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Task Force Report

NAMS task force report on Venous thromboembolism

National Academy of Medical Sciences (India), New Delhi, India.*

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PREFACE

There is a perceived gap in the utilization of appropriate prophylaxis for the prevention of venous thromboembolism (VTE) and its guidelines-based management across different strata of the healthcare system. In view of the aging population of India and the increasing burden of non-communicable diseases along with infectious diseases affecting healthcare service delivery, there is a dire need to have an early impact on the incidence and burden of deep venous thrombosis (DVT) and pulmonary embolism (PE) in India.

The measures required to be taken, call for stakeholders to take effective action to create a future for India where:

(a) The population at large is knowledgeable about the risk factors, triggering events, and symptoms of VTE, and individuals feel empowered to talk with their healthcare providers about VTE whenever appropriate.
(b) Evidence-based practices for the screening, prevention, diagnosis, and treatment of DVT/PE are clearly understood and routinely applied by all medical professionals in all settings.
(c) New scientific evidence is constantly being uncovered to fill gaps in knowledge, and these findings are quickly and easily disseminated to the public and put into practice by healthcare professionals.

The overall results of the above action agenda will be to save many lives each year and to reduce the suffering of many more. Implementing the vision for a VTE-free healthcare system, as proposed in this document, will not be an easy task, and undoubtedly, progress will take time. Many barriers will emerge; however, solutions must be found and, more importantly, set into motion sooner than later.

We will need the energy and commitment of individuals, families, the healthcare system, private sector organizations, and government systems at all levels to work together to build solutions that will bring better health to Indians. With these dedicated efforts, we can make this vision a reality. This document has been prepared by a the National Academy of Medical Sciences (India) (NAMS) Task Force and is intended to be a synthesis of a cross-section of available professional society guidelines focused on the prevention and management of VTE for the Government of India to issue suitable guidelines for implementation across the primary healthcare system. This initiative was wholeheartedly supported and encouraged by Prof SK Sarin, President of NAMS, and Prof Umesh Kapil, Secretary of NAMS.

EXECUTIVE SUMMARY

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). It can result in significant mortality, morbidity, and healthcare costs. Approximately 30% of patients with symptomatic VTE manifest with PE, and others with DVT. The incidence of DVT in India in the general population is about 1.79 per thousand. More than 50% of post-surgical procedure patients are at risk of developing VTE. The prevailing notion that the incidence of VTE in Asians is less than that in the Western population has been disproved by recent reports.

Increasing age, male gender, trauma, surgery, prolonged hospitalization, malignancy, neurologic disease, central venous catheter, prior superficial vein thrombosis, and varicose veins have been identified as some of the major risk factors for developing VTE. In women, oral contraceptive pill use, pregnancy, and hormone replacement therapy are established as independent risk factors. Some of the important risk factors for surgical patients developing VTE are age, type of surgery, length of procedure, and duration of immobilization.

An extensive review of up-to-date published literature and consensus statements/guidelines was undertaken by a Task Force (TF) of the NAMS, specifically focusing on the prevention and management of VTE. These guidelines have emerged therefrom.

The TF has recommended that consensus be achieved among the various stakeholders in the health of the people of India toward a national Vision, that is, a *VTE-free healthcare system and eventually a VTE-free population.*

The key issues identified by the TF on taking recourse to a systems approach to appropriate prevention and management of VTE include but are not limited to lack of *trained human resources* (healthcare professionals); inadequate *laboratory diagnostic support*; inadequate *availability of pharmaceutical supplies; lack of awareness in the community*; *need for suitable research along with equitable distribution of facilities for the management of VTE.*

Efficient use of healthcare resources is extremely crucial, and diagnostic testing without significant clinical utility is not recommended as per multiple specialty societies, including the current American College of Chest Physicians (ACCP) and American Society of Hematology (ASH) guidelines. Reduction of the risk of VTE can be done by screening patients pre- and postoperatively with accurate diagnostic testing. By diagnosing VTE early, treatment could be provided to halt progression and avoid morbidity and mortality associated with acute VTE. Screening "at-risk" patients is impractical and too expensive to be undertaken outside of clinical trials.

Recommendations have been made to bridge critical gaps/deficiencies as identified, including capacity building. Presently, there is no formal system for the upgradation and verification of skill sets of healthcare professionals in managing and prescribing prophylaxis for VTE. Recommendations have been made by the TF to address this suitably.

There needs to be concerted efforts by policymakers and medical professional bodies to focus attention on the policy gaps and also India-specific recommendations on awareness and training for the prevention of VTE. Consideration may also be given in due course to the identification of high-risk populations for screening and further management as per treatment guidelines.

Thus, there is a need for budgetary allocation of funds and policy initiatives, for assigning research priorities, and a need for convergence of medical specialties, to better serve the Indian population.

A community-based strategy is recommended to create awareness periodically. This is recommended to be steered by a special Committee or Cell that may be established by the Ministry of Health and Family Welfare, with the cooperation of the Indian Society of Hematology & Blood Transfusion, in coordination with the Indian Public Health Association.

After due deliberations on the need for current evidence about thromboprophylaxis practices, the NAMS TF has proposed the conduct of a rapid multicentric cross-sectional study on a pan India basis to ascertain a representative view of the VTE burden and real-world prophylaxis practices. This is intended to be undertaken to develop indigenous VTE risk assessment tools and prophylaxis strategies.

INTRODUCTION

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). It can result in significant mortality, morbidity, and healthcare costs. Approximately 30% of patients with symptomatic VTE manifest with PE, and others with DVT. The annual incidence of PE ranges from 39 to 115 per 100,000 population, and for DVT, the incidence ranges from 53 to 162 per 100,000 population. VTE not only disables patients but also prolongs hospital stay, leading to an increase in the cost of treatment.

PE is one of the most common causes of sudden unexplained deaths in hospitalized patients. An early diagnosis and prompt, effective treatment is crucial, as the mortality rate of untreated PE is about 30%, and nearly 30% of untreated DVTs suffer severe swelling or ulceration of the lower limbs. With timely diagnosis and treatment, PE-related deaths are less than 1%. Venous thrombosis (VT) generally lacks specific signs and symptoms, which can lead to a delayed or inaccurate diagnosis and inferior patient outcomes. Hence, awareness creation amongst treating physicians is a key approach to combating VTE.

The most common presentations of VT are DVT of the lower extremity and PE. These can result in significant mortality, morbidity, and healthcare costs. The causes of VT can be divided into two groups: hereditary and acquired, and are often multiple in a given patient. A major theory delineating the pathogenesis of VTE, often called Virchow Triad, proposes that VTE occurs as a result of:

(a) Alterations in blood flow (i.e., stasis)
(b) Vascular endothelial injury
(c) Alterations in the constituents of the blood (i.e., inherited or acquired hypercoagulable state)

A risk factor for thrombosis can be identified in over 80% of patients with VT. Furthermore, there is often more than one factor at play in a given patient. Accordingly, many patients with VTE fulfill most or all of Virchow's triad of stasis, endothelial injury, and hypercoagulability. As examples:

(a) Fifty percent of thrombotic events in patients with inherited thrombophilia are associated with the additional presence of an acquired risk factor (e.g., surgery, prolonged bed rest, pregnancy, oral contraceptives). Some patients have more than one form of inherited thrombophilia or more than one form of acquired thrombophilia and appear to be at even greater risk for thrombosis.
(b) In a population-based study of the prevalence of VTE, 56% of the patients had three or more of the following six risk factors present at the time of VTE: > 48 hours of immobility in the preceding month; hospital admission,

surgery, malignancy, or infection in the past three months; or current hospitalization.

BACKGROUND

The incidence of DVT in India in the general population is about 1.79 per thousand. Approximately 30% of patients with symptomatic VTE have PE, and others have DVT. More than 50% of post-surgical procedure patients are at risk of developing VTE. The risk of VTE following total knee arthroplasty (TKA) is 72.2%, following abdominal or thoracic surgeries is 40%, and following total hip arthroplasty (THA) is 42.9%. Idiopathic DVT is noted in 43% of patients, with 52% of patients developing DVT after a precipitating event and 6% of patients showing recurrence of DVT. The incidence of DVT after major lower limb surgery in Indian patients is comparable to Western data.

Increasing age, male gender, trauma, surgery, prolonged hospitalization, malignancy, neurologic disease, central venous catheter, prior superficial vein thrombosis, and varicose veins have been identified as some of the major risk factors for developing VTE. In women, oral contraceptive pill use, pregnancy, and hormone replacement therapy have been established as independent risk factors. Some of the important risk factors for surgical patients developing VTE are age, type of surgery, length of procedure, and duration of immobilization.

VTE is a major cause of cardiovascular morbidity and mortality and has a known genetic contribution. Genetic risk factors predispose to thrombophilia and play the most important etio-pathogenic role in VTE in people younger than 50 years. At least one inherited risk factor could be found in about half of the cases with a first episode of idiopathic VTE. A revolutionary contribution to the genetic background of VTE was brought by the achievements of the genome-wide association studies which analyze the association of a huge number of polymorphisms in a large sample.

The detection of hereditary thrombophilia has an impact on the management of the anticoagulation in children with purpura fulminans, and pregnant women at risk of VTE and may be useful in the assessment of the risk for recurrent thrombosis in patients presenting an episode of VTE at a young age (<40 years) and in cases with positive family history regarding thrombosis. Data showing the clinical usefulness and benefits of testing are limited or nonexistent, as are data supporting the benefit of primary or secondary VTE prophylaxis based on thrombophilia status alone. Patients with inherited thrombophilia can often be identified by coagulation experts on the basis of the patient's personal and family history of VTE, even without knowledge of test results. Factors associated with the presence of an inherited thrombophilia include VTE at a young age (often considered to be less than 40–50 years of age); a strong family history of VTE, VTE in conjunction with weak provoking factors at a young age; recurrent VTE events; and VTE in an unusual site such as the central nervous system or splanchnic veins.

While acute precipitants and clinical risk factors are often the focus of determining the cause of VTE, a small minority of patients have a mutation in a limited number of genes leading to an inherited thrombophilia. To that end, hypercoagulability and/or genetic testing can identify some uncommon genetic mutations such as factor V Leiden, antithrombin deficiency, protein C or S deficiency, or a prothrombin gene mutation. However, standard testing is usually unrevealing, with mutations present in only about 5% of the general population. Thus, for many patients with VTE, no clear precipitant or risk factor is ever identified.

When a patient experiences a VTE event without an acute precipitant such as recent surgery, immobilization, or trauma, one often considers clinical risk factors and contemplates testing for a handful of known monogenic thrombophilia disorders. However, the use of thrombophilia testing has fallen out of favor in part due to the low yield in terms of the number of patients identified. Given the genetic backdrop, the studies done in India have certain limitations, which include but are not limited to sample size being quite limited and the studies having been done in the context of VTE with some other co-morbidity. Further, mostly targeted polymorphisms have been analyzed, with no study involving a global approach at the genome-wide level. Indian data depict that the established thrombophilia genetic markers Factor V Leiden and Prothrombin G20210A have a limited role from the Indian perspective. Several studies have shown the role of Factor V Leiden in VTE risk but only with certain comorbidity in the Indian population. In recently published landmark studies regarding the genetics of VTE in the journals *Blood* and *Nature Genetics*, in contrast to uncommon thrombophilias, genome-wide association studies were used to identify 297 independent single nucleotide polymorphisms associated with VTE, from which a polygenic risk score was developed. These data demonstrate that consideration of broader polygenic risk can identify a much larger proportion of patients at risk for VTE and is a stronger predictor than many chronic clinical risk factors. We need to extend these kinds of studies in the Indian population to get a comprehensive genetic view on VTE.

Preventing fatal PE is the primary goal of anticoagulant prophylaxis for VTE. Prevention of VTE also avoids significant post-VTE morbidity. Conditions that can develop despite appropriate treatment of VTE are post-thrombotic syndrome (PTS), chronic thromboembolic pulmonary hypertension

(CTEPH), and post-PE syndrome. The prevalence and potential severity of these conditions must be considered when determining the potential benefits of preventing VTE. Averting sudden death and reducing post-PE morbidity are not the only benefits of anticoagulant prophylaxis, and prevention of VTE is important to avoid patient discomfort, anticoagulant treatments and their associated risks, specialist visits, delays in procedures, and the potential for additional testing.

Terms of Reference for the Task Force

The Executive Council of the National Academy of Medical Sciences (India) had assigned the following terms of reference for the Task Force (TF) on VTE in April 2022. All recommendations of the TF were to be placed before the Executive Council of the NAMS by the end of July 2022, for approval and onward submission to the Government of India.

(a) The TF was required to make recommendations to the Government of India for the prevention and control of VT and embolism in India at the health policy and implementation levels.
(b) The TF would prepare a "White Paper" which may include the existing morbidity and mortality status, if available due to VT and thromboembolism.
(c) The TF would identify existing lacunae and deficiencies in the thematic area and make recommendations to address these.

METHODOLOGY

On receipt of the terms of reference from the NAMS Executive Council, the TF was convened under the Chairmanship of Lt Gen Velu Nair with membership from a cross-section of domain experts enlisted in the task force.

Through a process of discussions in the virtual mode, a consensus was reached among the members of the TF, on the methodology to be adopted for developing ibid guidelines. The task at hand was divided into sections, and members allocated the sections based on their specific domain expertise.

An extensive literature review was undertaken using the websites PubMed and Google Scholar using the search terms "Venous Thromboembolism" AND "Management" AND "Prophylaxis" AND "Prevention" for English language documents, with a preference for review articles, clinical trials, consensus statements and guidelines. Professional society websites were browsed for the latest guidelines and consensus statements. Contribution from the scientific committee was requested through personal communication from the Chairperson to all members of the Indian Society for Hematology. Thus, almost all published work from India was reviewed along with all similar international work on VTE. A synthesis of the obtained literature was prepared and deliberated upon by the TF.

A series of weekly meetings were conducted in virtual mode for reviewing the progress being made and to discuss the allocated sections of the White Paper. Minutes of the meetings were prepared and circulated within the TF for information and guidance.

While developing the document, the PICO framework was relied upon to define the various at-risk patient groups and recommend the interventions required. Iterations of the document developed with the contributions of the members were circulated and discussed sequentially over the term of the TF. This modification of the Delphi technique was essential for the process of eventual consensus, as the guidelines required reference to the latest evidence and conformity with professional society guidelines, keeping in view the requirements of the country and the best interests of the patient population.

SITUATIONAL ANALYSIS

Current situation in India

The prevailing notion that the incidence of VTE in Asians is less than that in the Western population has been disproved by recent reports. The incidence of postoperative DVT in Indian patients undergoing major lower limb surgery is as high as seen in the Western world (43.2% and 60% of patients in the groups with and without prophylaxis, respectively). In a study covering 549 patients, acute DVT without PE, acute DVT with PE, and PE alone were reported in 64%, 23%, and 13% of patients, respectively. The mean age was 47 (±16) years, and 70% of the patients were males. A history of DVT (34%), surgery including orthopedic surgery (28%), trauma (16%), and immobilization >3 days (14%) were the most common risk factors for VTE. Hypertension (25%), diabetes (19%), and neurological disease (other than stroke) (8%) were the most common comorbidities. Most (94%) were treated with heparin alone (82%) or fondaparinux (2%) for initial anticoagulation; low molecular weight heparin alone (5%) or warfarin/acenocoumarol (76%) for long-term anticoagulation.

