API DK LAHARI

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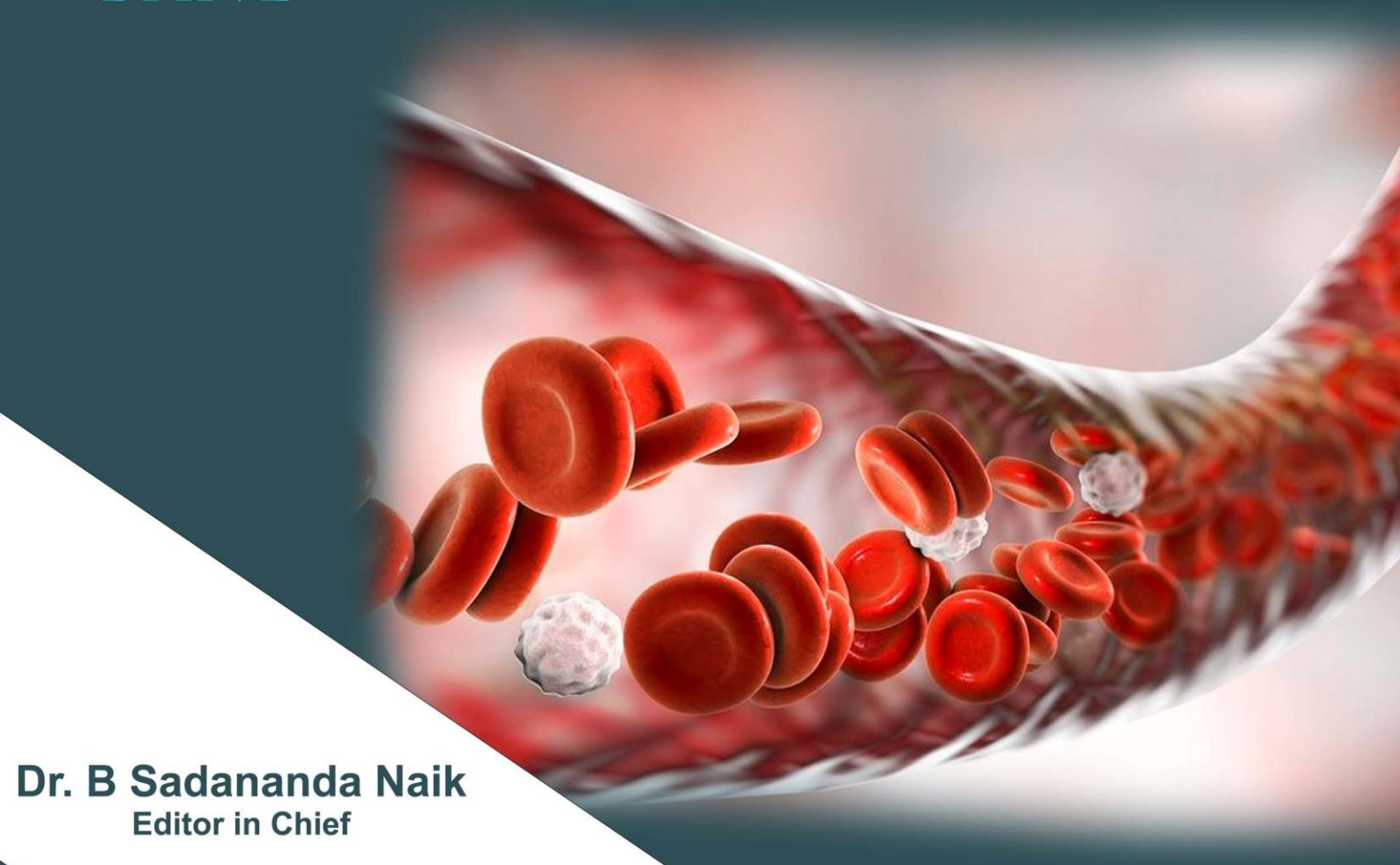
ANTICOAGULANTS - BOON OR BANE



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Dr. Akshatha Nayak U
Guest Editor

PRESIDENTS MESSAGE

Respected Readers,

I am overwhelmed again to be part of third issue of LAHARI for the year 2022 – 2023. It has been a great learning experience as president of API. I thank all the API members for making MAPICON and Physician Day great success.

The present issue of Lahari with caption ANTICOAGULANTS – BOON OR BANE has come up very well. It's very important to know when and when not to use anti coagulants. My special thanks to Dr. Akshatha Nayak U, Guest editor for this issue. She has covered usage of anti-coagulants in various conditions and its practical implications.

Finally, I thank editorial board for giving me this experience and opportunity. I well come incoming president Dr. Prabha Adhikari. I wish new team all the best.

Thanking you.

Dr. Suresh. G

President- API DK Chapter

SECRETARY'S REPORT

Dr. SHAMA PRAKASH K

Greetings from API D.K. Chapter.

The monthly meeting of October 2022 was held on 21st at Hotel Gold Finch at 8pm. Dr. Sandeep Satsangi, Consultant Hepatologist, Apollo Hospital, Bengaluru gave a talk on Novel Extracorporeal therapy in patients suffering with acute on chronic liver failure. Meeting was attended by 55 members.

The monthly meeting of November 2022 was held on 18th at Hotel Avatar at 8pm. Dr Prashantha B, Consultant Haematologist, gave a talk on What is new in Thrombocytopenia?. Dr Venkatesh B M, Professor of Medicine was the Chairperson. It was followed by a talk by CA Hari GR, the topic being Taxation of Gifts. Meeting was attended by about 70 members.

The Mangaluru API Conference (MAPICON 2022) was held on 16.12.2022 and 17.12.2022 at Avishkar Hall, 7th floor,ABSMIDS, Nitte University Campus, Deralakatte, Mangaluru by Department of General Medicine K S Hegde Medical Academy in association with API DK chapter.A total of 214 Delegates participated in the conference. The postgraduates from KSHEMA and neighbouring colleges were given the opportunity to present interesting clinical cases. They had fruitful discussions with teachers from all over Karnataka and Kerala who moderated the sessions. Eminent speakers from around Mangaluru also delivered their talks on important current issues in Medicine. Oration programmes were conducted on the occasion of the conference, in honour of 3 great physicians of Mangaluru. Dr Amarnath Hegde oration was delivered by Dr Govind Babu, Chairman, Karnataka API chapter on the topic "Impact of bio markers in oncology". Dr. K. P. Ganesan Memorial Oration was delivered by Dr. M. Shantharam Shetty, Hon. Pro-Chancellor, NITTE DU on the topic "Osteoporosis and osteoporotic related fractures- current challenges".

Dr. V. V. Mody Memorial Oration was delivered by Dr. J.P. Alva, Senior Physician, Ex-Dean FMMC on the topic “Medical education at crossroads”. Paper presentation and poster presentation were also held for the postgraduates. 45 papers and 28 posters were presented on this occasion. Cash prize for the best paper and poster were awarded to the winners in the valedictory function.

The Physician’s day was held on 16.12.2022 at Hotel Maya International ,Mangaluru. Eminent physicians namely Dr H Prabhakar (Senior Interventional cardiologist,FMMCH) and Dr. Mohammed Ismail H(Professor, KMC, Mangaluru) were honoured.Dr B M Venkatesh read the citation about Dr H Prabhakar and Dr Harish Rao read the Citation about Dr Mohammed Ismail H. Dr Joe Verghese(Former Professor, KMC, Mangaluru) was not able to attend the event due to unavoidable circumstances.Dr Damodar Shenoy read the citation in absentia. Dr Govind Babu, Chairman,API Karnataka was the chief guest. About 80 members attended this event.

The monthly meeting of January 2023 was held on 20th at Hotel AJ Grand at 8pm. Dr Jostol Pinto, Dr Deepak Madi, Dr Akshay Desai and Dr Bharath Biju gave talks on Stroke prevention in AF and the role of various anticoagulants. Dr Tanmay Bhat was the chairperson. Meeting was attended by about 50 members.

The monthly meeting of February 2023 was held on 17th at Hotel Goldfinch at 8pm. Dr Sahana Shetty gave a talk on Overcoming barriers to Insulinization in people of Type 2 DM. Dr Pavan M R was the chairperson.Dr Ganesh H K gave a talk on Indian realities and choosing right insulin. Dr Sadananda Naik was the chairperson. Meeting was attended by about 50 members.

The monthly meeting and AGM was held on 17th March 2023 at Hotel Oceanpearl at 8PM. Dr B.V.Tantry gave a talk on Decompensation in Cirrhosis. Dr E.V.S.Maben was the chairperson.Dr Ranjith Rao, Consultant Surgical Gastroenterologist, KMC, Mangaluru(Who replaced Dr Rajiv Lochan due to unavoidable circumstances) gave a talk on Who needs a transplant and what happens to those who undergo it. Dr Prabha Adhikari was the chairperson. Dr Prabha Adhikari took over as the President of API DK Chapter for 2023-24. Meeting was attended by 48 members.


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Association of Physicians of India
Dakshina Kannada Chapter
Mangaturu
Karnataka, India


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MAPICON - 2022


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EDITORIAL

Anticoagulation therapy has become an essential component of medical care. Anticoagulants play a crucial role in preventing thromboembolic events, atrial fibrillation , such as deep vein thrombosis (DVT), pulmonary embolism (PE), and stroke. Anticoagulation therapy, in combination with antiplatelet agents, has revolutionized the management of acute coronary syndromes (ACS), including unstable angina and myocardial infarction. Patients with mechanical heart valves require anticoagulation to prevent clot formation on the valve, which can lead to valve malfunction or thromboembolic events. Anticoagulants are crucial in preventing thromboembolic events in high-risk situations such as major surgeries, immobilization, and certain medical conditions like cancer.

Bleeding complications: Anticoagulants can increase the risk of bleeding, ranging from minor bruising to life-threatening haemorrhages. This risk is particularly elevated in patients with certain conditions, such as gastrointestinal ulcers, intracranial hemorrhage, or recent surgery. The severity of bleeding complications can vary depending on the type of anticoagulant used and individual patient factors.

Drug interactions: Anticoagulants can interact with other medications, leading to reduced effectiveness or increased bleeding risk. For example, nonsteroidal anti-inflammatory drugs (NSAIDs), certain antibiotics, and antiplatelet agents can potentiate the anticoagulant effect, potentially increasing the risk of bleeding. It is essential for healthcare providers to be aware of these interactions and adjust the anticoagulant therapy accordingly.

Reversal challenges: In emergency situations or when rapid reversal of anticoagulation is required, some anticoagulants pose challenges. Traditional anticoagulants, like warfarin, have reversal agents available, such as vitamin K and prothrombin complex concentrates. However, newer anticoagulants, such as direct oral anticoagulants (DOACs) like dabigatran, rivaroxaban, apixaban, and edoxaban, have limited specific antidotes available, making reversal more difficult.

Monitoring requirements: Anticoagulants like warfarin require regular monitoring of the International Normalized Ratio (INR) to ensure appropriate dosing and therapeutic range. This necessitates frequent blood tests and close follow-up, potentially increasing the burden on patients. In contrast, DOACs generally do not require routine monitoring, which can be an advantage in terms of convenience.

Individual variability: Anticoagulant response can vary significantly among individuals. Factors like age, body weight, genetics, liver function, and interactions with other medications can influence the response to anticoagulants. Finding the right dose for optimal effectiveness while minimizing the risk of bleeding can be challenging, requiring individualized adjustment and careful monitoring.

Patient adherence: Anticoagulant therapy often requires long-term or lifelong treatment. Strict adherence to the prescribed regimen is crucial for maintaining the desired therapeutic effect and preventing complications. However, some patients may struggle with medication adherence due to factors like forgetfulness, difficulty with complex dosing regimens, or concerns about side effects.

Cost: The cost of anticoagulant medications can vary significantly depending on the specific drug and healthcare system. Newer anticoagulants, such as DOACs, may be more expensive than traditional options like warfarin. Affordability and insurance coverage can affect patients' access to these medications.

It is important to note that the benefits of anticoagulants generally outweigh the potential disadvantages and complications, particularly in patients with a high-risk thromboembolism . Healthcare providers must carefully evaluate the risks and benefits for each individual before initiating anticoagulant therapy, considering factors such as the indication for treatment, patient characteristics, and potential contraindications. Regular monitoring, patient education, and open communication between patients and healthcare providers are crucial for maximizing the benefits while minimizing the risks associated with anticoagulant therapy.

This volume of Lahari aims to critically review anticoagulation therapy by examining its impact on different diseases and health outcomes.

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Guest editorial

ANTICOAGULATION- BOON OR BANE

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Life is short, and the art long, the occasion fleeting, experiences fallacious, and judgement difficult.

Hippocrates

Blood or Haem as we say it has to remain in its original liquid state inside the vasculature in our body supplying essential nutrients and oxygen to and removing toxins and carbon dioxide from various organs in the body ; except at the sites of injury where to achieve immediate hemostasis it has to clot immediately thereby following the rules of the Virchow's Triad. However, at times if thrombus forms inside the vasculature the blood supply to the organ gets curtailed and the organ suffers ischemia followed by infarction which is not desired in order to maintain homeostasis inside the human body.

The discovery of Antithrombotic agents or anticoagulants helped us avoid these issues and they have been in clinical use for over half a century which include the time-tested Warfarin and Heparin and currently the newer brigade of multiple novel agents which include DOACs, Direct Thrombin inhibitors and various low molecular weight heparins. Both oral and parenteral agents exist each with various indications and therapeutic targets, dosing variability, onerous monitoring, drug-drug, and drug- environment interactions. The new drugs bring with them new challenges such as lack of specific antidotes, increased cost, and lack of familiarity.

Proper management of anticoagulant therapy requires striking a safe balance between preventing further thromboembolic events and limiting potential side effects, the most concerning of which is bleeding. These issues are regularly the focus of medicolegal proceedings. It is necessary to ensure that comprehensive communication occurs regarding the risks and benefits of treatment, the importance of therapeutic monitoring, and the need for timely follow up should a change in dosage be required.

Physicians should keep themselves abreast with the most recent practice guidelines- ACCP , ASH and AHA guidelines to ensure that management is in keeping with current evidence-based guidelines.

Through this compilation we have tried to include various sub-specialties and their experiences with use of anticoagulation and the side effects of its management . In addition, hematologists have tried to cover certain topics of clinical importance which are commonly faced by the physicians in their routine practice and later hematology is involved for comprehensive management. We hope this editorial is educative and fruitful to all the readers here as learning is a continuous process as aptly quoted by Hippocrates.

Happy Reading !

Heparin Induced Thrombocytopenia

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Heparin-induced thrombocytopenia (HIT) is drug-induced thrombocytopenia mediated by platelet-activating antibodies of the immunoglobulin G class that target multi-molecular complexes of platelet factor 4 (PF4) and heparin. It results in thrombotic complications rather than bleeding as seen with other drug-induced thrombocytopenia. The incidence of HIT is 5.6 in Indian population and it depends on type of anticoagulant used. The incidence is more with unfractionated heparin than low molecular weight heparin. Highest frequencies approximately 10% are reported in patients with ventricular assist devices who are receiving therapeutic doses of UFH. Delay in diagnosis and initiation of appropriate therapy are associated with an initial 6.1% daily risk of thromboembolism, limb loss, and death and a cumulative thrombotic risk of 38% to 53% at 30 days. [1-3]

The first to identify the central features of the HIT syndrome --thrombocytopenia, thrombosis, and its immune pathogenesis were Dr Silver, Rhodes, and Dixon.[1]An immune basis for this syndrome was suggested by increased numbers of bone marrow megakaryocytes and a rapid recurrence of the thrombocytopenia after heparin re-exposure. A circulating heparin-dependent, platelet-activating substance (later identified as Immunoglobulin) was found in the patients' blood, which caused aggregation of donor platelets in the presence of heparin.

PATHOPHYSIOLOGY :

Heparin-induced thrombocytopenia (HIT) is a transient pro-thrombotic disorder initiated by heparin. Its central feature is thrombocytopenia resulting from immunoglobulin G (IgG)–mediated platelet activation, leading to in vivo thrombin generation and increased risk of venous and arterial thrombosis**.**[2,3]

HIT can cause both arterial and venous thrombosis.[4]HIT induces a pro-thrombotic state .The reason behind this hypercoagulable state could be due to the following proposed mechanisms -
a) HIT antibodies could bind to and injure endothelial cells, thereby initiating coagulation;
b) HIT antibodies could bind to monocytes and release tissue factor
c) HIT antibodies induce a platelet procoagulant response.

Clinical Features:

Venous thrombosis predominates except in patient populations with arteriopathy (e.g., postcardiac or vascular surgery.[5]Lower-limb DVT is the most common thrombotic complication of HIT ; Upper-limb DVT associated with the use of upper-limb catheters.[6] Pulmonary embolism possibly the most common cause of HIT-associated mortality.

Diagnosis

The diagnosis of HIT remains a clinical one, supported by confirmatory laboratory testing. The criteria for diagnosis of HIT include: [7]

- normal platelet count before the commencement of heparin
- Thrombocytopenia defined as a drop in platelet count by 30% to <100×10^9/l or a drop of >50% from the patient's baseline platelet count.
- onset of thrombocytopenia typically 5–10 days after initiation of heparin treatment, which can occur earlier with previous heparin exposure (within 100 days)
- acute thrombotic event
- the exclusion of other causes of thrombocytopenia
- the resolution of thrombocytopenia after cessation of heparin
- HIT antibody seroconversion.

