Gut Microbiome and Venous Thromboembolism: Emerging Insights and Diagnostic Potential

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Abstract

The role of the gut microbiome in modulating systemic health has become a focal point in recent research, particularly in the context of venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism. This review explores the potential of microbiome analysis in VTE diagnostics, highlighting recent insights into microbiome profiles associated with thrombotic risk, mechanisms linking gut microbial alterations to clot formation, and emerging diagnostic applications. Microbiome-based diagnostics, through tools such as metabolite profiling and microbial risk scoring, represent a promising, non-invasive approach to identifying individuals at high risk for VTE. However, challenges such as inter-individual variability and the influence of external factors on the microbiome need to be addressed. Advancing our understanding of the microbiome's influence on thrombotic risk could pave the way for innovative, personalised diagnostics and preventive strategies. This review proposes a framework for integrating microbiome-derived biomarkers into existing VTE diagnostic algorithms, highlighting opportunities for precision medicine.

Key Points

1. Venous thromboembolism remains a leading cause of cardiovascular morbidity and mortality worldwide, yet current diagnostic strategies have limitations, highlighting the need for novel biomarkers that improve risk stratification and early detection.

2. This narrative review examined evidence linking the gut microbiome to venous thromboembolism, summarising microbial signatures, mechanistic pathways, and emerging microbiome-based diagnostic approaches identified through literature published to June 2025.

3. Gut microbial dysbiosis and metabolites such as trimethylamine-N-oxide show promise as biomarkers of thrombotic risk, although standardisation, prospective validation, and integration with established clinical risk models are required before clinical implementation.

INTRODUCTION

Venous thromboembolism (VTE), encompassing both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of cardiovascular morbidity and mortality worldwide, with an estimated 10 million cases annually.[1] The condition imposes a substantial economic burden on healthcare systems globally.[2-4] Hospitalised patients are at increased risk for VTE, accounting for approximately one-half to two-thirds of VTE incidence worldwide.[5] Other risk factors include old age, male sex, obesity, smoking, Factor V Leiden, long-haul flight, pregnancy, surgery, antiphospholipid syndrome, and cancer.[4,6,7] While the mortality rates of VTE have been relatively stable since 2008, with slight increments recorded during the COVID-19 pandemic,[8] the systemic underuse of prophylactic treatment in hospitalised patients and high risk of recurrence continue to fuel the burden of this condition.[4]

The clinical signs and symptoms of DVT usually include lower extremity (calf) pain, swelling, erythema, and tenderness.[1,9,10] PE typically presents with dyspnoea, pleuritic chest pain, haemoptysis, tachycardia, or, in severe cases, haemodynamic instability.[11-14] This non-specificity in symptomatology accounts for the limited accuracy of VTE diagnosis using clinical signs and symptoms, with only half of patients with VTE reporting symptoms or positive findings on physical examination.[15]

The current diagnostic paradigm for VTE includes a combination of clinical pretest probability, D-dimer testing, and imaging.[14] The Wells score and revised Geneva score are commonly used to estimate the likelihood of a DVT and PE diagnosis, respectively.[16,17] Imaging modalities, such as compression ultrasonography for DVT and CT pulmonary angiography for PE, are commonly used following assessment of clinical pretest probability and D-dimer testing.[18] Although effective, these approaches may result in diagnostic delays, increased imaging utilisation, and reduced diagnostic accuracy in certain high-risk populations, including patients with cancer.[14,19,20]

Increasing evidence suggests that the gut microbiome plays an active role in thrombosis. Experimental studies have demonstrated that the absence of gut microbiota (GM) is associated with reduced von Willebrand factor (VWF) expression and impaired thrombus formation, indicating a direct influence of microbial signals on haemostasis.[21,22] Human studies further show that gut microbial dysbiosis and increased production of metabolites such as trimethylamine-N-oxide (TMAO) are associated with enhanced platelet reactivity and an elevated risk of cardiovascular and thrombotic events, including VTE related outcomes.[23-26] Given the established role of the gut microbiome in regulating immune, metabolic, and inflammatory pathways,[27-29] these findings suggest a plausible mechanistic link between gut microbial composition and thrombotic risk.[30]

This review examines current evidence linking the gut microbiome to VTE, explores the underlying biological mechanisms, and evaluates the potential role of microbiome based diagnostic approaches.

