericardial, intraocular, retroperitoneal) • Untreated major bleeding disorder • Acquired systemic coagulopathy • Platelet count less than 50 x 10^9/L

In these patients, mechanical thromboprophylaxis should be considered. However, pharmacological prophylaxis should be started when the contraindication resolves.

2.3 Contraindications for Mechanical Thromboprophylaxis

Patients should not receive mechanical thromboprophylaxis if they have one or more of the following conditions:

Table 4. Contraindications for Mechanical Thromboprophylaxis
• Acute stroke with immobility (unable to walk independently to the toilet) for GCS use • Peripheral vascular disease with absent pedal pulses • Severe peripheral neuropathy • Skin breakdown, ulcers, gangrene, cellulitis, or dermatitis • Skin grafting within last 3 months • Allergy to stocking or compression cuff materials • Unable to size or apply properly due to leg deformity, severe edema, recent surgery or trauma

3. Thromboprophylaxis Recommendations

Based on the wealth of evidence that pharmacological prophylaxis is effective and safe, and the limited evidence for mechanical methods, pharmacological thromboprophylaxis using an anticoagulant is the method of first choice at VCH-PHC. Mechanical thromboprophylaxis should not be used alone except when a contraindication exists that significantly reduces the safety of anticoagulant administration.

The recommended anticoagulant for inpatient prophylaxis is low molecular weight heparin (LMWH). This decision is based on several considerations: 1) the convenience and safety of once-daily administration over multi-injections; 2) the availability of single-use, prefilled safety syringes for LMWH; 3) the lower risk of heparin-induced thrombocytopenia (HIT) compared with unfractionated heparin (UFH); 4) the lower incidence of bleeding and higher cost-effectiveness compared with UFH in medical patients; 5) the efficacy in all patient populations and the superior efficacy over UFH in the highest risk patients; and 6) the simplicity and consistency of using one drug regimen in almost all patients in the hospital.

The only exceptions to this recommendation are: 1) in patients with severe renal failure (eGFR less than 10mL/min or dialysis dependent), UFH 5000 units twice daily (BID) should be used given the limited evidence for LMWH; 2) in patients who are candidates for neuraxial anesthesia and pain management and are awaiting urgent surgery without a definite surgery time, UFH 5000 units BID should be used; 3) in patients with HIT, UFH and LMWH are contraindicated and fondaparinux is an acceptable alternative. Its use will be restricted and a Hematology consult is recommended where available. Aspirin is not considered an adequate agent for thromboprophylaxis in patients admitted to hospital. Selected novel oral anticoagulants (NOACs) have regulatory approval for prophylaxis following hip or knee replacement surgery, stroke prevention in non-valvular atrial fibrillation, and treatment of DVT and PE. However, none have approval for prophylaxis in hospitalized medical or non-orthopedic surgical patients. It is recommended that economical analyses using local costs be performed to examine the relative value of UFH and LMWH in surgical populations lacking robust evidence to ensure fiscally-responsible practice as well as patient safety.

The choice of anticoagulant thromboprophylaxis will be determined by the Regional P&T Committee and updated as needed based on new evidence regarding efficacy, safety and cost. Without direct comparative evidence on the relative efficacy and safety of various LMWH preparations in all clinical settings, it is not possible to recommend one LMWH over another. Each LMWH agent has a different indication and regulatory profile, safety characteristics, as well as acquisition cost. These and other relevant issues will be considered by the Regional Pharmacy &Therapeutics Committee in its decision.

The recommended thromboprophylaxis regimens at VCH-PHC are summarized below according to broad patient groups described in this document. However, it is recognized that deviations may be necessary in individual cases or groups of patients with very high risks of thrombosis and bleeding (e.g. neurosurgery, acute spinal cord injury with multiple trauma). Deviations from this guideline are also acceptable in the setting of a Research Ethics Board (REB)-approved clinical trial evaluating the relative efficacy and safety of different agents or methods for thromboprophylaxis. To ensure transparency and communication, deviations from these recommendations must be documented in the patient's chart (preprinted order [PPO] or progress notes), citing reasons for the deviation and recording the discussion with the patient (or designated decision maker).

3.1 Medical Patients

- All patients admitted for acute medical conditions should receive thromboprophylaxis if they have moderate or high risk of VTE (see Section 5.1).
- Pharmacological prophylaxis with LMWH is recommended as the method of choice in patients without severe renal failure (eGFR less than 10 mL/min) or contraindications to anticoagulants.
- Pharmacological prophylaxis with UFH 5000 units BID is recommended as the method of choice in patients with severe renal failure (eGFR less than 10 mL/min). It may be considered in those with eGFR 10 – 30 mL/min who are receiving prophylaxis for longer than 10 days.
- For patients weighing less than 40 kg, LMWH dose reduction is recommended.

- For patients with a BMI greater than 40 kg/m^2, increasing the dose of LMWH or UFH is recommended.
- Routine monitoring of the platelet count is not necessary.
- In patients with a recent history of HIT, fondaparinux is an acceptable option. Hematology consult is recommended.
- Pharmacological prophylaxis should be given at the same time each day. Evening administration (e.g., 18:00) is encouraged to allow a minimum of a 12-hour window after the last dose of LMWH if an invasive procedure is required on the following day.
- Patients already receiving anticoagulant therapy (e.g., warfarin, NOACs) should continue with the same regimen during hospitalization, unless a contraindication exists. LMWH or UFH should be given while the INR is subtherapeutic.
- Patients receiving antiplatelet therapy (e.g., aspirin, clopidogrel) for medical conditions may continue antiplatelet agents while receiving prophylaxis doses of LMWH or UFH. See Section 3.2.4 re caution regarding epidural use and antiplatelet therapy.
- When pharmacological prophylaxis is absolutely contraindicated, mechanical methods may be considered although there is no evidence to support their use in general medical patients. The exception group is patients admitted with acute stroke with immobility, where sequential compression devices (SCD) can reduce the risk of DVT.
- When the contraindication to anticoagulation resolves, patients should receive pharmacological prophylaxis. Daily assessment for initiating anticoagulant prophylaxis should be performed.
- Insertion of an inferior vena caval filter should not be performed for primary prevention of VTE.
- Prophylaxis should continue during hospitalization until the patient is no longer at increased risk of VTE.

3.2 Surgical Patients

3.2.1 Pre-operative setting

- In outpatients being admitted for elective surgery, pharmacologic prophylaxis with a single subcutaneous dose of UFH 5000 units prior to surgery is recommended in those with an increased risk of VTE (see Section 5.2) and without contraindications to anticoagulants (e.g., history of HIT).
- In patients who are candidates for neuraxial anesthesia, all efforts should be made to administer the single dose of UFH **AFTER** the placement of neuraxial block.
- In hospitalized patients awaiting urgent surgery, LMWH prophylaxis should be withheld a minimum of 12 hours prior to surgery and be switched to UFH 5000 units BID (if there is no booked surgery time) to accommodate neuraxial blockade.
- Mechanical prophylaxis with graduated compression stockings (GCS) or SCD should be applied prior to surgery only in patients in whom pharmacological prophylaxis is absolutely contraindicated before and after surgery.

3.2.2 Intra-operative and post-anesthetic care setting

- If applied preoperatively, mechanical prophylaxis should continue during surgery and in the post-anesthetic care unit.

3.2.3 Post-operative setting

- All patients after surgery or have significant trauma should receive thromboprophylaxis if they have an increased risk of VTE (see Section 5.2).
- Pharmacological prophylaxis with LMWH is recommended as the method of choice in patients without severe renal failure (eGFR less than 10 mL/min) or contraindications to anticoagulants.
- Pharmacological prophylaxis with an approved NOAC is an acceptable alternative to LMWH in patients after major hip or knee replacement surgery if they do not have significant renal impairment (eGFR < 30 mL/min). Rivaroxaban is currently the NOAC on formulary for this indication.