Scoring system in HIT

4 T scoring system:

Element	The 4T score for heparin-induced thrombocytopenia
Thrombocytopenia	2 points if the fall in platelet count is >50% of the previous value, or the lowest count (nadir) is 20–100 × 10^9/liter 1 point if the fall is 30–50% or the nadir is 10–19 × 10^9/liter No points if the fall is less than 30% or the nadir is <10 × 10^9/liter.
Timing	2 points if the fall is between days 5–10 after commencement of treatment 1 point if the fall is after day 10. If someone has been exposed to heparin within the last 30 days and then has a drop in platelet count within a day of re exposure, 2 points are given. If the previous exposure was 30–100 days ago, 1 point. If the fall is early but there has been no previous heparin exposure, no points.
Thrombosis	2 points in new proven thrombosis, skin necrosis (see below), or systemic reaction 1 point if progressive or recurrent thrombosis, silent thrombosis or red skin lesions No points if there are no symptoms.
Alternative cause possible	2 points if no other cause 1 point if there is a possible alternative cause No points if there is a definite alternative cause.

HIT Expert Probability (HEP) Score

clinical Feature	Presentation	Score
Magnitude of fall in platelet count (measured from peak to nadir since heparin exposure)	< 30%	-1
	30-50%	+1
	>50%	+3
Timing of fall in platelet count	***For patients in whom typical onset HIT is suspected:***	
	Fall begins < 4 days after heparin exposure	-2
	Fall begins 4 days after heparin exposure	+2
	Fall begins 5-10 days after heparin exposure	+3
	Fall begins 11-14 days after heparin exposure	+2
	Fall begins > 14 days after heparin exposure	-1
	For patients with previous heparin exposure in the last 100 days in Whom rapid onset HIT is suspected.	
	Fall begins < 48 hours after heparin exposure	+2
	Fall begins > 48 hours after heparin exposure	-1
Nadir platelet count	$\leq 20 \times 10^9\ L^{-1}$	-2
	$> 20 \times 10^9\ L^{-1}$	+2
Thrombosis (select no more than one)	***For patients in whom typical onset HIT is suspected:***	
	New VTE or ATE $\geq$ 4 days after heparin exposure	+3
	Progression of pre-existing VTE/ATE while receiving heparin	+2
	For patients in whom rapid onset HIT is suspected:	
	New VTE or ATE after heparin exposure	+3
	Progression of pre-existing VTE /ATE while receiving heparin	+2
Skin necrosis	Skin necrosis at subcutaneous heparin injection sites	+3
Acute systemic reaction	Acute systemic reaction after intravenous heparin bolus	+2
Bleeding	Presence of bleeding, petechiae, or extensive bruising	-1

Other causes of thrombocytopenia (select all that apply)	Presence of a chronic thrombocytopenic disorder	-1
	Newly initiation non-heparin med known to cause thrombocytopenia	-2
	Severe infection	-2
	Severe DIC (fibrinogen < 100 mg/dL and D-dimer > 5 mcg/ml)	-2
	Indwelling intra-arterial device (IABP, VAD, ECMO)	-2
	Cardiopulmonary bypass within previous 96 hours	-1
	No other apparent cause	+3
VTE=venous thromboembolism; ATE=arterial thromboembolism; DIC=disseminated intravascular coagulation		

CLINICAL FEATURES :

Lower-limb DVT is the most common thrombotic complication of HIT

Upper-limb DVT associated with use of upper-limb catheters

Pulmonary embolism possibly the most common cause of HIT-associated mortality

Adrenal vein thrombosis associated with adrenal haemorrhagic necrosis

Arterial thrombosis: Lower-limb arteries > cerebral arteries > coronary arteries.

DIAGNOSIS:

Clinical suspicion along with laboratory tests, confirm the diagnosis of HIT. Laboratory tests include -They are solid-phase assay and particle gel immunoassays.[8,9] They have high sensitivity (>99%) and rapid turnaround time. These tests have poor specificity of around 30-70% across various studies because they detect non-pathogenic antibodies.[7] When there is positive ELISA, a decrease in the optical density by around 50% after addition of excess heparin confirms the presence of heparin-dependent antibodies. This is based on the principle that excess heparin inhibits agglutination. ELISAs while not complex are not generally available on a urgent basis.Hence newer tests with short turnaround time such as PF4 Rapid test which is a single use, semi-quantitative assay contained in a cartridge. It is designed to detect anti-PF4-heparin antibodies in human serum and/or plasma with a total assay time of 15 minutes.

Functional assays are considered the gold standard for diagnosis of HIT.They include serotonin release assay (SRA) and heparin-induced platelet aggregation (HIPA). SRA is based on HIT antibodies causing platelets to aggregate and release serotonin requires radiolabelled platelets. [10-14]

HIPA is a platelet-activation test in which the patient's serum is mixed with donor platelets in the presence of heparin. Presence of antibodies to the heparin–PF4 complex results in aggregation of the donor platelets.[15,16]

The PF4-dependent P-selectin expression assay, which uses platelets pre-treated with PF4 as targets for antibody detection are considered more sensitive and specific than SRA. This test had higher diagnostic accuracy (area under the curve, 0.92 vs 0.82; P = .02) than the SRA. [17]

TREATMENT :

The treatment of HIT includes withholding heparin, including flushes and heparin coated devices along with immediate administration of non heparin anti-coagulation.

Many clinicians still consider withholding heparin alone is sufficient and the thrombosis risk is negligible, but a retrospective data from 1996 suggest 30-days risk of thrombosis is up to 50%.

Bivaluridin is an attractive anticoagulant for HIT therapy in critically ill patient,because it has predominantly proteolytic elimination (only 20% renal clearance),with immediate onset of action and lack of need for an initial bolus, a low risk for immunogenicity and a short half-life of ~ 25 min, the potential for rapid dose titration and minimal interference with the PT/INR. [18-22]

Fondaparinux is alternative commonly used factor Xa inhibitor for the treatment of HIT because of once daily dosing with no need for monitoring and less bleeding and good anti thrombotic efficacy and less bleeding compared to other factor Xa inhibitors.[26]

The ideal alternative to heparin for patients receiving dialysis is Argatroban because it is not excreted by the kidneys and does not require dose adjustment in these patients

DURATION OF ANTICOAGULATION :

The risk of thrombosis is seen up to 8 weeks so anticoagulation is recommended for at least 2 to 3 months after the diagnosis of HIT.

In view of increased thrombin generation and further decrease in protein C and S by warfarin, this cannot be used initially, it can be used once the platelet count increased to near normal range and after initiation of another non-heparin anticoagulant and INR reaches more than 3, and when used should be at low dose, of less than 5mg.

REFERENCES:

1. Kelton JG, Warkentin TE. Heparin-induced thrombocytopenia: a historical perspective. 2008; Available from: www.bloodjournal.org

2. Warkentin TE. HEPARIN-INDUCED THROMBOCYTOPENIA [Internet]. [cited 2019 Mar 28]. Available from: https://www.clinicalkey.com/service/content/pdf/watermarked/3-s2.0-B9780323357623001335.pdf?locale=en_US

3. Warkentin TE, Aird WC, Rand JH. Platelet-Endothelial Interactions: Sepsis, HIT, and Antiphospholipid Syndrome I. ENDOTHELIAL-PLATELET INTERPLAY IN SEPSIS. Hematology. 2003.

4. Franchini M. Heparin-induced thrombocytopenia: an update. Thromb J [Internet]. 2005 Oct 4 [cited 2019 Mar 28];3(1):14. Available from: http://thrombosisjournal.biomedcentral.com/articles/10.1186/1477-9560-3-14

5. Levy JH, Tanaka KA, Hursting MJ. Reducing thrombotic complications in the perioperative setting: An update on heparin-induced thrombocytopenia. Anesthesia and Analgesia. 2007.

6. Gollomp K, Kim M, Johnston I, Hayes V, Welsh J, Arepally GM, et al. Neutrophil accumulation and NET release contribute to thrombosis in HIT. JCI Insight [Internet]. 2018 Sep 20 [cited 2019 Jun 14];3(18)

7. Watson H, Davidson S, Keeling D. Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition. Br J Haematol. 2012;

8. TE W, JA S. Testing for heparin-induced thrombocytopenia antibodies. Transfus Med Rev. 2006;

9. Tawfik NM, Hegazy MA, Hassan EA, Ramadan YK, Nasr AS. Egyptian experience of reliability of 4T's score in diagnosis of heparin induced thrombocytopenia syndrome. Blood Coagul Fibrinolysis. 2011;

10. Just SJ, Brighton T, Kondo M, Prawitha D. Review of Serotonin Release Assay (SRA) results for confirmation of Heparin Induced Thrombotic Thrombocytopenia (HITT). Int J Lab Hematol. 2012;

11. Warkentin TE, Greinacher A. Laboratory Testing for Heparin-Induced Thrombocytopenia. In 2011.

12 . Harenberg J, Huhle G, Giese CH, Wang LC, Feuring M, Song XH, et al. Determination of serotonin release from platelets by enzyme immunoassay in the diagnosis of heparin-induced thrombocytopenia. Br J Haematol. 2000;

13. Warkentin TE, Arnold DM, Nazi I, Kelton JG. The platelet serotonin-release assay. Am J Hematol. 2015;

14. Brighton TA, Kondo M, Prawitha D, Just S. Serotonin Release Assay (SRA) results for confirmation of Heparin Induced Thrombotic Thrombocytopenia (HITT). J Thromb Haemost. 2013

15. Boon DMS, Kappers-Klunne MC, Michiels JJ, Stibbe J, van Vliet HHDM. Heparin-induced thrombocytopenia and thrombosis: a potential fatal complication in a routine treatment. Neth J Med. 1995;46(3).

16. Minet V, Dogné J-M, Mullier F. Functional Assays in the Diagnosis of Heparin-Induced Thrombocytopenia: A Review. Mol A J Synth Chem Nat Prod Chem [Internet]. 2017 Apr 11 [cited 2019 Jun 19];22(4). Available from: http://www.ncbi.nlm.nih.gov/pubmed/28398258

17. Padmanabhan A, Jones CG, Curtis BR, Bougie DW, Sullivan MJ, Peswani N, et al. A Novel PF4-Dependent Platelet Activation Assay Identifies Patients Likely to Have Heparin-Induced Thrombocytopenia/Thrombosis. Chest. 2016

18. Tardy B, Tardy-Poncet B, Fournel P, Venet C, Jospe R, Dacosta A. Lower limb veins should be systematically explored in patients with isolated heparin-induced thrombocytopenia [5]. Thrombosis and Haemostasis. 1999.

19. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. Am J Med [Internet]. 1996 Nov [cited 2019 Jun 13];101(5):502–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8948273

20. Bibbo C, Hatfield PS. Lower extremity manifestations and treatment of heparin-induced thrombocytopenia syndromes: A cohort study. J Foot Ankle Surg. 2011;50(1).

21. Joseph L, Casanegra AI, Dhariwal M, Smith MA, Raju MG, Militello MA, et al. Bivalirudin for the treatment of patients with confirmed or suspected heparin-induced thrombocytopenia. J Thromb Haemost [Internet]. 2014 Jul [cited 2019 Jun 13];12(7):1044–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24766902

22. Koster A, Dyke CM, Aldea G, Smedira NG, McCarthy HL, Aronson S, et al. Bivalirudin During Cardiopulmonary Bypass in Patients With Previous or Acute Heparin-Induced Thrombocytopenia and Heparin Antibodies: Results of the CHOOSE-ON Trial. Ann Thorac Surg. 2007

23. Kiser TH, MacLaren R, Fish DN, Hassell KL, Teitelbaum I. Bivalirudin versus unfractionated heparin for prevention of hemofilter occlusion during continuous renal replacement therapy. Pharmacotherapy. 2010

24. Joseph L, Casanegra AI, Dhariwal M, Smith MA, Raju MG, Militello MA, et al. Bivalirudin for the treatment of patients with confirmed or suspected heparin-induced thrombocytopenia. J Thromb Haemost. 2014

25. L. T. Bivalirudin dosing requirements for treatment of heparininduced thrombocytopenia in renal dysfunction. J Thromb Thrombolysis. 2011;

26. Cuker A, Arepally GM, Chong BH, Cines DB, Greinacher A, Gruel Y, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood advances. 2018.

Antiphospholipid syndrome (APS) : Diagnosis, investigations, and Treatment

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Definition

APS is a systemic autoimmune syndrome characterized by venous or arterial thrombosis and/or pregnancy morbidity in the presence of antiphospholipid antibodies (aPL) that persist over time (more than 12 weeks).

Clinically leads to arterial or venous thrombosis and/or obstetric morbidity secondary to aPL

APS can occur as a

1. Primary condition, when it is idiopathic
2. Secondary if it occurs in the presence of systemic lupus erythematosus (SLE) or another systemic autoimmune disease.
3. Catastrophic APS (CAPS)

Pathophysiology

Animal studies do suggest that aPL is directly prothrombotic. Many mechanisms (1) for thrombosis in APS have been suggested, such as increased expression of tissue factor and endothelial cells, interference in the protein C anticoagulant pathway, inhibition of fibrinolysis and inhibition of annexin V binding to phospholipids. Antibody-b2GPI complexes bind to a variety of receptors and may trigger intracellular signalling and inflammatory responses. Pregnancy failure may be due to thrombosis in the placental bed, although alternative pathogenic mechanisms may apply, and may not fully explain the tendency to early embryo losses.

Diagnosis

Diagnosis of APS needs both clinical and laboratory criteria to be fulfilled (2)

1. Clinical criteria: Consider the diagnosis when either/ or

a. Thrombotic: Arterial or venous or small vessel thrombosis

b. Obstetric:

i. 3 or more spontaneous embryonic losses at or under 10 week gestation with anatomic, hormonal and chromosomal causes excluded,

ii. One or more foetal death of morphologically normal foetus after 10 weeks gestation,

iii. Preterm birth due to eclampsia, severe preeclampsia or placental insufficiency.

2. Laboratory criteria: This consists of presence of antibodies which are persistent on 2 or more occasions when checked 12 weeks apart. These antibodies are

a. Anticardiolipin (aCL) IgG and/ or IgM serotype present in medium or high titre (i.e.>40GPL units or MPL units, or >the 99th centile).

b. Anti-beta2 glycoprotein I (anti-beta2GPI) IgG and/or IgM serotype (in titre>the 99th centile)

c. Lupus anticoagulant (LA)

Signs and Symptoms

1. Unexplained/ Unprovoked arterial or venous thrombosis
2. Bad obstetric outcomes as described in diagnostic criteria
3. Thrombosis associated with livedo, valvular heart disease, and/or neurologic findings such as cognitive deficits and white matter lesions suggestive of a prior stroke
4. Thrombosis/ bad obstetric outcome in a patient with features or diagnosis of systemic autoimmune disease
5. Abnormal routine laboratory results showing mild thrombocytopenia, prolongation of the activated partial thromboplastin time (aPTT), or a history of a false-positive serologic test for syphilis (Venereal Disease Research Laboratory (VDRL))
6. History should focus on the thrombotic events, whether they are provoked or not, the outcomes of pregnancies in females, including reason for bad outcomes, thrombocytopenia, and other risk factors for thrombosis, which may include immobility, use of estrogen-containing medications, and/or family history of thrombophilia.
7. Symptoms associated with systemic lupus erythematosus (SLE) or other connective tissue diseases such as photosensitivity, malar rash, discoid rash, Livedo reticularis, livedo racemose , arthritis, serositis, oral ulcers, hair loss, and Raynaud phenomenon.
8. Digital ischemia or gangrene, sequelae of deep vein thrombosis (leg oedema, skin changes)

Differential Diagnosis

The following conditions need to be excluded clinically along with history and investigations if required.

1. Provoked thrombosis: Secondary to immobility, drugs or other causes
2. Heparin-induced thrombocytopenia (HIT).
3. Inherited and acquired thrombophilia
4. Anatomic vascular obstruction,
5. Paroxysmal nocturnal haemoglobinuria (PNH)
6. Myeloproliferative neoplasms (MPN).
7. Vaccine-induced immune thrombotic thrombocytopenia (VITT)
8. Anatomical or chromosomal causes of miscarriage

Laboratory and Other tests

1. Complete blood count (CBC) – Thrombocytopenia may be seen in patients with APS.
2. Baseline coagulation testing – The prothrombin time (PT) and activated partial thromboplastin time (aPTT) are important prior to starting anticoagulation, especially if they will be used for monitoring. The aPTT is used for lupus anticoagulant (LA) testing.
3. Serum creatinine level and urinalysis helps to identify kidney involvement in APS; abnormal findings may also suggest a concomitant or alternative diagnosis (eg, SLE).
4. Anticardiolipin antibodies (aCL); IgG and IgM by enzyme-linked immunosorbent assay (ELISA).
5. Anti-beta2 glycoprotein I (anti-beta2GPI) antibodies; IgG and IgM by ELISA.
6. Lupus Anticoagulant assay, which is a three-step procedure:

a) Demonstration of a prolonged phospholipid-dependent screening test of hemostasis

b) This is followed by mixing patient plasma with normal plasma which fails to correct the prolonged screening test. This shows that an inhibitor is present, rather than factor deficiency.

c) The third step involves addition of excess phospholipid to correct the prolonged coagulation test thus demonstrating phospholipid dependence.

7. Antinuclear antibody testing (ANA profile and indirect immunofluorescence tests as indicated), C3, C4 and double stranded DNA
8. Relevant radiological tests such as Doppler ultrasound, Computerised tomography pulmonary angiogram (CTPA), etc based on clinical signs.

Timing of testing

1. Initial aPL testing is usually done at the time of the thrombosis or adverse pregnancy outcome. An acute thrombotic event may falsely normalize the aPTT and hence LA may be inaccurate.

a. Hence Lupus anticoagulant is not recommended immediately after initial thrombotic event.

b. The immunoassays (ELISAs for aCL or beta2GPI) are not affected by acute thrombotic events or anticoagulants and hence may be done.