In the MEGA study, patients who were tested for thrombophilia after a first episode of VTE were analyzed for the outcomes of testing and for reduction in the risk of recurrence. It was observed that despite thrombophilia testing at the time of first VTE, 35% of patients had recurrent VTE during follow-up compared with 30% of patients who did not have recurrent VTE. This indicated that testing at the time of the first VTE did not reduce the risk of recurrence of VTE. Testing for inherited thrombophilia does not reduce the recurrence of VT. The recurrence risk for VTE is determined by the clinical situation (e.g., provoked vs. unprovoked) along

with non-Mendelian risk factors (e.g., body mass index and age) rather than the inherited thrombophilia panel.

The proportion of Indian patients at risk for VTE (53.6%) was similar to that of the global patients at risk for VTE (51.8%). However, ENDORSE data showed that globally, 50.2% of at-risk patients received ACCP-recommended prophylaxis, whereas in India, only 17.4% of at-risk patients received such prophylaxis. Among at-risk patients, 18.5% of surgical and 22.4% of medical patients received any VTE prophylaxis. Similarly, 16.3% of surgical and 19.1% of medical patients received ACCP-recommended thromboprophylaxis. In a prospective registry on venous thromboembolic events (PROVE) conducted in 19 countries, 3,526 patients with symptomatic DVT were enrolled, out of which 667 were from India. Prior VTE prophylaxis had been given to only 5% of enrolled Indian patients compared to 12% in the overall PROVE population.

Thus, thromboprophylaxis in India may not be routine practice in most institutions other than tertiary care hospitals. This large population of patients at-risk for VTE identifies an unmet need. There is thus a need to understand the incidence and prevalence of VTE in various medical and surgical settings better.

The most common reasons for the underutilization of pharmacological thromboprophylaxis are varied and often include (but are not limited to) lack of knowledge, ignorance, fear of bleeding, and any contraindication to anticoagulants. This can be interpreted to imply poor awareness of the risks of VTE in patients. The current paradigm for diagnosis and management of thrombosis has provided a variety of tools. However, it has also left some unanswered questions, such as methods for risk stratification to predict the risk for recurrent VTE requires aggressive anticoagulation.

Current infrastructure, facilities, technologies, policies, programs, etc., in India in the context of the problem of VTE

The ICMR has recently launched a National Hospital-based Registry on Venous Thromboembolic Disorders (i-RegVeD) with the aim of establishing a nationwide surveillance network through selected hospitals for the collection of data for generating evidence on VTE prevalence. This will be of relevance for planning suitable, calibrated responses and strengthening healthcare facilities across different treatment settings. This registry is based on a standard reporting framework with data capture using electronic information technology for timely analytics of patterns of disease distribution, treatment, and outcomes of VTE patients. The data are intended to be used for relevant and appropriate research and innovation, including identifying risk factors for VTE disease. It is anticipated that the registry shall contribute to improving patient management for VTE and related manifestations, and also guide policy and health planning in the future.

Presently, there is no formal campaign or system for the upgradation and verification of skill sets of healthcare professionals in managing and prescribing prophylaxis for VTE. Online consensus statements and guidelines are available from international professional societies which can be accessed by any interested healthcare professional; however, there is no focused initiative to regulate or standardize the approach across the Indian healthcare system.

Across the healthcare hierarchy in India, in the governmental public healthcare system, the availability of laboratory diagnostic capabilities and pharmaceutical supplies for managing, monitoring, and providing prophylaxis for VTE is not uniform. This problem is especially acute at the peripheral levels of the healthcare system, from the district hospital downward, compounded by the problem of a relative lack of trained and specialist human resources. In the private healthcare system, which accounts for the majority of tertiary healthcare sought by the Indian population with considerable out-of-pocket expense being incurred, the management of VTE among other conditions is dependent mostly on perceived commercial considerations.

With the Indian Public Health Standards being formulated to address the human resource and equipment needs across a standard template and scale, in an ideal scenario, the requirements of trained human resources have been addressed. However, ground reality indicates otherwise, with scorecards from the Niti Aayog revealing the realities. So far, there has been no comprehensive assessment of the competence per se of such trained personnel across a spectrum of clinical domains, leave alone VTE as a focus area.

The National Essential Diagnostics List was promulgated in 2019, with states being empowered to augment the list and provide equipment to suit their specific inclinations or areas of focus in disease and health management. This guideline serves to provide a generic template for states to plan service delivery. The framework for VTE management thus can capture the parameters outlined in this document to provide support to states in planning their response.

Key issues/gaps identified in the context of VTE

These include but are not limited to the following:

(a) *Trained human resources* (healthcare professionals): Availability of an adequate number of personnel adequately oriented toward VTE and skilled suitably to manage VTE in different clinical settings and provide thromboprophylaxis as required.
(b) *Laboratory diagnostic support*: Facilities that are commensurate with the basic minimum requirements to

screen for, diagnose, and manage VTE at different levels of the healthcare system.

(c) *Availability of pharmaceutical supplies*: Appropriate drug stocking and replenishment systems, including required logistics, for the healthcare facilities to provide appropriate care and manage VTE at different levels of the healthcare system.

(d) *Awareness in the community*: Awareness about VTE and the risks posed to health. To inculcate required healthcare-seeking behavior with specific reference to prevention and early recognition.

(e) *Research and future direction*: To study the incidence and prevalence in the Indian population and undertake research to identify suitable protocols for screening, diagnosis, and management appropriate for the country.

(f) *Equitable distribution of facilities for management of VTE*: Availability of healthcare facilities that are adequate and accessible, affordable and sustainable, appropriate and acceptable in the geographical vicinity of at-risk population clusters.

RECOMMENDATIONS

Vision

It is recommended that consensus be achieved amongst the various stakeholders in the health of the people of India toward a national vision, that is, a *venous thromboembolism-free healthcare system and eventually a VTE-free population*.

The National Academy of Medical Sciences (India) envisions a healthcare system in India, both in the public sector and the private healthcare system, in which a collaborative, multidisciplinary approach will ensure a VTE-free population and a VTE-free healthcare system through standardized, evolving, evidence-based guidelines, to deliver sustainable, high-quality, affordable, and patient-focused care.

Further to National Health Policy 2017, the goal of a VTE-free healthcare system and VTE-free population, being proposed by the National Academy of Medical Sciences (India), is for the attainment of the highest possible level of health and well-being for all, at all ages, through a preventive and promotive healthcare orientation, and universal access to good-quality healthcare services without anyone having to face financial hardship as a consequence, by eliminating incidence of VTE amongst other initiatives of the Government of India.

Recommendations made to bridge critical gaps/ deficiencies

Presently, thromboprophylaxis as an approach in the management of patient populations at risk is underutilized in India; hence, measures to overcome this unmet need are warranted [Annexure 1]. There is also a need to have focused, simple guidelines with algorithms and charts for care providers for early diagnosis of VTE and prompt management in different VTE settings (including at the community level). In addition [Annexures 2–5], it is important to increase awareness among treating physicians regarding guidelines on testing for VTE, while avoiding unnecessary testing. These need to be undertaken in the backdrop of promoting health literacy on a broader palette for the larger population [Annexure 6].

The various recommendations of the NAMS TF include but are not limited to the following Table 1

Table 1: VTE : Key recommendations of NAMS TF

Key Focus areas/ Gaps	Action Recommended
Trained human resources	Periodically updated online training modules be made available for healthcare personnel nationally, with regional mentoring by medical institutions of eminence.
Laboratory diagnostic support	The National Essential Diagnostics List 2019 and the relevant facility-wise Indian Public Health Standards be utilized to standardize the laboratory requirements for basic minimum requirements to screen for, diagnose, and manage VTE at different levels of the healthcare system.
Availability of pharmaceutical supplies	States be advised to refine their Essential Drugs List to include/retain appropriate drugs and ensure stocking and replenishment systems, including required logistics, for their healthcare facilities to provide appropriate care and manage VTE at different levels of the healthcare system.
Awareness in the community	Periodic campaigns be launched regionally with standard content about VTE and the risks posed to individual health. Behavior change campaigns may also be promoted to inculcate required healthcare-seeking behavior with specific reference to prevention and early recognition of VTE.
Research and future direction	Funding be made available to study the incidence and prevalence in the Indian population and undertake research to identify suitable protocols for screening, diagnosis, and management appropriate for the country.
Equitable distribution of facilities for the management of VTE	State governments may be advised to plan for the availability of healthcare facilities that are adequate and accessible, affordable and sustainable, appropriate and acceptable in the geographical vicinity of at-risk population clusters.

NAMS: National Academy of Medical Sciences (India); TF: Task Force; VTE: venous thromboembolism.

WAY FORWARD

The NAMS TF, after due deliberations on the need for current evidence about thromboprophylaxis practices has proposed the conduct of a rapid multicentric cross-sectional study on a pan India basis to ascertain a representative view of the VTE burden and real-world prophylaxis practices. This is intended to be undertaken to develop indigenous VTE risk assessment tools and prophylaxis strategies.

Efficient use of healthcare resources is extremely crucial, and diagnostic testing without significant clinical utility is not recommended as per multiple specialty societies, including the current ACCP and ASH guidelines. There are two major ways to reduce the risk of VTE. The first is to screen patients pre- and postoperatively with accurate diagnostic testing. By diagnosing VTE early, treatment could be provided to halt progression and avoid morbidity and mortality associated with acute VTE. Unfortunately, contrast venography is expensive, painful, and impractical to perform outside of clinical studies. Less invasive studies, such as venous ultrasonography (US), are less sensitive in asymptomatic patients than in symptomatic patients. Screening "at-risk" patients is impractical and too expensive to be undertaken outside of clinical trials.

The second approach is to undertake measures to prevent VTE. General measures, such as encouraging early ambulation after surgery, can be adopted universally without harm. In addition, active prophylaxis with either mechanical or pharmacologic means has been proven to lower the risk of VTE. Mechanical prophylaxis refers to devices, such as graduated compression stockings and intermittent pneumatic compression devices, which decrease venous stasis in the lower extremities. Mechanical prophylaxis does not carry a risk of bleeding but can be uncomfortable, and prolonged use can lead to skin breakdown and other cutaneous complications.

Suggested policy activities and advocacy for policy makers

DVT and PE have been recognized to be major public health problems across the world today. Clinicians and hospitalists are assumed to know how to reduce the morbidity and mortality resulting from DVT/PE, yet it is perceived that this knowledge is mostly not being applied systematically at the population level or even uniformly across healthcare facilities [Annexure 7]. Without a concerted effort to stem the public health crisis that unrecognized VTE poses, the incidence and burden of these diseases will only grow larger as the population in India ages.

The key actions required to be taken by policymakers in various settings have been given in Annexures 8, 9.

The recently launched ICMR registry for VTE is recommended to be actively promoted for voluntary participation by healthcare facilities across the country.

Recommendations for healthcare professionals

It is proposed that a focused, continuing professional education campaign be conceptualized and launched, targeting healthcare professionals. An outline of such an educational module is given in Annexure 8. This is proposed to be done in tandem with a suitably structured patient and community-focused campaign.

Suggestions to create awareness among general public, NGOs, and community stakeholders

A community-based strategy is recommended to create awareness periodically [Annexure 6]. This is recommended to be steered by a special committee or cell that may be established by the Ministry of Health and Family Welfare, with the cooperation of the Indian Society of Hematology in coordination with the Indian Public Health Association.

The specific areas of focus of community-focused campaigns may include but not be limited to the following:

(a) All about healthcare-associated VTE, including risk factors
(b) All about blood clots and travel
(c) All about blood clots and pregnancy
(d) All about blood clots and cancers.

The intent would be to provide information as appropriate, with a regional flavor, and to promote healthcare-seeking behavior on a broader palette of behavior change communication aimed at health literacy.

Areas of future research

In the current scenario, establishing a thrombophilia testing setup in the Indian population is difficult as there is a relative lack of well-designed, population-based studies that could associate genetic risk factors with disease prevalence. A large-scale population-based genome-wide association study is thus essential to identify the genetic associations with VTE. Details are further outlined in Annexure 10.

DOCUMENTS REFERRED BY THE TF

Technical documents from various professional societies, such as the ASH, ACCP, etc., were perused. Apart from these, landmark peer-reviewed articles over the past two decades were also reviewed.

"Suggested further reading," includes some of the relevant articles/documents referred to by the TF.

ANNEXURE 1

Annexure 1 briefly outlines the task force VTE prophylaxis recommendations through Tables I–XV appended below

VTE PROPHYLAXIS: RECOMMENDATIONS

Table I: VTE prophylaxis recommendations in medical patients

Medical patients			
Risk stratification	**Score**	**Choice of VTE prophylaxis**	**Remarks**
IMPROVE VTE[1] **IMPROVE Bleeding Risk Score[2]**	IMPROVE VTE score < 3	Nil	
	IMPROVE VTE score ≥ 3 & IMPROVE Bleeding risk score < 7	LMWH UFH or Fondaparinaux	If • CrCl < 30 mL/min or • cost constraints then, UFH can be used as an alternative • LMWH is preferred over DOAC
	IMPROVE VTE score ≥ 3 & IMPROVE Bleeding risk score ≥ 7	Mechanical prophylaxis with graduated compression stockings or intermittent pneumatic compression	Switch to pharmacologic prophylaxis once the bleeding risks return to normal.

IMPROVE: International Medical Prevention Registry on Venous Thromboembolism; VTE: Venous thromboembolism; LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; CrCl: Creatinine clearance; DOAC: Direct oral anticoagulant.
Source: [1]Spyropoulos AC, *et al*. Chest 2011 Sep;140(3):706-714; [2]Decousus H, *et al.* Chest 2011 Jan;139(1):69-79.

Duration:

- For the period of hospitalization (UFH/LMWH) or
- Extended prophylaxis up to 40 days (Rivaroxaban)

Table II: VTE prophylaxis recommendations in general surgery patients

Surgical patients			
Risk stratification	**Score**	**Choice of VTE prophylaxis**	**Remarks**
Caprini score[1]	**<0** At **very low risk** for VTE	• Early ambulation is recommended. • No specific pharmacologic or mechanical prophylaxis	
	1–2 At **low risk** for VTE	• Mechanical prophylaxis, preferably with intermittent pneumatic compression	
	3–4 At **moderate risk** for VTE	• LMWH/UFH or • intermittent pneumatic compression	
	≥5 At **high risk** for VTE	• Combined prophylaxis	
Duration		• Extended antithrombotic prophylaxis (6 weeks) is preferred over short-term antithrombotic prophylaxis	LMWH or UFH preferred
		• Early or delayed antithrombotic prophylaxis (>12 hours) is acceptable.	
In case of high bleeding risk		• Mechanical prophylaxis • IVC filters are not to be used	

VTE: Venous thromboembolism; LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; IVC: Inferior vena cava.
Source: Adapted from Caprini JA, *et al.* Semin Thromb Hemost 1991;17 Suppl 3:304-12. PMID: 1754886.

