Strategies for Perioperative Anticoagulant Reversal in Orthopedic Surgery: A Review

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AIM: The administration of anticoagulation therapy during major orthopedic surgeries is a clinical challenge due to the risk of thrombotic events and bleeding complications. This review aims to evaluate the current strategies and emerging developments in perioperative anticoagulation reversal.

METHODS: We conducted a literature review on the management of perioperative anticoagulant therapy, which included the current status of anticoagulant reversal agents, as well as personalized medicine, pharmacogenomics, artificial intelligence (AI), and novel drug delivery systems.

RESULTS: The review indicates that reversal agents such as idarucizumab and andexanet alfa are crucial in managing bleeding associated with direct oral anticoagulants (DOACs). Personalized medicine, guided by pharmacogenomics, allows for tailored anticoagulation regimens. AI and machine learning (ML) algorithms can enhance the predictive capabilities for bleeding and thrombotic risks. Additionally, nanotechnology and biomarkers offer innovative approaches to drug delivery and personalized treatment.

CONCLUSIONS: Integrating evidence-based guidelines with innovative reversal agents, personalized medicine, AI and nanotechnology opens a new era in perioperative anticoagulation management. These advancements can ensure patient safety, minimize bleeding risks, and improve surgical outcomes. Future research should focus on the clinical validation of these strategies to ensure their effectiveness across diverse patient populations.

Keywords: orthopedic surgery; anticoagulation therapy; venous thromboembolism (VTE); perioperative management; anticoagulant reversal; pharmacogenomics; artificial intelligence (AI); nanotechnology in drug delivery

Introduction

Optimizing anticoagulation therapy is crucial for reducing the risk of venous thromboembolism (VTE) in patients undergoing major orthopedic surgeries, such as hip and knee replacements or fracture repair [1]. Anticoagulation therapy should be carefully administered before and after surgery to reduce the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) [2, 3]. However, it is challenging to effectively maintain the delicate balance between the perioperative risk of thrombosis and excessive bleeding [4].

For instance, insufficient anticoagulation can lead to thromboembolic complications, which is a leading cause of morbidity and mortality in patients undergoing orthopedic surgery. Conversely, excessive anticoagulation enhances the risk of bleeding, leading to surgical complications and recovery delays, thereby contributing to longer hospital stays [5]. The incidence of orthopedic surgery with perioperative long-term anticoagulation therapy is growing with aging. These therapies include utilizing direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) for managing chronic comorbidities and providing prophylaxis against thromboembolic diseases [3, 6, 7]. These increasing trends of administering perioperative anticoagulants pose significant challenges in clinical decision-making that must be addressed using evidence-based guidelines and personalized risk assessment [5].

Perioperative anticoagulation reversal strategies are utilized for managing the high risk of bleeding or the patients requiring an urgent surgical intervention [1]. These strategies include temporarily inhibiting the anticoagulants before surgery, utilizing reversal agents, or employing mechanical methods to prevent thrombosis when anticoagulants are stopped [8, 9]. Reversal agents such as prothrombin complex concentrates (PCC), idarucizumab for dabigatran, and andexanet alfa for factor Xa inhibitors rapidly neutralize the effects of anticoagulants, minimizing the risk of excessive bleeding during surgery [1, 8, 9]. However, they must be carefully utilized, considering their economic implications and the potential risk for rebound thrombosis associated with these agents. For this reason, developing and implementing effective reversal strategies require a multidisciplinary approach involving the assistance of

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surgeons, anesthesiologists, and hematologists [8, 9, 10]. Therefore, this collaborative effort has been performed to suggest strategies for maintaining the balance between perioperative bleeding and thrombosis, improving surgical outcomes, ensuring patients' safety, and optimizing healthcare resource allocation in orthopedic surgery.

Current Landscape of Anticoagulation Reversal in Orthopedic Surgery

Overview of DOACs and VKAs in Orthopedic Surgery

The advent of DOACs has significantly altered anticoagulation management in patients undergoing orthopedic surgery. Traditionally, VKAs such as warfarin were the mainstay for preventing thromboembolic events in these patients. Recently, DOACs such as dabigatran, rivaroxaban, apixaban, and edoxaban have widely been utilized as the preferred choice due to their predictable pharmacokinetics, reduced risk of drug interactions, and the lack of routine monitoring requirements [11, 12, 13]. Despite these advantages, DOACs still present unique challenges regarding their cessation time before surgery and the need for rapidly reversing anticoagulation during urgent surgery or severe bleeding [14, 15].

VKAs, although effective, require careful management due to their narrow therapeutic range and the need for regular International Normalized Ratio (INR) monitoring [12]. Anticoagulation therapy utilizing DOACs during orthopedic surgery is more convenient and simpler. However, preferring DOACs over VKAs requires careful consideration regarding patient-specific factors, such as renal function and the risk of drug-drug interactions [11, 13]. Recent studies comparing the efficacy and safety of DOACs and VKAs in patients undergoing orthopedic surgery have found no significant differences in terms of thromboembolic events and bleeding outcomes, suggesting that DOACs are a viable alternative to VKAs in this patient population [12, 16].

Current Practices in Perioperative Anticoagulation Management

The perioperative management of anticoagulation requires a sophisticated approach to reducing the risk of thromboembolic events and surgical bleeding. Current practices include assessing the risks and advantages of anticoagulation therapy, considering the use of bridging anticoagulation, and determining the postoperative timing for resuming the anticoagulants [15, 17]. For patients administered with VKAs, discontinuing the VKA several days before surgery and considering the bridging with low-molecular-weight heparin based on the patient's thromboembolic risk are the common practices. Conversely, DOACs generally require shorter cessation period due to their shorter half-lives and are often used without bridging therapy [17, 18].

Anticoagulation reversal agents play a crucial role in urgent surgery or severe bleeding where rapid reversal of anticoagulation is necessary. For VKAs, vitamin K and PCC are the preferred reversal options [19]. Whereas, for DOACs, specific reversal agents like idarucizumab for dabigatran and andexanet alfa for factor Xa inhibitors have been developed and are frequently available. However, they must be carefully utilized considering the clinical context and the potential risk for thrombosis [19, 20].

Personalized perioperative anticoagulation-management strategies are continually evolving. Anticoagulation strategies are most effectively determined through a multidisciplinary approach, involving surgical, medical, and anesthesiology teams, balancing the risks of thrombosis and bleeding, thereby improving patients' outcomes. Moreover, the ongoing research and development of new anticoagulants and reversal agents would improve the efficacy of perioperative anticoagulation therapies in patients with orthopedic surgery [21].

Advancements in Specific Reversal Agents

Types of Reversal Agents for DOACs

The field of anticoagulation reversal has significantly advanced with the introduction of targeted reversal agents for DOACs. For instance, idarucizumab and andexanet alfa offer effective management of acute bleeding complications and provide rapid reversal strategies in patients who underwent DOAC therapy.

Idarucizumab, a monoclonal antibody, can effectively reverse the anticoagulant effects by specifically neutralizing the dabigatran. It exhibits the capability of rapidly reversing the anticoagulant effects of dabigatran, providing remarkable safety for managing patients experiencing severe bleeding or requiring urgent surgical interventions. Clinical trials and real-world use of idarucizumab have revealed its reliability in critical care settings based on its improved efficacy and enhanced safety [22].