METHODS

Study Design

This is a narrative review examining evidence linking the gut microbiome to VTE and exploring microbiome-informed diagnostic strategies. A narrative review style was chosen due to heterogeneity of the available data.

Literature Search

The authors conducted a focused literature search using PubMed and Google Scholar from inception through June 2025, combining terms related to "venous thromboembolism," "gut microbiome," and "diagnostics." Additional keywords were adapted as necessary to capture relevant variations. Studies were screened by title and abstract to identify relevant human studies, reviews, and mechanistic articles. Inclusion criteria were: publications in English, human-based or translational studies with relevance to VTE and the gut microbiome, and review articles providing mechanistic or diagnostic insights. Exclusion criteria were: non-English publications, animal-only studies without translational relevance, and articles unrelated to the research question. Reference lists of included studies were also reviewed to identify additional relevant sources. Given the narrative nature of the review, no formal risk-of-bias tool was applied and the inclusion was at the authors' discretion to support the narrative synthesis.

MICROBIOME PROFILES LINKED TO VTE RISK

The GM of healthy adults is predominantly composed of obligate anaerobic bacteria, with over 95% of microbial species belonging to the phyla *Firmicutes* and *Bacteroidetes*.[31] Emerging research has identified specific microbiome signatures that may correlate with an increased risk of VTE.[32] Alterations in the diversity and composition of gut bacteria are commonly observed in individuals with cardiovascular diseases and inflammatory conditions, both of which are established risk factors for thromboembolic events. Dysbiosis, characterised by imbalances in gut microbial populations, frequently occurs in these high-risk populations.[33,34]

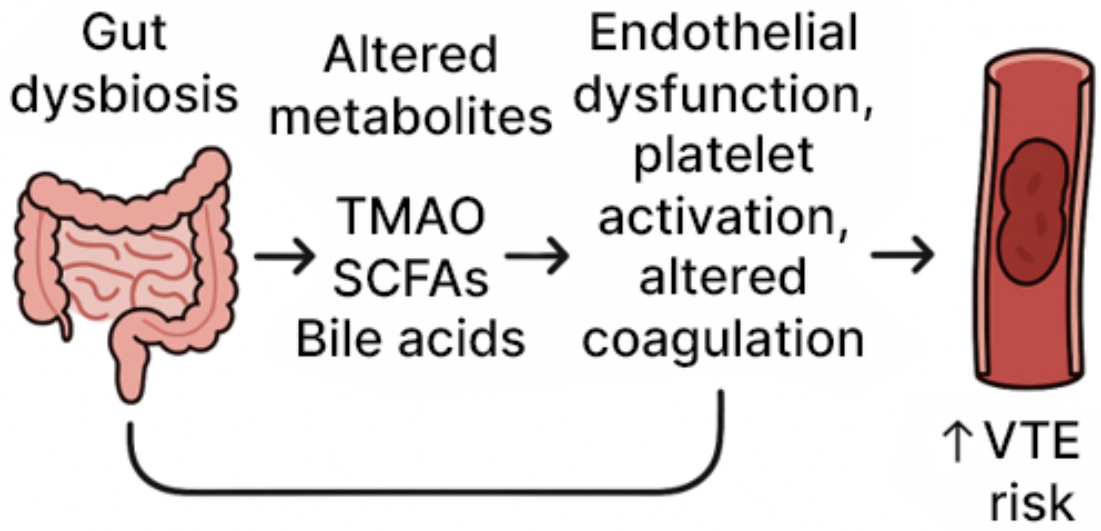
Reduced microbial diversity and an imbalance in the abundance of specific bacterial taxa, such as *Firmicutes* and *Bacteroidetes*, have been associated with metabolic dysfunction and inflammation. For instance, individuals with a higher prevalence of *Prevotella* and a relative paucity of *Bacteroides* are more likely to develop metabolic syndrome, a condition that increases VTE risk.[35] Additionally, dysbiosis observed in those with cardiovascular disease often overlaps with the microbiome profiles found in individuals predisposed to thrombosis.[36,37]

Certain high-risk populations, including individuals with autoimmune diseases, obesity, and metabolic syndrome, exhibit distinct microbiome patterns. These patterns may serve as potential biomarkers for VTE risk, highlighting the need to identify specific microbial signatures in groups prone to thrombotic events.[38]