- Pharmacological prophylaxis with UFH 5000 units BID is recommended as the method of choice in patients with severe renal failure (eGFR less than 10 mL/min). It may be considered in those with eGFR 10 – 30 mL/min who are receiving prophylaxis for longer than 10 days.
- For patients weighing less than 40 kg, LMWH dose reduction is recommended.
- For patients with a BMI greater than 40 kg/m^2, increasing the dose of LMWH or UFH is recommended.
- Routine monitoring of the platelet count is not necessary.
- In patients with a recent history of HIT, fondaparinux is an option. Hematology consult is recommended.
- Pharmacological prophylaxis should generally start within 12 – 24 hours after surgery once hemostasis is achieved. The surgeon must state when the first post-operative dose should be given.
- Subsequent doses should then be given at the same time once daily and this should be consistent for the same patient population.
- Evening administration (e.g., 18:00) is encouraged to allow a minimum of a 12-hour window after the last dose of LMWH if an invasive procedure is required on the following day.
- Patients already receiving anticoagulant therapy (e.g., warfarin, NOACs) should continue with the same regimen during hospitalization, unless a contraindication exists. LMWH or UFH should be given while the INR is subtherapeutic.
- Patients receiving antiplatelet therapy (e.g., aspirin, clopidogrel) for medical conditions may continue antiplatelet agents while receiving prophylaxis doses of LMWH or UFH. See Section 3.2.4 regarding caution regarding epidural use and antiplatelet therapy.
- When pharmacological prophylaxis is absolutely contraindicated, mechanical methods may be used if there are no contraindications (Section 6.2).
- When the contraindication to anticoagulation resolves, patients should receive pharmacological prophylaxis. Daily assessment for initiating anticoagulant prophylaxis should be performed.
- Insertion of an inferior vena caval filter should not be performed for primary prevention of VTE.
- Prophylaxis should continue during hospitalization until patient is no longer at increased risk of VTE.
- Continuing thromboprophylaxis for 14 days for total knee replacement is recommended and until 30 days after surgery in patients having surgery for cancer in the abdomen or pelvis, hip fracture, or hip replacement.
- Continuing thromboprophylaxis after discharge may be considered in other patients with ongoing and multiple risk factors for VTE.

3.2.4 Use of Neuraxial Blockade

The following recommendations are based on the American Society of Regional Anesthesia (ASRA) and Pain Medicine Evidence-Based Guidelines (third edition) on regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy. The Peri-Operative Pain Service (POPS) recommendations on the use of epidural analgesia and antithrombotic therapy should also be followed. If there are discrepancies between these and the POPS guideline, the more conservative approach should be taken.

- The risk benefit of neuraxial blockade versus the risk of of spinal hematoma and the risk of thromboembolic complications should be considered in each individual case.
- Neuraxial blockade should be avoided in patients receiving more than 10,000 units of UFH daily because the safety and risk of spinal hematoma have not been established.
- If a single dose of UFH is indicated before planned elective surgery, all efforts should be made to administer it **AFTER** the placement of neuraxial anesthesia.
- In patients receiving once-daily prophylaxis doses of LMWH, needle placement should occur no sooner than 12 hours after the last dose of LMWH.
- Indwelling neuraxial catheters may be maintained while patients are receiving prophylaxis with LMWH, but the catheter should be removed no sooner than 12 hours after the last dose of LMWH.
- LMWH administration should occur no sooner than 2 hours after epidural catheter removal.
- The first post-operative dose of LMWH should be administered no sooner than 8 hours after surgery in those with an epidural catheter.

- If there is blood during needle and catheter placement, initiation of LMWH should be delayed for 24 hours postoperatively.
- Twice-daily dosing of LMWH prophylaxis is NOT recommended because it is associated with an increased risk of spinal hematoma.
- Patients receiving antiplatelet therapy (other than ASA 81 mg daily) for medical conditions who stopped the antiplatelet agent prior to surgery (e.g., NSAIDs, clopidogrel) can resume the antiplatelet agent(s) when hemostasis is achieved and only after epidural catheter removal (if applicable). The risk of delaying the start of antiplatelet therapy should be weighed against the benefit of epidural analgesia.
- Fondaparinux and novel oral anticoagulants (NOACs) (e.g., dabigatran, rivaroxaban, apixaban) are contraindicated in patients with an indwelling epidural catheter due to the paucity of safety data.

3.3 Pediatric Patients

There are no specific recommendations in the ACCP Evidence-Based Clinical Practice Guidelines (9th edition) on antithrombotic therapy for prevention of VTE in hospitalized neonates and children. Consequently, given the very low rates of VTE in pediatric patients:

- Routine thromboprophylaxis is not recommended in hospitalized pediatric patients.
- Thromboprophylaxis in particularly high risk patients (see Section 5.3) should be discussed with a trained pediatric hematologist with experience in managing pediatric patients with VTE.

The contact information for the Pediatric Thrombosis service at BC Children's Hospital:

- Immediate help needed: 604-875-2161 to page the Pediatric Hematologist on call
- Non-urgent consultations: 604-875-2000 ext. 7058 (Thrombosis Nurse)

3.4 Obstetrical Patients (Pregnancy and Post Partum Period)

The following recommendations are based a review of the ACCP, NICE and the Royal College of Obstetricians and Gynaecologists guidelines (see Appendix). Based on sparse evidence, physicians may consider offering VTE prophylaxis to a woman who is admitted to hospital while pregnant or within 6 weeks of delivery if she has an increased risk of VTE (see Section 5.4):

- Pharmacological prophylaxis using LMWH (or UFH for patients with renal failure) may be offered to those without contraindications to anticoagulants.
- Mechanical VTE prophylaxis may be offered to those with contraindications to anticoagulation.

3.5 Special Populations (high risk of thrombosis and bleeding)

A single regimen for thromboprophylaxis cannot be recommended in these groups because of their very high risk of thrombosis and bleeding, frequently changing status and the lack of robust evidence to guide therapy. It is recommended that physicians adhere to the following when prescribing thromboprophylaxis:

- The balance of the risk of thrombosis and risk of bleeding should be considered.
- Pharmacological prophylaxis using LMWH (or UFH for patients with severe renal failure) should be offered to those whose risk of VTE outweighs the risk of bleeding.
- Mechanical VTE prophylaxis may be offered to patients whose risk of bleeding exceeds that of thrombosis.
- Daily reevaluation of the optimal thromboprophylaxis method should be performed.

4. Background and Rationale

4.1 Burden of VTE

Venous thromboembolism (VTE) is a common and potentially fatal complication in hospitalized patients.[1,2] Hospital-acquired VTE also accounts for approximately 70% of all VTE events in the general population and is the most preventable cause of death in the hospital setting.[3-5] In British Columbia, the number of patients with hospital-acquired VTE is estimated to be 3000 annually. This is based on an annual incidence of VTE 1 per 1,000 persons in the general population and that 70% of events are related to hospitalization. With up to one-third of patients with VTE developing long-term complications such as

post-thrombotic syndrome or chronic pulmonary hypertension, and many cases will prolong hospitalization, the burden of hospital-acquired VTE on healthcare resources is substantial.[6-9]

Among patients admitted to hospital, multiple risk factors are often present that contribute to the development of VTE during and shortly following hospitalization.[1,2,10] Up to 90% of patients admitted for an acute medical condition have one or more risk factors for VTE and all patients undergoing major surgery have an increased risk of VTE.[11,12] Evidence from numerous clinical trials have shown that thromboprophylaxis in medical and many surgical settings is efficacious, safe and cost effective,[1,2,6-9,13,14] and it has been identified as the most important patient safety practice in hospitalized patients.[15] It is estimated that for every 1000 medical admissions, 8 patients would have a symptomatic DVT and 4 patients could experience a fatal PE without thromboprophylaxis. The numbers would be reduced by approximately 50% with pharmacologic prophylaxis, with 3 patients having a symptomatic DVT and 2 experiencing a fatal PE. Therefore, an institutional-wide approach to risk assessment for VTE and the provision of appropriate thromboprophylaxis are important patient safety and cost-saving strategies for all hospitals. However, to ensure such practice also meets each patient's individual needs, clinicians must be able to estimate the patient's baseline risk of VTE, the absolute risk reduction and the risk of bleeding to determine the optimal method of prophylaxis.

