National Academy of Medical Sciences (India)
NAMS House, Ansari Nagar New Delhi-110029

NAMS National Virtual Graduated Medical CME(Navigate Medico CME) Programme

Navigate Medico CME

For Students (MD,MS,DNB)
Two Hours Online Session
Theme: Effective Management of Common Hematological disorders

National Academy of Medical Sciences (India)

Diagnosis and Management of VTE

Lt Gen Velu Nair, PVSM, AVSM, VSM** (Retd)

MD(Med), FRCP (London) , FRCP (Glasgow) FACP (USA), FICP, FAMS, FIACM, FUICC (UK), FISHTM,

Group Head- Medical Services

&

Chief Consultant – Haematto-Oncology & Bone Marrow Transplant

Apollo HOSPITALS CBCC

The next frontier of Cancer Care

Ahmedabad, India

Saturday, 3rd Jun 2023

OUTLINE

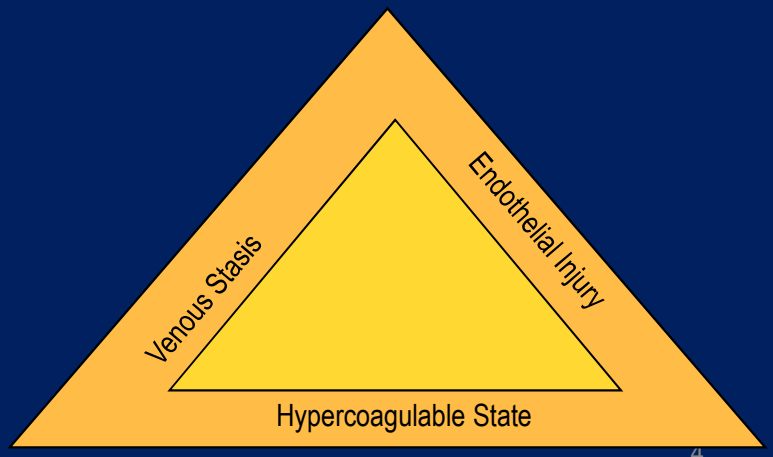
1. History & Incidence and of VTE
2. VTE in India
3. Complications of VTE
4. Thromboprophylaxis
5. Diagnostics & Approach to a case of VTE
6. CAT & CRT
7. DOACS
8. COVID-19 and VITT
9. High Altitude and Thrombosis

HISTORY

Discoveries and developments in the field of DVT		
First descriptions	The Raoul story (Guillaume de Saint Pathus)	1271
Understanding DVT's physiopathology	Wiseman Alteration of blood	1676
	Hunter Vein occlusion by blood clot	1793
	Virchow Relationship between DVT and PE and its famous triad?	1856
Discovery and development of anticoagulants	Haycraft Hirudin	1884
	Mclean and Howel The true heparin	1916 1937
	Charles and Scott Pure heparin	1933
	Link Dicoumarol /Warfarin	1941 1948
Modern molecules	LMWH	1982[1]
	New oral anticoagulants	1996

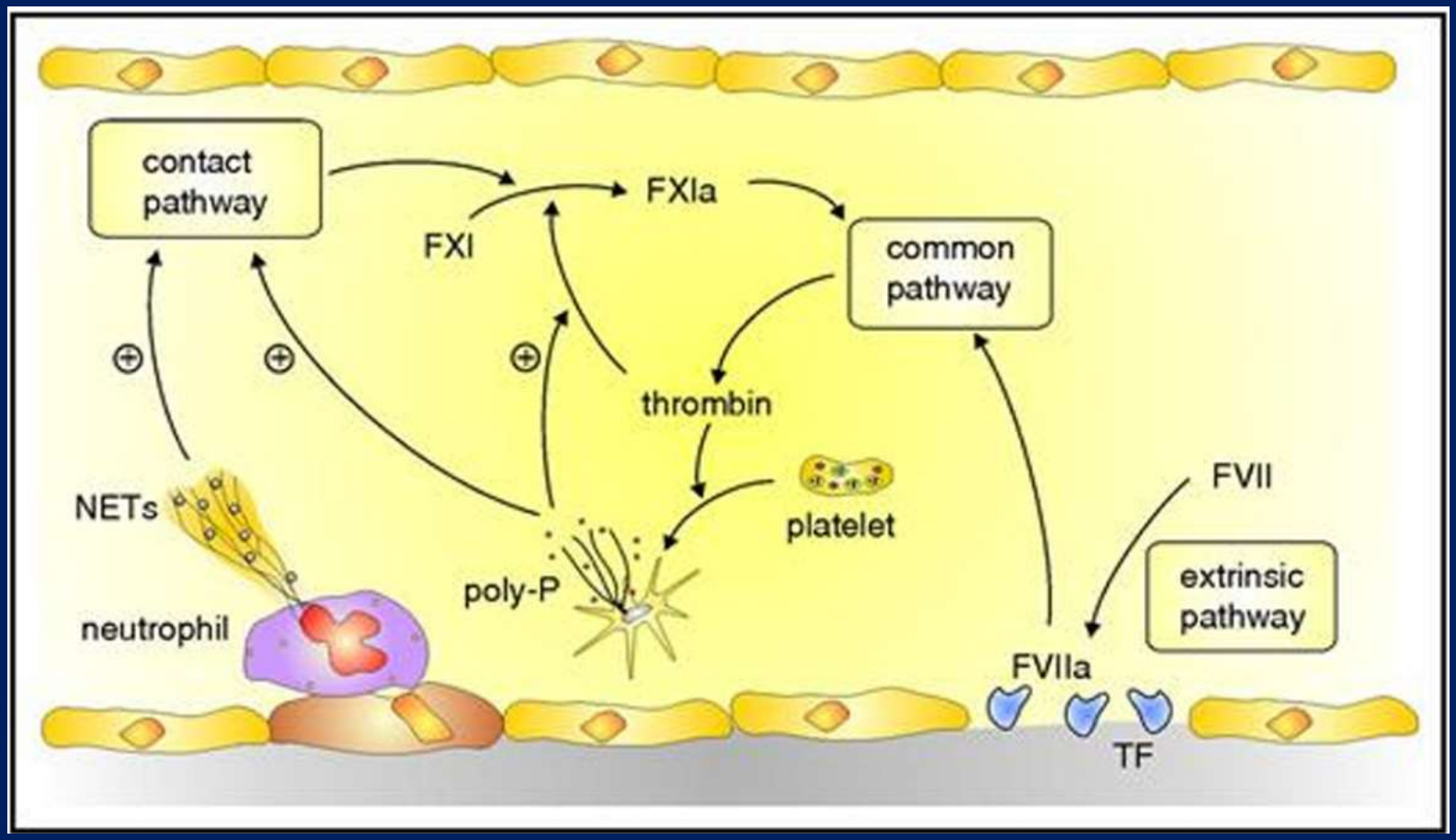
1. J Clin Prev Cardiol2017;6:125-6.

Rudolf Virchow
(1821–1902)
Courtesy of the National Library of Medicine.



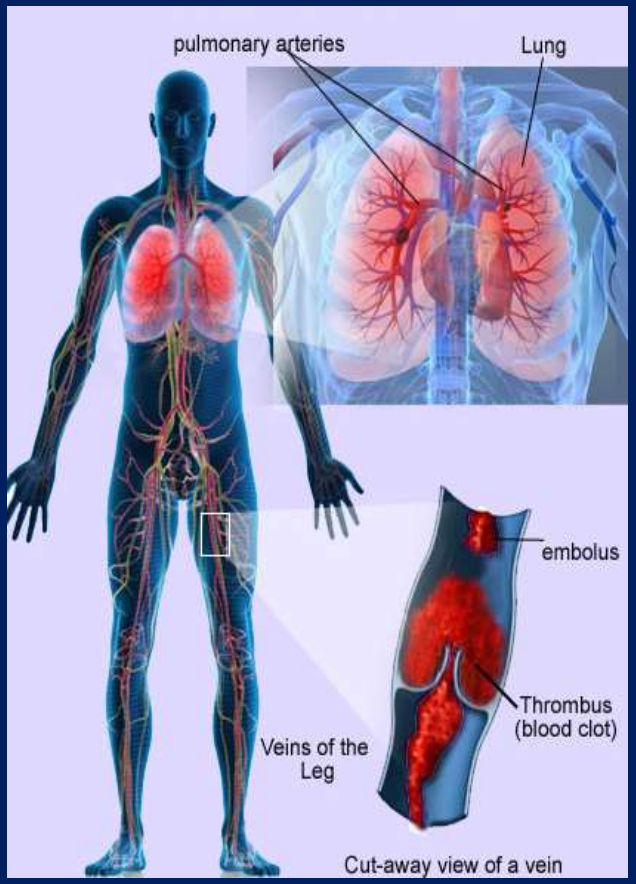
Virchow's triad

Initiators of coagulation



Noel C Chan et al F1000Research 2020, 9(Faculty Rev):1206

Venous Thrombo Embolism : VTE



Pulmonary Embolism

When DVT BLOOD CLOT breaks off and travels from vein of the leg to lungs

Deep Vein Thrombosis

BLOOD CLOT in the leg

VTE

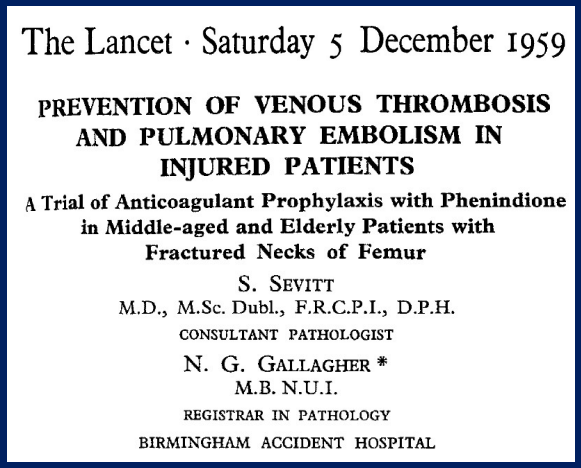
A Major Disease Burden

Wendelboe AM, Raskob GE Circ Res. 2016 Apr 29;118(9):1340-7.

1959: First Study of Oral Anticoagulant in Hip Fracture Patients

1. Elderly hip fracture patients (N=300)
2. Treatments
   1. Oral anticoagulation (n=150)
   2. Controls (n=150)

3. **Total mortality reduced 40%**
   1. Pulmonary embolism was the cause of death in 8% in the oral anticoagulant group vs 26% in the control group



The Lancet · Saturday 5 December 1959

PREVENTION OF VENOUS THROMBOSIS AND PULMONARY EMBOLISM IN INJURED PATIENTS

A Trial of Anticoagulant Prophylaxis with Phenindione in Middle-aged and Elderly Patients with Fractured Necks of Femur

S. SEVITT
M.D., M.Sc. Dubl., F.R.C.P.I., D.P.H.
CONSULTANT PATHOLOGIST
N. G. GALLAGHER *
M.B. N.U.I.
REGISTRAR IN PATHOLOGY
BIRMINGHAM ACCIDENT HOSPITAL

The evidence indicates that **phenindione** effectively prevents thrombosis in veins and eliminates the risk of pulmonary embolism in patients under its influence provided that the drug is given early, for sufficient time, and under laboratory control.

Sevitt S and Gallagher NG. *Lancet.* 1959; ii: 981-989

DVT/PE

1. In 1970s DVT treated , more as a local disorder and treated as a Surgical problem !!

2. Now DVT is considered as a Systemic disorder !

3. Multidisciplinary approach : Clinical Hematologist / Cardiologist / Critical Care Spl / Vascular Surgeon

4. DVT Clinics

Estimated incidence of venous thromboembolism by age, race, and gender

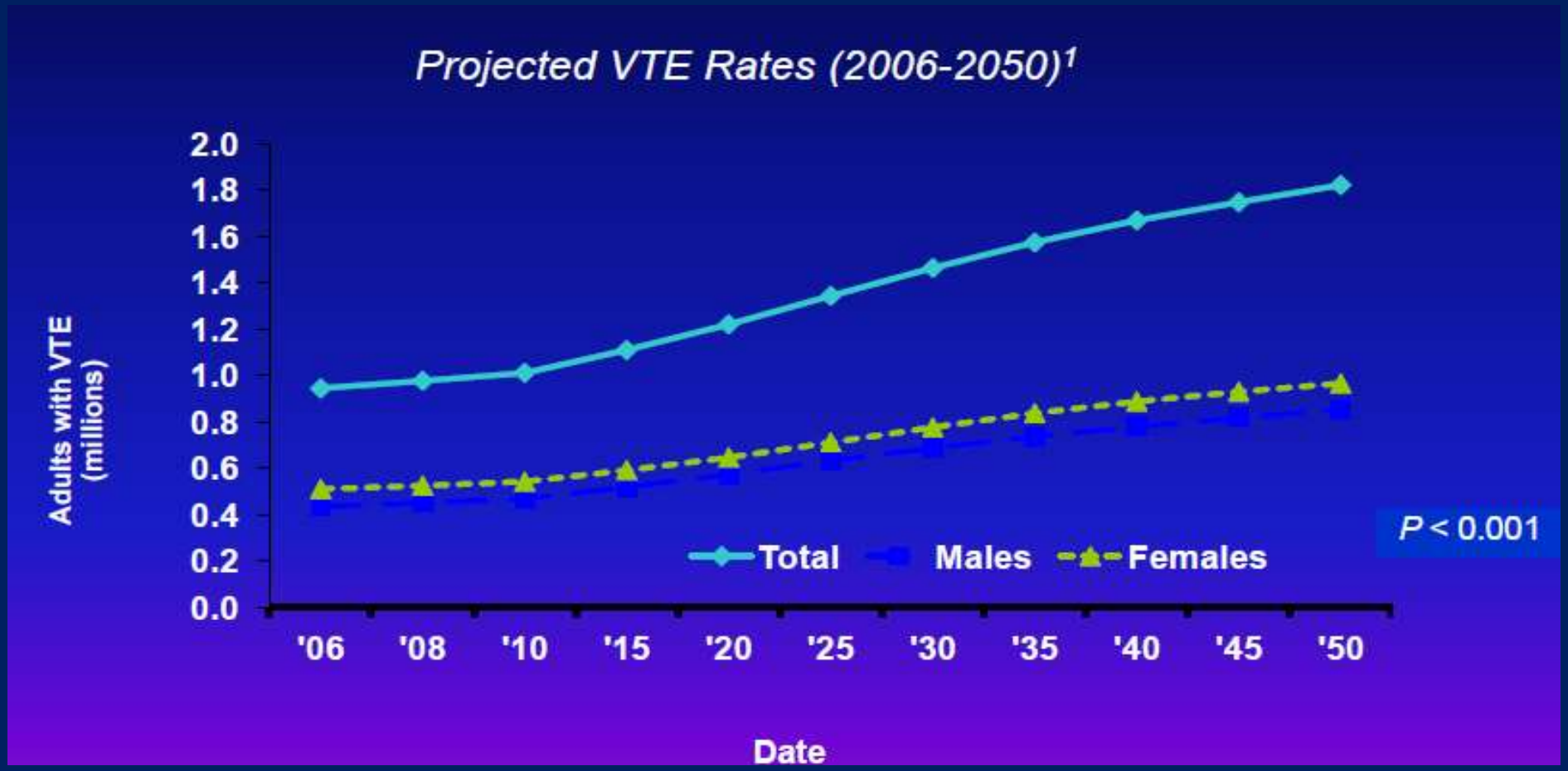
Characteristics	Annual incidence per 1000
Race/ethnicity	
White	1.17[3]
Black	0.77[6]–1.41[5]
Hispanic	0.61[7]
Asian	0.29[7]
Age (years)	
<15	<0.5[3,8]
15–44	1.49[3]
45–79	1.92[9]
≥80	5–6[3,4,8,9]
Gender	
Male	1.3[3]
Female	1.1[3]
Overall	1–2[3–5]

- VTE deaths 60,000-100,000
- DVT/PE recurrence in 10 years- 33%.
- Inherited thrombophilias- 5 - 8%

Beckman et al / Am J Prev Med 2010;38(4S):S495–S501

https://www.cdc.gov/ncbddd/dvt/data.html, February 7, 2020

Trends in VTE: Prevalence to Double by 2050



Deitelzweig SB, et al. American J Hematology. 2011 86:217-220.