MECHANISMS CONNECTING THE MICROBIOME TO THROMBOTIC RISK

The principal pathways through which gut microbial dysbiosis may contribute to venous thrombosis are summarised in Figure 1. The relationship between GM composition and thrombotic risk is mediated through several interconnected mechanisms, including the production of metabolites, inflammatory modulation, and endothelial function regulation.[21,23] Several diseases with an increased risk of VTE are associated with an imbalance in the gut microbiome, characterised by a decrease in commensal anaerobic bacteria and an increase in the abundance of pathogenic

Figure 1: Proposed mechanisms linking gut microbiome dysbiosis to venous thromboembolism.



TMAO: trimethylamine-N-oxide; SCFA: short-chain fatty acid; VTE: venous thromboembolism.

bacteria, of which the most common is the gram-negative *Enterobacteriaceae*.[23] Key pathways include lipopolysaccharide-mediated immunothrombosis, trimethylamine-N-oxide (TMAO) associated platelet activation, toll-like receptor signalling, inflammatory cytokine release, dysbiosis associated endotoxaemia, and the altered production of microbiota derived metabolites such as short chained fatty acids and tryptophan metabolites. The main microbiome-related mechanisms implicated in thrombosis are summarised in Table 1.

Lipopolysaccharides

Bacterial lipopolysaccharides (LPS), the glycolipids found on the outer membrane of gram-negative bacteria, is one of the links between the microbiome and hypercoagulability. Support for this mechanistic relationship has also been demonstrated in germ-free and microbiota-depleted mouse models. In a stenosis induced deep vein thrombosis model, depletion of microbiota significantly reduced circulating LPS levels, thrombus formation, and inflammatory activation, whereas restoration of microbial associated LPS signalling enhanced thrombotic susceptibility.[57] These findings provide casual experimental evidence that gut microbiota derived endotoxins contribute directly to venous thrombogenesis. LPS binds to toll-like receptors to activate endothelial cells and platelets, leading to activation of the coagulation cascade.[23]

In the intrinsic pathway, LPS triggers the kallikrein-kinin system, leading to the activation of factor XII and subsequent coagulation and inflammation.[39] High molecular weight kininogen, a key LPS carrier, is essential for this process, as its absence reduces LPS-induced mortality.[39] Factor FXII activation by LPS also amplifies cytokine release, such as IL-1, IL-6, and IL-23, linking coagulation with inflammatory responses.

In the extrinsic pathway, LPS enhances tissue factor activity through the externalisation of phosphatidylserine, mediated by caspase-11 (Casp11).[40] This promotes thrombin generation and platelet aggregation, which are key drivers of

Table 1: Proposed mechanisms linking the gut microbiome to thrombotic risk and venous thromboembolism.

Mechanism	Microbial component/ metabolite	Pathophysiologic pathway	Impact on thrombosis	Key references
LPS	Gram-negative bacteria (e.g., *Enterobacteriaceae*)	Binds TLR → activates endothelial cells and platelets; triggers kallikrein-kinin system → FXII activation; enhances TF activity via caspase-11	Coagulation cascade activation, platelet hyperreactivity, immunothrombosis	21,23,39,40
TMAO	Microbial metabolism of choline, carnitine, phosphatidylcholine	Increases platelet aggregation and thrombus formation; U-shaped mortality association in VTE	Modulates thrombosis risk; potential therapeutic target via microbiome modulation	23-26
TLR signalling	PAMPs	Activates platelet and endothelial responses; increases VWF expression	Promotes platelet aggregation and thrombus growth	21,22,41-43
Inflammatory cytokines	Various gut bacteria	Release of IL-6, TNF-α→ endothelial damage, ↓ nitric oxide→ impaired vasodilation	Endothelial dysfunction → increased clotting tendency	44,45
Dysbiosis	Overgrowth of *Enterobacteriaceae*	↑ LPS production + gut barrier permeability	Systemic endotoxemia → hypercoagulability	23,46,47
Gut–liver axis and intestinal inflammation	Gut-derived endotoxins, inflammatory cytokines, microbial metabolites	Increased intestinal permeability and portal translocation of microbial products alter hepatic inflammatory signalling and coagulation factor synthesis	Promotes systemic hypercoagulability, endothelial dysfunction, and thrombo-inflammatory activation associated with VTE	23,48-52
Tryptophan metabolites	Indole derivatives, kynurenine pathway metabolites	Activates AhR; modulates immune and endothelial responses	Dysregulated signalling may promote inflammation and thrombotic susceptibility	53,54
Short-chain fatty acids	Butyrate, acetate, propionate	Maintains gut barrier integrity; modulates inflammation and endothelial function; regulates platelet activity	Reduced inflammation and endothelial dysfunction may protect against thrombosis	55,56