Andexanet alfa acts as a decoy receptor for factor Xa inhibitors such as rivaroxaban, apixaban, and edoxaban, and can effectively reverse their anticoagulant activity, therefore frequently utilized in clinical practice [23]. A meta-analysis suggests that it demonstrates a certain level of effectiveness in treating severe bleeding events but may be associated with a higher risk of thrombotic events [22].

Additionally, ciraparantag and VMX-C001 have also demonstrated exceptional anticoagulant reversal capabilities. Ciraparantag is a broad-range and potent neutralizer of anticoagulants, targeting DOACs such as apixaban and rivaroxaban, as well as traditional anticoagulants such as low molecular weight heparins (LMWH) [24]. It binds to DOACs and LMWH through non-covalent hydrogen bonding and electrostatic interactions, preventing their interaction with clotting factors including Xa and IIa and rapidly restoring normal hemostasis [25]. VMX-C001 is a novel reversal agent developed from a modified human zymogen factor X, providing a hemostatic solution or bleeding prevention strategy for patients on direct factor Xa inhibitors. It can restore thrombin generation in the presence

Table 1. Comparison of different DOAC reversal agents.

Reversal agent	Mechanism of action	Indications	Dosage	Side effects and precautions
Idarucizumab	Monoclonal antibody that specifically neutralizes dabigatran and its metabolites	Reversal of dabigatran in cases of bleeding or need for urgent reversal before emergency surgery	5 g intravenous infusion as a single dose	Potential side effects include hypotension, headache; monitor for allergic reactions and thrombotic events
Andexanet alfa	Recombinant modified factor Xa protein, binds to and sequesters factor Xa inhibitors	Reversal of anticoagulation effects of factor Xa inhibitors in cases of serious bleeding	Initial dose (400 or 800 mg) followed by continuous infusion (4 or 8 mg/min over 2 hours)	Potential side effects include bleeding, hypersensitivity reactions; monitor for thrombotic risks, dosage and infusion rate
Ciraparantag	Broad and potent neutralizing capabilities against a range of anticoagulants, specifically targeting DOACs such as apixaban and rivaroxaban, as well as traditional anticoagulants like LMWH	Reversal of the anticoagulant effects of DOACs or LMWH	Dosage and administration are not established; further research required	Side effects not fully established; further research required; note its broad neutralizing capability may affect different anticoagulants
VMX-C001	Novel reversal agent designed based on a modified human zymogen factor X, aimed at restoring thrombin generation in the presence of DOACs while avoiding excessive elevation of ETP	Reversal of anticoagulation effects of direct factor Xa inhibitors	Dosage and administration not established; further research required	Side effects not fully established: further research required; note its impact on ETP may differ from andexanet alfa

DOACs, direct oral anticoagulants; LMWH, low molecular weight heparins; ETP, endogenous thrombin potential.

of DOACs without significantly elevating the endogenous thrombin potential (ETP), unlike the andexanet alfa [20, 26]. However, their pharmacokinetic profile in humans, optimal dosing, long-term safety, and real-world clinical utilization require validation through extensive investigations and larger-scale clinical trials.

Despite these advancements, using these agents requires careful considerations regarding their appropriate indications, dosages, and potential adverse effects (Table 1) [27]. Idarucizumab and andexanet alfa are crucial in managing DOAC-treated patients in emergent situations, yet their cost and availability may limit their widespread implementation.

Mechanisms of Action and Clinical Efficacy in Reversing DOACs

The mechanisms of action of idarucizumab and andexanet alfa are fundamental to their role in anticoagulant reversal. Idarucizumab binds specifically and with high affinity to dabigatran and its metabolites, offering a rapid and effective reversal of their anticoagulant activity [28]. Idarucizumab may not only reverse anticoagulation in case of urgent surgery or invasive procedures but can also manage excessive bleeding associated with dabigatran [29]. The RE-VERSE AD prospective study revealed that only a single intravenous dose of idarucizumab can rapidly achieve a complete reversal of dabigatran's anticoagulant effect with improved bleeding symptoms observed in 100% of patients and a mild rate of thrombotic events within 90 days (NCT02104947||clinicaltrials.gov, 2014-05-06) [30]. Another study on Chinese populations (NCT03343704||clinicaltrials.gov, 2018-03-26) further validates its high reversal efficacy with a median reversal rate of 100% and low complication risk [29, 31].

Andexanet alfa, a recombinant factor Xa protein, mimics the endogenous factor Xa (FXa) and, by binding effectively to its inhibitors, neutralizes their anticoagulant effect [32]. Numerous clinical trials and observational studies have suggested the efficacy of andexanet alfa in reducing the anticoagulation effects of factor Xa inhibitors and its impact on hemostasis [33]. The phase III ANNEXA trials series (NCT02207725 and NCT02220725||clinicaltrials.gov, 2014-03 and 2014-05) [34] further substantiated the safety and efficacy of andexanet alfa in managing serious or uncontrolled bleeding in patients administered with apixaban

or rivaroxaban. Furthermore, it was identified that a bolus dose (400 or 800 mg) followed by continuous infusion (4 or 8 mg/min for more than 2 hours) rapidly and significantly reduced anti-FXa activity and maintained it low till the end of infusion. Consequently, more than 80% of the patients achieved good to excellent hemostasis in the primary bleeding assessment.

The clinical efficacy of these reversal agents has been a subject of extensive research. Outcomes from their use in life-threatening bleeding events and prior to urgent surgeries have underscored their importance in patient care [22, 23]. Although highly effective, continuous assessment of their safety profile and real-world efficacy remains essential for optimizing their use in clinical practice [27].

In conclusion, the advent of idarucizumab and andexanet alfa has significant advancements in the management of DOAC-related bleeding complications. Their development and integration into clinical practice highlight the evolving nature of anticoagulant therapy and the crucial role of targeted reversal strategies. As with any medical intervention, a comprehensive and personalized approach will ensure the optimal and effective use of these novel agents.

Innovation in Personalized Anticoagulant Reversal Strategies

The Emergence of Personalized Therapy in Anticoagulation Reversal

Personalized therapy, characterized by tailoring the medical treatment to the individual characteristics of each patient, is gaining traction across various medical fields, including anticoagulation management. This approach is particularly relevant in the context of anticoagulation therapy, where the balance between the risk of thrombosis and severe bleeding can be precarious and highly individualized. The advent of pharmacogenomics—using a patient's genetic profile to personalize the treatment—has introduced novel strategies for managing anticoagulation therapy.

Traditionally, the one-size-fits-all approach to warfarin dosing has been challenging due to its narrow therapeutic range and the significant variability in patient response [35]. The incorporation of genetic information, specifically variants in the cytochrome P450 2C9 (*CYP2C9*) and vitamin K epoxide reductase complex subunit 1 (*VKORC1*) genes, into dosing algorithms has shown promise in achieving more rapid and stable anticoagulation control, thereby reducing the time to reach therapeutic INR levels and improving overall treatment safety and efficacy [35, 36]. Additionally, integrating pharmacogenomic data into clinical practice is paving the way for more sophisticated and personalized anticoagulation management strategies, potentially decreasing the incidence of adverse drug reactions and improving clinical outcomes [37].