2. Confirmatory aPL testing – In patients with initial positive testing for aPL, testing should be repeated after ≥12 weeks to confirm persistence of the aCL, anti-beta2GPI, or LA.
3. Transiently elevated levels of IgG or IgM aCL, as well as a positive LA test, can occur with certain infections or drug exposures and hence not significant.
4. Positive results from aPL testing on 2 tests ≥12 weeks apart is essential for diagnosis
5. The IgG isotype of aCL and anti-beta2GPI has a stronger association with thrombotic and obstetric events compared with IgM isotypes.
6. Triple positive aPL is also more significant.

Transient antiphospholipid antibodies (aPL)

1. Transient aPL may be detected in the following settings where patient may have a thrombosis. This will disappear in the second test after 12 weeks and hence are not diagnostic

2. Infections – Bacterial sepsis, leptospirosis, syphilis, Lyme disease, tuberculosis, leprosy, infective endocarditis, post-streptococcal rheumatic fever, and Klebsiella infections. Viral infections such as Hepatitis A and B; mumps; human immunodeficiency virus (HIV); human T-lymphotropic virus type 1 (HTLV-I); cytomegalovirus; varicella-zoster; Epstein-Barr virus (EBV); adenovirus; parvovirus; rubella; and Covid19, Parasitic infestations such as Malaria, Pneumocystis jirovecii, and visceral leishmaniasis.

3. Medications – These include phenothiazines (chlorpromazine), phenytoin, hydralazine, procainamide, quinidine, quinine, ethosuximide, alpha interferon, amoxicillin, chlorothiazide, oral contraceptives, and propranolol

4. Malignancy – Solid tumors (lung, colon, cervix, prostate, kidney, ovary, breast, and bone); Hodgkin disease and non-Hodgkin lymphoma; MPN (primary myelofibrosis, polycythemia vera); and myeloid and lymphocytic leukemias.

Screening Recommendation (3)

1. There is no evidence to routinely screen all patients with thrombosis or stroke.
2. Patients with unprovoked proximal DVT or PE after stopping anticoagulation (for at least 7 days) should be screened as the presence of aPL will help to make decision regarding long-term anticoagulant therapy or cessation of therapy
3. Women with recurrent pregnancy loss (3 pregnancy losses) before 10 weeks gestation should be screened for aPL
4. Young adults under 50 years with ischemic stroke should be screened
5. Patients with connective tissue disease who develop thrombotic or obstetric complications should be screened.

Treatment of Primary APS: Thrombosis (4,5)

1. Primary thrombosis prophylaxis is not recommended in patients with incidental laboratory detection of aPL without clinical criteria.
2. Recommended anticoagulation is heparin (low molecular weight heparin is preferred) or Vitamin K antagonists (VKA) such as warfarin.
3. Long term anticoagulation is recommended for APS associated thrombosis
4. Evidence for DOACs is still insufficient at present to recommend its use in APS patients and hence it is not preferred.
5. If patient who is already on DOAC for venous thrombosis with good response may continue it if it is patient preference.
6. DOAC is not recommended for arterial thrombosis or triple positive aPL.
7. The target INR for VKA therapy in APS should be 2·5 (target range 2·0–3·0).

Treatment of Primary APS: Obstetric

1. For women with APS with recurrent (3 or more) pregnancy loss, antenatal administration of heparin prophylaxis (Low molecular weight heparin (LMWM) is preferred) combined with low dose aspirin is recommended throughout pregnancy and 6 weeks post-partum.
2. For women with APS and a history of pre-eclampsia or fetal growth retardation, low dose aspirin is recommended.
3. Women with aPL should be considered for post-partum thrombo-prophylaxis for 6 weeks.
4. VKA is contraindicated in pregnancy in view of birth defects. LMWH is preferred during pregnancy in view of its convenience over unfractionated heparin

Treatment of secondary APS:

1. Anticoagulation for thrombosis and / or obstetric management is similar to that of primary APS
2. Optimal treatment of underlying connective tissue disorder is essential and increased thrombosis is seen during active disease. Treatment includes assessing the degree of severity of connective tissue disease and starting immunosuppressive medications which consists of combination of steroids and steroid sparing agents such as Mycophenolate mofetil, Azathioprine, Hydroxychloroquine sulphate.
3. If disease is not controlled with the conventional therapies, biological treatment as Rituximab, Belimumab should be considered.
4. Mothers should be counselled regarding APS and should have combined follow up with their treating doctors.

Catastrophic APS(CAPS)

CAPS is a rare, life-threatening form of APS characterized by thrombotic complications (macrovascular and microvascular) affecting multiple organs that develop simultaneously or over a short period of time. Combinations of treatments are typically used including anticoagulation with heparin/warfarin. Immunomodulatory therapies including plasmaphaeresis, intravenous human immunoglobulins (IVIg), corticosteroids and rituximab have been employed. This needs aggressive treatment in intensive care settings and early suspicion and diagnosis is essential based on unexplained severe, widespread thrombosis.

References

a. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost.* (2006) 4:295–306. 10.1111/j.1538-7836.2006.01753.x

b. Meroni PL, Borghi MO, Raschi E, Tedesco F. Pathogenesis of antiphospholipid syndrome: understanding the antibodies. *Nat Rev Rheumatol.* (2011) 7:330–9.

c. David Keeling, Ian Mackie, Gary W. Moore, Ian A. Greer, Michael Greaves, Guidelines on the investigation and management of antiphospholipid syndrome British Committee for Standards in Haematology. https://doi.org/10.1111/j.1365-2141.2012.09037

d. Cohen H, Hunt BJ, Efthymiou M, Arachchillage DR, Mackie IJ, Clawson S, et al.Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. *Lancet Haematol.* (2016) 3:e426–36. 10.1016/S2352-3026(16)30079-5

e. Deepa R. J. Arachchillage, Keith Gomez, Raza Alikhan, Julia A. M. Anderson, Will Lester, Mike Laffan Addendum to British Society for Haematology Guidelines on Investigation and Management of Antiphospholipid syndrome, 2020. https://doi.org/10.1111/bjh.16308

Cancer Associated Thrombosis

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Malignancy is a pro-thrombotic state and patients with cancer are at increased risk of developing venous thromboembolism including deep venous thrombosis and pulmonary thromboembolism.

Cancer associated thrombosis includes deep venous thrombosis , pulmonary embolism , catheter associated thrombosis. It is the second leading cause of death in cancer patients . It is associated with increased risk of recurrence and anti coagulation associated bleeding

The pathophysiology of cancer associated thrombosis is multi-factorial . There are direct and indirect mechanisms for thrombosis. Direct mechanisms include expression of tissue factor ,micro particles , podoplanin,plasminogen activator inhibitor(PAI),tumor derived platelet agonist by the tumor. Malignant tissue involving endothelial and tumor cells constitutively expresses TF. Indirect mechanisms include the hypoxic micro environment provided by the tumor , cytokines and damage associated molecular patterns (DAMP) released by the dying tumor cells , mucin produced by certain solid tumors and chemotherapy ; nausea and vomiting leading to dehydration are contributing factors for thrombosis.[1]

RISK ASSESSMENT OF VTE:

The Khorana Risk Score is one well-known tool that can help to assess the risks of first VTE in cancer patients undergoing treatment with chemotherapy. Based on five pre-chemotherapy clinical characteristics (site of cancer, platelet count, hemoglobin level, leukocyte count, and body mass index), patients are divided into three risk categories: low, intermediate, and high-risk, with significantly different risks of VTE in 3 months (0.3%, 2%, and 6.7% in the validation cohort, respectively). For recurrent VTE, the Ottawa score has been developed to identify risk factors for recurrent VTE in cancer patients. The researchers identified four factors—gender, type of cancer, stage of cancer, and history of VTE for risk assessment. A score ≤0 corresponds with a low risk (≤4.5%) and score ≥1 corresponds with a high risk (≥19%) of VTE recurrence within 6 months

MANAGEMENT :

The International Initiative on Thrombosis and Cancer (ITAC) guidelines recommend low molecular weight heparin (LMWH) in the initial treatment of established venous thrombosis , when the Creatinine clearance is >30 ml/min for the first 5-10 days, then subsequently change to vitamin K antagonist(VKA).[2]Unfractionated heparin (UFH) is recommended for patients with reduced renal function.

'CLOT' - randomized trial conducted across several nations comparing the efficacy of LMWH versus VKA for prevention of recurrent VTE in cancer patients proved the superiority of LMWH over VKA, with reduced risk of VTE in the LMWH arm than VKA arm .[2]

ASCO recommends prophylaxis for hospitalized medically ill medical oncology patients with additional risk factors for VTE. It does not recommend thromboprophylaxis in patients admitted for chemotherapy or stem cell transplantation.[3]

DOACs are recently approved for treatment of cancer associated thrombosis . DOACs are suitable for cancer patients who are ambulatory and have intact upper gastrointestinal tract with adequate absorption and in those patients where no surgical intervention is planned. However they are not indicated in patients who have creatinine clearance <30 ml/min, obese ,pregnant , severe hepatic impairment, luminal gastrointestinal or genitourinary lesions.The ease of administration ,lack of drug interactions, freedom from drug monitoring has made DOACs quite a popular option for treatment of cancer associated VTE.

Several trials such as SELECT D [4] , where Rivaroxaban 15 mg twice a day for 3 weeks followed by 20 mg once a day for 6 months was compared to Dalteparin 200 IU /kg daily for one month followed by 150IU/kg once a day from 2 -6 months for VTE/PE showed recurrence rate of 4% for Rivaroxaban arm versus 11% for

Dalteparin arm. Recurrence rates being higher for patients presenting with symptomatic VTE and those with solid tumors in stomach, pancreas . Major bleeding episodes were higher with Rivaroxaban than Dalteparin . However , overall survival was similar in both arms (75% vs 70% respectively).

ADAM VTE trial comparing Apixaban versus Dalteparin showed non inferiority of the Apixaban over Dalteparin in VTE treatment . Carvaggio trial [5]compared Apixaban with Dalteparin for treatment of VTE showed superiority of Apixaban over Dalteparin , with similar recurrence rates (203% vs 2.6%) , major bleeding events (3.3vs 5.5%)and similar mortality rates (23.4vs 26.4%) . Apixaban had overall better EFS than the Dalteparin arm .[6]

Duration of anti-coagulation:

Optimal duration of anti-coagulation in cancer associated VTE patients is around 3-6 months. Beyond 6 months continuation of anti-coagulation is only indicated if there are risk factors such as ongoing active malignancy and or cancer treatment. Studies showed that the risk of recurrent thrombosis or major bleeding is higher during the first 3-6 months, with an ongoing risk of recurrent thrombosis beyond 6 months.

Anti-coagulation in patients with thrombocytopenia:

In the setting of an acute VTE, the ISTH guideline, based on expert consensus, recommends a therapeutic dose of anti-coagulation for patients with platelet count ≥50 × 10^9/L. If platelet count <50 × 10^9/L, platelet transfusion is recommended to allow for therapeutic anti-coagulation, or alternatively, insertion of retrievable IVC filter until the platelet count is safe for anticoagulation. For patients with subacute or chronic VTE, the ISTH guideline recommends the LMWH dose be reduced in patients with platelet count <50 × 10^9/L, and held altogether if the platelet count is <25 × 10^9/L.[3]

Recurrence of thrombosis :

In patients on DOACs ; switch to a treatment regimen of LMWH, such as Dalteparin 200 IU once daily for one month, followed by 150 IU once daily thereafter, or Enoxaparin 1 mg/kg every 12 hours. For patients with thrombosis progression while receiving LMWH, increase the dose of LMWH by 20-25%. The algorithm for treatment of recurrent thrombosis while on anticoagulation is depicted in figure 1.

Conclusion :

Cancer associated thrombosis is associated with increased morbidity and mortality. There is increased recurrence rates and need for prolonged anticoagulation. LMWH is the anticoagulant of choice in treatment of cancer associated VTE. However ,in the recent years DOACs has been approved for treatment of cancer associated VTE .

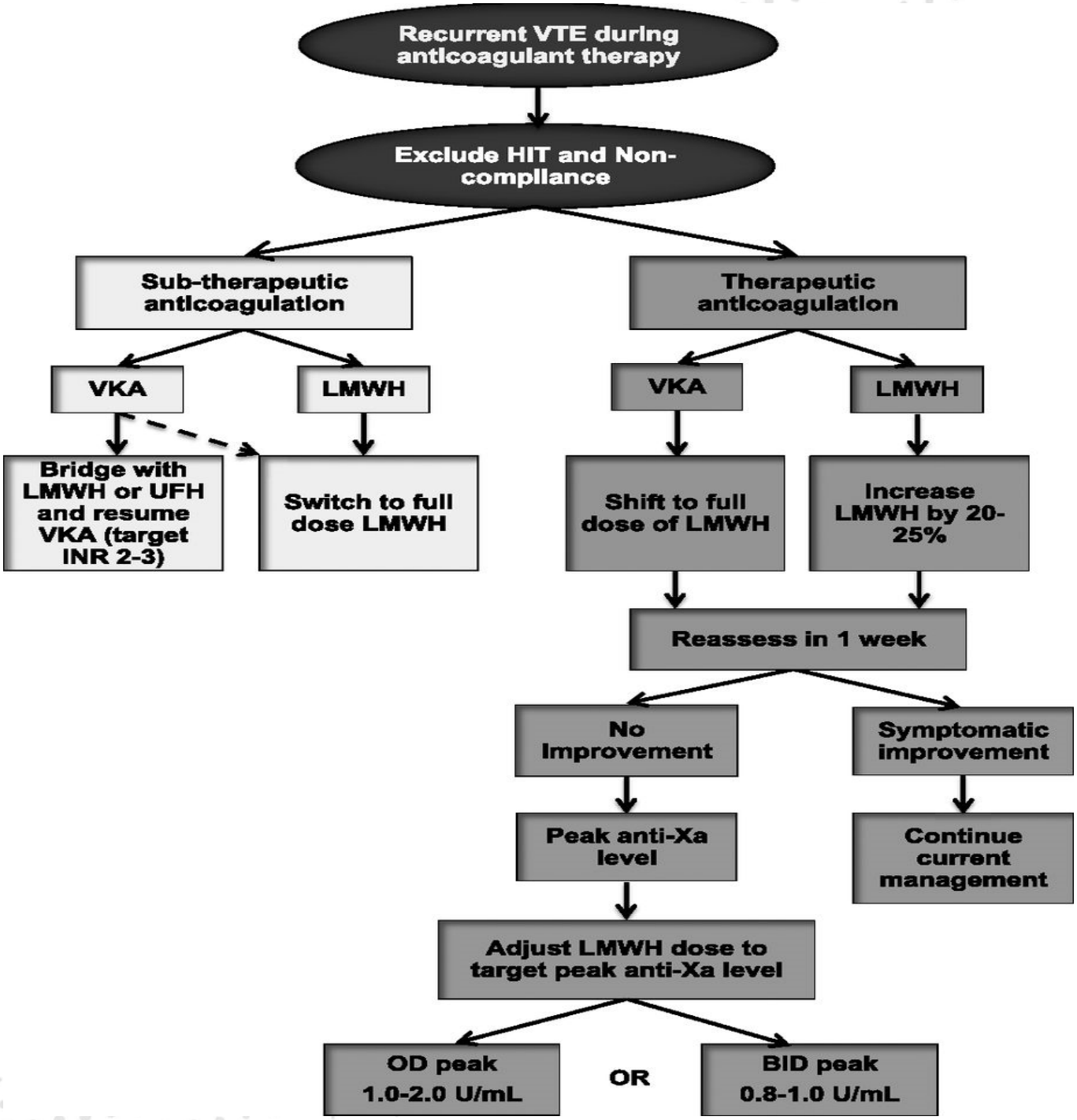

Figure 1 image taken from blood journal [7]

REFERENCES :

1. Norbaini Binti Abdol Razak , Gabrielle Jones, Pat Metharom et al . Cancer associated thrombosis: An overview of mechanisms ,risk factors,and treatment.Cancers.2018 Oct ;10(10): 380
2. Lee AYY,Levine MN,Baker RI et al.Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer.N Engl J Med. 2003; 349: 146-153.
3. Farge D ,Debourdeau P ,Beckers M et al.International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer.J Thromb Haemost. 2013; 11: 56-70
4. Young AM, Marshall A,Thirlwall J et al.Comparison of an oral factor xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol. 2018; 36: 2017-2023
5. Agnelli G,Becattini C,Meyer G et al.Apixaban for the treatment of venous thromboembolism associated with cancer.N Engl J Med. 2020; 382: 1599-1607
6. McBane 2nd, RD,Wysokinski WE, Le-Rademacher JG et al.Apixaban and dalteparin in active malignancy-associated venous thromboembolism: the ADAM VTE trial.J Thromb Haemost. 2020; 18: 411-421
7. Agnes Y. Y. Lee,Erica A. Peterson, Treatment of cancer-associated thrombosis, Blood, 2013

Thrombophilia testing: Boon or Bane

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Thrombophilia is the term used to describe hereditary and/or acquired conditions which predispose to thrombosis. There is a great interest in identifying the factors associated with increased predisposition to thrombosis. But with research and experience, it was realized that the relationship between the factors such as elevated levels of procoagulant proteins or deficiency of anticoagulant proteins with thrombosis is not straightforward. There are many acquired factors such as obesity which can tilt the direction toward a prothrombotic state. Secondly, our understanding of all the procoagulant genes and their phenotype correlation is not complete. Thirdly, some proteins such as factor V have both pro- and anticoagulant effects.[1]

The most clearly identified heritable thrombophilias include factor V Leiden (FVL) variant, prothrombin gene variant (G20210A), protein C deficiency (PC), protein S deficiency (PS), and antithrombin deficiency (AT). Other hereditary thrombophilia such as methylenetetrahydrofolate reductase (MTHFR) and elevated factor VIII levels have doubtful attribution to thrombosis and are no longer being tested routinely.[2] Acquired thrombophilias include antiphospholipid (APS), paroxysmal nocturnal hemoglobinuria (PNH), myeloproliferative disorder (MPN), and JAK2 mutation in absence of an MPN phenotype.[3]

With the availability of tests readily, there is a dilemma as to whom to test and how to use the results. Testing for inherited thrombophilia has been debated and is controversial. For example, the American Society of Hematology choosing wisely recommends against testing for thrombophilia in adults with VTE who have major transient risk factors.[4] Similarly, other guidelines have also advised limiting testing to a narrow range of specific clinical situations.[5,6] These have been in response to its indiscriminate use and fallacy regarding its interpretation in clinical practice.[1]

Pitfalls in Thrombophilia testing

The problem with thrombophilia testing arises from the fact that many thrombophilia results do not affect the decision-making and outcomes including death. The risk of recurrence is also not significantly different between those who test positive from those who are negative. But the positive results can falsely affect the decision-making and make the physician unduly overtreat whereas those who test negative are unduly reassured especially when there is a family history of venous thromboembolism. Another pitfall of thrombophilia testing includes testing these in the acute state which leads to false low levels as protein C, protein S, and antithrombin are consumed in the acute thrombotic process. Similarly, testing while the patient is on anticoagulation leads to erroneous interpretation. The proteins C and S are low while the patient is on warfarin and antithrombin activity is affected by heparin. Direct oral anticoagulants (DOAC) also affect many serological tests performed for thrombophilia and must be stopped before testing.[7] Another argument as to why these tests need not be sent from emergency departments is that the initial management is unlikely to be affected by the thrombophilia results.

