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CUH Ospidéil Ollscoile Chorcaí Cork University Hospitals | UCC Coláiste na hOllscoile Corcaigh University College Cork, Ireland

MAJOR TRAUMA CENTRE

Management guidance for the thrombo-prophylaxis and consideration for recommencement of Antithrombotic therapy in patients presenting with Traumatic Brain Injury to Cork University Hospital.

Reference Number:	Revision No:	Review Cycle: 2 years
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1. SCOPE OF GUIDELINES

- This document aims to provide clinicians with guidance on the use of pharmacological thromboprophylaxis to reduce the risk of venous thromboembolism (VTE) in patients with traumatic intra-cranial haemorrhage (tICrH). This document also aims to guide the re-commencement or continuation of anti-platelet and anticoagulation agents in patients prescribed these medications prior to tICrH.
- The CUH guidance document is anchored on the assessment of thromboembolic and re-bleeding risk in patients with tICrH with the aim of preventing an expansion of an existing brain bleed as well mitigating the risk of VTE development.
- It is expected that this guideline will provide a structured approach to the assessment and suitability of these therapies in patients who are at low risk for expansion of their tICrH.
- The clinical decision to commence pharmacological thromboprophylaxis or other antiplatelet or anticoagulation agents remains the discretion of the treating consultant. This document intends to serve as a guidance for decision making.

1. 1 Background

- The natural history of tICrH as a disease is important in this context for understanding when the acute event ends, that is, the cessation of hematoma expansion and stabilization of clot. Hematoma expansion in tICrH is very common in the first 24 hours, much less so by 48 hours and rare by 72 hours.
- VTE is a recognised complication of traumatic brain injury and is associated with increased morbidity and mortality. Failure to commence pharmacological thromboprophylaxis within an appropriate time frame in tICrH increases the likelihood of VTE.[i] In the absence of randomized trials and a definitive time target, restart practice in tICrH is highly variable—ranging from 3 days to several months to never.
- Among the TBI population, up to 54% may develop VTE in the absence of any form of prophylaxis and in 20%–30% of patients despite mechanical prophylaxis.[iiiii]
- Those trauma centers that provide pharmacologic prophylaxis within 24 hours after TBI have significantly lower rates of VTE with no difference in rates of late neurosurgical intervention.
- The optimal timing for the initiation of pharmacological thromboprophylaxis in patients with traumatic brain injury (TBI) is controversial. National guidelines are vague on this topic, with the Brain Trauma Foundation simply stating that prophylactic low-molecular-weight heparin (LMWH) or low-dose unfractionated heparin should be used in conjunction with a means of mechanical prophylaxis at some point in a TBI patient's convalescence, and that pharmacological prophylaxis carries a risk for propagation of brain injury.
- The other recent, major guidelines on initiating pharmacological prophylaxis after TBI are those of the American College of Chest Physicians, who suggest that mechanical prophylaxis be used until the risks of intracranial bleeding expansion are felt to have abated enough that pharmacological prophylaxis can be safely initiated.
- NICE guidance document on reducing the risk of hospital-acquired deep vein thrombosis/pulmonary embolism in patients with major trauma and patients undergoing neurosurgery recommends mechanical thromboprophylaxis and frequent reassessment of bleeding and VTE risk with consideration toward pharmacological thromboprophylaxis as soon as the risk of VTE outweighs the risk of bleeding. This should be continued for a

minimum of 7 days. NICE advises that patients with tICrH should not be offered pharmacological thromboprophylaxis until the lesion has been secured or the condition has stabilised[iv].

- The American Association for the surgery of Trauma recommend that thromboprophylaxis should be initiated as soon as possible following traumatic brain injury (TBI), balancing the risks of hemorrhagic expansion and VTE. The available literature supports initiation of prophylaxis 24–72hours following admission, pending stability of intracranial/extra cranial hemorrhage and in conjunction with neurosurgical consultation.[v]
- This lack of empirical evidence leaves clinicians prone to conservative attitudes about anticoagulant agents in this context.
- More recently, a systematic review from 2020 evaluated 17 studies, and concluded that early chemoprophylaxis 24–72hours after injury is associated with reduced VTE incidence without increasing ICH in patients with TBI with a stable repeat head CT[vi]
- Importantly, progression of TBI occurs in about 10% of patients with a stable follow-up CT, regardless of whether pharmacologic prophylaxis is provided or not.
- With regard to restarting anticoagulation, based on existing literature, the risk of rebleeding is <1% by 1 week after traumatic intracranial haemorrhage [vii] [viii] [ix]. Early restarting of anticoagulation should reduce thrombotic events with only a very small increase in major bleeding (v). However, that conclusion is based on observational studies, and there are no randomized trial data.
- Chipman et al reported a retrospective single centre study of 50 patients with tICrH concomitant with PE. There was no significant difference in ICH expansion between patients who started anticoagulation therapy within 7 days of injury and those who started anticoagulation 7 days after injury. None of the patients required neurosurgical intervention due to ICH expansion. [x]
- This guideline classifies patients with tICrH as low, moderate, or high risk for spontaneous progression of their intracranial hemorrhage (ICH) pattern and tailors a pharmacological prophylaxis regimen to each arm. This approach is adopted from the 'Parkland Protocol' which was expansion of the work of Berne and Norwood, who had promulgated a set of intracranial injury patterns that could safely receive enoxaparin 30 mg subcutaneously beginning 24 h after injury if a repeat CT scan of the head was stable.