Table III: VTE prophylaxis recommendations in patients posted for orthopedic surgery

Orthopedic Surgical Cases			
Procedure	**Duration**	**Options**	**Remarks**
Total hip arthroplasty or TKA	Minimum of 10–14 days	Any one of LMWH Fondaparinux Apixaban Dabigatran Rivaroxaban, UFH Vit K antagonist Aspirin	Direct oral anticoagulants (DOACs) are preferred over low-molecular-weight heparin
Hip fracture repair	Minimum of 10–14 days	Any one of LMWH UFH Fondaparinaux Vit K antagonist Aspirin Intermittent pneumatic compression	
Arthroscopic knee surgery Foot or ankle surgery Upper limb surgery	6–12 hours after surgery for 14 days (Prophylaxis recommended only if any of the conditions mentioned under Remarks column apply)	LMWH	• if total anesthesia time is >90 minutes • person's risk of VTE outweighs their risk of bleeding • Immobilization is required postoperative period

TKA: Total Knee Arthroplasty; LMWH: Low molecular weight heparin; UFH: Unfractionated heparin.

- Extended thromboprophylaxis is recommended in the outpatient period for up to 35 days from the day of surgery rather than for only 10–14 days.
- Dual prophylaxis may be preferred over mono-prophylaxis.
- For asymptomatic patients following major orthopedic surgery, Doppler ultrasound screening before hospital discharge is not needed.

Table IV: VTE prophylaxis recommendations in patients presenting with polytrauma

POLYTRAUMA	
Category	**Recommendation**
Major trauma and low to moderate risk for bleeding	LMWH or UFH
High bleeding risk	Do not use pharmacologic prophylaxis

LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; VTE: venous thromboembolism.

Table V: VTE prophylaxis recommendations in patients presenting with acute spinal cord injuries

ACUTE SPINAL CORD INJURIES	
Recommendation	**Remarks**
Mechanical prophylaxis And/Or pharmacological prophylaxis	Consider adding pharmacological VTE prophylaxis with LMWH 24 hours after initial admission if no surgery is planned in the next 24–48 hours, if the benefit of reducing the risk of VTE outweighs the risk of bleeding.
	Continue VTE prophylaxis in people with spinal injury for 30 days or until the person is mobile or discharged, whichever is sooner

VTE: Venous thromboembolism; LMWH: Low molecular weight heparin.

Table VI: VTE prophylaxis recommendations in patients admitted for urological surgery

UROLOGIC SURGERY	
Category	**Recommendation**
Transurethral resection of the prostate	Do not use pharmacologic prophylaxis Instead, consider mechanical prophylaxis
Radical prostatectomy	
An extended node dissection and/or open radical prostatectomy	May consider LMWH/UFH
VTE risk factors	May consider LMWH/UFH

LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; VTE: venous thromboembolism.

Table VII: VTE prophylaxis recommendations in patients admitted for vascular surgery

VASCULAR SURGERY	
Category	**Recommendation**
In routine surgeries	Do not use pharmacologic prophylaxis Instead, consider mechanical prophylaxis
Open vascular surgery or major endovascular procedures, including endovascular aneurysm repair, when risk of VTE outweighs risk of bleeding	Consider pharmacological VTE prophylaxis with LMWH for a minimum of 7 days.

VTE: Venous thromboembolism; LMWH: Low molecular weight heparin.

Table VIII: VTE prophylaxis recommendations in patients admitted for laparoscopic surgery

LAPAROSCOPIC SURGERY	
Category	**Recommendation**
In routine surgeries	Do not use pharmacological prophylaxis Instead, consider mechanical prophylaxis
If risk factors for VTE are present	Consider pharmacological prophylaxis

VTE: Venous thromboembolism.

Table IX: VTE prophylaxis recommendations in patients admitted for gynecological surgery

GYNECOLOGICAL SURGERY	
Category	**Recommendations**
Major surgery	LMWH or UFH

LMWH: Low molecular weight heparin; UFH: Unfractionated heparin.

Table X: VTE prophylaxis recommendations in patients admitted for neurosurgery

NEUROSURGERY	
Recommendation	**Remarks**
In routine, mechanical prophylaxis is indicated	Do not use pharmacological prophylaxis routinely.
If prolonged immobilization is anticipated, then plan for post-operative pharmacologic prophylaxis	

Table XI: VTE prophylaxis recommendations in patients admitted for bariatric surgery

BARIATRIC SURGERY	
Recommendation	**Remarks**
LMWH or UFH or Intermittent pneumatic compression	Duration: for 10–15 days Dual prophylaxis if risk factors +, • age > 55 years • BMI > 55 • history of VTE • OSA • hypercoagulability • PAH

OSA: Obstructive sleep apnea; PAH: Pulmonary arterial hypertension; BMI: Body mass index; VTE: Venous thromboembolism; UFH: Unfractionated heparin; LMWH: Low molecular weight heparin.

Table XII: VTE prophylaxis recommendations in oncological patients

MALIGNANCY		
Category	**Prophylaxis**	**Remarks**
Hospitalized cancer patients	LMWH or UFH	Till discharge
Cancer patients undergoing surgery	LMWH or Fondaparinaux or Mechanical prophylaxis (only if the risk of bleed is high)	Should be prescribed pharmacological prophylaxis in the postoperative period
Ambulatory patients (Risk stratification by Khorana score)	If score < 2 No VTE prophylaxis	If receiving chemotherapy and at low risk for thrombosis
	If score ≥ 2 Rivaroxaban or Apixaban	Those who are receiving systemic anticancer therapy and are at intermediate-to-high risk of VTE
Multiple myeloma patients	Aspirin or low-dose Vit K Antagonists or LMWH	For those receiving lenalidomide, thalidomide, or pomalidomide-based regimens
Outpatients with cancer and indwelling central venous catheters	No role of routine prophylaxis with LMWH or UFH or Vit K Antagonists	

VTE: Venous thromboembolism; UFH: Unfractionated heparin; LMWH: Low molecular weight heparin.
Source: Adapted from Dutia M *et al.* Cancer. 2012 Jul 15;118(14):3468-76.

Table XIII: VTE prophylaxis recommendations in long distance travellers (travel time > 4 hours)

LONG-DISTANCE TRAVELERS (travel time > 4 hours)	
No risk factors for VTE	**High VTE risk**
	Recent surgery, h/o VTE, postpartum, active malignancy, hormone replacement therapy, obesity, or pregnancy
No prophylaxis recommended	Graduated compression stockings or LMWH or Aspirin

VTE: Venous thromboembolism; LMWH: Low molecular weight heparin.

Table XIV: VTE prophylaxis recommendations in pregnancy

PREGNANCY	
Category	**Recommendation**
Women undergoing assisted reproductive therapy	Routine prophylaxis **Not** recommended
If they develop severe ovarian hyperstimulation syndrome	Prophylactic antithrombotic therapy with aspirin/LMWH recommended
Women who have a history of VTE	Postpartum anticoagulant prophylaxis recommended
Women with a history of VTE that was unprovoked or associated with a hormonal risk factor	Antepartum anticoagulant prophylaxis recommended

(*continued*)

Table XIV: Continued

Pregnant women having	Family history of VTE		
	None	With family history	Regardless of family history
Antithrombin deficiency		Postpartum prophylaxis	
Antithrombin deficiency or are homozygous for prothrombin mutation	Antepartum prophylaxis to prevent a first VTE event **Not** recommended		
Heterozygous for Factor V Leiden or prothrombin mutation		Postpartum prophylaxis **Not** recommended	
Heterozygous for Factor V Leiden or prothrombin mutation/protein C or S deficiency			Antepartum prophylaxis to prevent a first VTE event **Not** recommended
Heterozygous for the factor V Leiden mutation or prothrombin mutation or who have antithrombin, protein C, or protein S deficiency	Postpartum prophylaxis **Not** recommended		
protein C, or protein S deficiency,		Postpartum prophylaxis with LMWH ×6 weeks	
Antithrombin deficiency, and for those who are homozygous for Factor V Leiden mutation or have combined thrombophilias		Antepartum prophylaxis	Antepartum prophylaxis
combined thrombophilias or are homozygous for Factor V Leiden mutation or prothrombin mutation			Postpartum prophylaxis with LMWH or Vit K antagonists targeted at an INR of 2.0–3.0 for 6 weeks

Note: Wherever not specifically mentioned, no anticoagulation is recommended.
VTE: Venous thromboembolism; LMWH: Low molecular weight heparin; INR: International normalized ratio.

Table XV: VTE prophylaxis by health care workers are different levels of health care practice

Level of healthcare	Prophylaxis of VTE by HealthCare Workers					
	Patient/Family members	ASHA	ANM	Community Health Officer	Medical officer	Specialist
Community Level	Follow treatment as prescribed	Advise patients to follow treatment as prescribed				
Health & Wellness Centre				Advise patients to follow treatment as prescribed		
Primary Health Centre					Advise patients to follow treatment as prescribed Counsel on medication compliance	
Community Health Centre						Prescribe treatment as per guidelines
District Hospital						
Medical College Hospital						

VTE: venous thromboembolism; ASHA: Accredited Social Health Activist; ANM: Auxiliary Nurse Midwife.

ANNEXURE 2

VTE MANAGEMENT: RECOMMENDATIONS

Annexure 2 briefly outlines the task force VTE treatment recommendations through Tables I–XIV and Figure 1 appended below

Table I: Indications for outpatient management of VTE in settings

Outpatient Treatment (Home based)		
In DVT	Uncomplicated DVT and PE at low risk for complications	Uncomplicated DVT – No comorbid illness requiring admission – Low bleeding risk – No evidence of limb-threatening DVT – No Phlegmasia cerulea dolens, or limb ischemia
In PE	HESTIA[1] score 0	Low-risk PE + No RV dysfunction + Normal cardiac biomarker

DVT: Deep vein thrombosis; PE: Pulmonary embolism; RV: Right ventricle; VTE: venous thromboembolism.
Source: Adapted from [1]Zondag W, *et al.* J Thromb Haemost 2011 Aug;9(8):1500-7.

Table II: Preferred anticoagulant agent for VTE management

Choice of anticoagulant			
DOAC	**VKA preferred**	**UFH**	**LMWH**
Preferred agent in all settings other than those discussed under alternative agents	• Moderate to severe liver disease • eGFR < 30mL/min • APLA • Inhibitors or inducers of P-gp or • Strong inhibitors or inducers of CYP3A4 • Breast feeding mother • Financial constraints	• e GFR < 15 mL/min; • PE with hemodynamic instability	• Bridge for – VKA – Dabigatran – Edoxaban; Pregnancy; • APLA • Malignancy if DOAC cannot be used

eGFR: estimated glomerular filtration rate; APLA: Antiphospholipid syndrome; DOAC: Direct oral anticoagulants; VKA: Vitamin K antagonists; LMWH: Low molecular weight heparin; PE: Pulmonary embolism; VTE: venous thromboembolism.

Table III: Recommended duration of anticoagulation in VTE

Duration of anticoagulation		
Category	**Primary phase**	**Secondary Phase**
VTE provoked by transient risk factors	3 months	
VTE provoked by chronic (persistent) risk factors	3 months	Indefinite anticoagulation with periodic assessment (annual) for risk factors of bleeding and risk factors for VTE
Unprovoked VTE	3 months	Indefinite anticoagulation with periodic assessment for risk factors of bleeding
HAS-BLED score ≥ 4		Avoid indefinite anticoagulation

VTE: Venous thromboembolism.

Remarks

- **Secondary treatment phase**
  Vit K Antagonist @ INR 2-3 (A)
  Low-dose DOAC (Apixaban/Rivaroxaban) is as good as standard dose DOAC
- Aspirin 75 mg or 150 mg daily in people who decline extended anticoagulation treatment or patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy.
- Routine use of prognostic scores HERDOO2, Vienna and DASH scores, D Dimer testing, or ultrasound to detect residual vein thrombosis is no longer recommended in unprovoked VTE.

APPROACH TO MANAGEMENT

Annexure 2

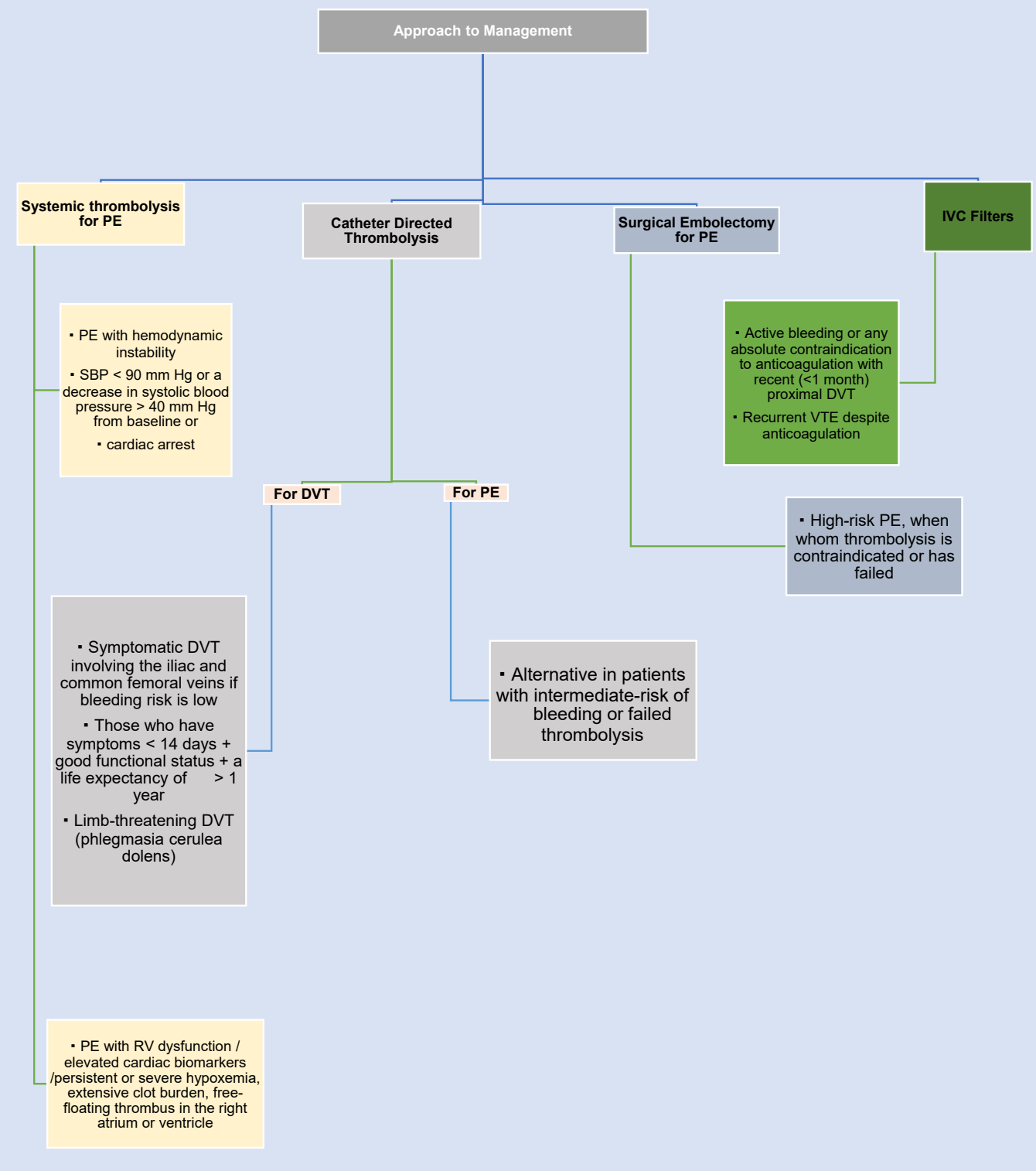

Figure 1: Approach to management of pulmonary embolism
DVT: Deep venous thrombosis; IVC: Inferior vena cava; PE: Pulmonary embolism; VTE: Venous thromboembolism; SBP: Systolic blood pressure.