4.2 Under Utilization of Thromboprophylaxis

Despite evidence that the burden of VTE is high and the effectiveness of thromboprophylaxis is established, studies have shown that physician's incorporation of evidence-based guidelines for thromboprophylaxis into their practice is suboptimal.[11,12,16-19] Universally, utilization of thromboprophylaxis is alarmingly low at less than 40%. In a 2002 Canadian study, thromboprophylaxis utilization was assessed during a 3-week period in 1894 consecutive medical patients admitted to 29 hospitals (academic or community) across 6 provinces.[12] Using recommendations from the American College of Chest Physicians (ACCP) Clinical Practice Guideline on Antithrombotic and Thrombolytic Therapy as the benchmark of practice, the study found that 90% of medical patients met the criteria for requiring thromboprophylaxis. However, only 16% received appropriate thromboprophylaxis.[12] These results are consistent with international surveys, national registries and other studies evaluating thromboprophylaxis utilization.[11,16-19] The Canadian Medical Protective Association (CMPA) also has recognized that the failure or delay to prescribe an anticoagulant when indicated is a serious risk management issue for physicians. In its June 2009 Risk Identification report, the CMPA indicated that cases involving anticoagulant therapy resulted in fewer favourable outcomes for physicians in comparison to all other cases leading to legal actions.[20]

The reasons for such deficient performance are not clear. Barriers to improving in-hospital thromboprophylaxis utilization are many, and include the lack of physician familiarity or agreement with guidelines, underestimation of VTE risk, excessive concern over the risk of anticoagulant-related bleeding, and that complex, resource-intensive processes are often necessary for institutional practice change. The lack of a simple, prospectively validated VTE risk assessment model has further hampered the widespread integration of VTE assessment and thromboprophylaxis prescription into inpatient practice. Obviously, a multifaceted approach that involves education, simple but effective tools and hospital administration commitment to reduce VTE are important components to improve thromboprophylaxis utilization and enhance patient safety.

To enhance thromboprophylaxis utilization and, thereby, improve patient safety during hospitalization and reduce health resource utilization, a VCH-PHC Thromboprophylaxis Policy has been established to mandate routine VTE risk assessment and provision of appropriate thromboprophylaxis in all patients upon admission to hospital and at the time of transfer of care between services or units. This policy is in line with national and international efforts to reduce hospital-acquired VTE and is consistent with the CMPA's recommended practices.[20-24]

5. VTE Risk Assessment

Given that hospitalized patients are a heterogeneous group with varying risks of VTE, it is important to assess the risk of VTE in each patient to determine whether thromboprophylaxis is indicated. This is best

performed using a validated risk assessment model that can identify patients in whom the risk of VTE is sufficiently high to warrant prophylaxis or identify those with an acceptably low risk in whom prophylaxis can be safely withheld. However, such a model that can be applied to all hospitalized patients is lacking. Furthermore, there is no risk model available to predict for bleeding to help clinicians estimate the net risk benefit of prophylaxis in individual patients. This has hampered the general integration of VTE risk assessment into daily inpatient practice and contributes to the poor compliance with the use of thromboprophylaxis.

One strategy for thromboprophylaxis is to provide routine thromboprophylaxis to all patients unless a specific contraindication is present. This ensures uniformity and simplicity, but may result in over treatment of patients who do not need thromboprophylaxis and cause excessive bleeding. Another strategy is to classify patients into broad risk categories, such as low, moderate and high, and provide uniform thromboprophylaxis within each risk group. A recent study in a US tertiary care hospital found such an approach to be highly effective in improving the percentage of patients receiving adequate prophylaxis from 58% in 2005 up to 93% in 2007 (P<0.001).[25] More importantly, in combination with educational rounds, real-time daily feedback and audits, the program reduced the risk of hospital-acquired VTE significantly over the 2-year period, from 1 in 76 to 1 in 122 patients (relative risk reduction 39%; P<0.001) and the risk of preventable hospital-acquired VTE dropped dramatically from 1 in 221 to 1 in 1601 patients (relative risk reduction 86%; P<0.001).[25] This high success rate was achieved without any increase in bleeding or HIT, an uncommon but potentially life- or limb-threatening complication from heparin exposure. It is important to note that the risk assessment model was incorporated into the flow of patient care by using mandatory, standardized order sets.

In January 2010, the United Kingdom (UK) National Institute for Health and Clinical Excellence (NICE) clinical guideline on VTE prophylaxis in hospitalized patients was published.[26] It is a comprehensive review of the literature and provided cost-effectiveness analyses for various thromboprophylaxis methods. It outlined criteria that identified patients at increased risk of VTE and recommended provision of thromboprophylaxis in these patients. In general, thromboprophylaxis is recommended in any patient with significant reduced mobility for 3 days or more, in medical patients with reduced mobility and an additional risk factor for VTE, and in surgical patients having surgery lasting 60 minutes or longer, with inflammatory or intra-abdominal disease, significant reduction in mobility, or have risk factors for VTE. The NICE guideline also outlines recommendations for obstetrical patients, critical care patients, and other subspecialty groups.

At VCH-PHC, a VTE risk assessment approach will be used to classify patients into two risk categories: low risk and moderate-high risk. This classification was chosen largely based on the NICE guideline and because it dichotomizes patients into those who require and do not require thromboprophylaxis. This is considered to be the most practical, simple, efficient approach and can be applied consistently across different patient populations. Although it is not a validated model, it is consistent with the recommendations of evidence-based consensus guidelines, including the NICE guideline,[26] ACCP guideline,[1,2] and other consensus guidelines published by various subspecialties (see Appendices). It was also developed in consultation with content experts and local stakeholders. It is recommended that each inpatient service program at VCH-PHC apply this risk assessment approach to its specific patient group and incorporate it into their routine admission/transfer PPO set (or create a new PPO if one currently does not exist) and prescribe the appropriate thromboprophylaxis accordingly.

The following sections outline the VTE risk assessment recommendations in medical, surgical, pediatric, and obstetrical patients.

5.1 Medical Patients

Admission for a medical illness is independently associated with an 8-fold risk for VTE.[10] Approximately 10-20% of hospitalized medical inpatients not receiving thromboprophylaxis will develop DVT.[1] Moreover, 75% of all VTE occurs in medical patients.[16] Although this patient group is very heterogeneous, up to 90% of medical patients admitted to hospitals in Canada have at least one or more risk factors for

VTE.[11,12] Therefore, appropriate thromboprophylaxis in these patients represents a great opportunity to reduce the overall burden of VTE.

To-date, a validated patient-specific model is still lacking to estimate the risk of VTE in medical hospitalized patients.[2] Proposed models are being tested and appear to be promising tools for risk stratification,[27] but none are not considered "standard of care" due to the lack of evidence on improving patient outcomes.

Based on available evidence, thromboprophylaxis should be provided to medical patients admitted to hospital if they:

- Have had or are expected to have significantly reduced mobility for 3 days or more; **OR**
- Are expected to have ongoing reduced mobility (compared to their usual state) AND have one or more of the following risk factors:

Table 5. Risk Factors for VTE	

• Age 60 years or over
• Active cancer or cancer treatment
• Previous VTE
• Critical care admission
• Obesity (BMI > 30 kg/m^2)
• Known thrombophilia
• First degree relative with VTE
• Varicose veins with phlebitis
• Estrogen-containing contraception
• Hormone replacement therapy
	• One or more significant medical conditions:
	  • Sepsis or severe acute infection
	  • Heart disease
	  • Respiratory pathology
	  • Inflammatory condition
	  • Rheumatological disease
	  • Nephrotic syndrome
	  • Antiphospholipid syndrome
	  • Acute stroke

Medical patients who do not meet the above criteria do not require routine thromboprophylaxis with pharmacological or mechanical methods. Ambulation in those with reduced mobility should be encouraged.