What are the complications of DVT ?

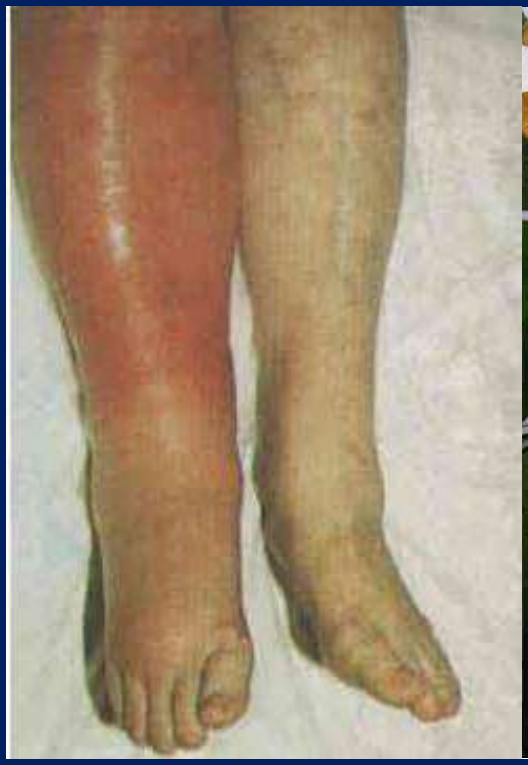
1. **Acute Complications**
    1. PE
    2. Venous Gangrene
2. **30% DVT cases develop symptomatic PE**
3. **50%-60% DVT cases develop asymptomatic PE**

Fatal Pulmonary Embolism is responsible for approx 10% of hospital deaths

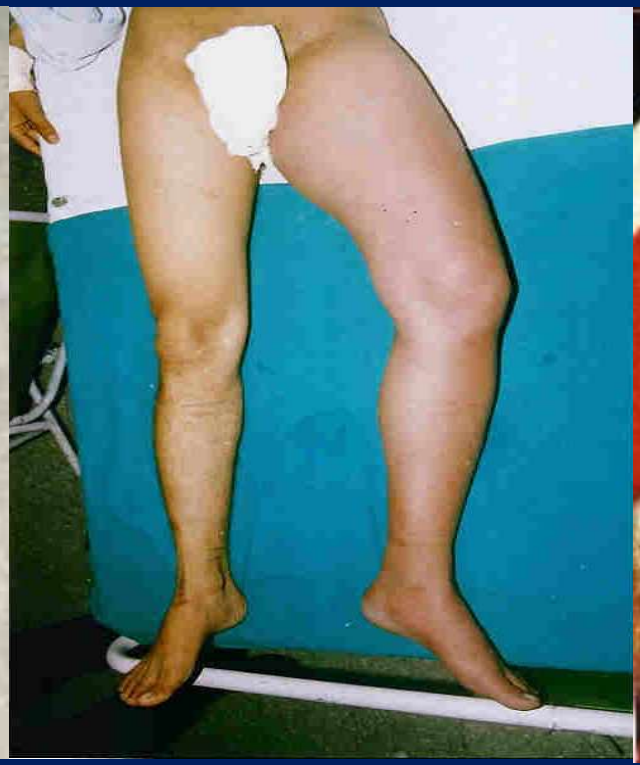
4. **Chronic Complications**
    1. Recurrent VTE
    2. Chronic Pulmonary Arterial Hypertension
    3. Chronic Limb Venous Hypertension :Post Phlebitic Syndrome (PPS).
    4. **PPS varies from 20 to 35% 3 years; 49% at 5 years**

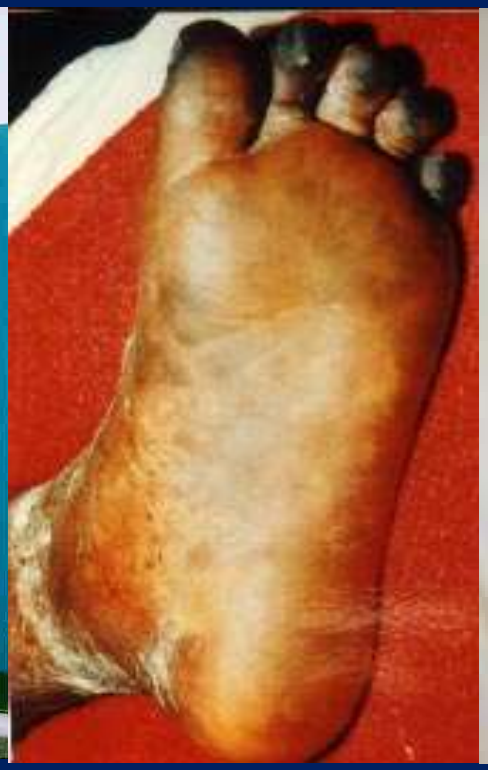
Sandler DA et al, J Royal Soc Med.1989;82:203
O'Donnel J.Surg.Res.1977

Stages of DVT

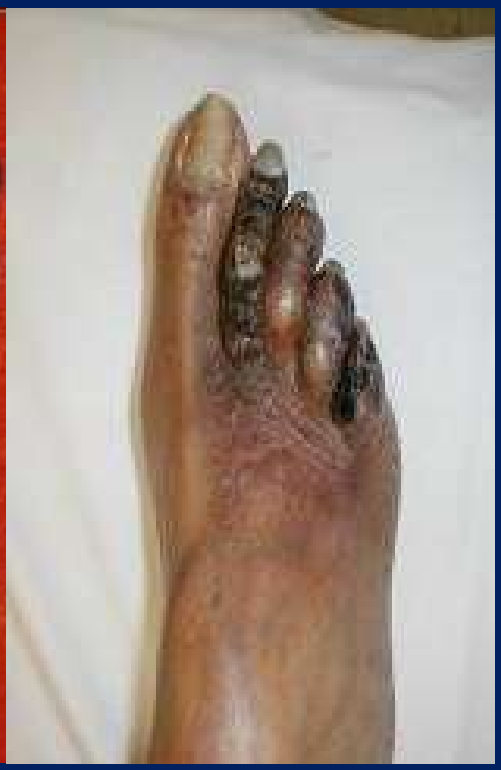


Acute DVT





Symptomatic Acute DVT



Venous Gangrene

Risk of recurrence after a first episode of unprovoked VTE

Risk factors for DVT recurrence		
Proximal DVT location	Male sex	Persistence of residual vein thrombosis at ultrasound
Obesity	Non- O blood group	High D-dimer values
Old age	Early PTS development	Role of inherited thrombophilia is controversial

Clinical prediction rules assessing risk of recurrent VTE after first episode of unprovoked VTE[71]			
Score	**Vienna prediction model**	**DASH score**	**HERDOO-2**
Parameters	• D-dimer level at 3 weeks and 3, 9, 15, 24 months after stopping anticoagulation • Male sex • VTE location (Distal DVT, Proximal DVT, PE)	• Abnormal D-dimer 3–5 weeks after stopping anticoagulation • Male sex • Age<50 years • VTE not associated with oestrogen-progestatif therapy in women	• Abnormal D-dimer before stopping anticoagulation • Post thrombotic symptoms (hyperpigmentation, edema and redness) • Age ≥65 years • BMI ≥30
Validation study	Yes	Yes	Yes
Commentaries	Different nomograms are available to calculate risk of VTE recurrence at different time	Patients with low score (≤1) have an annual recurrence rate of 3.1%	It is applicable in women only. Women with low score (≤1) have an annual recurrence rate of 1.3%

European Heart Journal (2018) 39, 4208–4218

Post-Phlebitic Syndrome (PPS)/Post-Thrombotic Syndrome (PTS)

1. 20-50% PTS develops in DVT patients[1]
2. Reduces QOL & costly to Rx
3. What are the risk factors ?
    1. Raised D-dimer after completion of OAC.
    2. Proximal > Distal DVT
    3. Extensive illiofemoral DVT
    4. Recurrent ipsilateral DVT
    5. Obesity & older age
    6. No-impact of 'heritable thrombophilia'
4. Early ambulation and continued physical activity reduces risk of propagation of DVT or PPS /PTS

Circulation. 2014;130:1636-1661.

Prevention of VTE

Is

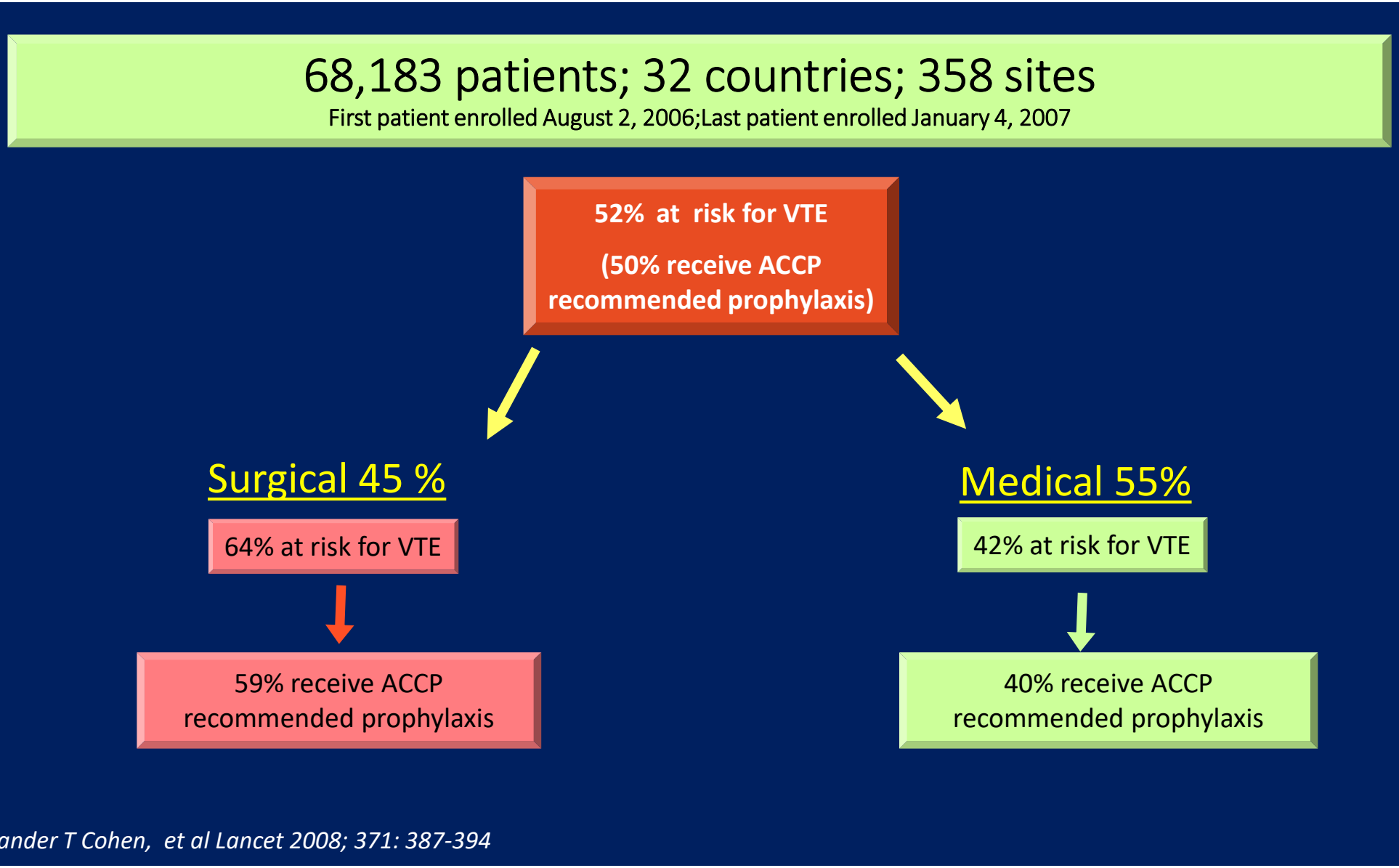
Better Than Cure

VTE Prophylaxis / Thromboprophylaxis

Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study

ENDORSE : WORLDWIDE
(Lancet 2008; 371: 387-394)

Alexander T Cohen, et al Lancet 2008; 371: 387-394

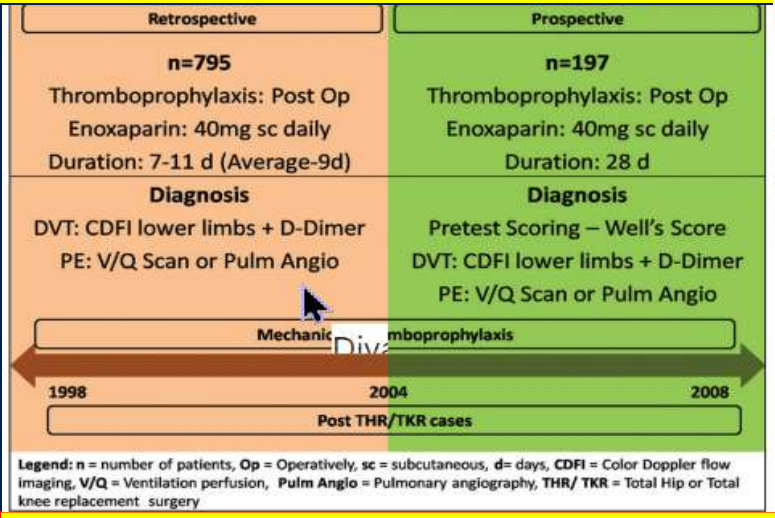

68,183 patients; 32 countries; 358 sites
First patient enrolled August 2, 2006;Last patient enrolled January 4, 2007
52% at risk for VTE
(50% receive ACCP recommended prophylaxis)
Surgical 45 %
64% at risk for VTE
59% receive ACCP recommended prophylaxis
Medical 55%
42% at risk for VTE
40% receive ACCP recommended prophylaxis
Alexander T Cohen, et al Lancet 2008; 371: 387-394

Original Article

Comparative study of extended versus short term thromboprophylaxis in patients undergoing elective total hip and knee arthroplasty in Indian population

Velu Nair, Ratheesh Kumar[1], Bikram Kumar Singh[2], Ajay Sharma[3] Gururaj R Joshi[4], Kamal Pathak[5]

Primary outcome-incidence of VTE



Outcome	Prospective (*n*=197)					Retrospective (*n*=795)				
	Hip		Knee		Total	Hip		Knee		Total
	Unilateral	Bilateral	Unilateral	Bilateral		Unilateral	Bilateral	Unilateral	Bilateral	
DVT	00	00	00	00	00	04	00	02	00	06
PTE	00	00	00	01	01	07	00	11	02	20
VTE	00	00	00	01	01	11	00	13	02	26