AhR: aryl hydrocarbon receptor; FXII: factor XII; LPS: lipopolysaccharide; PAMP: pathogen-associated molecular patterns; TLR: toll-like receptor; TMAO: trimethylamine-N-oxide; VTE: venous thromboembolism; VWF: von Willebrand factor.

hypercoagulability.[40] This convergence of coagulation activation, platelet hyperreactivity, and inflammatory signalling supports the role of immunothrombosis in VTE and identifies potential therapeutic targets, such as Casp11 or tissue factor, for managing LPS-driven hypercoagulable states.

Trimethylamine-N-oxide

Western diets are rich in trimethylamine-containing nutrients such as choline, carnitine, and phosphatidylcholine.[24] The gut microbiota converts these nutrients from the host's diet into metabolites such as TMAO.[23-25] Elevated TMAO levels have been associated with increased platelet aggregation and thrombus formation.[23-25] Interestingly, a U-shaped association has been observed between TMAO levels and mortality in elderly patients with acute VTE, with the lowest mortality risk occurring at moderate TMAO levels around 4 µmol/L.[26] This suggests that both deficient and

excessive TMAO levels could have adverse effects, underscoring the complexity of TMAO's role in thrombosis and systemic outcomes.[26] Modulating the gut microbiome to target balanced TMAO levels may be an innovative approach for decreasing the risk of thrombosis.[23]

Toll-Like Receptor Signalling

The microbiota produces pathogen-associated molecular patterns, such as peptidoglycans, which leak into circulation and activate toll-like receptor (TLR) signalling. This not only influences immune function but also regulates haemostatic processes in endothelial cells and platelets. TLR stimulation directly evokes platelet responses,[22,41-43] mediates endothelial responses to pathogen-associated molecular patterns, and can promote coagulation by endothelial cells. TLR engagement also leads to enhanced VWF expression in the liver, facilitating platelet aggregation and thrombus growth.[21] Reduced VWF levels in germ-free and TLR2-deficient mice correlate with impaired thrombus growth, suggesting a critical regulatory role for microbial patterns in maintaining normal VWF levels.[21]

Inflammatory Cytokines

Some gut bacteria may promote the release of inflammatory cytokines like IL-6 and TNF-α, which have been linked to thrombotic processes. Chronic inflammation can damage endothelial cells, leading to dysfunction and increased clotting risk. Gut-derived metabolites and pro-inflammatory cytokines can compromise endothelial cell integrity, impairing vascular function.[44,45] The microbiome's influence on nitric oxide production, critical for vasodilation, can thus impact vascular tone and reactivity, fostering conditions conducive to thrombus formation. As endothelial dysfunction is a precursor to thrombosis, the microbiome's role in affecting vascular health directly ties to its potential influence on VTE risk.

Dysbiosis

Genetic and environmental factors can cause dysbiosis, characterised by an overgrowth of *Enterobacteriaceae* and a reduction in microbial diversity.[23,46,47] This overgrowth increases LPS production in the gut lumen, which can pass through a compromised gut epithelial barrier into the portal and systemic circulation.[23,46,47] The mechanism of LPS is outlined above.

Short-Chain Fatty Acids

Short-chain fatty acids (SCFA), primarily acetate, propionate, and butyrate, are produced through bacterial fermentation of dietary fibre in the colon.[55,56] These metabolites play an important role in maintaining intestinal barrier integrity, regulating immune responses, and preserving endothelial function.[55,56,58] Reduced SCFA production has been associated with systemic inflammation and endothelial dysfunction, both of which contribute to thrombotic susceptibility.[55,58]

Among SCFAs, butyrate has demonstrated anti-inflammatory and antithrombotic properties through inhibition of pro-inflammatory cytokine production and modulation of platelet activation pathways.[55] SCFAs also help maintain gut epithelial integrity, thereby limiting translocation of prothrombotic bacterial products such as lipopolysaccharides into the systemic circulation.[56,58] Experimental studies suggest that depletion of SCFA producing bacteria may contribute to a prothrombotic state through enhanced inflammation and vascular dysfunction, although direct evidence specifically linking SCFAs to VTE remains limited.