Pharmacogenomics and its Potential to Tailor Reversal Agent Dosage

The role of pharmacogenomics in anticoagulation therapy extends beyond optimizing the efficacy and safety of traditional anticoagulants like warfarin, encompassing the emerging field of personalized reversal strategies. Since, DOACs are frequently utilized, effective anticoagulant reversal agents during urgent surgical interventions and severe perioperative bleeding have been needed. For this reason, specific reversal agents like idarucizumab for dabigatran and andexanet alfa for factor Xa inhibitors have been developed and found significantly effective. However, the individual responses to these agents may vary due to genetic variations among patients [38, 39].

Therefore, pharmacogenomic testing is crucial in identifying the optimized dosage strategies for these reversal agents and susceptibility regarding their adverse impacts on patients. For instance, variability in genes encoding drug-metabolizing enzymes and transporter proteins could influence the pharmacodynamics and pharmacokinetics of warfarin, DOACs, and their respective reversal agents [40, 41]. Identifying genetic variants influencing drug action and metabolism could provide significant insights into customizing anticoagulant reversal strategies that are effective and exhibit minimal side effects.

Moreover, investigating the genomics of anticoagulant response not only aids in selecting the most appropriate anticoagulant and reversal agent for each patient but also assists in determining the optimal dosing, thereby enhancing the safety and efficacy of anticoagulation therapy [42, 43]. As pharmacogenomic testing becomes more widely available and integrated into routine clinical practice, it has the potential to significantly enhance the personalization of anticoagulation therapy, including the use of reversal agents, ultimately resulting in better patient outcomes and safety for those at risk of thromboembolic events [44].

In conclusion, integrating pharmacogenomics into anticoagulation management represents a considerable shift toward individualized care, offering the potential for significant improvement in treatment outcomes. As research progresses, developing guidelines, such as incorporating pharmacogenomic data, will be vital in fully realizing the benefits of personalized medicine in anticoagulation reversal.

Integrating Artificial Intelligence in Reversal Strategy Optimization

Application of Artificial Intelligence in Predicting Bleeding and Thrombotic Risks

Integrating artificial intelligence (AI) and machine learning (ML) into healthcare has shown promising potential, particularly in the complex domain of anticoagulation management. AI approaches, such as ML algorithms, have the potential to revolutionize patient blood management by offering more accurate predictions of bleeding and thrombotic risks [45]. These advanced technologies can analyze ex-

tensive datasets, including laboratory findings, clinical outcomes, and patient-specific factors, to identify patterns and predictors that may not be apparent through traditional analysis methods.

AI can significantly optimize reversal strategies for anticoagulated patients [46]. AI models developed to predict the risk of bleeding during procedures such as total joint arthroplasty and robot-assisted surgeries have demonstrated higher accuracy than conventional risk stratification tools [47, 48]. These models can assist clinicians in making informed decisions about the timing of anticoagulation reversal, selection of reversal agents, and the need for additional hemostatic interventions.

Furthermore, AI-based approaches can aid in managing intraoperative bleeding during surgical procedures, major bleeding episodes during anticoagulation therapy for VTE, and acute gastrointestinal bleeding, predicting treatment outcomes, and optimizing therapeutic interventions [49, 50, 51]. Through predictive analytics, healthcare providers can prioritize high-risk patients for aggressive intervention, while managing lower-risk individuals with less invasive strategies.

ML Algorithms for Individualized Treatment Plans

ML, a branch of AI, can substantially enhance the personalization of treatment plans for patients undergoing anticoagulation therapy. ML algorithms can develop highly individualized predictive models by incorporating diverse patient data, including genetic markers, comorbidities, medication usage, and lifestyle factors [52]. These models provide more precise predictions of individual patients' risks for thromboembolism or bleeding than conventional methods.

Integrating pharmacogenomics into ML models is a prime example of how individual patient characteristics can optimize anticoagulation management [53]. A pharmacogenomics trial on warfarin for preventing deep vein thrombosis (NCT01006733||clinicaltrials.gov, 2011-03) indicated that genotype-guided dosing reduced the combined risk of major bleeding, INR $\geq$4, VTE, or death compared to clinically guided dosing among patients undergoing elective hip or knee arthroplasty [54]. This implies that genes affecting anticoagulant metabolism and therapeutic response, such as *CYP2C9*, *VKORC1*, and *CYP4F2*, can be integrated with clinical data to tailor anticoagulant dosing and reversal strategies [54]. This tailored approach improves patient outcomes and minimizes the risk of adverse events.

Moreover, the advancement in imaging diagnostics and the integration of AI have facilitated the early identification of conditions like VTE and large vessel occlusion in ischemic stroke [55, 56]. ML models can now analyze imaging data with high accuracy, enabling timely interventions that significantly enhance patient outcomes.

In conclusion, applying AI and ML in anticoagulation management offers a transformative shift toward optimizing reversal strategies and personalizing treatment plans. Using these technologies, clinicians can improve the safety and efficacy of anticoagulant therapies, ultimately leading to better patient care and outcomes. The dynamic synergy between advanced algorithms and clinical expertise begins a new era in medicine, where decision-making is increasingly data-driven and personalized to the specific needs of each patient.

Exploring Novel Drug Delivery Systems for Reversal Agents

Innovations in Nanotechnology and Targeted Drug Delivery

Recent advancements in nanotechnology have paved the way for the development of innovative drug delivery systems, especially in thrombosis and cardiovascular diseases [57]. Nanoparticles, nanorobots, and nanoencapsulation represent a new frontier in targeted drug delivery, with the potential to revolutionize the administration of reversal agents and antithrombotic therapies [58]. These nanosystems are designed to deliver drugs directly to the site of action, thereby increasing therapeutic efficacy while reducing systemic side effects and bleeding risks commonly associated with traditional anticoagulant therapies [59, 60].

Targeted nanorobotics and smart drug delivery systems that respond to physiological triggers have demonstrated promise in preclinical studies, indicating the potential of precision medicine in perioperative care and anticoagulation management [58, 61]. These nanotechnologies can specifically target fibrin, platelets, and other components of the coagulation cascade, offering a more localized and controlled approach to reversing anticoagulation or enhancing thrombolytic agents [59]. Furthermore, the development of nano-systems carrying antithrombotic drugs aims to address the limitations of current therapies by delivering drugs directly to thrombotic sites, thus reducing the incidence of severe bleeding complications [62].

Enhancing the Efficacy and Safety of Perioperative Anticoagulation Reversal

Integrating novel drug delivery systems into perioperative anticoagulation reversal strategies can significantly enhance both efficacy and safety [43]. By employing targeted delivery mechanisms, these nano-systems can improve the precision of anticoagulant reversal, ensuring that the reversal agents are concentrated precisely where they are needed, thereby minimizing the risk of bleeding while efficiently restoring hemostasis [59, 63]. For instance, targeted nanotherapeutics for thrombosis utilize ligand modifications to specifically target thrombotic sites, enabling localized drug release and diminishing the systemic side effects typically associated with conventional anticoagulation therapy [62].

