health
Department:
Health
REPUBLIC OF SOUTH AFRICA

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 2: BLOOD AND BLOOD FORMING ORGANS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 -2019)

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the chapter for BBFO conditions.

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED
2.2 Anaemia, iron deficiency		
- *Treatment*	Ferrous sulfate, oral	Description and dosing amended, including when there is poor tolerance
	Ferrous fumarate, oral	Added
- *Prophylaxis*	Ferrous sulfate, oral	Description and dosing amended, including when there is poor tolerance
	Ferrous fumarate, oral	Added
Parenteral iron:	Iron sucrose, IV	Added as an example of parenteral iron
- *Iron, IV*	Iron dextran, IV	Added as an example of parenteral iron
- *Iron, IM*	Iron polymaltose, IM	Not added as an example of parenteral iron
2.8 Febrile neutropenia	Piperacillin/tazobactam, IV	Retained
	Amikacin, IV	Added
	Cefepime, IV	Retained and dose increased
2.11 Immune thrombocytopenia (ITP)	Prednisone, oral	Retained
– *Acute active life-threatening bleeding and surgery*	Tranexamic acid, IV	Not added
2.14 Venous thrombo-embolism		
- *Treatment*	LMWH, SC	Amended to first line option
	Enoxaparin, SC	Retained as an example of LMWH class (listed in STG) and dosing amended
	Dalteparin, SC	Added as an example of LMWH class
	Nadoparin, SC	Added as an example of LMWH class
	Unfractionated heparin (UFH), SC	Amended to second line option
	Fondaparinux, SC	Added as a therapeutic option to LMWH/UFH (this is an antithrombotic agent)
- *Prophylaxis*	LMWH, SC	Amended to first line option
	Enoxaparin, SC	Retained as an example of LMWH class (listed in STG)
	Dalteparin, SC	Added as an example of LMWH class
	Nadoparin, SC	Added as an example of LMWH class
	Unfractionated heparin (UFH), SC	Amended to second line option; indication(s) not amended
	Fondaparinux, SC	Added as a therapeutic option to LMWH/UFH, but indication restricted (this is an antithrombotic agent)

2.2 ANAEMIA, IRON DEFICIENCY

ORAL IRON SUPPLEMENTS:

Treatment

Ferrous sulfate, oral: *description and dosing amended (including when there is poor tolerance)*

Ferrous fumarate, oral: *added*

Aligned with PHC recommendations that was accepted by NEMLC at the meeting of 12 April 2018 – see below:

PHC Nutrition and anaemia NEMLC report of 12 April 2018:

Treatment: Adults

Ferrous sulfate, oral: description and dosing amended

Dosing: Lower dosing of oral iron recommended for anaemia:

- *Open-label randomised controlled trial[1] showed that low-dose iron treatment is effective in elderly patients with iron-deficiency anaemia. Iron doses of 15 mg per day increased haemoglobin (Hb) levels from 10.0 g/dL to 11.3 g/dL; 150 mg per day increased Hb from 10.2 g/dL to11.6 g/dL over 60 days. Adverse drug reactions (abdominal discomfort, nausea, vomiting, changes in bowel movements and black stools were significantly more common at higher iron doses).*
- *Aligned with Adult Hospital Level STGs and EML, 2015*

Recommendations: *Dosing for ferrous sulfate and ferrous fumarate be made consistent with Adult Hospital Level STGS and EML, 2015, section 2.2 Anaemia, iron deficiency.*

Level of Evidence: III Disease-oriented RCT, Guidelines

Description: Amended to be aligned with SAMF 2016 and MCC/SAHPRA registered package insert (s) of product(s) currently available on tender[2]:

Adults

- *Ferrous sulfate compound BPC (dried), oral, 170 mg (± 55 ~~65~~ mg elemental iron) ~~8~~12 hourly with meals.*

OR

Ferrous fumarate, oral, 200 mg (± 65 mg elemental iron) ~~8~~12 hourly.

