Executive Summary for revision of Venous Thromboembolism (VTE) Prophylaxis and addition of Treatment Guidelines at the R Adams Shock Trauma Center 2018

The last guidelines for venous thromboembolism (VTE) for the R Adams Cowley Shock Trauma Center were developed in 2013. These did not include guidelines for treatment of VTE. The present document represents an update and revision of the VTE prophylaxis and addition of treatment guidelines for the R Adams Cowley Shock Trauma Center.

The major resource for references still remains the Chest Guidelines 2012 and the more recent 2016 issue, which addresses up to date changes in treatment strategies.

Sections I (General Guidelines) and II (Special Considerations) deal with only prophylaxis. The major change in prophylaxis strategy is the timing for the use of anticoagulants (including antiplatelet agents) in the presence of **brain and spinal injury** (Sections II.5 and II.6). Prophylaxis in the patient with brain injury and blunt cerebrovascular injury (BCVI) is also addressed (section II.7)
Extended prophylaxis for the non-weight bearing orthopedic trauma patient (beyond inpatient hospitalization) has been lengthened to be 35 days from date of last orthopedic procedure.
Dosing and monitoring of LMWH/UFH for VTE prophylaxis and treatment have been added (Section II.9).

ASA is mentioned for prophylaxis in orthopedic trauma patients: there has not been a consensus on its use, however, the **PCLOT study** is ongoing and will not be finished until sometime in 2020 (Section VI.1 Addendum).

Sections III (General Guidelines) and IV (Special Considerations) deal with Treatment of VTE. There have been major changes in treatment strategies. First, the **duration of treatment** using oral anticoagulants is determined by whether or not the VTE was **provoked or unprovoked** (Section III.2). Also, included are guidelines for Distal Lower extremity VTE and Upper extremity VTE (Section IV.1 and IV.2). Second, since 2010, there are more choices for the treatment modality regarding oral agents for anticoagulation (Section I.a). There are direct inhibitors of either factor IIa or Xa. The present nomenclature refers to them as "DOACs" (**D**irect **O**ral **A**nti**C**oagulants), rather than "NOACs" (Novel or Non Vitamin K Oral Anticoagulants).

The **FDA** has relaxed their stance on "**where**" patients with pulmonary embolism may be treated: inpatient versus outpatient. In prior years, outpatient treatment with anticoagulation was deemed "off label" (not enough data to support its safety). This has been relaxed so that patients may be treated as outpatients if they are considered reliable and are not a cardio-pulmonary cripple (Section VI.5)

Section III.1.a, addresses Pulmonary Thromboendarterectomy, thrombolytics (both systemic and catheter directed) and ECMO protocols.

The suggested treatment of **distal lower extremity VTE** is now determined by the severity of symptoms and risk of thrombus extension more proximally (Section IV.1).

The guideline for **full anticoagulation** in the **presence of TBI** for various causes (A-Fib, BCVI,VTE) is given in Section IV.3.

There is a Miscellaneous Section (V) which addresses all reversal agents, a chart on how to convert from one anticoagulant to another, and the use of DOACs in patients with mechanical heart valves.

Approved by STC Oversight Committee May 2, 2018

Venous Thromboembolism (VTE) Prophylaxis and Treatment Guidelines at the R Adams Shock Trauma Center 2018

(Revision of Prophylaxis guidelines 2013 and addition of Treatment)

I. *PRACTICE GUIDELINE: VENOUS THROMBO-EMBOLISM (VTE) PROPHYLAXIS in the trauma population*

OBJECTIVE:

To provide guidelines for venous thrombo-embolism prophylaxis in the trauma patient.

Legend: AC= anticoagulation, ASCI= acute spinal cord injury, ASA=aspirin, AT= antithrombin, BCVI= Blunt Cerebrovascular Injury, DVT= deep venous thrombosis, DOAC= Direct Oral AntiCoagulant , GCS=graded compression stockings, HIT= heparin induced thrombocytopenia, IPC=intermittent pneumatic compression, IVCF= inferior vena cava filter, LDUH=low dose unfractionated heparin, LMWH= low molecular weight heparin, NSAIDS= non steroid anti-inflammatory drugs PE= pulmonary embolism, SC=subcutaneous, VKA= vitamin K antagonist, VTE= venous thrombo-embolism.

1. **All Trauma patients** expected to be admitted for over 24 hours should be considered at **high risk** for deep venous thrombosis and should be considered candidates for DVT prophylaxis.

2. **The following prophylaxis should be considered until the patient is discharged from the hospital**.
   a. **Mobilization** – all patients should be mobilized out of bed as soon as possible and when feasible; however mobility alone is not adequate prophylaxis in the high risk patient.
   b. **Low molecular weight heparin** – enoxaparin and leg compression devices in *all* patients except when contraindicated or there exists a special consideration (see below: "Section II.9 Special Considerations: Dosing of LMWH for Prophylaxis" for dosing).
   c. **Pneumatic compression devices (IPC)** (either calf or foot pumps) should be used in all patients when feasible. If calf compression devices cannot be placed on both lower extremities then **foot pumps** should be applied.
   d. **Graded compression stockings** (TEDs) may be used as an alternative to mechanical compression if there is patient non-compliance to IPC. Patients should be inspected for skin breakdown. However, GCS are no longer considered beneficial for preventing post-thrombotic syndrome and are therefore not used routinely to prevent post-thrombotic syndrome.(Ref 1 pg 315 and 337)
   e. **Aspirin** 81 mg P.O. BID:
      i. In the non-orthopedic trauma population, LMWH is considered superior to ASA for VTE prophylaxis. (ref. 2 pg. 237s: 2.9)

      ii. However, in the orthopedic fracture population, ASA is not considered as efficacious as LMWH (Ref 2 pg.296s; 2.3.3 and Table 15, fig.s S33, S34 and Table S12), but appears to have less bleeding complications. Therefore, ASA may be used as an alternative, and

is best when used in conjunction with a heparinoid. ASA is superior to no prophylaxis in orthopedic trauma patients (Ref 2 p e237, p e286-290, and Ref.s 3 and 4). This issue is presently under investigation in the STC as the Prevent Clot study (PCLOT) in patients with pelvis, acetabulum or lower extremity fractures needing operation. (See Addendum #1).