Table IV: Recommendations for VTE treatment in pregnancy

PREGNANCY	
Drug of choice	**LMWH over UFH**
As soon as the patient is in labor, heparin should be stopped immediately	
⇩	
Spinal/epidural anesthesia or analgesia should be used 12 hours after prophylactic and 24 hours after therapeutic LMWH, while these techniques can be used 6 hours after stopping conventional heparin.	
⇩	
Heparins should be restarted at least 4–6 hours after removal of an epidural catheter.	
⇩	
At discharge, the patient may be transitioned to VKAs (safe during breastfeeding).	
⇩	
Total duration of anticoagulation for pregnancy associated DVT should be at least 3 months of anticoagulants or 6 weeks postpartum whichever is later.	

LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; VKAs: Vitamin K antagonist; VTE: venous thromboembolism; DVT: Deep venous thrombosis.

Table V: Recommendations for VTE treatment in malignancy

MALIGNANCY	
DOAC preferred	Apixaban Rivaroxaban Edoxaban
if DOAC cannot be used	LMWH
Alternative if patient does not accept injectable therapy	Vitamin K Antagonist
Duration	At least 6 months; Reassess the risk of recurrent VTE and bleeding before deciding on continued anticoagulation.

DOAC: direct oral anticoagulant; LMWH: Low molecular weight heparin; VTE: Venous thromboembolism.

Table VI: Recommendations for cerebral venous thrombosis treatment

CEREBRAL VENOUS THROMBOSIS		
Initial phase	**Primary & secondary phase**	**Duration**
LMWH or UFH	Warfarin or DOAC	3 months if transient risk factors
		At least 6 months if unprovoked
		Indefinite if persistent hypercoagulability identified

DOAC: direct oral anticoagulant; LMWH: Low molecular weight heparin; UFH: Unfractionated heparin.

Table VII: Recommendations for splanchnic venous thrombosis (SVT) treatment

SPLANCHNIC VEIN THROMBOSIS	
Acute SVT	**Incidental chronic SVT**
• DOACs should be considered in noncirrhotic patients • DOACs are contraindicated in Child-Pugh class C liver disease and for rivaroxaban in class B and C liver disease. • LMWH or VKAs if contraindications to DOACs. • Indefinite anticoagulation: unprovoked or persistent risk factors • Prophylactic banding should be instituted in cirrhotic patients to decrease variceal bleeding	Anticoagulation if malignancy or extensive SVT

SVT: Splanchnic venous thrombosis; DOAC: direct oral anticoagulant; LMWH: Low molecular weight heparin; VKA: Vitamin K antagonists.

Table VIII: Recommendations for VTE in Anti Phospholipid Antibody syndrome (APLA) syndrome

APLA (Anti Phospholipid Antibody syndrome)	
Triple positive APLA or Arterial thrombosis or patients with small vessel thrombosis or aPL-related cardiac valvular disease	Vit K Antagonists preferred over DOAC Indefinite anticoagulation.

APLA: Anti Phospholipid Antibody syndrome; DOAC: direct oral anticoagulant.

Table IX: Recommendations for superficial venous thrombosis treatment (SfVT)

SUPERFICIAL VEIN THROMBOSIS	
Anticoagulation if	**Options:**
• SfVT > 5 cm • proximity to SFJ • other risk factors for VTE – male sex – >65 years – cancer – systemic inflammation – previous VTE – no contraindications to anticoagulation	Fondaparinux 2.5 mg SC OD × 45 days Rivaroxaban 10 mg OD or Enoxaparin 40 mg OD × 30 days

SfVT: Superficial venous thrombosis; SFJ: Saphenofemoral junction; VTE : Venous thromboembolism; SC: subcutaneously; OD: once daily.

Table X: Recommendations for isolated distal deep venous thrombosis treatment

ISOLATED DISTAL DVT	
Serial imaging of the deep veins for 2 weeks over anticoagulation	If severe symptoms or risk factors for extension are absent – Elevated D-dimer – Thrombosis is extensive (e.g., >5 cm in length, multiple veins, >7 mm in maximum diameter) – Thrombosis is close to the proximal veins – No reversible provoking factor for DVT – Active cancer – History of VTE – Inpatient status

DVT: deep venous thrombosis; VTE : Venous thromboembolism.

Table XI: Recommendations for isolated subsegmental pulmonary embolism

ISOLATED SUBSEGMENTAL PULMONARY EMBOLISM	
Clinical surveillance if low risk for recurrent VTE	Anticoagulation if high risk for recurrent VTE due to following risk factors: – Inpatient status – Reduced mobility – Active cancer – No reversible risk factor for VTE – Pregnancy

VTE: venous thromboembolism

Table XII: Recommendations for thrombosis associated with heparin induced thrombocytopenia (HIT)

Management of HIT	
4T score > 4	***4T score 4–5***
Pretest probability of HIT is intermediate/high	Pretest probability intermediate
⇩	⇩
Discontinue heparin	Anticoagulation for patients with suspected HIT + Prophylactic dose if bleeding risk is high
⇩	⇩
Switch to alternate anticoagulant • Argatroban/Bivaluridin/ Danaparoid • Fondaparinux • DOAC	No Vit K Antagonists No prophylactic platelet transfusion

Table XII: Continued

Choice of anticoagulant in HIT	
Critical illness, high bleeding risk or potential need for urgent procedure.	Argatroban/Bivalirudin
Clinically stable	Fondaparinux/DOAC
Life or limb threatening thrombosis.	Argatroban/Bivalirudin/ Danaparoid Fondaparinux
Child-Pugh Class B and C	Avoid DOAC or Argatroban
⇩	
Transition to DOAC when patient is clinically stable	
⇩	
Start DOAC • within 2 hours of stopping argatroban or bivalirudin infusion, • within 8–12 hours after stopping Danaparoid infusion, • 24 hours after last dose of fondaparinux VKAs if platelet count > 1.5L/ul: Overlap parenteral agent with warfarin for ≥ 5 days and until INR: 2–3	
Duration of anticoagulation	**3 months** **or** **till platelet recovery if no DVT**

HIT: heparin induced thrombocytopenia; DOAC: direct oral anticoagulants; VKAs: Vitamin K antagonist; INR: International normalized ratio.

Table XIII: Recommendations for management of post thrombotic syndrome (PTS)

POST THROMBOTIC SYNDROME (PTS)	
Prophylaxis	Optimal anticoagulation is key for PTS prevention.
	Use of compression stockings is not recommended
Catheter directed thrombolysis	▪ For DVT involving the iliac and common femoral veins if bleeding risk is low ▪ Those who have symptoms <14 days, ▪ good functional status, ▪ a life expectancy of >1 year
Management	<u>All cases</u> ▪ Elastic compression stockings, ▪ leg elevation, ▪ weight loss, ▪ exercise
	Pentoxifylline may be used for treating venous ulcers on its own or with compression stockings.
	<u>Moderate-to-severe PTS</u> Endovascular recanalization or surgical bypass or disobliteration may be considered in patients with chronic venous occlusion class CEAP 4–6
	<u>Severely symptomatic patients with PTS</u> Segmental vein valve transfer or venous transposition may be considered

PTS: post thrombotic syndrome; DVT: deep vein thrombosis; CEAP: Clinical Etiological Anatomical Pathophysiological.

Table XIV: VTE management recommendations at various levels of healthcare delivery

Level of healthcare	Management of VTE by healthcare worker					
	Patient/family members	ASHA	ANM	Community health officer	Medical officer	Specialist
Community Level	Follow treatment as prescribed	Advise patients to follow treatment as prescribed				
Health & Wellness Centre				Advise patients to follow treatment as prescribed		
Primary Health Centre					Advise patients to follow treatment as prescribed Counsel on medication compliance	
Community Health Centre						Advise patients to follow treatment as prescribed
District Hospital						
Medical College Hospital						

VTE: venous thromboembolism; ASHA: Accredited Social Health Activist; ANM: Auxiliary Nurse Midwife.

ANNEXURE 3

Annexure 3 describes the various scoring systems recommended by the task force for VTE treatment and prophylaxis through Tables I–IX.

SCORING SYSTEMS

Table 1: Scoring systems for VTE prophylaxis in medical and surgical patients

Scoring system	Population at risk	Outputs and risk categories	Lowest risk category	Highest risk category	Comments
Caprini[1]	Surgical patients	Risk of VTE at 3 months	Lowest risk <0.7% (0 points)	Highest risk 10.7% (≥9 points)	No formal validation with original study. External validation studies in surgical subpopulations.
Padua Prediction Score[2]	Medical inpatients	Risk of VTE at 3 months	Lowest risk 1.1% (<4 points)	Highest risk 3.5% (≥4 points)	Internal validation showing 32-fold variation in VTE risk across 11 studies An external validation in patients with sepsis did not find correlation with VTE risk.
IMPROVE Score[3]	Medical inpatients	Risk of VTE at 3 months	Lowest risk 0.4% (0 points)	Highest risk 5.7% (≥4 points)	Validation includes 1 retrospective, 1 case control, and 1 prospective multicenter study*
Khorana Score[4]	Ambulatory cancer patients	Risk of VTE at 2.5 months	Lowest risk 0.8% (0 points)	Highest risk 7.1% (≥3 points)	Internal development and validation cohort included in original study. Multiple prospective and retrospective validation studies

*AUC 0.69–8.77 for predicting VTE.
Negative predictive value 98.5%, Positive predictive value 6.7%, C-static = 0.7.
VTE: venous thromboembolism.
Source: [1]Caprini JA, *et al.* Semin Thromb Hemost 1991;17 Suppl 3:304-12. [2]Vardi M, *et al.* J Thromb Haemost 2013 Mar;11(3):467-73. [3]Spyropoulos AC *et al.* Chest 2011 Sep;140(3):706-14. [4]Dutia M *et al.* Cancer 2012 Jul 15;118(14):3468-76.

Table II: PADUA scoring systems for VTE prophylaxis in medical patients

PADUA score	
VTE risk factor	**Points**
Decreased mobility	3
Thrombophilia	3
Previous trauma or surgery within the last month	2
Age ≥ 70	1
Heart or respiratory failure	1
Ischemic stroke or acute myocardial Infarction	1
Acute rheumatologic disorder and/or acute infection	1
Obesity	1
Hormonal therapy	1

Score < 4	**Low risk**	Confers a <0.3% 90-day risk of symptomatic VTE in patients who do not receive anticoagulation during hospitalization
Score ≥ 4	**High risk**	Confers an 11% risk of symptomatic VTE

VTE: Venous thromboembolism.
Source: Vardi M, *et al.* J Thromb Haemost 2013 Mar;11(3):467-73.

Table III: IMPROVE VTE scoring systems for VTE prophylaxis in medical patients

IMPROVE VTE score	
VTE Risk Factor	**VTE risk score**
Previous VTE	3
Known thrombophilia	2
Current lower limb paralysis or paresis	2
History of cancer	2
ICU/CCU stay	1
Complete immobilization ≥1 day	1
Age ≥ 60 years	1

IMPROVE: International Medical Prevention Registry on Venous Thromboembolism (VTE); CCU/ICU: Cardiac/Intensive Care Unit.

Score < 3	**Low risk**	Confers a <1.5% VTE risk
Score ≥ 3	**High risk**	Confers an >4% risk of symptomatic VTE

Source: Spyropoulos AC *et al.* Chest 2011 Sep;140(3):706-14.

Table IV: 4T score for heparin induced thrombocytopenia risk stratification and portability

4T Score			
Category	**2 points**	**1 point**	**0 point**
Thrombo-cytopenia	>50% fall, or nadir ≥20 × 10^9/L	30–50% fall, or nadir 10–19 × 10^9/L	< 30% fall, or nadir <10 × 10^9/L
Timing of the decrease in platelet count	Days 5–10, or ≤ day 1 with recent heparin (past 30 days)	> Day 10 or timing unclear, or < day 1 if heparin exposure within past 30–100 days	< Day 4 (no recent heparin)
Thrombosis or other sequelae	Proven thrombosis, skin necrosis, or acute systemic reaction after heparin bolus	Progressive, recurrent, or silent thrombosis; erythematous skin lesions	None
Other causes of thrombo-cytopenia	None evident	Possible	Definite

Score	Probability	Risk of HIT
0–3	**Low**	<1%
4–5	**Intermediate**	~10%
6–8	**High**	~50%

Source: Lo GK, *et al.* J Thromb Haemost 2006 Apr;4(4):759-65.

Table V: IMPROVE bleeding risk assessment method for calculating bleed risk on anticoagulants

IMPROVE BLEED RAM	
Risk Factors	**Point**
Moderate renal failure (CrCI 30–50 mL/min)	1
Male sex	1
Age 40–84 years	1.5
Active cancer	2
Rheumatic disease	2
Central venous catheters	2
Admission in intensive care	2.5
Severe renal failure (CrCI < 30 mL/min.)	2.5
Liver insufficiency (INR > 1.5)	2.5
Age ≥ 85	3.5
Thrombocytopenia (<50 × 10^9 cell/L)	4
Recent (3 months) bleeding	4
Active gastrointestinal ulcer	4
High bleeding risk when total score ≥ 7	4

Score	Risk	Implication
<7	**Low**	Has a major bleed risk of approximately 0.4%
≥7	**High**	Has a major bleed risk of 4.1%

INR: International normalized ratio; CrCI: Creatinine clearance.
Source: Adapted from Decousus H *et al.* IMPROVE Investigators. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. Chest 2011 Jan;139(1):69-79.