- *……*

Level of Evidence: III Guidelines

Poor tolerance to oral iron supplements

Evidence for alternate dosing of oral iron supplements for treating iron deficiency anaemia is limited and of low quality: underpowered, may not be generalisable to the local setting, study design provides pharmacokinetic and pathophysiological information rather than clinical meaningful inferences.

Hepcidin, which regulates body iron homeostasis was shown to increase with increased dosing of oral iron decreasing iron absorption: 24 hours after doses ≥60 mg, serum hepcidin increased by 35%, p<0.01 and fractional iron absorption decreased by 45%, p<0.01. [3]

Poor tolerance: Pragmatic option would be to recommend alternate day dosing of iron if daily iron cannot be tolerated.

Recommendation: Alternate day dosing of oral iron recommended for treatment of iron deficiency anaemia, where daily dosing is poorly tolerated.

Rationale: Pragmatic option provided for poor tolerance of daily oral iron supplements as alternate day dosing. Limited evidence suggests that hepcidin levels increase with increasing doses of oral iron, and the alternate day dosing regimen recommended to minimise use of parenteral iron in patients who cannot tolerate or who are not responding to oral iron supplements.

Level of Evidence: III Pharmacokinetic[4]/pharmacodynamics studies, Expert opinion

[1] Rimon E, Kagansky N, Kagansky M, Mechnick L, Mashiah T, Namir M, Levy S. Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. Am J Med. 2005 Oct;118(10):1142-7. https://www.ncbi.nlm.nih.gov/pubmed/16194646

[2] Contract cirvular HP09-2016SD

[3] Moretti D, Goede JS, Zeder C, Jiskra M, Chatzinakou V, Tjalsma H, Melse-Boonstra A, Brittenham G, Swinkels DW, Zimmermann MB. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood. 2015 Oct 22;126(17):1981-9. https://www.ncbi.nlm.nih.gov/pubmed/26289639

[4] Stoffel NU, Cercamondi CI, Brittenham G, Zeder C, Geurts-Moespot AJ, Swinkels DW, Moretti D, Zimmermann MB. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. Lancet Haematol. 2017 Nov;4(11):e524-e533. https://www.ncbi.nlm.nih.gov/pubmed/29032957

Prophylaxis

Ferrous sulfate, oral: *description and dosing amended*

Ferrous fumarate, oral: *added*

Aligned with PHC recommendations that was accepted by NEMLC at the meeting of 14 December 2017 – see below:

PHC Obstetrics and Gynaecology NEMLC report of 14 December 2017:

Iron: *(Refer to the medicine review: Intermittent iron supplementation in pregnancy, 6 November 2017).*

Recommendation: *Based on the evidence review, the PHC Committee was of the opinion that intermittent iron is not appropiate as antenal supplementation for all pregnant women. Iron supplementation in pregnancy should be recommended as daily iron dosing. However, if iron is poorly tolerated, intermittent iron supplemenattion should be considered as an alternative.*
Rationale: Current low quality evidence suggests that intermittent iron supplementation is as efficacious as daily dosing in pregnant women. Furthermore, local prevalence study estimates that 30-40% of pregnant women have anaemia.
Level of Evidence: I Systematic review[5], Prevalence study[6]

PARENTERAL IRON:

Indications amended from:

Parenteral iron is **only** indicated when oral iron is:
» expected to be ineffective, e.g. malabsorption, patients on haemodialysis and erythropoietin therapy, or
» not tolerated.

To:

Parenteral iron is **only** indicated when oral iron is:
» ineffective, defined as lack of response after three months of oral iron therapy, or
» iron deficiency anaemia from 36 weeks of pregnancy, or
» expected to be ineffective, e.g. malabsorption, patients on haemodialysis and erythropoietin therapy, or
» not tolerated.

Level of Evidence: III Guidelines[7]

i) Iron IV

Iron sucrose, IV: *added as an example of parenteral iron*

Iron dextran, IV: *added as an example of parenteral iron*

Therapeutic members of the parenteral iron class (administered IV) includes iron sucrose and iron dextran. The dosing for both iron sucrose and iron dextran be included in the text of the STG, with a test dose only required for administration of iron dextran.