See "II Special Considerations: 10" regarding trauma patients with acute hip replacement who are not in the PClot study

At present, we address only ASA as an antiplatelet agent, and will not address other antiplatelet drugs for VTE prophylaxis.

f. Absolute Contraindications to an anticoagulant
    i. Known allergy to the medication
    ii. LMWH and UFH: HIT within the last 100 days (Ref 5) (Link to HIT guidelines)

g. Relative Contraindication to an anticoagulant for prophylaxis:
    i. Traumatic brain injury with *hemorrhage* on CT (SDH, EDH, SAH, ICH): hold all forms of AC or antiplatelet medications for at least 72 hours, then confer with Neurosurgery or Neuro-trauma Critical Care regarding starting prophylaxis with either AC or an antiplatelet agent. (see Section II.6 Special Considerations).
    ii. Spinal cord injury: hold AC or ASA for first 72 hours, if hemorrhage on CT/MRI. Confer with Orthopedic spine service or Neurosurgery Trauma Service. (See Sections II.5 and II.6: VTE prophylaxis for Acute Spinal Cord Injury (ASCI) and VTE prophylaxis for Orthopedic and Neuro-Trauma Spine Patients with Spine Column Surgery)
    iii. Brain/Spinal cord injury AND the presence of BCVI (that requires either antiplatelet medications or full AC): generally, hold ASA for first 72 hours, then may add clopidogrel on day 5, then may use AC on day 7 if indicated by the grade of BCVI, but **must confer with either Neurosurgery or Neuro-trauma Critical Care in all cases.**
    iv. Bleeding diathesis (until resolved)
    v. Solid viscous injury (liver, spleen, kidney) until clinically safe
    vi. Ophthalmology: globe trauma (retro-bulbar hematoma, retina, etc). Consult with ophthalmology)

3. Extended prophylaxis,(i.e. VTE prophylaxis continued once discharged from the hospital).
    a. Patients with lower extremity injuries that mandate *non-functional* weight bearing status , should have 35 days of VTE prophylaxis from date of last orthopedic surgery with LMWH (see below Section I.5)
    b Cancer patients: Cancer patients who have had recent pelvic or abdominal surgery for cancer should have extended prophylaxis for at least 4 weeks post operatively. LMWH is the preferred agent. (Ref 2 pgs. 228s and 262s; 3.6.6, and Ref 6)

4. **Vena Caval Filters**

a. For prevention of PE in the Presence of DVT or PE (see addendum 7)

Vena caval filters should be considered in the following circumstances:

i. Recurrent pulmonary embolus (PE) despite adequate anticoagulation
ii. Proximal DVT and major bleeding while on appropriate levels of anticoagulation
iii. Progression of ilio-femoral clot despite adequate anticoagulation
iv. Large free-floating thrombus in a femoral vein, iliac vein or inferior vena cava
v. after massive PE in which recurrent emboli could prove fatal
vi. In the presence of a PE/DVT with absolute contraindications to anticoagulation: the presence of active or recent bleeding that would be of danger to the patient (brain or spinal cord injury with bleeding, solid organ injuries with bleeding, gastro-intestinal hemorrhage, etc.)

b. <u>Prophylactic Vena Caval Filters (in the absence of DVT or PE)</u> <u>(see addendum 7)</u>

Consider prophylactic vena caval filters in patients who are at extremely high risk (spinal cord or spinal column injuries ,previous DVT/PE), **<u>and</u>** may not receive an anticoagulant for an extended period, **<u>and</u>** external pneumatic compression cannot be used (e.g. bilateral lower extremity fractures). (Ref 2, pg. e270(s):8.4.4, and Ref 7).

c. Do not use prophylactic IVCF as primary prophylaxis against PE, unless **both** anticoagulant **and** mechanical prophylaxis are not able to be used (see Section I.4.b above).

5. <u>Shock Trauma Orthopaedic DVT Screening and Prophylaxis Guidelines</u>

<u>DVT Screening</u>

<u>Qualification</u>	*<u>Screening Recommendation</u>*
1. Trauma Patients with Orthopaedic Injuries Transferred after 24 hours from time of Injury.	1.Bilateral LE Duplex prior to Pneumatic Compression Devices or Surgery
2. Trauma Patients with Orthopaedic Injuries admitted to STC directly from Injury.	Nothing

DVT Prophylaxis (Inpatient) ***

<u>Qualification</u>	*<u>Prophylaxis Recommendation*</u>
Trauma Patients with Orthopaedic Injuries	Enoxaparin 30 mg SC BID
Trauma Patients with Orthopaedic Injuries (pre-op)	Enoxaparin 30 mg SC BID (**Hold pre-op am dose**)
Trauma Patients with Orthopaedic Injuries (post-op)	Enoxaparin 30 mg SC BID, start **12 hours** after surgery

DVT Prophylaxis (Outpatient after discharge)

Qualification	*Prophylaxis Recommendation*
-Pelvic/Acetabular Fractures (treated by manipulation and/or surgery)	Enoxaparin 30 mg SC BID x 35 days (after last surgery)
-Hip Fractures (femoral neck, peri-trochanteric fractures)	Enoxaparin 30 mg SC BID x 35 days (after last surgery)
-Lower Extremity Fractures/Injuries (Patients that are not ambulatory**)	Enoxaparin 30 mg SC BID x 35 days (after last surgery)
-Lower Extremity Fractures/Injuries (Patients that are ambulatory**)	Nothing extended
-Upper Extremity Fractures/Injuries	Nothing extended

Key:

* Change dosing schedule to Enoxaparin 40 mg q day if indwelling epidural catheter.

