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Drug delivery systems for the treatment of venous thrombosis

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ABSTRACT

Venous thrombosis (VT) is defined by the formation of a blood clot within a vein, leading to partial or complete obstruction of blood flow. This condition may result in severe sequelae, including chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome. As a multifactorial and episodic disorder, VT constitutes a significant contributor to global morbidity and mortality. In this review, we first seek to provide a comprehensive understanding of the intricate pathophysiological mechanisms underlying VT. Next, the diagnostic challenges posed by the nonspecific nature of clinical signs and symptoms were explored, offering an overview of current strategies aimed at enhancing diagnostic accuracy. Furthermore, treatment modalities for VT, primarily consisting of anticoagulation therapy, along with thrombolysis or surgical intervention when indicated, are discussed in detail. Considering the urgent need for safer and more effective therapeutic options, the development of nanoparticle-based drug delivery systems (DDS) capable of specific sites of thrombosis is crucial. Thus, this review further examines recent advancements in DDS for the treatment of VT. Finally, we will evaluate the prospects and significant challenges currently facing the field, offering a comprehensive overview of the research and treatment of VT.

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1. Introduction

Venous thrombosis (VT) occurs when a blood clot, made of fibrin, erythrocytes, platelets, and leukocytes, forms in a vein, causing partial or complete blockage of the blood vessel. VT is a disorder with substantial morbidity and mortality rates worldwide, which represents the third most prevalent vascular disease, following myocardial infarction and stroke [1]. VT encompasses a range of disorders, including superficial vein thrombosis (SVT), deep vein thrombosis (DVT), and pulmonary embolism (PE) [2]. SVT arises from the formation of clots in veins located near the skin's surface, commonly in the legs or arms. As superficial veins drain into the deep veins, untreated SVT can progress to DVT [3]. DVT results from the abnormal coagulation of blood within the deep veins, which impedes blood return to the heart. The thrombus may propagate retrogradely or anterogradely, potentially involving the entire venous system of the lower extremities and causing swelling and pain in the affected limbs [4]. If a thrombus in the deep vein dislodges and travels to the pulmonary arteries, it can cause PE, resulting in impaired pulmonary circulation and respiratory dysfunction [5]. Notably, DVT and PE are collectively termed as venous thromboembolism, representing distinct stages of the same disease [6].

VT is a multifactorial and episodic disease whose pathophysiology is commonly explained by the Virchow's triad, encompassing stasis, endothelial injury, and hypercoagulability [7]. It is generally believed that VT originates within the valve cusps of large veins, regions vulnerable to stasis, a significant reduction or cessation of venous blood flow [8]. The resultant stasis creates localized hypoxia, inducing endothelial cells (ECs) dysfunction and endothelial injury, which may lead to the downregulation of the natural anticoagulant properties of ECs, thereby fostering hypercoagulability. Increasing evidence suggests inflammation and coagulation are intricately linked through a bidirectional interplay, forming a vicious cycle that promotes thrombus formation and progression [9,10]. In general, therapeutic strategies targeting these pathological features, specifically stasis, endothelial injury, hypercoagulability, and inflammation, are crucial in mitigating VT [11,12].

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The complex pathogenesis of VT, combined with the nonspecific nature of its clinical signs and symptoms, leads to a low clinical detection rate as well as a high incidence of underdiagnosis and misdiagnosis, which ultimately results in elevated mortality [13]. The diagnostic approach to suspected VT involves a comprehensive evaluation strategy, including clinical probability assessment, measurement of D-dimer levels, and imaging [14]. The combination of clinical pretest probability assessment and D-dimer testing provides a noninvasive and rapid approach for ruling out VT. However, such methods can be affected by various clinical conditions due to their limited sensitivity and specificity, confirmatory imaging remains typically required [15]. Regrettably, universal imaging for all suspected VT cases is impractical, as diagnostic imaging modalities are not only time-consuming and costly but also carry risks of radiation exposure and potential adverse effects, including contrast-induced nephropathy or allergic reactions [16]. Therefore, selective use of diagnostic modalities is crucial for reducing diagnostic errors, lowering healthcare costs, and enhancing diagnostic accuracy, ultimately facilitating the development of personalized diagnostic and therapeutic strategies for VT patients [17].

The primary treatment for VT focuses on promoting thrombolysis, restoring vascular patency, preserving valve function, and preventing the development of chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome [18]. In patients with suspected VT, anticoagulation should be initiated promptly, pending diagnostic confirmation, provided that the risk of bleeding is deemed low. Fixed-dose direct oral anticoagulants (DOACs) have emerged as the preferred treatment for acute VT in most patients, eliminating the need for routine pharmacologic monitoring [19]. Compared to conventional anticoagulation, thrombolysis has demonstrated efficacy in not only alleviating pain and edema but also preventing damage to the venous valves. Nonetheless, it is often associated with an increased risk of bleeding. In patients with proximal DVT, the use of vena cava filters has been shown to effectively reduce the short-term risk of PE although their impact on long-term mortality remains uncertain [20]. As therapeutic strategies continue to evolve, the indications and efficacy of various treatments are becoming better defined [21].

Thrombolytic and anticoagulant agents, including heparin, urokinase plasminogen activator (uPA), and tissue plasminogen activator (tPA), are commonly utilized in management of VT due to their ability in dissolving or inhibiting thrombus formation [22]. However, these drugs have some limitations, such as short half-lives, susceptibility to allergic reactions, and potential inactivation [23]. Therefore, the effective delivery of therapeutic agents to the thrombus site, with enhanced local drug concentration and minimized systemic side effects, is essential [24]. Since the emergence of nanomedicine in the late 1990s, numerous nanoparticle (NP)-based drug delivery systems (DDS) have been developed, including polymeric NPs, metal NPs, silica NPs, carbon-based nanostructures, and metal-organic frameworks [25]. By optimizing the shape, size, physicochemical properties, and surface area-to-volume ratio of these NPs, it is possible to improve their half-life in blood circulation, targeting efficiency, and bioavailability, as well as reduce toxicity [26]. Therefore, DDS, leveraging nanotechnology and thrombus-specific targeting, hold promise to improve VT therapy by maximizing efficacy while minimizing off-target effects [27].

Although several reviews have reported the pathogenesis, diagnosis, or conventional treatments of VT [28], there remains a paucity of systematic summaries regarding NP-based DDS for VT management. To our knowledge, this represents the first comprehensive review evaluating both the clinical translation potential of these technologies and their synergistic effects with existing therapies. We begin by a thorough exploration of their pathophysiology, with particular emphasis on the roles of immune cells and coagulation factors in the embolization process. We then summarize the current diagnostic and therapeutic practices, with the objective of proposing an integrated platform for the detection and management of VT. Finally, we review the NP-based DDS employed in therapy, analyzing their advantages and limitations, with the aim of developing more streamlined and effective thrombus-targeted treatments in the future. These advancements are crucial for enhancing the clinical efficacy and safety of targeted antithrombotic therapies.

2. Pathophysiology of VT

Virchow's triad, the cornerstone model for understanding thrombus formation in VT, has been progressively refined through advances in cellular and molecular pathophysiology (Fig. 1). Increasing evidence now underscores the pivotal roles of inflammation and oxidative stress in VT pathogenesis [29]. The following section will examine the pathogenesis of VT in light of these emerging insights.

2.1. Stasis

Stasis, characterized by the transition from pulsatile to streamline flow, results in severe hypoxia in the deeper regions of the venous valve cusps, ultimately causing endothelial dysfunction and damage [30]. Local hypoxia triggers the nicotinamide adenine dinucleotide phosphate oxidase system, leading to excessive reactive oxygen species (ROS) production. ROS serves as a stimulus for the activation of ECs, triggering the exocytosis of Weibel-Palade bodies, which subsequently fuse with the plasma membrane to release P-selectin and vWF, facilitating the recruitment of neutrophils, leukocytes, platelets, and tissue factor (TF)-positive particles to the vessel wall [31]. TF-positive particles and monocytes activate the FVII-dependent coagulation cascade, while platelets adhere to activated ECs or leukocytes, forming small and heterogeneous aggregates that further amplify the local coagulation response [32,33].