Level of Evidence: III Guidelines[8] [9]

ii) Iron IM

Iron polymaltose, IM: *not added as an example of parenteral iron*

Rationale: The adverse effects of permanent discolouration, pain and allergic reactions associated with IM administration of parenteral iron precludes this agent from inclusion to the Adult Hospital Level EML. Intravenous iron is included as a parenteral option on the EML.

Level of Evidence: III Expert opinion

[5] Pena-Rosas JP, De-Regil LM, Gomez Malave H, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. The Cochrane database of systematic reviews. 2015(10):CD009997. https://www.ncbi.nlm.nih.gov/pubmed/26482110

[6] Tunkyi K, Moodley J. Prevalence of anaemia in pregnancy in a regional health facility in South Africa. S Afr Med J. 2015;106(1):101-4. https://www.ncbi.nlm.nih.gov/pubmed/26792317

[7] SAMF, 2016

[8] Goddard AF, James MW, McIntyre AS, Scott BB; British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia. Gut. 2011 Oct;60(10):1309-16. https://www.ncbi.nlm.nih.gov/pubmed/21561874

[9] SAMF, 2016

2.7 ANAEMIA, SICKLE CELL

Chronic management

Hydoxyurea, oral: *retained*

Folic acid, oral: *retained*

NEMLC recommended that[10] guidance for chronic management of sickle cell anaemia be retained in the chapter; as chronic management of sickle cell anaemia could be provided by specialists at regional level facilities. South African Medical Association concurred with NEMLC's recommendation.

2.8 FEBRILE NEUTROPENIA

Piperacillin/tazobactam, IV: *retained*

Amikacin, IV: *added*

Cefepime, IV: *retained and dose increased*

Aligned with Infections chapter (section 9.1.3: Hospital-acquired pneumonia (HAP)) that has been updated and accepted at NEMLC meeting of 1 February 2018[11].

Rationale: NICD surveillance data[12] reports of approximately 28% resistance of Pseudomonas to piperacillin/tazobactam nationally; and approximately 30% resistance of Pseudomonas to cefepime; and thus dosing recommended as 2 g 12 hourly.[13]

Level of Evidence: III Local surveillance data

2.11 IMMUNE THROMBOCYTOPENIA (ITP)

Prednisone, oral: *retained*

Aligned with guideline recommendations.

Level of Evidence: III Guidelines[14] [15]

Acute active life-threatening bleeding and surgery

Tranexamic acid, IV: *not added*

External comment to consider tranexamic acid (TXA), IV in this clinical setting was not accepted.

Rationale: RCTs[16] [17] are currently underway to evaluate the efficacy and safety of TXA therapy in thrombocytopenia. At present, there is insufficient evidence for TXA for the prevention of bleeding in patients with insufficient platelets[18]; and anecdotal evidence[19] suggests that antifbrinolytics are associated with bleeding and transfusion rates; but outcomes from RCTs would probably inform decision-making going forward.

Level of Evidence: III Case series

[10] Minutes of the NEMLC meeting of 27 September 2018

[11] Minutes of the NEMLC meeting of 1 February 2018.

[12] NICD AMR surveillance for ESKAPE, 1 January 2016 to 31 December 2016.

[13] SAMF, 2016.

[14] Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, Chong BH, Cines DB, Gernsheimer TB, Godeau B, Grainger J, Greer I, Hunt BJ, Imbach PA, Lyons G, McMillan R, Rodeghiero F, Sanz MA, Tarantino M, Watson S, Young J, Kuter DJ. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010;115(2):168.

[15] Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA, American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117(16):4190.