Tryptophan Metabolites

The GM also influences host tryptophan metabolism, generating bioactive metabolites including indole derivatives and kynurenine pathway products.[53,54] These metabolites interact with host immune and vascular pathways, particularly through activation of the aryl hydrocarbon receptor, an important regulator of inflammation and endothelial homeostasis.[53,54,59]

Altered tryptophan metabolism has been implicated in chronic inflammatory and cardiovascular disease associated

with increased thrombotic risk.[53,60] Dysregulation of microbiota derived tryptophan metabolites may promote endothelial dysfunction, oxidative stress, and inflammatory activation, thereby creating a vascular environment conducive to thrombosis.[54,59,60] Although the relationship between tryptophan metabolites and VTE remains incompletely understood, emerging evidence suggests that these pathways may contribute to thrombo-inflammatory processes and represent potential targets for future diagnostic and therapeutic investigations.

Intestinal Inflammation, Infection, and the Gut–Liver Axis

Clinical conditions characterised by intestinal inflammation or infection provide additional evidence supporting a relationship between the gut microbiome and VTE. Patients with inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, exhibit a significantly increased risk of VTE compared with the general population, particularly during periods of active disease and hospitalisation.[48-50] Chronic intestinal inflammation in IBD promotes endothelial dysfunction, platelet activation, and systemic hypercoagulability through sustained cytokine release and disruption of the intestinal epithelial barrier.[49,50]

Similarly, intestinal infections may contribute to thrombotic risk through microbiota disruption, endotoxemia, and activation of inflammatory and coagulation pathways. Increased intestinal permeability during enteric infections facilitates translocation of microbial products such as lipopolysaccharides into the systemic circulation, promoting immunothrombosis and endothelial activation.[23,39] These observations further support the concept that intestinal barrier dysfunction and microbial dysbiosis may contribute to systemic thrombo-inflammatory states relevant to VTE pathogenesis.

The gut–liver axis also represents an important mechanistic link between the intestinal microbiome and thrombosis. Through the portal circulation, gut-derived microbial metabolites and endotoxins directly influence hepatic immune signalling and coagulation factor synthesis. Dysbiosis-associated endotoxemia may stimulate hepatic inflammatory responses and alter production of prothrombotic mediators including fibrinogen, VWF, and coagulation factors.[51,52] Given the liver's central role in regulating haemostasis, perturbations within the gut–liver axis may substantially influence thrombotic susceptibility. Emerging evidence suggests that this bidirectional interaction between the gut microbiota and hepatic coagulation pathways may represent an important contributor to VTE development and progression.

POTENTIAL FOR DIAGNOSTIC APPLICATIONS

Microbiome analysis has emerged as a valuable tool in the diagnosis and management of various gastrointestinal disorders. For example, in IBD, gut microbiome profiling reveals significant alterations in microbial composition. Studies have demonstrated that patients with IBD often have reduced levels of beneficial bacteria such as *Faecalibacterium prausnitzii*, a species known for its anti-inflammatory properties. This reduction correlates with heightened disease activity and an increased risk of relapse.[61]

In the context of VTE, emerging evidence suggests a dynamic interplay between GM dysbiosis and thrombotic processes. Among the metabolites of interest, TMAO has also attracted attention for its potential diagnostic value. Rather than reiterating its mechanistic role, recent evidence suggests that TMAO may hold potential as a qualitative biomarker for risk stratification. In a cross-sectional study of 859 patients with acute VTE, elevated TMAO levels were associated with arterial thrombotic events, including myocardial infarction and stroke, as well as increased mortality.[26] Notably, the risk of recurrent VTE did not significantly differ across patients with low, medium, or high TMAO levels,[26] suggesting that while absolute concentrations may not predict recurrence, the presence of elevated TMAO could still indicate a broader prothrombotic state.