0.5% **Vs** **$P < 0.018$** **3.27%**

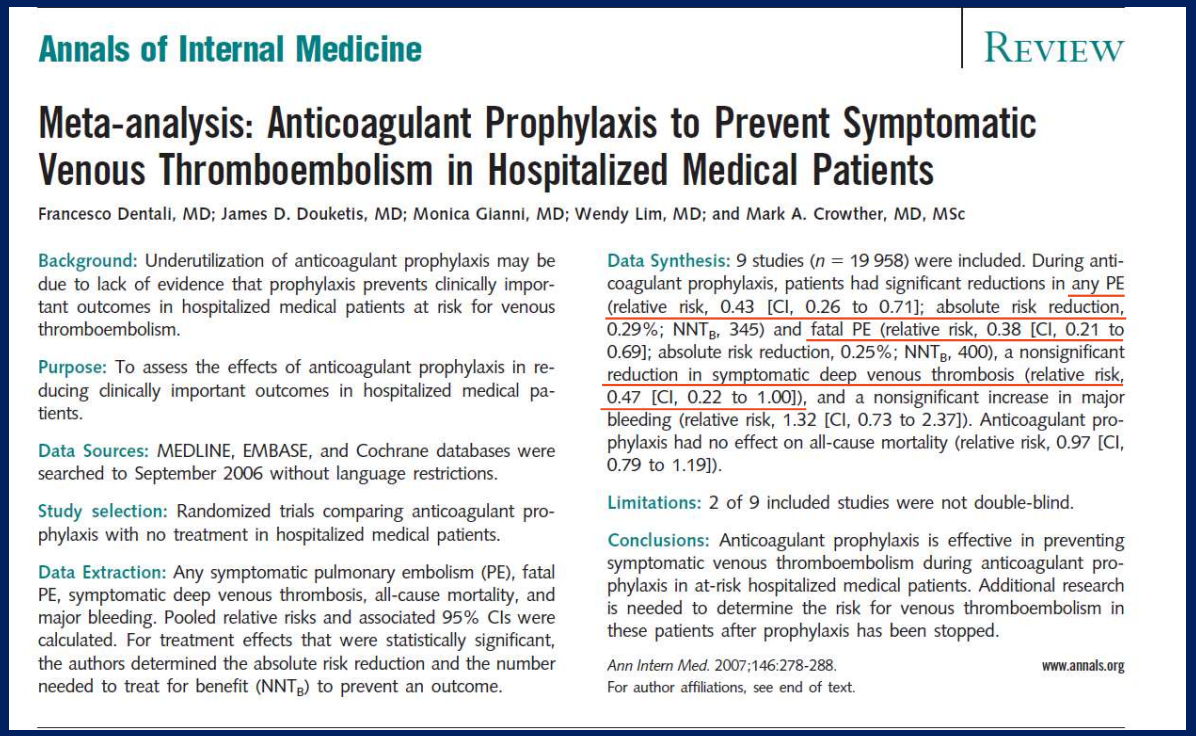
Odds Ratio = 0.15 (95% Confidence Interval = 0.03-0.86) *P* value; DVT = Deep vein thrombosis; PTE = Pulmonary thromboembolism; VTE Venous

Conclusion

Extended thromboprophylaxis (for 4 weeks) was found to be more effective than short term thromboprophylaxis in minimizing the risk of postoperative VTE in patients who underwent THA/TKA.

VTE Prophylaxis in 19,958 Medical Patients, 9 Studies (Meta-Analysis)

1. 62% reduction in fatal PE
2. 57% reduction in nonfatal PE
3. 53% reduction in DVT



Annals of Internal Medicine | REVIEW

Meta-analysis: Anticoagulant Prophylaxis to Prevent Symptomatic Venous Thromboembolism in Hospitalized Medical Patients

Francesco Dentali, MD; James D. Douketis, MD; Monica Gianni, MD; Wendy Lim, MD; and Mark A. Crowther, MD, MSc

Background: Underutilization of anticoagulant prophylaxis may be due to lack of evidence that prophylaxis prevents clinically important outcomes in hospitalized medical patients at risk for venous thromboembolism.

Purpose: To assess the effects of anticoagulant prophylaxis in reducing clinically important outcomes in hospitalized medical patients.

Data Sources: MEDLINE, EMBASE, and Cochrane databases were searched to September 2006 without language restrictions.

Study selection: Randomized trials comparing anticoagulant prophylaxis with no treatment in hospitalized medical patients.

Data Extraction: Any symptomatic pulmonary embolism (PE), fatal PE, symptomatic deep venous thrombosis, all-cause mortality, and major bleeding. Pooled relative risks and associated 95% CIs were calculated. For treatment effects that were statistically significant, the authors determined the absolute risk reduction and the number needed to treat for benefit (NNT_B) to prevent an outcome.

Data Synthesis: 9 studies (n = 19 958) were included. During anticoagulant prophylaxis, patients had significant reductions in any PE (relative risk, 0.43 [CI, 0.26 to 0.71]; absolute risk reduction, 0.29%; NNT_B, 345) and fatal PE (relative risk, 0.38 [CI, 0.21 to 0.69]; absolute risk reduction, 0.25%; NNT_B, 400), a nonsignificant reduction in symptomatic deep venous thrombosis (relative risk, 0.47 [CI, 0.22 to 1.00]), and a nonsignificant increase in major bleeding (relative risk, 1.32 [CI, 0.73 to 2.37]). Anticoagulant prophylaxis had no effect on all-cause mortality (relative risk, 0.97 [CI, 0.79 to 1.19]).

Limitations: 2 of 9 included studies were not double-blind.

Conclusions: Anticoagulant prophylaxis is effective in preventing symptomatic venous thromboembolism during anticoagulant prophylaxis in at-risk hospitalized medical patients. Additional research is needed to determine the risk for venous thromboembolism in these patients after prophylaxis has been stopped.

Ann Intern Med. 2007;146:278-288. www.annals.org
For author affiliations, see end of text.

Dentali F, et al. Ann Intern Med 2007; 146: 278-288

VTE Awareness in 2000s…..2020s…..!

1. Growing interest in VTE's as a public health threat (Covid incl)
2. Publicity increasing in health care professionals; Patient advocacy a reality
3. **Known as the most preventable illness in hospitalized patients.**
4. **Concept of ''DVT –FREE'' hospitals born.**
5. Most States have adopted months for **"Thrombosis Awareness"**
6. Medicare has declared certain DVTs or PEs as "**Never Events**" **and will not reimburse !!**

VENOUS THROMBOEMBOLISM (VTE) STUDY GROUP

Hematology : *Core Group Leader :* **V Nair**, Army Hospital (R&R), Delhi.
MB Agarwal, Bombay Hospital Institute of Medical Sciences, Mumbai. A Bhave, Lilavati Hospital & Research Centre, Mumbai. Lt Col A Sharma, Army Hospital (R&R), Delhi. S Shah, Jaslok Hospital, Mumbai. B George, Christian Medical College Hospital, Vellore. S Apte, Sahyadri Speciality Hospital, Pune.

Surgery : *Core Group Leader :* **A Choudhary**, Sir Ganga Ram Hospital, Delhi.
KS Vijayraghavan, Sri Ramchandra Medical College and Research Institute, Chennai. M Gore, Lokmanya Tilak Municipal Medical College, Mumbai. R Kannan, Cancer Institute, Adyar, Chennai. P Shukla, Tata Memorial Hospital, Mumbai. VK Kapoor, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow. G Srikanth, Manipal Hospital, Bangalore. CV Kantharia, King Edward Memorial Hospital, Mumbai.

Oncology : *Core Group Leader :* **P Jagannath**, Raheja Hospital, Mumbai.
BK Smruti, Lilavati Hospital & Research Centre, Mumbai. TB Yuvaraja, Tata Memorial Hospital, Mumbai. C Ramchandra, Kidwai Memorial Institute of Oncology, Bangalore. S Gupta, Tata Memorial Hospital, Mumbai. BS Awasthy, Batra Hospital, New Delhi.

Vascular Surgery : *Core Group Leader :* **R Parakh**, Sir Ganga Ram Hospital, Delhi
M Patel, Sterling Hospital, Ahmedabad. KR Suresh, Jain Institute of Vascular Sciences, Bangalore. N Shekhar, Apollo Hospital, Chennai. D Kamerkar, Ruby Hall Clinic, Pune. PR Pai, Bombay Hospital, Mumbai. P Patel, Lilawati Hospital, Mumbai. A Johri, Jaslok Hospital, Mumbai. U Vasudeva Rao, Manipal Hospital, Bangalore. N Bhushan, Manipal Hospital, Bangalore. RK Pinjala, Nizam's Institute of Medical Sciences, Hyderabad. N Shastry, Apollo Hospital, New Delhi.

Critical Care : *Core Group Leader(s) :* **RK Mani**, Apollo Hospital, Delhi. **F Kapadia**, PD Hinduja Hospital, Mumbai.
R Bajwa, Regency Hospital, Kanpur. A Sarkar, Peerless Hospital, Kolkata. S Ramasubban, Apollo Gleneagles Hospital, Kolkata. Ramakrishnan, Apollo Hospitals, Chennai.

Orthopedics : *Core Group Leader(s) :* **S Agarwala**, Hinduja Hospital, Mumbai. **R Malhotra**, All India Institute of Medical Sciences, New Delhi.
N Rajgopalan, St. John's Medical College Hospital, Bangalore. PV Vijayaraghavan, Sri Ramchandra Medical College and Research Institute, Chennai. SR Rao, Apurva Hospital, Rajkot. AK Maru, Madhuram Hospital, Rajkot. MS Ghosh, Kothari Medical Centre, Kolkata. MS Diggikar, B.J. Medical College, Pune. A Rajgopal, Fortis Hospital, NOIDA. KJ Reddy, Apollo Hospital, Hyderabad. S Mehta, Advanced Ortho Centre, Thane, Mumbai. PK Banerjee, Peerless Hospital, Kolkata. A Bhattacharya, AMRI Hospital, Kolkata. A Bandyopadhya, Peerless Hospital, Kolkata.

Gynae & Obstetrics : *Core Group Leader :* **SK Ghai** Bhandari, Sir Ganga Ram Hospital, Delhi.
NB Vaid, University College of Medical Sciences & Guru Teg Bahadur Hospital, Delhi. S Mittal, All India Institute of Medical Sciences, New Delhi. H Khullar, Sir Ganga Ram Hospital, Delhi. I Ganguli, Sir Ganga Ram Hospital, Delhi. Tarakeshwari, Fernandez Hospital, Hyderabad. A Maheshwari, Tata Memorial Hospital, Mumbai. P Kumar, Kasturba Medical College & Hospital, Manipal. N Venkatesh, St. Philomenas, Bangalore. N Bhatacharya, Kalyani Hospital, Kolkata. JK Gupta, Apollo Gleneagles, Kolkata.

011-26589791 vte.bms@gmail.com App Login

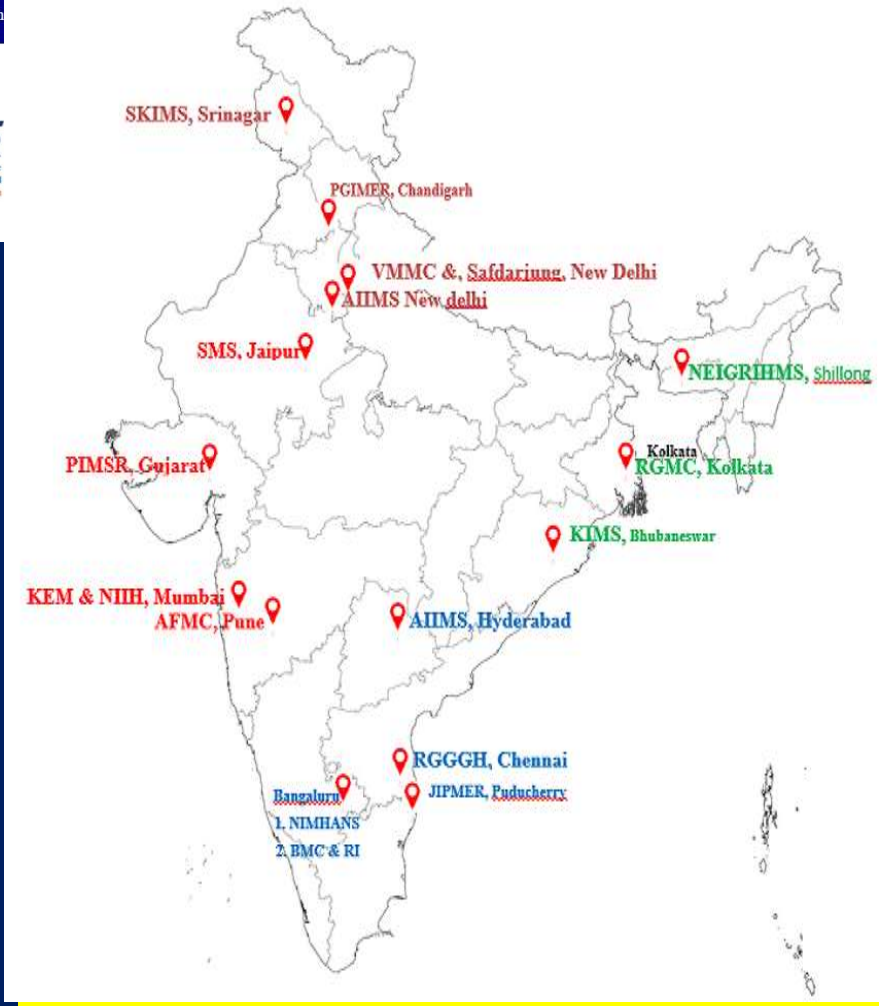
Ministry of Health & Family Welfare

ICMR-National Hospital Based Registry on Venous Thromboembolism Disorders (i-RegVED)

i-ऋग्वेद

ICMR INDIAN COUNCIL OF MEDICAL RESEARCH

1. **National Hospital based Registry on Venous Thromboembolic Disorders** (i-RegVeD) aims to establish a nationwide surveillance network through selected hospitals and collect data for generating evidence on VTE prevalence for planning response, and strengthening healthcare facilities across different treatment settings.
2. This registry is based on standard reporting framework and data capture using electronic information technology for timely analytics of patterns of disease distribution, treatment and outcomes of VTE patients. The data will be used for relevant and appropriate research and innovation



Registered Patient

Total Enrolled Patients= 28

National Academy of Medical Sciences, India
VTE Task Force

1. National Academy of Medical Sciences, India (NAMS) formed a Taskforce to draft a Whitepaper on VTE.
2. The taskforce will make recommendations to the Government of India for prevention and control of Venous Thrombosis and Embolism in India at the health policy and implementation levels
3. Composition of TF
    1. Lt Gen (Dr) Velu Nair (Retd) - ***Chairperson***
    2. Col (Dr) MP Cariappa, (Retd) - ***Secretary***
    3. Dr Pankaj Malhotra
    4. Dr Manisha Madkaikar
    5. Dr Sonia Nityanand
    6. Dr Sukesh Nair
    7. Prof Mohammad Zahid Ashraf


NAMS
Inaugural NAMS Public Oration
On
"Law And Medicine"
by
Shri Justice N.V.Ramana
on
Justice N. V. Ramana
Dr. Shiv K Sarin
President


REPORT OF TASK FORCE
ON
VENOUS THROMBOSIS & EMBOLISM
IN INDIA
NATIONAL ACADEMY OF MEDICAL SCIENCES
2022

Approach to a case of Suspected Venous Thromboembolism (VTE)

Clinical prediction rules (PTP) for DVT:

Wells Score for Leg DVT	
Component	**Points**
Active cancer	1
Localized tenderness	1
Entire leg swollen	1
Calf swelling > 3 cm	1
Pitting edema	1
Collateral superficial veins	1
Previous DVT	1
Bedridden/surgery	1
Paralysis	1
Alternate diagnosis	-2

Score ≥ 3: high PTP (≥ 50% prevalence)
Score 1 to 2: intermediate PTP (~25%)
Score 0 or lower: low PTP (≤ 10%)

