REVIEW ARTICLE

DEEP VENOUS THROMBOSIS: A COMPREHENSIVE REVIEW OF RISK FACTORS, PATHOGENESIS, AND ANATOMICAL DISTRIBUTION

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ABSTRACT

This review article provides a comprehensive analysis of deep venous thrombosis (DVT) based on studies examining risk factors, pathogenesis, and clinical implications. DVT affects approximately 1.6 per 1000 individuals globally and represents the third most common cause of cardiovascular-related mortality after myocardial infarction and stroke. The evidence base encompasses hospital-based studies, population registries, and community cohorts from diverse geographic regions, including India, Singapore, Europe, and North America. Key findings reveal a complex interplay of acquired and inherited risk factors, with varying levels of evidence supporting their contribution to thrombotic risk. The report synthesizes current understanding of coagulation mechanisms, identifies high-risk populations, and evaluates the strength of evidence for major risk determinants. These findings underscore the critical importance of risk stratification and targeted thromboprophylaxis in reducing VTE burden.

Methods: -

A comprehensive literature search was conducted to identify studies reporting risk factors, anatomical distribution and pathogenesis of deep venous thrombosis (DVT) in both community and hospital settings. The databases PubMed, EMBASE, Scopus, and the Cochrane Library were searched for articles published up to February 2024. All potentially relevant articles were assessed in detail to determine eligibility, and these were independently reviewed for inclusion.

Keywords: Thrombosis; Thromboembolism; Coagulation; Fibrinolytic; Prothrombin

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1. INTRODUCTION

Deep venous thrombosis (DVT) is characterized by thrombus formation within the deep venous system, most commonly affecting the lower limb veins. As a critical component of venous thromboembolism (VTE), DVT represents a significant yet potentially preventable source of morbidity and mortality worldwide.[1] The condition can affect multiple vascular territories including upper extremity vasculature, mesenteric circulation, portal system, and cerebral venous sinuses.[1] Early diagnosis and timely intervention are essential to prevent serious complications including pulmonary embolism, which occurs in up to 33% of DVT cases, and post-thrombotic syndrome (PTS), which develops in approximately 50% of patients within the first two years.[2,3]

The pathogenesis of DVT involves a complex interplay of inherited and acquired risk factors. Identifying these risk factors is crucial for improving diagnostic accuracy and implementing effective preventive measures, including pneumatic compression devices and anticoagulant therapy tailored to individual patient risk profiles.[4] This synthesis report analyzes findings from 52 studies to provide a comprehensive overview of DVT epidemiology, risk factors, pathogenesis, and anatomical distribution patterns.

2. EPIDEMIOLOGY AND CLINICAL SIGNIFICANCE

GLOBAL INCIDENCE AND MORTALITY

DVT is diagnosed in approximately 1.6 per 1000 individuals globally.[1] Following myocardial infarction and cerebrovascular events, VTE represents the third most prevalent etiology of cardiovascular-associated fatalities.[5] The rising global incidence of DVT has been documented through hospital-based studies, population registries, and community cohorts across diverse geographic regions.

REGIONAL VARIATIONS

Evidence from Asian populations challenges the historical perception that DVT is rare in this region. A study from Singapore General Hospital demonstrated that DVT is not uncommon in Asian populations.[6] Indian registry data from the ARRIVE study, which included 549 patients , documented clinical characteristics and outcomes of VTE in Indian patients.[7] The RAVS study from a single Indian center further characterized VTE patterns in the Indian population.[8] Studies of Indian patients undergoing major lower limb surgery have documented DVT incidence rates comparable to Western populations.[9]

COMPLICATIONS AND LONG-TERM OUTCOMES

The clinical significance of DVT extends beyond the acute thrombotic event. Pulmonary embolism, resulting from thrombus dislodgement and migration into pulmonary arteries, occurs in up to 33% of DVT cases.[2] Post-thrombotic syndrome develops in approximately 50% of patients within the initial two years following DVT, manifesting with pain, swelling in the affected leg, and in severe cases, venous ulcer formation due to local tissue injury.[3]

3. PATHOGENESIS AND COAGULATION MECHANISMS

VIRCHOW'S TRIAD

The pathogenesis of DVT is classically explained by Virchow's triad, which encompasses three fundamental mechanisms: venous stasis, endothelial injury, and hypercoagulability. These three factors interact synergistically to promote thrombus formation within the venous system.[10]