This raises the possibility that TMAO measurement could be explored as part of a qualitative screening panel, flagging patients with a heightened thrombotic phenotype, rather than as a standalone quantitative predictor of VTE recurrence. Supporting this concept, two prospective clinical studies have demonstrated strong association between elevated plasma TMAO levels and an increased risk of major adverse cardiovascular events, emphasising the potential relevance of these metabolites in integrated thrombotic risk assessment models.[62]

Advanced sequencing technologies, including next-generation sequencing and 16S rRNA gene sequencing, have provided significant insights into the role of the gut microbiome in VTE pathogenesis. These methods enable the identification of microbial taxa and metabolites associated with thrombotic risk, offering promising avenues for innovative diagnostic applications. For example, Mendelian randomisation analyses have been employed to investigate the causal role of gut microbiota composition and plasma metabolite levels in VTE development. By utilising single nucleotide polymorphisms as instrumental variables, these studies have identified microbial taxa with protective roles against VTE, while highlighting others that may contribute to its pathogenesis.[63]

The potential of microbiome profiling as a diagnostic tool for VTE risk assessment is a developing but promising field. Microbiome-based diagnostics could offer non-invasive methods to assess VTE risk. Integrating microbiome data with traditional risk factors such as age, BMI, and comorbid conditions can enable the creation of more accurate risk scoring models. Such scoring systems could provide a personalised assessment of VTE risk, improving the precision of diagnostic processes. The development of predictive models through machine learning and bioinformatics could further refine microbiome-based diagnostics.

CHALLENGES AND FUTURE DIRECTIONS

Despite the promising potential of microbiome-based diagnostics in VTE, significant challenges remain that must be addressed to facilitate widespread clinical implementation. Firstly, there is currently no standardised definition of a healthy gut microbiome. There are no standard cut-offs for effect sizes.[64,65] This lack of standardisation leads to inconsistent findings across studies.

Secondly, many microbiome-based prediction models lack rigorous external validation and remain susceptible to overfitting. In a recent systematic review quantitatively analysing human gut microbiome classification studies (n=102), only 12% (n=12) of included studies reported a bona fide test set area under the receiver operating curve, casting serious doubt on the diagnostic potential of gut microbiome.[66]

Thirdly, microbiome composition is strongly influenced by factors such as diet, medications (particularly antibiotics), and lifestyle, making diagnostic interpretation challenging.[67] In addition, the high cost of omics technologies, including metatranscriptomics, metabolomics, and metaproteomics, may limit widespread adoption, particularly in resource limited settings.

Beyond these technical challenges, important knowledge gaps remain. Large scale prospective studies are needed to establish temporal and causal relationships between specific microbiome signatures and VTE. Similarly, interventional studies evaluating dietary modification, probiotic or prebiotic therapies, and targeted microbial metabolite modulation remain limited and have not yet demonstrated clear clinical benefit in VTE prevention or diagnosis. Furthermore, few studies have examined how microbiome profiles interact with established VTE risk factors, such as immobility, surgery, and cancer, or how they may be incorporated into existing risk prediction models. The absence of standardised protocols for

sample collection, sequencing, and data analysis further limited reproducibility across studies. Future research should focus on adequately powered longitudinal studies to identify microbial taxa and metabolites associated with incident VTE, while interventional trials should evaluate whether microbiome targeted therapies can reduce thrombotic risk or improve diagnostic accuracy. Equally important is the development of cost-effective, standardised, and reproducible microbiome assays suitable for routine clinical practice. Finally, integrating microbiome derived biomarkers with traditional clinical risk factors through advanced analytical approaches, including machine learning, may facilitate more personalised VTE risk prediction and prevention strategies.

CONCLUSION

The emerging evidence linking the gut microbiome to VTE risk highlights the potential of microbiome profiling as a diagnostic tool. While the field remains in its early stages, microbiome-based diagnostics could offer a non-invasive, cost-effective approach to identifying individuals at high risk for thrombotic events. As research progresses, addressing challenges related to variability, standardisation, and causality will be crucial in refining these diagnostic tools. Integrating microbiome-based diagnostics with traditional risk assessment methods could ultimately lead to more personalised and effective approaches to VTE prevention and management, contributing to better patient outcomes in thrombosis care.

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