2. Management

2.1 Consideration for the commencement of Pharmacological Thromboprophylaxis on Admission

1) All patients presenting with a traumatic intracranial haemorrhage should be discussed with the on call Neurosurgical team.
2) All patients should have mechanical VTE prophylaxis measures (TEDS/ pneumatic compression devices) prescribed where no contraindications exist.
3) All patients should have their anticoagulation and antiplatelet medication held on arrival pending review of same as per 2.2/2.3
4) Patients should be risk stratified in relation to the severity of their tICrH at the time of admission. (Table 1)
5) Assess the bleeding and Thrombotic risk of a patient presenting with a tICrH (Table 2)
6) If low risk criteria are met, a repeat CT scan is arranged for 24 post the admission scan.
7) All High risk patients should have repeat CT at 72 hours post admission scan
8) If repeat imaging is stable, prophylactic dose LMWH may be commenced taking into account patients weight and renal function
9) If repeat imaging shows progression pt is now deemed to have progressed to moderate risk category and commencement is to be guided by the Neurosurgical team.
10) Please see attached Flow diagram (Appendix 1)

2.2 Consideration for the recommencement of anticoagulation

- Please follow points 1-5 as per 2.1
- If the patient is on Warfarin or a Direct Oral Anticoagulant (DOAC) e.g. rivaroxaban, apixaban, edoxaban or dabigatran, clarify the agent, dose and indication.
- Calculate the patient's creatinine clearance (CrCl).
- Please follow guidance re prophylactic enoxaparin as per 2.1
- If deemed necessary to continue therapeutic dose anticoagulation please risk stratify the patient in relation to the severity of their tICrH as per Table 1
- If Low risk, with stable appearances after interval CT scan, and deemed necessary to continue with anticoagulation as per relevant indications, anticoagulation can be commenced after 1 week.
- Patients on Warfarin to link in with Warfarin Clinic at 1 week post TBI if deemed suitable to recommence at that time.
- If moderate to high risk – decision to recommence lies with the Neurosurgical team.
- Decisions re anticoagulation prescription in patients with biological/ mechanical valves should be discussed with Cardiothoracics and Neurosurgery at the earliest opportunity.
- Please see attached Flow diagram (Appendix 1)

2.3 Consideration for the recommencement of antiplatlets

- Please follow points 1-5 as per 2.1
- If a patient is taking aspirin for primary prevention, the risk of ischaemic events is low and aspirin can be held on admission
- Among patients with previous percutaneous coronary intervention (PCI), in the absence of a very high bleeding risk (moderate to high risk as per table 1**), discuss with Cardiology and Neurosurgery re suitability to recommence Aspirin. Low-dose aspirin should be held initially pending discussion.**
- **For patient who have had recent stenting with Interventional radiology, these patients should also be discussed with Interventional radiology when withholding and restarting antiplatelets.**
- For patients with high peri-operative bleeding risk (e.g. undergoing spinal surgery or certain neurosurgical or ophthalmological operations) aspirin should be discontinued for at least 7 days.
- For patients with moderate to high bleeding risk aspirin should be discontinued for at least 7 days and recommenced following discussion with the neurosurgical team.
- Patients treated with P2Y12 inhibitor monotherapy as part of a de-escalation strategy after PCI/ acute coronary syndrome (ACS), or due to a recent stroke, peripheral arterial disease (PAD), or aspirin intolerance, will require a careful interdisciplinary evaluation of tICrH expansion vs. ischaemic risk, and individual decisions based on the tICrH expansion and ischaemic risk.
- In low risk tICrH patients, the preferred management of patients on dual antiplatelet therapy (DAPT) due to PCI is to **discontinue both aspirin monotherapy and P2Y12 inhibitors initially**. **Early discussion with cardiology and Neurosurgery for suitability to re commence Mono-therapy with Aspirin and for the recommencement of the P2Y12 inhibitor.**
- Please see attached Flow diagram (Appendix 1)