Thrombophilia tests

Following inherited and acquired thrombophilias are commonly tested in clinical practice and the methods of their testing are summarized below.

Inherited

Increased procoagulants:

Factor V Leiden mutation is detected either by activated protein C resistance (APCR) or polymerase chain reaction (PCR) for factor V Leiden mutation. Heterozygosity for factor V Leiden is common in some populations and can be up to 5-8%.

Prothrombin gene mutation is detected by PCR-based test.

Decreased anticoagulants:

Protein C, protein S, and antithrombin are measured by activity-based assays.

Acquired

Lupus anticoagulant – lupus anticoagulant is measured by in vitro clotting tests based on APTT (acquired partial thromboplastin time) and dRVVT (diluted Russell viper venom time). The other 2 tests anticardiolipin (IgM and IgG) and beta-2 glycoprotein I (IgM and IgG) are measured by ELISA-based tests.

PNH panel – evaluated by flow cytometry for the absence of GPI-anchored proteins including CD 55 and CD59.

JAK2 V617F (Janus Kinase), CALR (Calreticulin), and MPL (myeloproliferative leukaemia virus oncogene) are evaluated by PCR-based or NGS(Next Generation Sequencing) method to look for pathological mutations.[1]

What, when, and whom to test for thrombophilia?

Some factors which suggest inherited thrombophilia in patients with venous thromboembolism include factors such as young age (<50 years), strong family history, recurrent venous thromboembolism (VTE) events, and VTE in unusual sites such as splanchnic and cerebral veins.

Provoked VTE – Patients who have VTE which is precipitated by strong transient risk factors such as major surgery, trauma, immobility, or recent hospitalization have a low risk of recurrence. It is estimated to be 1% within 1 year and 3% within 5 years.[8] Even patients who test positive for thrombophilia do not require longer-term anticoagulation. Hence, many societies including ASH choosing wisely have recommended against testing for provoked VTE.

Unprovoked VTE – Unprovoked VTE has a significant risk of recurrence with around 10% in the first year and up to 40% at 5 years. But again, the recurrence risk has been predicted by prediction models such as the Vienna prediction model, DASH score, and HERDOO2 scores, and thrombophilia is not part of any of them.[9,10,11] Thrombophilia testing does not add much value when tested in the acute period and can be done later (usually after 3 months) once there is a consideration for stopping the anticoagulation. Testing can be considered in young-age VTE with weak provoking factors, in a family with a strong history of recurrent VTE, or in a female family member of childbearing age. Antiphospholipid antibodies can be evaluated especially if associated with arterial thrombosis and it also affects the choice of anticoagulation (Warfarin for triple positive APLS compared to direct oral anticoagulants- VKAs VS DOACs).

Thrombosis at unusual sites -

Splanchnic vein thrombosis (portal, mesenteric, splenic, hepatic veins) – Paroxysmal nocturnal hemoglobinuria (PNH) and JAK2 mutation have been associated with increased risk of splanchnic vein thrombosis hence are routinely tested. Though there might be a local factor that has to be evaluated first which increases the risk of thromboses such as cirrhosis of the liver, extrinsic compression from a tumour, or abdominal infections.[12]

Cerebral vein thrombosis – Cerebral venous sinus thrombosis (CVST) is a rare entity accounting for <1% of all strokes. The cause of CVST can be identified in the majority of the cases such as combined direct cranial trauma, neurosurgical procedures, infections (e.g. bacterial meningitis), combined hormonal pills, pregnancy, antiphospholipid syndrome (6%), Behcets disease, dehydration due to diarrheal illness in children, myeloproliferative neoplasm (MPN), paroxysmal nocturnal hemoglobinuria, malignancy and cancer treatments such as cisplatin, L-asparaginase, tamoxifen.[13] The utility of testing inherited thrombophilia is not well established in patients with unusual sites of thrombosis. The British society of haematology guideline state that they do not recommend testing for inherited thrombophilia if the only indication for testing is thrombosis as the association is weak. Evaluation for MPN, PNH, JAK2, and APS testing is done in these patients who do not have a clear provoking factor.[3]

Retinal vein occlusion – There is no evidence of association with inherited thrombophilia. Some studies show an increased prevalence of antiphospholipid antibodies with retinal vein occlusion. Testing for aPL may be considered in patients without local risk factors, hypertension, diabetes, and hypercholesterolemia.

Thrombophilia testing in relation to pregnancy outcomes - Multiple studies have found very weak or no associations between hereditary thrombophilia and placentally mediated pregnancy complications such as placental abruption, pre-eclampsia, recurrent first-trimester pregnancy loss, and stillbirth. Hence it is recommended that these tests are not done for women with recurrent miscarriages or adverse pregnancy outcomes.[3,14,15] However, acquired thrombophilia antiphospholipid syndrome (APS) has been associated with placenta-mediated pregnancy complications. According to revised Sapporo criteria for APS, clinical criteria are satisfied if there are three or more unexplained consecutive spontaneous abortions before 10 weeks gestation not related to chromosomal or anatomical abnormalities in parents, unexplained death of a morphologically normal fetus at or beyond week 10 of gestation and premature birth of a morphologically normal neonate before 34 weeks gestation as a result of eclampsia, severe preeclampsia, or placenta insufficiency. Low molecular weight heparin (LMWH) and aspirin have been shown to benefit in the reduction of early pregnancy losses.[16]

A brief note on acquired thrombophilia states -

Antiphospholipid syndrome - Antiphospholipid antibody syndrome is associated with both venous and arterial thrombosis. The spectrum of disorder is wide ranging from a single venous thrombosis to catastrophic life-threatening thrombosis. Many patients can have transient antiphospholipid antibodies positivity hence it is advised to repeat the tests in 3 months to recheck for persistent antibodies. The problem with antiphospholipid antibodies is the risk they confer, with lupus anticoagulant being significantly associated with thrombosis than anticardiolipin and anti-beta2 glycoprotein I antibodies. The triple-positive confers an even higher thrombotic risk with both venous and arterial events. Studies have found that arterial events with Rivaroxaban were higher compared to Warfarin. This led to the recommendation by the European Medical Agency (EMA) that DOACs should not be used for the secondary prevention of APS.[17]

Paroxysmal nocturnal haemoglobinuria (PNH) - PNH is a condition in which uncontrolled complement activity leads to systemic complications, principally through intravascular hemolysis and platelet activation. It arises through a somatic mutation of the phosphatidylinositol glycan A (*PIG-A*) gene in bone marrow stem cells, resulting in disruption to glycosylphosphatidylinositol (GPI) biosynthesis and thereby a deficiency of all GPI-anchored proteins on the cell membrane. Among the deficient proteins are the complement regulatory proteins CD55 and CD59, resulting in increased complement sensitivity of PNH cells, intravascular hemolysis, promotion of inflammatory mediators, and systemic hemoglobin release.[18] Thrombosis in PNH may occur at any site. Common sites include the intraabdominal and cerebral veins, for reasons still unknown, making thrombosis a leading cause of morbidity as well as mortality.

Myeloproliferative disorders (MPN) - They are characterized by clonal expansion of an abnormal hematopoietic stem/progenitor cell. The three main myeloproliferative disorders are polycythemia vera (PV), essential thrombocythaemia (ET), and primary myelofibrosis (PMF). Their understanding was massively improved after unveiling the molecular basis mainly represented by the V617F mutation in *JAK2* exon 14, which involves >95% of PV and ~60% to 70% of ET and PMF patients. Myeloproliferative disorders can lead to both arterial (coronary artery disease, nonhaemorrhagic stroke) and venous thrombosis (Budd Chiari syndrome, Portal vein thrombosis, Pulmonary embolism) and microcirculatory problems (vascular headaches, dizziness, visual disturbances, distal paresthesia, acrocyanosis, and erythromelalgia).[19] Thrombosis may be the heralding event in 20% of the MPN. *JAK2*V617F screening in splanchnic vein thrombosis (SVT) patients without typical hematologic MPN features was identified in 17.1% and 15.4% of screened BCS and PVT patients, respectively.[20]

Conclusions -

The thrombophilia testing in VTE is a complex one as the development of VTE is multifactorial with environmental and acquired causes contributing over and above the inherited ones. Hence there is a need for carefully selecting the patients for testing, the right time to test, and interpreting the testing results in the context of optimal management for the patient.

References:

1. Connors JM. Thrombophilia Testing and Venous Thrombosis. N Engl J Med. 2017 Sep 21;377(12):1177–87.
2. Colucci G, Tsakiris DA. Thrombophilia screening revisited: an issue of personalized medicine. J Thromb Thrombolysis. 2020;49(4):618–29.
3. Arachchillage DJ, Mackillop L, Chandratheva A, Motawani J, MacCallum P, Laffan M. Thrombophilia testing: A British Society for Haematology guideline. Br J Haematol. 2022;198(3):443–58.
4. American Society of Hematology | Choosing Wisely [Internet]. 2015 [cited 2023 Feb 13]. Available from: https://www.choosingwisely.org/societies/american-society-of-hematology/
5. Chong LY, Fenu E, Stansby G, Hodgkinson S. Management of venous thromboembolic diseases and the role of thrombophilia testing: summary of NICE guidance. BMJ. 2012 Jun 27;344:e3979.
6. Baglin T, Gray E, Greaves M, Hunt BJ, Keeling D, Machin S, et al. Clinical guidelines for testing for heritable thrombophilia. Br J Haematol. 2010 Apr;149(2):209–20.
7. Siriez R, Dogné JM, Gosselin R, Laloy J, Mullier F, Douxfils J. Comprehensive review of the impact of direct oral anticoagulants on thrombophilia diagnostic tests: Practical recommendations for the laboratory. Int J Lab Hematol. 2021;43(1):7–20.

8. Kearon C, Akl EA. Duration of anticoagulant therapy for deep vein thrombosis and pulmonary embolism. Blood. 2014 Mar 20;123(12):1794–801.
9. Tosetto A, Iorio A, Marcucci M, Baglin T, Cushman M, Eichinger S, et al. Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). J Thromb Haemost JTH. 2012 Jun;10(6):1019–25.
10. Houghton D, Moll S. HERDOO2 Score: How Long to Treat With Anticoagulation? The Hematologist [Internet]. 2017 Jul 1 [cited 2023 Feb 13];14(4). Available from: https://doi.org/10.1182/hem.V14.4.7468
11. Tritschler T, Méan M, Limacher A, Rodondi N, Aujesky D. Predicting recurrence after unprovoked venous thromboembolism: prospective validation of the updated Vienna Prediction Model. Blood. 2015 Oct 15;126(16):1949–51.
12. Ageno W, Dentali F, Squizzato A. How I treat splanchnic vein thrombosis. Blood. 2014 Dec 11;124(25):3685–91.
13. Ropper AH, Klein JP. Cerebral Venous Thrombosis. N Engl J Med. 2021 Jul 1;385(1):59–64.
14. Arachchillage DRJ, Makris M. Inherited Thrombophilia and Pregnancy Complications: Should We Test? Semin Thromb Hemost. 2019 Feb;45(1):50–60.
15. Ormesher L, Simcox LE, Tower C, Greer IA. 'To test or not to test', the arguments for and against thrombophilia testing in obstetrics. Obstet Med. 2017 Jun;10(2):61–6.
16. Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis. 2019 Oct 1;78(10):1296–304.
17. Fazili M, Stevens SM, Woller SC. Direct oral anticoagulants in antiphospholipid syndrome with venous thromboembolism: Impact of the European Medicines Agency guidance. Res Pract Thromb Haemost. 2019 Dec 12;4(1):9–12.
18. Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood. 2013 Jun 20;121(25):4985–96.
19. Barbui T, Finazzi G, Falanga A. Myeloproliferative neoplasms and thrombosis. Blood. 2013 Sep 26;122(13):2176–84.
20. Smalberg JH, Arends LR, Valla DC, Kiladjian JJ, Janssen HLA, Leebeek FWG. Myeloproliferative neoplasms in Budd-Chiari syndrome and portal vein thrombosis: a meta-analysis. Blood. 2012 Dec 13;120(25):4921–8.

Choosing the right DOAC for your patient

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Direct Oral Anticoagulants (DOACs) are increasingly being used for anticoagulation for a wide range of patients. Easy administration, reliable duration of action, acceptable bleeding profile and the lack of need for frequent monitoring are making DOACs preferable alternatives to the time tested Vitamin K antagonists (VKA). DOACs are mainly of 2 groups:

1. Direct thrombin Inhibitors (dabigatran)
2. Oral Factor X-a Inhibitors (Rivaroxaban , Apixaban , Edoxaban and Betrixaban . The latter two are not available India as yet).

Since 2010 , when dabigatran was approved, several Randomized clinical trials have justified the use of each of the molecules as potential alternatives to VKAs. Each of the trials were designed to prove non inferiority or superiority to VKAs in a variety of conditions ranging from Atrial Fibrillation to Deep Venous Thrombosis (DVT). With RCT data backing each molecule choosing the right DOAC for your patient sometimes becomes challenging and needs practical and pharmacokinetic considerations.

Indications:

The primary use case scenario for DOACs include the prevention of stroke in patients with Non-Valvular AF (NVAF). NVAF includes all AF patients except those with prosthetic heart valves and more than moderate mitral stenosis (usually rheumatic).

The reason for excluding the above said conditions has more to do with the non-availability of significant data rather than actual harm (as these two conditions were excluded from major DOAC trials). There was a small study though (Re-Align), of prosthetic heart valves and dabigatran VS warfarin which showed more thrombotic and bleeding events with Dabigartran, clearly making it less favourable in this subset. The following is a table comparing the FDA approved indications of the three DOACs.

Approved indications for DOACs:

	Dabigatran	Rivaroxaban	Apixaban
Stroke prevention in NVAF	✓	✓	✓
Treatment of deep vein thrombosis and pulmonary embolism	✓	✓	✓
Prevention of recurrent deep vein thrombosis and pulmonary embolism	✓	✓	✓
Prevention of thromboembolism after total knee and hip replacement	✓	✓	✓
Prevention of major cardiovascular events in patients with chronic CAD/peripheral artery disease		✓	
Prevention of thromboembolism in hospitalized acutely ill medical patients		✓	✓
Treatment of heparin-induced thrombocytopenia;			✓
Prevention and treatment of cancer-associated DVT			✓

Pharmacodynamic and Pharmacokinetic differences:

While all DOACs have a rapid onset of action and offset of action (peak plasma levels within 2-3 hrs of ingestion), there are a few significant pharmacokinetic difference which affect the choice of DOAC used. Dabigatran is a prodrug with a bio-availability of 6.5% while both rivaroxaban and apixaban are active molecules with good bioavailability (>80% and > 50% respectively). Dabigatran is only 35% protein bound while the latter two are highly protein bound. This makes dabigatran dialyzable. Also, 80% of dabigatran is excreted renally while only 33% of rivaroxaban and 25% of apixaban are excreted from kidneys. Both rivaroxaban and apixaban have predominant biliary excretion. The low protein binding and the predominant renal excretion have implications in choosing dabigatran in patients with renal insufficiency as will be discussed later. One of the major advantages of DOACs over VKAs is the lack of any interaction with food.

Monitoring and reversal agents:

General monitoring of DOACs for therapeutic efficacy is not required. Specific tests like Factor Xa assay drug plasma concentrations can be performed in exceptional situations. The commoner indication for monitoring would be when drug compliance is questionable (or in case of DOAC related bleeding) and can be done with Prothrombin time (All DOACs tend to prolong) and APTT and TT (only dabigatran tends to prolong).

Bleeding related to DOACs is usually managed with supportive therapy. Since all molecules have a very rapid offset of action, tiding over the crisis for 12-24 hrs with supportive therapy usually is sufficient. Reversal agents are required in case of major or life threatening bleeding or when emergency surgery dictates reversal of anticoagulation. For elective surgeries, stopping the drug for a minimum of 24 hrs (rivaroxaban) to 48 hrs (apixaban and dabigatran) is usually sufficient. There are two specific reversal agents (antidotes) approved for reversal of a DOAC: idarucizumab is approved for reversal of the direct thrombin inhibitor dabigatran, and andexanet alfa is approved for reversal of the direct FXa inhibitors apixaban and rivaroxaban.