**Attending Orthopaedic Surgeon will make determination if patient is truly "ambulatory" or "not ambulatory"

*** Pending the results of the PCLOT study: see addendum 1.

NB: Other forms of chemoprophylaxis may be considered such as Fondaparinux, or LDUH, however they are considered to be less efficacious than LMWH. ASA (325 BID or 650 BID) has been considered, but is also considered less efficacious than LMWH (Ref 2, pg. e296s: 2.3.3 and Table 15 , Figs S33, S34, and Table S12). The PClot trial is underway presently to address this issue (see addendum 1).

II. VTE GUIDELINES: Special Considerations for VTE Prophylaxis

1. **Epidural catheter insertion**
   Due to the danger of spinal epidural hematoma in patients with an indwelling epidural catheter, patients:
   a. Should receive enoxaparin 40 mg once a day (NOT 30 mg BID) while the catheter is indwelling

   b. Should follow a strict protocol for insertion and removal:
      i. enoxaparin is withheld **12 hours prior** to insertion of epidural (hold the night dose)
      ii. First dose **post-insertion** is at least 24 hours after placement of the epidural catheter
      iii. Hold enoxaparin for at least 12 hours **prior to removal** of epidural catheter
      iv. Wait at least **2 hours** after pulling catheter prior to first dose

      OR

   c. LDUH 5,000 units every 8 hours may be used as an alternative to the above use of LMWH, (although less efficacious than LMWH in non-orthopedic patients for VTE prophylaxis).

   d. Patients may receive NSAIDs while the catheter is indwelling; however, take caution in the performance of neuraxial techniques if the concurrent use of other medications affecting clotting mechanisms, such as other (non-NSAID) antiplatelet agents, oral anticoagulants, UFH, and LMWH, is anticipated in the early postoperative period because of the increased risk of bleeding complications(e.g. spinal epidural hematoma).

   e. Fondaparinux (Ref 27) (used for VTE prophylaxis in patients with a recent history of HIT) Refer to APMS.

2. **Chronic Renal failure**: if the creatinine clearance is less than 30 ml/min, then the dose of Lovenox should be 30 mg once a day for the trauma patient, or half of the daily prophylactic dose. Alternatively, LDUH 5,000 units every 8 hours may be used. (see Addendum 8 for monitoring levels of enoxaparin)

3. **Routine Surveillance Duplex Scanning**
   Duplex scanning should be performed if any evidence of DVT is found such as limb swelling or pulmonary emboli. The routine use of Duplex for surveillance in the asymptomatic trauma patient is not warranted (Ref 2 pg. 270, 8.4.5). For patients transferred from another facility, a screening duplex scan is recommended.

4. **VTE prophylaxis for Acute Spinal Cord Injury (ASCI), without Spinal Column surgery**

   a. Thrombo-prophylaxis should be provided for all patients with acute SCI.
   b. Do not use LDUH, GCS, or IPC as single prophylaxis modality.
   c. **Prophylaxis with LMWH** should be commenced once primary hemostasis is evident, usually after 24 hours (confer with the Orthopedic or Neurosurgical spine services). Use a combination of IPC and either LDUH or LMWH as alternatives to LMWH alone. (Ref 8) Both chemical and mechanical used together are better than either alone. (ref 1 pg 315-352)
   d. Use IPC and/or GCS when anticoagulant prophylaxis is contraindicated early after injury.
   e. **Do not** use prophylactic IVCF as primary prophylaxis against PE, unless **both** anticoagulant **and** mechanical prophylaxis are not able to be used.
   f. During rehabilitation phase (greater than 2 weeks), recommend the continuation of LMWH prophylaxis over LDUH (Ref 9). Conversion to an oral agent for 8-12 weeks may be considered, either VKA (INR 2.0-3.0) (Ref 2 pg e270s 8.3 and Ref 10 pg 247) or a DOAC. Some authors consider oral coagulation alone not as effective as LMWH (Ref 10 pg 244 and 252).

5. **VTE prophylaxis for Orthopedic and Neuro-Trauma Spine Injured Patients with Spine Column Surgery (with or without ASCI)**

   a. Anterior cervical discectomy and fusion (ACDF) **OR** posterior fusion **WITHOUT** laminectomy: after 24 hours postoperative, standard VTE prophylaxis may be initiated .

   b. Posterior fusion **WITH** a laminectomy: after 48 hours postoperative VTE standard prophylaxis may be initiated.

   c. Laminectomy only: after48 hours postoperative standard VTE prophylaxis may be initiated.