Table VI: Caprini scoring systems for VTE prophylaxis in surgical patients

Caprini score			
-35 points	**3 points**	**2 points**	**1 point**
• Stroke (in the previous month) • Fracture of the hip, pelvis, or leg • Elective arthroplasty • Acute spinal cord injury (in the previous month)	• Age 75 years • Prior episodes of VTE • Positive family history for VTE • Prothrombin 20.210A • Factor V Leiden • Lupus anticoagulants • Anticardiolipin antibodies • High homocysteine • Heparin-induced thrombocytopenia • Other congenital or acquired thrombophilia	• Age 61–74 years • Arthroscopic surgery • Laparoscopy lasting >45 minutes • General surgery lasting >45 minutes • Cancer • Plaster cast • Bed bound for >72 hours • Central venous access	• Age 41–60 years • BMI > 25 kg/m^2 Minor surgery • Edema in the lower extremities • Varicose veins • Pregnancy • Postpartum • Oral contraceptive • Hormonal therapy • Unexplained or recurrent abortion • Sepsis (in the previous month) • Serious lung disease such as pneumonia (in the previous month) • Abnormal pulmonary function test • Acute myocardial infarction • Congestive heart failure (in the previous month) • Bed rest • Inflammatory bowel disease

BMI: Body mass index; VTE: venous thromboembolism.

Score < 2	Low risk
Score 3–4	Moderate risk
Score ≥ 5	High risk

Source: Caprini JA, *et al.* Clinical assessment of venous thromboembolic risk in surgical patients. Semin Thromb Hemost 1991;17(Suppl 3):304-12.

Table VII: Khorana scoring systems for VTE prophylaxis in oncology patients

Khorana Score	
Patients' characteristics	**Risk score**
Site of cancer	
• Very high risk (stomach, pancreas)	2
• High risk (lung, lymphoma, gynecological, bladder, or testicular)	1
Pre chemotherapy platelet count ≥ 350 × 10^9/L	1
Pre chemotherapy hemoglobin level < 100 g/L or use of red cell growth factors	1
Pre chemotherapy leukocyte count > 11 × 10^9/L	1
Body Mass Index ≥ 35 kg/m^2	1

Score 0	**Low risk**
Score 1–2	**Intermediate risk**
Score > 2	**High risk**

VTE: venous thromboembolism.
Source: Dutia M, White RH, Wun T. Risk assessment models for cancer-associated venous thromboembolism. Cancer 2012 Jul 15;118(14):3468-76.

Table VIII: HESTIA criteria
HESTIA Criteria
If any of the below are answered "Yes," the patient should NOT be treated as an outpatient.
1. Hemodynamically unstable?
2. Thrombolysis or embolectomy necessary?
3. Active bleeding or high risk of bleeding?
4. Oxygen supply to maintain oxygen > 90% > 24 hours?
5. Pulmonary embolism diagnosed during anticoagulant treatment?
6. In severe pain needing IV pain medication > 24 hours (or multiple doses in the ED)?
7. Medical or social reason for treatment in hospital > 24 hours?
8. Creatinine clearance less than 30 mL/min?
9. Severe liver impairment or disease?
10. Pregnant?
11. Documented history of heparin-induced thrombocytopenia?
Source: Adapted from Zondag W, *et al.* J Thromb Haemost 2011 Aug;9(8): 1500-7.

Table IX: HAS-BLED score for bleeding risk assessment on anticoagulant use	
HAS-BLED-Score	
Risk-factor	**Scores**
Hypertension	1
Abnormal-renal/liver function	1 or 2
Strokes	1
Bleeding tendency	1
Labile-INR	1
Age (e.g., >65)	1
Drugs-(e.g., concomitant aspirin, NSAIDs,) or alcohol	1 or 2
Maximum-score	9
Notes: Hypertension is defined as a systolic blood pressure >160 mmHg. 1 point is awarded for each of abnormal renal or liver function, and drugs or alcohol. INR: International normalized ratio; NSAID: Nonsteroidal anti-inflammatory drugs.	

Score	**Risk of Bleeding**
0–2	**Low risk**
Score ≥ 3	**High risk**
Source: Adapted from Pisters R, *et al.* Chest 2010 Nov;138(5):1093-100.	

ANNEXURE 4

DIAGNOSIS OF VTE

Ineffectively managed lower extremity DVT has risks associated with it (e.g., pulmonary emboli) as also the inherent risks of anticoagulation (e.g., resultant major or life-threatening bleeding); hence, the accurate diagnosis of VTE is essential [Figure 1]. Features of lower extremity DVT are usually nonspecific, and many patients are asymptomatic.

History: DVT should be suspected in patients who present with leg swelling, pain, warmth, and erythema. Information that should be sought from patients and informants include:

(a) History of immobilization or (prolonged) hospitalization
(b) Recent surgery or trauma (typically within 12 weeks of surgery or trauma)
(c) Obesity
(d) Previous VTE
(e) Malignancy or symptoms suggestive of malignancy
(f) Use of oral contraceptives or hormone replacement therapy
(g) Pregnancy or postpartum status
(h) Stroke with hemiplegia or immobility
(i) Age > 65 years
(j) Family history of VTE
(k) Heart failure
(l) Inflammatory bowel disease

Physical examination—A thorough physical examination of the legs, abdomen, and pelvis should be performed in patients with suspected DVT to look for the following by the "Look–Touch–Measure" technique:

(a) Dilated superficial veins
(b) Unilateral edema or swelling with a difference in calf or thigh diameters
(c) Unilateral warmth, tenderness, erythema
(d) Pain and tenderness along the course of the involved major veins
(e) Local or general signs of malignancy.

Note: Initial diameters should be recorded at presentation to maintain a baseline. A larger calf diameter is the most useful finding in the presentation. Subsequent measurements are not of much significance, with pain and tenderness being a more reliable indicator. Homans' sign (calf pain on passive dorsiflexion of the foot) is unreliable for the presence of DVT.

Laboratory Routine laboratory tests (e.g., complete blood count, routine biochemistry tests, liver function tests, coagulation studies) are not useful diagnostically but may provide clues as to the underlying cause and may influence treatment decisions if DVT is confirmed.

Young patients (<40 years) with an episode of unprovoked VTE in unusual sites (cerebral venous sinuses and splanchnic circulation) and those with a history of VTE in the family or recurrent VTE will warrant a screen for inherited thrombophilia. The duration of anticoagulation varies from long term in recurrent VTE to short term (3 months) in the presence of reversible risk factors like surgery. All non genetic tests for thrombophilia (PC, PS, AT, APC-R) should be done after withdrawal of anticoagulation for a period of 4 weeks. However, genetic tests such as FVL,

prothrombin gene mutation, and Methylenetetrahydrofolate reductase (MTHFR) gene mutations can be tested during anticoagulation.

In the Indian population, most of the studies have been limited to certain variants only. Many Indian studies have reported the role of MTHFR polymorphisms in VTE risk; however, a recently published report suggests MTHFR polymorphisms should not be a part of inherited thrombophilia testing and eliminating MTHFR from thrombophilia testing will reduce patient concerns and decrease healthcare costs.

Suspected first DVT (risk stratification)

An approach that incorporates clinical assessment of the pretest probability (PTP) and D-dimer testing in selected patients is recommended. This approach allows for the strategic use of US for diagnosis or alternative imaging modalities such as CT or MRI. The goal of diagnostic testing is to "rule-in" (>85% posttest probability of DVT) or "rule out" DVT (<2 % posttest probability of VTE in the next 3 months) with an acceptable level of certainty, thereby justifying instituting or withholding anticoagulant therapy, respectively.

Assessment of clinical PTP In patients with suspected first DVT, we recommend estimation of the clinical PTP. Subsequent measurement of the D-dimer level and compression US are dependent upon the assigned PTP of DVT. We may use the Wells score for the purpose of estimating PTP. Some experts, due to reproducibility, prefer the revised Geneva system as it also overcomes the interobserver variability.

Table I: Wells criteria for the prediction of deep vein thrombosis (DVT)

Wells Score	
Clinical feature	**Score**
Active cancer (treatment ongoing or within previous 6 months or palliative care)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for >3 days or major surgery, within 4 weeks	1
Localized tenderness along the distribution of deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared to the asymptomatic leg (measured below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (non varicose)	1
Alternative diagnosis as likely or more likely than that of DVT	−2

Score	Classification
3–8	High probability
1–2	Moderate probability
≤0	Low probability

Source: Modi *et al.* World Journal of Emergency Surgery (2016) 11:24.

Table II: Revised Geneva Score

Items	Points
Previous PE or DVT	1
Heart Rate	
75–94 BPM	1
≥95 BPM	2
Previous surgery or fracture	1
Hemoptysis	1
Active cancer	1
Unilateral leg pain	1
Pain on lower limb palpation and unilateral edema	1
Age > 65 Years	1

PE: Pulmonary embolism; DVT: Deep vein thrombosis; BPM: Beats per minute.

3 Point Score	Clinical Probability
≥5	High
2–4	Intermediate
0–1	Low

2 Point Score	Clinical Probability
≥3	PE Likely
0–2	PE Unlikely

Source: Le Gal G, *et al.* Ann Intern Med 2006 Feb 7;144(3):165-71.

In patients with suspected first DVT, it is recommended that based on the clinical PTP, further action should be taken:

(a) Low probability—In patients with a **low** PTP for DVT, we recommend that D-dimer levels be obtained. Patients in whom the D-dimer level is normal (e.g., <500 ng/mL) do **not** need further testing, while those in whom the D-dimer is positive (e.g., ≥500 ng/mL) should have US of the lower extremities. Patients can proceed directly to US if the D-dimer is expected to be positive due to another condition. DVT is diagnosed

if US is positive; no further testing is required if US is negative.

(b) Moderate probability—In patients with **moderate** PTP for DVT, we recommend that D-dimer levels be obtained. Patients in whom the D-dimer level is normal do **not** need further testing, while those in whom the D-dimer is positive should have US of the lower extremities. Patients can proceed directly to US if the D-dimer is expected to be positive due to another condition. DVT is diagnosed if US is positive. When neither proximal nor distal DVT is identified on the whole leg US, no further testing is required; in contrast, in those in whom the proximal US is negative, repeat proximal US should be performed at one week to detect extension of distal DVT into the proximal veins.

(c) High probability—For patients with a **high** PTP for DVT, we suggest that US be performed. DVT is diagnosed if US is positive. If DVT is not identified, options include high sensitivity D-dimer level measurement (if not expected to be positive due to another condition), repeat proximal compression ultrasonography (CUS) at one week (off anticoagulation), whole leg US (if not already performed), or iliac vein US (when iliac vein DVT is suspected). Choosing among these options should be individualized. In general, if one or more of these tests are negative in a patient without proximal DVT on ultrasound, then no further testing is required.

D-dimer

D-Dimer is a degradation product of cross-linked fibrin and is elevated in nearly all patients with acute DVT. However, it is nonspecific since elevated levels are found in many other conditions (e.g., malignancy, sepsis, recent surgery or trauma, pregnancy, renal failure), i.e., D-dimer has high sensitivity but poor specificity for VTE. Hence a negative result (e.g., <500 ng/mL) is useful for ruling out DVT, particularly in those with a low or moderate PTP for thrombosis; however, a negative test is obtained in about 30% of outpatients (lower in inpatients or if there has been a previous VTE). A positive result (e.g., ≥500 ng/mL) is not diagnostic and indicates the need for further investigation. D-dimer testing is of limited value in patients with high PTP since the negative predictive value is lower in this population. In summary, D-dimer assay should not be used as a stand-alone test in patients suspected of having DVT but rather should be used in conjunction with clinical PTP and/or US.

Imaging

CUS with Doppler is the diagnostic test of choice in patients with suspected DVT. In general, the sensitivity and specificity of proximal CUS is greater than 95%. Duplex US has less accuracy than CUS since the specificity of an abnormal duplex ultrasonogram is lower than that of an abnormal compression ultrasonogram. Point-of-care-US is not recommended for diagnosis unless the situation is urgent or emergent.

Ultrasonography interpretation—Interpretation of CUS in patients with a first suspected DVT:

(a) ***Positive***
   (i) Using ultrasound probe pressure, the presence of thrombus is diagnosed by demonstrating the noncompressibility of the imaged vein. Veins that can be assessed for compressibility are proximal (e.g., the common femoral, femoral, and popliteal veins) and distal veins (e.g., peroneal, posterior and anterior tibial, and muscular veins); iliac veins often cannot be assessed for compressibility.
   (ii) Lack of compressibility of a vein with the ultrasound probe is the most sensitive (>95%) and specific (>95%) sonographic sign for **proximal** vein thrombosis.
   (iii) The addition of color flow Doppler does not improve the sensitivity but can provide supportive evidence of thrombus and also help to identify calf veins.
   (iv) Variation of venous size with the Valsalva maneuver has a low sensitivity and specificity for the diagnosis.
   (v) In contrast, CUS is less sensitive for the detection of calf vein and iliac vein thrombus since these veins are less readily compressed (particularly calf veins).

(b) **Negative**—A negative study is one that demonstrates full compressibility of all imaged veins.

(c) **Nondiagnostic**—A nondiagnostic study is one where there is uncertainty about whether DVT is present or absent.
   (i) Nondiagnostic findings are less common in outpatients compared with inpatients, with less than 5% of outpatients expected to have nondiagnostic findings of the proximal veins.
   (ii) Nondiagnostic findings are also less common when imaging the proximal veins compared with the distal veins (i.e., with whole leg US); however, nondiagnostic findings that are confined to the distal veins are also less important and can usually be managed by withholding anticoagulant therapy while doing serial ultrasound testing.

(iii) The main reasons for a nondiagnostic examination are:
  (aa) difficulty visualizing the deep veins because of morbid obesity, edema, recent surgery or trauma, skin lesions, contractures, or leg casts.
  (ab) although the deep veins are well visualized, small or atypical appearing abnormalities of uncertain significance may be identified.
  (ac) in patients with previous DVT, when a thrombus is present, it is often difficult to assess if it is acute or old (residual thrombosis can persist indefinitely).

Further investigation(s) (e.g., repeat proximal CUS at three and seven days) in those with nondiagnostic studies should be individualized and depend upon why the US is considered nondiagnostic, the extent and position of the venous segment (e.g., distal or proximal veins) that is nondiagnostic, clinical PTP, results of D-dimer testing, and the clinician's overall assessment of the risk associated with undiagnosed DVT.

Imaging at first occurrence

For patients who are not initially stratified according to clinical PTP of low, moderate, or high risk, the initial test of choice is US.

(a) When the whole leg US is negative, no further investigations are necessary unless iliac vein thrombosis is suspected.
(b) When the proximal CUS is negative, options include whole leg US (to detect distal DVT), repeat proximal CUS at 3–7 days (to detect extension of distal DVT into the proximal veins), measuring a high-sensitivity D-dimer level, or assessing clinical PTP (low PTP excludes DVT with a negative proximal CUS).

Diagnostic compressive US

(a) Proximal CUS—In most patients with suspected DVT, CUS with Doppler is the imaging test of choice. The presence of DVT is diagnosed by demonstrating noncompressibility of the imaged vein.
(b) Whole leg CUS—Both proximal and whole leg US have a high sensitivity for the detection of thrombus in the proximal veins (i.e., common femoral, femoral, and popliteal veins). Whole leg US additionally examines the veins in the calf (peroneal, posterior and anterior tibial, and muscular veins) and can, therefore detect isolated distal DVT.