Moreover, the advent of drug-releasing coatings for medical devices exposed to blood flow represents an innovative approach for locally inhibiting coagulation [64]. These coat-

Table 2. Comparing the pros and cons of different drug delivery systems.

Type of drug delivery system	Advantages	Limitations
Traditional oral medication	High patient compliance Easy to distribute and manage	Susceptible to gastrointestinal absorption effects May require multiple dosing
Transdermal patches	Avoid first-pass effect Sustained drug release	Limited by drug type and dosage May cause skin reactions
Injectable agents	Rapid achievement of therapeutic concentration Suitable for patients who cannot take oral medication	Requires administration by healthcare professionals May have lower patient compliance
Nanoparticle delivery systems	Improve drug targeting Enhance drug solubility and stability	High manufacturing costs Long-term safety unknown
Liposomes	Protect drugs from degradation Increase drug circulation time	Complex production process May cause immune reactions
Microcapsules	Control drug release rate Protect drugs from body environment effects	May affect drug release Limited material choices
Nanorobots	Highly targeted Programmable drug release	Technology still in research phase Regulatory and ethical issues
Drug release coatings	Provides targeted drug release to minimize systemic side effects Reduces risk of thrombosis in implanted devices	Difficult to control release rates precisely Durability and biocompatibility are concerns for sustained effectiveness

ings can gradually release antithrombotic agents at the implantation, alleviating the risk of thrombosis without necessitating systemic anticoagulation, thereby reducing associated risks [64]. Advances in nanomedicine further improve the performance of existing drugs by enhancing their stability, safety, and patient compliance through novel delivery systems [65, 66]. For example, mitochondria-targeted drug delivery systems have demonstrated improved tumor accumulation and stability in the systemic circulation, highlighting the potential of nanotechnology to optimize drug delivery in complex clinical scenarios [66]. The advantages and limitations of various drug delivery systems are presented in Table 2.

In conclusion, exploring novel drug delivery systems, particularly those using nanotechnology, holds significant promise for advancing anticoagulation reversal and perioperative management. These innovative approaches aim to achieve a balance between preventing thrombosis and minimizing bleeding risk, tailoring therapy to meet individual patient needs. As research continues in this dynamic field, it is anticipated that targeted drug delivery systems will contribute to enhancing the safety and efficacy of anticoagulation reversal, ultimately improving patient outcomes in perioperative settings and beyond.

The Role of Biomarkers in Perioperative Anticoagulation Management

Identification and Validation of Biomarkers for Anticoagulation Reversal

The emergence of biomarkers in perioperative anticoagulation management represents a significant advancement in personalized medicine. Accurate identification and validation of these biomarkers are crucial for anticoagulation reversal. These biomarkers help assess a patient's thrombosis risk and guide clinical decisions and adjustments to anticoagulation treatment protocols [67, 68]. For instance, biomarkers such as Von Willebrand Factor (VWF), fibrinopeptide A, and D-dimer have demonstrated potential in improving the detection and management of thrombotic risk in orthopedic surgery patients [67, 69]. Additionally, the postoperative decrease in antithrombin III may serve as a predictive factor for thrombotic events, further emphasizing the necessity for personalized treatment plans in perioperative management [67]. The dynamic changes in these biomarkers require continuous monitoring to adjust anticoagulation regimens, ensuring therapeutic effectiveness while minimizing the risk of bleeding.

Use of Biomarkers to Guide Personalized Treatment Strategies

Using biomarkers during the orthopedic perioperative period offers the possibility of highly personalized anticoagulation therapy. By analyzing a patient's biomarker profile, it is possible to predict the individual's response to specific anticoagulant treatments, enabling precise dosing adjustments and the design of personalized treatment plans [70, 71]. For example, in atrial fibrillation patients, the analysis of blood biomarkers allows for more accurate stroke risk management by considering each patient's unique biochemical and genetic characteristics [72]. Moreover, integrating data from pharmacokinetic and pharmacodynamic models can predict individual drug exposure, reducing the risk of

clinical non-response or adverse bleeding events [70]. This strategy is expected to significantly enhance patient satisfaction and reduce the risks associated with anticoagulation therapy.

Furthermore, using predictive scores and anticoagulation reversal strategies incorporating biomarkers can optimize the management of bleeding in patients under anticoagulant treatment. This approach enhances the efficacy of anticoagulation reversal and mitigates the risk of adverse events associated with inappropriate reversal. Thromboelastography is an essential tool for evaluating coagulation status during the perioperative period, aiding in formulating tailored anticoagulation strategies and exemplifying the broader utility of biomarkers in clinical decision-making [73, 74].

In summary, the role of biomarkers in perioperative anticoagulation management is advancing rapidly, with promising implications for patient care. Identifying and validating specific biomarkers are crucial for refining anticoagulation reversal strategies and tailoring treatment to individual needs. By integrating these biomarkers into clinical practice, healthcare providers can achieve a more comprehensive understanding of each patient's coagulation risk, resulting in safer and more effective perioperative management.

Economic Considerations in Anticoagulation Reversal

Cost-Effectiveness of Different Reversal Agents and Strategies

Assessing the economic aspects of anticoagulation reversal highlights the importance of cost-effectiveness analysis in healthcare decision-making [75]. The rapid development of anticoagulation therapies, particularly with the introduction of DOACs and their corresponding reversal agents like idarucizumab for dabigatran and PCC for factor Xa inhibitors, has necessitated a reassessment of the financial impact of these treatments [76]. The Danish study indicates that while the initial costs of these novel agents might be higher, their potential to reduce hospital stays, lower complication rates, and avoid additional invasive procedures could render them more cost-effective in the long run [77].

The economic burden of DOAC-related major bleeding, especially before the widespread availability of specific reversal agents, underscores the financial strain on healthcare systems [76]. However, introducing these antidotes has shifted the cost-benefit analysis, suggesting that investment in these agents may lead to greater overall savings through better bleeding management [76]. Furthermore, cost-effectiveness analyses comparing DOACs to warfarin in specific patient populations, such as those with nonvalvular atrial fibrillation (NVAF) and venous thromboembolism (VTE), highlight the complexities of determining economic significance. Crucial factors such as postoperative care, dosage adjustments, and managing bleeding complications, are critical in assessing the economic implications of these treatment modalities [78].

Economic Impact on Healthcare Systems and Patient Outcomes

The economic impact of anticoagulation therapy on healthcare systems is multifaceted, including direct medical costs, patient treatment outcomes, and quality of life. Research has indicated that managing major bleeding events related to DOACs or warfarin in elderly patients with atrial fibrillation can lead to substantial utilization of healthcare resources and associated costs. However, the introduction of DOAC-specific reversal agents can potentially reduce the rate of hospital resource utilization, particularly in emergencies requiring rapid reversal for urgent surgeries or life-threatening bleeds [76]. Decreased resource use could result in significant cost savings for healthcare systems while also offering clinical and economic benefits.