2.2. Endothelial dysfunction

The pathogenic mechanisms of VT are closely interconnected and often initiated by damage to the vascular wall [34]. Oxidative stress-induced endothelial dysfunction represents a critical pathogenic factor in VT. Oxidative stress drives the direct reaction between ROS and nitric oxide (NO) in ECs, generating peroxynitrite, which mediates both oxidative and nitrosative damage to cellular membranes, proteins, and DNA, while concurrently reducing NO bioavailability and promoting thrombus formation [35]. Additionally, inflammation induces an imbalance favoring procoagulant and antifibrinolytic components, shifting vascular ECs from an anticoagulant and anti-inflammatory phenotype to a proinflammatory and prothrombotic state [36].

2.3. Hypercoagulability

Hypercoagulability is a pathophysiological state characterized by excessive activation of coagulation pathways due to hereditary or acquired risk factors, concomitant with impaired anticoagulant and fibrinolytic systems, leading to a pathological predisposition to thrombosis [37]. From a genetic perspective, thrombosis can arise from two main mechanisms, including the loss of function of endogenous anticoagulant pathways, as well as the hyperactivation of procoagulant pathways [38–40]. Additionally, increasing evidence reveals a bidirectional relationship between inflammation and thrombosis: inflammatory mediators promote coagulation factor release, increasing thrombotic risk, while coagulation activation stimulates pro-inflammatory factors that amplify the inflammatory response [41,42].

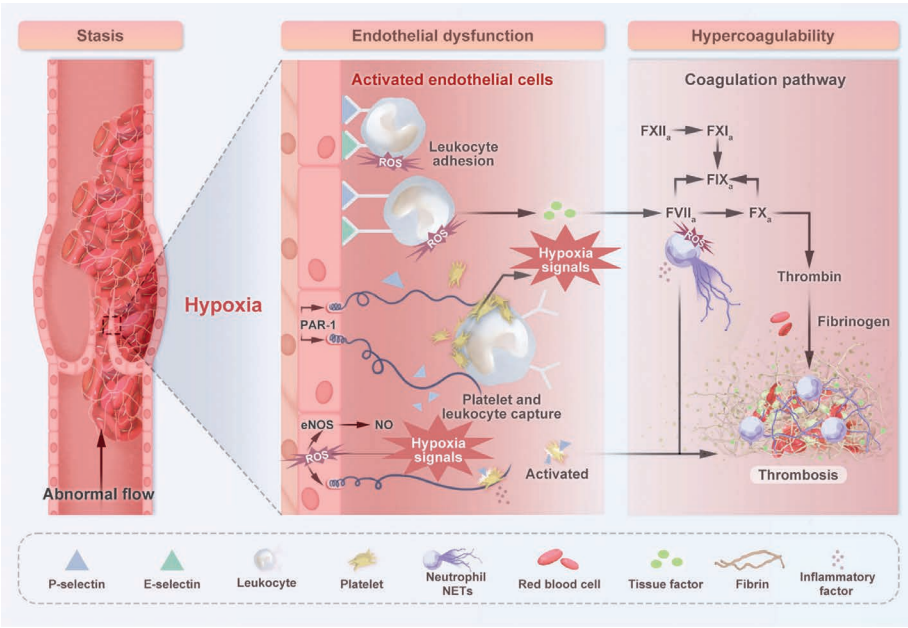


Fig. 1. VT is thought to originate in the valvular sacs of large veins, which are prone to stasis leading to hypoxia or inflammation. Procoagulant activation of venous ECs increases the expression of adhesion molecules like P-selectin and E-selectin, facilitating the binding of leukocytes and platelets. Activated leukocytes express TF, triggering the extrinsic coagulation pathway and thrombin production. Increased ROS production decreases endothelial NO production, leading to the release of vWF and P-selectin from Weibel-Palade bodies, which enhances platelet aggregation and activation. Finally, fibrin, vWF, and neutrophil extracellular traps (NETs) form a scaffold for platelet and erythrocyte adhesion, promoting thrombus formation and growth.

3. Diagnosis of VT

Timely and accurate diagnosis is crucial for appropriate prevention and treatment of thrombus extension, thus reducing in morbidity and mortality associated with VT. Due to the nonspecific nature of symptoms in VT, diagnosis based solely on clinical presentation is unreliable. Therefore, a comprehensive diagnostic approach is adopted, incorporating clinical probability assessment, D-dimer testing, and imaging (Fig. S1 in Supporting information) [43]. The following section outlines four widely used clinical diagnostic methods for VT (Table S1 in Supporting information).

3.1. Clinical probability assessment

The initial step in the diagnostic algorithm for suspected VT is the clinical pretest probability assessment to guide risk stratification and inform subsequent diagnostic testing. Predictive probability can be evaluated through clinical prediction rules, which are developed through multivariate regression modeling on patient cohorts, aiming to identify independent clinical predictors of VT [44]. Commonly used clinical prediction rules include the Wells Score and Modified Geneva Score for suspected PE, and the Wells Score for suspected DVT [45,46]. However, traditional clinical probability assessment often fails to capture the complex interactions among multiple risk factors. Artificial neural networks, a type of machine learning algorithm, can enhance DVT risk stratification by analyzing key variables, such as sex, age, D-dimer levels, and Wells score components [47]. By mimicking the brain's learning process, artificial neural networks optimize their predictive accuracy, allowing for more precise individualized risk assessment.

3.2. D-dimer testing

D-dimer is a fibrin degradation product resulting from the breakdown of thrombin-generated fibrin clots by fibrinolytic enzymes which reflects the dynamics of coagulation and fibrinolysis *in vivo* and serves as a key marker of hypercoagulable states and thrombosis [48]. D-dimer testing demonstrates high sensitivity (>93%) for ruling out VT, therefore negative D-dimer results are particularly valuable in excluding VT. However, D-dimer exhibits relatively low specificity (approximately 50%), primarily because elevated levels can also result from various factors such as advanced age, pregnancy, infections, chronic inflammatory states, and malignancies [49]. Consequently, positive D-dimer results necessitate further confirmation of VT through imaging [50]. Advanced D-dimer detection methods, such as mass spectrometry, electrochemical analysis, and optical immunoassays, outperform traditional immunoassays in sensitivity, specificity, and analytical precision [51]. These innovations may significantly improve the accuracy and reliability of D-dimer testing.

3.3. Compression ultrasonography

Compression ultrasound, a routine non-invasive modality, has largely replaced venography as the primary diagnostic tool for DVT. The technique encompassed two main approaches, including whole-leg compression ultrasound and limited compression ultrasound. Whole-leg compression ultrasound evaluates the entire deep venous system, from the groin to the calf, while limited compression ultrasound targets the popliteal and femoral veins [52]. Additionally, the technique is less effective in obese patients, in veins of cast-immobilized limbs, and in pelvic veins. In such instances, alternative imaging modalities such as computed tomography (CT) venography, magnetic resonance venography, or magnetic resonance direct thrombus imaging are often preferred [53]. Recently, an artificial intelligence (AI)-guided compression ultrasound (ThinkSono Guidance system) with remote expert review for DVT can be a safe and effective method to reduce the number of duplex ultrasound scans and D-dimer testing needed [54].

3.4. Computed tomography pulmonary angiography (CTPA)

The continuous advancement of non-invasive diagnostic techniques has led to the replacement of ventilation-perfusion scan

and pulmonary angiography by CTPA as the first-line imaging modality for PE due to its superior sensitivity and specificity [55]. CTPA provides clearer and more intuitive visualization of the thrombus location, size, shape, and degree of vascular obstruction in the pulmonary arteries, aiding in both diagnosis and assessment of PE severity [56]. Recently, photon counting CT has emerged as an advanced CT technique, utilizing an energy-resolved photon counting detector to enhance spatial resolution, reduce noise, improve contrast, and minimize radiation exposure, while also allowing for the use of alternative contrast agents [57,58]. Similarly, low-dose CTPA with iterative reconstruction maintains diagnostic accuracy and image quality at significantly lower radiation levels [59]. Therefore, combining additional imaging techniques in clinical practice may improve both the detection rate and safety of PE diagnosis [60,61].