5.2 Surgical Patients

Patients undergoing major surgery have an increased risk of VTE. Depending on the type of surgery and presence of other VTE risk factors, the incidence of post-operative VTE have been reported in historical literature to range from 10% to 60%.[1,2]

However, the true present day risk of VTE after different surgeries is less certain. Emphasis on early mobilization after surgery and minimally invasive surgical techniques may have reduced the risk of VTE, yet older patients having surgery and the performance of more complex procedures may in fact increase the incidence. The shorter duration of hospital stay may also create the perception that the risk of VTE is lower than previously reported because patients are discharged home prior to the peak incidence of post-operative thrombosis. Furthermore, the shorter duration of inpatient prophylaxis may lead to a higher incidence of VTE in the community. There is also evidence that patients undergoing hip arthroplasty, hip fracture surgery, or abdominal or pelvic surgery for malignancy have a prolonged risk of VTE.[1,28-30] A large, prospective cohort study of almost one million middle-aged (age 50 – 64 years) women in the United Kingdom showed that the increased risk of symptomatic VTE persists up to 12 weeks after any surgery, and the peak risk for symptomatic VTE occurs at 3 weeks post-operatively.[31]

Based on available evidence, surgical patients have an increased risk of VTE and should receive thromboprophylaxis if they have one or more of the following:

Table 6. Specific Risk Factors for VTE in Surgical Patients (Including Day Surgery)
• Surgical procedure with a total anesthetic and surgical time 60 minutes or longer • Acute surgical admission with inflammatory or intra-abdominal condition • Expected significant reduction in mobility • Have one or more risk factors shown in Table 5

Surgical patients who do not meet these criteria do not require thromboprophylaxis with pharmacological or mechanical methods. Early ambulation should be encouraged in all patients, regardless of VTE risk status.

For patients who received thromboprophylaxis in hospital, VTE assessment should be done at the time of discharge to determine if they should continue thromboprophylaxis beyond hospitalization. This is particularly important for patients who had abdominal or pelvic surgery for cancer, hip or knee arthroplasty, or those with multiple risk factors for VTE.

5.3 Pediatric Patients

Unlike their adult counterparts, hospitalized pediatric patients are less likely to acquire a venous thromboembolic event. However, VTE is more likely to occur in a hospitalized pediatric patient (5.3 per 10,000 children) versus general pediatric patients (0.07 to 0.14 per 10,000 children) and this number is rising.[32-35] In fact, a recent study suggests the prevalence of VTE in hospitalized pediatric patients has climbed from 0.3 per 10,000 admissions from 1992-1995 to 28 per 10,000 admissions in 2005.[34] As more children survive more complicated illnesses in tertiary care centers, it is anticipated that their risk of hospital-acquired VTE will continue to increase.[35]

There are no VTE risk assessment models for hospitalized children. However, those with the following risk factors have a higher risk of thrombosis and may be considered for thromboprophylaxis:

Table 7. Specific Risk Factors for VTE in Children Admitted to Hospital

- Use of central venous catheters
- Malignancy
- Congenital heart disease
- Renal disease
- Immobility
- Multiple trauma
- Inherited thrombophilia (homozygosity or double heterozygosity)
- L-asparaginase

5.4 Obstetrical Patients (Pregnancy and Post Partum Period)

Pregnancy and the early (first 6 weeks) post partum periods are hypercoagulable states. In fact, VTE remains the leading direct cause of maternal death in developed countries. The estimated incidence of VTE is 1.72 per 1000 deliveries.[36]

Women who are admitted to the hospital while pregnant or during the first 6 weeks after delivery have a higher risk of thrombosis than an age-matched population.[37,38] Based largely on expert opinion and clinical observation, the risk is higher if these women have general risk factors for VTE (see Table 5) or the following obstetrical-specific risk factors: [26]

Table 8. Specific Risk Factors for VTE in Hospitalized Obstetrical Patients[26]

- Ovarian hyperstimulation
- Hyperemesis gravidarum
- Multiple pregnancy
- Preeclampsia
- Emergency caesarean section
- Obesity (pre-pregnancy or early-pregnancy BMI > 30 kg/m^2)

5.5 Special Populations

In addition to children and pregnant women, there are many other populations in whom the risk of VTE remains poorly characterized. These include patients admitted in critical care units, patients with newly acquired long-term immobility (such as those after a spinal cord injury or stroke), long term care facility residents, palliative care patients, and others. There are also a multitude of surgical procedures and disciplines in which the risk of VTE and bleeding are not well studied.

For all of these groups, it is likely that they share the same risk factors (see Table 5) as the general population, but their risk benefit ratios of thromboprophylaxis may differ from the general medical or surgical population. It is recommended that individual VTE risk assessment be performed using the patient category listed above that is most similar to the individual patient. The risk category and rationale should be documented clearly in the patient's chart.

6. Methods of Thromboprophylaxis

Two major methods are available for thromboprophylaxis: pharmacological and mechanical. Pharmacological methods are well studied and consistently shown to produce significant reduction in venous thrombosis in hospitalized patients.[1,2] Mechanical methods, on the other hand, are not well studied in most patient populations, lack standardization and provide much weaker evidence of efficacy in reducing clinically significant thrombotic events.[1,2]

6.1 Pharmacological thromboprophylaxis

Anticoagulants remain the cornerstone of pharmacological thromboprophylaxis. In hospitalized patients, two anticoagulants are commonly used: UFH and LMWH. Both are parenterally administered via subcutaneous injections. UFH is typically given twice- or three-times daily, while LMWH is usually given once a day. The relative advantages of these agents are outlined in Table 9.

Table 9. Comparison of UFH and LMWH Prophylaxis

	UFH	LMWH
Advantages	• inexpensive • useful in renal insufficiency • very low risk of spinal hematoma in neuraxial blockade	• Once-daily dosing (reduce nursing time and increase patient comfort) • Available in single-use prefilled safety syringes (reduce dosing error and needle stick injuries) • Lower risk of HIT[39-42]

Warfarin is also an effective anticoagulant for thromboprophylaxis. However, it is not ideal for short term use for in-patient thromboprophylaxis because of its delayed onset of action and its multiple drug and food interactions. Patients who are receiving long-term warfarin for any indication do not require additional prophylaxis with LMWH or UFH when the INR has reached a therapeutic level of 2.0 or above.

Other pharmacological agents commercially available for prophylaxis include fondaparinux, rivaroxaban, apixaban, and dabigatran. These agents are only available for restricted use only or are currently not available on the VCH-PHC formulary. Fondaparinux is a synthetic, indirect inhibitor of factor Xa given by once-daily subcutaneous injection. Well-designed randomized controlled trials have shown that it is effective in reducing VTE in orthopedic surgery, general surgery and medical patients.[43-45] Fondaparinux is a useful alternative to heparins in patients with HIT although it is not approved for this indication.[46,47] Rivaroxaban and apixaban, two oral, direct factor Xa inhibitors, and dabigatran, an oral direct thrombin inhibitor, have Health Canada approval for prophylaxis in patients undergoing elective total hip or knee arthroplasty and stroke prevention in non-valvular atrial fibrillation. Of these NOACs, only rivaroxaban is on hospital formulary for routine thromboprophylaxis following hip or knee arthroplasty. None of these NOACs have approval for prophylaxis in hospitalized medical patients or non-orthopedic surgical patients due to the lack of studies.

Although pharmacological prophylaxis has the strongest evidence for preventing VTE, it is not recommended in patients with bleeding concerns. Contraindications for pharmacological thromboprophylaxis are outlined in Table 10.

Table 10. Contraindications for Pharmacological Thromboprophylaxis
• Active bleeding of clinical significance • High risk of serious bleeding that might be life-threatening • High risk of bleeding into a critical site (e.g., intracranial, intraspinal, pericardial, intraocular, retroperitoneal) • Untreated major bleeding disorder • Acquired systemic coagulopathy with bleeding • Platelet count less than 50 x 10^9/L

6.2 Mechanical Thromboprophylaxis

Three types of mechanical methods are available for thromboprophylaxis: sequential compression devices (SCD; also called intermittent pneumatic compression devices [IPC]), graduated compression stockings (GCS; also called thromboembolic deterrent stockings) and foot pumps. They are designed to reduce the risk of VTE by reducing venous stasis. To achieve optimal results, they must be properly fitting and applied almost continuously. They should only be removed only for a short time each day to allow for skin assessment, bathing, toileting, and mobilization.