Dosage of DOACs:

Stroke prevention for AF

	Dabigatran	Rivaroxaban	Apixaban
CrCl >50 ml/min	150 mg BID Or 110 mg BID	20 mg OD	5mg BID
Cr Cl (30-50 ml/min)	150 mg BID Lower dose if bleeding risk is high	15 mg OD	5 mg BID*
Cr Cl (15-30 ml/min)	75 mg BID (in US)	15 mg OD	2.5 mg BID
Cr Cl < 15 ml/min			2.5 mg BID (in US)
Dialysis			5 mg BID *

In Cr Cl < 15 VKAs are preferred

*Apixaban dose is reduced to 2.5 mg BID if 2/3 are met: 1. Age > 80 yrs , 2. Weight < 60 Kg and 3. Creatinine > 1.5 mg/dl

DVT:

For acute DVT, parenteral anticoagulation can be given for 5 days and then switched over to any of the full doses of DOACs. Oral alone Apixaban (10 mg BID for 7 days followed by 5 mg BID) or oral alone Rivaroxaban (15 mg BID for 21 days followed by 20 mg OD) can also be used.

When Switching over from VKA to DOAC, it is recommended to stop VKA and initiate DOAC only when the INR is < 2 or in therapeutic range. It is important to remember that DOACs can elevate INR values and hence the test should be done before starting a DOAC.

Articles of interest:

1. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383:955–962.
2. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019;74:104–132.
3. Jan Steffel, Ronan Collins, Matthias Antz, Pieter Cornu, Lien Desteghe, Karl Georg Haeusler, Jonas Oldgren, Holger Reinecke, Vanessa Roldan-Schilling, Nigel Rowell, Peter Sinnaeve, Thomas Vanassche, Tatjana Potpara, A John Camm, Hein Heidbüchel, External reviewers, 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation, *EP Europace*, Volume 23, Issue 10, October 2021, Pages 1612–1676,

Thromboprophylaxis in ICU

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FAST HUGS BID- Feeding, Analgesia, Sedation, Thromboprophylaxis, Head end elevation, Ulcer prophylaxis, Glucose, Bowel-bladder, Indwelling catheter and De-escalation- mantra of ICU.

***Thromboprophylaxis is an essential part of day-to-day ICU care*.**

Anticoagulation in ICU- Prophylactic and therapeutic. Conditions like Pulmonary thromboembolism or cortical venous thrombosis, mechanical heart valves, atrial fibrillation, NSTEMI, idiopathic pulmonary hypertension require therapeutic doses of anticoagulation. Other critically ill patients also will need anticoagulation but in prophylactic doses to prevent complications like pulmonary embolism or deep venous thrombosis. Mechanical ventilation, central venous catheterization, immobilization, sepsis, vasopressor requirement and platelet transfusions remain risk factors for venous thromboembolism in Intensive care unit.

5 to 20 % of critically ill patients develop deep venous thrombosis despite of receiving DVT prophylaxis. Pharmacological prophylaxis reduces risk of DVT by 50%. Intermittent pneumatic compression devices are recommended for patients who can not receive pharmacological thromboprophylaxis. They have shown to reduce DVT risk by 30%. The Pneumatic Compression for Preventing Venous Thromboembolism (PREVENT) trial showed no benefit of combining Pharmacological and mechanical DVT.

PROTECT (PROphylaxis for ThromboEmbolism in Critical Care Trial) showed Low molecular weight heparin (LMWH) to be more efficacious than Unfractionated heparin (UFH) in medical as well as surgical groups of critically ill patients. Dalteparin in comparison with UFH showed less incidence of Venous thromboembolism, however risk of proximal DVT remained same.

LMWH is preferred over UFH for routine prophylaxis. UFH, Dalteparin or low dose LMWH is preferred in case of renal insufficiency. Fondaparinux is contraindicated in severe renal insufficiency.

active gastroduodenal ulcer, prior bleeding history in the 3 months before admission, low platelet count (less than 50,000), hepatic failure (international normalized ratio higher than 1.5), and activated partial thromboplastin time (APTT) increased (10 s increased) without an anticoagulation agent are the contraindications for pharmacological prophylaxis.

DVT prophylaxis if GFR > 30 ml/min

Enoxaparin (low molecular-weight heparin) is the preferred agent. Less frequent dosing, reduced risk of heparin induced thrombocytopenia and more efficacy makes it superior to unfractionated heparin.

Dose is 40 mg enoxaparin subcutaneous daily. If Weight <50 kg, decrease the dose to 30 mg sc daily.

Weight >120 kg, increase dose to 0.25 mg/kg enoxaparin twice daily. As a routine measuring factor Xa activity is not practical, however edema, vasoconstrictor use and renal failure situations may warrant measuring factor Xa activity to know the effectiveness of enoxaparin activity.

Fondaparinux 2.5mg subcutaneous once daily can be used alternatively.

DVT prophylaxis if GFR <30 ml/min

Unfractionated heparin 5,000 IU subcutaneous TID.
Dalteparin 5000 IU SC OD
Enoxaparin 20 mg SC OD
Newer oral anticoagulants are not preferable in critical illness due to rapidly changing pathophysiology. Associated organ dysfunctions like liver and renal dysfunctions in critically ill patients limit their use.

Monitoring anticoagulation:

LMWH effectiveness ideally needs anti-Xa activity to be maintained between 0.1 and 0.4 IU/mL. Routine measurement is debatable. In the setting of Extracorporeal membrane oxygenation, renal failure and in patients where immediate reversal of anticoagulation required unfractionated heparin is preferred. Monitoring in such a scenario is done using Activated Partial Thromboplastin Clotting Time or Activated clotting time (ACT) of Anti Xa activity.

Conclusion:

In critically ill patients' selection of ideal anticoagulant is difficult. Understanding pathophysiology of illness, modifying thromboprophylaxis according to coagulation profile, renal and liver function is extremely important to maintain thin balance between clotting and bleeding.

References:

1. Cauchie, P.; Piagnerelli, M. What Do We Know about Thromboprophylaxis and Its Monitoring in Critically Ill Patients?Biomedicines 2021, 9, 864. https://doi.org/10.3390/ biomedicines9080864
2. Y.M. Arabi, F. Al-Hameed, K.E.A. Burns, S. Mehta, S.J. Alsolamy, M.S. Alshahrani et al. Adjunctive Intermittent Pneumatic Compression for Venous Thromboprophylaxis. n engl j med 380;14
3. Helms J , Middeldorp S, Spyropoulos AC. Thromboprophylaxis in critical care. Intensive Care Med (2023) 49:75–78
4. Tang X, Lyu W R, Jin Y, Wang R , Li X Y , Li Y et al. Modern thromboprophylaxis protocol based on guidelines applied in a respiratory intensive care unit: a single-center prospective cohort study. Thrombosis Journal (2022) 20:76 https://doi.org/10.1186/s12959-022-00439-2
5. Minet C, Potton L , Bonadona A , Hamidfar-Roy R , Somohano C A , Lugosi M. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. Critical Care (2015) 19:287 DOI 10.1186/s13054-015-1003-9

Anticoagulation in neurology

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With the ever increasing incidence of stroke and thromboembolic diseases with progressive age in our population, anticoagulation has been gaining importance in clinical practice.

Coagulation is the process of formation of a clot to prevent bleeding. Primary hemostasis shall lead to cessation of hemorrhage by vasoconstriction and platelet plug formation. If this proves insufficient this shall be followed by the Secondary hemostasis leading to formation of the clot(1).The clot formation occurs as a result of the clotting cascade which involves interaction of various clotting factors, designated I to XIII leading to the formation of fibrin, which intercalates and forms the clot. The extrinsic pathway triggered by the external trauma and the intrinsic pathway triggered by the internal pathway leading to the common pathway and fibrin clot formation is the final end point in the clotting cascade.

The neurological indications of anticoagulants are:

1) Cardioembolic stroke
2) Cerebral Venous thrombosis
3) DVT prophylaxis

1) <u>Cardioembolic stroke</u>

Atrial fibrillation is considered as major cause of cardioembolic stroke and it is imperative to carefully identify AF in patients with stroke, as this could lead to prevention of recurrent stroke with anticoagulation. Left atrial appendage clot is identified to be associated with 90% of stroke associated with AF. Non-valvular atrial fibrillation (NVAF), prosthetic heart valve (PHV), dilated cardiomyopathy (DCMP), and left atrial myxoma are the other causes(2).

Vitamin K antagonists and four new direct acting oral anticoagulant agents are the main therapeutic agents used for the prevention of stroke. DOACS have been found to be associated to have lesser chances of bleeding along with improved stroke rates on the basis of RE-LY trial, ROCKET AF, ARISTOTLE and ENGAGE AF TIMI trial.

The AHA guidelines ,2021 for Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack(3) states that

1. In patients with nonvalvular AF and stroke or TIA, oral anticoagulation (eg, Apixaban, Dabigatran, Edoxaban, Rivaroxaban, or Warfarin) is recommended to reduce the risk of recurrent stroke(Level 1A)
2. In patients with AF and stroke or TIA, oral anticoagulation is indicated to reduce the risk of recurrent stroke regardless of whether the AF pattern is paroxysmal, persistent, or permanent (Level 1 B-R)

3. In patients who do not have moderate to severe mitral stenosis or a mechanical heart valve, Apixaban, Dabigatran, Edoxaban, or Rivaroxaban is recommended in preference to Warfarin to reduce the risk of recurrent stroke.

4. In patients with stroke or TIA and LV thrombus, anticoagulation with therapeutic warfarin for at least 3 months is recommended to reduce the risk of recurrent stroke

5. In patients with stroke or TIA in the setting of acute anterior MI with reduced ejection fraction (EF<50%) with no evidence of LV thrombus, anticoagulation for 3 months may be considered to prevent recurrent stroke.

When to initiate anticoagulation?

1. In the setting of TIA in the setting of non valvular AF patient may be started on anticoagulants immediately after index events

2. In patients with low risk of haemorrhagic transformation, it is advisable to wait for 2-14 days before initiation of anticoagulants .

3. In patients with high risk of haemorrhagic transformation, a delay of 14 days is advisable before the initiation of oral anticoagulants.

4. In patients who cannot tolerate life long anticoagulation, but can tolerate it for upto 45 days, closure of left appendage with watchman device may be performed for prevention of stroke .

5. In patients with ESRD or on dialysis, apixaban or warfarin would be the recommended choice for anticoagulation.

Cerebral venous thrombosis

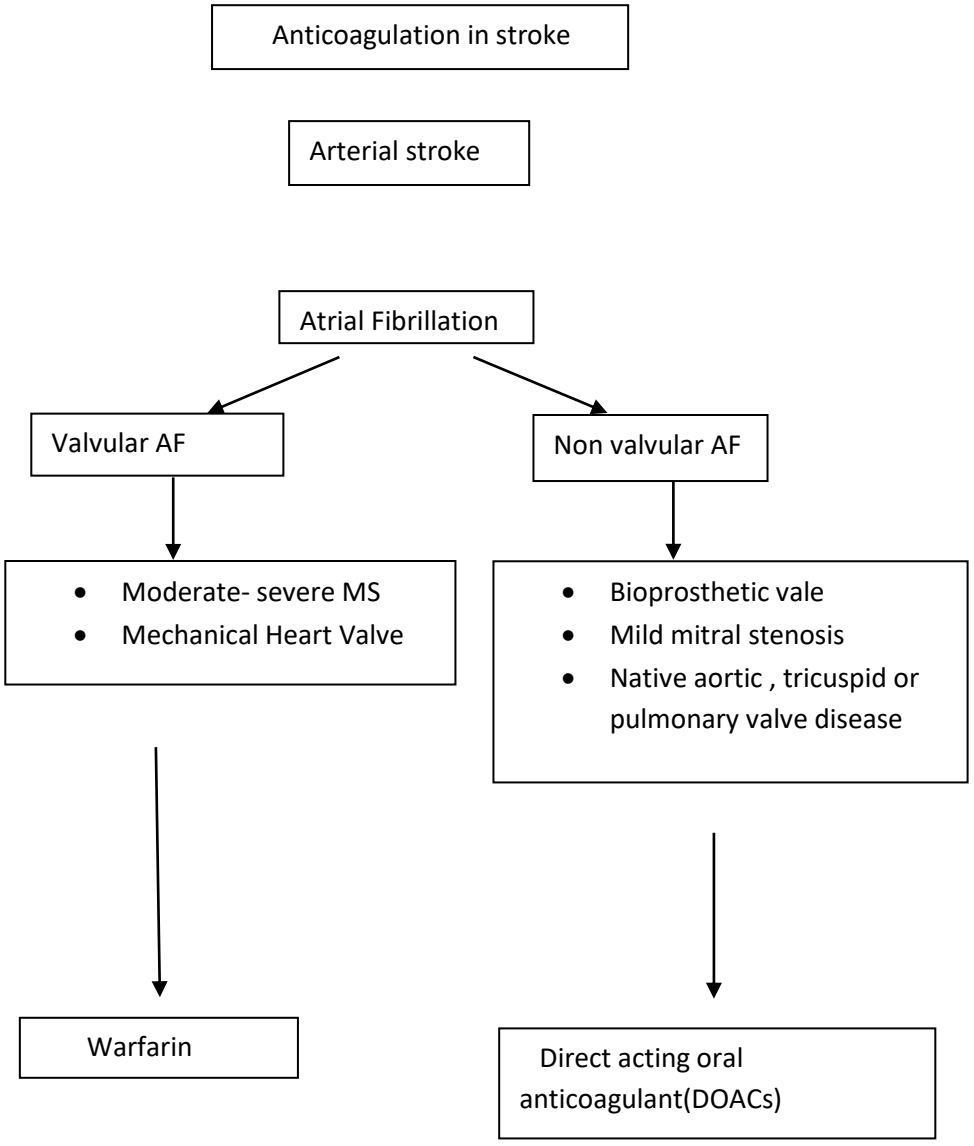
CVT is an important cause of young stroke, with a preponderance among the females. This is due to the occlusion of the cerebral venous sinus and the smaller cortical veins (4).Anticoagulant needs to be initiated as soon as the diagnosis of CVT has been confirmed to prevent further complications.

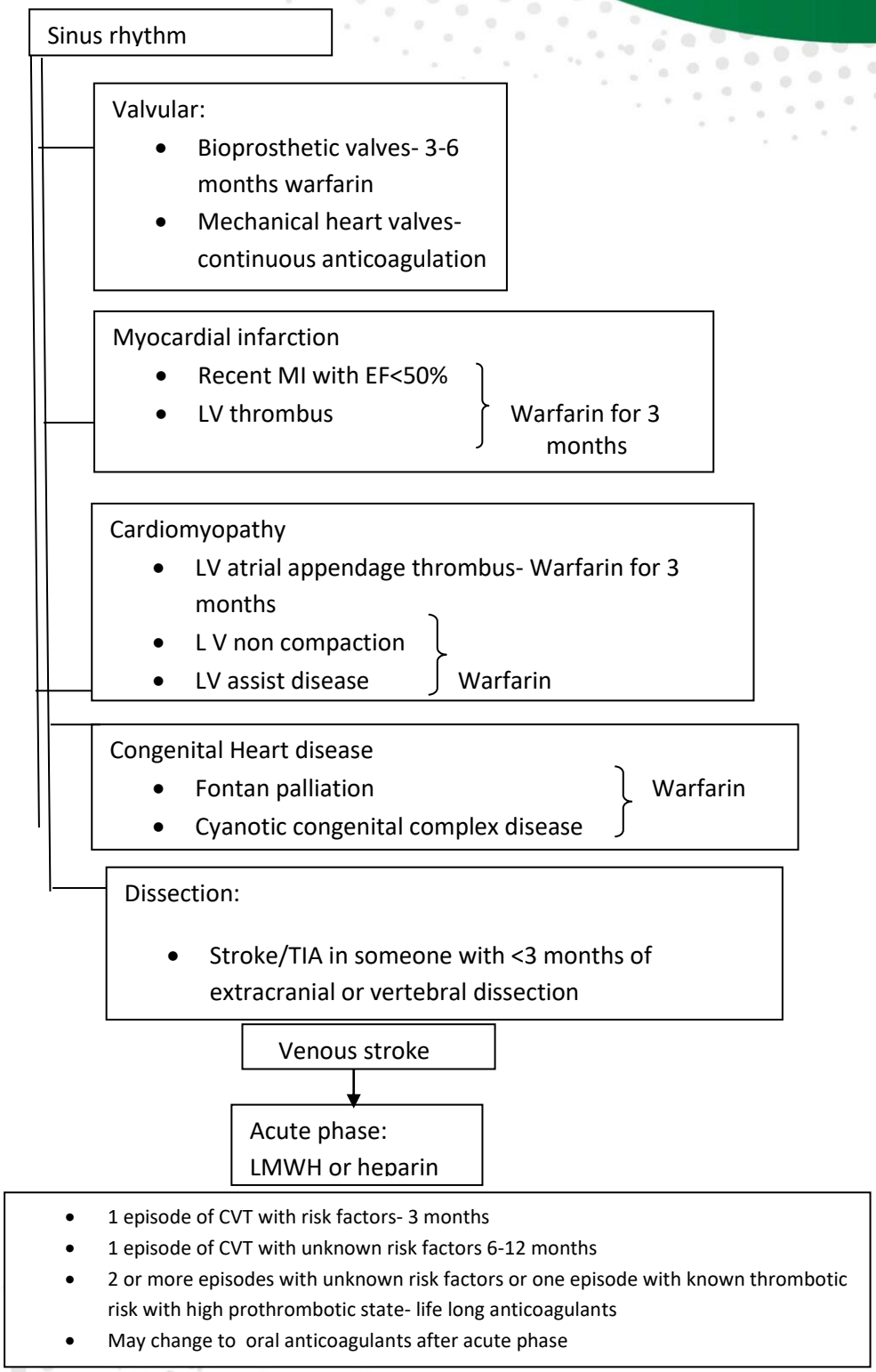
ESO guidelines (5) states that

1. The initiation of anticoagulation with LMWH/ UFH at therapeutic dosages have been recommended.
2. The duration of anticoagulation is decided based on the number of episodes of CVT and associated risk factors,

- In patients with one episode of CVT and transient risk factors (dehydration, drugs (eg, oral contraceptives), infections, trauma, surgical interventions) -anticoagulation for 3–6 months is recommended
- In patients with one episode of CVT of unknown cause anticoagulation for 6–12 months is recommended.
- In patients with two or more CVTs (or one episode and a severe prothrombotic condition with a high ongoing thrombotic risk) lifelong anticoagulation is recommended.
- After the acute phase of CVT, a shift to oral anticoagulants can be considered.