Imaging in Recurrence

For most patients with suspected ipsilateral DVT recurrence, proceeding directly to US (proximal or whole leg US) or using an approach similar to that described for the first suspected DVT is appropriate. When an ultrasonographic abnormality is identified in patients with suspected recurrence, it may be difficult for the clinician to determine whether it is due to an old or new thrombus. The availability of a previous ultrasound report that documents the extent of residual thrombosis greatly improves the accuracy of ultrasound for recurrent DVT. In the absence of a previous ultrasound report, magnetic resonance direct thrombus imaging (MRDTI) may be useful.

Alternative imaging modalities—For patients with suspected DVT, contrast-enhanced computed tomographic venography (CTV) and magnetic resonance venography (MRV) are rarely used diagnostically, unless there is uncertainty about iliac vein or IVC thrombosis after US. Ascending contrast venography, which was the earlier gold standard for DVT diagnosis, and impedance plethysmography are now not recommended to be used.

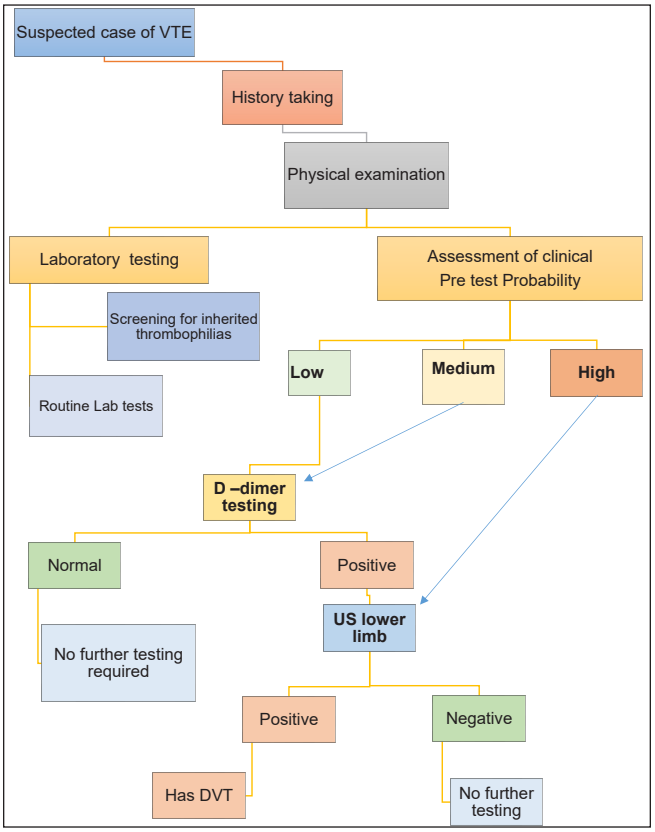

Figure 1: Clinical Decision Aid – Diagnostic workup of a suspected case of VTE
DVT: Deep venous thrombosis; VTE: Venous thromboembolism; US: Ultrasonography.

ANNEXURE 5

MOLECULAR ASPECTS AND GENETIC BACKDROP OF VTE

Ordering thrombophilia tests is easy; determining whom to test and how to use the results is not (Connors 2017).

To understand the Indian perspective of genetic risk factors in VTE, a literature review was undertaken to identify the genetic variants that have been reported in association with VTE [Table I].

Indian data depict that the established thrombophilia genetic markers FV Leiden and Prothrombin G20210A have a limited role from the Indian subcontinental perspective. Several studies have shown the role of FV Leiden in VTE risk, however, only with certain comorbidities in the Indian population. To understand this limited role, we reviewed the literature from other Asian countries also. The data show no role of established genetic markers in the Chinese and Thai populations as well. The prevalence of the FV Leiden phenotype, shown by Ridker *et al*. is 0.4% in an Asian population.

In the Indian population, most of the hospital-based studies have been limited to certain variants only. Many studies have reported the role of MTHFR polymorphisms in VTE risk; however, a recently published report suggests MTHFR polymorphisms should not be a part of inherited thrombophilia testing and eliminating MTHFR from thrombophilia testing will reduce patient concerns and healthcare costs.

Table I: VTE variants studied and reported in India

Variant	Association	Sample Size	Author & Journal
Factor V Leiden G1691A mutation and prothrombin G20210A	Significantly associated in the Kashmiri population	250 patients 250 controls	Shafia *et al*., **Gene** (2018)
MTHFR C677T polymorphism	No significant association in the Kashmiri population		
EDN T1370G (endothelin gene)	Significant association with VTE occurrence	133 patients with VTE 164 controls	Kumari *et al*., **Clinical and Applied Thrombosis/ Hemostasis** (2017)
CYP4F2 1347 G> A polymorphism	Significant association with PVT (portal vein thrombosis)	91 PVT cases 136 controls	Kalpana *et al*., **Medicine** (2019)
JAK2V617F mutation	May increase the risk of thrombosis in patients with Philadelphia negative chronic myeloproliferative neoplasms.	65 (46 males and 19 females) CMPN cases	Singh *et al*., **Indian J Pathol Microbiol** (2018)
FV Leiden	Inherited APCR in patients with DVT—significant association	50 APCR + patients 50 controls	Sharma *et al*., **Clinical and Applied Thrombosis/ Hemostasis** (2017)
Factor V leiden (FVL) mutation and PAI 4G/4G homozygosity	Increase DVT risk in pregnant women in Western India	Prevalence of DVT in 34,720 prenatal women	Vora *et al*. **Thrombosis** (2007)
Factor V Leiden	Significant Association with Myocardial Infarction Patients	120 patients of MI (age < 40) 100 controls	Khare *et al*., **Indian Journal Of Medical Sciences** (2004)
MTHFR 677TT polymorphism	Increased risk of thrombosis in patients with hyperhomo-cysteinemia	124 patients with DVT	Paradkar *et al*., **Indian Journal of Clinical Biochemistry** (2020)
MTHFR 677C/T	Contribute toward susceptibility to thrombosis	93 male patients 102 controls	Kumari *et al*., **Thrombosis** (2014)
PAI-1 −844G/A, fibrinogen-β −455G/A	Protective role		
FVL (1691G/A), pro-thrombin (20210G/A), and TFPI (−536C/T)	Limited role in Indian population		
eNOS894G/T and 2479G/A polymorphisms	Possess the risk of VTE	100 cases of DVT 200 controls	Akhter*et al*., **Clinical Laboratory** (2022)

Table I: Continued

Variant	Association	Sample Size	Author & Journal
MTHFR C677T and prothrombin G20210A mutation	No significant association in west Indian population	Cases of DVT 252 males 180 females	Ghosh *et al*., **Clinical and Applied Thrombosis/ Hemostasis** (2001)
Variant allele 4G of PAI-1 4G/5G polymorphism	Significantly associated with ischemic stroke in young Indians	100 cases 100 controls	Akhter *et al*., **Clinical and Applied Thrombosis/ Hemostasis** (2017)
TFPI polymorphisms (polymorphisms (33T > C, 399C > T, and 536C > T))	33T > C protective and 399C > T as risk factors	100 DVT patients 100 controls	Kamal *et al*., **Blood Cells, Molecules, and Diseases** (2017)
CYP2C9 polymorphisms (rs1799853, rs1057910, rs1057909, and rs28371686), VKORC1 promoter polymorphism (rs9923231)	CYP2C9 and VKORC1 polymorphisms, suggested that an increase in the anti-coagulant drug dose may be necessary for Indian patients	124 patients with DVT	Arunkumar *et al*., **Drug Discoveries & Therapeutics** (2017)

VTE: venous thromboembolism; PVT: Portal vein thrombosis; DVT: Deep vein thrombosis; MI: Myocardial infarction; APCR: Activated protein C Resistance; CMPN: Chronic Myeloproliferative Neoplasms.

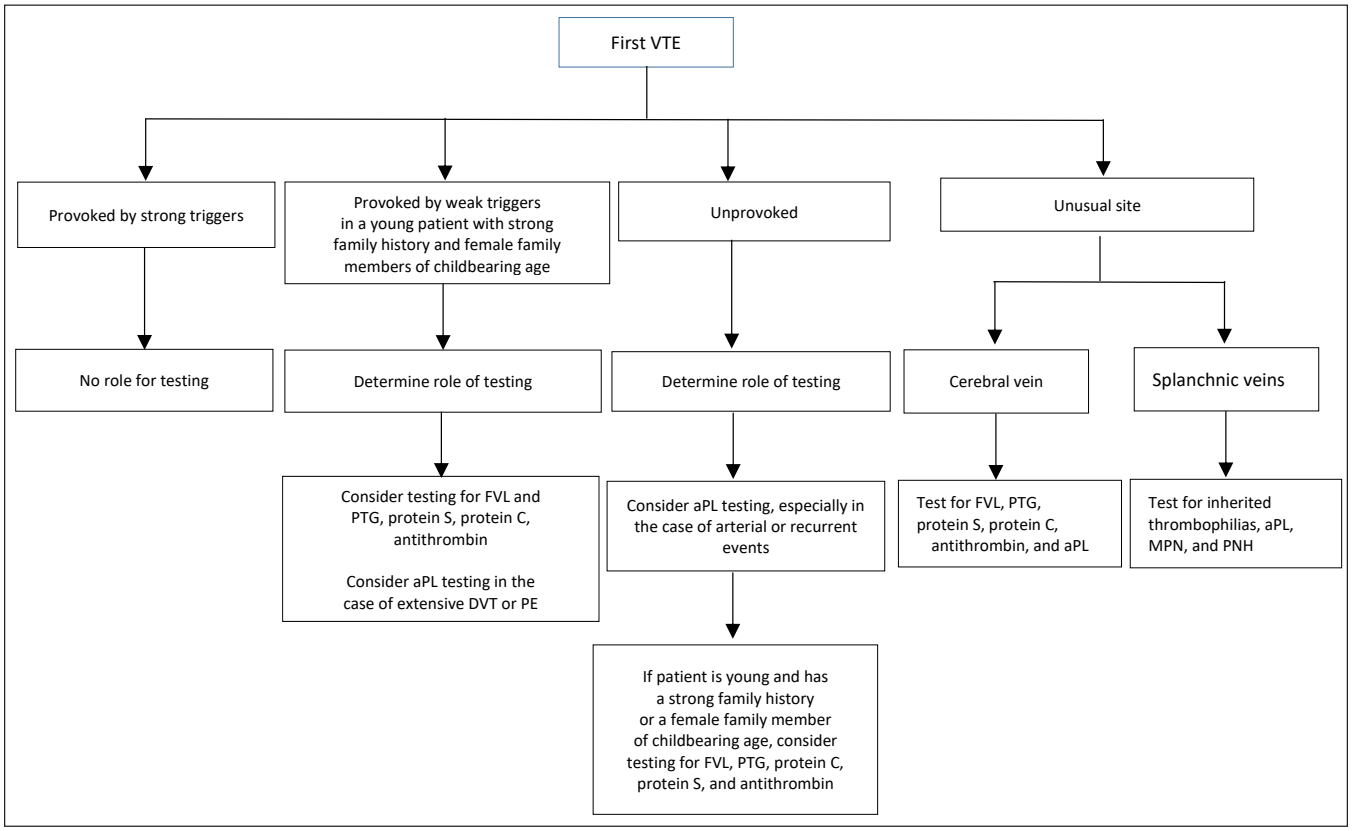

Figure 1: Algorithm for Selecting Patients with a First VTE episode for Thrombophilia Testing.
VTE: venous thromboembolism; FVL: Factor V leiden; PTG: Prothrombin gene mutation; MPN: myeloproliferative neoplasms; PNH: Paroxysmal Nocturnal Hemoglobinuria; aPL: Antiphospholipid antibody.
(Source: N Engl J Med 2017;377:1177–87)

We also reviewed the literature regarding European and American populations and a recently published trans-ancestry meta-analysis, and also another independent study that tested approximately 13 million DNA sequence variants for association with VTE and reported the variants associated with VTE [Figure 1]. A similar approach could be replicated in the Indian population, and validation of these variants in the context of different regional/ethnic population groups could be considered to identify a set of variants uniquely associated with Indian population (if at all).

Hence, a large-scale population-based genome-wide association study is recommended amongst the Indian population with representation from different regional and ethnic groups to identify the genetic associations with VTE.

ANNEXURE 6

PUBLIC HEALTH RESPONSE TO REDUCING DVT AND PE

DVT and PE are major public health problems across the world today. It is essential for policymakers to direct public health responses to reducing the burden of VTE, in various settings. The required set of actions is ideally organized by the CARE framework to be customized to the requirement and context on a regional basis:

(a) *Communication* refers to the provision of information to motivate and empower individuals and healthcare professionals in various settings to catalyze change that will lead to more effective prevention, diagnosis, and treatment of first-time and recurrent DVT/PE.
(b) *Action* refers to interventions and activities that will assist various stakeholders in preventing, screening, diagnosing, and managing medical conditions or diseases more effectively.
(c) *Research* into the various aspects of VTE that may be required to be addressed or investigated further.
(d) *Evaluation* refers to the ongoing assessment of the various activities and interventions for VTE to ascertain their practicality, feasibility, cost benefit, etc.

Note: The US Surgeon General's "call to action to prevent DVT and PE" (2008) provides an excellent framework which can be suitably adapted to the Indian context.

Setting: Communities

The community, which comprises individuals and their families, needs to understand DVT and PE as threats to their health and life; they need to understand the risk factors for these conditions and to learn how to reduce these risks. They need to recognize the signs and symptoms and to know about available medical management modalities. Patients and their family members should actively discuss these conditions when interacting with their healthcare providers. The goal is to raise awareness among patients and their family members and empower them to ask their healthcare providers about preventive treatment during hospitalization, after a traumatic event, or in other high-risk situations.

A broad-based health risk communication campaign can play a major role in raising awareness at the community level. From a public education and social marketing standpoint, communication campaigns can disseminate structured health messages aimed at educating individuals about DVT/PE. It is essential to harness social and other media to address gaps that exist in the availability of appropriate educational materials pertaining to VTE, among other medical conditions. Emphasis should be placed on opportunities for communication at the family and community level, with a specific focus on high-risk groups.

Communication

Policymakers and healthcare administrators need to take the following steps, among others:

(a) Increasing public knowledge of DVT/PE and the severity of the burden these disorders place on society.
(b) Educating people about the signs, danger signs, and precipitating circumstances, including medical procedures, hospital stays, and trauma.
(c) Educating the general public on genetic predispositions to DVT/PE.
(d) Supporting public education by letting people know how serious the issue is in terms of incidence and mortality/morbidity.
(e) Publication of specific patient tales via news channels and social media, as human interest stories frequently have a greater impact than statistics alone.
(f) Highlighting the substantial gap between what is understood about how to prevent and treat DVT/PE and what is happening in practice today.
(g) Facilitating the development and dissemination of uniform messages about DVT/PE that are consistent with existing guidelines.