As a group, mechanical thromboprophylaxis methods have important advantages and limitations.[1] The major advantage of mechanical methods is that they do not increase the risk of bleeding, but they do cause more skin breakdown[48-50] and are contraindicated in patients with the following conditions:

Table 11. Contraindications for Mechanical Thromboprophylaxis (GCS, IPC, foot pumps)
• Acute stroke with immobility (unable to walk independently to the toilet) should not use GCS • Peripheral vascular disease with absent pedal pulses • Severe peripheral neuropathy • Skin breakdown, ulcers, gangrene, cellulitis, or dermatitis • Skin grafting within last 3 months • Allergy to stocking or compression cuff materials • Unable to size or apply properly due to leg deformity, severe edema, recent surgery or trauma

The recommendation against the use of GCS in acute stroke patients comes from a large randomized trial in the UK (CLOTS-1 trial) which found that thigh-high GCS caused more skin breakdown, including ulcers, blisters and skin necrosis without any benefit in reducing the incidence of proximal DVT.[49] In contrast, IPC device was found to be effective in reducing the risk of DVT in this same patient population in the CLOTS-3 trial.[48] But similar to the CLOTS-1 data, IPC is associated with more skin breaks on the legs. Therefore, clinicians must recognize that although mechanical methods do not cause bleeding, they can lead to skin damage, with blistering and ulceration, vessel damage, damage to soft tissue due to a tourniquet effect, as well as compartment syndrome. Other concerns about the use of mechanical methods are that they may delay the start of pharmacological prophylaxis and that they discourage or impede early ambulation. Poor compliance is also a serious problem and obviously reduces the effectiveness of these devices.[26,51-53] Education of nursing staff and patients is very important in ensuring proper fitting and optimal compliance.[54] Lastly, inappropriate use leads to substantial cost wasting.

7. Efficacy and Safety of Thromboprophylaxis

The efficacy and safety of thromboprophylaxis have been proven in many randomized trials, across many different patient populations and hospital settings. The strongest evidence is available for anticoagulant prophylaxis. Mechanical methods are not well studied and provide much weaker evidence of efficacy in reducing clinically significant thrombotic events.[1,2] There are a few studies that have compared

pharmacological and mechanical methods directly, but they are small and have important methodological limitations. Using a combination of pharmacological and mechanical prophylaxis has been recommended for patients with the highest risks of thrombosis, but the evidence supporting better efficacy over the use of a pharmacological or mechanical method alone is also weak.

Despite the decades of research supporting the use of thromboprophylaxis, skepticism still exists. Some of the criticism is focused on the use of screening investigations, such as venography or ultrasonography, to detect DVT or PE in clinical trials rather than using symptomatic outcomes. Also, some argue that patient samples in clinical trials may not be representative of all patients admitted to hospital, with the major concern being the exclusion of patients with a high risk of bleeding. Lastly, cost-effectiveness studies comparing various drugs and methods are often criticized for not including all relevant variables, making controversial assumptions, using estimates from outdated sources, and being funded mostly by pharmaceutical companies with a vested interest in the outcomes.

7.1 Medical Patients

7.1.1 Pharmacological Thromboprophylaxis

There are no placebo-controlled randomized trials studying the efficacy and safety of UFH in hospitalized medical patients. One open-label trial found UFH 5000 units three-times daily (TID) was associated with a lower mortality than those receiving no treatment but treatment allocation was open to bias.[55] Another large open-label trial in patients with infectious disease showed no difference in mortality during hospitalization or fatal PE among patients assigned to receive UFH 5000 units BID or no prophylaxis.[56] No studies have directly compared UFH 5000 units BID versus TID in medical patients. A meta-analysis comparing the two dosing regimens across different studies concluded that UFH TID was associated with a greater reduction in the risk of DVT than BID dosing.[57]

The most recent and well-conducted trials of thromboprophylaxis in medical patients have studied LMWH or fondaparinux.[42, 54, 55] These trials compared an anticoagulant against placebo in hospitalized medical patients with reduced mobility and at least one or more risk factors for VTE. The relative risk reductions of VTE in these studies were approximately 50% and differences in major bleeding between anticoagulant and placebo groups were not observed. Although these trials used venography or ultrasonography screening for DVT, two trials did show significant reductions in proximal vein thrombosis. It can also be argued that detection of asymptomatic events leads to an underestimation of symptomatic events because treatment initiated for asymptomatic thrombosis would have prevented the evolution to symptomatic disease. It is also not uncommon for hospitalized patients to not have typical symptoms of DVT because of their reduced mobility. One meta-analysis has found that during anticoagulant prophylaxis, patients had significant reductions in any PE (RR 0.43; 95%CI 0.26 – 0.71) and fatal PE (RR 0.38; 95%CI 0.21 – 0.69), a nonsignificant reduction in symptomatic DVT (RR 0.47; 95%CI 0.22 – 1.00), and a nonsignificant increase in major bleeding (RR 1.32; 95%CI 0.73 – 2.37).[13]

A meta-analysis by the Cochrane Collaboration also found that anticoagulant prophylaxis with either UFH or LMWH significantly reduce the risk of DVT by 60% (RR 0.40; 95%CI 0.31 – 0.53; P<0.00001) and PE by 42% (RR 0.58; 95%CI 0.43 – 0.80; P=0.0007) compared with no treatment or placebo.[58] No statistically significant difference in efficacy was found between LMWH and UFH. It also demonstrated that heparin resulted in a significant increase in major hemorrhage (RR 2.18; 95%CI 1.28 – 3.72; P=0.004) and minor bleeding (RR 1.74; 95%CI 1.26 – 2.41; P=0.0008) and that LMWH was associated with a 72% risk reduction in major bleeding compared with UFH (RR 0.28; 95% CI 0.10 – 0.78; P=0.02).[58] Another advantage of LMWH over UFH is the much lower incidence of HIT.[39,41,59] In a large retrospective study of 10,121 adult medical patient admissions to a tertiary care centre, the incidence of HIT was 0.51% in patients receiving UFH versus 0.084% in those given LMWH.[39] There is also consistent evidence that LMWH is more cost effective than UFH for prophylaxis in medical patients.[26,60] The cost-effectiveness of LMWH using local costs for drugs, labour and tests has recently been verified in the medical population (personal communication L.Lynd, CHEO)

Summarizing the evidence from published literature, the baseline VTE risk and the number needed to treat (NNT) and number needed to harm (NNH) in medical patients receiving anticoagulant prophylaxis with either UFH or LMWH are: [13,26,58]

Table 12. Baseline Risk and Number Needed to Treat or Harm in Medical Patients Receiving Anticoagulant Prophylaxis

	Baseline VTE Risk, %	NNT/NNH
Symptomatic or proximal DVT	0.84%	212
Non-fatal PE	0.5%	300
Fatal PE	0.4%	400
Major bleed	0.4%	430
Fatal bleed	0.6%	2270

A recently published large randomized trial did raise questions about the usefulness of LMWH for prophylaxis in medical hospitalized patients. In this study that was conducted primarily in Asia (India and China contributed 73% of the patients), enoxaparin failed to reduce overall 30-day mortality compared with placebo (4.9% vs. 4.8%).[61] The study also found no difference in major bleeding (0.4% vs. 0.3%). The limitations of this study include the insufficient power to detect a 25% reduction in death (the primary objective of the study), the inadequate duration of prophylaxis (patients did not receive prophylaxis throughout hospital stay), and the lack of generalizability to most western populations. Importantly, the study also did not include symptomatic VTE as an endpoint and did not systematically capture this outcome. Given that the goal of VTE prophylaxis is VTE reduction, this study is not able to address this question.