6. **VTE Prophylaxis for Brain Injured Patients**
   a. At 72 hours post injury, may start enoxaparin 30 mg q 12 hr for the duration of the hospital stay. However, in all cases, Neuro-Trauma Critical Care and/or Neurosurgery must be consulted.
   b. Use IPC and/or GCS when anticoagulant prophylaxis is contraindicated early after injury.
7. **DVT Prophylaxis for Traumatic Brain Injury with associated BCVI**

   For patients with a brain and/spinal cord injury AND the presence of BCVI (requiring either ASA or full AC), start ASA at 72 hours, and then may add clopidogrel on day 5. If indicated by the grade of BCVI, full AC may be started at day 7 but **must confer with either Neurosurgery or NeuroTrauma Critical Care**. (**Link to BCVI Protocol)**

   In all cases, the grade of the BCVI and the risk of stroke with no AC, must be weighed against the severity of the cerebral bleed and the risk of worsening bleed with

anticoagulation.

8. **Heparin Induced Thrombocytopenia (HIT)**
   The heparin molecule (either UFH or LMWH, but not fondaparinux) may cause HIT. HIT should be considered if the platelet count decreases to either **below 100,000 or less that 50% of the patient's baseline** in the absence of other causes. Heparin should be discontinued immediately and argatroban should be started. **Warfarin should NOT be started until the platelet count has recovered to at least above 150,000** (Ref 11). (**Link to HIT guidelines**)

9. **Dosing of LMWH for Prophylaxis: Obesity and Renal failure**
   a. A standard dose of enoxaparin 30 mg q 12 hours is generally used for patients with a BMI<30 kg/m2.
      - Patients with renal dysfunction and a CrCl <30 ml/min, should receive a dose of enoxaparin 30 mg only ONCE a day. However in patients with AKI, UFH may be used alternatively.

   b. For prophylaxis in obese patients,
      - BMI >30 = enoxaparin 40 mg SC q12h (normal renal function)

   c. Monitoring: Certain patient populations such as obese patients, underweight patients and patients with renal insufficiency, need monitoring of heparin dosing (UFH and LMWH). See Addendum 8 for the **Guidelines for Anti-Xa Monitoring for Enoxaparin in Shock Trauma Center** and reference 13**.**

10. In Orthopedic patients who have a **total hip replacement** during the index admission (i.e. not elective), **AND** are **NOT** in the PClot study, then ASA (rather than enoxaparin) would be an option for VTE prophylaxis. Orthopedics must confer with the Team regarding the choice of prophylaxis.

III. *PRACTICE* GUIDELINE: VENOUS THROMBO-EMBOLISM TREATMENT in the trauma population

OBJECTIVE:

To provide guidelines for venous thrombo-embolism treatment in the trauma patient.

Legend: AC= anticoagulation, ASCI= acute spinal cord injury, ASA=aspirin, AT= antithrombin, BCVI= Blunt Cerebrovascular Injury, DVT= deep venous thrombosis, DOAC= Direct Oral AntiCoagulant , GCS=graded compression stockings, HIT= heparin induced thrombocytopenia, IPC=intermittent pneumatic compression, IVCF= inferior vena cava filter, LDUH=low dose unfractionated heparin, LMWH= low molecular weight heparin, NSAIDS= non steroid anti-inflammatory drugs PE= pulmonary embolism, SC=subcutaneous, TBI= traumatic brain injury, VKA= vitamin K antagonist, VTE= venous thrombo-embolism.

1. Treatment MODALITY (see addendum 3 for list of anticoagulants and their targets)
In all cases, check for contraindications to anticoagulation, especially TBI.

a. INPATIENT VTE treatment:

i. If a DVT or PE is detected, then either systemic IV UFH or enoxaparin SC may be given.

Enoxaparin: 1 mg/kg SC every 12 hours should be implemented unless anticoagulation is contraindicated. Special attention should be given in the obese and renal failure patients. (ref 13 and Addendum 8 for monitoring for Anti-Xa monitoring). Also, at the STC, we, prefer to use the “Moderate Dose” heparin nomogram (aPTT 60-80 sec) for VTE treatment in trauma patients.

UFH: The weight based nomogram for heparin therapy can be found in the UMMC Guidelines: goals for the levels of anticoagulation should be determined depending on the clinical situation where unwarranted bleeding would pose a danger (e.g. TBI, severe liver/spleen injury, post-operative orthopedic patient). Pay special attention to the differences in medium and high dose goals nomograms. (**Link to Heparin Nomogram for moderate dose**) (**Link to Heparin Nomogram for Low Dose**). At the STC, we prefer to use the "Moderate Heparin Nomogram” for trauma patients.

Special attention should be given in the obese and renal failure patients (ref 13 and Addendum 8 for monitoring guidelines).

UFH IV is preferred over LMWH if there is concern for dangerous bleeding: UHF IV has a shorter half-life than LMW and UFH is 100% reversible whereas LMWH is only 60% reversible with protamine. Patients may be started on oral AC when deemed safe. (**Link to Oral AC Reversal Guidelines**)

ii. **DOACs** are preferred over VKA as oral agents, in patients without cancer: they are as

effective with less bleeding complications.

For use of DOACs, refer to the "UMMC Clinical Practice Guideline: Direct Oral Anticoagulants", (**Link to Guidelines for use of DOACs**) (Ref. 1, pgs. 323-325, table 2). The bleeding risk is less with rivaroxaban than with other oral AC. (see Addendum 2 and Ref 14).

Rivaroxaban (Xaralto) and apixaban (Eliquis) may be started immediately without first using either LMWH or UFH. (see below III.1.a.iv). Current recommendations are not to give a DOAC if the patient's weight is greater than 120 kg. For patients weighing over 120 kg; warfarin is the anticoagulant of choice.

LMWH is preferred over VKA or NOACs in **cancer patients** ("cancer associated thrombosis").(Ref 1; pg. 325).