4. Conventional treatment strategies for VT

Antithrombotic drugs can be classified into three major categories based on their mechanisms of action: anticoagulants, thrombolytics, and antiplatelet agents (Table S2 in Supporting information). Risk stratification is essential for identifying high-risk patients and facilitating the timely initiation of thrombolysis, interventional treatment, or surgery as appropriate [62]. This section reviews commonly employed treatment approaches in clinical practice (Fig. 2).

4.1. Anticoagulation

Anticoagulation therapy is a key approach for the prevention and treatment of VT, which can inhibit thrombus extension, promote thrombolysis, and enhance vascular recanalization, thereby reducing the incidence and mortality of PE [63]. In the acute phase of VT, rapid-acting parenteral anticoagulants are typically used to achieve immediate therapeutic anticoagulation and minimize early recurrence and mortality [64]. Parenteral anticoagulation should be continued until the international normalized ratio reaches the therapeutic range, after which patients should transition to long-term anticoagulants (*e.g.*, warfarin) for a minimum of 3 months [65].

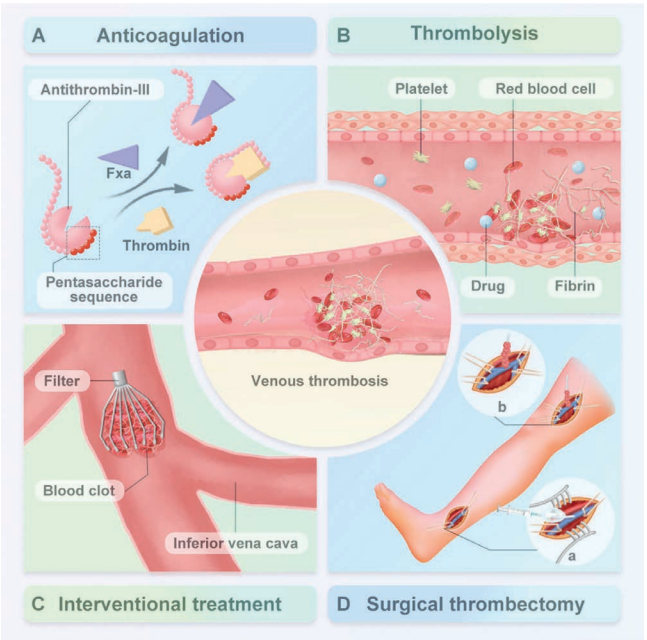


Fig. 2. Conventional treatment strategies for VT. (A) Anticoagulation. VT is initially treated with fast-acting parenteral anticoagulants, which activate antithrombin to inactivate thrombin and Factor Xa. (B) Thrombolysis. Thrombolysis breaks down the clot, restoring vein patency. (C) Interventional treatment. Interventional treatment involves inserting a device at the embolism site to dissolve and remove the thrombus through various physical methods. (D) Surgical thrombectomy. Surgical thrombectomy refers to the surgical removal of the thrombus from the vein.

4.2. Thrombolysis

Thrombolysis effectively dissolves thrombus and restores venous patency through either systemic administration or catheter-directed delivery of thrombolytic agents [66], which converts plasminogen to plasmin, resulting in fibrinolytic degradation of thrombotic clots [67]. In clinical practice, systemic thrombolysis is primarily used for massive PE, promoting rapid reperfusion and reducing mortality and recurrence in severe cases [68,69]. Compared to systemic thrombolysis, targeted catheter-directed thrombolysis using side-hole infusion catheters achieves localized thrombus dissolution with significantly reduced thrombolytic dosage, while enhancing local drug concentration and contact area, thereby minimizing bleeding risk and improving safety profiles [70,71].

4.3. Interventional treatment

Interventional treatment is a minimally invasive approach that delivers therapeutic devices to the site of vascular embolism *via* puncture [72]. Percutaneous mechanical thrombolysis utilizes a catheter-based mechanical device to remove thrombus through rotational cutting, ultrasonic fragmentation, and rheological aspiration [73]. Unlike treatments that dissolve, fragment, or aspirate thrombi, the placement of an inferior vena cava filter does not directly treat VT. Instead, it serves as a physical barrier to prevent thrombus migration from the lower extremities to the lungs [74].

4.4. Surgical thrombectomy

Surgical thrombectomy is an effective method for thrombus removal, rapidly alleviating venous obstruction and preserving valve function. This procedure can be performed retroperitoneally, *via* femoral vein incision, or through a femoral-popliteal collateral approach [75]. In current clinical practice, surgical thrombectomy is primarily indicated for patients with large emboli, particularly when thrombolysis is ineffective or contraindicated [76]. Surgical thrombectomy may be a useful strategy to prevent further severe thromboembolism in cases at high risk of embolism [77].

5. NP-based DDS for the prevention and treatment of VT

Antithrombotic drugs exhibit diverse physicochemical properties due to their distinct chemical structures. In terms of solubility, highly water-soluble drugs like heparin dissolve easily, enabling rapid systemic absorption and fast action [78]. Conversely, poorly soluble drugs like clopidogrel often have low bioavailability, requiring specialized formulations to enhance dissolution and absorption. Currently, most clinically used antithrombotics are administered systemically, which lacks thrombus-specific targeting capability. Additionally, some drugs exhibit short half-lives (1–2 h), requiring continuous intravenous infusion to maintain therapeutic plasma concentrations. Oral administration presents additional challenges, including degradation by digestive enzymes and instability in the acidic gastrointestinal environment. The most critical concern is the elevated risk of hemorrhage—a potentially life-threatening complication resulting from improper application of antithrombotic agents. Under physiological conditions, disruption of endothelial barrier integrity exposes tissue factor in extravascular spaces, providing a compensatory hemostatic mechanism. However, when drug-induced vascular dysfunction

combines with impaired coagulation, this synergy promotes blood extravasation [79]. Anticoagulants exacerbate bleeding risk by prolonging clotting time while increasing capillary fragility and permeability. Therefore, it is urgent to develop efficient delivery systems for the prevention and treatment of VT [80].

NPs have emerged as a promising DDS, facilitating the incorporation of multimodal therapeutic strategies to improve targeted delivery efficacy (Table S3 in Supporting information) [81,82]. Organic NPs, including liposomes, polymeric NPs, and dendritic macromolecules, are composed of biodegradable materials, while inorganic NPs encompass metal, ceramic, and semiconductor-based NPs [83]. Additionally, biomimetic membrane technology has advanced to a stage where cellular membrane-coated NPs are gaining attention for their improved biocompatibility and ability to evade immune system clearance [84]. Therefore, the rational design of NP-based DDS holds promise for extending circulation time, minimizing drug-related side effects during transit to the target site, and achieving precise temporal and spatial localization of drug action [85]. This section highlights recent advances in NP-based DDS for the prevention and treatment of VT (Table S4 in Supporting information).