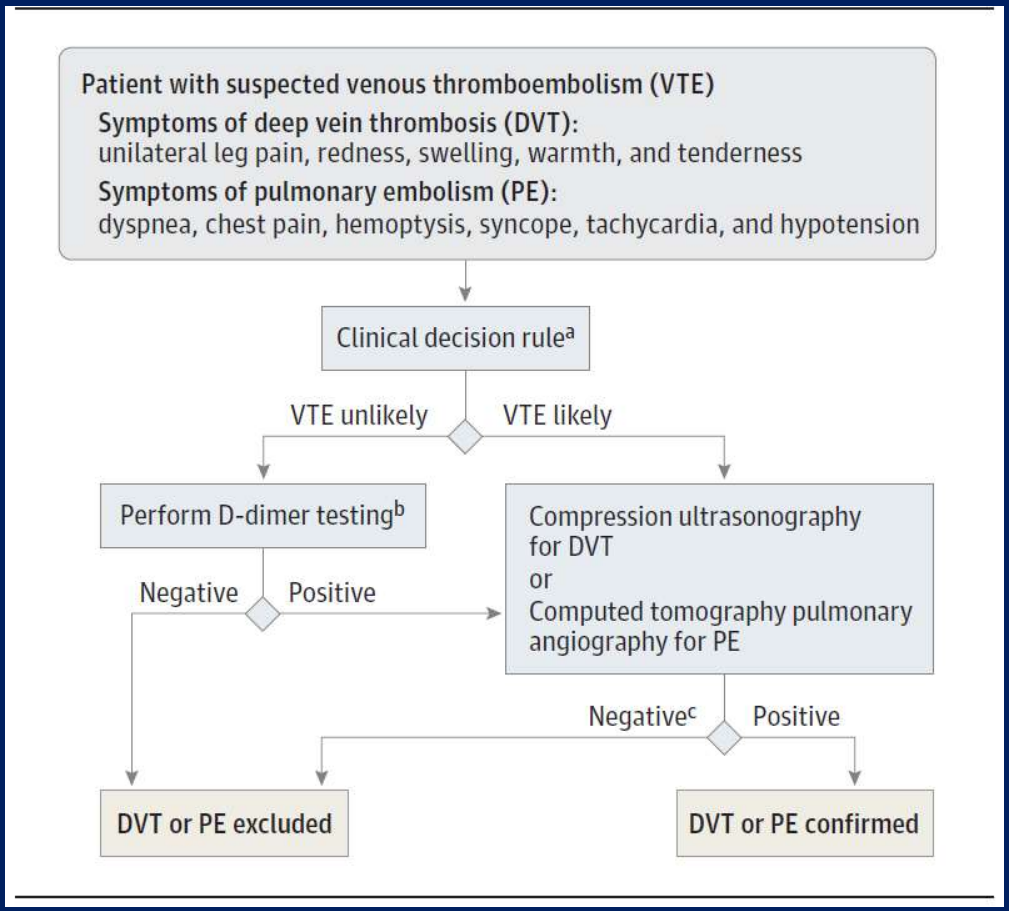
Constans Score for Upper Extremity DVT	
Component	**Points**
Venous material (central catheter, pacemaker)	1
Localized pain	1
Unilateral edema	1
Alternate diagnosis	-1

Score 2 to 3: likely PTP (~40% prevalence)
Score ≤ 1: unlikely PTP (~10%)

PTP-Pretest probability

Wells NEJM 2003
Constans Thromb Haemost 2008
Kleinjan Ann Intern Med 2014

Diagnostic Management of Patients With Suspected DVT or PE



[a]Wells score for suspected DVT and Wells score or revised Geneva score for suspected PE.

[b]Age-adjusted D-dimer threshold, calculated as the patient's age multiplied by 10 ng/mL (fibrinogen-equivalent units) for patients older than 50 years with suspected PE.

[c]Repeat compression ultrasonography 1 week after initially normal finding in patients with high clinical probability and positive D-dimer levels if initial imaging was not whole-leg ultrasonography.

JAMA. 2018;320(15):1583-1594. doi:10.1001/jama.2018.14346

The Sensitivity and Specificity of Various Diagnostic Tests

Test	Sensitivity %	Specificity %
Contrast Venography	97	96-99
Real time B-mode compression Ultrasonography[2]	100	100
Doppler Ultrasonography[3]	99	88
Duplex Ultrasonography [4]		
Symptomatic Proximal DVT	100	98
Symptomatic Distal DVT	94	75
MRI[5]	91.5	94.8
D-Dimer (ELISA)[6]	94	53

1. Am J Neuroradiol 31:527–35 Mar 2010 DOI 10.3174/ajnr.A1869
2. Thromb Haemost . 1993 Sep 1;70(3):404-7.
3. Shahzad et al.; JPRI, 32(18): 1-5, 2020; Article no.JPRI.57641
4. Cardiovasc Ultrasound. 2008; 6: 53.
5. Eur Radiol. 2007 Jan;17(1):175-81.
6. Int J Lab Hem. 2017;39(Suppl. 1):98–103

Q. Significance of D-dimer test in the diagnosis of DVT ?

Central laboratory D-dimer assays frequently used in VTE clinical trials

Assay	DVT sensitivity	DVT specificity
Asserachrom D-dimer	98% (91-100%)	47% (29-65%)
Clearview Simplify D-dimer	100% (92-100%)	48% (43-53%)
Hemosil D-dimer HS 500	100% (85-99%)	45% (41-49%)
Innovance D-dimer	99% (97-99%)	40% (38-40%)
MiniQuant D-dimer	96% (95-98%)	44% (40-47%)
STA-Liatest D-dimer	96% (90-100%)	47% (33-76%)
TinaQuant D-dimer	99% (90-100%)	46% (39-72%)
Vidas D-dimer	100% (82-100%)	42% (37-46%)

DVT Sensitivity 96-100%

DVT Specificity 40-48%

Abbreviations: DDU, D-dimer units; DVT, deep vein thrombosis; FEU, fibrinogen equivalent units.
[a]Values as per Manufacturer Package Insert, FDA Memorandum, and Independent expert comparison. References: 5,26–37. Other studies might report other sensitivities/specificities. Reported ranges represent 95% CI.

Johnson ED, Schell JC, Rodgers GM.The D-dimer assay.Am J Hematol. 2019;94:833–839.

Point-of-care D-dimer assays frequently used in VTE clinical trials

Assays	DVT sensitivity	DVT specificity
LABGEO	99% (93-100%)	53% (38-68%)
Roche Cardiac D-dimer	95% (88-99%)	62% (58-67%)
PATHFAST D-dimer	98% (94-100%)	40% (35-44%)
SimpliRED D-dimer	94% (84-95%)	67% (56-84%)
TRIAGE	97% (93-100%)	48% (44-53%)

Abbreviations: DDU, D-dimer units;
[a]Values as per Manufacturer Packag
other sensitivities/specificities. Repc

ı. References: 5,26–37. Other studies might report

DVT Sensitivity 94-100%

DVT Specificity 40-62%

- Elisa tests more sensitive than Latex & whole blood assays
- Sensitivity more for Proximal DVT
- Extrapolation not possible across methodology

Johnson ED, Schell JC, Rodgers GM.The D-dimer assay.Am J Hematol. 2019;94:833–839.

- Introduction
- Emergency p
- Magnetic res
- V/Q single-ph

V/Q single-photon emission computed tomography (CT)

JAMA. 2018;320(15):1583-1594. doi:10.1001/jama.2018.14346

Major Diagnostic Advances in Venous Thromboembolism

Source	Type of Evidence	No. of Studies	No. of Patients	Diagnostic Management	Conclusion
Clinical Decision Rules					
Singh et al,[22] 2013	Meta-analysis	12	14 844	PERC rule	PERC can safely rule out PE in low-clinical-probability populations.
Penaloza et al,[25] 2017	Cohort	1	1773	PERC rule	PERC may safely rule out PE in patients with low implicit clinical probability in a European setting.
Freund et al,[26] 2018	Cluster randomized trial	1	1916	PERC rule	PERC safely rules out PE in patients with low implicit clinical probability in a European setting.
D-Dimer Testing					
Van Es et al,[16] 2016	Meta-analysis	6	7268	Conventional vs age-adjusted D-dimer threshold	Age-adjusted D-dimer threshold increases proportion of patients in whom imaging can be withheld, and also in high-risk subgroups
Diagnostic Algorithm					
Van der Hulle et al,[27] 2017	Cohort	1	3465	Diagnostic algorithm	YEARS diagnostic algorithm can safely rule out PE.
Imaging for Suspected DVT					
Pomero et al,[28] 2013	Meta-analysis	16	2379	Emergency physician-performed ultrasonography	Emergency physician-performed ultrasonography has a high sensitivity and specificity for diagnosis of DVT.
Abdalla et al,[29] 2015	Meta-analysis	23	1121	Magnetic resonance venography	Magnetic resonance venography is a potential alternative for diagnosis of DVT when ultrasonography is not feasible.
Imaging for Suspected PE					
Da Costa Rodrigues et al,[30] 2016	Meta-analysis	15	6991	Lower limb ultrasonography	Proximal lower limb ultrasonography can confirm but cannot rule out PE.
Squizzato et al,[31] 2017	Meta-analysis	13	1170	Magnetic resonance imaging	Magnetic resonance imaging has high specificity but limited sensitivity for diagnosis of PE, and one-fifth of results are inconclusive.
Phillips et al,[32] 2015	Meta-analysis	19	5923	Ventilation/perfusion SPECT	Ventilation/perfusion SPECT and computed tomography pulmonary angiography have similar performance and are both superior to planar ventilation/perfusion imaging.

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; PERC, Pulmonary Embolism Rule-Out Criteria; SPECT, single-photon emission computed tomography.

JAMA. 2018;320(15):1583-1594. doi:10.1001/jama.2018.14346

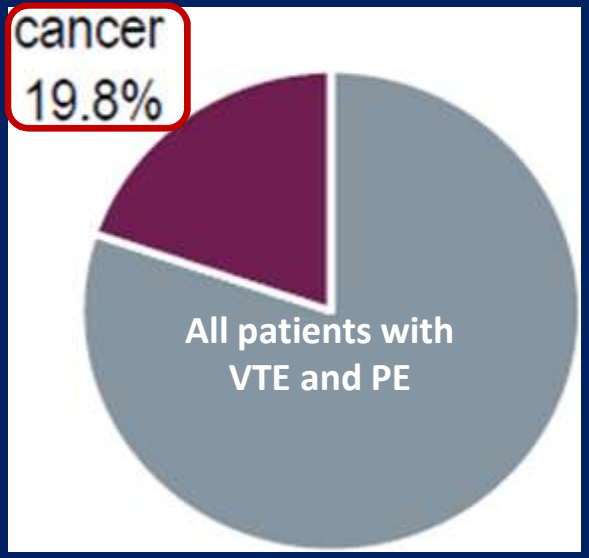
VTE

&

Cancer Associated Thrombosis(CAT)

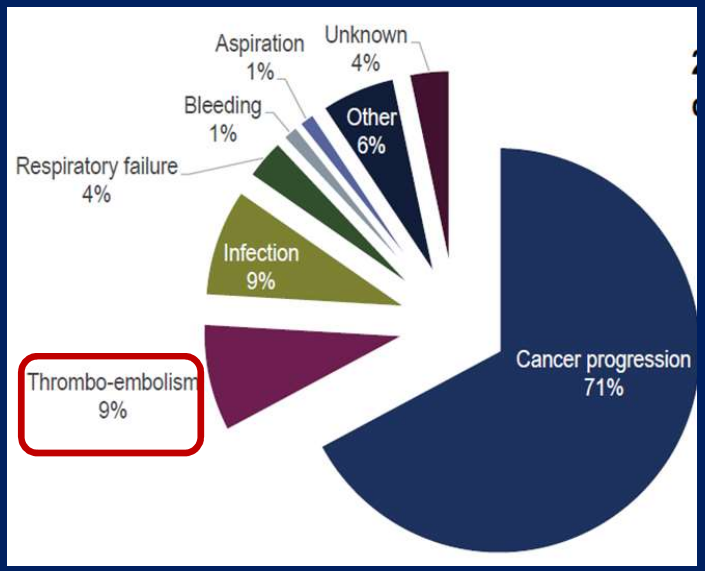
Overview: Cancer Associated Thrombosis (CAT)

About 20% of all VTE Cases Occur in Cancer[1]



- CAT is common complication in patients with malignancies.[2]
- CAT is independent risk for early mortality during first 4 cycles of chemotherapy.[1]
- **Indian ARRIVE registry:** 7% malignancy with VTE[3]
- **Large Indian observational study (2021):**[4]
  - ✓10.3% malignancy with VTE.
  - ✓16.3% deaths in cancer patients with PE.

VTE: 2nd Leading Cause of Mortality in Cancer[1]

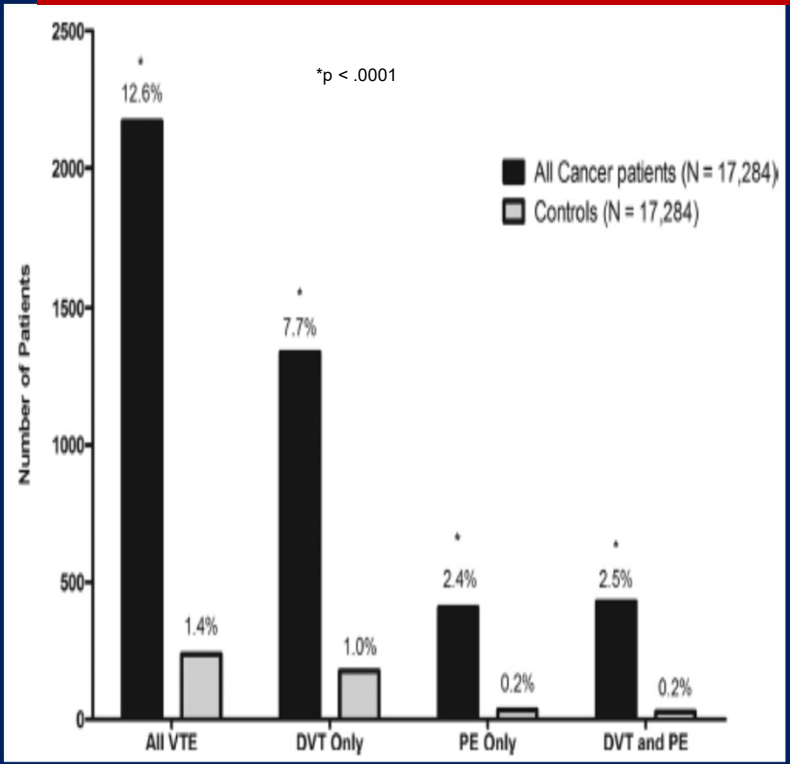


VTE is the 2nd most common preventable cause of death in patients with cancer.[5]

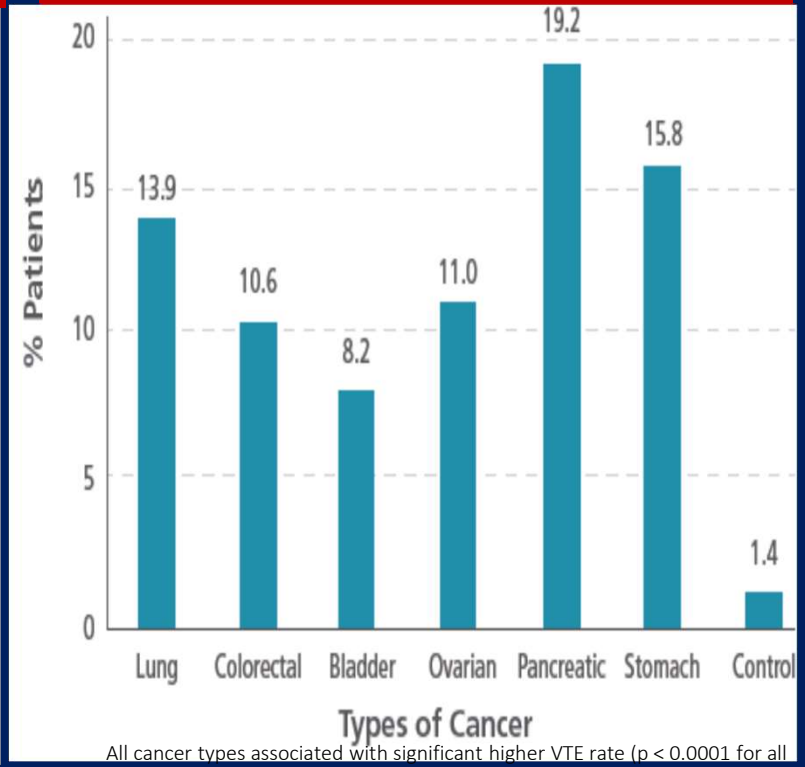
1. ESMO Management Of Cancer Associated Thrombosis [Internet]. Available at: https://oncologypro.esmo.org/content/download/127803/2410452/1/E-Learning-Management-of-Cancer-Associated-Thrombosis.pdf. Accessed on 31 Oct 2020. 2. Streiff MB, Abutalib SA, Farge D, Murphy M, Connors JM, Piazza G. Update on Guidelines for the Management of Cancer-Associated Thrombosis. Oncologist. 2021 Jan;26(1):e24-e40. 3. Kamerkar DR, John MJ, Desai SC,. Arrive: A retrospective registry of Indian patients with venous thromboembolism. Indian J Crit Care Med 2016;20:150-8. 4. Muralidharan TR, Ramesh S, Kumar BV, et al. Clinical profile and management of patients with acute pulmonary thromboembolism - a single centre, large observational study from India. Pulm Circ. 2021 Feb 16;11(1):2045894021992678. 5. Thrombosis and cancer [Internet]. Available at: https://cancerworld.net/e-grandround/thombosis-and-cancer/. Accessed on 31 Oct 2020.