Action

Actions that need to be initiated by policymakers and medical administrators include but are not limited to:

(a) Forming community coalitions to sponsor public awareness campaigns.
(b) Developing tools and materials that patients can use when talking with their physicians and other health professionals.
(c) Creating local networks and peer support programs for patients and their family members.
(d) Working with volunteer groups, professional societies, and the media as part of a national awareness campaign intended to educate both the public and health professionals about the incidence of the disease, along with its symptoms and risk factors.

(e) Making available to the media accurate messages about DVT/PE for news stories and media programming, including television shows or podcasts.
(f) Encouraging community-based advertising campaigns.
(g) Consider using a celebrity spokesperson to deliver messages about these conditions, especially a celebrity who may have had a personal experience related to either DVT or PE.

Research and Evaluation

It is recommended for policymakers and healthcare system administrators to assign priority to this often neglected aspect of interventions focused on medical conditions. This is essential to:

(a) Gain a better understanding of what the public already knows about DVT/PE, gaps in their understanding, and how best to address those gaps.
(b) Develop and test messages to determine which approaches work best to educate the public, inform them of when they are at risk, and empower them to raise issues proactively with their clinicians.
(c) Investigate, in a culturally and linguistically appropriate manner, why certain ethnic groups are more or less likely to develop these conditions.
(d) Investigate the causes of age- and gender-based variations in the incidence and recurrence of these diseases, including why men are more susceptible to a recurrence.
(e) Research the role (if any) that behavior modification (e.g., smoking cessation, increased physical activity, weight loss) plays in reducing risk.
(f) Conduct research to better understand why obesity increases risk.
(g) Investigate the role that prolonged immobility due to travel (air, car, rail), hospitalization, or confinement to bed plays in increasing risk.
(h) Conduct an analysis of the economic toll of DVT/PE on individuals, families, communities, and the nation as a whole. This analysis should include not only the direct costs (i.e., healthcare expenditures) but also indirect costs such as lost productivity and wages due to time away from work.
(i) Evaluate the impact of communication and social marketing programs, including pre- and post-evaluation levels of consumer awareness and knowledge.
(j) Conduct formative research to ensure that media messages are positive, realistic, relevant, consistent, and effective.

Setting: The Healthcare System

The healthcare system is uniquely positioned to implement interventions aimed at reducing the incidence and burden of DVT/PE, as the majority of cases occur within the healthcare system itself. There is a gap between the implementation of a required standard of care with broad compliance to evidence-based guidelines and ground realities.

Healthcare systems in the public and private sectors and also medical colleges have a crucial role to play in preventing and reducing the burden of DVT/PE. Much is left to be done—to apply evidence-based medicine in real-world settings and to investigate the gaps in knowledge related to the management of VTE.

Communication

Actions that need to be initiated by policymakers and healthcare administrators include but are not limited to:

(a) Informing healthcare professionals and administrators about the problem of DVT/PE in terms of mortality, morbidity, and direct and indirect costs.
(b) Promoting evidence-based practice by sharing existing guidelines with healthcare professionals on the prevention, diagnosis, and treatment in specific at-risk populations.
(c) Promoting the findings and recommendations from expert groups such as professional societies related to the importance of screening all hospitalized patients for risk for these diseases and providing appropriate preventive treatment based on those screenings.
(d) Educating healthcare professionals about the availability of genetic testing wherever feasible, about when it may be appropriate to discuss with and test patients, and the importance of counseling for those who test positive.
(e) Educating healthcare professionals at all levels about the relative risks of excessive bleeding from properly managed anticoagulation therapy versus the risks of not using such therapy.
(f) Informing healthcare professionals about the availability and appropriate use of treatment options, including anticoagulation therapy and clot dissolving/clot removal therapies.

Action

Actions that need to be initiated by policymakers and healthcare administrators include but are not limited to:

(a) Convening a TF, such as the NAMS TF, to forge consensus on a single set of clear, standardized, evidence-based guidelines in those areas where multiple and/or conflicting guidelines currently exist.
(b) Instituting formal systems related to risk assessment and the provision of preventive therapy (prophylaxis) to appropriate high-risk individuals in the healthcare system and community.

(c) Consistently tracking performance on current and future DVT measures that are endorsed by professional societies and developing quality improvement initiatives designed to improve performance on these measures over time.
(d) Developing and improving easy-to-use tools (such as Internet-based apps) that provide ready access to relevant data and information at the point of care. These tools will help healthcare professionals to follow existing evidence-based guidelines and assist in enhancing their patient care service delivery.
(e) Developing and/or refining tools and/or algorithms to determine who should undergo diagnostic imaging tests for DVT/PE. These tools could incorporate clinical manifestations, biomarkers and genetic profiles, patient and family history, the results of simple tests, and other information to determine who should be screened.
(f) Identifying and supporting healthcare professionals who can provide evidence-based preventive, diagnostic, and therapeutic care and serve as models in their respective hospitals.
(g) Encouraging medical and nursing colleges to provide adequate education and training to ensure that the new generations of doctors and nurses are aware of the magnitude of the problem and how to prevent, diagnose, and treat DVT/PE in accordance with the latest scientific evidence.
(h) Encouraging medical and nursing colleges, and other organizations to incorporate training into continuing medical education and recertification processes such as renewal of registrations.
(i) Supporting the development of hospital- and community-based support programs for patients with DVT/PE and their family members.

Research and Evaluation

It is recommended for policymakers and healthcare system administrators to assign priority to this often neglected aspect of interventions focused on medical conditions. This is essential to:

(a) Conduct further research into the benefits and risks associated with various strategies (pharmacological, mechanical, and surgical) for dissolving or removing clots and for determining which patients, if any, would benefit from these approaches (as an alternative to anticoagulation therapy).
(b) Conduct further research into the pathophysiology of DVT/PE, including the roles of inflammation, obesity, stasis, and the basic endothelial cell biology and vessel response to stasis and thrombosis. This research can lead to the development of novel prevention and treatment strategies.
(c) Investigate whether more biomarkers can be identified that will allow for the development of individualized risk profiles for primary and recurrent DVT/PE and chronic venous insufficiency. These biomarkers can possibly be used to help predict an individual's response to therapy.
(d) Investigate the role of prolonged air, car, boat, or rail trips (and other situations causing long periods of immobility) on raising risk, both for the general population and certain high-risk groups, such as women on oral contraceptives or individuals with a genetic predisposition to DVT/PE.
(e) Investigate the role of CUS in diagnosing isolated calf DVT, and study the benefits and costs associated with treatment.
(f) Continue to study the effectiveness of various tests, including the D-dimer and other tests, in diagnosing the recurrence of the disease.
(g) Investigate the safety and effectiveness of various approaches to diagnosing DVT/PE in pregnant women.
(h) Conduct further research into the best drugs, dosing strategies, and treatment regimens for anticoagulation therapy for certain patient populations, including children (from infancy through adolescence), obese individuals, and those with renal insufficiency.
(i) Conduct further research on the benefits and risks of preventive and therapeutic anticoagulation therapy for certain patient populations, including children, pregnant women, individuals with a genetic predisposition to DVT/PE (with or without prior events), cancer patients, and the elderly. Such research should also address how to treat individuals with multiple risk factors, such as pregnant women or children with genetic predisposition.
(j) Conduct further research into the appropriate duration of anticoagulation therapy in specific patient populations, including whether some high-risk groups should remain on the therapy indefinitely.
(k) Investigate the role that pharmacogenetics can play in determining optimal warfarin dosing in individuals.
(l) Investigate and evaluate the various approaches (e.g., pharmacological, mechanical, and/or a combination) to reduce the risk and impact of chronic venous insufficiency.
(m) Conduct research into when genetic testing is appropriate, including whether and when to test the asymptomatic family members of those with a genetic predisposition to DVT/PE.
(n) Conduct further research into optimal therapy for those with genetic predisposition and how that therapy might vary depending upon the number of genetic and other acquired risk factors or triggering events. Research should focus on the impact of specific thrombophilic disorders on anticoagulant therapy management and the identification of optimal prophylactic strategies for asymptomatic individuals during high-risk situations.

(o) Conduct research into how upper extremity DVT—a less common and less studied form than DVT in the legs—should best be evaluated, diagnosed, and managed.

Setting: Policymakers and Governments

Healthcare policymakers at the state and national levels have a crucial role to play in raising awareness and encouraging the development and use of evidence-based guidelines. The scientific community and professional societies, such as the National Academy of Medical Sciences (India), Indian Society of Hematology, Indian Public Health Association, and the Indian Medical Association, must seek to collaborate, partner, facilitate, and steer actions required for advocacy with all stakeholders. Governments at the state and the national level, along with the scientific community, must work together to focus on the following areas:

(a) **Communication**
   (i) Raise policymakers' awareness of DVT/PE and the magnitude of the problems caused by the disease, as well as the need to support research and infrastructure that are consistent with the provision of evidence-based care.
   (ii) Support public awareness campaigns.
   (iii) Support the education of health professionals, including the dissemination of evidence-based guidelines.

(b) **Action**
   (i) Review Ayushman Bharat reimbursement policies to ensure that they encourage the provision of evidence-based prevention, diagnosis, and treatment. Subsequently, to make recommendations to the Government of India for necessary action as may be required.
   (ii) Support the formation of community-based regional and national multi stakeholder coalitions dedicated to raising awareness about these VTEs.
   (iii) Form TFs, steering committees, or advisory committees dedicated to addressing the problems resulting from VTE.
   (iv) Support actions that lead to enhanced awareness about DVT/PE among healthcare professionals and obtain better adherence to evidence-based practices.

(c) **Research and Evaluation**
   (i) Support basic, clinical, and epidemiological research that is intended to fill critical gaps in the current knowledge about DVT/PE.
   (ii) Support translational research and the development of other tools that are intended to speed the adoption of new scientific knowledge into the everyday practice of medicine.
   (iii) Support the training of scientific investigators and healthcare professionals who are interested in VTE.

ANNEXURE 7

VTE TRAINING AND EDUCATION FOR HEALTHCARE PROFESSIONALS

It is recommended that an online training course for healthcare professionals be proposed by NAMS to be hosted on the Government of India website for training (www.igot.gov.in). This training course may be updated periodically as per evolving evidence and peer-reviewed best practices.

An outline template for such a training course may be taken from

https://www.cdc.gov/ncbddd/dvt/training.html#accreditation

Stop the Clot®: What Every Healthcare Professional Should Know

Course Overview: A self-paced, online course providing the most current foundational information on assessing, treating, and managing patients who have blood clots and clotting disorders.

Target Audience: Physicians, Nurses, and other healthcare professionals

Content:

1. Basics of blood clots
2. Thrombophilia and blood clots
3. Anticoagulation medications
4. Post-thrombotic syndrome
5. Pulmonary hypertension
6. Prevention of blood clots

Course Objectives

At the conclusion of this proposed training course, participants should be able to do the following:

1. Explain three signs and symptoms of DVT and pulmonary embolism (PE).
2. Describe three factors that increase the risk of developing a blood clot in the form of a DVT and/or PE.
3. Describe three management considerations for the use of anticoagulant medications.
4. Explain three signs and symptoms of post-thrombotic syndrome that providers should include in patient education plans for blood clot survivors.
5. Explain two facts about pulmonary hypertension and its relationship to PE.
6. Describe three appropriate treatment/management options to prevent blood clot recurrence and secondary complications.

ANNEXURE 8

Table I: Theoretical Framework: Prevention of VTE

PERIOD OF PRE PATHOGENESIS			**PERIOD OF PATHOGENESIS** *This is the stage when VTE has set in.*		
Disease Process	*This is the stage when conditions within the body predispose to VTE, however VTE has not set in as yet.*		DEATH Chronic State Disability Illness Signs & Symptoms Clinical Horizon RECOVERY		
LEVELS OF PREVENTION	**Primary Prevention**		**Secondary Prevention**	**Tertiary Prevention**	
MODES OF INTERVENTION	**Health Promotion**	**Specific Protection**	**Early Diagnosis & Treatment**	**Disability Limitation**	**Rehabilitation**

VTE: venous thromboembolism.

ANNEXURE 9

Comprehensive primary healthcare framework approach: prevention of VTE

Table I: Primary prevention

	Actions at - Level	Actions by	Remarks
Health Promotion	Community level	ASHA/ ANM	Conduct of community level Health Education campaigns *to promote healthy lifestyles and promote early healthcare seeking behaviour*
	Health & Wellness Centre level	CHO	Conduct of outreach health education for communities and support for ASHA/ ANM
	Primary Health Centre level	MO	Supervision and conduct of outreach health education activities for communities and patients, including support and guidance to CHOs
	Community Health Centre level	MO/ Specialist	Supervision and conduct of outreach health education activities for communities and patients, including support and guidance to MOs

	District Hospital level	Specialist	Supervision and conduct of outreach health education activities for communities and patients, including support and guidance to MOs and Specialists
	Medical College level	Specialist	Conduct of outreach health education activities, in rural / urban field practice areas, providing support and guidance to MOs and Specialists
	Tertiary Hospital level	Specialist / Sub Specialist	Conduct of health education activities for inpatients and relatives / caregivers, providing support and guidance to MOs and Specialists
Specific Protection			**Nil**

Table II: Secondary prevention

	Actions at - Level	**Actions by**	**Remarks**
Early Diagnosis	Community level	ASHA/ ANM	Early recognition of symptoms with prompt referral Training module (online) can be developed for early recognition at the community level
	Health & Wellness Centre level	CHO	
	Primary Health Centre level	MO	
	Community Health Centre level	MO/ Specialist	Early recognition of signs and symptoms , with a high degree of clinical suspicion Training module (online) can be developed for early diagnosis at the health care facility level
	District Hospital level	Specialist	
	Med College level	Specialist	
	Tertiary Hospital level	Specialist / Sub Specialist	

	Actions at - Level	Actions by	Remarks
Prompt Treatment	Community level	ASHA/ ANM	Referral without delay, and encouragement to patient to seek medical attention urgently.
	Health & Wellness Centre level	CHO	
	Primary Health Centre level	MO	Commence treatment as per Guidelines and referral as per criteria.
	Community Health Centre level	MO/ Specialist	
	District Hospital level	Specialist	
	Med College level	Specialist	
	Tertiary Hospital level	Specialist / Sub Specialist	Management as per Guidelines.

Table III: Tertiary prevention
This is the phase where long term anti coagulation is indicated, adhering to guidelines

	Actions at - Level	Actions by	Remarks
Disability Limitation	Community level	ASHA/ ANM	To brief patients in the domestic setting to comply with prescribed medications and follow up at required frequency, with self care as applicable. Referral as needed.
	Health & Wellness Centre level	CHO	To brief patients attending OPD in the HWC to comply with prescribed medications and follow up at required frequency, with self care as applicable. Referral as needed
	Primary Health Centre level	MO	To brief patients attending OPD in the PHC to comply with prescribed medications and follow up at required frequency, with self care as applicable. Referral as needed
	Community Health Centre level	MO/ Specialist	To undertake required investigations, and monitor patients for health status and ascertain compliance with prescribed medications. Referral as needed.
	District Hospital level	Specialist	
	Med College level	Specialist	
	Tertiary Hospital level	Specialist / Sub Specialist	To undertake investigations and management as needed.