5.1. Polymeric NPs

Polymeric NPs refers to solid colloidal particles with size ranging from 10 nm to 1000 nm [86]. Self-assembled polymer systems, such as polymeric drugs, protein-polymer conjugates, and polymeric micelles, can be functionalized with antibodies or antibody fragments to enable precise targeting to specific organs, tissues, or even cells [87–89]. Polymeric NPs can be prepared either from preformed polymers or by directly polymerizing monomers directly through conventional polymerization or polymerization reactions. The particle size and surface charge vary depending on the type of polymer used [90]. Among various polymers, chitosan, a naturally occurring cationic polymer characterized by biodegradable and non-toxic properties, is suitable for the delivery of a wide range of macromolecules. Pazhani *et al.* developed edoxaban tosylate monohydrate-loaded chitosan NPs (ETM-CS-NPs) using the tripolyphosphate ion-gelation method, creating chitosan-based shielded NPs for enhanced bioavailability of orally administered Edoxaban tosylate monohydrate. ETM-CS-NPs prolonged activated partial thromboplastin time to 75 s (peak at 4 h), compared to the free drug's maximum of 78 s at 2 h, demonstrating sustained release and more stable anticoagulation. Oral Edoxaban tosylate monohydrate administration faces major clinical limitations due to its low bioavailability and poor gastrointestinal absorption, resulting from its high anionic charge density, large molecular size, and enzymatic degradation susceptibility. This novel nanoplateform may result in safer and more effective treatment choices for VT patients, lowering the possibility of bleeding problems from systemic anticoagulant medication. As the first-line medication low-molecular-weight heparin (LMWH), a hydrophilic natural glycosaminoglycan, is recommended for DVT treatment due to its potent anticoagulation. However, LMWH is only available as parenteral route which restricts its clinical applicability. Fan *et al.* prepared LMWH-loaded NPs (pH-TCS/OCMCS@LMWH) by ionic crosslinking the positively charged amino groups of thiolated chitosan and *o*-carboxymethyl chitosan with the negatively charged HP55 [91,92]. Seven-day oral administration of pH-TCS/O-CMCS@LMWH (200 IU/100 g) reduced wet and dry thrombus weights by 70 % and 67.4 %, respectively, representing 4.05-fold and 11-fold greater efficacy than free LMWH. Besides, Paliwal *et al.* quaternized chitosan to enhance its efficacy as an absorption enhancer at neutral pH, and then proposed an alternative *N*-trimethyl chitosan (TMC) chitosan-based nano-system to enhance the oral bioavailability of LMWH [93]. Pharmacokinetic studies showed TMC-NPs had 2.4-fold higher bioavailability (0.39 %) than free LMWH. Fluorescence imaging confirmed enhanced intestinal uptake of TMC-NPs *versus* both CS-NPs and free dye within 1 h. This system showed improved intestinal epithelial permeability and drug absorption. Hence, this nanoplatform holds promising clinical application for oral delivery of LMWH, paving the way for improved DVT treatment.

DVT during pregnancy can lead to a range of severe complications, including PE, recurrent miscarriage, and fetal growth restriction, posing significant threats to maternal-fetal health. Given the unique physiological characteristics of pregnancy, NPs with combined antithrombotic, anti-inflammatory, and antioxidant properties, along with limited transplacental transport capacity, represent a safe and effective therapeutic strategy for pregnancy-associated DVT. In line with this, Cheng *et al.* designed a biologically active amphiphilic compound (TLH) by simultaneously conjugating two bioactive and biocompatible moieties (*i.e.*, Tempol and linoleic acid (LA)) onto LMWH that assembles into multifunctional NPs (TLH NPs) for treating gestational DVT [94]. LMWH is a clinically well-recognized antithrombotic agent that does not cross the placental barrier, while its associated bleeding risks may contribute to adverse pregnancy outcomes. In rat models of gestational DVT, TLH NPs could effectively target and dissolve thrombi, achieving approximately 70 % reduction in thrombus weight and over 50 % decrease in length, while restoring vascular patency, and prevent the recurrence of thromboembolism. Importantly, TLH NPs demonstrate no observable maternal or fetal toxicity at doses up to 10-fold higher than the therapeutic concentration. The promising results encourage further clinical translation studies of the examined nanotherapies for DVT or other cardiovascular diseases during pregnancy.

To investigate the impact of nanodrug on lower extremity DVT and its correlation with susceptibility genes, Chang *et al.* constructed primary NP using lauric acid and stearic acid (LSA), then fabricated CTAB-$HAuCL_4$-TEOS (CHT) complexes through the incorporation of cetyltrimethyl ammonium bromide, chloroauric acid, and tetraethyl orthosilicate [95]. Subsequently, these components were conjugated with urokinase to prepare UK-LSA-CHT nanocomposites. The study revealed that the G and T alleles of the NOS3 rs1799983 polymorphism may represent key risk factors for the development of lower extremity DVT. UK-LSA-CHT significantly lowered endothelin-1, interleukin-6, and nuclear factor-κB levels within 12 h post-surgery compared to urokinase and LSA controls, indicating thrombotic microenvironment stabilization through dual suppression of endothelial activation and inflammation. These results highlighted its potential for DVT therapy. In addition to natural enzymatic proteins and antithrombotic drugs, the degradation of biopolymers by free radicals from chemical reagents provides an effective approach for clot dissolution [96]. Because of their inherent reactivity, the generation of radicals must be tightly controlled and localized to prevent collateral damage by freely diffusing species. In this context, Walker *et al.* synthesized a water-soluble PEGylated gold NP combined with enediyne diamine (Z)-octa-4-en-2,6-diyne-1,8-diamine, generated 1,4-diradical species upon visible light excitation [97]. These photothermal radicals created macroporous structures (>2.0 μm) in the fibrin matrix while decreasing 1.5–2.0 μm micropores. Quantitative analysis showed a 10 % increase in macropore ratio and enhanced overall porosity after irradiation. This microchannel formation within the initially dense thrombus network ultimately enabled complete clot perfusion. This approach has broad clinical therapeutic potential, provided its unique mechanism—the localized, on-demand generation of radicals *via* photothermal activation, proves effective for managing VT.

It was found that myeloid-related protein 14 (MRP-14), a key regulator of vascular inflammation and thrombosis, was identified

as an optimal molecular target for cardiovascular nanomedicine [98,99]. Accordingly, Park *et al.* developed an MRP-14-targeting delivery system to achieve tissue specificity [100]. Through screening, suitable MRP-14-targeting peptides were identified and conjugated to vectors, such as tobacco mosaic virus (TMV) and cowpea mosaic virus (CPMV) to formulate NPs. Fluorescence imaging analysis revealed that CPMV-MTP2 and TMV-MTP2 showed 2.5- and 2-fold stronger thrombus fluorescence signals than PEGylated controls, confirming MRP-14 targeting enhances NP accumulation. CPMV-MTP2 treatment also reduced thrombus weight and area by approximately 50% *versus* phosphate buffered saline (PBS) group. Therefore, these NPs demonstrated a favorable profile that has broad clinical potential for the development of next-generation diagnostics and safer therapeutic interventions, with the goal of reducing disease burden and improving long-term outcomes. Furthermore, Wei *et al.* introduced a novel pH-responsive prodrug nanodelivery platform for antithrombotic agents [101]. The system, based on polymeric prodrugs synthesized *via* Schiff base bonding with polyethylene glycol (PEG), self-assembled into micelles in aqueous solutions with diosgenin derivatives as the core and PEG as the corona. The prodrug micelles extended tail bleeding time to 703 s, significantly longer than aspirin (666 s), diosgenin (577 s), and the control group (344 s), indicating reduced bleeding risk. Additionally, prodrug micelles and diosgenin decreased infarct volumes from 37.73% to 21.64% and 30.45%, respectively. These diosgenin-based pre-drug micelles demonstrated reduced bleeding risk and effectively prevented thrombosis, providing a new insight for developing a novel selective carrier system for thrombus-targeted therapy.

5.2. Mesoporous silica NPs

Mesoporous silica NPs are nanoscale porous materials composed of silica molecules with large pore sizes [102]. Their unique topology enables the independent functionalization of three distinct structural domains: the silica framework, the nanopore channels, and the outermost surface, which are particularly well-suited for integrating essential drug delivery functions [103]. Their uniform mesoporous structure, ease of functionalization, and excellent biocompatibility have garnered significant attention for biomedical uses. However, this unique pore structure offers high drug loading capacity and excellent prevention of drug crystallization, but poses a risk of drug leakage [104]. Xu *et al.* developed urokinase-loaded gold-mesoporous silica core-shell NPs, a thrombus-targeting nanoplatform [105]. Upon near-infrared (NIR) irradiation, the photothermal effect of gold NPs induces a phase transition in the eutectic mixed fatty acids, facilitating the controlled urokinase release from the nanopores. Under static *in vitro* conditions, NPs with NIR irradiation achieved complete thrombus dissolution within 60 min (with visible color lightening), significantly outperforming urokinase alone (partial dissolution at 120 min), NIR alone (90 min), and untreated controls (no dissolution). These results opened up new prospects for clinically developed controllable and accurate delivery of thrombolytic agents for thrombus sites in the body.