[16] TRial to EvaluAte Tranexamic Acid Therapy in Thrombocytopenia (TREATT). - https://clinicaltrials.gov/ct2/show/NCT03136445

[17] American Trial Using Tranexamic Acid in Thrombocytopenia (A-TREAT) - https://clinicaltrials.gov/ct2/show/NCT02578901

[18] Desborough M, Hadjinicolaou AV, Chaimani A, Trivella M, Vyas P, Doree C, Hopewell S, Stanworth SJ, Estcourt LJ. Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review. Cochrane Database Syst Rev. 2016 Oct 31;10:CD012055. https://www.ncbi.nlm.nih.gov/pubmed/27797129 (provided after the meeting)

[19] Mayer B, Salama A. Successful treatment of bleeding with tranexamic acid in a series of 12 patients with immune thrombocytopenia. Vox Sang. 2017 Nov;112(8):767-772. https://www.ncbi.nlm.nih.gov/pubmed/28952160

2.14 VENOUS THROMBO-EMBOLISM

LMWH VS HEPARIN MEDICINE REVIEW:

Evidence review was done to review comparative evidence of low molecular weight heparin (LMWH) vs unfractionated heparin (UFH) for the management of venous thromboembolism (VTE) and other acute coronary syndromes (ACS); and to determine the appropriate therapeutic alternatives within the LMWH therapeutic group.

Refer to the medicine review, LMWH for VTE and ACS (April 2018) below:

LMWH for VTE and ACS - Adult review_A

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendations: Based on this evidence review, the Adult Hospital Level Committee reccommends that:

- LMWH preparations be reccomended as the preferred therapeutic agent of choice versus UFH for the following indications:
  - VTE prophylaxis after major surgery.
  - VTE prophylaxis for hospitalised medically ill patients with prolonged immobilization; but that criteria for management with LMWH be clearly defined using an appropiate risk scoring tool.
  - Tretament of VTE (from proximal DVT to pulmonary embolism).
  - Acute coronary syndromes (unstable angina or non-ST segment elevation MI).
- In renal impairment the dose of LMWH should be reduced based on locally agreed protocols (see Appendix A which describes dosing issues).
- LMWH dosing for VTE treatment recommended as either once daily or twice daily - see Appendix A.
- LMWH recommended as a therapeutic group for specific indications (medicines in the group includes enoxaparin, dalteparin, fondaparinux and nadoparin) – see Appendix B.

Rationale:

- Compared with UFH, LMWH preparations are at least as effective and as safe as classic intravenous heparin therapy and have the advantage of being more convenient to administer.
- The simplified therapy provided by LMWH may allow patients with uncomplicated proximal deep-vein thrombosis to be cared for in an outpatient setting.
- The LMWH have greater convenience in the ability to administer by subcutaneous injection without laboratory monitoring and the possible associated cost reduction resulting from reduced hospital stay and also a lower incidence of heparin-induced thrombocytopenia (HIT).
- LMWHs appear to be as safe and effective as UFH for the treatment of venous thrombosis and pulmonary embolism and at least as safe and effective as UFH for the treatment of patients with unstable angina.
- Availability of UFH: Heparin 25000 IU/ml has recently been discontinued from the South African market.
- While the Fixed-Dose Heparin (FIDO) RCT suggested that fixed-dose, weight-adjusted S.C. UFH, without PTT monitoring, was comparable to fixed-dosed, unmonitored S.C; this may not be generalisable to the South African population (public sector patients with VTE may have multiple co-morbidities, are thinner and younger than the study participants).

Level of Evidence: I non-inferiority RCTs and Systematic Reviews

Other factors and considerations:

- Cost
- Within class therapeutic alternatives – refer to Appendix B

FONDAPARINUX ECONOMIC ANALYSIS:

Background: An extensive motivation with evidence, was submitted by the Western Cape Provincial Pharmaceutics and Therapeutics Committee to consider fondaparinux (FPX) as an alternative to heparin and LMWH for management of VTE and ACS. Initial scoping review was done by the Adult Hospital Level Committee and it was concluded that FPX was too expensive, but the agent could be considered for inclusion in the antithrombotic therapeutic grouping of LMWH and UFH (provided for by the National Health Council approved NDoH Therapeutic Policy).

Refer to the fondaparinux economic analyses below:


Fondaparinux for NSTEMI -Economic a


Fondaparinux for STEMI-Economic an


Fondaparinux for VTE treatment-Econ


Fondaparinux for VTE prophylaxis-Eco

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

(Appendix I and II are available on the NDoH website but can be forwarded on request).