DOAC medications dosage:

As a general rule, any oral anticoagulant (VKA or DOAC) should not be used in the critically ill or unstable patient: unforeseen emergency procedures may be necessary and renal function may be variable. (**Link to Guidelines for use of DOACs**)

Rivaroxaban: Xaralto: Factor Xa inhibitor; Dose: start 15 mg PO **twice daily** for 21 days, then 20 mg **once** daily until end of treatment:

Do not need heparin overlap

Apixaban: Eliquis : Factor Xa inhibitor; Dose: start 10 mg PO **twice daily** for 7 days, then 5 mg **twice daily** until end of therapy.

Do not need heparin overlap

Dabigatran: Pradaxa: Direct Thrombin Inhibitor; Dose: 150 mg PO **twice daily**

The patient needs to be *another form of full anticoagulation for 5-10 days* prior to starting dabigatran.

Note: Dabigatran is contraindicated in patients with moderate/severe mitral stenosis or mechanical heart valves for VTE prophylaxis. Coumadin should be used in these patients (see ref 15 and 16).

As of this writing, In patients with AF and VHD (other than moderate/severe mitral stenosis or mechanical heart valves) it appears that the DOACs are attractive alternatives to VKAs because the coexistence of VHD with AF, does not affect the overall relative efficacy or safety of DOACs (Ref. 16)

iii: VKA: Warfarin: The standard starting dose is 5 mg per day, however this may be adjusted especially in underweight or overweight patients. The goal is to adjust the dose to achieve an INR of 2.0-3.0. A higher starting dose (7.5 mg-10 mg) may be

considered for special situations.(see Addendum 9)

Warfarin must be overlapped with either UFH or LMWH.

iv. Oral AC and **timing of Initial parenteral anticoagulation.**
Initial parenteral anticoagulation
-is given 5-10 days **before** dabigatran is started,
-is **not given before** rivaroxaban and apixaban,
-is **overlapped** with VKA therapy.

v **Reversal Agents for DOACs**: refer to UMMC Clinical Practice Guidelines Pre- and Peri-Procedural Management of Anticoagulation, Management of Bleeding in the Setting of Anticoagulation, Intracranial Hemorrhage, and Dilutional coagulopathies. (**Link to Oral AC Reversal Guidelines**)

vi. **Thrombolytic Therapy**: Catheter directed or IV
IV thrombolytic therapy: Patients with **PE and hypotension** (systolic BP<90 for 15 minutes) and **low** bleeding risk should be considered for IV thrombolytic therapy . (Ref 1, pg 341) For the use of alteplase (recombinant plasminogen activation factor rt-PA), go to the following link for use in "Cardiac Arrest and Suspected PE". (**Link to Protocol for Alteplase and Suspected PE**). For weight base dosing of alteplase, go to "Acute Ischemic Stroke IV Alteplase Weight Dosing". (**Link to Alteplase Weight Based Dosing**).

A trans-thoracic ECHO (TTE) may be considered to assess for right heart strain.

Patients with PE and hypotension that is **transient** and there do not appear to be signs of shock, and/or there is a moderate to high bleeding risk, should be considered for IV UFH therapy instead of thrombolytic therapy. (Ref 1, pg 341)

Catheter directed thrombolysis (**CDT**), and **catheter directed thrombectomy without thrombolysis** (**CDWT**), may be considered if the expertise is available. If both are available, CDT is preferred over CDWT in the patient with low risk of bleeding, whereas CDWT is preferred in the patient with a moderate to high bleeding risk (Ref 1, pg 343)

However, the CHEST Guidelines 2016 (Ref 1, pg 343) still prefer IV thrombolysis over CDT; this is due to of lack of comparative evidence .For a more detailed description of this complex problem(Reference 1 pg.s 341-342).

vii. **Pulmonary Thromboendarterectomy** : for patients with chronic thromboembolic pulmonary hypertension, consult Cardio-Thoracic service regarding pulmonary embolectomy.

viii. **ECMO**: considered for patients with PE and severe cardio-respiratory compromise as a potential bridge to open pulmonary embolectomy (Ref 17)

b. OUTPATIENT VTE treatment: Note: "Extended AC therapy" refers to treatment of VTE and has **no specific stop date**.

i. **DVT** may be treated as an outpatient with LMWH then switched to either VKA (bridged) or a DOAC, and has been shown to be safe and efficacious. A DOAC is preferred over VKA. (Ref 1, pg 316). Apixaban (Eliquis) or rivaroxaban (Xaralto) may be started without bridging with either UFH or LMWH.

ii. **PE** Outpatient: LMWH then bridging to either VKA or a DOAC can be administered safely in an outpatient setting, but **only in patients with PE who are deemed to be reliable and safe, may be treated as outpatients** (see addendum 6).

In all settings, patients are converted either to VKA (to achieve an INR of 2.0-3.0) or a DOAC, and may be followed as outpatients. DOACs are preferred over VKA. (Ref 13 and Ref 1)
Exception: See special circumstances for cancer patients in section IV.