In recent years, both unfractionated heparin (UH) and urokinase, commonly used antithrombotic agents, have shown efficacy in treating VT, but their combined use in direct therapy has been found to significantly reduce their therapeutic effectiveness. To address this issue, Zhong *et al.* developed a multifunctional and sequential drug-release thrombolytic platform consisting of polydopamine-modified hollow mesoporous silica NPs (HMSNs) loaded with UH and urokinase, augmented by dual physical mechanisms, NIR-II irradiation and air bubbles [106]. Under NIR-II irradiation, UH released rapidly within 30 min, followed by sustained urokinase release triggered by D-menthol phase transition-induced microbubbles, achieving 80.67% ± 2.15% cumulative release by 40 min, significantly higher than the non-irradiated control (17.33% ± 1.82%), confirming the photothermal-microbubble synergy. These results will provide new ideas for the clinical development of safe, efficient, rapid, and accurately targeted thrombolytic drugs in some deeper tissue area. In addition to the NIR-assisted physical therapy described above, optimizing the size of the NP delivery system to ensure physical compatibility can further enhance its efficacy in various thrombolytic therapies. Accordingly, Wang *et al.* developed mesoporous silica NPs coated with platelet membranes (PM) of different sizes for the delivery of urokinase [107]. Their study demonstrated that UNP-L showed efficacy similar to 200 U/g urokinase in VT achieving a 53.23% ± 7.82% occlusion rate and reducing thrombus wet weight to 8.61 ± 1.16 mg/cm. In arterial thrombosis, UNP-S performed comparably to high-dose urokinase, with a 63.29% ± 9.10% occlusion rate and 63.29 ± 9.10 mg/cm thrombus wet weight. The hematoxylin and eosin (H&E) staining results also illustrated intermediate/small particles showed limited VT efficacy and larger particles displayed reduced arterial thrombosis effectiveness. These findings suggested that adjusting the particle size of the nano delivery system enabled targeted thrombolysis of both arterial and venous thrombi.

5.3. Magnetic NPs

Magnetic NPs are a class of materials with strong magnetic properties, typically consisting of a magnetic core made of metal oxides such as iron, cobalt, or nickel, surrounded by a shell of polymer, silica, or hydroxyapatite [108,109]. Due to their biocompatibility, low toxicity, ease of surface modification, and magnetic properties, magnetic NPs have found wide applications in disease detection and treatment, particularly as drug carriers in targeted DDS and as effective agents for hyperthermia-based therapies [110,111]. Leveraging these advantages, Ouyang *et al.* developed a magnetic-targeted DDS with photothermal properties, where polyethyleneimine and iron oxide NPs (Fe_3O_4) functionalized black phosphorus nanosheets for heparin delivery [112]. *In vitro* and *in vivo* studies demonstrated that this system exhibited high heparin loading capacity, precise magnetic targeting, and excellent biocompatibility, with enhanced thrombolytic efficacy under NIR laser-assisted photothermal treatment.

Recent studies have shown that thermosensitive liposomes enable targeted drug release at the temperature corresponding to their lipid gel-liquid crystal phase transition, which significantly improving the efficacy of antitumor therapies during hyperthermic treatments [113]. Building on this concept, Hsu *et al.* developed a polyethylene glycol-modified thermosensitive magnetic liposome system for the magnetic-targeted delivery of recombinant tissue-type plasminogen activator (rtPA) to thrombus sites [114]. This system allows for temperature-controlled, triggered drug release in the presence of an alternating magnetic field. The results demonstrated that the thrombolytic activity of TML-rtPA at 43 °C was superior to that at 37 °C, attributed to the synergistic effects of enhanced drug release and increased enzyme activity at elevated temperatures. These NPs represented a promising magnetic-targeted nanodrug system with temperature-responsive drug release capabilities, potentially improving clinical thrombolytic therapy.

5.4. Liposomes

Liposomes are spherical vesicles composed of amphiphilic phospholipids, where a lipid bilayer encapsulates an aqueous core [115]. This unique amphiphilic property enables liposomes to efficiently encapsulate and deliver a broad spectrum of drugs, protecting them from natural degradation processes, such as enzy-

matic breakdown and immune or chemical inactivation [116,117]. Since the primary components of liposomes are lipids naturally found in cell membranes, they exhibit excellent biocompatibility and biodegradability [118]. However, the incorporation of non-physiological additives can enhance the delivery efficiency and bioavailability of liposomes, though they may also introduce potential toxicity as a result of chemical modifications [119]. Cationic liposomes, commonly employed as non-viral vectors for gene delivery, utilize their positive charge to electrostatically interact with and condense negatively charged DNA molecules. Inspired by the structural similarities between DNA and LMWH, Bai *et al.* developed PEGylated cationic liposomes as a promising vehicle for inhalable LMWH formulations [120]. Safety and efficacy evaluations of these inhalable PEG-liposomal formulations demonstrated that once-every-other-day inhalation dosing yielded comparable effects to once-daily subcutaneous administration with respect to clot reduction, without inducing significant lung damage. Additionally, in a feasibility study evaluating this formulation for the treatment of DVT and PE, conventional distearoyl-*sn*–glycero-3-phosphoethanolamine liposomes, as well as long-circulating PEGylated liposomes (DSPE-PEG-2000 and DSPE-PEG-5000), were prepared using a hydration method to assess their anticoagulant and antithrombotic properties [121]. The results indicated that PEG-2000-modified liposomes administered daily or alternate-day for 8 days equally reduced thrombus weight (0.6 ± 0.1 mg and 0.6 ± 0.7 mg, respectively), matching daily subcutaneous LMWH efficacy (0.5 ± 0.5 mg). In contrast, alternate-day free LMWH showed inferior results (3.5 ± 0.6 mg), confirming PEG-2000 liposomes enable less frequent dosing without compromising efficacy. These results suggested that inhalable pegylated liposomes of LMWH could be a potential noninvasive approach for DVT and PE. Additionally, these liposomes significantly reduced thrombus weight and accelerated thrombus clearance in DVT. Furthermore, a clinical trial evaluating the efficacy and safety of a topical liposomal heparin spraygel (LHSG) was conducted involving 46 outpatients presenting clinical signs of SVT [122]. The trial demonstrated that LHSG was comparable to subcutaneous LMWH injections in terms of pain relief and erythema reduction, with no significant adverse effects in the LHSG group. These results suggested that LHSG and LMWH offer similar efficacy and safety for the topical management of SVT. Notably, to our knowledge, this represents the sole clinical trial to explore the application of nanotechnology for treating VT.

Recent studies have highlighted the specific binding affinity of the RGD peptide for activated platelet GPIIb/IIIa, establishing it as an ideal ligand for thrombus targeting. In this context, Liang *et al.* developed cRGD-functionalized urokinase liposomes (cRGD-UK-LIP) aimed at enhancing thrombolytic efficacy and extending the half-life of urokinase [123]. Histological analysis of 60 randomly selected pulmonary arterioles (80–120 μm) revealed that the cRGD-UK-LIP treatment group exhibited significantly fewer thrombus-containing vessels (6.7 ± 3.2) compared to both the UK group (10.3 ± 2.6) and the APMTE/NS control group (14.5 ± 0.7), with thrombi displaying looser organization and higher recanalization rates. Despite these advancements, localized treatment of DVT remains challenging due to the presence of extensive obstructive zones and significant thrombus thickness [124]. To overcome these challenges, Yang *et al.* engineered a thrombus-responsive, whole-layer infiltrating, non-pharmacological liposome responsive to thrombin for imaging-guided DVT treatment [125]. This liposome employed a dual-targeting strategy utilizing surface-modified cell-penetrating peptide and a fibrin-binding ligand (PFP-ACPP-FTP). Upon exposure to low-intensity focused ultrasound, the perfluoropentane core of the liposome underwent rapid vaporization, facilitating thrombus disruption and reduction in size, thereby enabling effective non-pharmacological ultrasonic thrombolysis. After 60 min of LIFU treatment, dual-targeted PFP-ACPP-FTP achieved 47.8 % ± 9.1 % thrombus reduction in 60 min - significantly greater than single-targeted (PFP-ACPP: 34 % ± 8.9 %; PFP-FTP: 30.1 % ± 5.6 %), non-targeted PFP (26.3 % ± 3.7 %), and saline control (7.4 % ± 2.5 %), demonstrating synergistic targeting's superior thrombolytic efficacy. This non-invasive and highly localized non-pharmacological thrombolytic strategy represented an improvement over existing clinical approaches by minimizing systemic side effects compared to conventional long-term drug therapies. Moreover, Fan *et al.* proposed an innovative therapeutic approach that utilized ultrasound to activate acoustic sensitizers, triggering an acoustochemical reaction that generated toxic ROS [126]. The combination of deep tissue penetration capabilities of mechanical ultrasound with the thrombolytic efficacy of urokinase enabled the development of an acoustic-responsive nanoliposomal capsule (ULU). Digital subtraction angiography showed no flow restoration in control, liposome, or ultrasound-only groups. Free urokinase achieved only partial recanalization by 60 min, whereas ULU + US therapy produced complete thrombolysis (major recanalization at 15 min; full restoration by 30 min). The results represented good thrombolytic properties for acute PE, which provides a new strategy for clinical acute pulmonary embolism thrombolysis.