NEMLC Recommendations:

- The Adult Hospital STGs to include FPX, enoxaparin (EPX), dalteparin and nadoparin in an antithrombotic therapeutic group that can be used interchangeably for management of appropriate acute coronary syndromes in adults. Enoxaparin to be listed as an example in the STG, and the other therapeutic agents to be listed in the therapeutic interchange database.

Rational: Available evidence suggests that FPX is comparable to enoxaparin. There are huge price disparities between the agents and creating a LMWH therapeutic group may encourage competition.

Level of Evidence: I Systematic reviews[20] [21] [22] [23] [24], RCTs[25] [26]

Treatment

LMWH, SC: *amended to first line option*
Enoxaparin, SC: *retained as example of class (listed in the STG) and dosing amended*
Dalteparin, SC: *added as example* of *LMWH class*
Nadoparin, SC: *added as an example of LMWH class*
Unfractionated heparin: *amended to second line option*
Fondaparinux, SC: *added as a therapeutic option to LMWH/UFH – it is an antithrombotic agent*

Dosing for the various LMWH agents has been described in the LMWH medicine review, appendix B (see above).

Treatment of ACS: However, for treatment of Acute Coronary Syndrome; guidance has been restricted to enoxaparin, aligned with European ACS Guidelines[27] as enoxaparin is the most studied LMWH with the most clinical experience.

Enoxaparin dosing: For acute treatment of proximal venous thrombosis and/or pulmonary embolism, the recommended dosing is either enoxaparin 12 hourly or enoxaparin, SC, 1.5 mg daily.

[20] Dong K, Song Y, Li X, Ding J, Gao Z, Lu D, et al. Pentasaccharides for the prevention of venous thromboembolism (Review). Cochrane Database Syst Rev. 2016;(10):Art. No.: CD005134.
[21] Alikhan R, Forster R, Cohen AT. Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction). Cochrane Database of Systematic Reviews 2014. Issue 5. Art. No.: CD003747. DOI: 10.1002/14651858.CD003747.pub4.
[22] Castellucci LA, Cameron C, Le Gal G, Rodger MA, Coyle D, Wells PS, et al. Clinical and Safety Outcomes Associated With Treatment of Acute Venous Thromboembolism: A Systematic Review and Meta-analysis. JAMA. 2014;312(11):1122–35.
[23] Brito V, Ciapponi A, Kwong J. Factor Xa inhibitors for acute coronary syndromes (Review). Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD007038.
[24] Brito V, Ciapponi A, Kwong J. Factor Xa inhibitors for acute coronary syndromes (Review). Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD007038.
[25] Buller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al. Subcutaneous Fondaparinux versus Intravenous Unfractionated Heparin in the Initial Treatment of Pulmonary Embolism. New England Journal of Medicine. 2003;349:1695–702.
[26] Peters, Ron JG, Campbell Joyner, Jean-Pierre Bassand, Rizwan Afzal, Susan Chrolavicius, Shamir R. Mehta, Jonas Oldgren et al. "The role of fondaparinux as an adjunct to thrombolytic therapy in acute myocardial infarction: a subgroup analysis of the OASIS-6 trial." European heart journal 29, no. 3 (2008): 324-331.
[27] Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bet al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)]. G Ital Cardiol (Rome). 2016 Oct;17(10):831-872.

Prophylaxis

LMWH, SC: *amended to first line option*
Enoxaparin, SC: *retained as example of class (listed in the STG)*
Dalteparin, SC: *added as example* of *LMWH class*
Nadoparin, SC: *added as an example of LMWH class*
Unfractionated heparin: *amended to second line option*
Fondaparinux, SC: *added as a therapeutic option to LMWH/UFH, but indication restricted*

Fondaparinux: Guidance for DVT prophylaxis for fondaparinux restricted to major risk surgery with additional patient-related risk factors or very high-risk procedures (orthopaedic or trauma surgery) aligned with Guidelines[28].