Overall VTE incidence & VTE by cancer types

Overall VTE Incidence Rates[1]



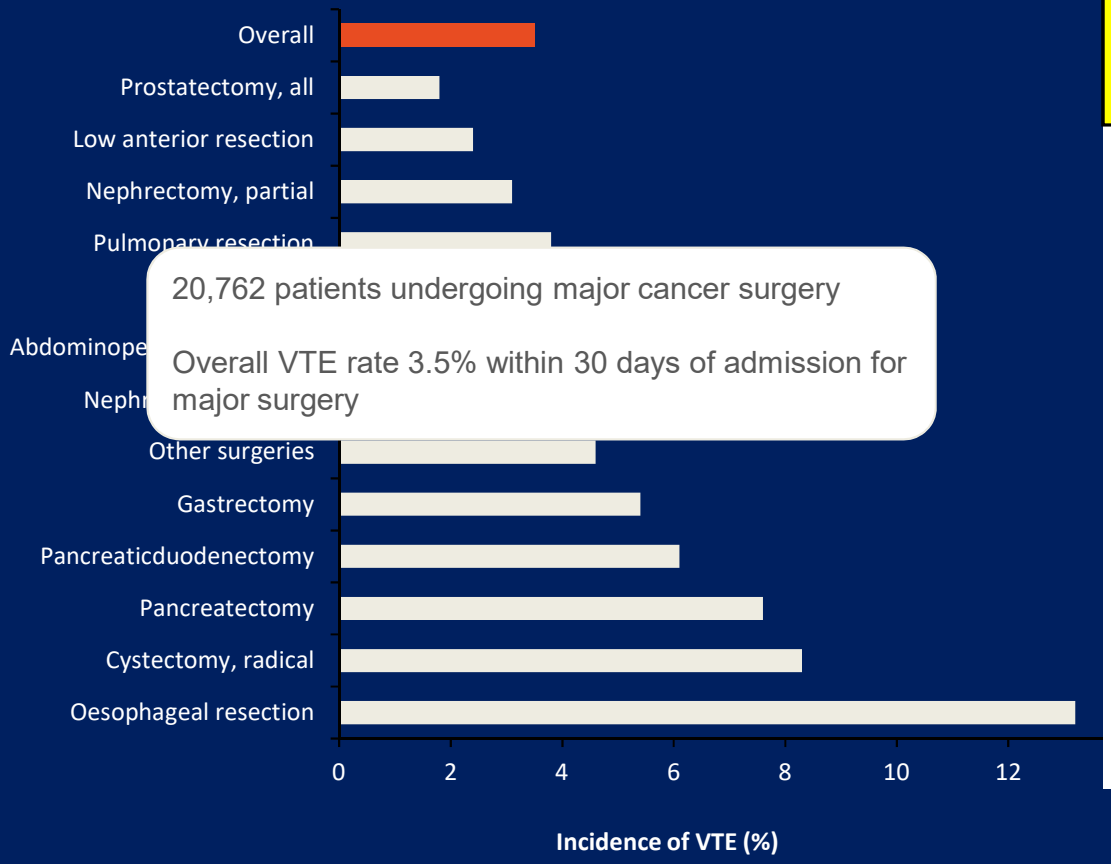
Incidence Rates of VTE by Cancer Types[2]



All cancer types associated with significant higher VTE rate ($p < 0.0001$ for all comparisons vs. controls)

1. Khorana AA, Dalal M, Lin J, Connolly GC. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. *Cancer.* 2013 Feb 1;119(3):648-55. **2.** Khorana A, Hahn D. Thrombosis and cancer: A major complication of cancer care [Internet]. Available at: http://www.pusulamedikal.com/assets/thrombosis-and-cancer-a-major-complication-of-cancer-car.pdf. Accessed on Jan 23, 2019.

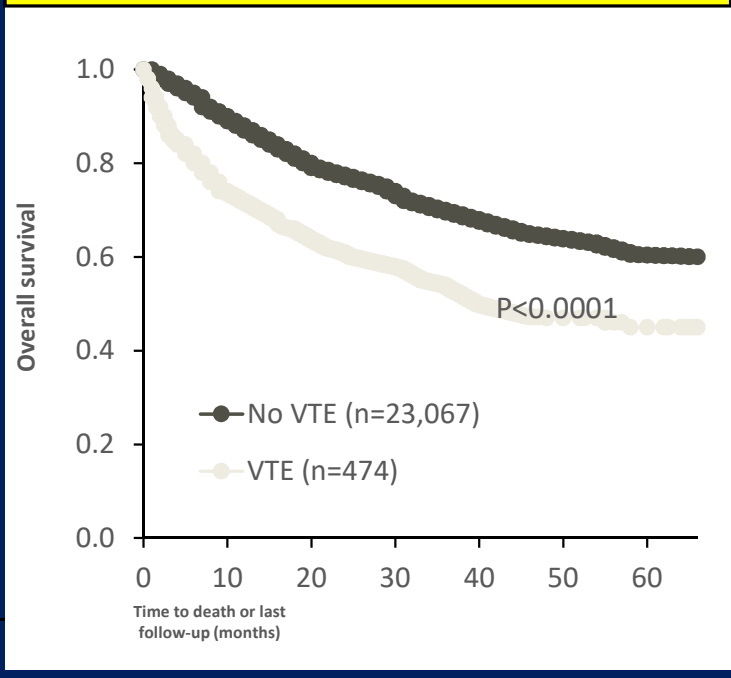
Incidence of Venous Thromboembolism After Cancer Surgery



20,762 patients undergoing major cancer surgery

Overall VTE rate 3.5% within 30 days of admission for major surgery

Prevention : Thromboprophylaxis !!



Hammond J *et al*, *Ann Surg Oncol* 2011;18:3240–3247

Risk Factors for Developing VTE in Cancer Patients

Patient-related

- Medical comorbidities (CCI ≥3)
- Presence of varicose veins
- Prior VTE
- Hereditary risk factors (e.g., factor V Leiden)

Tumour-related

- Site of cancer:
  - Very high: stomach, pancreas, brain
  - High: lung, haematological, gynaecological, renal, bladder
- Histological grade of a tumour
- Stage of cancer/metastases
- Time since cancer diagnosis

Treatment-related

- Platinum-based and other chemotherapy
- Anti-angiogenesis agents
- Hormonal therapy
- Surgery
- Radiotherapy
- Blood transfusion
- Central venous catheters
- Immobility and hospitalization

Biomarkers

- Haematological biomarkers (e.g. platelet, haemoglobin, leukocyte counts)
- D-dimer, P-selectin,
- Prothrombin fragment 1 + 2
- Thrombin generation potential
- MP-tissue factor activity
- C-reactive protein

CRPs and D-dimer testing may not be as accurate or as useful in patients with cancer.
Radiological means are better

Ay C *et al*, *Thromb Haemost* 2017;117:219–230

Risk Assessment for VTE in cancer patients

Table 1. Venous thromboembolism (VTE) risk scoring comparison between Khorana, Vienna CATS, and Protecht clinical prediction models.

Risk variable	Khorana Risk Score (points)	Vienna CATS Score (points)	Protecht Score (points)
Very high-risk tumor (i.e. pancreatic or gastric)[a]	2	2	2
High-risk tumor (i.e. bladder, testicular, lymphoma, gynecological, lung)	1	1	1
Pre-chemotherapy platelet count $\geq 350 \times 10^9$/L	1	1	1
Pre-chemotherapy leukocyte count $\geq 11 \times 10^9$/L	1	1	1
Pre-chemotherapy hemoglobin <100 g/L or use of erythropoietin stimulating agents	1	1	1
Body mass index (BMI). ≥ 35 kg/m^2	1	1	N/A
D-Dimer ≥ 35 mg/L	N/A	1	N/A
Soluble P-selectin ≥ 53.1 ng/L	N/A	1	N/A
Platinum chemotherapy	N/A	N/A	1
Gemcitabine chemotherapy	N/A	N/A	1

[a]Brain tumors are included in the 'very high-risk' tumor category for Vienna CATS Score calculation.

Table 2. Risk category stratification and percent risk of venous thromboembolism (VTE) for Khorana, Vienna CATS, and Protecht clinical prediction models.

Risk model	Risk Score	Risk category	Percent (%) VTE risk
Khorana Risk Score	0	Low	0.8% at 2.5 months[a]
	1–2	Intermediate	1.8% at 2.5 months
	≥ 3	High	7.1% at 2.5 months
Vienna CATS Score	0	Low	1.5% at 6 months
	1	Intermediate	3.8% at 6 months
	2	Intermediate	9.6% at 6 months
	≥ 3	High	17.7% at 6 months
Protecht Score	0–2	Low-intermediate	2% at 4 months
	≥ 3	High	8.1% at 4 months

[a]Data presented from Khorana Score derivation cohort.

Blood. 2010;116(24):5377-5382
Journal of Oncology Pharmacy Practice 27(4)

Treatment of CAT : LMWH vs DOACs

	Hokusai VTE Cancer 2018		SELECT-D 2018		ADAM VTE 2020		Caravaggio 2020	
	Edoxaban (n = 522)	Dalteparin (n = 524)	Rivaroxaban (n = 203)	Dalteparin (n = 203)	Apixaban (n = 150)	Dalteparin (n = 150)	Apixaban (n = 576)	Dalteparin (n = 579)
Males (%)	277 (53.1)	263 (50.2)	116 (57.1)	98 (48.3)	72 (48.0)	73 (48.7)	292 (50.7)	276 (47.7)
Age, mean (SD) or median (range)	64.3 (11.0)	63.7 (11.7)	67 (22-87)	67 (34-87)	64.4 (11.3)	64 (10.8)	67.2 (11.3)	67.2 (10.9)
Metastatic disease (%)	274 (52.5)	280 (53.4)	118 (58.1)	118 (58.1)	96 (64.0)	97 (64.7)	389 (67.5)*	396 (68.4)*
GI cancers (%)	165 (31.6)	140 (26.7)	91 (45.0)	86 (42.4)	48 (32.0)	57 (38.0)	188 (32.6)	187 (32.3)
Recurrent VTE (%)	34 (6.5)	46 (8.8)	8 (3.9)	18 (8.8)	1 (0.7)	9 (6)	32 (5.6)	46 (7.9)
Major bleeding (%)	29 (5.6)	17 (3.2)	11 (5.4)	6 (3.0)	0 (0)	2 (1.4)	22 (3.8)	23 (4.0)
CRNMB (%)	64 (12.3)	43 (8.2)	25 (12.3)	7 (3.5)	9 (6.0)	7 (4.7)	52 (9.0)	35 (6.0)

MB : Drop in Hb $\geq$ 2gm/dL, transfusion of $\geq$ 2-unit RCC, critical site bleeds, fatal bleeds, bleeding necessitating surgery
CRNMB: Bleeding compromising hemodynamics, hematoma > 25 cm^2, bleeding from venipuncture > 5 mins, epistaxis or gingival bleed requiring intervention, macroscopic hematuria, hemoptysis, per-rectal bleed

Conclusion across all studies:

Lower VTE recurrence with DOACs than LMWH

Higher bleeding risk (Major and CRNMB) in GI & GU cancers with DOACs

Ramcharitar et al. ACA 2020; https://www.acc.org/latest-in-cardiology/articles/2020/05/05/08/31/treatment-of-malignancy-associated-venous-thromboembolism

CENTRAL VENOUS ACESS DEVICE (CVAD)

CENTRAL VENOUS CATHETER (CVC)

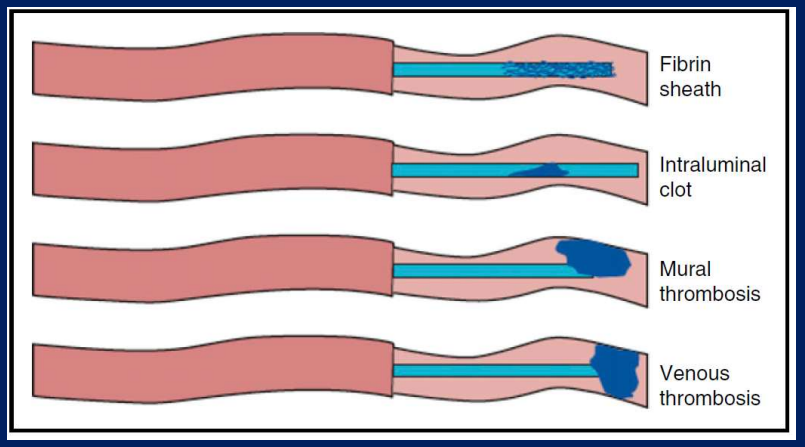
CATHETER-RELATED THROMBOSIS (CRT)

Upper Extremity DVT(UE-DVT)

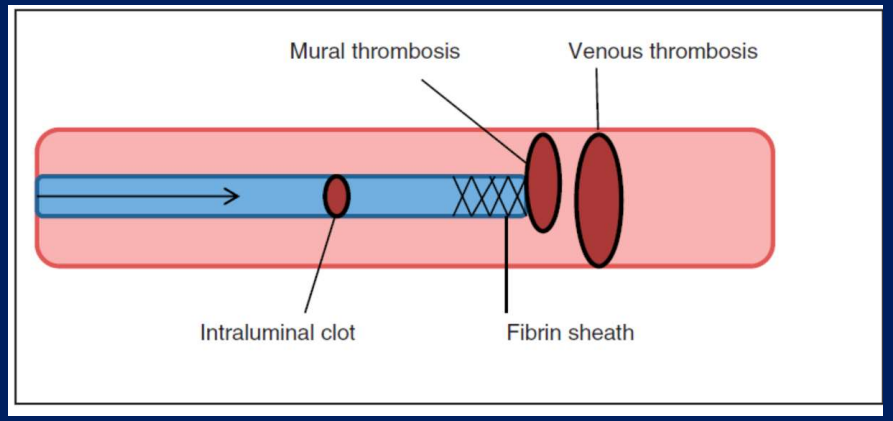
1. Advent of HDC and BMT has led to increasing use of central catheters
2. PE high in this group-15 to 33%
3. Classical Features of DVT are lacking
4. CUS not useful for centrally placed thrombosis (catheter induced)
5. Venography, CT and MR Angiography useful

Pathophysiology of VTE in CVC use

1. CVCs predispose to VTE & impact each component of Virchow's triad: stasis, hypercoagulability, and endothelial injury.
2. CVCs in the vessel lumen slows blood flow, leading to stasis.
3. CVCs likely activate coagulation
4. Endothelial injury.
    1. Insertion results in local vessel wall injury
    2. Turbulent inflow and the toxic effects of some medications promote endothelial injury.