2. DURATION of AC treatment;(Ref 1 pg. 321)

a. PROVOKED VTE (i.e. trauma or surgery)

i. **Proximal DVT** leg or **PE** and **no cancer:** 3 months treatment. A **DOAC** is preferred over VKA and LMWH, except in PREGNANCY: DOACs and VKA are contraindicated and LMWH or UFH may be used instead.

ii**. Proximal DVT** leg or **PE** and **no cancer** provoked by NON surgical TRANSIENT risk factor (i.e. pregnancy, estrogen therapy, etc.) :3 months treatment.
A **DOAC** is preferred over VKA and LMWH, except in PREGNANCY: DOACs and VKA are contraindicated and LMWH or UFH may be used instead.

iii. **Proximal DVT** of the leg or **PE** and **cancer**: minimum 3 months. **LMWH** is preferred over VKA or DOACs.

iv .If **isolated distal** DVT provoked by surgery or by a nonsurgical transient risk, refer to Section I.V.1 regarding which patient receives treatment: If the decision is to treat, then treatment with AC for 3 months.

b. UNPROVOKED VTE

i. Unprovoked **DVT** (proximal or distal leg) or **PE**: 3 months AC then re-evaluate at 3 months for risk /benefit of continued treatment. See the following for duration depending on risk of bleed.
ii. If unprovoked proximal DVT or PE and **low bleed to moderate** bleed risk: Extended AC therapy: no stop date

iii. If unprovoked proximal DVT or PE and **high bleed** risk: 3 months AC therapy.

c. <u>ACTIVE CANCER</u> and DVT or PE, then Extended AC therapy, no stop date
LMWH is preferred over oral AC agents. (Ref 1 pg 317).

IV. VTE Treatment: Special Considerations

1. Distal DVT (below knee)(Ref 1, pgs. 317 and pg. 333)

a. In patients with a distal DVT that does **not exhibit severe symptoms or risk factors** for extension, serial US surveillance should be performed over 2 weeks. If the thrombus does not extend, then continue with no AC. If the thrombus does extend, then AC should be started in the same manner as with a proximal DVT.

b. If the distal DVT **exhibits severe symptoms or there are risk factors for extension**, AC should be initiated.

2. Upper Extremity DVT (Ref 1: 319 and 344)

Patients with DVT of the upper extremity veins (axillary and more proximal) should have a course of full anticoagulation similar to the lower extremity DVT. Thrombolysis is also a consideration. Thrombolysis is most likely to be of benefit in patients who meet the following criteria: (a) severe symptoms; (b) thrombus involving most of the subclavian vein and the axillary vein; (c) symptoms for <14 days; (d) good functional status; life expectancy of >1 year; (e) and low risk for bleeding.

3. TBI and Anticoagulation

For **therapeutic anticoagulation** in patients with traumatic brain injury (TBI):
ONLY and after consultation with Neuro-Trauma and/or Neurosurgery:

a. Initiate an unfractionated heparin continuous infusion at 15 units/kg/hr.(NO BOLUS) to achieve a goal aPTT 60-80 seconds.

b. Once the patient is within the therapeutic aPTT range for two consecutive checks, obtain a head CT 6 hours after the second of these two therapeutic aPTTs. If the head CT shows no progression of bleeding, then may continue anticoagulation. If there is progression of bleeding, then heparin is stopped.

c. At 24 hours of being therapeutic, obtain another head CT. If the head CT is stable, then consider converting to low molecular weight heparin (enoxaparin 1 mg/kg SC q12h in patients with CrCl >30 mL/min), and eventually an oral AC.

d. A head CT might be repeated daily if indicated.

4. <u>Cancer patients:</u> LMWH is preferred over VKA or DOACs. All active cancer patients should have extended treatment, no stop date. (Ref 1, pg 316)

V. Miscellaneous

1. Reversal agents for various AC agents

For exact details, refer to the UMMC Clinical Practice Guidelines: Pre- and Peri-Procedural Management of Anticoagulation, Management of Bleeding in the Setting of anticoagulation, Intracranial Hemorrhage, and Dilutional Coagulopathies (Ref 18) **(**Link to Oral AC Reversal Guidelines**)**

In general, the reversal scheme will depend on the severity of bleeding, as outlined in Reference 18.

In all cases, when 4-factor prothrombin complex concentrates (PCC4, Kcentra®) or Factor VIII Inhibitor Bypassing Activity (FEIBA NF®) are being considered, special permission must be given by the appropriate clinical authority.

a. Warfarin: see sections H and K in "Oral AC Reversal Guidelines" link above.
b. DOACs: see sections I in "Oral AC Reversal Guidelines" link above
   i. Dabigantran: idarucizumab (Praxiband) or FEIBA NF® (See Ref 18, or with link above Section I, page 9)
   ii. Rivaroxaban and Apixaban: PCC4 (see Ref 18, or link above section J pg 10)
c. Parenteral Anticoagulants (see Ref 18 or section K in "Oral AC Reversal Guidelines" link above)
   i. UFH: protamine (100% reversible))
   ii. LMWH: protamine (60% reversible)
   iii. Fondaparinux: no know antidote as of this writing.

2. To convert from one form of AC to another form of AC, refer to the UMMC guidelines. (Link to Guidelines for Use of DOAC). Also see below:

FROM	TO	HOW
NOACs		
Rivaroxaban	Warfarin	Stop Rivaroxaban and start parenteral UFH or LMWH. Start warfarin at next scheduled Rivaroxaban dose. Stop UFH/LMWH when INR is acceptable.
Rivaroxaban	UHF/LMWH	stop Rivaroxaban and give the first dose of the AC when the next dose of Rivaroxaban is due
Apixaban	Warfarin	stop Apixaban and start parenteral UFH or LMWH, and warfarin at next scheduled Apixaban dose. Then stop UFH/LMWH when the INR is acceptable.
Apixaban	UHF/LMWH	stop Apixaban and give the first dose of the AC when the next dose of Apixaban is due
Dabigatran	Warfarin	IF CrCl>50 ml/min: start warfarin and stop dabigatran 3 days later. If CrCl=31-50 ml/min, then start warfarin and stop dabigatran 2 days later. If CrCl=15-30, then start warfarin and stop dabigatran 1 day later.
Dabigatran	UHF/LMWH	IF CrCl >30 ml/min: start UFH/LMWH 12 hours after the last dose of dabigatran

N.B. Dabigatran can alter the INR.