5.5. Cell membrane camouflaged NPs

Cell membrane camouflaged NPs, consisting of a NP core enveloped by a cell membrane, represent an innovative class of biomimetic nanotherapeutics. These NPs replicate the biological functions of their source cells, enabling immune evasion, prolonged circulation time, and targeted delivery to disease sites through the homing properties of membrane proteins [127–129]. Initially, these biomimetic NPs were fabricated using a co-extrusion process, wherein erythrocyte membrane shells were combined with poly(lactic-*co*-glycolic acid) (PLGA) cores to form a core-shell structure. Subsequently, a variety of cell membranes, including those derived from platelets, albumin, cancer cells, and exosomes, have been explored as carriers for drug delivery across diverse therapeutic areas [130–133]. In addition to drug delivery, biomimetic membrane technology holds promise for applications in image-guided photothermal therapy (PTT), photodynamic therapy (PDT), immunomodulation, and detoxification [134]. Notably, PM-coated NPs have emerged as a promising strategy for thrombosis targeting, capitalizing on the biological link between DVT, inflammation, and platelets. The presence of membrane proteins such as CD62p and CD41, on the platelet surface endows the encapsulated NPs with crucial biological properties, including immune evasion and precise clot targeting [135]. In the context of PM-based thrombolytic therapies, Li *et al.* first reported a platelet-mimetic porphyrin-based, covalent organic framework-engineered melanin nanoplatform (HMPC@PM), which combined hirudin with PTT and PDT therapies for targeted thrombus treatment [136]. The study demonstrated that HMPC@PM effectively extended the circulation half-life of hirudin and enabled targeted accumulation at the thrombus site, leveraging the natural thrombus-homing properties of the PM. Additionally, the combination PTT/PDT significantly enhanced thrombolytic efficacy (85.7 %) while preventing secondary embolism of large fragments. Subsequent high-loading (97 %) and sustained-release hirudin (14 days) effectively inhibited thrombus recurrence without inducing thrombocytopenia. The tremendous biosafety and efficacy indicated that this short-term thrombolytic and long-term anticoagulant nanosystem has a promising future in thrombosisrelated diseases. PM-derived NPs facilitate multimodal imaging, enabling a deeper understanding of the role of platelet membrane proteins in platelet-mimetic, targeted drug delivery at the molecular level [137]. Xiao *et al.* developed a platelet-derived aminated mesoporous silica NPs (AMSNP) to co-deliver recombinant hirudin, a direct thrombin inhibitor, and apixaban, a factor Xa

inhibitor, to sites of DVT [138]. The distribution and aggregation of these bionic nanoplatforms at the DVT site were monitored using multiple imaging techniques. The results demonstrated that PM-modified AMSNPs exhibited a significantly prolonged plasma elimination half-life of 7.31 h, compared to 0.58 h for unmodified AMSNPs. This extended circulation characteristic markedly enhanced the drug's *in vivo* retention time, enabling effective elimination of DVT lesions while achieving therapeutic efficacy at half the dosage. In this investigation, the potential for increased platelet aggregation was counteracted by the incorporation of recombinant hirudin within the NPs. The promising safety profile and specific therapeutic benefits of nanoplateform suggested potential clinical utility.

6. Conclusions and perspectives

VT is a major vascular disease with a multifactorial etiology and diverse clinical manifestations, posing significant challenges for accurate diagnosis and effective treatment. The primary goal of VT treatment is to prevent thrombus extension, embolism, cardiopulmonary failure, mortality, recurrence, and long-term complications. Due to patient variability in age and physical condition, treatment strategies must be individualized. Anticoagulation therapy remains the cornerstone of VT management and is typically combined with other therapies, such as pharmacologic thrombolysis and surgical intervention for optimal outcomes. Given the structural and functional diversity of therapeutic agents, it is crucial to select appropriate carriers and delivery strategies to achieve precise thrombus-targeted drug delivery. NPs, as emerging drug delivery vehicles, offer significant potential to enhance drug localization at the target site while minimizing systemic and off-target effects. The integration of NPs with external stimuli, such as magnetic fields, NIR light, and ultrasound, further augments thrombolytic efficacy, while potentially reducing the risk of bleeding and other adverse outcomes. Currently, to our knowledge, apart from the aforementioned clinical trial, no additional approved clinical trials exist investigating NP-based DDS for VT treatment. Nevertheless, these innovative approaches hold promise for improving VT management and are expected to optimize patient prognosis and quality of life in the future. The discussion of key considerations is provided in Text S1 (Supporting information).

CRediT authorship contribution statement

Li Yang: Writing – original draft, Methodology, Investigation, Conceptualization. **Yuhong Gong:** Writing – original draft, Methodology, Investigation. **Liqing Mo:** Writing – original draft, Visualization, Methodology. **Ting Zhu:** Writing – original draft, Investigation. **Yingxuan Dai:** Writing – original draft, Validation. **Xinrui Hu:** Writing – original draft. **Yuxi Zhu:** Writing – review & editing, Validation. **Yi Zhao:** Writing – review & editing, Visualization, Project administration. **Jianhua He:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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References