Another pharmacological option for VTE prophylaxis is the NOACs. Although they are approved for orthopedic prophylaxis, they have not been evaluated for non-orthopedic surgical patients. There have been randomized trials evaluating rivaroxaban and apixaban for extended prophylaxis in medical hospitalized patients,[62,63] and the results showed that these agents are noninferior to enoxaparin for prophylaxis in the first 6 – 10 days but they are associated with a higher risk of bleeding when prophylaxis with these agents is continued for up to 30 – 35 days. Consequently, extended prophylaxis in medically ill patients is not recommended. Until further evidence is available to support the use of NOACs in hospitalized medical patients, LMWH will remain the agent of choice in this setting.

7.1.2 Mechanical Thromboprophylaxis

There are no studies evaluating the efficacy of mechanical prophylaxis in general medical patients. In patients with acute stroke who are unable to walk independently to the toilet, there is now good evidence that supports the use of SCD/IPC devices but against the use of GCS for VTE prophylaxis. In the CLOTS-1 trial thigh-high GCS caused more skin breakdown, including ulcers, blisters and skin necrosis without providing any benefit in reducing the incidence of proximal DVT.49 Thigh-high GCS also failed to reduce VTE compared with below-knee stockings in the CLOTS-2 trial.50 In contrast, the CLOTS-3 trial found that SCD/IPC significantly reduced the absolute risk of DVT by 3.6% (from 12.1% to 8.5%), but they also caused more skin breaks (3% vs. 1%; p=0.002).48 In a subgroup analysis, SCD did not reduce VTE among those patients who can lift both legs off the bed. There was also no significant reduction in VTE among those who also received an anticoagulant. Therefore, the CLOTS 3 results should not be generalized to non-stroke medical patients, who are usually more ambulatory or are candidates for anticoagulant prophylaxis. None of these trials addressed which method of prophylaxis (anticoagulant vs. SCD prophylaxis) is more effective in stroke patients. In the all three CLOTS trials, some patients also received anticoagulant prophylaxis at their clinician's discretion.

7.1.3 Summary of Evidence

Overall, the evidence in medical patients is strongest and most favourable for LMWH thromboprophylaxis. Compared with UFH, it is safer in terms of bleeding and the risk of HIT, more convenient with once-daily dosing, and more cost effective. Fondaparinux is a reasonable choice in patients with HIT. The NOACs do not have regulatory approval for VTE prophylaxis in medical hospitalized patients and are not recommended. Among those admitted with an acute stroke and immobility, SCD is an effective option in those with contraindications for anticoagulant prophylaxis. GCS are contraindicated in this subgroup of patients.

7.2 Surgical Patients

The efficacy and safety of thromboprophylaxis in surgical patients is well established. A large randomized trial published in 1975 showed that low-dose UFH was associated with a decrease in the incidence of fatal PE.[64] Since then, numerous studies and meta-analyses have confirmed the benefit of pharmacological thromboprophylaxis in reducing post-operative VTE, total and fatal PE.[14,65] Consequently, thromboprophylaxis has been accepted for decades as the standard of care in patients undergoing surgery.[1]

7.2.1 Pharmacological Thromboprophylaxis

Comparable efficacy and safety between LMWH and UFH have been demonstrated in the general surgery setting.[1,65] But for patients having the highest risks of VTE, including those having hip or knee arthroplasty,[1] those with major trauma,[66] and those admitted with an acute stroke,[67] LMWH is more effective than UFH. As in medical patients, the incidence of HIT is lower with LMWH than UFH use after surgery.[40,59] Cost-effective analyses have been done in different surgical settings. Depending on the risk of major bleeding, findings favour different modalities. In the NICE guidelines, GCS alone was the most cost effective for general surgery patients but the results are highly sensitive to baseline risk of major bleeding and baseline risk of PE. For patients are lowest risk of major bleeding, combination prophylaxis is cost-effective, rather than mechanical prophylaxis alone.[26] However, compliance with mechanical methods is a major concern, with studies showing fewer than half of the patients wore GCS in a correct manner or had proper fitted GCS or SCDs.[26]

Summarizing the evidence from published literature, the baseline risk of VTE and NNT/NNH in patients having major general surgery with either UFH or LMWH are:

Table 13. Baseline Risk and Number Needed to Treat or Harm in Patients Receiving Anticoagulant Prophylaxis after Major General Surgery

	Baseline Risk, %	NNT/NNH
Symptomatic or proximal DVT	1.3%	20 – 106
Non-fatal PE	1.3%	110 – 150
Fatal PE	0.7%	200
Major bleed	1.4%	70 – 100
Re-operation	0.3%	250

Uncertainty, however, remains concerning: 1) the role of thromboprophylaxis in minimally invasive or day procedures; 2) the role of thromboprophylaxis in different types of surgery; and 3) the optimal duration of prophylaxis.

As surgical and anesthetic techniques advance, more and more procedures are being performed as day surgery, where patients are admitted, undergo their procedure and discharged within 24 hours. Typically, thromboprophylaxis is not provided for these patients. Although recovery time is shortened in most cases, some patients still have limited mobility afterwards and their other risk factors for VTE. Also, minimally invasive surgeries, such as laparoscopy, vary in their complexity and associated risk of VTE, making it difficult to determine whether routine withholding of thromboprophylaxis is safe in these

patients. This uncertainty is evident in the guideline for deep vein thrombosis prophylaxis during laparoscopic surgery from the Society of Gastrointestinal and Endoscopic Surgeons, which recommends individualizing therapy, and offering either pharmacological or mechanical thromboprophylaxis in patients with risk factors.[68]

Similarly, evidence on the risk benefit of thromboprophylaxis is limited in most types of surgery. The risks of VTE and bleeding are clearly dependent on the type of surgery and the comorbid features of the patients. The most comprehensive summary of evidence in different types of surgery is available in the ACCP guideline and NICE guideline.[1,26] For most surgeries, pharmacological prophylaxis is recommended in patients with an increased risk of VTE, unless the bleeding risk is sufficiently high.

Traditionally, prophylaxis is continued during hospitalization and is stopped when patients are discharged. This provided approximately 7 – 10 days of thromboprophylaxis and it is the duration used in most clinical trials and recommended by evidence-based guidelines. It is unknown whether shorter duration of thromboprophylaxis is sufficient but studies have shown that prolonged thromboprophylaxis up to 30 – 35 days after surgery reduces symptomatic VTE in patients having hip arthroplasty or hip fracture repair,[28,69] and all VTE in patients having abdominal or pelvic surgery for cancer.[70] The recent Million Women study in the UK confirms that the risk of symptomatic VTE persists up to 12 weeks after any surgery, and the risk is particularly high after orthopedic, vascular or cancer surgery.[31]

7.2.2 Mechanical Thromboprophylaxis

Evidence for mechanical thromboprophylaxis comes primarily from the surgical literature. Most of the studies are methodologically weak and open to bias, and all are too small to have sufficient power to demonstrate clinically important differences. Also, many of the studies were performed in the 1980s and 1990s, so it is difficult to know if changes in design or material have occurred that would have changed the performance of these devices. Compression devices differ with respect to their length, single-chamber vs sequential compression, asymmetric versus circumferential compression, cycle frequency, and pressure generation characteristics. Many commercially available devices have never been standardized or assessed in clinical trials. Consensus guidelines also tend to group mechanical methods as a whole and fail to distinguish GCS from SCD.[1,26] But these are clearly different devices that have different performance characteristics and variable costs associated with their use, maintenance and disposal. The recent CLOTS trials in patients with acute stroke and immobility confirm there are differences in the efficacy between SCD/IPC and GCS. This should be taken into account when mechanical prophylaxis is being considered in other medical and the surgical patient populations.[48-50]

In 2009 the Cochrane Collaboration published a meta-analysis of elastic compression stockings in preventing VTE after surgery. It included 7 randomized controlled trials conducted between 1971 and 1996 that looked the effect of GCS alone.[71] Stockings were applied on the day of admission or on the day of surgery and were worn until discharge or the patients were fully mobile. Screening tests were done to detect DVT but it is not clear that blinded outcome assessment was performed. The VTE rates were 15% in the GCS group and 29% in the control group. The Peto's odds ratio was 0.36 (95% CI 0.26 – 0.49; P<0.00001) in favour of GCS. There was no evidence that symptomatic VTE is reduced with GCS.