Rajasekhar & Streiff, Blood (2017) 129 (20): 2727–2736



Journal of the Intensive Care Society 2016, Vol. 17(2) 160–167

Commonly encountered CVCs

Venous catheter	Common brands	Lumens	Duration	General indications
Non-tunnelled	NA	2–4	Temporary: 1–3 weeks	Critical care
Tunnelled	Hickman® Broviac® Groshong®	1–3	Semi-permanent >30 days	Long-term uses: chemotherapy, parenteral nutrition, etc.
Implanted port	Port-a-cath®	1	Semi-permanent >30 days	Infrequent but long-term requirements Paediatrics
Peripherally inserted central catheter (PICC)	NA	1–3	Intermediate >7 days	Outpatient chemotherapy, intermediate-term access for sampling, antibiotics, etc.

Journal of the Intensive Care Society 2016, Vol. 17(2) 160–167

Summary of recommendations by clinical guidelines on the prevention and treatment of CRT

Guideline	Prevention
ACCP 2012, 2016	In outpatients with cancer and indwelling CVAD**, suggest against routine prophylaxis** with LMWH or LDUH (grade 2B) or VKAs (grade 2C).
American Society of Clinical Oncology 2013	In cancer patients with CVADs: **Routine thromboprophylaxis is not recommended**. Routine CVAD flushing with saline is recommended. Data are insufficient to recommend routine thrombolytics to prevent catheter occlusion.
European Society for Medical Oncology 2015	In cancer patients with CVADs: **Routine thromboprophylaxis is not recommended.** Prophylaxis with thrombolytic agents is not recommended (grade I, A). Saline flushing is recommended (grade III, C).
International Guideline 2013	In cancer patients with CVADs: **Routine thromboprophylaxis is not recommended (grade 1A).** Catheters should be inserted on the right side, in the jugular vein, with catheter tip in the junction of the SVC and the right atrium (grade 1A).
National Comprehensive Cancer Network 2013	In cancer patients with CVADs: **Routine thromboprophylaxis is not recommended (grade 2A).**

Rajasekhar & Streiff, Blood (2017) 129 (20): 2727–2736

CRT - Treatment

Anticoagulation

- **Who to treat:**
  - Anticoagulation is beneficial in CRT but must be balanced with hemorrhagic risks
- **What to treat with:**
  - Choice of agent is unclear: LMWH, VKA and NOACs may be effective
  - LMWH monotherapy or LMWH bridged to warfarin are most commonly used
- **Treatment duration:**
  - Unclear; ISTH guidelines suggest a period of 3 months

Cathether removal

- **Should be considered if:**
  - Associated infection present
  - Defective/dysfunctional line
  - Line no longer necessary

Treatment strategies for CRT in the context of malignancy. CRT, catheter-related thrombosis; ISTH, International Society on Thrombosis and Hemostasis; LMWH, low-molecular-weight heparin; NOACs, novel oral anticoagulants; VKA, vitamin K antagonist.

Marin A, Bull L, Kinzie M, et al. BMJ Supportive & Palliative Care 2021;11:371–380.

Treatment Goals of VTE

Aim of initial treatment

1. Assess bleeding risk & rule out any contraindications to use of anticoagulation
2. To prevent local extension of the thrombus
3. To prevent embolisation
4. Relief of symptoms
5. Reversal of vascular occlusion

Long-term goal

1. To prevent recurrent VTE
2. To prevent post-thrombotic syndrome (PTS)
3. To prevent Chronic pulmonary arterial hypertension (CPAH)

Bleeding risk assessment models

	HAS-BLED[38]	mOBRI[39]	ATRIA[78]	HEMORR$_2$HAGES[40]
Risk factors				
Age ≥64 y		1 point		
Age >65 y	1 point			
Age >75 y			2 points	1 point
Previous bleeding	1 point		1 point	2 points
Previous gastrointestinal bleeding		1 point		
Hepatic or renal disease				1 point
Renal failure/insufficiency	1 point		3 points	
Liver failure	1 point			
Previous stroke	1 point	1 point		1 point
Anemia			3 points	1 point
Antiplatelet therapy	1 point			
Labile international normalized ratio	1 point			
CYP2C9 single-nucleotide polymorphisms				1 point
Excessive fall risk				1 point
Reduced platelet count or function				1 point
History of hypertension	1 point		1 point	1 point
Recent myocardial infarction, renal insufficiency, diabetes, or anemia		1 point		
Drugs/alcohol use	1 point			
Risk stratification				
Low risk	0 points	0 points	0 to 3 points	0 to 1 points
Intermediate risk	1 to 2 points	1 to 2 points	4 points	2 to 3 points
High risk	>2 points	>2 points	>4 points	>3 points

Klok et al. Blood. 2020;135:724-734

Why new oral anticoagulants ?

- Warfarin- sole oral anticoagulant for 60 years.
- Limitations-
  - Narrow therapeutic index
  - Delayed onset & offset of action
  - Mandatory lab monitoring
  - Drug interactions

- **Novel Oral Anticoagulants**

Warfarin Therapy

when starting a DOAC /NOAC

- Finances – Very Important in Indian Scenario !!!
- Baseline labs: CBC, creatinine, AST, ALT, T.Bil
- GFR > 30 ml/min and BMI
- Dosing of various DOACs
- Drug to Drug interactions

DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Atrial Fibrillation	FDA approved	FDA approved	FDA approved	FDA approved
VTE Treatment	FDA approved	FDA approved	FDA approved	FDA approved
VTE Prevention, ortho surgery	FDA approved	FDA approved	FDA approved	Not approved???

[Last Updated: Jan 2022]

DOACs : Drug to Drug Interactions

	CYP 3A4	P-gp
Inducers (may **reduce** NOAC plasma levels)	• **Chemotherapy:** paclitaxel • **Targeted therapies:** vemurafenib • **Hormonal therapies:** enzalutamide • **Immune modulators:** dexamethasone, prednisone	• **Chemotherapy:** vinblastine, doxorubicin • **Immunomodulators:** dexamethasone
Inhibitors (may **increase** NOAC plasma effect)	•**Chemotherapies:** Several anti-mitotic agents, etoposide, doxorubicin, idarubicin, cyclophosphamide, ifosphamide, lomustine •**Targeted therapies:** imatinib, crizotinib and other tyrosine kinase inhibitors •**Hormonal therapies:** tamoxifen, anastrozole, bicalutamide, abiraterone •**Immunomodulators:** cyclosporine, sirolimus, temsirolimus & tacrolimus •**Supportive care:** aprepitant, fosaprepitant, fentanyl, methadone, acetaminophen	•**Targeted therapies:** imatinib, nilotinib, lapatinib, sunitinib, crizotinib, vandetanib •**Hormonal therapies:** tamoxifen, enzalutamide, abiraterone •**Immunomodulators:** cyclosporine, temsirolimus, tacrolimus

[Source adapted from: Short NJ et al. The Oncologist 2014: Lee AYY et al. Blood 2013]

Costs involved

Drug	Brand Name	Manufacturer	MRP
Dabigatran	**Pradexa**	**Boehringer Ingelheim**	**110mg*10tabs ~ 718/-**
	Generic	8 companies	110mg*10tabs ~ 240 to 300 /-
Dabigatran	**Pradexa**	**Boehringer Ingelheim**	**150mg*10Tabs ~ 718/-**
	Generic	14 companies	150mg*10Tabs ~ 280/- to 439/-
Rivoroxaban	**Xarelto**	**Bayer Zydus**	**10mg*7 tabs ~ 885/-**
	Generic	20 companies	10mg*7 tabs ~ 70/ to 279/-
Apixaban	**Eliquis**	**Pfizer**	**5mg*10tabs – 638/-**
	Generic	2 companies	5mg*10tabs – 185/- to 755/-
Enoxaparin	**Clexane**	**Sanofi Aventis**	**Clexane 40mg (0.4ml) Injection ~ 489**
	Generic	8 companies	Clexane 40mg (0.4ml) Injection ~ 319/- to 510/-
Edoxaban	Edoxaban	Edoxaban	Edoxaban 30mg

DOACs Reversal

Drug	Dose	DOAC's Effects
Idarucizumab (Monoclonal antibody fragment)	Idarucizumab 5mg	Dabigatran Reversal
Andexanet (Recombinant modified human factor Xa decoy protein)	Andexanet Bolus dose - 400mg; Infusion dose - 480mg	For patients who had taken apixaban or rivaroxaban more than 7 hours
	Andexanet Bolus dose - 800mg; Infusion dose - 960mg	For patients who had taken enoxaparin, edoxaban, or rivaroxaban 7 hours or less before the administration of the bolus dose or at an unknown time

N Engl J Med 2017; 377:431-441
N Engl J Med 2016; 375:1131-1141

DVT treatment phases

Initial treatment (first 5-21 days)	Long term treatment (first 3-6 months)	Extended treatment (following initial 3-6 months)
Apixaban 10 mg bid for 7 days	Apixaban 5mg bid; Apixaban 2,5mg bid beyond 6 months	
Dabigatran 150 mg bid preceded by LMWH for 5-10 days		
Edoxaban 60 mg od (30mg od if ClCreat 50-30<ml/min or concomitant potent P-P inhibitors) preceded by LMWH for 5-10 days		
Rivaroxaban 15 mg bid for 21 days	Rivaroxaban 20mg od; Rivaroxaban 10 mg or 20 mg od beyond 6 months	
VKA to achieve INR 2-3 preceded by LMWH for 5-10 days		

European Heart Journal (2018) 39, 4208–4218

Major Therapeutic Advances

1. Graduated compression stockings are no longer recommended for PTS
2. Non cancer-provoked VTE, anticoagulation is recommended for 3 months. In patients with cancer-associated VTE, anticoagulation may be given until the cancer is cured. DOACs, are non inferior to LMWH in cancer patients.
3. DOACs are also non inferior to VKAs for prevention of recurrent VTE. VKAs are, however, preferred inpatients with severe renal impairment or when significant drug-drug interactions exist with DOACs.
4. The 2016 ACCP guidelines suggest that ultrasound surveillance only is preferred over anticoagulation in isolated " Distal DVT" patients to monitor for thrombus extension.

JAMA. 2018;320(15):1583-1594. doi:10.1001/jama.2018.14346

Major Therapeutic Advances

1. The ATTRACT trial suggested no benefit of CDT over anticoagulation alone in initial treatment of acute proximal DVT. CDT is currently only recommended in patients with threatened limb loss.

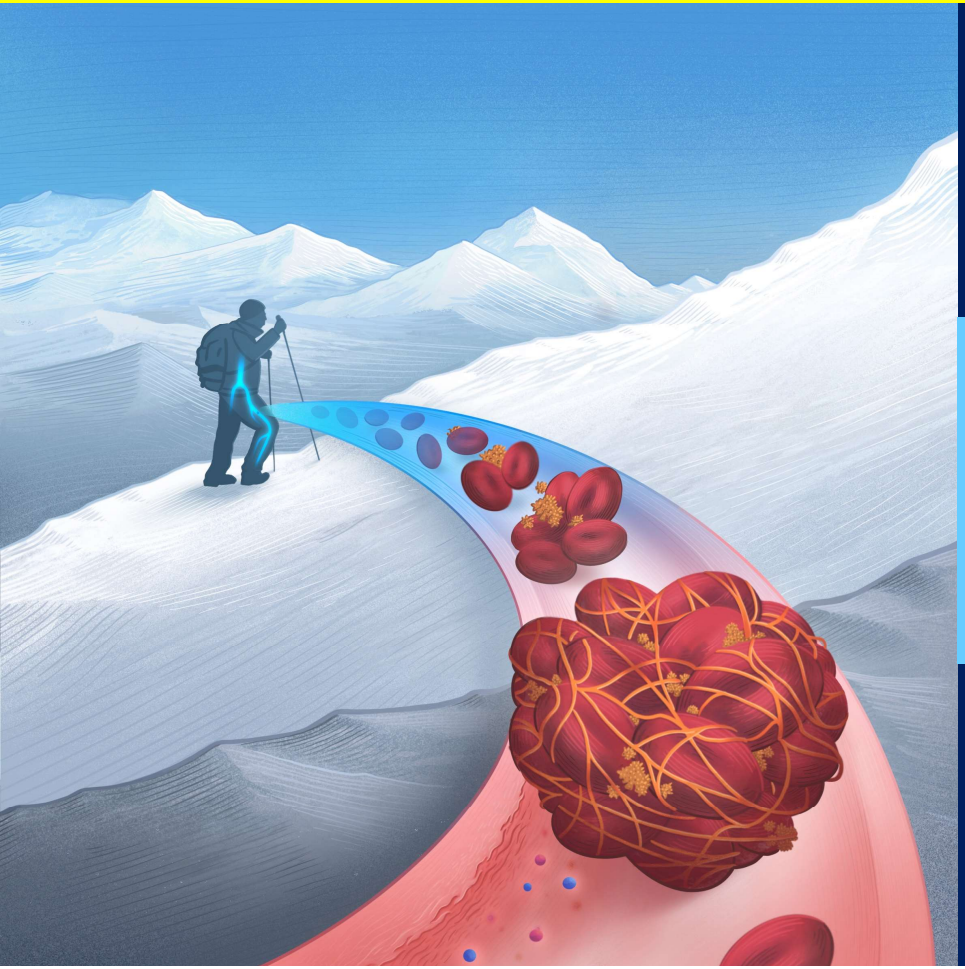
1. Currently, IVC filters may only be used in proximal DVT and PE patients with an absolute contraindication to anticoagulation.

2. There is currently insufficient evidence to support the use of DOACs in patients with antiphospholipid syndrome, heparin-induced thrombocytopenia, or venous thrombosis at unusual sites, such as splanchnic vein thrombosis.

3. Lack of prospectively validated bleeding risk score is another current knowledge gap.

JAMA. 2018;320(15):1583-1594. doi:10.1001/jama.2018.14346

Thrombosis at High Altitude
The Plot Behind The Clot !



High Altitude

&

Thrombosis

Peculiarities of thrombosis at HA

1. Despite a thorough screening, at sea level, VTE still occurs
2. Thrombosis at unusual sites
3. Sparse data, as it is very labour and capital intensive!
4. Impacts our Operational capability!
5. Young healthy subjects afflicted
6. Highland natives rarely affected

Free Preview

PRINT | E-MAIL | DOWNLOAD CITATION | PERMISSIONS

ORIGINAL ARTICLE ARCHIVE

Acute Mountain Sickness

Inder Singh, M.B. (Rangoon), F.R.C.P.E., F.R.C.P. (Glasg.), F.A.M.S., P. K. Khanna, M.D. (Poona), D.M. Cardiology (A.I.I.M.S.), M. C. Srivastava, M.D., Madan Lal, M.D. (Poona), Sujoy B. Roy, M.B. (Rangoon), F.R.C.P.E., and C. S. V. Subramanyam, M.D. (Poona)

N Engl J Med 1969; 280:175-184 | January 23, 1969 | DOI: 10.1056/NEJM196901232800402

Share:

Access this article: Subscribe to NEJM | Purchase this article

Access includes the full-text article, media, slides, and article PDF.
Preview of article PDF below.