Additional research has demonstrated that compared to PCC, the use of idarucizumab to reverse dabigatran in patients with NVAF and VTE is associated with lower healthcare resource utilization and reduced total hospital costs [78]. This suggests that adopting novel anticoagulant reversal agents can improve patient care and outcomes and enhance the efficiency of healthcare resource allocation and cost-effectiveness within public health systems. This decrease in resource utilization could result in significant cost savings, highlighting the clinical and economic benefits of these agents [79].

The economic evaluation of anticoagulation reversal strategies underscores the need to consider the broader implications of thromboembolism prevention. Anticoagulant and reversal therapies must be evaluated regarding overall healthcare costs and in terms of preventing complications and improving patient quality of life [80]. Identifying the most effective and efficient approaches requires a comprehensive assessment that includes clinical efficacy, direct and indirect costs, and patient-centered outcomes. The clinical efficacy and cost-effectiveness analysis of commonly used reversal strategies are presented in Table 3.

In conclusion, economic considerations are critical in advancing and implementing anticoagulation reversal strategies. As healthcare systems aim to provide high-quality, cost-effective care, evaluating the financial implications of novel therapies and their impact on patient outcomes is crucial. Ongoing research and collaboration among clinicians, policymakers, and researchers are required to ensure that anticoagulation management optimizes both clinical benefits and economic outcomes for patients and healthcare systems.

Table 3. Clinical efficacy and cost-effectiveness analysis of common reversal strategies.

Reversal strategy	Clinical outcomes	Cost-effectiveness factors
Idarucizumab	Rapid reversal of dabigatran effect Effective in emergency bleeding scenarios	High acquisition cost Potential reduction in hospital stay duration
Andexanet alfa	Effective reversal for factor Xa inhibitors Improved coagulation in severe bleeding	Development and production costs Cost-effective for specific patient populations
Ciraparantag	Broad-spectrum reversal potential Under clinical investigation	Research and development costs Potential for widespread application pending clinical validation
PCC	Rapid reversal for VKAs Established use in bleeding episodes	Lower cost compared to novel agents Risk of thromboembolic events requiring management
Vitamin K	Slow but effective reversal for VKAs Standard of care for minor bleeding	Low cost Time to onset may limit effectiveness in urgent situations
Nanoparticle technology	Targeted drug delivery Reduced systemic side effects	High research and development costs Long-term cost-effectiveness yet to be determined
Personalized medicine approach	Tailored treatment based on pharmacogenomics Optimized dosing and selection of anticoagulants	Cost of genetic testing and analysis Reduction in Costs Associated with Ineffective Treatments

VKAs, vitamin K antagonists; PCC, prothrombin complex concentrates.

Challenges and Future Directions

Addressing Current Limitations in Anticoagulation Reversal Strategies

Anticoagulation reversal is critical for managing bleeding risks during surgeries or emergencies. Nonetheless, current reversal strategies encounter significant limitations, including the variable efficacy of agents across different patient populations and the potential risk for thrombotic complications following reversal [81, 82]. Reversal agents, such as PCC and specific antidotes like idarucizumab for dabigatran, and andexanet alfa for factor Xa inhibitors (e.g., rivaroxaban and apixaban), exhibit varying efficacy and safety profiles, underscoring the need for a more personalized approach to their application. Moreover, accurately assessing the real-world benefits of these strategies beyond the confined environment of clinical trials remains a substantial challenge [12, 28, 31, 83].

Factors that further complicate reversal of anticoagulation include the timing of intervention, dose adjustments based on renal function, and the precise identification of patients who would benefit most from these approaches [84]. These challenges underscore the importance of comprehensive guidelines that can adapt to the rapidly evolving landscape of anticoagulation therapy and its reversal strategies.

Future Research Directions, Including New Agents and Personalized Medicine

Future research focuses on establishing new reversal agents with improved safety profiles and adapting personalized medicine approaches. Targeting factor XI for anticoagulation, which presents a lower bleeding risk, is emerged as a promising approach for prevention and reversal [85]. Additionally, using biomarkers to guide the personalized application of reversal agents could significantly enhance the efficacy of these strategies.

Personalized medicine in anticoagulation reversal necessitates integrating patient-specific factors, including genetic predispositions [86, 87], to customize the selection and dosing of reversal agents. This approach, combined with the advent of novel agents and diagnostic methods, can potentially address the current limitations and improve patient outcomes. The future of anticoagulation reversal is moving towards a more individualized care model, where treatment decisions are guided by a comprehensive understanding of patient risk factors and the pharmacological properties of anticoagulants and their antidotes.

Prospects

Looking ahead, the deployment of intelligent monitoring systems through wearable technology stands at the forefront [88, 89], providing real-time data on critical hemodynamic parameters that can inform immediate and precise adjustments to anticoagulation therapy. This real-time monitor-

ing is expected to revolutionize the dynamic management of perioperative risks. Effective cross-disciplinary collaboration will be crucial in advancing these innovations, incorporating insights from various fields to develop a more comprehensive approach to perioperative care. Finally, incorporating patient-reported outcomes as a core component in treatment evaluation ensures that patient perspectives are central to the development of new anticoagulation strategies, highlighting the importance of a patient-centered approach.

The prospects of the field are undeniably promising, with the potential to significantly improve patient outcomes through a comprehensive understanding of individual risk factors and using advanced technology. As we advance and refine our strategies, the future of anticoagulation reversal in major orthopedic surgery appears bright, promising safer, more effective, and personalized care.

Conclusions

In conclusion, perioperative anticoagulation management in major orthopedic surgery is poised for substantial change through innovative approaches that aim to refine the balance between thrombotic and bleeding risks. The integration of precision medicine, particularly the advent of gene-editing technologies like CRISPR-Cas9 [90], offers the potential to personalize anticoagulant strategies at a genetic level, enhancing both efficacy and safety profiles. Moreover, using AI in decision support systems is expected to enhance clinical decision-making. By leveraging ML algorithms to analyze extensive patient data, we can anticipate a new standard of care that is highly individualized and proactive. Additionally, the advancement of drug delivery through nanotechnology offers promising frontier, with targeted nano-systems designed to release therapeutic agents in response to specific physiological signals, thereby improving the therapeutic window of anticoagulants and reducing off-target effects.

Abbreviations

VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists; INR, International Normalized Ratio; PCC, prothrombin complex concentrates; LMWH, low molecular weight heparins; ETP, endogenous thrombin potential; AI, artificial intelligence; ML, machine learning; CYP, cytochrome P450; VKORC1, vitamin K epoxide reductase complex subunit 1; VWF, Von Willebrand Factor; NVAF, non-valvular atrial fibrillation.

Availability of Data and Materials

Not applicable.

Author Contributions

MH and XYZ were responsible for literature search and screening. YYF and MH were responsible for data extraction and initial analysis and organization. YYF wrote the main manuscript text. All authors critically reviewed and revised the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Talari G, Demertzis ZD, Summey RD, Gill B, Kaatz S. Perioperative management of anticoagulation. Hospital Practice (1995). 2020; 48: 231–240.