	Actions at - Level	Actions by	Remarks
Rehabilitation	Community level	ASHA/ ANM	Counselling for maintenance of healthy lifestyle and risk reduction as applicable, with information on early recognition, and encouragement to health care seeking behaviour.
	Health & Wellness Centre level	CHO	
	Primary Health Centre level	MO	
	Community Health Centre level	MO/ Specialist	Advice on healthy lifestyle and risk reduction as applicable, with provision of physiotherapy services if available.
	District Hospital level	Specialist	
	Med College level	Specialist	Advice on long term rehabilitation as applicable , at the post VTE recovery stage
	Tertiary Hospital level	Specialist / Sub Specialist	

ASHA: Accredited Social Health Activist; ANM: Auxiliary Nurse Midwife; CHO: Community Health officer; MO: Medical Officer.

ANNEXURE 10

AREAS OF RESEARCH/FUTURE DIRECTIONS

Advances in technology and pharmacology have already improved our ability to predict and prevent VTE. However, the following major barriers to improving VTE prevention still exist:

(a) the limitations on the overall benefit to thromboprophylaxis inherent to current anticoagulant medications.
(b) the imperfect science of individualizing VTE risk stratification and the inherent complexity of predicting multifactorial and competing phenomena.

As per various position papers, future direction can be focused toward therapeutics and technology, including the importance of antithrombotic options with less bleeding and technological advances, including artificial intelligence and machine learning to refine risk stratification and facilitate their implementation.

A more pragmatic approach to pharmacologic prevention is what is necessitated in India today given the diversity in healthcare settings. Over the past decade, the tolerability, acceptability, and quality of life for patients at risk of VTE have changed with the advent of effective oral therapies for VTE treatment and prevention. In those with cancer, patient-reported quality of life is better with oral anticoagulant treatment compared to daily subcutaneous LMWH injection. While not as rigorously studied, quality-of-life improvements with oral therapies are likely similar in the prophylactic setting.

Novel agents for pharmacologic prophylaxis are currently being developed that target various factors. If these trials or other new agents are successful at reducing VTE without substantially increasing the risk of bleeding, existing approaches to VTE prevention could change dramatically.

Efforts to predict and prevent venous thromboembolic disease are predicated on our ability to accurately identify patients at risk. The benefits of thromboprophylaxis must be weighed against the financial costs and potential for increased bleeding. Understanding which patients are at greatest risk can help healthcare professionals and their patients to make informed decisions about the use of anticoagulants to prevent VTE. We must continue to collect and analyze large datasets on patient-specific and acquired risk factors and how they interact to improve existing risk assessment models.

The discovery and evaluation of novel biomarkers to risk-stratify patients may be an area of significant interest going forward, and serum biomarkers such as Vascular Endothelial Growth Factor (VEGF), Interferon-alpha, Interleukin-15 (IL-15), and Citrullinated histone H3 (H3cit) may see further investigation for this purpose.

The development and validation of prediction models should seek to increase the accuracy of prediction without sacrificing usability. As we seek to individualize preventive efforts, the primary obstacles that affect the implementation of risk assessment models will be the complications and complexity of any proposed algorithm. Scoring systems and other risk-assessment models can be implemented for use by healthcare professionals if they are easily accessible and understood, but developing sufficient predictive power for VTE often requires the combination of several variables. Scoring systems can quickly become time-consuming for use by physicians, and hiring additional data entry personnel adds significant cost. Predictive algorithms that appropriately consider and calculate bleeding risks for individual patients to avoid harm from VTE prophylaxis increase complexity and add additional workload. Scoring systems developed in the present times must not lose sight of the practical challenges of implementation by treating clinicians in busy hospital settings.

We have made tremendous progress in understanding the epidemiology and prevention of VTE and have transitioned from studies detailing the benefits of "mini-dose" unfractionated heparin given to postoperative patients to sophisticated algorithms that leverage patient-specific and acquired risk factors to determine which patients will derive the greatest benefit from VTE prophylaxis. As scoring systems and other decision support tools increase in accuracy and complexity, we risk overburdening overworked clinicians, and hence, we need to be aware of this pitfall.

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OPERATIONAL DEFINITION OF TERMS USED

Pulmonary embolus refers to obstruction of the pulmonary artery or one of its branches by material (e.g., thrombus, tumor, air, or fat) that originated elsewhere in the body. Patients with ***acute PE*** typically develop symptoms and signs immediately after obstruction of pulmonary vessels. Some patients with PE may also present ***subacutely*** within days or weeks following the initial event. Patients with ***chronic PE*** slowly develop symptoms of pulmonary hypertension over many years (i.e., chronic thromboembolic pulmonary hypertension; CTEPH).

Symptomatic PE refers to the presence of symptoms that usually leads to the radiologic confirmation of PE, whereas ***asymptomatic PE*** refers to the incidental finding of PE on imaging (e.g., contrast-enhanced computed tomography performed for another reason) in a patient without symptoms.

LIST OF ABBREVIATIONS

ACCP: American College of Chest Physicians

AHA: American Heart Association

APLA: Anti-phospholipid antibody syndrome

ASCO: American Society of Clinical Oncology

ASH: American Society of Hematology

BMI: Body mass index

CrCl: Creatinine clearance

DOAC: Direct acting oral anticoagulant

DVT: Deep venous thrombosis

ENDORSE: Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting

ESA: European Society of Anesthesiology

ESC: European Society of Cardiology

HIT: Heparin-induced thrombocytopenia

IPC: Intermittent pneumatic compression

ISHBT: Indian Society of Hematology & Blood Transfusion

ITAC: International Initiative on Thrombosis and Cancer

IVC: Inferior vena cava

LMWH: Low molecular weight heparin

NICE: National Institute of Clinical Excellence

OSA: Obstructive sleep apnea

PAH: Pulmonary artery hypertension

PE: Pulmonary embolism

PICO: Population, intervention, comparator, and outcome

PTS: Post-thrombotic syndrome

RV: Right ventricle

SVT: Splanchnic vein thrombosis

TF: Task Force

UFH: Unfractionated heparin

VKA: Vitamin K antagonist

VTE: Venous thromboembolism

VT: Venous thrombosis

SUGGESTED READINGS

1. Cohen H, Cuadrado MJ, Erkan D, Duarte-Garcia A, Isenberg DA, Knight JS, *et al*. 16th International Congress on Antiphospholipid Antibodies Task Force. Report on Antiphospholipid Syndrome Treatment Trends: Lupus 2020;29:1571–93.
2. Agarwala S, Bhagwat AS, Modhe J. Deep vein thrombosis in Indian patients undergoing major lower limb surgery. Indian J Surg 2003;65:159–62.
3. American Heart Association. The Postthrombotic Syndrome-Guidelines. Circulation 2014;130:1636–61.
4. American Society of Hematology. 2018 guidelines for management of venous thromboembolism: Venous thromboembolism in the context of pregnancy. Blood Adv 2018;2:3317–59.
5. American Society of Hematology. 2019 guidelines for management of venous thromboembolism: Prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv 2019;3:3898–944
6. American Society of Hematology. 2020 guidelines for management of venous thromboembolism: Treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020;4:4693–738
7. American Society of Hematology. 2021 guidelines for management of venous thromboembolism: Prevention and treatment in patients with cancer. Blood Adv 2021;5:927–74
8. Anghel L, Sascău R, Radu R, Stătescu C. From Classical laboratory parameters to novel biomarkers for the diagnosis of venous thrombosis. Int J Mol Sci 2020;21:1920.
9. American College of Chest Physicians. Antithrombotic Therapy and prevention of thrombosis, evidence-based clinical practice guidelines. Chest 2012;141:e419S–e494S
10. American College of Chest Physicians. Antithrombotic therapy for VTE disease guideline and expert panel report. Chest 2016;149:315–52
11. American College of Chest Physicians. Antithrombotic therapy for VTE disease: Second update of the CHEST guideline and expert panel report. Chest 2021;160:2247–59
12. Anghel L, Sascău R, Radu R, Stătescu C. From classical laboratory parameters to novel biomarkers for the diagnosis of venous thrombosis. Int J Mol Sci 2020;21:1920.
13. Bagaria V, Modi N, Panghate A, Vaidya S. Incidence and risk factors for development of venous thromboembolism in Indian patients undergoing major orthopaedic surgery: Results of a prospective study. Postgrad Med J 2006;82:136–9.
14. 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;149:209–20.
15. Basavanthappa RP, Vivek Vardhan JP, Gangadharan AN, Desai SC, Anagavalli Ramswamy C, Luthra L, *et al*. RAVS Study: An Indian single center analysis of patients with VTE. Ann Vasc Dis 2019;12:205–9.
16. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 2005;293:715–22.
17. Cohen AT, Tapson VF, Bergmann JF, Goldhaber SZ, Kakkar AK, Deslandes B, *et al*. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): A multinational cross-sectional study. Lancet 2008;371:387–94.
18. Dantkale SS, Dalal SK, Gunaki RB. Is thromboprophylaxis really justified among Indian population with femur shaft fractures treated with IM nailing? Int J Orthop Sci 2018;4:492–5.
19. Dhillon KS, Askander A, Doraismay S. Postoperative deep-vein thrombosis in Asian patients is not a rarity: A prospective study of 88 patients with no prophylaxis. J Bone Joint Surg Br 1996;78:427–30.
20. Duranteau J, Taccone FS, Verhamme P, Ageno W, ESA VTE Guidelines Task Force. European guidelines on perioperative venous thromboembolism prophylaxis. Eur J Anaesthesiol 2018;35:142-6.
21. Jain V, Dhal AK, Dhaon BK. Deep vein thrombosis after total hip arthroplasty in Indian patients with and without Enoxaparin. J Orth Surg (Hong Kong) 2004;12:173–7.
22. Jakhetiya A, Shukla NK, Deo SVS, Garg PK, Thulkar S. Deep vein thrombosis in indian cancer patients undergoing major thoracic and abdomino-pelvic surgery. Indian J Surg Oncol 2016;7:425–9.
23. Kamerkar DR, John MJ, Desai SC, Dsilva LC, Joglekar SJ. Arrive: A retrospective registry of Indian patients with venous thromboembolism. Indian J Crit Care Med 2016;20:150-8.
24. Kapoor CS, Mehta AK, Patel K, Golwala PP. Prevalence of deep vein thrombosis in patients with lower limb trauma. J Clin Orthop Trauma 2016;7(Suppl 2):220–4.
25. Lee AD, Stephen E, Agarwal S, Premkumar P. Venous Thrombo-embolism in India. Eur J Vasc Endovasc Surg 2009;37:482–5.
26. Mavalankar AP, Majmundar D, Sudha R. Routine chemoprophylaxis for DVT in Indian patients. Indian J Orthop 2007;41:188–91.

27. Nair V, Kumar R, Singh BK, Sharma A, Joshi GR, Pathak K. Comparative study of extended versus short term thromboprophylaxis in patients undergoing elective total hip and knee arthroplasty in Indian population. Indian J Orthop 2013;47:161–7.
28. Nair V, Singh S, Ashraf MZ, Yanamandra U, Sharma V, Prabhakar A, *et al.* Epidemiology and pathophysiology of vascular thrombosis in acclimatized lowlanders at high altitude: A prospective longitudinal study. The Lancet Regional Health - Southeast Asia 2022;3:100016
29. NICE (UK). Venous thromboembolism Guidelines; 2018 & 2020.
30. Nicholson M, Chan N, Bhagirath V, Ginsberg J. Prevention of Venous Thromboembolism in 2020 and Beyond. J Clin Med 2020;9:2467.
31. Office of the Surgeon General (US); National Heart, Lung, and Blood Institute (US). The surgeon general's call to action to prevent deep vein thrombosis and pulmonary embolism. Rockville (MD): Office of the Surgeon General (US); 2008.
32. Parakh R, Kakkar VV, Kakkar AK; Venous Thromboembolism (VTE) Core Study Group. Management of venous thromboembolism. J Assoc Physicians India 2007;55:49–70.
33. Pawar P, Ayyappan MK, Jagan J, Rajendra N, Mathur K, Raju R. Analysis of patients with venous thromboembolism in a multi-specialty tertiary hospital in South India. Indian J Vasc Endovasc Surg 2020;7:29–33.
34. Pinjala R, ENDORSE-India Investigators. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE), a multinational cross-sectional study: Results from the Indian subset data. Indian J Med Res 2012;136:60-7.
35. Prabhudesai A, Shetty S, Ghosh K, Kulkarni B. Dysfunctional fibrinolysis and cerebral venous thrombosis. Blood Cells Mol Dis 2017;65:51–5.
36. Sahoo DR, Dorairajan G, Palanivel C. Risk stratification for venous thrombosis in post–partum women in a tertiary care setup in south India. Indian J Med Res 2020;152:523–6.
37. Saket R, Aggarwal S, Kumar V, Kumar P, Patel S. Acute venous thromboembolism in Indian patients of isolated proximal femur fractures. J Clin Orthop Trauma 2019;10:917–21.
38. ESC Working Group. Second consensus document on diagnosis and management of acute deep vein thrombosis: Group on aorta and peripheral vascular diseases and the ESC Working Group on pulmonary circulation and right ventricular function. Eur J Prev Cardiol 2022;29:1248–63
39. Sehrawat A, Mittal GS, Sundriyal D, Chaturvedi A, Gupta D. Cancer–associated venous thromboembolism in ambulatory solid organ malignancy patients: Experience from a cancer research institute. Indian J Surg Oncol 2021;12:246–50.
40. Sen RK, Kumar A, Tripathy SK, Aggarwal S, Khandelwal N, Manoharan SR. Risk of postoperative venous thromboembolism in Indian patients sustaining pelvi–acetabular injury. Int Orthop 2011;35:1057–63.
41. Shrikhande SV, Verma M. A prospective observational study to determine rate of thromboprophylaxis in oncology patients undergoing abdominal or pelvic surgery. Indian J Surg Oncol 2021;12:279–85.
42. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: A 25-year population-based study. Arch Intern Med 1998;158:585–93.
43. Singh G, Rathi AK, Singh K, Sharma D. VTE in cancer patients – magnitude of problem, approach, and management. Indian J Cancer 2017;54:308–12.
44. Singh S, Kapoor S, Singh B, Tandon R, Singla S, Singla T, *et al.* Real world data on clinical profile, management and outcomes of venous thromboembolism from a tertiary care centre in India. Indian Heart J 2021;73:336–41
45. Spirk D, Sebastian T, Hans Beer J, Mazzolai L, Aujesky D, Hayoz D, *et al.* Role of age, sex, and specific provoking factors on the distal versus proximal presentation of first symptomatic deep vein thrombosis: Analysis of the SWIss Venous Thrombo Embolism Registry (SWIVTER). Intern Emerg Med 2022;17:799–803.

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