The newer anticoagulants have ushered in a new era for anticoagulation with lesser risk of bleeding, lesser hospital stays and cost. However, risks of hemorrhage cannot be discounted and hence physicians should appropriately use the HASBLED scale for assessment of risk of bleed before administration of anticoagulants.


Anticoagulation in stroke
Arterial stroke
Atrial Fibrillation
Valvular AF
Non valvular AF
Moderate- severe MS
Mechanical Heart Valve
Bioprosthetic vale
Mild mitral stenosis
Native aortic , tricuspid or pulmonary valve disease
Warfarin
Direct acting oral anticoagulant(DOACs)


Sinus rhythm
Valvular:
Bioprosthetic valves- 3-6 months warfarin
Mechanical heart valves- continuous anticoagulation
Myocardial infarction
Recent MI with EF<50%
LV thrombus
Warfarin for 3 months
Cardiomyopathy
LV atrial appendage thrombus- Warfarin for 3 months
L V non compaction
LV assist disease
Warfarin
Congenital Heart disease
Fontan palliation
Cyanotic congenital complex disease
Warfarin
Dissection:
Stroke/TIA in someone with <3 months of extracranial or vertebral dissection
Venous stroke
Acute phase:
LMWH or heparin
1 episode of CVT with risk factors- 3 months
1 episode of CVT with unknown risk factors 6-12 months
2 or more episodes with unknown risk factors or one episode with known thrombotic risk with high prothrombotic state- life long anticoagulants
May change to oral anticoagulants after acute phase

Bibliography

1. Batta A, Kalra BS, Khirasaria R. Critical issues and recent advances in anticoagulant therapy: a review. Neurology India. 2019 Sep 1;67(5):1200.
2. Verma R. Role of anticoagulation in neurological practice. Indian J Med Res. 2016 Apr;143(4):392-4.
3. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, Kamel H, Kernan WN, Kittner SJ, Leira EC, Lennon O. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. Stroke. 2021 Jul;52(7):e364-467.
4. Ulivi L, Squitieri M, Cohen H, Cowley P, Werring DJ. Cerebral venous thrombosis: a practical guide. Practical neurology. 2020 Oct 1;20(5):356-67.
5. Ferro JM, Bousser MG, Canhão P, Coutinho JM, Crassard I, Dentali F, di Minno M, Maino A, Martinelli I, Masuhr F, de Sousa DA. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis–endorsed by the European Academy of Neurology. European stroke journal. 2017 Sep;2(3):195-221.

GASTROINTESTINAL SAFETY OF ANTICOAGULATION

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"No anticoagulant can reduce the risk of thrombosis without increasing the risk of bleeding".

Anticoagulants are commonly used to prevent or treat thrombosis in various medical conditions, but they can increase the risk of gastrointestinal (GI) bleeding. Therefore, it is important to follow standard guidelines when using anticoagulants in patients with GI bleeding to ensure optimal management and outcomes. [1]Recent data suggest that DOACs account for approximately 62% of new anticoagulant prescriptions.[2] The safety of DOACs compared to warfarin in the context of gastrointestinal bleeding has been studied extensively. Randomized controlled trials, systematic reviews, and observational studies have demonstrated a 25%–30% increased risk of GI bleeding with DOACs when compared to warfarin.[3, 4, 5]

The following are some general guidelines:

- Risk stratification: Patients with GI bleeding should be risk-stratified based on the severity of bleeding, comorbidities, and the indication for anticoagulant use. This helps to determine the appropriate management strategy.
- Hold anticoagulants: In most cases, anticoagulants should be temporarily held in patients with active GI bleeding until the bleeding is controlled. This may involve the reversal of anticoagulation if necessary, such as with vitamin K antagonists (e.g., warfarin), direct oral anticoagulants (DOACs), or heparin.
- Reversal agents: Reversal agents may be used to reverse the effects of anticoagulation and facilitate haemostasis. For example, patients on warfarin may require vitamin K or fresh frozen plasma, while those on DOACs may benefit from specific reversal agents such as idarucizumab for dabigatran, Andexanet alfa for factor Xa inhibitors, and ciraparantag.
- Resumption of anticoagulation: Once the bleeding is controlled, the decision to resume anticoagulation should be based on the patient's individual risk-benefit profile. This involves assessing the risk of recurrent thromboembolism and the risk of recurrent bleeding.
- Alternative anticoagulants: In some cases, it may be appropriate to switch to an alternative anticoagulant that has a lower risk of GI bleeding. For example, DOACs have a lower risk of GI bleeding compared to warfarin.
- Surveillance and follow-up: Patients who have had GI bleeding while on anticoagulants should be closely monitored for signs of recurrent bleeding and managed accordingly. They should also receive appropriate follow-up care to ensure that their anticoagulant therapy is optimized.

It is important to note that the management of GI bleeding in patients on anticoagulants should be individualized based on the patient's clinical presentation, comorbidities, and the specific anticoagulant used. Therefore, the guidelines should be used as a framework for clinical decision-making rather than as strict rules.

Pathogenesis of anticoagulant associated bleeding

- Loss of vascular integrity.
- micro bleeds (HTN- subcortical bleeds , amyloid associated- lobar hemorrhage).
- mechanical cause- (trauma, tumor, thrombosis).
- Endothelial cell dysfunction- sepsis, hypoxia etc.

Risk Factors [4]

Patient Related Risk Factors	Risk Factor Related To Anticoagulant
• Age • Sex • Race • Genetic factors. • Comorbidities – liver failure, renal failure, cancer & cancer therapy. • Thrombocytopenia, bleeding disorders, hemophilia & coagulation factor deficiencies. • Prior history of bleeding.	• Class of the drug- (warfarin> DOAC'S). • Dosage. • Initiation of anticoagulation-Pts who have a bleeding episode with in first 3 months of initiation of anticoagulation, have higher risk of bleeding risk in future.
Risk Factors For GI Bleeding • GI tumors. • Prior history of GI bleeding. • Gastro esophageal varices. • Excess alcohol consumption. • Gastritis, peptic ulcer disease etc. • Concomitant use of antiplatelets & NSAIDS. • Use of chemotherapy agents.	

Gastrointestinal bleeding

- In a Cohort Study , the Incidence of hospital admission for GI bleeding was found to be 115 per 10,000 pt years (1.15 per 100 pt years). [5]

I. Rivaroxaban – 144 per 10,000 pt years.
II. Dabigatran -120 per 10,000 pt years.
III. Warfarin- 113 per 10,000 pt years.
IV. Apixaban- 73 per 10,000 pt years.

- Apixaban had the most favourable GI bleeding profile and rivaroxaban had the least favourable GI safety profile. The clarification of age-related increase in GI bleeding among all DOACs is particularly important.

Gastric protection

Gastric protection with Proton Pump Inhibitor (PPI) is better than H2 blocker.

In 2022, meta-analysis of 6 observational studies & 1 randomized trial that included pts receiving anticoagulation, showed a reduced risk of GI bleeding with the use of PPI's. (RR- 0.67) & this risk reduction was greatest in individuals with higher baseline risk of GI Bleeding such as use of NSAIDS, GI tumor etc.[6]

A retrospective cohort study done in 2018, that included >1.6 million patients receiving an anticoagulant, found that PPI co-therapy was associated with a lower risk of hospitalization for gastrointestinal bleeding (incidence rate ratio [IRR] 0.66, 95% CI 0.62-0.69).Bleeding requiring hospitalization was most likely with rivaroxaban.[7]

Periprocedural Management of Patients on Anticoagulation

Following factors need to be investigated.

- Estimation of thromboembolic risk
- Estimation of bleeding risk.
- Decide on whether to interrupt anticoagulation.
- Timing of Interruption of anticoagulation.

Estimation of thromboembolic risk [8]
High thrombotic risk • Recent venous thromboembolism (3 months) • Severe thrombophilia- deficiency of protein c, protein s, antithrombin, antiphospholipid antibodies. • AF- CHADS2- Score 5-6 (or) CHA2DS2VASc Score7-9, recent stroke(3 months), rheumatic valvular disease. • Any mitral valve prosthesis.
Moderate thrombotic risk • VTE in past 3-12 months. • Non severe thrombophilia – heterozygous factor 5 Leiden mutation etc. • CHADS2 score 3-4, or CHA2DS2VASc score 4-6 • Bi-leaflet aortic valve prosthesis with h/o AF, or IHD, Congestive heart failure etc.
Low thrombotic risk • VTE – 12 MONTHS • CHADS2 score 0-2 or CHA2DS2VASc Score0-3 • Bi-leaflet aortic valve prosthesis without any risk factors for stroke.

- Reversal of anticoagulation.

Estimation of bleeding risk.
High risk procedures • Esophagogastroduodenoscopy (EGD) with variceal ligation. • EGD with esophageal dilation. • Percutaneous endoscopy gastrostomy tube placement etc. • Colonoscopy with polypectomy of large polyp >1cm • ERCP with biliary or pancreatic sphincterotomy. • EUS with FNA • PEG/ PEJ placement • RFA/ Tumor ablation
Low risk procedures • Upper GI endoscopy including mucosal biopsy. • Colonoscopy including mucosal biopsy. • ERCP without sphincterotomy. • ERCP with biliary stent placement etc • Balloon dilatation of luminal stenosis • EUS without FNA • Video capsule endoscopy

Interrupting Anticoagulation [9,10]

WARFARIN

Pts with low to moderate risk of thromboembolic events- • Discontinue warfarin- 5 days prior to procedure. • Confirm INR <1.5 On the day of procedure. • Restart warfarin on the evening of the day of procedure, provided good haemostasias is achieved. • Bridging is generally not needed for pts at low risk of thromboembolic events. Pts undergoing sphincterotomy – high risk of bleeding • Restart warfarin after 3 days. • DOACS- after 5 days.	**High risk patients** • Discontinue warfarin – 5 days prior to the procedure • Bridging with heparin. • Unfractionated heparin > low mol wt heparin. • INR <1.5 on the day of procedure.
Management of acute bleeding 1. For patients on warfarin who are hospitalized or under observation with acute GI bleeding, we suggest against fresh frozen plasma (FFP) administration (conditional recommendation, very low certainty of evidence). 2. For patients on warfarin who are hospitalized or under observation with acute GI bleeding, we suggest against the use of vitamin K (conditional recommendation, very low certainty of evidence).	

DOACS

- Short half lives.
- Bridging therapy is not required.
- **Dabigatran** – 12 to 17hrs- (2.5 to 3.5 days after the last dose). 80-85% renal
- **Rivaroxaban**- 5 to 9hrs – (1-2 days after the last dose). 35% renal
- **Apixaban** – 8 to 15hrs – (1.5 to 3 days after the last dose). 25% renal
- **Edoxaban** – 6 to 11hrs – (1.3 to 2 days after the last dose). 35% renal.
- Anticoagulation is assumed to be fully resolved after 5 half lives.

Patients undergoing low risk procedure	**Patients undergoing high risk procedures**
• Stop DOACS, 48hrs prior to procedure and restart 48hrs after the procedure. • Usually no bridging required.	• Stop DOACS, 48hrs prior to procedure • Bridging is not required for DOACS- rapid onset of action • Restart DOACS after **5 days**.

Management of acute bleeding

- Dabigatran – **Idarucizumab**- 5mg (2.5 mg vials iv bolus or infusion)
- Rivaroxaban, apixaban, edoxaban- **Andexanate alfa**
- Low dose- 400 mg bolus at 30 mg/ min f/b 480 mg at 4mg/min, over 120 min.
- High dose- 800 mg iv bolus at 30 mg/min f/b 960 mg infusion at 8mg/min.
- Prothrombin complex concentrate (PCC).
- 4 Factor PCC

Conclusion

GI bleeding is a significant source of morbidity among patients initiating anticoagulation and is one of the key issues to consider when assessing the risk–benefit trade-offs. This is especially important among the elderly, as GI bleeding often has a poor prognosis and can significantly affect quality of life. As DOACs become more commonly prescribed among patients with AF, assessing the risk of GI bleeding becomes more critical. Individualizing treatment preferences based on patient indication, age, and preference for anticoagulation is practical in choosing appropriate anticoagulant for patients after incorporating other information about the safety, efficacy, and effectiveness of these agents, as well as their cost and patients' preferences regarding anticoagulant therapy.

1. Husted S.,Lip G.Y.,De C Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH: comment.J Thromb Haemost. 2015; 13: 2130-2132
2. Desai N.R,Krumme A, Schneeweiss S.et al.Patterns of initiation of oral anticoagulants in patients with atrial fibrillation- quality and cost implications.Am J Med. 2014; 127: 1075-1082
3. Abraham N.S.,Singh S.,Alexander G.C.et al.Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. BMJ. 2015; 350: h1857
4. Holster I.L, Valkhoff V.E.,Kuipers E.J. et al.New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis.Gastroenterology. 2013; 145: 105-112
5. Ray WA, Chung CP, Murray KT, et al. Association of Oral Anticoagulants and Proton Pump Inhibitor Co therapy With Hospitalization for Upper Gastrointestinal Tract Bleeding. JAMA. 2018;320(21):2221–2230.
6. Kurlander JE, Barnes GD, Fisher A, Gonzalez JJ, Helminski D, Saini SD, Sengupta N, Yang YX, Scheiman J, Laine L. Association of Antisecretory Drugs with Upper Gastrointestinal Bleeding in Patients Using Oral Anticoagulants: A Systematic Review and Meta-Analysis. Am J Med. 2022 Oct;135(10):1231-1243.
7. Ray WA, Chung CP, Murray KT, Smalley WE, Daugherty JR, Dupont WD, Stein CM. Association of Oral Anticoagulants and Proton Pump Inhibitor Cotherapy With Hospitalization for Upper Gastrointestinal Tract Bleeding. JAMA. 2018 Dec 4;320(21):2221-2230.
8. Abraham NS, Hartman C, Richardson P, et al. Risk of lower and upper gastrointestinal bleeding, transfusions, and hospitalizations with complex antithrombotic therapy in elderly patients. Circulation2013;128:1869-77.
9. Hippisley-Cox J, Coupland C. Predicting risk of upper gastrointestinal bleed and intracranial bleed with anticoagulants: cohort study to derive and validate the QBleed scores. BMJ2014;349:g4606
10. Abraham, N S. Barkun, A N Sauer,B G et al American College of Gastroenterology-Canadian Association of Gastroenterology Clinical Practice Guideline: Management of Anticoagulants and Antiplatelets During Acute Gastrointestinal Bleeding and the Periendoscopic Period. The American Journal of Gastroenterology 117(4):p 542-558, April 2022

Anticoagulation In Renal Disease

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Introduction- cardiovascular events in chronic kidney disease

Chronic kidney disease (CKD) is defined as a persistent (>3 month) decline in renal function, culminating in end stage renal disease (ESRD) when the estimated glomerular filtration rate (eGFR) is less than 15 mL/min/1.73 m^2. It is estimated that almost a tenth of the world's population are suffering from CKD, with an estimated jump of about 40% in incidence over the last three decades.[1]

Risk for venous thromboembolism (VTE) is two to three times greater in patients with chronic kidney disease (CKD) than the general population[2]. Nephrotic syndrome is associated with an additional risk of upto 44% for thromboembolic events,[3,4] with the risk being highest for the initial one month after diagnosis.[5] The prevalence of atrial fibrillation (AF) in CKD is three times as much as in the general population. Risk of AF remains high despite being initiated on hemodialysis or undergoing renal transplant.[6,7] Moreover, a study reported three times higher risk of progression of CKD to ESRD in patients with coexisting chronic AF.[8] Reduced GFR and proteinuria have been reported as independent risk factors for poor cardiovascular outcomes.

As many as half the deaths in the CKD population have been attributed to cardiovascular disease.[9,10] Anticoagulation, hence, ideally should have been extensively studied in CKD and ESRD patients. However there is a general dearth of information and guidelines about safety, dosing and indications for anticoagulation in people with impaired renal function.

The conundrum of conflicting pathophysiology

ESRD is a peculiar situation where the patient is in both a prothrombotic state as well as a pro hemorrhagic state. Hypercoagulable (prothrombotic) state is thought to be due to altered prothrombotic particles like thrombin, due to reduced levels of antithrombin III. Hypoalbuminemia induces hepatic synthesis of amino acids which includes prothrombotic proteins like prothrombin 1, prothrombin 2, fibrinogen, and tissue factor.

Activation of RAAS and altered vessel wall contractility due to chronic inflammation provides a nidus for emboli to lodge. A coexistent heart disease increases risk for atrial fibrillation and, thereby, thrombus generation.