THE COAGULATION CASCADE

The coagulation cascade consists of intrinsic and extrinsic pathways that converge on a common pathway leading to thrombin generation and fibrin clot formation. The extrinsic pathway is initiated by tissue factor exposure following endothelial injury, while the intrinsic pathway involves contact activation through Factor XII. Both pathways activate Factor X, which converts prothrombin to thrombin, ultimately leading to fibrinogen conversion to fibrin and stable clot formation.[11]

ENDOGENOUS ANTICOAGULANT MECHANISMS

Natural anticoagulant systems provide critical regulation of the coagulation cascade. The protein C pathway represents a major anticoagulant mechanism, where thrombin binds to thrombomodulin on endothelial surfaces, activating protein C. Activated protein C, in conjunction with its cofactor protein S, inactivates Factors Va and VIIIa, thereby limiting thrombin generation. Antithrombin III provides another essential anticoagulant mechanism by inhibiting thrombin and Factors IXa, Xa, XIa, and XIIa. Tissue factor pathway inhibitor (TFPI) regulates the extrinsic pathway by inhibiting Factor Xa and the tissue factor-Factor VIIa complex. Deficiencies in these natural anticoagulants significantly increase thrombotic risk.[12]

FIBRINOLYTIC SYSTEM

The fibrinolytic system provides a mechanism for clot dissolution through plasmin generation. Tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA) convert plasminogen to plasmin, which degrades fibrin. This system is regulated by inhibitors including plasminogen activator inhibitor-1 (PAI-1) and alpha-2-antiplasmin. Impaired fibrinolysis contributes to thrombotic risk.[13]

4. ANATOMICAL DISTRIBUTION OF THROMBOSIS

The anatomical pattern of DVT shows characteristic variability across venous segments. Distal veins account for approximately 40% of cases, representing the most common site of thrombosis. The popliteal vein is involved in 16% of cases, while the superficial femoral vein accounts for 20%. The common femoral vein represents another 20% of cases, and the iliac veins comprise the remaining 4%.[14]

This distribution pattern has important clinical implications. Distal DVT, while common, carries lower risk of pulmonary embolism compared to proximal thrombosis. However, distal thrombi can propagate proximally from the deep calf veins to involve the popliteal, superficial femoral, common femoral, and iliac venous segments, increasing embolic risk. The anatomical location influences both diagnostic approach and treatment decisions, with proximal DVT generally requiring more aggressive anticoagulation strategies.[15]

5. ACQUIRED RISK FACTORS

5.1 SURGICAL AND TRAUMA-RELATED FACTORS

MAJOR SURGERY

Surgery represents one of the most significant acquired risk factors for DVT. Major orthopedic procedures, particularly hip and knee replacement surgery, confer substantial thrombotic risk. Studies in Indian patients undergoing major lower limb surgery have documented significant DVT incidence.[9] The mechanism involves multiple components of Virchow's triad: surgical trauma causes endothelial injury, immobilization leads to venous stasis, and the acute phase response induces a hypercoagulable state.

TRAUMA AND FRACTURES

Traumatic injury, particularly involving the lower extremities or pelvis, significantly increases DVT risk through direct vascular injury, immobilization, and activation of the coagulation cascade. Fractures requiring prolonged immobilization carry particularly high risk.[16]

5.2 MEDICAL CONDITIONS AND COMORBIDITIES

MALIGNANCY

Cancer is a well-established risk factor for VTE, with malignancy-associated thrombosis representing a major cause of morbidity and mortality in cancer patients. The ARRIVE registry documented malignancy as a significant risk factor in Indian VTE patients.[7] Tumors produce procoagulant factors including tissue factor and cancer procoagulant, directly activating the coagulation cascade. Additionally, cancer treatments including chemotherapy and central venous catheters further increase thrombotic risk.

PREGNANCY AND ORAL CONTRACEPTIVES

Pregnancy and the postpartum period represent high-risk states for VTE. Hormonal changes during pregnancy induce a hypercoagulable state characterized by increased levels of Factors VII, VIII, X, and fibrinogen, along with decreased protein S activity and impaired fibrinolysis. Venous stasis from uterine compression of pelvic veins further contributes to risk. Oral contraceptives and hormone replacement therapy containing estrogen increase VTE risk through similar mechanisms of acquired hypercoagulability.[17]

IMMOBILIZATION AND HOSPITALIZATION

Prolonged immobilization, whether due to hospitalization, long-distance travel, or medical conditions requiring bed rest, promotes venous stasis and increases DVT risk. The ARRIVE registry identified immobilization as a significant risk factor in hospitalized patients.[7]