FROM	TO	HOW
VKA		
Warfarin	Rivaroxaban	stop Warfarin and start Rivaroxaban **when INR is <2.0 (manufacturer recommends <3.0)**
	Apixaban	stop Warfarin and start Apixaban **when INR is <2.0**
	dabigatran	stop Warfarin and start dabigatran **when INR is <2.0**
	LMWH	stop Warfarin and start LMWH **when INR is <2.0**
	UFH	stop Warfarin and start UFH **when INR is <2.0**
Heparins		
UFH	all NOACs	stop UHF infusion and start NOAC at the same time
LMWH	Rivaroxaban	start Rivaroxaban 0-2 hours prior to the next scheduled evening administration of LMWGH: then omit Rivaroxaban
	Apixaban	start Apixaban 0-2 hours prior to the next scheduled evening administration of LMWGH: then omit Apixaban

3. Use of DOACs in mechanical heart valve patients:

The RE-ALIGN study did not support the use of dabigatran as an alternative to warfarin in patients with mechanical heart valves (ref.s 15 and 16). As of this writing dabigatran is contraindicated in patients with mechanical heart valves (company insert warning). Studies are ongoing as to the use of the other DOACs and mechanical valves.(ref.s 15 and 16)

VI. ADDENDUM ; VTE Guidelines for Prophylaxis and Treatment

1. **PCLOT Study** : **Purpose**: To perform a pragmatic randomized controlled trial of the use of low molecular weight heparin (LMWH) BID versus ASA 81 mg BID for VTE prophylaxis in patients with high-risk fractures. **Specific Aims:** (1) To compare the bleeding complication outcomes associated with LMWH (enoxaparin) versus ASA in patients receiving VTE prophylaxis following high-risk fractures. (2) To compare the incidence of clinically important VTE events associated with LMWH (enoxaparin) versus ASA for VTE prophylaxis in patients receiving VTE prophylaxis following high-risk fractures. (3) To compare the 6-month treatment costs associated with VTE prophylaxis using either LMWH or ASA for high-risk orthopedic trauma patients.

2. In a recent meta-analysis, the **risk of major bleeding** was **reduced with rivaroxaban** (Xaralto) (RR = 0.55, 95 % CI 0.35–0.89) and similar with dabigatran (Pradaxa) (RR = 0.84, 95 % CI 0.51–1.39) and apixaban (Eliquis) (RR = 0.31, 95 % CI 0.15–0.62) **compared to warfarin** for treatment of acute venous thromboembolism (Ref 14)

3. Anticoagulants and their targets.

a. VKAs inhibit the synthesis of Factors II, VII, IX and X.
b. Rivaroxaban (Xaralto), Apixaban (Eliquis) and edoxaban (Savaysa) directly inhibit Factor Xa
c. Dabigatran (Pradaxa) is a direct thrombin inhibiter.
d. Argatroban: is a direct thrombin inhibiter.
e. The heparins:
   UFH: activates antithrombin 3 (AT3), which then inactivates Factors Xa and II (equally). It also inhibits Factors IXa, XIa, and XIIa depending on the dosing.
   LMWH: inhibits Factor Xa primarily, through AT3, but in high doses it also inhibits Factor II (the ratio of antiXa/anti-IIa = 3.9 with enoxaparin)
   Fondaparinux: indirectly inhibits just Factor Xa alone via AT3.

4. HIT: The first screening test in someone suspected of having **HIT** is aimed at detecting antibodies against heparin-PF4 complexes. This may be with a laboratory test of the ELISA (enzyme-linked immunosorbent assay) type. The ELISA test, however, detects all circulating antibodies that bind heparin-PF4 complexes, and may also falsely identify antibodies that do not cause HIT. Therefore, those with a positive ELISA are tested further with a functional assay. This test uses platelets and serum from the patient; the platelets are washed and mixed with serum and heparin. The sample is then tested for the release of serotonin, a marker of platelet activation. If this serotonin release assay (SRA) shows high serotonin release, the diagnosis of HIT is confirmed. The SRA test is difficult to perform and is usually only done in regional laboratories.

5. The change by the FDA has led to the development of programs in which clinically stable patients with **PE are treated at home**, at substantial cost savings. The ACCP guidelines suggest

that patients with low-risk PE and who have acceptable home circumstances be discharged early from hospital (ie, before the first five days of treatment. (Ref 1 pg 339,).

6. Three different guidelines have been published on the use of **prophylactic IVC filters** in trauma patients, with differing recommendations. The most recently released guidelines were published in 2008 by the Inflammation and Host Response to Injury Collaborative Research Project. Their recommendations are for prophylactic IVC filter placement in patients with contraindications to low molecular weight heparin (LMWH) that are expected to persist beyond 72 hours.; namely spinal cord injury with tetraplegia or paraplegia, complex pelvic fractures in association with long bone fractures, multiple long bone fractures, some solid organ injuries where increased bleeding would be unsafe (Ref 19).