Table 1; Risk Stratification of patients with tICrH

Low Risk	Moderate Risk	High Risk
• A subdural hemorrhage ≤8 mm at its thickest point, • Epidural hemorrhage ≤8 mm thick, • No more than a single parenchymal contusion per lobe, • All contusions ≤20 mm in their greatest diameters, • And/or any amount of subarachnoid hemorrhage or intraventricular hemorrhage	• Any injury larger than the low-risk criteria, but not undergoing craniotomy or monitor placement	• Any TBI that underwent craniotomy or monitor placement.

Table 2. Assessing the bleeding and thrombotic risk of a patient presenting with a tICrH					
1.	Is the patient on an anticoagulant	Yes/No	Agent		Dose/ INR;
	Indication for anticoagulation				
2.	Is the patient on an antiplatelet	Yes/No	Agent		Dose
	Indication for antiplatelet				
3.	Estimate the thrombotic risk for the patient – Table 3				
4.	What is the creatinine clearance				

Table 3. Adapted from the American College of Chest physicians (CHEST) for patient specific patient periprocedural Thromboembolism

Risk Category	Atrial Fibrillation	Venous Thromboembolism
High (>10%/year risk of ATE or >10%/month risk of VTE)	CHA2DS2VASc score (Appendix 2) of ≥7 or CHADS2 score of 5 or 6 or recent (<3 month) stroke or TIA or Rheumatic valvular heart disease	Recent VTE (<3 month and especially 1 month) Severe thrombophilia (deficiency of protein C, protein S or antithrombin; homozygous factor V Leiden or prothrombin gene mutation or double heterozygous for each mutation, multiple thrombophilias) Antiphospholipid antibodies Associated with vena cava filter Active cancer associated with high VTE risk*
Moderate (4%–10%/year risk of ATE or 4%–10%/month risk of VTE)	CHA2DS2VASc score of 5 or 6 or CHADS2 score of 3 or 4	VTE within past 3-12 months Recurrent VTE Non-severe thrombophilia (heterozygous factor V Leiden or prothrombin gene mutation) Active cancer or recent history of cancer**
Low (<4%/year risk of ATE or <2%/month risk of VTE)	CHA2DS2VASc score of 1-4 CHADS2 score of 0–2 (and no prior stroke or TIA)	VTE more than 12 months ago

*Includes pancreatic cancer, myeloproliferative disorders, primary brain cancer, gastric cancer, esophageal cancer