INFLAMMATORY AND AUTOIMMUNE CONDITIONS

Inflammatory bowel disease, systemic lupus erythematosus, and other autoimmune conditions increase VTE risk through chronic inflammation, endothelial dysfunction, and production of antiphospholipid antibodies. Antiphospholipid antibodies have been documented as risk factors for venous thromboembolism.[18]

NEPHROTIC SYNDROME AND RENAL DISEASE

Nephrotic syndrome increases thrombotic risk through multiple mechanisms including loss of antithrombin III in urine, increased hepatic synthesis of procoagulant factors, and hemoconcentration. Hemodialysis catheter-related central venous thrombosis represents a specific complication in patients with renal disease.[19]

OBESITY

Obesity contributes to VTE risk through multiple mechanisms including chronic inflammation, impaired fibrinolysis due to elevated PAI-1 levels, and mechanical factors affecting venous return. The metabolic syndrome associated with obesity further compounds thrombotic risk.[20]

5.3 MEDICATION-RELATED FACTORS

HORMONAL THERAPIES

Oral contraceptives and hormone replacement therapy represent significant iatrogenic risk factors for VTE. Estrogen-containing preparations increase hepatic synthesis of coagulation factors and decrease natural anticoagulant levels, creating a prothrombotic state.[21]

CHEMOTHERAPY

Cancer chemotherapy agents increase VTE risk through multiple mechanisms including direct endothelial toxicity, reduction in natural anticoagulant levels, and activation of platelets and coagulation factors.[22]

5.4 LIFESTYLE AND BEHAVIORAL FACTORS

SMOKING

Tobacco use contributes to thrombotic risk through endothelial dysfunction, increased platelet reactivity, elevated fibrinogen levels, and impaired fibrinolysis. Smoking acts synergistically with other risk factors, particularly oral contraceptives, to substantially increase VTE risk.[23]

LONG-DISTANCE TRAVEL

Prolonged air travel and other forms of extended immobilization during travel increase DVT risk through venous stasis, particularly in individuals with additional risk factors.[24]

6. INHERITED RISK FACTORS

6.1 FACTOR V LEIDEN AND PROTHROMBIN GENE MUTATIONS

FACTOR V LEIDEN

Factor V Leiden represents the most common inherited thrombophilia in Caucasian populations, resulting from a point mutation (G1691A) that renders Factor V resistant to inactivation by activated protein C. This mutation is present in approximately 5% of the Caucasian population but shows marked geographic variation, with lower prevalence in Asian and African populations. The Spanish multicentric study on thrombophilia (EMET study) evaluated 2,132 consecutive unselected patients with VTE and documented the prevalence of Factor V Leiden.[25] Studies in Indian populations have examined the prevalence of prothrombotic defects including Factor V Leiden.[26]

Heterozygous Factor V Leiden carriers have approximately 5-fold increased risk of VTE, while homozygotes face 50-80 fold increased risk. The mutation is particularly significant in combination with other risk factors, demonstrating important gene-environment interactions.[27]

PROTHROMBIN G20210A MUTATION

The prothrombin gene mutation (G20210A) results in elevated plasma prothrombin levels and approximately 3-fold increased VTE risk. This mutation is present in about 2% of Caucasian populations but is rare in Asian and African populations. The EMET study documented prothrombin gene mutation prevalence in European VTE patients.[25]

6.2 NATURAL ANTICOAGULANT DEFICIENCIES

PROTEIN C DEFICIENCY

Protein C deficiency represents a significant inherited thrombophilia with heterozygous prevalence of approximately 0.2-0.4% in the general population. The Leiden Thrombophilia Study demonstrated that protein C deficiency is an infrequent but clear risk factor for venous thrombosis in unselected outpatients.[28] Heterozygous deficiency increases VTE risk approximately 7-fold, while homozygous deficiency typically presents with neonatal purpura fulminans, a life-threatening condition.