The literature on SCDs is also weak.[1] These trials have been performed in total hip or knee arthroplasty,[72,73] gynecological surgery,[74,75] urological surgery,[76,77] and neurosurgery.[78] These procedures are associated with higher bleeding risks so alternatives to anticoagulant prophylaxis are often preferred. Most of these trials were small, did not use appropriate control groups, used tests such as fibrinogen leg scanning and impedance plethysmography (both tests are no longer used and have poor sensitivity and specificity for diagnosing DVT), and unblinded assessment. None were sufficiently large to show reduction in symptomatic VTE.

The efficacy of combining pharmacological prophylaxis and SCD in surgical patients was examined in a 2009 Cochrane Collaboration meta-analysis.[79] It concluded that the combined method is more effective than single methods (pharmacological or mechanical) alone. However, only 6 randomized controlled trials were included and many did not use concealed treatment allocation, blinded outcome assessment or

proper randomization methods. In the 2 randomized trials that compared combined prophylaxis with anticoagulants, GCS was used in the anticoagulant group as well. In effect, these studies compared SCDs with GCS. Therefore, there is no solid evidence that combining anticoagulant and SCD provides better efficacy than using anticoagulant alone.

Despite the lack of evidence, mechanical methods are often preferred because they do not cause bleeding and so there had been general consensus that there is no harm in using them. But the CLOTS-1, CLOTS-2 and CLOTS-3 trials in patients with acute stroke found that SCD/IPC and GCS do cause more skin breakdown.[48-50] Also, practical issues limit the effectiveness of mechanical thromboprophylaxis. Patients generally find them uncomfortable and most have trouble putting GCS on. Proper fitting is essential to avoid a tourniquet effect but this is not always possible for patients. There is also a concern for falls as stockings are slippery. Compression devices are also noisy and the tubing connecting the sleeves to the machine is a tripping hazard. They must be applied almost continuously to be effective but this impedes ambulation. Studies have even questioned whether they produce the pressures claimed by the manufacturers and raised issues regarding compliance.[80] Also, the cost of SCDs are substantial. Replacement cost of a pair of knee-high compression sleeves is approximately $40 - $70 for a new pair and $20 for a reprocessed pair (2012 pricing, VCH, Biomedical Engineering). Besides the purchase cost, considerable expense is also used for maintenance, storage, distribution, tracking, delivering, and other logistical resources. The cost of sleeve purchase alone in 2012 at VCH-PHC is estimated to be approximately $900,000 (Biomedical Engineering).

7.2.3 Summary of Evidence

Overall, the evidence in surgical patients is strongest and most favourable for pharmacological thromboprophylaxis. Mechanical methods do not cause bleeding but they can cause skin breakdown. The data for efficacy are generally weak and poor compliance seriously reduce efficacy. LMWH once daily and UFH three-times daily are comparable in efficacy and bleeding risk but LMWH is safer in terms of a lower risk of HIT, dosing errors and needle stick injuries. Cost effectiveness varies in different surgical procedures depending on the risk of major bleeding. The frequency of use of post-op neuraxial blockade in specific populations needs to be considered because concomitant UFH three-times daily is not recommended with an epidural; for these patients LMWH should be used.

7.3 Pediatric Patients

There are no level I trials evaluating the efficacy and safety of thromboprophylaxis in hospitalized children. The low incidence of VTE and the diversity of patient groups make research in this field particularly challenging. Also, the epidemiology and natural history of VTE are different even among pediatric patients as the hemostasis and coagulation systems are evolving as children age. Consequently, there are no specific guidelines on thromboprophylaxis for the pediatric population.[35] Therefore, expert recommendations are largely based on extrapolations from adult studies and clinical experience. This is not ideal as pharmacodynamics and pharmacokinetics of antithrombotic drugs, as well as their dosing and monitoring are different in pediatric patients compared to adults.[81,82]

Given that the incidence is very low, it is reasonable to conclude that the vast majority of hospitalized pediatric patients do not warrant routine thromboprophylaxis. However, higher risk groups, such as those with congenital heart disease, cancer, indwelling central venous catheters, may sometimes benefit from thromboprophylaxis. Because of the complexity and the rapidly changing status of such conditions in these children, the decision to use thromboprophylaxis should always be made with the aid of a trained pediatric hematologist with experience in managing pediatric patients with VTE. It is recommended that the Pediatric Thrombosis service at BC Children's hospital be contacted for advice for specific cases.

7.4 Obstetrical Patients (Pregnancy and Post Partum Period)

Evidence for thromboprophylaxis in obstetrical patients admitted to the hospital is sparse.[83] The few available trials evaluated women after caesarean section are small and have methodological limitations.[26] Because of the lack of evidence, it is not possible to make conclusive recommendations.

Overall, given that the absolute risk of VTE is low, routine thromboprophylaxis of these women admitted to hospital is likely not warranted. However, because the presence of VTE risk factors (Table 5) and specific obstetrical conditions (Table 8) may significantly increase the risk of VTE during hospitalization, it is recommended that women with these risk factors be considered for thromboprophylaxis if they are admitted to hospital during pregnancy or within the first 6 weeks after delivery.[26]

7.5 Special Populations

Although strong evidence is not uniformly available for anticoagulants in all patient types and all hospital settings, the consistent and overwhelming evidence available argue in favour of a simple and unified approach to provide effective thromboprophylaxis in most, if not all, patients admitted to the hospital. Therefore, in patient groups not specifically addressed here, the recommended approach is to consider the relative risks of thrombosis and bleeding in individual patients. If the risk of thrombosis outweighs the risk of bleeding, then pharmacological prophylaxis is recommended. In patients in whom the risk of bleeding is high (see Table 10), mechanical prophylaxis should be considered.

Based on evidence available, LMWH (or UFH in those with severe renal impairment) is recommended as the pharmacological agent of choice for all medical patients, patients admitted with stroke, patients with major trauma including acute spinal cord injury, and surgical populations frequently using neuraxial blockade. For other populations, LMWH is preferred over UFH to simplify and streamline prophylaxis practice throughout the institution. This uniform approach is likely to reduce confusion and errors. A more complicated cost-conscious approach would be to examine the incremental cost of using LMWH over UFH in patient populations currently lacking robust evidence and specify the use of UFH in some patient populations and LMWH in others. To do this, appropriate cost-effectiveness analyses using local drug costs, as well as costs associated with adverse effects, nursing time, risks of dosing errors and needle sticks, disposal, education, etc. are necessary.

For patients undergoing major hip or knee arthroplasty, robust, level 1 evidence from large, randomized clinical trials have demonstrated recently that LMWH and NOACs are comparable in efficacy and safety.[84] Because of the convenience of a once-daily oral medication over once-daily injections, the anticoagulant prophylaxis of choice in many North American and European centres has shifted from LMWH to NOACs in this patient population. At VCH, Rivaroxaban is currently on formulary for this indication. LMWH remains a good choice and should be used in those with a higher risk of bleeding, requiring neuraxial analgesia, or receiving warfarin for long-term anticoagulation for other reasons. The use of LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose UFH, adjusted-dose vitamin K antagonist, and aspirin *over no prophylaxis* was given grade 1B support by the 2012 ACCP guidelines.[84] However, the ACCP guidelines still recommend the use of LMWH in preference to other agents in this patient group.

Several patient groups requiring special mention are those with renal insufficiency or obesity, because the dosing and choice of anticoagulants differ in these patients from the general population, and those patients receiving neuraxial blockade because of the risk of spinal hematoma.

7.5.1 Patients with Renal Insufficiency

Anticoagulant thromboprophylaxis in patients with renal sufficiency has been studied. Because LMWH is excreted via the kidney, there is a potential for accumulation in patients with impaired renal function. Overall, the evidence supports that therapeutic doses of LMWH is associated with a higher risk of bleeding in patients with severe renal insufficiency than in patients with normal renal function.[85] UFH is considered to be safer in those with renal impairment because it is cleared primarily by the liver at therapeutic doses.