[2] Yamashita Y, Morimoto T, Kimura T. Venous thromboembolism: Recent advancement and future perspective. Journal of Cardiology. 2022; 79: 79–89.

[3] Tritschler T, Kraaijpoel N, Le Gal G, Wells PS. Venous Thromboembolism: Advances in Diagnosis and Treatment. JAMA. 2018; 320: 1583–1594.

[4] Kai AM, Vadivelu N, Urman RD, Shukla S, Schonberger R, Banack T. Perioperative Considerations in the Management of Anticoagulation Therapy for Patients Undergoing Surgery. Current Pain and Headache Reports. 2019; 23: 13.

[5] Ghasemi MA, Ghadimi E, Shamabadi A, Mortazavi SJ. The Perioperative Management of Antiplatelet and Anticoagulant Drugs in Hip Fractures: Do the Surgery as Early as Possible. The Archives of Bone and Joint Surgery. 2022; 10: 490–500.

[6] Backus B, Beyer-Westendorf J, Body R, Lindner T, Möckel M, Sehgal V, *et al*. Management of major bleeding for anticoagulated patients in the Emergency Department: an European experts consensus statement. European Journal of Emergency Medicine: Official Journal of the European Society for Emergency Medicine. 2023; 30: 315–323.

[7] Gibler WB, Racadio JM, Hirsch AL, Roat TW. Management of Severe Bleeding in Patients Treated with Oral Anticoagulants: Proceedings Monograph From the Emergency Medicine Cardiac Research and Education Group-International Multidisciplinary Severe Bleeding Consensus

Panel October 20, 2018. Critical Pathways in Cardiology. 2019; 18: 143–166.
[8] Lenzen-Großimlinghaus R. Perioperative management of platelet function and anticoagulation in geriatric patients. Der Chirurg; Zeitschrift Fur Alle Gebiete Der Operativen Medizen. 2022; 93: 266–273. (In German)
[9] Shaw JR, Kaplovitch E, Douketis J. Periprocedural Management of Oral Anticoagulation. The Medical Clinics of North America. 2020; 104: 709–726.
[10] Briete LD, Towers WF, Bone R, Nair R, Steck M, Cutshall BT, *et al*. Perioperative Anticoagulation Management. Critical Care Nursing Quarterly. 2022; 45: 119–131.
[11] Ripoll JG, Klompas AM, Smith BB, Smith MM. Contemporary Perioperative Management of Direct Oral Anticoagulants. Advances in Anesthesia. 2022; 40: 93–109.
[12] Chen AT, Patel M, Douketis JD. Perioperative management of antithrombotic therapy: a case-based narrative review. Internal and Emergency Medicine. 2022; 17: 25–35.
[13] Budd AN, Wood B, Zheng W, Rong LQ. Perioperative Management of Direct Oral Anticoagulants in Cardiac Surgery: Practice Recommendations Based on Current Evidence. Journal of Cardiothoracic and Vascular Anesthesia. 2022; 36: 4141–4149.
[14] von der Forst M, Morath B, Schwald M, Weigand MA, Schmitt FCF. Principles of the perioperative management of direct oral anticoagulants. Die Anaesthesiologie. 2022; 71: 565–576. (In German)
[15] Sachdev D, Khalil L, Gendi K, Brand J, Cominos N, Xie V, *et al*. Perioperative Management of Traditional and Direct Oral Anticoagulants in Hip Fracture Patients. Orthopedic Reviews. 2024; 16: 115605.
[16] Gong LN, Li JY, Li XF, Chu J. Effect of preinjury use of direct oral anticoagulants vs. Vitamin K antagonists on outcomes of hip fracture: a systematic review and meta-analysis. European Review for Medical and Pharmacological Sciences. 2021; 25: 6260–6270.
[17] Rostagno C, Rubbieri G, Zeppa M, Cartei A, Ceccofiglio A, Mannarino GM, *et al*. Management and 1-Year Outcome in Elderly Patients with Hip Fracture Surgery Receiving Anticoagulation (Warfarin or DOAc) or P2Y12 Antiplatelet Agents. Journal of Clinical Medicine. 2023; 12: 6178.
[18] You D, Xu Y, Krzyzaniak H, Korley R, Carrier M, Schneider P. Safety of expedited-surgery protocols in anticoagulant-treated patients with hip fracture: a systematic review and meta-analysis. Canadian Journal of Surgery. Journal Canadien De Chirurgie. 2023; 66: E170–E180.
[19] Milling TJ, Jr, Ziebell CM. A review of oral anticoagulants, old and new, in major bleeding and the need for urgent surgery. Trends in Cardiovascular Medicine. 2020; 30: 86–90.
[20] van Es N, De Caterina R, Weitz JI. Reversal agents for current and forthcoming direct oral anticoagulants. European Heart Journal. 2023; 44: 1795–1806.
[21] Hagedorn JC, 2nd, Yates SG, Chen J, Adkins BD. Direct Oral Anticoagulants: How Do These Drugs Work, How to Monitor, and What Is Their Role in Orthopaedic Surgery. The Journal of the American Academy of Orthopaedic Surgeons. 2023; 31: e347–e355.
[22] Gómez-Outes A, Alcubilla P, Calvo-Rojas G, Terleira-Fernández AI, Suárez-Gea ML, Lecumberri R, *et al*. Meta-Analysis of Reversal Agents for Severe Bleeding Associated with Direct Oral Anticoagulants. Journal of the American College of Cardiology. 2021; 77: 2987–3001.
[23] Siegal DM. What we have learned about direct oral anticoagulant reversal. Hematology. American Society of Hematology. Education Program. 2019; 2019: 198–203.
[24] Chan NC, Weitz JI. Ciraparantag as a potential universal anticoagulant reversal agent. European Heart Journal. 2022; 43: 993–995.
[25] Ansell J, Laulicht BE, Bakhru SH, Burnett A, Jiang X, Chen L, *et al*. Ciraparantag, an anticoagulant reversal drug: mechanism of action, pharmacokinetics, and reversal of anticoagulants. Blood. 2021; 137: 115–125.
[26] Gómez-Outes A, Suárez-Gea ML, Lecumberri R. When and How to Use Reversal Agents for Direct Oral Anticoagulants? Current Cardiology Reports. 2023; 25: 371–380.
[27] Zhao S, Hong X, Cao J, Zhang J, Ma P. Current Evidence for Pharmacologic Reversal Using Direct Oral Anticoagulants: What's New? American Journal of Cardiovascular Drugs: Drugs, Devices, and other Interventions. 2020; 20: 117–123.
[28] Kaide CG, Gulseth MP. Current Strategies for the Management of Bleeding Associated with Direct Oral Anticoagulants and a Review of Investigational Reversal Agents. The Journal of Emergency Medicine. 2020; 58: 217–233.
[29] Yang Y, Ma C, Zhou J, Liu S, Wang L, Wang J, *et al*. Reversal effect of idarucizumab on the anticoagulant effect of dabigatran etexilate in Chinese population. Chinese Journal of Cardiac Arrhythmias. 2022; 26: 553–560. (In Chinese)
[30] Pollack CV, Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, *et al*. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. The New England Journal of Medicine. 2017; 377: 431–441.
[31] van der Horst SFB, Martens ESL, den Exter PL, Bos MHA, van Mens TE, Huisman MV, *et al*. Idarucizumab for dabigatran reversal: A systematic review and meta-analysis of indications and outcomes. Thrombosis Research. 2023; 228: 21–32.
[32] Sible AM, Nawarskas JJ. Andexanet Alfa for Reversing Factor Xa Inhibition. Cardiology in Review. 2019; 27: 108–111.
[33] Chaudhary R, Singh A, Chaudhary R, Bashline M, Houghton DE, Rabinstein A, *et al*. Evaluation of Direct Oral Anticoagulant Reversal Agents in Intracranial Hem-