A study of 150 families with inherited thrombophilia documented different risks of thrombosis associated with various coagulation defects, including protein C deficiency.[29] Studies in young patients with venous thrombosis have documented the frequency of type I heterozygous protein C deficiency.[30] The condition has been reviewed as part of hypercoagulable states.[31]

PROTEIN S DEFICIENCY

Protein S serves as a cofactor for activated protein C, and its deficiency increases thrombotic risk. Heterozygous protein S deficiency occurs in approximately 0.03-0.13% of the general population and increases VTE risk approximately 5-10 fold. The condition was documented in studies of young patients with venous thrombosis 30 and in the study of 150 families with inherited thrombophilia.[29]

Studies in outpatients with deep vein thrombosis have documented deficiencies of coagulation-inhibiting and fibrinolytic proteins.[32] Japanese studies have identified protein S gene mutations in deep vein thrombosis patients.[33] Indian studies have documented protein S deficiency in patients with venous thromboembolism.[26,34]

ANTITHROMBIN DEFICIENCY

Antithrombin deficiency is the rarest of the major inherited thrombophilias, with heterozygous prevalence of approximately 0.02% in the general population. However, it confers the highest relative risk among natural anticoagulant deficiencies, with approximately 10-20 fold increased VTE risk. The study of 150 families documented thrombotic risks associated with antithrombin deficiency.[29] Deficiencies have been documented in outpatients with DVT 32 and in Indian populations.[26,34]

6.3 OTHER INHERITED THROMBOPHILIAS

HYPERHOMOCYSTEINEMIA

Elevated homocysteine levels, whether due to genetic polymorphisms in enzymes involved in homocysteine metabolism (particularly MTHFR C677T) or nutritional deficiencies (folate, vitamin B12, vitamin B6), increase VTE risk through endothelial dysfunction and prothrombotic effects. The condition has been reviewed as part of hypercoagulable states.[35]

ELEVATED FACTOR VIII

Persistently elevated Factor VIII levels (>150 IU/dL) increase VTE risk approximately 5-fold. While Factor VIII elevation can be acquired (acute phase reactant), some individuals have constitutively elevated levels with a hereditary component.[36]

DYSFIBRINOGENEMIA

Rare inherited abnormalities in fibrinogen structure or function can predispose to thrombosis through impaired fibrin clot structure or resistance to fibrinolysis.[37]

7. SYNERGISTIC EFFECTS AND RISK STRATIFICATION

The risk of DVT is not simply additive when multiple risk factors coexist; rather, risk factors often interact synergistically to substantially amplify thrombotic risk. This synergistic effect has important implications for risk stratification and prophylaxis decisions.[38]

GENE-GENE INTERACTIONS

Individuals with multiple inherited thrombophilias face disproportionately elevated risk compared to single defects. For example, combined heterozygosity for Factor V Leiden and prothrombin G20210A mutation increases VTE risk more than the sum of individual risks. The study of 150 families documented different risks associated with various combinations of coagulation defects.[29]

GENE-ENVIRONMENT INTERACTIONS

Inherited thrombophilias interact significantly with acquired risk factors. Oral contraceptive use in women with Factor V Leiden increases VTE risk approximately 30-fold compared to women without the mutation who do not use oral contraceptives. Similarly, surgery in individuals with inherited thrombophilia carries substantially higher risk than in those without genetic predisposition.

Studies in young patients with low-risk venous thromboembolism have examined inherited risk factors.[39] The EMET study provided data on thrombophilia prevalence in unselected VTE patients.[25] Indian studies have characterized venous thromboembolism in young patients from western India 34 and documented prothrombotic defects in north Indian populations.[26]

RISK STRATIFICATION MODELS

Clinical risk assessment models incorporate multiple risk factors to estimate individual VTE risk and guide prophylaxis decisions. The Caprini score and other validated tools assign weighted points to various risk factors, enabling categorization of patients into low, moderate, high, and very high-risk groups. This stratification approach allows tailored prophylaxis strategies, balancing thrombotic risk against bleeding risk associated with anticoagulation.[40]

8. STRENGTH OF EVIDENCE ASSESSMENT

HIGH-QUALITY EVIDENCE (STRONG SUPPORT)

The following risk factors are supported by high-quality evidence from multiple large studies, systematic reviews, and meta-analyses:

ACQUIRED RISK FACTORS:

Major orthopedic surgery (hip/knee replacement): Supported by numerous prospective studies and randomized trials. Evidence includes Indian studies of major lower limb surgery[9] and international data. Strength: High

Active malignancy: Documented in large registries including the ARRIVE study[7] and extensive international literature. Strength: High

Pregnancy and postpartum period: Well-established through population-based studies and cohort analyses. Strength: High

Prolonged immobilization/hospitalization: Consistently demonstrated across multiple studies including the ARRIVE registry.[7] Strength: High

INHERITED RISK FACTORS:

Factor V Leiden: Extensively studied in multiple populations including the EMET study [25] and studies in various ethnic groups.[26] Strength: High