The EAST published similar guidelines in 2002. Noting the lack of conclusive evidence, they make only a level 3 recommendation for the use of prophylactic IVC filters in very high-risk trauma patients who cannot receive anticoagulation because of increased bleeding risk (intracranial hemorrhage, ocular injury with associated hemorrhage, solid intra-abdominal organ injury and/or pelvic or retroperitoneal hematoma requiring transfusion, and/or medical conditions that predispose to coagulopathy or bleeding) or have specific injury patterns including severe closed head injury (Glasgow Coma Scale [GCS] < 8), incomplete spinal cord injury with paraplegia or quadriplegia, complex pelvic fractures with associated long bone fractures, or multiple long bone fractures. The EAST guidelines also note the increased risk of thromboembolism with age and suggest there may be an increased need to place a prophylactic IVC filter in an older patient with the injuries just described (Ref 20).

These recommendations are in contrast to the 2008 American College of Chest Physicians (ACCP) guidelines that state, “We do not recommend the use of an IVC filter as thromboprophylaxis, even in patients who are at high risk for VTE. IVC filter insertion is indicated for patients with proven proximal DVT, and either an absolute contraindication to full-dose anticoagulation or planned major surgery in the near future. In either case, even with an IVC filter, therapeutic anticoagulation should be commenced as soon as the contraindication resolves.” Also see Reference 7.

In “A Clinical Trial of Vena Caval Filters in the Prevention of Pulmonary Embolism in Patients with Proximal Deep-Vein Thrombosis” Hervé Decousus**,** demonstrated the initial efficacy of filters for the prevention of pulmonary embolism in patients presumed to be at high risk who had proximal deep-vein thrombosis and were receiving anticoagulants. However, because of the observed excess rate of recurrent deep-vein thrombosis and the absence of any effect on mortality among patients receiving filters, their systematic use cannot be recommended in this population. In addition, this study showed that low-molecular-weight heparin was as effective

and safe as unfractionated heparin for the initial treatment of proximal deep-vein thrombosis in patients presumed to be at high risk. (Ref 19)

7. Guidelines for Anti-Xa Monitoring for Enoxaparin in Shock Trauma Center

LMWH can be used in most patient care settings without regular therapeutic drug monitoring as compared to unfractionated heparin (UFH). However, some concerns arise about whether or not dosage adjustment is required for certain patient population, such as obese patients, underweight patients and patients with renal insufficiency. Currently, it is recommended to check LMWH anti-Xa in patients who are obese, elderly, pediatric, or have severe renal impairment (ref 21-26)

Based on the current literature, monitoring anti-Xa activity may be warranted for VTE **prophylaxis** and **treatment** in certain trauma patients:

1. Obese patients: Body Mass Index (BMI) > 30 kg/ m^2.
2. Elderly (age >65)
3. Severe renal impairment (Creatinine clearance [CrCl]<30 ml/min)
4. Critically ill trauma patients (patients admitted to Shock Trauma ICU)
5. Patients weight <35 kg
6. Patients underweight: BMI<20 kg/ m^2.

ENOXAPARIN DOSING and MONITORING:

For DVT prophylaxis (patients without severe renal impairment)

BMI	Dose	Anti-Xa Goal
≤30	30 mg every 12 hours	0.2 – 0.4 unit/ml
≥31	40 mg every 12 hours*[2, 3]	0.2 – 0.4 unit/ml

*This is a recommendation for the initial dose, and anti-Xa level **must be checked** 4 hours after the 4th dose for appropriate dose adjustment if needed.

For DVT and PE treatment (patients with stable renal function)

CrCl (ml/min)	Dose	**Anti-Xa Goal**
< 30	1 mg/kg[%] Subcutaneously every 24 hours	0.6 – 1 unit/ml
≥ 30	1 mg/kg[%] Subcutaneously every 12 hours	0.6 – 1 unit/ml

[%]Dose should be calculated based on Actual Body Weight (ActBW) up to 190 kg (11). If a patient weight is >190 kg, parenteral heparin is recommended for VTE treatment.

MONITORING (DVT prophylaxis):

Procedure:

1. Patients should receive at least 4 doses of enoxaparin before measuring the serum anti-Xa activity to ensure the drug is at the steady state concentration.
2. The blood sample must be drawn at 4 hours after the dose (peak concentration).
3. At Shock Trauma Center, for twice-daily DVT prophylaxis dosing of enoxaparin, the medication will be given at 10 am and 10 pm. The anti-Xa level of enoxaparin will be drawn at 2 pm.
4. Anti-Xa activity is a time-sensitive assay, so the **University main lab (not Shock Trauma Lab)** needs to process the blood sample within 30 minutes after it is drawn. **Nurses or technicians must drop off the blood samples directly to the University main lab.**
5. The dose of enoxaparin should be adjusted in increments of 10 mg.
6. Once the dose of enoxaparin is adjusted, repeat step #1 for monitoring.
7. If the drug level is at the therapeutic range, the anti-Xa level of enoxaparin should be rechecked one week later. Further anti-Xa level of enoxaparin may not need to be checked unless the patient becomes hemodynamically unstable or develops acute kidney injury.

8. VTE Treatment and Monitoring with enoxaparin in Obesity:

For patients with BMI ≥35 **OR their weight is between 150 kg to 190 kg,** anti-Xa activity for enoxaparin should be monitored 4 hours after the 4th enoxaparin dose. Otherwise, **for any patient who is ≥190 kg, parenteral heparin is recommended for anticoagulation therapy**.

9. Regarding the starting warfarin dose in special situations:

Warfarin inpatient Guidelines for Use 7.5 mg –10 mg can be considered for patients who:

a) <40 years of age

b) who are obese

c) with significant vitamin K intake or enteral feeds

d) with concurrent medications known to inhibit warfarin

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