VTE prophylaxis risk scoring: The STG defines "medical patients" that would require prophylaxis therapy and furthermore, provides criteria for VTE prophylaxis using appropriate risk scoring tool(s).

The following guidance was added to the STG, aligned with the South African Society of Thrombosis and Haemostasis VTE Practice Guidelines.

Risk Assessment

Risk assessment is essential, and treatment needs to be individualised. Risk factors for VTE can be divided into predisposing factors (i.e. patient characteristics) and exposing factors (i.e. underlying medical conditions, nature of surgical intervention, etc.).

SUBCATEGORIES OF VTE RISK IN SURGICAL AND NON-SURGICAL PATIENTS

	Surgical patients	***Medical patients***
Low VTE risk	» Surgery lasting <30 minutes » Injuries without or with only minor soft-tissue trauma » No or only minor additional predisposing risk factors	» Infection or acute inflammatory diseases without bed rest » Central venous catheters » No or only minor additional predisposing risk factors
Moderate VTE risk	» Surgical procedures of longer duration » Immobilisation of lower limb with plaster cast » Lower limb arthroscopic procedures. » No or only minor additional predisposing risk factors	» Acute cardiac insufficiency (NYHA III/IV) » Acute decompensated COPD without ventilation » Infection or acute inflammatory diseases with bed rest » Malignant disease » No or only minor additional predisposing risk factors
High VTE risk	» Major surgical procedures for malignancy » Multiple trauma or severe trauma of the spine, vertebra or » lower limbs » Major orthopaedic surgery, e.g. hip or knee replacement » Major surgical procedure of cardiothoracic and pelvic region	» Stroke with paralysis » Acute decompensated COPD with ventilation » Sepsis » ICU patients

Level of Evidence: III Guidelines[29]

[28] SAMF, 2016

[29] Jacobson BF, Louw S, Büller H, Mer M, de Jong PR, Rowji P, Schapkaitz E, Adler D, Beeton A, Hsu HC, Wessels P, Haas S; South African Society of Thrombosis and Haemostasis. Venous thromboembolism: prophylactic and therapeutic practice guideline. S Afr Med J. 2013 Feb 15;103(4 Pt 2):261-7. https://www.ncbi.nlm.nih.gov/pubmed/23547704

As no one score is used uniformly throughout South Africa, the following url links to tools to assess VTE risk were included in the STG:

Some risk assessment models for assessing VTE risk:

Model	Url link to tool
Padua Prediction Score[30]	https://www.mdcalc.com/padua-prediction-score-risk-vte
IMPROVE VTE risk score[31]	https://www.outcomes-umassmed.org/IMPROVE/risk_score/vte/index.html
Geneva risk score[32]	https://www.mdcalc.com/geneva-risk-score-venous-thromboembolism-vte-prophylaxis

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)

- ***Note:*** *Information sourced from NEMLC ratified minutes and NEMLC-approved documents.*

[30] Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, De Bon E, Tormene D, Pagnan A, Prandoni P. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost. 2010 Nov;8(11):2450-7. https://www.ncbi.nlm.nih.gov/pubmed/20738765

[31] Rosenberg D, Eichorn A, Alarcon M, McCullagh L, McGinn T, Spyropoulos AC. External validation of the risk assessment model of the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) for medical patients in a tertiary health system. J Am Heart Assoc. 2014 Nov 17;3(6):e001152. https://www.ncbi.nlm.nih.gov/pubmed/25404191

[32] Geneva risk score for VTE prophylaxis: Nendaz M, Spirk D, Kucher N, Aujesky D, Hayoz D, Beer JH, Husmann M, Frauchiger B, Korte W, Wuillemin WA, Jäger K, Righini M, Bounameaux H. Multicentre validation of the Geneva Risk Score for hospitalised medical patients at risk of venous thromboembolism. Explicit ASsessment of Thromboembolic RIsk and Prophylaxis for Medical PATients in SwitzErland (ESTIMATE). Thromb Haemost. 2014 Mar 3;111(3):531-8. https://www.ncbi.nlm.nih.gov/pubmed/24226257