A pro-hemorrhagic state is much simpler to explain. CKD is known to have platelet dysfunction, producing lesser levels of procoagulants like thrombaxane A_2 and platelet activating factor. Oxidative stress due to chronic inflammation causes platelet inactivation.

There is impaired platelet adhesion and aggregation because of increased levels of fibrinogen (because of uremia), compromised function of GPIIb/IIIa receptor complex, and defective interaction of GPIIb with von Willebrand factor on the defective endothelium. Anemia which is very common in CKD causes decreased ADP release and inactivation of prostaglandin I_2. Extrinsic factors like drugs (concomitant antiplatelets, NSAIDs and certain antibiotics like cephalosporins), injection of systemic heparin during hemodialysis, platelet activation at dialyzer membrane etc all add up to the prothrombotic state in a patient of CKD, and more so, ESRD.

About 20 lakh people are estimated to be on maintenance hemodialysis (MHD) worldwide.[11] Patients on MHD are at a greater risk for both thrombosis and hemorrhage. Access devices like catheters and fistula grafts provide an active nidus for thrombus formation, with regular manipulation with needles only amplifying that risk. Systemic anticoagulation with heparin with each dialysis session puts them at an additional risk for developing significant hemorrhage and complications associated with heparin use like heparin induced thrombocytopenia or osteoporosis.

Anticoagulants and altered pharmacokinetics with impaired renal clearance

1. Vitamin K antagonists

The prototypical drug warfarin is one of the oldest and most studied among anticoagulants. Vitamin K antagonists deactivate clotting factors II, VII, IX, and X. American heart association (AHA) recommends use of warfarin in all stages of CKD.[12] Dosage is guided by the patient's INR, with therapeutic range being 2 to 3 for most indications. Clinicians generally prefer using the ‘start low go slow’ approach in initiating warfarin.

However in CKD its narrow therapeutic index, long half life and unpredictable dosage provide challenges to regular use. Warfarin also has a variable response, depending on various factors like diet and drug interactions, vitamin K deficiency, and volume status variations of the individual.[13]

2. Direct oral anticoagulants (DOACs)

They inhibit either thrombin (dabigatran) or factor Xa (apixaban rivaroxaban and edoxaban). They have a shorter half life, and are generally safer than warfarin. Most of them are cleared by the renal pathway and hence need dose adjustment. Few randomised controlled trials have demonstrated the benefit of DOACs over Warfarin in reduction in the number of fatal side effects in the general population as well as in CKD stages 1 to 3. Dose in CKD stages 4 and 5 remains uncertain. Many landmark trials that recommend the dose of DOACs have strictly excluded patients with a GFR less than 30 mL/min.

3. Parenteral anticoagulants

Unfractionated heparin (UFH) is the oldest drug of this group. It is preferred because of its short half life and easy availability. Dosing is generally the same for CKD patients like in the normal population. Long term usage might warrant reduction in dose by a third in ESRD to prevent complications, and can be accurately monitored based on target aPTT level (usually 1.5 to 2).[14,15]

Low molecular weight heparins (LMWH) like dalteparin and enoxaparin are gaining popularity because of their predictable pharmacokinetics, lesser dosage frequency, and monitoring-free usage. However dose reduction is needed in late stages of CKD (with GFR less than 30 mL/min). Anti-Xa level can be monitored to optimise the level of LMWH with 0.1 to 0.3 IU/mL being recommended for prophylaxis and 0.4 to 1.0 IU/mL for therapeutic dose.[16] Fondaparinux is a factor Xa inhibitor (heparinoid) which can be used in patients of CKD, who develop heparin induced thrombocytopenia.[14]

Pharmacokinetics of common anticoagulants[13,17]

DRUG	TARGET	HALF LIFE (hours)	RENAL ELIMINATION	DIALYSABLE
Warfarin	Vit K dependent clotting factors	40	nil	No
Dabigatran	Thrombin (direct)	12-17	80%	Yes
Apixaban	Factor Xa (direct)	12	27%	Partial
Rivaroxaban	Factor Xa (direct)	5-9	66%	No
Edoxaban	Factor Xa (direct)	10-14	50%	No
Heparin	Xa and IIa, via AT III	1 to 1.5	Negligible	Partial
LMWH	Factor Xa (selective)	3-6	Main route	Partial
Fondaparinux	Factor Xa (indirect)	17-21	Main route	Partial

Table 1: Pharmacokinetics of common anticoagulants

Suggested dosing in reduced GFR as per KDIGO and ESC[18,19,20]

DRUG	eGFR 30-59 mL/min	eGFR 15-29 mL/min	eGFR <15 mL/min or On MHD
Warfarin	Adjust to INR 2-3	Adjust to INR 2-3	Adjust to INR 2-3
Dabigatran	110-150 mg BID	Consider 75 mg BID	Not recommended
Apixaban	2.5 mg to 5 mg BID	Consider 2.5 mg BID	Consider 2.5 mg BID
Rivaroxaban	15 mg QD	consider 15 mg QD	Unknown
Edoxaban	30 mg QD	Consider 30 mg QD	Not recommended
Heparin	As per indication and regimen chosen	As per indication and regimen chosen	Dose may be reduced by 30% for loading, then as per aPTT
Enoxaparin	1 mg/kg BD	1 mg/kg QD	1 mg/kg QD
Fondaparinux	50% of recommended dose (of 2.5 to 10 units SC QD)	Not recommended	Not recommended

Table 2: Suggested anticoagulant dose in renal impairment

Indications of anticoagulation in patients with impaired GFR

1. Nephrotic syndrome

Nephrotic syndrome (NS) is a clinical complex characterised by proteinuria exceeding 3 g/day. Hypoalbuminemia and reduced oncotic pressure seem to be independent risk factors for cardiovascular adverse effects, causing people with NS to have poor cardiovascular outcomes. Among various causes of nephrotic syndrome like minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and membranous nephropathy (MN), MN has a higher risk of thrombosis due to non selective proteinuria and increased loss of anticoagulants in urine. Around 10% of adults and 2% of children with nephrotic syndrome can have one clinical episode of thromboembolism.[21]

An update from KDIGO in 2021[21] expands upon the targets for anticoagulation in NS. Therapeutic anticoagulation is indicated in those that have had an event like venous thrombosis, arterial thrombosis or pulmonary emboli in the past or those with non valvular AF. Intravenous UFH is recommended, later to be bridged to oral warfarin (target INR between 2 and 3). Oral Xa inhibitors and direct thrombin inhibitors have not been systematically studied enough to formulate guidelines as they have high albumin binding properties which makes dosing in hypoalbuminemia difficult.

Prophylactic anticoagulation is recommended for those with the following risk factors for adverse cardiovascular effects- serum albumin < 20-25 g/L, proteinuria > 10 g/d, BMI > 35 kg/m^2, heart failure with NYHA class III/IV, a genetic disposition for thromboembolism, recent orthopaedic or abdominal surgery and expected prolonged immobilisation. Recommended drug is subcutaneous UFH at 5000 U twice daily with LMWH as an alternative option. In case of people with high bleeding risk, an alternative is to give a single antiplatelet (aspirin) as prophylaxis.

Contraindications to anticoagulation include bleeding diathesis, history of GI bleed, and mutations that impair warfarin metabolism.

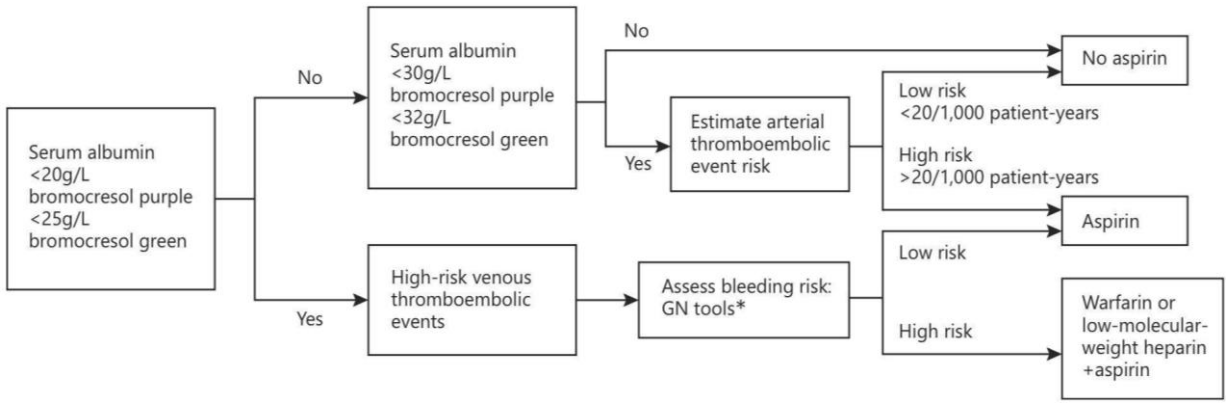

Figure 1: Recommendations in nephrotic syndrome

2. Non-valvular AF

AF in kidney disease is associated with both increased cardiovascular risks in the form of thromboembolism and faster progression of CKD itself. Oral anticoagulants are recommended for patients with GFR upto 30 mL/min by a number of statutory bodies like European Heart Rhythm Association (EHRA),[23] American Heart Association (AHA)[24] and by KDIGO conference update. Warfarin is the preferred drug, however DOACs are non inferior.

For stage 4 CKD, while warfarin remains the recommendation by both guidelines, DOACs are not formally recommended. EHRA and KDIGO guidelines 'suggest' that they can be used. U.S. FDA and European Medical Agency have approved low dose dabigatran (75 mg twice a day) in stage 4 CKD, although the same hasn't been reflected in the guidelines as of this writing.

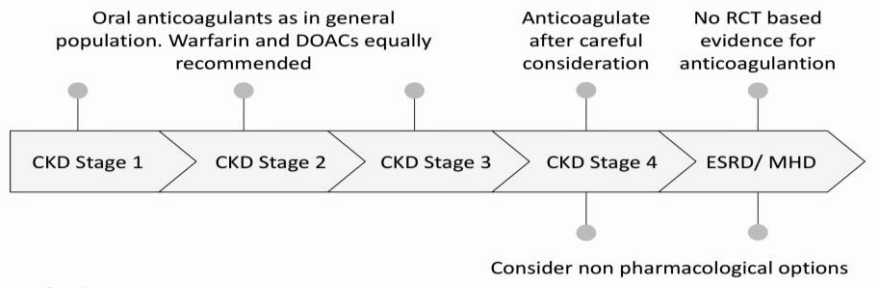

Figure 2: Recommendations in non valvular AF in patients of CKD

Patients with ESRD or on MHD were excluded from most of these studies. There are no randomised control trial based recommendations for anticoagulants in these patients. KDIGO Controversies Conference did not find enough 'high quality' evidence to warrant recommending warfarin as a preventive measure of stroke in those with non-valvular AF on hemodialysis.[25] However, an AHA update in 2019 says warfarin and apixaban can be used, but that further studies were warranted. Newer trials are currently on going in this regard, namely AXADA (comparing apixaban and warfarin in ESRD and AF), RENAL AF (evaluation of apixaban versus warfarin in patients on hemodialysis with AF), and AVKDIAL (studying the cumulative incidence of severe bleeding or thrombosis in ESRD with AF on warfarin).[26]

3. Hemodialysis

Not using anticoagulation during HD has a reported risk of tubing thrombosis of upto 10% and subsequent blood loss of upto 150 mL. Routinely used anticoagulant is heparin. It can be administered as a single bolus at the start of HD, as repeated boluses, or as a bolus followed by continuous infusion based on patient requirement and bleeding risk. In order to achieve an ideal balance between anticoagulation and risk of bleeding during HD, especially during prolonged sessions like SLED and CRRT, it is recommended to monitor the effect of heparin by ACT (activated clotting time) keeping a target ACT of 80% above the baseline. For all its ease of use and universal availability, heparin is not without its share of complications like HIT. LMWH and fondaparinux were featured in successful studies but are still limited in clinical practice by their lack of widespread availability and high costs. Another alternative in HD is Regional Citrate Anticoagulation (RCA) where blood is mixed with trisodium citrate in the extracorporeal circuit. Citrate chelates ionic calcium (factor V of coagulation cascade) from the blood, thereby interrupting the coagulation process and prevents thrombosis. Calcium chloride is again infused to the patient separately in a continuous fashion to prevent hypocalcemia.

Problems with anticoagulant use in patients of CKD

1. Complications with warfarin

a. Calciphylaxis

Inhibition of vitamin K by warfarin also inhibits a protein called matrix G1a, which has a role in prevention of vascular calcification. Matrix G1a is dependent on vitamin K dependent carboxylation for effective functioning. In end stage renal patients with an excess calcium and phosphorus burden, vascular calcification is associated with poorer cardiovascular and renal outcomes.

b. Anticoagulant nephropathy

A specific adverse effect that has been studied with warfarin is presence of a biopsy proven nephropathy occurring more frequently in those with CKD[(27)]. It is an unexplained increase in creatinine by atleast 0.3 mg/dL within 7 days of INR reaching atleast 3. It is postulated to be due to glomerular microhemorrhages and tubular obstruction with hematic cylinders. In CKD patients, it carries a mortality of above 30% in one year.[(28)]

c. Skin necrosis

It is seen in the first week of therapy due to subcutaneous necrosis because of an acquired protein C deficiency. It occurs more commonly in those with innate protein C or protein S deficiency. Management includes vitamin K and FFP administration apart from prompt withdrawal of warfarin.

d. Purple toe syndrome

It is a late complication, developing 3 to 8 weeks after initiation of therapy. It is thought to be due to cholesterol microemboli getting lodged in the end vessels of peripheral circulations of hands and feet. Management involves stopping warfarin.

2. Complications with heparin

a. Heparin induced thrombocytopenia (HIT)

Use of heparin has traditionally been associated with thrombocytopenia in some cases. Two distinctive forms of HIT have been described. Type 1, where thrombocytopenia is dose dependent and predictable, is usually benign and can be reversed by stopping heparin. The more dangerous clinically is type 2 which is due to autoantibodies against platelet factor 4 (PF-4) in susceptible which causes consumption thrombocytopenia and widespread embolic phenomenon. It carries higher mortality risk than type 1. Treatment for type 2 remains symptomatic and prompt changeover to fondaparinux. Warfarin can be an alternative once thrombocytopenia resolves.

b. Miscellaneous

Dyslipidemia can occur due to activation of lipoprotein lipase. Anaphylactoid reactions are mostly limited to pruritus. Life threatening respiratory distress or hypotension is reported, but rare. Osteoporosis is well known with long term heparin use. Aldosterone is sometimes suppressed, causing hyperkalemia. Warfarin should be withdrawn should suspicion arise for any of these conditions.

3. Practical issues with anticoagulants

a. Bleeding manifestations

Although anticoagulants tend to be under-dosed in patients with renal impairment, overdosing can occur because of a variety of reasons leading to unwanted bleeding. It can range from simple derangement of coagulation parameters which just requires withholding of the drug, to life threatening intracranial bleeds needing transfusion of blood products.

b. Therapeutic drug reversal

Use of specific antidotes is useful in severe bleeding complications. Fresh frozen plasma, recombinant factors VIIa and VIII are useful as general stabilizers. Vitamin K orally (2.5 to 5 mg as a single dose) or parenterally (10 mg intravenous in three doses 12 hours apart) is given for warfarin overdose. Idracusizumab and protamine sulphate are specific antidotes for dabigatran and heparin respectively. Hemodialysis is reportedly useful for dabigatran overdose.[13] Andexanet alfa is useful for rivaroxaban and apixaban.

c. Difficulty in dosing in acute worsening of renal clearance

For those patients of chronic kidney disease presenting with an acute kidney insult due to any reason, need for anticoagulation and dosing tend to change. Maintaining a balance between benefit and risk becomes difficult. Most centers implement switching over to UFH when a patient on anticoagulation gets admitted with an acute illness.

Newer avenue- factor XI as a potential therapeutic target

Majority of available guidelines and recommendations focus on vitamin K antagonists, heparin or DOACs.[29] Among the lesser studied targets is factor XI. It is a component of the intrinsic coagulation cascade, activated by factor XIIa. It is understood to play a role in amplification of thrombus that is already formed than in hemostasis actively.[30] In people with congenital deficiency of factor XI, it was found that the risk of bleeding diathesis was milder when compared to hemophilia.[31] It is therefore speculated that selective therapeutic blockade of factor XI might have lesser risk of fatal bleed than by conventional anticoagulants. A number of phase 2 clinical trials are underway aimed at factor XI blockers like milvexian, asundexian, osocimab, abelacimab. There are trials targeted at CKD population namely EMERALD[32] (ISIS 416858), RE-THINC[33] (BAY 2976217, and CONVERT[34] (osocimab), which aim at testing the safety and tolerability of this group of drugs in those with renal failure.

Conclusion- the known and the unknown

That patients with CKD and especially those with nephrotic syndrome are at an increased risk of developing thromboembolic complications is well known. Treatment of such complications once they occur is fairly straightforward, with drugs and dosing established. It is in the context of prophylactic anticoagulants where there is most indecision. There is a widespread under-dosage in prescribing maintenance anticoagulants in renal disease, primarily because of non availability of standard guidelines in severe renal impairment. Studies which include CKD stages 4 and 5 need to be conducted and recommendations updated. Initiation of anticoagulation in ESRD is still a debatable issue. Trials with newer agents like factor XI inhibitors and safety of anticoagulants in patients undergoing hemodialysis are close to finishing, and will hopefully yield much needed data in this field of uncertainty.