orrhage: A Systematic Review and Meta-analysis. JAMA Network Open. 2022; 5: e2240145.
[34] Favresse J, Hardy M, van Dievoet MA, Sennesael AL, Douxfils J, Samama CM, *et al*. Andexanet alfa for the reversal of factor Xa inhibitors. Expert Opinion on Biological Therapy. 2019; 19: 387–397.
[35] Sridharan K, Sivaramakrishnan G. A network meta-analysis of CYP2C9, CYP2C9 with VKORC1 and CYP2C9 with VKORC1 and CYP4F2 genotype-based warfarin dosing strategies compared to traditional. Journal of Clinical Pharmacy and Therapeutics. 2021; 46: 640–648.
[36] Al-Metwali BZ, Rivers P, Goodyer L, O'Hare L, Young S, Mulla H. Personalised Warfarin Dosing in Children Post-cardiac Surgery. Pediatric Cardiology. 2019; 40: 1735–1744.
[37] Lin B, Chung WK. Cases in Precision Medicine: The Role of Pharmacogenetics in Precision Prescribing. Annals of Internal Medicine. 2019; 170: 796–804.
[38] Hassan R, Allali I, Agamah FE, Elsheikh SSM, Thomford NE, Dandara C, *et al*. Drug response in association with pharmacogenomics and pharmacomicrobiomics: towards a better personalized medicine. Briefings in Bioinformatics. 2021; 22: bbaa292.
[39] Sadee W, Wang D, Hartmann K, Toland AE. Pharmacogenomics: Driving Personalized Medicine. Pharmacological Reviews. 2023; 75: 789–814.
[40] Chang GSW, Tan DSY. Using Pharmacogenetic Testing to Tailor Warfarin Therapy: The Singapore Experience and What the Future Holds. European Cardiology. 2020; 15: e53.
[41] Gabriel RA, Burton BN, Urman RD, Waterman RS. Genomics Testing and Personalized Medicine in the Preoperative Setting. Surgical Oncology Clinics of North America. 2020; 29: 73–86.
[42] Pirmohamed M. Pharmacogenomics: current status and future perspectives. Nature Reviews. Genetics. 2023; 24: 350–362.
[43] Zhou Y, Koutsilieri S, Eliasson E, Lauschke VM. A paradigm shift in pharmacogenomics: From candidate polymorphisms to comprehensive sequencing. Basic & Clinical Pharmacology & Toxicology. 2022; 131: 452–464.
[44] Eljilany I, Elarref M, Shallik N, Elzouki AN, Mohammed A, Shoman B, *et al*. Periprocedural Anticoagulation Management of Patients receiving Warfarin in Qatar: A Prospective Cohort Study. Current Problems in Cardiology. 2021; 46: 100816.
[45] Li B, Eisenberg N, Beaton D, Lee DS, Al-Omran L, Wijeysundera DN, *et al*. Predicting inferior vena cava filter complications using machine learning. Journal of Vascular Surgery. Venous and Lymphatic Disorders. 2024; 101943.
[46] Rashidi HH, Bowers KA, Reyes Gil M. Machine learning in the coagulation and hemostasis arena: an overview and evaluation of methods, review of literature, and future directions. Journal of Thrombosis and Haemostasis: JTH. 2023; 21: 728–743.
[47] Shohat N, Ludwick L, Sherman MB, Fillingham Y, Parvizi J. Using machine learning to predict venous thromboembolism and major bleeding events following total joint arthroplasty. Scientific Reports. 2023; 13: 2197.
[48] Checcucci E, Piazzolla P, Marullo G, Innocente C, Salerno F, Ulrich L, *et al*. Development of Bleeding Artificial Intelligence Detector (BLAIR) System for Robotic Radical Prostatectomy. Journal of Clinical Medicine. 2023; 12: 7355.
[49] Horita K, Hida K, Itatani Y, Fujita H, Hidaka Y, Yamamoto G, *et al*. Real-time detection of active bleeding in laparoscopic colectomy using artificial intelligence. Surgical Endoscopy. 2024; 38: 3461–3469.
[50] Mora D, Mateo J, Nieto JA, Bikdeli B, Yamashita Y, Barco S, *et al*. Machine learning to predict major bleeding during anticoagulation for venous thromboembolism: possibilities and limitations. British Journal of Haematology. 2023; 201: 971–981.
[51] Shung DL. Advancing care for acute gastrointestinal bleeding using artificial intelligence. Journal of Gastroenterology and Hepatology. 2021; 36: 273–278.
[52] Mishra A, Ashraf MZ. Using Artificial Intelligence to Manage Thrombosis Research, Diagnosis, and Clinical Management. Seminars in Thrombosis and Hemostasis. 2020; 46: 410–418.
[53] Sridharan K, Ramanathan M, Al Banna R. Evaluation of supervised machine learning algorithms in predicting the poor anticoagulation control and stable weekly doses of warfarin. International Journal of Clinical Pharmacy. 2023; 45: 79–87.
[54] Gage BF, Bass AR, Lin H, Woller SC, Stevens SM, Al-Hammadi N, *et al*. Effect of Genotype-Guided Warfarin Dosing on Clinical Events and Anticoagulation Control Among Patients Undergoing Hip or Knee Arthroplasty: The GIFT Randomized Clinical Trial. JAMA. 2017; 318: 1115–1124.
[55] Al Saiegh F, Munoz A, Velagapudi L, Theofanis T, Suryadevara N, Patel P, *et al*. Patient and procedure selection for mechanical thrombectomy: Toward personalized medicine and the role of artificial intelligence. Journal of Neuroimaging: Official Journal of the American Society of Neuroimaging. 2022; 32: 798–807.
[56] Wang Q, Yuan L, Ding X, Zhou Z. Prediction and Diagnosis of Venous Thromboembolism Using Artificial Intelligence Approaches: A Systematic Review and Meta-Analysis. Clinical and Applied Thrombosis/hemostasis: Official Journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2021; 27: 10760296211021162.
[57] Mao Y, Ren J, Yang L. Advances of nanomedicine in treatment of atherosclerosis and thrombosis. Environmental Research. 2023; 116637.
[58] Jaynes TL. "Compoundless Anaesthesia", Controlled Administration, and Post-Operative Recovery Accelera-