But it remains uncertain whether LMWH at prophylaxis doses is associated with an increase in bleeding in renally impaired patients. The pharmacodynamic studies conducted to examine this question typically use a surrogate endpoint of anti-Xa activity and are too small and underpowered to demonstrate differences in bleeding.[86] Also, the correlation between anti-Xa levels and bleeding is not well established. In general, such studies have found no evidence of LMWH accumulation in patients with

mild or moderate renal impairment but accumulation may occur with some of the LMWH agents in patients with severe renal impairment (eGFR less than 30mL/min).

A prospective study of 138 critically ill patients with a creatinine clearance of less than 30 mL/min found that dalteparin 5000 units once daily administered for 4 – 12 days (median 7 days) did not show any bioaccumulation.[87] Other studies have supported this finding.[88,89] In contrast, data for enoxaparin 40 mg once daily suggest that bioaccumulation can occur in patients with a creatinine clearance lower than 30 mL/min,[90,91] and so dose reduction is recommended.[86] Tinzaparin once daily does not appear to bioaccumulate in patients with impaired renal function, even at therapeutic doses.[90] This is due to its longer chain length that increases its clearance by the liver. However, tinzaparin does not have regulatory approval for prophylaxis in medical patients and a recent VTE treatment study in very elderly patients with renal impairment found a higher all-cause mortality rate in the tinzaparin treatment group.[92] Although this was not related to bleeding or any adverse effect of tinzaparin, it has resulted in a FDA Safety Review and a warning in the tinzaparin product monograph.

Overall, in patients with mild to moderate renal impairment, prophylaxis doses of LMWH do not require adjustment. In patients with severe renal impairment (eGFR 10 – 30 mL/min), dalteparin 5000 units once daily, tinzaparin 4500 units once daily or enoxaparin 30 mg once daily appear to be safe.[86,93] **Note that tinzaparin is a non-formulary drug*. UFH 5000 units BID should be used in those with eGFR less than 10 mL/min and could be considered in patients with eGFR 10 – 30 mL/min if LMWH prophylaxis is continuing beyond 10 days.

7.5.2 Patients with Extremes of Body Weight

Patients at extremes of body weight raise concerns regarding the efficacy and safety of fixed-doses of anticoagulants given for thromboprophylaxis. Clinical trials typically exclude these patients and comorbid conditions are likely more common in patients who are very underweight or are morbidly obese.

A few studies have been done to examine the need for dose adjustment in morbidly obese patients. In a retrospective subgroup analysis of 1118 obese, hospitalized medically ill patients, VTE rate in obese patients (BMI greater than 30 kg/m^2) was not statistically different between the dalteparin 5000 units once daily group and the placebo group (2.8% vs. 4.3%; RR 0.64; 95%CI 0.32 – 1.38).[94] This was largely due to no reduction in VTE in the highest weight group with a BMI 40 kg/m^2 or higher. For enoxaparin, a small study reported that a weight-based dose of 0.5 mg/kg once daily produced anti-Xa levels within the prophylaxis range, with no VTE or bleeding outcomes in 28 morbidly obese medical patients.[95] Studies in patients undergoing bariatric surgery also suggest that higher doses of enoxaparin is associated with low rates of post-operative VTE without any increase in bleeding, but properly designed randomized controlled trials have not been done.[96,97] Tinzaparin also has a weight-based thromboprophylaxis dose at 75 U/kg but lacks data in morbidly obese patients.[98] To date, there are no randomized controlled trials comparing standard and higher doses of LMWH in obese patients. Overall, the evidence supports the use of higher than standard doses of LMWH be used in obese patients.

There are no studies addressing the appropriate dose of LMWH for thromboprophylaxis in underweight adult patients (less than 40 kg or BMI less than 20 kg/m^2). The concern here is overdosing and an increased risk of bleeding. Because the available data suggest that higher doses are required in larger patients, it seems prudent to use lower doses in patients who are underweight.

There are no studies addressing the use of UFH prophylaxis in medical patients of extreme body weights.

7.5.3 Neuraxial Anesthesia and Analgesia

The concern with using antithrombotic therapy and neuraxial anesthesia and analgesia is well documented. The most serious consequence is the development of spinal hematoma, which, although rare, is a devastating complication and largely avoidable. The ASRA and Pain Medicine Evidence-Based Guideline (third edition) published in Jan 2010 outlines the evidence and rationale for precautions that should be taken when patients who receive neuraxial blockade.[99]

In general, neuraxial blockade can be used in patients receiving anticoagulant prophylaxis. However, the timing of needle placement, epidural catheter removal and when an anticoagulant is administered are critical to safeguard against the risk of spinal hematoma. There is also very little safety data on the risk associated with UFH doses of more than 10,000 units daily, so UFH 5000 units TID or 7500 units BID should be avoided in patients receiving neuraxial blockade. There appears to be a very low risk of spinal hematoma associated with UFH 5000 units BID and a low risk with once-daily LMWH prophylaxis regimens if needle placement or catheter removal occurs no sooner than 10 – 12 hours after an injection.

After catheter removal, patients should be monitored closely for neurological symptoms and LMWH or UFH should not be given within the next 2 hours. Twice-daily dosing of LMWH prophylaxis is associated with an increased risk of spinal hematoma and is not recommended. Also, ASRA recommends against the concomitant use of LMWH and antiplatelet therapy in patients receiving neuraxial blockade. Antiplatelet agents (e.g., NSAIDS, clopidogrel) that are stopped for surgery should not be restarted postoperatively until after epidural catheter removal.

Far less experience and no robust evidence are available to guide the use of NOACs in patients requiring neuraxial blockade. Although these agents are not recommended for VTE prophylaxis in medical and non-orthopedic patients, they are commonly used for orthopaedic VTE prophylaxis, stroke prophylaxis in atrial fibrillation or VTE treatment. Manufacturers of these agents provide very limited information and recommendations on the timing of neuraxial catheter placement or removal in patients who are taking these agents. There is general consensus that patients should NOT be receiving these agents if they have an indwelling epidural catheter. The Peri-Operative Pain Service (POPS) should be consulted for further advice in patients on NOACs who require neuraxial intervention.

Details of the recommendations regarding anticoagulant prophylaxis are outlined in Section 3.2.4 Thromboprophylaxis Recommendations Use of Neuraxial Blockade. The POPS recommendations on the use of epidural analgesia and antithrombotic therapy should also be followed. If there are discrepancies between these and the POPS guideline, the more conservative approach should be taken.

8. Roles and Responsibilities

All personnel with direct patient care have the responsibility to assess their patients for the risk of VTE and ensure appropriate thromboprophylaxis is prescribed and administered.

Physicians have a key role in VTE risk assessment and are responsible for ordering appropriate thromboprophylaxis. They must incorporate these actions in their routine practice. Educating patients regarding the risk of VTE, the relevant signs and symptoms and the risks and benefits of prophylaxis is also a responsibility of the physician.

Nurses play a major role in the daily assessment of patients' condition and VTE assessment should be part of this routine evaluation. Reminding physicians and patients about the risk of VTE and checking for the relevant signs and symptoms are invaluable contributions that nurses make to improve patient safety.

Pharmacists can assist physicians in assessing VTE risk and choosing the optimal regimen of thromboprophylaxis. They also have a vital role in reviewing potential drug interactions and need for post-discharge thromboprophylaxis.

To maximize compliance with the VTE prophylaxis policy, VTE risk assessment and thromboprophylaxis must be included in standard PPOs for hospital admission and interservice patient transfer. It is encouraged that these components are embedded in existing PPOs to facilitate use.

9. Appendices

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Expected Client/Family Outcomes

Reduction in preventable VTE associated with hospitalization.

Evaluation (Guideline Only)

Chart audit and feedback.

Documentation

Routine VTE risk assessment and orders for thromboprophylaxis will be added to admission preprinted order sets of all acute care services or units.

References

See Practice Guideline.

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