ACUTE MOUNTAIN SICKNESS*

Inder Singh, M.B. (Rangoon), F.R.C.P.E., F.R.C.P. (Glasg.), F.A.M.S., P. K. Khanna, M.D. (Poona), D.M. Cardiology (A.I.I.M.S.), M. C. Srivastava, M.D. (Poona), Madan Lal, M.D. (Poona), Sujoy B. Roy, M.B. (Rangoon), F.R.C.P.E., and C. S. V. Subramanyam, M.D. (Poona)

Abstract Observations on acute mountain sickness occurring between 11,000 and 18,000 feet, in 1925 men, 18, to 53 years old, showed no direct relation between altitude and severity of illness; mild, moderate and severe cases occurred at all altitudes. A time lag of six to 96 hours between arrival and onset of symptoms ruled out any direct relation between hypoxia and acute mountain sickness. During this period there was clinical evidence of respiratory dysfunction with slow, irregular or Cheyne-Stokes breathing, pulmonary congestion and antidiuresis. In one biopsy and two autopsy studies there was evidence of cerebral edema. Diuresis induced with furosemide provided effective routine therapy. Morphine and betamethasone were used as additional aids in severe cases. Clinical features of acute mountain sickness were ascribed to hypoxia, pulmonary congestion, increased cerebral blood flow, increased cerebrospinal-fluid pressure and cerebral edema.

Heart

Changes in transthoracic electrical impedance at high altitude.

R S Hoon, V Balasubramanian, S C Tiwari, et al.

Br Heart J 1977 39: 61-66
doi: 10.1136/hrt.39.1.61

British Heart Journal, 1977, **39**, 61–66

Changes in transthoracic electrical impedance at high altitude

RAGHUNATH SINGH HOON, V. BALASUBRAMANIAN, SURESH C. TIWARI, OOMMAN P. MATHEW, ARUN BEHL, SUBHASH CHANDER SHARMA, AND KANWAR S. CHADHA

From the Directorate General, Armed Forces Medical Services, Ministry of Defence, 'M' Block, New Delhi, 110001, India

Mean transthoracic electrical impedance (impedance) which is inversely related to intrathoracic extravascular fluid volume was measured in 121 normal healthy volunteers at sea-level and at 3658 metres altitude. Fifty (group A) reached the high altitude location after an hour's journey in a pressurised aircraft. Twenty-five (group D) underwent slow road ascent including acclimatisation en route. Thirty permanent residents (group B) and 16 temporary residents at high altitude (group C) were also studied. Serial studies in the 30 subjects of group A who developed symptoms of high altitude sickness showed a significant decrease of impedance up to the fourth day of exposure to high altitude which later returned to normal. The 4 volunteers who developed severe symptoms showed the largest drop in impedance. A case of acute pulmonary oedema developing at 4300 metres showed an impedance value of 24·1 ohms on admission. After effective treatment the impedance increased by 11·9 to 36·0 ohms. Twenty asymptomatic subjects of group A and 25 of group D showed a small average increase in impedance values at high altitude. These observations suggest that measurement of transthoracic electrical impedance may be a valuable means of detecting incipient high altitude pulmonary oedema.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

Effect of digoxin and diuretics on high altitude left ventricular dysfunction.

V Balasubramanian, A Behl, G S Das, A K Wadhwa, O P Mathew and R S Hoon

Circulation. 1978;57:1180-1185
doi: 10.1161/01.CIR.57.6.1180
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Effect of Digoxin and Diuretics on High Altitude Left Ventricular Dysfunction

V. Balasubramanian, M.D., Arun Behl, M.B.B.S., G. S. Das, M.B.B.S., A. K. Wadhwa, M.B.B.S., O. P. Mathew, M.B.B.S., and R. S. Hoon, M.B., F.R.C.P.(E.)

SUMMARY Systolic time intervals, stroke volume, cardiac output and (dZ/dt)/RZ index were serially estimated in 51 normal healthy volunteers at sea level, for ten days after air induction to 3658 m altitude and on return to sea level. The subjects were divided into three groups and were administered a diuretic, beta methyldigoxin and placebo in a double blind protocol. The group on placebo showed an increase in heart rate, reduction in stroke index and cardiac index during high altitude exposure with normalization on return to sea level. A deterioration in left ventricular function as manifested by prolongation of pre-ejection period, increase in PEP/LVET ratio, reduction in (dZ/dt)/RZ index and left ventricular ejection time was also noted at high altitude. The subjects on digoxin maintained normal stroke/cardiac index and did not show any significant change in the parameters of myocardial function. The diuretic group showed more deterioration in the parameters than the placebo group. No significant side effects were noted. Left ventricular dysfunction and reduction of stroke index at high altitudes may be causally related; digoxin administration may prevent them from occurring.

British Heart Journal, 1978, **40**, 276-285

Alterations in left ventricular function in normal man on exposure to high altitude (3658 m)

V. BALASUBRAMANIAN, O. P. MATHEW, S. C. TIWARI, A. BEHL, S. C. SHARMA, AND R. S. HOON

From The Stress Test and Noninvasive Laboratory, Army Hospital, Delhi Cantt, New Delhi 110010, India

SUMMARY Left ventricular function was estimated by noninvasive methods in 83 normal volunteers at sea level, at an altitude of 3658 m for 10 days, and on return to sea level. Of these subjects, 50 reached high altitude by air in 55 minutes and the rest by road in 6 hours. Controls comprised 56 permanent residents of high altitude and 59 lowlanders resident at high altitudes for 120 to 180 days. Simultaneous recording of electrocardiogram, phonocardiogram, carotid pulse, and first derivative of electrical impedance cardiogram yielded data in respect of pre-ejection period (PEP), left ventricular ejection time (LVET), PEP/LVET ratio, RZ interval, contractility index $\left(\frac{dZ/dt}{RZ}\right)$, stroke index, and cardiac index. A statistically significant reduction of stroke index, cardiac index, and depression of all indices of left ventricular function was observed from the second day of induction to high altitude despite increased urinary catecholamine excretion. On return to sea level all the values returned to normal by the third day. Permanent residents of high altitude had normal left ventricular function and temporary residents a

Published data

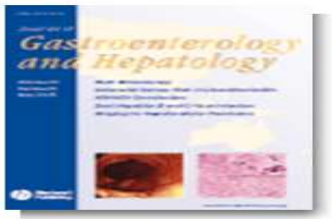
JGH Journal of Gastroenterology and Hepatology JGHF

Symptomatic portal system thrombosis in soldiers due to extended stay at extreme altitude

ANIL C ANAND, ANUPAM SAHA, AVNISH K SETH, GURVINDER S CHOPRA, VELU NAIR, VIVEK SHARMA

Article first published online: 15 MAR 2005
DOI: 10.1111/j.1440-1746.2005.03723.x

Issue



Journal of Gastroenterology and Hepatology
Volume 20, Issue 5, pages 777–783, May 2005

Fagenholz PJ, ... Department of Surgery, Mass...

Ashraf HM, Jave...

HIGH ALTITUDE MEDICINE & BIOLOGY
Volume 3, Number 1, 2002
© Mary Ann Liebert, Inc.

Stroke at High Altitude: Indian Experience

SUDHIR KUMAR JHA, ANIL C. ANAND, VIVEK SHARMA, NIKHIL KUMAR, and CHANDRA M. ADYA

...ematologica

THROMBOSIS RESEARCH

Effectiveness of homocysteine lowering vitamins in prevention of thrombotic tendency at high altitude area: A randomized field trial

Jyoti Kotwal[1], Atul Kotwal[2], Sandeep Bhalla[3], P.K. Singh[4], Velu Nair[5]

Nair V, Mohapatro AK, Sreedhar M, Indrajeet IK, Te... , Anand AC, Mathew OP: **A Case of Hereditary Protein S Deficiency Pres...ng with Cerebral Sinus Venous Thrombosis and Deep Vein Thrombosis at High Altitude.** *Acta Haematol 2008;119:158-161 (DOI: 10.1159/000126200)*

Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

BMJ

CASE REPORT

PAI-1 polymorphism as a cause of severe high altitude associated arteriovenous thrombosis

Velu Nair,[1] Uday Yanamandra,[2,3] Rai Kumud,[4] Kanjakya Ghosh[5]

[1]Armed Forces Medical Services, Army Medical Corps (Indian Army), New Delhi, India
[2]Department of Internal Medicine, Armed Forces Medical College, Pune, Maharashtra, India
[3]Department of Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, Chandigarh, India
[4]Department of Vascular Surgery, Max Super Specialty Hospital, New Delhi, Delhi, India
[5]Department of Immunohematology & Hematopathology, Surat Raktadan Kendra & Research Centre, Surat, Gujarat, India

Correspondence to
Dr Uday Yanamandra,
udayj2@gmail.com

Accepted 9 November 2016

SUMMARY

We present a 34-year-old man who developed disseminated intra-arterial and venous thrombosis following exposure to extreme high altitude. On evaluation, the patient was found to have thrombosis involving the aorta, bilateral iliac arteries and middle cerebral artery. On detailed evaluation for the cause of recurrent seizures, he was also found to have cerebral venous thrombosis of the superior sagittal sinus. The patient underwent amputation of 3 limbs due to gangrene. Procoagulant work up revealed increased plasminogen activator inhibitor-1 activity with 4G/4G polymorphism. This case highlights the life-threatening and limb-threatening thrombosis secondary to a rare inherited thrombophilia on exposure to extreme high altitude.

BMJ Nair V, et al. BMJ Case Rep 2016. doi:10.1136/bcr-2016-217361

Acta Haematologica

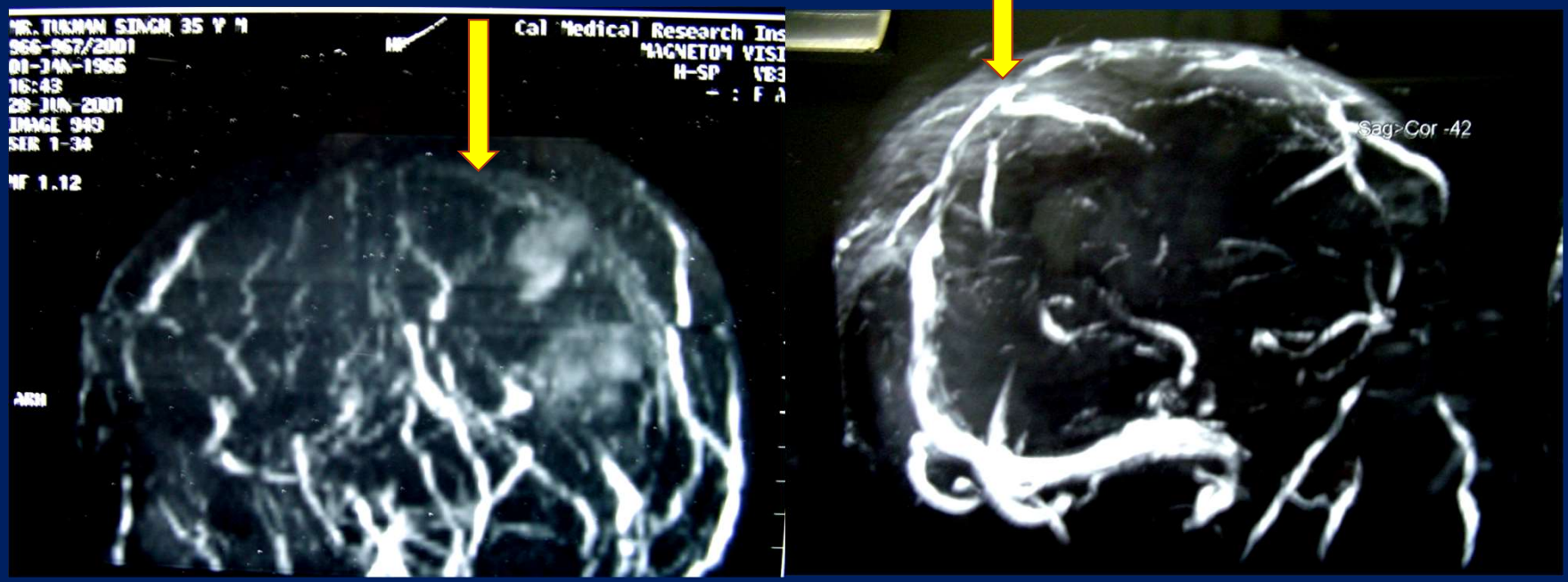
Nair V, Mohapatro AK, Sreedhar M, Indrajeet IK, Tewari AK, Anand AC, Mathew OP:
A Case of Hereditary Protein S Deficiency Presenting with Cerebral Sinus Venous Thrombosis and Deep Vein Thrombosis at High Altitude.
Acta Haematol 2008;119:158-161 (DOI: 10.1159/000126200)

Case vignette- 2

A 35-year-old healthy male with no history of any past medical illness developed severe headache, vomiting and drowsiness while at high altitude (4,572 m) in the eastern Himalayan ranges. He was evacuated to a tertiary-care hospital where he was diagnosed to have cerebral sinus venous thrombosis (CSVT) on magnetic resonance imaging, with deep vein thrombosis (DVT) of his right popliteo-femoral vein on color Doppler study. Investigation for thrombophilia revealed protein S (PS) deficiency in this patient. Family screening was positive.

Jun 2001

Dec 2001



THE LANCET Regional Health
Southeast Asia

Epidemiology and pathophysiology of vascular thrombosis in acclimatized lowlanders at high altitude: A prospective longitudinal study

Velu Nair,[a,b,c,1]* Surinderpal Singh,[d,e,1] Mohammad Zahid Ashraf,[f,g,1] Uday Yanamandra,[a,h,1] Vivek Sharma,[i,j] Amit Prabhakar,[f,k] Rehan Ahmad,[l,m] Tathagata Chatterjee,[n,o] Vineet Behera,[a,p] Vivek Guleria,[a,q] Seema Patrikar,[r] Shivi Gupta,[s,t] Madan Gopal Vishnoi,[s,u] Rigvardhan,[f] Kiran Kalshetty,[v,w] Prafull Sharma,[a,x] Nitin Bajaj,[y,z] Thyelnai D. Khaling,[d,aa] Tanaji Sitaram Wankhede,[d,bb] Srinivasa Bhattachar,[aa,cc] Rajat Datta,[q,dd] and Late Prosenjit Ganguli[l,ee,1]

Summary

Background Previous literature suggests that thrombosis is more common in lowlanders sojourning at high altitude (HA) compared to near-sea-level. Though the pathophysiology is partly understood, little is known of its epidemiology. To elucidate this, an observational prospective longitudinal study was conducted in healthy soldiers sojourning for months at HA.

Methods A total of 960 healthy male subjects were screened in the plains, of which 750 ascended, to altitudes above 15,000ft (4,472m). Clinical examination, haemogram, coagulogram, markers of inflammation and endothelial dysfunction, were studied at three time points during ascent and descent. The diagnosis of thrombosis was confirmed radiologically in all cases where a thrombotic event was suspected clinically. Subjects developing thrombosis at HA were labelled as Index Cases (ICs) and compared to a nested cohort of the healthy subjects (comparison group,(CG)) matched for altitude of stay.

Findings Twelve and three subjects, developed venous (incidence: 5,926/105 person-years) and arterial (incidence: 1,482/105 person-years) thrombosis at HA, respectively. The ICs had enhanced coagulation (FVIIa: $p<0.001$; FXa: $p<0.001$) and decreased levels of natural anticoagulants (thrombomodulin, $p=0.016$; tissue factor pathway inhibitor[TFPI]: $p<0.001$) and a trend to dampened fibrinolysis (tissue plasminogen activator tPA; $p=0.078$) compared to CG. ICs also exhibited statistically significant increase in the levels of endothelial dysfunction and inflammation markers (vascular cell adhesion molecule-1[VCAM-1], intercellular adhesion molecule-1 [ICAM-1], vascular endothelial growth factor receptor 3 [VEGFR-3], P-Selectin, CD40 ligand, soluble C-reactive protein and myeloperoxidase: $p<0.001$).