**Within 5 years if history of cancer, excluding non-melanoma skin cancer

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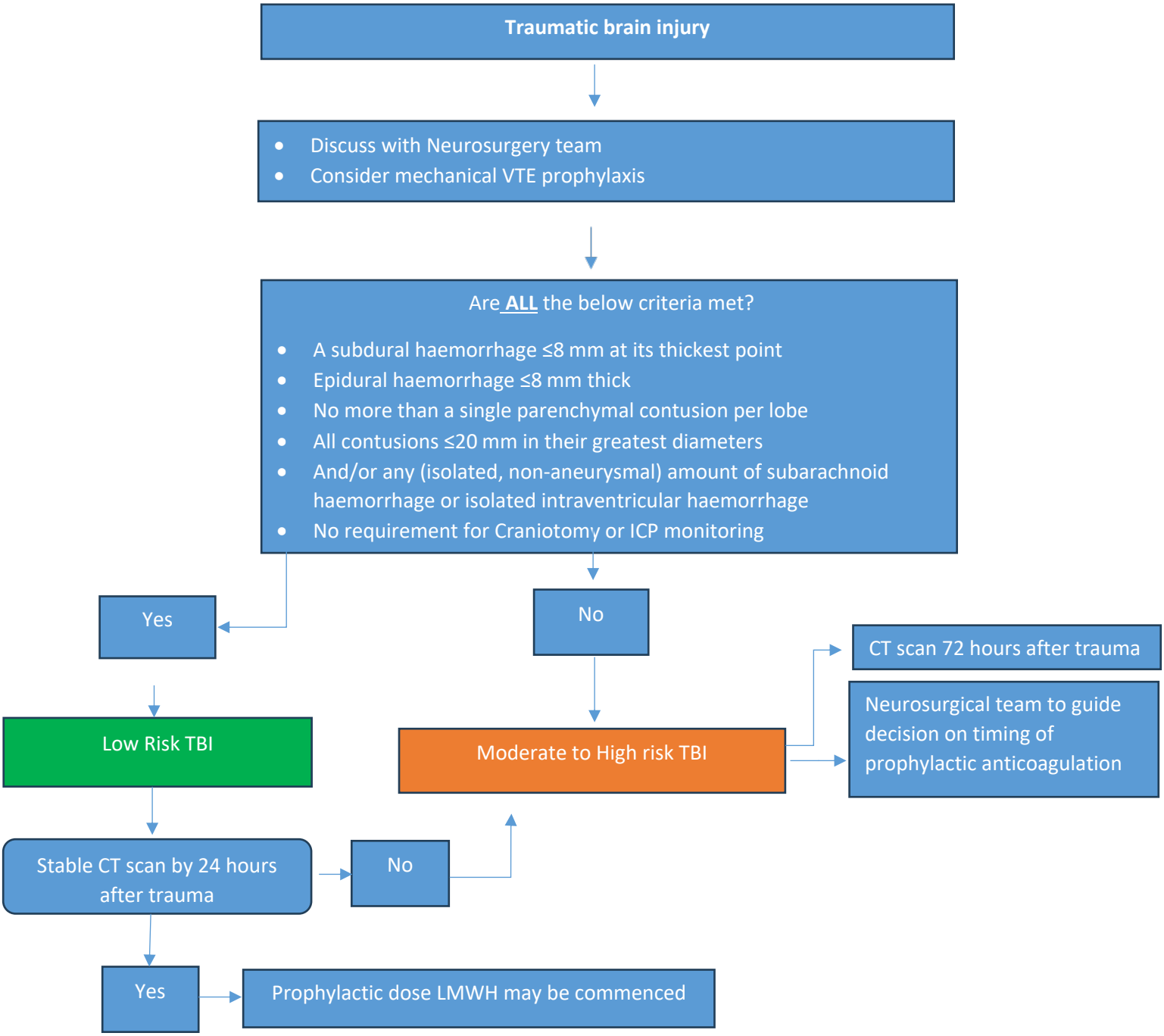
Appendix 1. : Guideline for Pharmacological Thromboprophylaxis post Traumatic Brain Injury (TBI) for Patients not on Antithrombotic Agents*.



*Antithrombotic agents include anticoagulants and antiplatelet agents.

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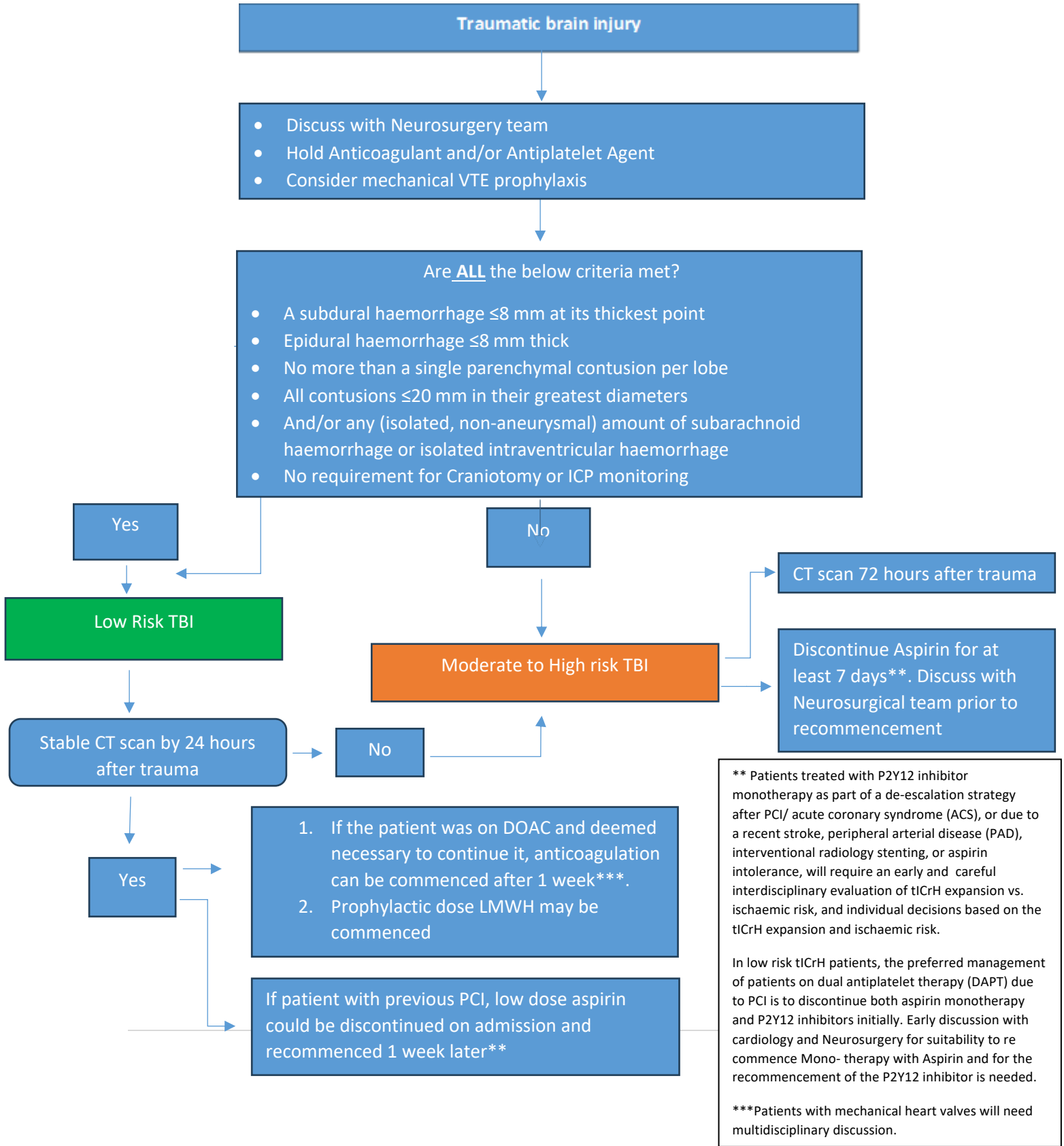
Appendix 2