Prothrombin G20210A mutation: Well-characterized in European populations [25] with consistent risk estimates. Strength: High

Protein C deficiency: Documented in the Leiden Thrombophilia Study,[15] family studies, [29] and multiple population studies [30,32]. Strength: High

Protein S deficiency: Supported by multiple studies including family cohorts, [29] outpatient serie, [32] Japanese studies, [33] and Indian populations [26,34]. Strength: High

Antithrombin deficiency: Documented in family studies, 29 outpatient cohorts, [32] and Indian populations.[26,34]. Strength: High

MODERATE-QUALITY EVIDENCE (MODERATE SUPPORT)

The following risk factors are supported by moderate-quality evidence from observational studies and smaller cohorts:

Oral contraceptives and hormone replacement therapy: Supported by multiple observational studies and cohort analyses, though randomized trial data is limited for ethical reasons. Strength: Moderate

Obesity: Documented in epidemiological studies with consistent associations, though mechanistic understanding continues to evolve. Strength: Moderate

Smoking: Supported by observational studies showing increased risk, particularly in combination with other factors. Strength: Moderate

Antiphospholipid antibodies: Documented in specific studies 41 with consistent findings in autoimmune populations. Strength: Moderate

Elevated Factor VIII levels: Supported by cohort studies with consistent risk estimates. Strength: Moderate

Hyperhomocysteinemia: Evidence from observational studies, 35 though intervention trials have not consistently shown benefit from homocysteine reduction. Strength: Moderate

EMERGING EVIDENCE (LIMITED BUT SUGGESTIVE)

The following areas have emerging evidence requiring further validation:

Long-distance travel: Supported by case-control studies and observational data, though absolute risk remains low in individuals without additional risk factors. Strength: Limited

Specific chemotherapy regimens: Growing evidence for particular agents, though data varies by cancer type and treatment protocol. Strength: Limited

Inflammatory bowel disease: Supported by cohort studies, though mechanisms require further elucidation. Strength: Limited[42]

GEOGRAPHIC AND ETHNIC VARIATIONS

Evidence quality varies by population studied. While Factor V Leiden and prothrombin mutations are well-characterized in Caucasian populations, [25] data in Asian populations is more limited. Studies from Singapore, [6] India [7–9,26,34,] and Japan [33] have begun to address this gap, demonstrating that DVT is not rare in Asian populations and documenting thrombophilia prevalence in these groups. However, larger population-based studies in diverse ethnic groups remain needed.

9. CLINICAL IMPLICATIONS AND PREVENTION STRATEGIES

RISK ASSESSMENT AND STRATIFICATION

The comprehensive understanding of DVT risk factors enables systematic risk assessment in clinical practice. All hospitalized patients should undergo formal VTE risk assessment using validated tools that incorporate both patient-specific factors (age, prior VTE, thrombophilia, comorbidities) and situational factors (surgery type, immobilization, acute illness). This stratification guides prophylaxis decisions and intensity.[43]

THROMBOPROPHYLAXIS STRATEGIES

Prevention strategies must be tailored to individual risk profiles, balancing thrombotic risk against bleeding risk. Mechanical prophylaxis using pneumatic compression devices provides effective prevention without bleeding risk and is appropriate for patients with contraindications to anticoagulation.[7] Pharmacological prophylaxis with anticoagulants (low-molecular-weight heparin, unfractionated heparin, fondaparinux, or direct oral anticoagulants) is indicated for moderate to high-risk patients without contraindications.

Current guidelines, including the CHEST guideline on antithrombotic therapy for VTE disease, provide evidence-based

recommendations for prophylaxis and treatment.[44] The duration and intensity of prophylaxis should be proportionate to risk, with extended prophylaxis considered for very high-risk situations such as major cancer surgery or orthopedic procedures.

SPECIAL POPULATIONS

Certain populations require tailored approaches:

Pregnancy: Prophylaxis decisions must consider both maternal thrombotic risk and fetal safety. Low-molecular-weight heparin is the preferred agent, as it does not cross the placenta.

Cancer patients: Thromboprophylaxis should be considered for hospitalized cancer patients and those receiving high-risk chemotherapy regimens. The ARRIVE registry documented VTE patterns in cancer patients.[7]

Thrombophilia carriers: Asymptomatic carriers of inherited thrombophilias generally do not require long-term anticoagulation but should receive prophylaxis during high-risk situations (surgery, pregnancy, prolonged immobilization).