Interpretation The incidence of thrombosis in healthy subjects at HA was higher than that reported in literature at near sea-level. This was associated with inflammation, endothelial dysfunction, aprothrombotic state and dampened fibrinolysis.

Funding Research grants from the Armed Forces Medical Research Committee, Office of the Director General of Armed Forces Medical Services (DGAFMS) & Defence Research and Development Organization (DRDO), Ministry of Defence, India.

Conclusion The ICs were noted to have a **prothrombotic state** with **suppressed naturally occurring anticoagulants, dampened fibrinolysis, endothelial activation, platelet activation and raised proinflammatory markers.** The incidence of clinically manifest thrombotic events, venous more than arterial, at HA2 (altitudes >15,000ft/ 4,572m) among the healthy subjects of this study was markedly higher than that reported at near sea level. **Altitude >15,000ft (4,572m) may be an independent risk factor for thrombosis, even in healthy subjects.**

Velu Nair et al. The Lancet Regional Health - Southeast Asia 2022; 00: 100016 Published online xxx https://doi.org/10.1016/j. lansea.2022.05.005

Summary of Results

1. 15 Healthy subjects developed thrombosis (Venous=12, Arterial=3)
2. Cases had prothrombotic state VIIa and Xa ($p<0.001$)
3. Decreased levels of natural anticoagulants (TM, $p=0.016$; TFPI< 0.001)
4. Trend to dampened fibrinolysis (TPA, $p=0.078$)
5. Significant increase ($P<0.001$) in endothelial dysfunction and pro-inflammatory markers (VCAM-1, ICAM-1, VEGFR-3, P-selectin, CD40, CRP and MPO)

High altitude thrombosis—Evidence for underlying mechanisms from a large prospective longitudinal study

Johann Wojta [a,b,*]

[a]Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria
[b]Ludwig Boltzmann Institute for Cardiovascular Research, Vienna, Austria

Despite constant progress in prevention and therapy, thrombotic events (arterial or venous), remain a major health concern world-wide due to morbidity and mortality.[1] Hypoxia and subsequent sojourn at high altitude have long been suggested as risk factors for thrombosis. A few small studies and case reports supporting this view have been earlier reviewed by Gupta & Ashraf.[2]

Besides increased blood viscosity, a reduced fibrinolytic capacity, a procoagulatory state and an inflammatory activation of the endothelium have been proposed as possible reasons for high altitude induced thrombosis.[3–6] Recently the long noncoding RNAs *LINC00659* and *UXT-AS1* have been identified as possible molecular modulators of high altitude induced thrombotic events.[7]

In this issue of *The Lancet Regional Health – Southeast Asia*, Velu Nair and colleagues[8] report the results of a challenging, large prospective longitudinal study that investigated thrombotic events in a cohort of 960 acclimatized lowlanders at high altitude.[8] Of these 960 male soldiers, 750 ascended to altitudes above 15,000ft (4472 m). Clinical screening and determination of markers of coagulation and fibrinolysis were performed in blood samples obtained from these individuals once at sea level and twice at high altitude (at 12–15,000ft and at >15,000ft, respectively).

The authors reported 15 thrombotic events in their cohort, of which twelve were venous and three were arterial. The affected individuals showed significantly higher levels of procoagulant Factor VIIa and Xa, and lower levels of the anticoagulant modulators thrombomodulin and tissue factor pathway inhibitor (TFPI) compared to healthy controls. Also, the fibrinolytic capacity in these individuals was affected by a moderate, albeit not significant, reduction in tissue-type plasminogen activator (tPA), a profibrinolytic serine protease. In addition, Velu Nair and colleagues[8] provide strong evidence that not only coagulation and fibrinolysis are affected by staying at high altitude but that such environment might also impact on activation of the endothelium as indicated by the increased levels of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM), and CD40 ligand in the individuals who experienced a thrombotic event. Such activation of the endothelium most likely can be linked to a generalized inflammatory state as evidenced by increased C-reactive protein (CRP) and myeloperoxidase (MPO) levels.

Intriguingly, already at sea level, plasma levels of MPO, the inflammatory mediator monocyte chemoattractant protein-1 (MCP-1) and plasmin-alpha-2-antiplasmin (PAP) complexes were significantly higher in those individuals who suffered a thrombotic event at high altitude as compared to the respective plasma levels in individuals of the control group. Thus, one could speculate that a particular marker profile would allow the identification of individuals at risk to develop thrombosis at high altitude. Therefore, adequately powered prospective studies to conclusively identify such biomarkers which might also include other biomolecules such as PA inhibitor-1 (PAI-1) or long noncoding RNAs that have been shown to be involved in high altitude induced thrombosis, seem warranted.[5–7] In conclusion, this challenging study improves our understanding on the mechanisms that might underly high altitude induced thrombosis.[8]

The Lancet Regional Health - Southeast Asia
2022;3: 100039
https://doi.org/10.1016/j.lansea.2022.100039

Contributors

JW conceptualised and wrote the paper.

Declaration of interests

None.

References

1 Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010:

DOI of original article: http://dx.doi.org/10.1016/j.lansea.2022.05.005

*Correspondence to: Department of Internal Medicine II, Medical University of Vienna, Waehringer Guertel 18-20, Vienna 1090, Austria.
E-mail address: johann.wojta@meduniwien.ac.at

Editorial

In this issue of The Lancet Regional Health Southeast Asia, Velu Nair and colleagues[8] report the results of a challenging, large prospective longitudinal study that investigated thrombotic events in a cohort of 960 acclimatized lowlanders at high altitude

In conclusion, this challenging study improves our understanding on the mechanisms that might underly high altitude induced thrombosis.

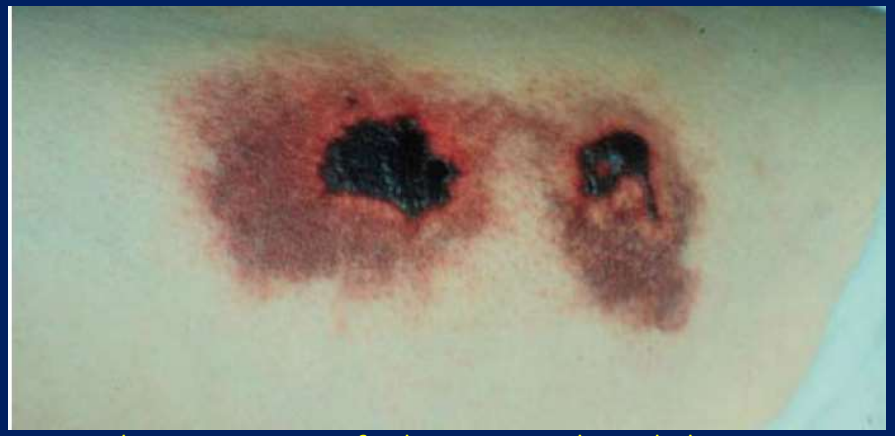
HIT

HEPARIN Induced Thrombocytopenia (HIT)

1. Common after continuous infusion of UFH
2. Diagnosis:
    1. High index of clinical suspicion
    2. Clinically, appearance of ecchymotic patches, DVT, venous gangrene
    3. Thrombocytopenia
    4. Four T's:
        1. **T**hrombocytopenia, **T**iming (5-10 days post heparin), **T**hrombosis,
        2. No other cause of **T**hrombocytopenia
3. Lab tests
    1. Antigenic immuno- assays: Easier to perform, sensitive but lacks specificity (IgG, IgM, IgA)
    2. Functional assays: HIPA and SRA. More specific

Risk factors for HIT

Heparin-related	Host-related
Type of heparin (UFH > LMWH)	Age (middle-aged and older adults > young adults and children)
Duration of heparin (~ 6 days > shorter courses)	Sex (female > male)
Patient population (surgical > medical > obstetric)	



Typical appearance of a heparin induced skin necrosis

Features that favor a diagnosis of HIT

Feature	Comment
Fall in platelet count $\geq$ 50%	Platelet count fall is 30%-50% in 10% of cases
Fall in platelet count begins 5-14 days after heparin exposure	Platelet count fall may occur immediately after heparin re-exposure in patients with a previous recent exposure (ie, rapid-onset HIT)
Nadir platelet count $\geq 20 \times 10^9$/L	May be lower in cases associated with DIC
Thrombosis	May be venous or arterial
Unusual manifestations	Skin necrosis at subcutaneous heparin injection sites; anaphylactoid reactions after intravenous heparin bolus; transient global amnesia
Absence of petechiae and significant bleeding	
Absence of other causes of thrombocytopenia	Such as infection, drugs other than heparin, CPB

NON-HEPARIN ANTICOAGULANTS FOR TREATMENT OF ACUTE HIT

Drug	Dosing	Laboratory Monitoring
Argatroban	Bolus: None Continuous infusion: Normal organ function → 2 µm/kg/min Liver dysfunction (bilirubin > 1.5 mg/dl) → 0.5–1.2 µm/kg/min Heart failure, anasarca, post-cardiac surgery → 0.5–1.2 µm/kg/min	Adjust to APTT 1.5–3.0 times baseline
Bivalirudin	Bolus: None Continuous infusion: Normal organ function → 0.15 mg/kg/h Renal or liver dysfunction → dose reduction may be appropriate	Adjust to APTT 1.5–2.5 times baseline
Danaparoid	Bolus: <60 kg, 1,500 units 60–75 kg, 2,250 units 75–90 kg, 3,000 units >90 kg, 3,750 units Accelerated initial infusion: 400 units/h × 4 h, then 300 units/h × 4 h Maintenance infusion: Normal renal function → 200 units/h Renal dysfunction → 150 units/h	Adjust to danaparoid-specific anti-Xa activity of 0.5–0.8 units/mL
Fondaparinux[1]	<50 kg → 5 mg daily 50–100 kg → 7.5 mg daily >100 kg → 10 mg daily	None
Apixaban[1,2]	HITT: 10 mg twice daily × 1 week, then 5 mg twice daily Isolated HIT: 5 mg twice daily until platelet count recovery	None
Dabigatran[1,2]	HITT: 150 mg twice daily after ≥5 days of treatment with a parenteral non-heparin anticoagulant Isolated HIT: 150 mg twice daily until platelet count recovery	None
Rivaroxaban[1,2]	HITT: 15 mg twice daily × 3 weeks, then 20 mg daily Isolated HIT: 15 mg twice daily until platelet count recovery	None

[1] *Not approved for treatment of acute HIT*

[2] *Dosing for treatment of acute HIT is not well-established. Suggested dosing is extrapolated from venous thromboembolism and based on limited published evidence*

Based on the 2018 American Society of Hematology (ASH) Clinical Practice Guidelines for Management of VTE: HIT

VTE & Covid

How to approach Thrombosis and COVID-19 ?

1. Ensure all patients are risk assessed for VTE as well as bleeding risk

2. Ensure those at risk receive appropriate thromboprophylaxis adjusted for **weight** and **renal function**

3. Have a high index of clinical suspicion for VTE

WHO Coronavirus disease (COVID-19): Vaccines

As of 12 January 2022, the following vaccines have obtained EUL

1. The Pfizer/BioNTech Comirnaty vaccine, 31 December 2020.
2. The SII/COVISHIELD and AstraZeneca/AZD1222 vaccines, 16 February 2021.
3. The Janssen/Ad26.COV 2.S vaccine developed by Johnson & Johnson, 12 March 2021.
4. The Moderna COVID-19 vaccine (mRNA 1273), 30 April 2021.
5. The Sinopharm COVID-19 vaccine, 7 May 2021.
6. The Sinovac-CoronaVac vaccine, 1 June 2021.
7. The Bharat Biotech BBV152 COVAXIN vaccine, 3 November 2021.
8. The Covovax (NVX-CoV2373) vaccine, 17 December 2021.
9. The Nuvaxovid (NVX-CoV2373) vaccine, 20 December 2021

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-(covid-19)-vaccines?adgroupsurvey={adgroupsurvey}&gclid=CjwKCAjwpuajBhBpEiwA_Ztfha6vEEYS5qcU_GYcWX_F50cMfQ7xux9vsbjpwIHIqQTdlWz92Mc_fBoCpfMQAvD_Bw

Case definition criteria for VITT

Vaccine induced Immune Thrombotic Thrombocytopenia

	Likelihood of VITT	Clinical and laboratory features	Recommended management
1		Onset of symptoms 5-30 days post COVID-19 vaccine (or up to 42 days if isolated DVT/PE) Documented thrombosis or severe and persistent headache Thrombocytopenia (platelet count <150 000/µL) D-dimer >4000 FEU (and >8x ULN) Positive anti-PF4/heparin IgG ELISA assay	
2	Definite VITT	Meets all five criteria	Anticoagulation, IVIG
3	Probable VITT	D-dimer > 4000 FEU (and >8x ULN), but one criteria not fulfilled (timing, thrombosis, Anticoagulation, IVIG thrombocytopenia, anti-PF4/heparin antibodies) or D-dimer unknown or 2000-4000 FEU (4-8 x ULN) with all other criteria present	Anticoagulation, IVIG
4	Possible VITT	D-dimer unknown or 2000-4000 FEU (4-8 x ULN) with one other criteria not fulfilled or two criteria not fulfilled (timing, thrombosis, thrombocytopenia, anti-PF4/heparin antibodies)	Anticoagulation, close clinical monitoring,
5	Unlikely	Platelet count <150 000/µL without thromboses, D-dimer <2000 FEU (<4x ULN), regardless of anti-PF4/heparin antibody result, and/or alternative diagnosis more likely	Anticoagulation only if thrombosis is present. Consider if ITP treatment is needed

*N Engl J Med 2021;385:1680-9; Greinacher et al. J Thromb Haemost. 2021;00:1–8 **Modified from Pavord et al.***

Fundamentals of Management of VITT

1. Anticoagulation - started in all patients with probable or definite VITT.
2. Less than 5% VITT patients present with severe headache ,**without** overt thrombosis&negative neuroimaging studies 5 days after vaccination, should be managed like VITT with anticoagulant (microvascular thrombosis);repeat imaging done a week later.
3. Heparin does not appear to be dangerous in the vast majority of VITT patients. **5% of VITT patients have antibodies that cross-react with PF4/heparin complexes.**
4. The hesitancy to use heparin likely stems from the fact that rapid exclusion of heparin cross-reactivity is usually not possible. Hence, it is recommended to use a non-heparin anticoagulant for initial treatment.

GREINACHER et al. J Thromb Haemost. 2021;00:1–8.

Fundamentals of Management of VITT

1. Dampening of the immune response- High-dose IVIG, 1-2 g/kg of actual body weight should be given.
2. Thrombocytopenia is not a contraindication to therapeutic dose anticoagulation in VITT.
3. The optimal duration of anticoagulation is 3–6 months
4. Antibodies persist for at least 5 months.
5. An increase in D-dimer without other explanation indicates ongoing clotting

GREINACHER et al. *J Thromb Haemost.* 2021;00:1–8.

CONCLUSION-1

1. Needs extensive edn of all Health Care providers and Public at large !
2. VTE Incidence needs close audit
3. Special situations eg HA , Travel
4. Preventable condition
5. Health Economics
6. Newer ,safer and cheaper Anticoagulants !
7. Aim for DVT Free Hospitals !!

CONCLUSION-2

1. Every hospital should develop a prevention program.
2. Grade 1A evidence for pharmacological DVT prophylaxis in patients with VTE risk factors.
3. Perioperative prophylaxis given +/-24 hr from surgery.
4. Evaluate each patient upon admission, and regularly thereafter, for the risk of developing DVT/VTE

Prevention of VTE

Is

Better Than Cure

Thank you