Guideline for Pharmacological Thromboprophylaxis and the Recommencement of Anticoagulant/ Antiplatelet therapy in patients post Traumatic Brain Injury (TBI) who are on Antithrombotic Agent(s) inclusive of anticoagulants and antiplatelet agents.



** Patients treated with P2Y12 inhibitor monotherapy as part of a de-escalation strategy after PCI/ acute coronary syndrome (ACS), or due to a recent stroke, peripheral arterial disease (PAD), interventional radiology stenting, or aspirin intolerance, will require an early and careful interdisciplinary evaluation of tICrH expansion vs. ischaemic risk, and individual decisions based on the tICrH expansion and ischaemic risk.

In low risk tICrH patients, the preferred management of patients on dual antiplatelet therapy (DAPT) due to PCI is to discontinue both aspirin monotherapy and P2Y12 inhibitors initially. Early discussion with cardiology and Neurosurgery for suitability to re commence Mono- therapy with Aspirin and for the recommencement of the P2Y12 inhibitor is needed.

***Patients with mechanical heart valves will need multidisciplinary discussion.

[i] Brandi G, et al. Delayed prophylaxis with unfractionated heparin increases the risk of venous thromboembolic events in patients with moderate to severe traumatic brain injury: a retrospective analysis. Anaesthesiol Intensive Ther. 2020;52(1):28-33.

[ii] American College of Surgeons. ACS TQIP best practices in the management of traumatic brain injury. Chicago. 2015. https://www.facs.org/quality-programs/trauma/ tqp/center-programs/tqip/best-practice (12 Oct 2020)

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[iv] Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. London: National Institute for Health and Care Excellence (NICE); 2019 Aug 13.

[v] Rappold JF, Sheppard FR, Carmichael Ii SP, Cuschieri J, Ley E, Rangel E, Seshadri AJ, Michetti CP. Venous thromboembolism prophylaxis in the trauma intensive care unit: an American Association for the Surgery of Trauma Critical Care Committee Clinical Consensus Document. Trauma Surg Acute Care Open. 2021 Feb 24;6(1):e000643.

[vi] Spano PJ, Shaikh S, Boneva D, Hai S, McKenney M, Elkbuli A. Anticoagulant chemoprophylaxis in patients with traumatic brain injuries: a systematic review. J Trauma Acute Care Surg 2020;88:454–60

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[x] Chipman, Amanda M. MD; Radowsky, Jason MD; Vesselinov, Roumen PhD; Chow, David BS; Schwartzbauer, Gary MD, PhD; Tesoriero, Ronald MD; Stein, Deborah MD, MPH. Therapeutic anticoagulation in patients with traumatic brain injuries and pulmonary emboli. Journal of Trauma and Acute Care Surgery 89(3):p 529-535, September 2020.