Surgical patients: Risk-stratified prophylaxis based on procedure type and patient factors is essential. Indian studies have documented DVT risk in patients undergoing major lower limb surgery.[9]

CATHETER-RELATED THROMBOSIS

Central venous catheters, particularly hemodialysis catheters, represent a specific risk factor requiring attention to catheter selection, insertion technique, and monitoring.[19]

10. GAPS IN CURRENT EVIDENCE AND FUTURE DIRECTIONS

GEOGRAPHIC AND ETHNIC DIVERSITY

While studies from Singapore [6], India [7–9,26,34,] and Japan [33] have expanded understanding of DVT in Asian populations, large population-based registries from diverse geographic regions remain limited. The prevalence and impact of specific thrombophilias vary substantially by ethnicity, and risk prediction models developed in predominantly Caucasian populations may not perform equally well in other ethnic groups.

MECHANISTIC UNDERSTANDING

While major risk factors are well-established, the precise molecular mechanisms underlying many gene-environment interactions require further elucidation. Understanding these mechanisms may enable development of targeted prevention strategies.

PERSONALIZED RISK ASSESSMENT

Current risk stratification tools provide population-level estimates but may not accurately predict individual risk. Integration of genetic, clinical, and biomarker data through machine learning and artificial intelligence approaches may enable more precise personalized risk assessment.

NOVEL ANTICOAGULANTS AND PROPHYLAXIS STRATEGIES

Direct oral anticoagulants have expanded options for VTE prevention and treatment, 44 but optimal selection, dosing, and duration for specific patient populations require ongoing study. Novel anticoagulant targets and delivery methods may further improve the benefit-risk ratio of prophylaxis.

POST-THROMBOTIC SYNDROME PREVENTION

While anticoagulation prevents recurrent VTE, strategies to prevent post-thrombotic syndrome, which affects approximately 50% of DVT patient, 3 remain suboptimal. Research into early thrombus removal strategies, optimal compression therapy, and interventions to preserve venous valve function is needed.

LONG-TERM OUTCOMES

Long-term follow-up studies are needed to better understand the natural history of DVT, optimal duration of anticoagulation for various patient populations, and strategies to minimize both recurrent VTE and bleeding complications.

11. CONCLUSION

Deep venous thrombosis represents a significant global health burden, affecting approximately 1.6 per 1000 individuals and ranking as the third leading cause of cardiovascular mortality.[1,5] This narrative review reveals a complex pathogenesis involving intricate interactions between acquired and inherited risk factors, with evidence quality ranging from high (major surgery, malignancy, Factor V Leiden, natural anticoagulant deficiencies) to moderate (hormonal therapies, obesity, smoking) to emerging (long-distance travel, specific inflammatory conditions).

The anatomical distribution of DVT shows characteristic patterns, with distal veins accounting for 40% of cases, followed by superficial femoral (20%), common femoral (20%), popliteal (16%), and iliac veins (4%)[14]. This distribution influences both diagnostic approach and treatment strategy. Complications including pulmonary embolism (up to 33% of cases) and post-thrombotic syndrome (approximately 50% within two years) underscore the importance of prevention.[2,3]

Evidence from diverse geographic regions, including studies from India [7–9,26,34,] Singapore, [6] Japan, [33] and Europe [25,28–30,32] demonstrates that DVT is a global problem requiring attention across all populations. The prevalence of specific thrombophilias varies by ethnicity, highlighting the need for population-specific risk assessment approaches.

Synergistic interactions between risk factors substantially amplify thrombotic risk beyond simple additive effects, emphasizing the importance of comprehensive risk stratification. Current evidence supports risk-stratified prophylaxis using mechanical and pharmacological approaches tailored to individual patient profiles.[4,44] The recognition that multiple risk factors often coexist and interact synergistically underscores the need for systematic risk assessment in all hospitalized patients and those undergoing high-risk procedures.

Key gaps in current evidence include limited data from diverse geographic and ethnic populations, incomplete understanding of molecular mechanisms underlying gene-environment interactions, and suboptimal strategies for preventing post-thrombotic syndrome. Future research should focus on personalized risk assessment integrating genetic, clinical, and biomarker data; novel anticoagulant strategies with improved benefit-risk profiles; and interventions to prevent long-term complications.

The synthesis of current evidence emphasizes that DVT is largely preventable through early recognition of risk factors and implementation of appropriate thromboprophylaxis. As our understanding of risk factors and mechanisms continues to evolve, opportunities for more precise, personalized prevention strategies will emerge, potentially reducing the substantial global burden of venous thromboembolism.

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