References

1. Bikbov B, Purcell CA, Levey AS, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020; 395:709–733.
2. Molnar AO , Bota SE , McArthur E, et al. Risk and complications of venous thromboembolism in dialysis patients. Nephrol Dial Transplant 2018; 33:874–80.
3. Llach F. Hypercoagulability, renal vein thrombosis, and other thrombotic complications of nephrotic syndrome. Kidney Int. 1985; 28:429 –39.
4. Rankin AJ, McQuarrie EP, Fox JG, Geddes CC, MacKinnon B, Scottish Renal Biopsy R. Venous thromboembolism in primary nephrotic syndrome - is the risk high enough to justify prophylactic anticoagulation? Nephron. 2017;135:39 –45.
5. Christiansen CF, Schmidt M, Lamberg AL, et al. Kidney disease and risk of venous thromboembolism: a nationwide population- based case control study. J Thromb Haemost. 2014; 12:1449–54.
6. Lau YC, Proietti M, Guiducci E, et al. Atrial fibrillation and thromboembolism in patients with chronic kidney disease. J Am Coll Cardiol. 2016; 68:1452-1464.
7. Liao JN, Chao TF, Liu CJ, et al. Incidence and risk factors for new onset atrial fibrillation among patients with end-stage renal disease undergoing renal replacement therapy. Kidney Int. 2015; 87:1209-1215.
8. Soliman EZ, Prineas RJ, Go AS, et al. Chronic Renal Insufficiency Cohort Study Group Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). Am Heart J. 2010; 159:1102-1107.
9. US Renal Data System. USDRS quarterly update: 2020. Available at: https://www.usrds.org/esrd-quarterly-update/

10. Bansal N. Use of oral anticoagulation for patients with ESRD on hemodialysis with atrial fibrillation: verdict 1. Clin J Am Soc Nephrol. 2016; 11:2093–2094.
11. Thomas B, Wulf S, Bikbov B, et al. Maintenance dialysis throughout the world in years 1990 and 2010. J Am Soc Nephrol. 2015; 26:2621–2633. doi: 10.1681/ASN.2014101017.
12. Bhatia HS, Hsu JC, Kim RK. Atrial fibrillation and chronic kidney disease: a review of options for therapeutic anticoagulation to reduce thromboembolism risk. Clin Cardiol. 2018; 41:1395-1402.
13. Jain N, Reilly RF. Clinical pharmacology of oral anticoagulants in patients with kidney disease. Clin J Am Soc Nephrol. 2019; 14(2):278-287.
14. Hughes S, Szeki I, Nash MJ, et al. Anticoagulation in chronic kidney disease patients- the practical aspects . Clin Kidney J 2014; 7:442–9.
15. Aursulesei V, Costache, II. Anticoagulation in chronic kidney disease: from guidelines to clinical practice . Clin Cardiol 2019; 42:774–82.
16. Arepally GM . Heparin induced thrombocytopenia. Blood 2017; 129:2864–72.
17. Lutz J, Jurk K, Schinze H, et al. Direct oral anticoagulants in patients with chronic kidney disease: patient selection and special considerations. Int J Nephrol Renovasc Dis. 2017; 10:135-143.
18. Konstantinides SV, Torbicki A, Agnelli G, et al. ESC guidelines on the diagnosis and management of acute pulmonary embolism. The task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Endorsed by the European Respiratory Society (ERS). Eur Heart J. 2014, 2014; 35:3033-3080.
19. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation – Web Addenda. Task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016; 37(3):267–315.
20. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with STsegment elevation. The task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018; 39:119–177.
21. Rovin BH, Adler SG, Barratt J, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney International 2021; 100:S1–276. doi: 10.1016/j.kint.2021.05.021.
22. Chan KE, Edelman ER, Wenger JB, et al. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. Circulation. 015; 131:972–979. doi: 10.1161/CIRCULATIONAHA.114.014113.
23. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018; 39:1330–93.

24. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ ACC/HRS Guideline for the Management of Pa- tients With Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guide- lines and the Heart Rhythm Society. J Am Coll Cardiol 2019; 74:104–32.
25. Turakhia MP, Blankestijn PJ, Conference Participants, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Eur Heart J. 2018; 39:2314–2325.
26. Nigwekar SU, Thadhani R. Long-Term Anticoagulation for Patients Receiving Dialysis. Circulation 2018; 138:1530–3. doi: 10.1161/circulationaha.118.037091.
27. Brodsky SV, Satoskar A, Chen J, et al. Acute kidney injury during warfarin therapy associated with obstructive tubular red blood cell casts: a report of 9 cases. Am J Kidney Dis 2009; 54:1121–6.
28. Potpara TS, Ferro CJ, Lip GYH. Use of oral anticoagulants in patients with atrial fibrillation and renal dysfunction. Nat Rev. 2018; 14:337-351.
29. Krüger T, Floege J. Vitamin K antagonists: beyond bleeding. Semin Dial. 2014; 27:37–41.
30. Weitz JI, Chan NC. Advances in antithrombotic therapy. Arterioscler Thromb Vasc Biol. 2019; 39:7–12.
31. Gomez K, Bolton-Maggs P. Factor XI deficiency. Haemophilia. 2008; 14:1183–1189.
32. Ionis Pharmaceuticals Inc. A study of ISIS 416858 administered subcutaneously to participants with end-stage renal disease on hemodialysis (EMERALD). Available at: https://clinicaltrials.gov/ct2/show/ NCT03358030.
33. Bayer. Factor XI LICA to reduce events such as heart attack and stroke in patients whose kidneys are no longer able to work as they should and require treatment to filter wastes from the blood: focus is on the safety of BAY2976217 and the way the body absorbs, distributes and removes the study drug (RE-THINc ESRD). Available at: https://clinicaltrials.gov/ct2/show/NCT04534114.
34. Bayer. Study to investigate the safety of a drug called osocimab at low and high doses in adult patients with kidney failure requiring regular hemodialysis (CONVERT). Available at: https://clinicaltrials.gov/ct2/show/NCT04523220.

Occupational Asthma :The Orphan of Indian Pulmonology - A brief Review

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Introduction :

Bronchial asthma affects a large number of people globally. It causes not only persistent morbidity, but also some degree of mortality.

Occupational asthma(OA) is a type of asthma that is related to exposure to substances at the workplace. Historically, Bernardino Ramazzini, the Italian physician (1633 – 1714), who has a treatise on asthma. He is hailed as the father of Occupational asthma. He noted that persons exposed to food grains suffered from asthma. The purpose of this review is to create an enquiring approach to the possibility of OA' this is the very first step.

There are two major mechanisms that cause OA. First is due to exposure to allergens at the workplace, sensitisation leading to immune mediated airway inflammation and bronchospasm. The other type is non-immune irritant reactions; this is based on the neurological pathway. This short review examines this entity. It is important in the contest that mostly asthma can only be alleviated by various therapeuticmeasures. In the case of OA, early diagnosis and cessation of continued exposure might result in total cure for the given individual.

What causes OA ?

Some common causes of OA are noted below

Job	Asthma triggers
Bakers, farmers	Cereal grains
Animal handlers , Vets	Animal proteins
Forest workers	Wood dust Eg Cedar wood dust
Metal workers	Cobalt, nickel
Painters, foam rubber welders, plastics, latex	
Epoxy resins	Chemicals

The most common causes are wood dust, grain dust, animal dander, fungi or chemical substances. Over 300 agents have been noted to cause OA at the global level. The immune mediated OA is mostly after a latent period of exposure to the offending agent. Work done by Kobayashi in Japan madeus interested in this area.

Prior to1985, we noted no example of occupational asthma were reported. A preliminary study was done in two small towns with one with no silk industry and the study group with two silk factories as the major industry. We noted that the control group had a prevalence of 4.2 % among men and women. The study group had a 12.5% prevalence of presumed OA.

A systematic study was then taken up, with a Doctoral PhD candidate. Field visits were performed after getting permission from the state -run silk filatures and informed consent by the owners of private cottage industries. At the workplace we had a proforma to collect needed data from the workers. Special reference to past or current pulmonary issues. In order to diagnose allergy to the silk antigens, these were prepared from the pupa and from the sericin. These allergens were used by performing skin prick tests on the control subjects and those with asthma. The degree of reactivity was noted. Serum samples from controls and the asthma subjects were collected. They were analysed for silk protein IgE levels in the control and asthma subjects. Peak flow rate was measured in the asthma subjects. The clinical setting was that the women weaving the silk thread were exposed to the hot water ; the thread was rolled on to the equipment .

Aerosol inhalation was likely in these conditions. In the grainages , where the seeds are developed in a disease-free environment. Tin this atmosphere too there is exposure to the fine dust emanated by the silk-worm moths. Here too, the individual might get sensitised and get OA later.

The study we conducted in 1984-1986 involved two silk centres – Kollegal and Ramanagara. The summary of the results are as follows.

A clinical survey in these silk filatures in Karnataka, revealed that 36.2 % of the study population engaged in processing of natural silk were suffering from bronchial asthma. A total of 16.9% of the total subjects had OA related to silk allergens. Skin prick tests with using crude silkworm cocoon and pupal antigen extracts, revealed that 28.8% of the subjects were sensitive to silkworm derived allergens. IgE antibodies specific to both cocoon and pupal allergens were demonstrable by Radio-allegro-sorbent test (RAST) .Another troubling situation we noted that infants and children were also inadvertently exposed to the offending allergens. Having diagnosed OA, need to find a solution to mitigate asthma morbidity. The ideal solution of total avoidance to allergen exposure was not feasible due to economic considerations. This holds true for both the state run and private setups for silk production. We tried to get conventional medications for asthma both oral and inhaled.This gave some but transient relief.

As mentioned earlier, there are a large number of potential OA causing agents in various industries. If some of these are examined in detail after taking a comprehensive history, there is a possibility of cessation of exposure. The need of collaborative applied research with the clinician and basic scientists. We hope young pulmonologists can do original work which is needed.

It has to be understood that this area of asthma is difficult because in large industries, the problem of compensation arises with confirmed diagnosis of OA. Thus both state run and private small industries are hesitant to cooperate.

References

1. Harindranath N, Prakash Om, Subba Rao PV. Prevalence of occupational asthma in silk filatures Ann. Allergy, 1985 Sep; 511-5

2. 2 Gowda G, Anagha M, Vijaeendra, Nagaraj C. A study of occupational asthma among workers of silk filatures in South India.Indian J Occup Environ Med 2014 May-Aug; 18(2)64-67
3. 3 Uragoda C G, Wijecoon P N B, Occupational Medicine 1991 41; 140- 142
4. Occupational Asthma – Symptoms and Causes – Mayo Clinic, 03-May-2022 www.mayoclinic.org >20375772

JOURNAL SCAN

Section Editors

Dr Chakrapani M

Dr B.Sadananda Naik

Summaries of important published articles

Aspirin or Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture

Major Extremity Trauma Research Consortium (METRC). Aspirin or low-molecular-weight heparin for thromboprophylaxis after a fracture. N Engl J Med 2023; 388:203-213.

In this pragmatic, multicentre, randomized, noninferiority trial the patients with extremity fractures that had been treated operatively or with any pelvic or acetabular fracture, thromboprophylaxis with aspirin was noninferior to low-molecular-weight heparin in preventing death and was associated with low incidences of deep-vein thrombosis and pulmonary embolism and low 90-day mortality.

Common Symptoms That Precede Diagnosis of Parkinson Disease

Bledsoe IO et al. Functional impairment preceding Parkinson disease diagnosis — What's in a prodrome? JAMA Neurol 2022 Dec 19; [e-pub]. (https://doi.org/10.1001/jamaneurol.2022.4157.

In this case-control study, researchers focused on functional impairment prior to PD diagnosis, to gain a better understanding of prodromal or unrecognized PD. The study revealed that the patients who eventually received PD diagnoses were three times more likely to report problems with balance. The study emphasized the inclusion of prodromal PD in the differential diagnosis when older patients report problems with mobility, strength, and balance.

Efficacy of antidepressants in chronic pain

Ferreira G E, Abdel-Shaheed C, Underwood M, Finnerup N B, Day R O, McLachlan A et al. Efficacy, safety, and tolerability of antidepressants for pain in adults: overview of systematic reviews BMJ 2023; 380 :e072415 doi:10.1136/bmj-2022-072415

In this overview of systematic reviews sourced from PubMed and many other data bases, the authors have found the efficacy of antidepressants in most of the chronic pain is inclusive and suggest that a more nuanced approach is needed when prescribing antidepressants for pain.

Comparison of torsemide with furosemide to reduce all-cause mortality in heart failure following hospitalization

Mentz RJ, Anstrom KJ, Eisenstein EL, et al. Effect of Torsemide vs Furosemide After Discharge on All-Cause Mortality in Patients Hospitalized With Heart Failure: The TRANSFORM-HF Randomized Clinical Trial. JAMA. 2023;329(3):214–223. doi:10.1001/jama.2022.23924

This is an open-label, pragmatic randomized trial that recruited 2859 participants hospitalized with heart failure (regardless of ejection fraction) at 60 hospitals in the United States. Among patients discharged after hospitalization for heart failure, torsemide compared with furosemide did not result in a significant difference in all-cause mortality.

Can thiazides prevent kidney stones?

Dhayat, Nasser A., et al. "Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence." New England Journal of Medicine 388.9 (2023): 781-791.

Thiazide diuretic agents are widely used for prevention of the recurrence of kidney stones. In this double-blind trial, researchers randomly assigned patients with recurrent calcium-containing kidney stones to receive hydrochlorothiazide at a dose of 12.5 mg, 25 mg, or 50 mg once daily or placebo once daily. Among patients with recurrent kidney stones, the incidence of recurrence did not appear to differ substantially among patients receiving hydrochlorothiazide once daily at a dose of 12.5 mg, 25 mg, or 50 mg or placebo once daily.

Publications of our members for this Quarter

Books

Dr Sadananda naik et al.

Pocket book of Poisoning protocols : Indian Society of Toxicology 1St Edition 2023

Medical Journals

Dr. Sadananda naik et al.

1. B Sadananda Naik When nurses break the rules in a patient's best interests British Journal of Nursing VOL. 32, NO. 4 | Comment normal https://doi.org/10.12968/bjon.2023.32.4.166

2. Sadananda Naik B, C S Jyothi, Sangram Biradar A Case of Contact Dermatitis to Venomous Snake J.Assoc Physicians India Feb 2023: 71: 96

3. *Naik S. B.* ***On Being a Physician to Celebrities!*** APIK J Int Med 2023;11(2):135-136 DOI: 10.4103/ajim.ajim_86_22

Dr. Archith Boloor et al.

1. Reiner RC Jr. A Boloor ; LBD Triple Burden Collaborators; Hay SI. The overlapping burden of the three leading causes of disability and death in sub-Saharan African children. **Nat Commun.** 2022 Dec 6;13(1):7457. doi: 10.1038/s41467-022-34240-6.
2. GBD 2019 Snakebite Envenomation Collaborators. Global mortality of snakebite envenoming between 1990 and 2019. **Nat Commun.** 2022 Oct 25;13(1):6160. doi: 10.1038/s41467-022-33627-9
3. Haeuser E, Serfes AL, , Boloor A, Dwyer-Lindgren L; Local Burden of Disease sub-Saharan Africa HIV Prevalence Collaborators. Mapping age- and sex-specific HIV prevalence in adults in sub-Saharan Africa, 2000-2018. **BMC Med.** 2022 Dec 19;20(1):488. doi: 10.1186/s12916-022-02639-z.

AUTHOR INSTRUCTIONS

API DK LAHARI is a quarterly published magazine of API D. K. Chapter, released in print version and on the www.apidk.org website with archival options of all the issues released stored in PDF format (each issue) also with a download option. The magazine will include academic and non-academic articles. The languages included will be English and Kannada.

We are hopeful that this will give a unique opportunity to all API members to share their vision and views on various aspects of our profession and beyond.

Submission Email Id: **editorapidk2020@gmail.com**

Instructions on preparation of the manuscript to be submitted

1. Manuscript may be in English/Kannada.

2. Font size -12 (Times New Roman), double spacing, 1.5 inches margins all around the page.

3. All the write-ups should include a Title page with author information

4. Title Page should contain the following: Full name/names of all the authors with contact address, cell number, email id, designation, position in the Institution and a passport-sized recent photo

Paper/write up categories

1. Scientific articles
2. Member‘s accomplishments
3. Obituaries
4. News and Views
5. Residents corner
6. Viewpoint
7. Medico legal pearls
8. Journal Watch
9. Patient page

10. Listen to the legend
11. Life beyond medicine [Non-medical topics]
12. General health articles [more for lay public]

SCIENTIFIC ARTICLES

- ✦ Case reports
  - Word count- 1500, Maximum of 03 tables & or figs, 07 Refs
- ✦ Review article
  - Word count- 3500, Maximum of 5 tables or figs
- ✦ Academic challenge
  - An interesting case presentation with detailed academic discussion
  - Abstract, word count -3500, Maximum of 5 tables or figs
- ✦ Diagnostic test and interpretation
  - Word count- 1500
- ✦ Images in Medicine
  - Photos with good resolution and quality, Word count -500
- An abstract is required for case report, Review article, Academic Challenge, and Diagnostic test and interpretation.
- Word count is inclusive of abstract.
- References should be in Vancouver style.
- ✦ Member's accomplishments
  - Brief information by self or others on the accomplishments of our API members in profession, public life, academics and other walks of life .Word count- 1000
- ✦ Obituaries
  - Condolence message and short write up on the deceased member, One message -500 words
- ✦ News and Views
  - Write up on medical happenings with an opinion expressed , Word count -1000

- ✦ Resident's corner
  - Medical articles by postgraduates/interns
  - Word count as per the criteria mentioned for the scientific articles by the members
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  - Write up on various problems or happenings in the field of medicine or medical profession
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  - Articles on medical-legal aspects including the consumer protection act and other acts applicable to the medical profession . No word limits
- ✦ Journal Watch
  - Short summary of recent journal articles .No word limits