[1] A.S. Wolberg, F.R. Rosendaal, J.I. Weitz, et al., Nat. Rev. Dis. Primers 1 (2015) 15006.
[2] Á. Dubois-Silva, C. Barbagelata-López, P. Piñeiro-Parga, et al., Thromb. Haemost. 121 (2021) 1650–1659.
[3] M.J.D. Almeida, A.T. Guillaumon, D. Miquelin, et al., J. Vasc. Bras. 18 (2019) e20180105.
[4] O. Moreno-Rocha, A.T. Obi, Med. Clin. North Am. 109 (2025) 923–929.
[5] L. Duffett, L.A. Castellucci, M.A. Forgie, BMJ 370 (2020) m2177.
[6] P.L. Lutsey, N.A. Zakai, Nat. Rev. Cardiol. 20 (2023) 248–262.
[7] S. Schulman, A. Makatsariya, J. Khizroeva, et al., Int. J. Mol. Sci. 25 (2024) 11447.
[8] S. Behravesh, P. Hoang, A. Nanda, et al., Thrombosis 2017 (2017) 3039713.
[9] C.T. Esmon, Blood Rev. 23 (2009) 225–229.
[10] C. Becattini, G. Agnelli, A. Schenone, et al., N. Engl. J. Med. 366 (2012) 1959–1967.
[11] N. Mackman, J. Clin. Invest. 122 (2012) 2331–2336.
[12] M. Koupenova, L. Clancy, H.A. Corkrey, J.E. Freedman, Circ. Res. 122 (2018) 337–351.
[13] M. Bhatt, C. Braun, P. Patel, et al., Blood Adv. 4 (2020) 1250–1264.
[14] A. Brill, Int. J. Mol. Sci. 22 (2021) 3853.
[15] P.S. Wells, R. Ihaddadene, A. Reilly, M.A. Forgie, Ann. Intern. Med. 168 (2018) 131–140.
[16] F. Khan, T. Tritschler, S.R. Kahn, M.A. Rodger, Lancet 398 (2021) 64–77.
[17] C.E.A. Dronkers, F.A. Klok, M.V. Huisman, J. Thromb. Haemost. 14 (2016) 1696–1710.
[18] T.L. Ortel, I. Neumann, W. Ageno, et al., Blood Adv. 4 (2020) 4693–4738.
[19] N. Chan, M. Sobieraj-Teague, J.W. Eikelboom, Lancet 396 (2020) 1767–1776.
[20] S. Balabhadra, J.D. Kuban, S. Lee, et al., JAMA Netw. Open 3 (2020) e2011079.
[21] R. Wallace, M.A. Anderson, K. See, et al., Intern. Med. J. 47 (2017) 436–446.
[22] A. Onishi, K. St Ange, J.S. Dordick, R.J. Linhardt, Front. Biosci. Landmark 21 (2016) 1372–1392.
[23] C. Broderick, L. Watson, M.P. Armon, Cochrane Database Syst. Rev. 1 (2021) Cd002783.
[24] G.Y. Chen, I. Roy, C.H. Yang, P.N. Prasad, Chem. Rev. 116 (2016) 2826–2885.
[25] Y. Li, Y.G. Wang, G. Huang, J.M. Gao, Chem. Rev. 118 (2018) 5359–5391.
[26] X. Pang, X. Liu, Y. Cheng, et al., Adv. Mater. 31 (2019) 1902530.
[27] P. Russell, C.E. Hagemeyer, L. Esser, N.H. Voelcker, Theranostics 12 (2022) 2773–2800.
[28] H. Tian, L. Lin, Z. Ba, et al., Chin. Chem. Lett. 32 (2021) 3665–3674.
[29] D. Pastori, V.M. Cormaci, S. Marucci, et al., Int. J. Mol. Sci. 24 (2023) 3169.
[30] E.G. Bovill, A. van der Vliet, Annu. Rev. Physiol. 73 (2011) 527–545.
[31] A. Brill, T.A. Fuchs, A.K. Chauhan, et al., Blood 117 (2011) 1400–1407.
[32] I. Budnik, A. Brill, Trends Immunol 39 (2018) 610–623.
[33] A. Janaszak-Jasiecka, A. Siekierzycka, A. Płoska, et al., Biomolecules 11 (2021) 982.
[34] J.W. Yau, H. Teoh, S. Verma, BMC Cardiovasc. Disord. 15 (2015) 130.
[35] C. Gutmann, R. Siow, A.M. Gwozdz, et al., Int. J. Mol. Sci. 21 (2020) 1918.
[36] A.R. Cyr, L.V. Huckaby, S.S. Shiva, B.S. Zuckerbraun, Crit. Care Clin. 36 (2020) 307–321.
[37] R.A. Baylis, N.L. Smith, D. Klarin, E. Fukaya, Circ. Res. 128 (2021) 1988–2002.
[38] S.P. Grover, N. Mackman, Arterioscler. Thromb. Vasc. Biol. 38 (2018) 709–725.
[39] D. Klarin, E. Busenkell, R. Judy, et al., Nat. Genet. 51 (2019) 1574–1579.
[40] B. Zöller, P.J. Svensson, B. Dahlbäck, et al., Expert Rev. Hematol. 13 (2020) 971–981.
[41] A. Saghazadeh, N. Rezaei, Crit. Rev. Oncol. Hematol. 99 (2016) 272–285.
[42] A. Rabinovich, J.M. Cohen, M. Cushman, et al., J. Thromb. Haemost. 13 (2015) 398–408.
[43] H. Patel, H.Z. Sun, A.N. Hussain, T. Vakde, Diagnostics 10 (2020) 365.
[44] Y. Li, Y. He, Y. Meng, et al., Sci. Rep. 12 (2022) 649.
[45] K. Xu, K. de Wit, G.J. Geersing, et al., J. Thromb. Haemost. 19 (2021) 1752–1758.
[46] H. Robert-Ebadi, A. Elias, O. Sanchez, et al., J. Thromb. Haemost. 19 (2021) 3044–3050.
[47] J. Willan, H. Katz, D. Keeling, Br. J. Haematol. 185 (2019) 289–296.
[48] M. Franchini, D. Focosi, M.P. Pezzo, P.M. Mannucci, Haematologica 109 (2024) 1035–1045.
[49] M. Sartori, L. Borgese, E. Favaretto, et al., Am. J. Hematol. 98 (2023) 1772–1779.
[50] J.I. Weitz, J.C. Fredenburgh, J.W. Eikelboom, J. Am. Coll. Cardiol. 70 (2017) 2411–2420.
[51] R. Zhao, M. Li, P. Xiao, et al., Anal. Bioanal. Chem. 416 (2024) 3737–3750.
[52] R. Chopard, I.E. Albertsen, G. Piazza, JAMA 324 (2020) 1765–1776.
[53] D. Liu, E. Peterson, J. Dooner, et al., Can. Med. Assoc. J. 187 (2015) 1288–1296.
[54] E. Avgerinos, S. Spiliopoulos, F. Psachoulia, et al., Eur. J. Vasc. Endovasc. Surg. 70 (2025) 517–522.
[55] S. Soffer, E. Klang, O. Shimon, et al., Sci. Rep. 11 (2021) 15814.
[56] M.H. Albrecht, M.W. Bickford, J.W. Nance, et al., Am. J. Roentgenol. 208 (2017) 495–504.

[57] P. Pannenbecker, H. Huflage, J.-P. Grunz, et al., Eur. Radiol. 33 (2023) 7830–7839.
[58] C.M.M. de Jong, L.J.M. Kroft, T.E. van Mens, et al., Thromb. Res. 238 (2024) 105–116.
[59] L. Wu, S. Wu, Q. Chen, X. Yu, Clin. Imaging 125 (2025) 110565.
[60] S.V. Konstantinides, A. Torbicki, G. Agnelli, et al., Eur. Heart J. 35 (2014) 3033–3080.
[61] S.V. Konstantinides, G. Meyer, C. Becattini, et al., Eur. Heart J. 41 (2020) 543–603.
[62] G. Gal, M.J. Kovacs, L. Bertoletti, et al., Ann. Intern. Med. 175 (2021) 29–35.
[63] L. Duffett, Ann. Intern. Med. 175 (2022) ITC129–ITC144.
[64] T.S. Field, V. Dizonno, M.A. Almekhlafi, et al., Stroke 54 (2023) 2724–2736.
[65] A.N. Frei, O. Stalder, A. Limacher, et al., Thromb. Haemost. 121 (2021) 1512–1522.
[66] Y. Haig, T. Enden, O. Grøtta, et al., Lancet Haematol. 3 (2016) e64–e71.
[67] A. Izcovich, J.M. Criniti, F. Popoff, et al., Blood Adv. 4 (2020) 1539–1553.
[68] S. Nakamura, H. Takano, Y. Kubota, et al., J. Thromb. Haemost. 12 (2014) 1086–1095.
[69] G. Meyer, E. Vicaut, T. Danays, et al., N. Engl. J. Med. 370 (2014) 1402–1411.
[70] L. Duarte-Gamas, F. Jácome, L.R. Dias, et al., Thromb. Haemost. 124 (2023) 89–104.
[71] S. Vedantham, Z. Goldhaber Samuel, A. Julian Jim, et al., N. Engl. J. Med. 377 (2017) 2240–2252.
[72] D.M. Dudzinski, J. Giri, K. Rosenfield, Circ. Cardiovasc. Interv. 10 (2017) e004345.
[73] R. Tyagi, D.C. Carr, P. Stibbs, O. Ahmed, J. Vasc. Interv. Radiol. 33 (2022) 249–254.
[74] T. Young, K.B. Sriram, Cochrane Database Syst. Rev. 10 (2020) Cd006212.
[75] M.U. Wagenhäuser, C. Dimopoulos, K. Antakyali, et al., J. Vasc. Surg. Venous Lymphat. Disord. 7 (2019) 333–343.
[76] A.J. Comerota, Semin. Vasc. Surg. 25 (2012) 2–12.
[77] Y. Yamazaki, Y. Tanaka, G. Uno, et al., JACC Case Rep. 30 (2025) 103996.
[78] Z. Wang, L. Chi, Chin. Chem. Lett. 29 (2018) 11–18.
[79] L. He, H. Du, Y. Yang, et al., Chin. Chem. Lett. 35 (2024) 109013.
[80] R. Liu, C. Luo, Z. Pang, et al., Chin. Chem. Lett. 34 (2023) 107518.
[81] T. Ren, Y. Mi, J. Wei, et al., Molecules 29 (2024) 2325.
[82] M. Zoulikha, Z. Chen, J. Wu, W. He, Chin. Chem. Lett. 36 (2025) 110225.
[83] F. Yang, J. Xue, G. Wang, Q. Diao, Front. Pharmacol. 13 (2022) 999404.
[84] Y. Liu, J. Luo, X. Chen, et al., Nano Micro Lett. 11 (2019) 100.
[85] Y. Song, H. Jing, L.B. Vong, et al., Chin. Chem. Lett. 33 (2022) 1705–1717.
[86] Kenry, T. Yeo, P.N. Manghnani, et al., ACS Nano 14 (2020) 4509–4522.
[87] I. Ekladious, Y.L. Colson, M.W. Grinstaff, Nat. Rev. Drug Discov. 18 (2019) 273–294.
[88] M. Gao, Y. Yang, A. Bergfel, et al., J. Nanobiotechnol. 18 (2020) 13.
[89] Y.S. Xu, H. Wang, Z.Y. Qiao, Chin. J. Chem. 40 (2022) 2815–2824.
[90] J.P. Rao, K.E. Geckeler, Prog. Polym. Sci. 36 (2011) 887–913.
[91] P. Pazhani, J.P. Dharmian, S. Arumugam, et al., J. Drug Target. 32 (2024) 1125–1138.
[92] B. Fan, L. Liu, Y. Zheng, et al., J. Drug Deliv. Sci. Technol. 78 (2022) 103955.
[93] R. Paliwal, S.R. Paliwal, G.P. Agrawal, S.P. Vyas, Int. J. Pharm. 422 (2012) 179–184.
[94] J. Cheng, S. Zhang, C. Li, et al., Nat. Commun. 13 (2022) 7166.
[95] R. Chang, C. Wang, X. Kong, et al., Bioengineered 15 (2021) 2003926.
[96] J. Lv, L. Zhang, W. Du, et al., J. Control. Release 345 (2022) 572–585.
[97] J.M. Walker, J.M. Zaleski, Chem. Mater. 26 (2014) 5120–5130.
[98] R. Dann, T. Hadi, E. Montenont, et al., J. Am. Coll. Cardiol. 71 (2018) 53–65.
[99] Y. Wang, H. Gao, C.W. Kessinger, et al., JCI Insight 2 (2017) e91356.
[100] J. Park, A.M. Wen, H. Gao, et al., Biomacromolecules 22 (2021) 2582–2594.
[101] Z. Wei, G. Xin, H. Wang, et al., Nanomed. Nanotechnol. Biol. Med. 14 (2018) 673–684.
[102] M. Vallet-Regí, F. Schüth, D. Lozano, et al., Chem. Soc. Rev. 51 (2022) 5365–5451.
[103] R.K. Kankala, Y.H. Han, J. Na, et al., Adv. Mater. 32 (2020) 1907035.
[104] Y. Zhao, J. Yuan, L. Zhu, Y. Fang, Chin. Chem. Lett. 35 (2024) 109065.
[105] J. Xu, Y. Zhou, H. Nie, et al., J. Mater. Chem. B 8 (2020) 787–793.
[106] Z. Zhong, C. Fang, S. He, et al., ACS Biomater. Sci. Eng. 6 (2020) 6790–6799.
[107] Y. Wang, L. Lv, H. Liang, et al., Chem. Eng. J. 441 (2022) 135982.
[108] Z. Zhou, L. Yang, J. Gao, X. Chen, Adv. Mater. 31 (2019) 1804567.
[109] T.H. Shin, Y. Choi, S. Kim, J. Cheon, Chem. Soc. Rev. 44 (2015) 4501–4516.
[110] A. Farzin, S.A. Etesami, J. Quint, et al., Adv. Healthc. Mater. 9 (2020) 1901058.
[111] L. Gloag, M. Mehdipour, D. Chen, et al., Adv. Mater. 31 (2019) 1904385.
[112] H. Ouyang, Z. Zheng, Y. Chen, et al., J. Mater. Chem. B 7 (2019) 6099–6108.
[113] M. de Smet, S. Langereis, S. den Bosch, H. Grüll, J. Control. Release 143 (2010) 120–127.
[114] H.L. Hsu, J.P. Chen, J. Magn. Magn. Mater. 427 (2017) 188–194.
[115] N. Filipczak, J. Pan, S.S.K. Yalamarty, V.P. Torchilin, Adv. Drug Deliv. Rev. 156 (2020) 4–22.
[116] F. Zahednezhad, M. Saadat, H. Valizadeh, et al., J. Control. Release 305 (2019) 194–209.
[117] G. Bozzuto, A. Molinari, Int. J. Nanomed. 10 (2015) 975–999.
[118] Z. Huang, X. Li, T. Zhang, et al., Asian J. Pharm. Sci. 9 (2014) 176–182.
[119] D.E. Large, R.G. Abdelmessih, E.A. Fink, D.T. Auguste, Adv. Drug Deliv. Rev. 176 (2021) 113851.
[120] S. Bai, V. Gupta, F. Ahsan, Eur. J. Pharm. Sci. 38 (2009) 165–171.
[121] S. Bai, F. Ahsan, J. Pharm. Sci. 99 (2010) 4554–4564.
[122] G. Gorski, P. Szopinski, J. Michalak, et al., Angiology 56 (2005) 9–17.
[123] C. Liang, T. Huang, X. Zhang, et al., Drug Des. Devel. Ther. 16 (2022) 801–816.
[124] T. Panpikoon, W. Phattharaprueksa, T. Treesit, et al., Thromb. J. 19 (2021) 99.
[125] A. Yang, B. Qiao, E.M. Strohm, et al., Biomater. Sci. 8 (2020) 4545–4558.
[126] Y. Fan, L. Liu, F. Li, et al., Front. Bioeng. Biotechnol. 10 (2022) 923365.
[127] P. Dash, A.M. Piras, M. Dash, J. Control. Release 327 (2020) 546–570.
[128] Y. He, S. Zhang, Y. She, et al., Exploration 4 (2024) 20230164.
[129] C. Feng, P. Tan, G. Nie, M. Zhu, Exploration 3 (2023) 20210263.
[130] N. Khosravi, E. Pishavar, B. Baradaran, et al., J. Control. Release 348 (2022) 706–722.
[131] Q. Jiang, K. Wang, X. Zhang, et al., Small 16 (2020) 2001704.
[132] Q. Jiang, Y. Liu, R. Guo, et al., Biomaterials 192 (2019) 292–308.
[133] L. Rao, L.L. Bu, J.H. Xu, et al., Small 11 (2015) 6225–6236.
[134] H. Wang, Y. Liu, R. He, et al., Biomater. Sci. 8 (2020) 552–568.
[135] J.B. Kral-Pointner, P. Haider, P.L. Szabo, et al., Arterioscler. Thromb. Vasc. Biol. 44 (2024) 954–968.
[136] S. Li, K. Zhang, Z. Ma, et al., Small 18 (2022) e2203184.
[137] S. Bai, J. Liao, B. Zhang, et al., Biomater. Sci. 8 (2020) 5047–5060.
[138] H. Xiao, X. Meng, S. Li, et al., Biomaterials 311 (2024) 122670.