tion: Musings on Theoretical Nanomedicine Applications. Journal of Clinical Medicine. 2022; 11: 256.
[59] Kwon YM. Targeted delivery of thrombolytic enzymes. BioImpacts: BI. 2021; 11: 85–86.
[60] Shen Y, Yu Y, Zhang X, Hu B, Wang N. Progress of nanomaterials in the treatment of thrombus. Drug Delivery and Translational Research. 2024; 14: 1154–1172.
[61] Russell P, Hagemeyer CE, Esser L, Voelcker NH. Theranostic nanoparticles for the management of thrombosis. Theranostics. 2022; 12: 2773–2800.
[62] Priya V, Viswanadh MK, Mehata AK, Jain D, Singh SK, Muthu MS. Targeted nanotherapeutics in the prophylaxis and treatment of thrombosis. Nanomedicine (London, England). 2021; 16: 1153–1176.
[63] Ferreira-Silva M, Faria-Silva C, Baptista PV, Fernandes E, Fernandes AR, Corvo ML. Drug delivery nanosystems targeted to hepatic ischemia and reperfusion injury. Drug Delivery and Translational Research. 2021; 11: 397–410.
[64] Reczyńska K, Major R, Kopernik M, Pamuła E, Imbir G, Plutecka H, *et al*. Surface modification of polyurethane with eptifibatide-loaded degradable nanoparticles reducing risk of blood coagulation. Colloids and Surfaces. B, Biointerfaces. 2021; 201: 111624.
[65] Tenchov R, Bird R, Curtze AE, Zhou Q. Lipid Nanoparticles─From Liposomes to mRNA Vaccine Delivery, a Landscape of Research Diversity and Advancement. ACS Nano. 2021; 15: 16982–17015.
[66] Fang L, Lin H, Wu Z, Wang Z, Fan X, Cheng Z, *et al*. In vitro/vivo evaluation of novel mitochondrial targeting charge-reversal polysaccharide-based antitumor nanoparticle. Carbohydrate Polymers. 2020; 234: 115930.
[67] Mansoor SN, Nadeem SM, Nadeem W, Nadeem SM. Plasma Antithrombin III Concentration: A Predictor of Thromboembolism in Orthopedic Surgery. Pakistan Journal of Medical and Health Sciences. 2020; 14: 309–311.
[68] Hijazi Z, Oldgren J, Siegbahn A, Wallentin L. Application of Biomarkers for Risk Stratification in Patients with Atrial Fibrillation. Clinical Chemistry. 2017; 63: 152–164.
[69] Dailiana ZH, Stefanou N, Varitimids S, Rigopoulos N, Dimitroulias A, Karachalios T, *et al*. Factors predisposing to thrombosis after major joint arthroplasty. World Journal of Orthopedics. 2020; 11: 400–410.
[70] Terrier J, Daali Y, Fontana P, Csajka C, Reny JL. Towards Personalized Antithrombotic Treatments: Focus on $P2Y_{12}$ Inhibitors and Direct Oral Anticoagulants. Clinical Pharmacokinetics. 2019; 58: 1517–1532.
[71] Hammer A, Schnaubelt S, Niessner A, Sulzgruber P. The personalized antithrombotic management of atrial fibrillation with intermediate thromboembolic risk: a case report. European Heart Journal. Case Reports. 2020; 4: 1–4.
[72] Kamtchum-Tatuene J, Jickling GC. Blood Biomarkers for Stroke Diagnosis and Management. Neuromolecular Medicine. 2019; 21: 344–368.
[73] Burton AG, Jandrey KE. Use of Thromboelastography in Clinical Practice. The Veterinary Clinics of North America. Small Animal Practice. 2020; 50: 1397–1409.
[74] Fan D, Ouyang Z, Ying Y, Huang S, Tao P, Pan X, *et al*. Thromboelastography for the Prevention of Perioperative Venous Thromboembolism in Orthopedics. Clinical and Applied Thrombosis/hemostasis: Official Journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2022; 28: 10760296221077975.
[75] Jones NR, Crawford W, Yang Y, Hobbs FDR, Taylor CJ, Petrou S. A Systematic Review of Economic Aspects of Service Interventions to Increase Anticoagulation Use in Atrial Fibrillation. Thrombosis and Haemostasis. 2022; 122: 394–405.
[76] Xu Y, Schulman S, Dowlatshahi D, Holbrook AM, Simpson CS, Shepherd LE, *et al*. Healthcare resource utilization and costs among patients with direct oral anticoagulant or warfarin-related major bleeding. Thrombosis Research. 2019; 182: 12–19.
[77] Nielsen A, Poulsen PB, Dybro L, Kloster B, Lorentzen A, Olsen J, *et al*. Total costs of treating venous thromboembolism: implication of different cost perspectives in a Danish setting. Journal of Medical Economics. 2019; 22: 1321–1327.
[78] Spyropoulos AC, Hartaigh BO, Cao Z, Lipkin C, Robinson SB, Caberwal H, *et al*. Healthcare Resource Utilization for Oral Anticoagulant Reversal Therapies in Non-Valvular Atrial Fibrillation/Venous Thromboembolism Patients. Cardiology Research. 2022; 13: 27–43.
[79] Korjian S, Daaboul Y, Laliberté F, Zhao Q, Mehran R, Bode C, *et al*. Cost Implications of Anticoagulation Strategies After Percutaneous Coronary Intervention Among Patients with Atrial Fibrillation (A PIONEER-AF PCI Analysis). The American Journal of Cardiology. 2019; 123: 355–360.
[80] Liao CT, Lee MC, Chen ZC, Ku LJE, Wang JD, Toh HS. Cost-Effectiveness Analysis of Oral Anticoagulants in Stroke Prevention among Patients with Atrial Fibrillation in Taiwan. Acta Cardiologica Sinica. 2020; 36: 50–61.
[81] Connolly SJ, Milling TJ, Jr, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, *et al*. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. The New England Journal of Medicine. 2016; 375: 1131–1141.
[82] Schulman S, Gross PL, Ritchie B, Nahirniak S, Lin Y, Lieberman L, *et al*. Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study. Thrombosis and Haemostasis. 2018; 118: 842–851.
[83] Milling TJ, Pollack CV. A review of guidelines on anticoagulation reversal across different clinical scenarios - Is there a general consensus? The American Journal of Emergency Medicine. 2020; 38: 1890–1903.
[84] Cuker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott EM, *et al*. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. American Journal of Hematology. 2019; 94: 697–709.

[85] Koulas I, Spyropoulos AC. A Review of FXIa Inhibition as a Novel Target for Anticoagulation. Hamostaseologie. 2023; 43: 28–36.
[86] Lippi G, Favaloro EJ. What We Know (and Do not Know) Regarding the Pathogenesis of Pulmonary Thrombosis in COVID-19. Seminars in Thrombosis and Hemostasis. 2023; 49: 27–33.
[87] Öncül Y, Akyay A, Özgen Ü. Thromboembolism in Children. Indian Journal of Pediatrics. 2024; 91: 696–701.
[88] Li L, Liang H, Fan Y, Yan W, Yan M, Cao D, *et al*. Development of intelligent monitoring system based on Internet of Things and wearable technology and exploration of its clinical application mode. Sheng wu yi xue gong cheng xue za zhi = Journal of biomedical engineering = Shengwu yixue gongchengxue zazhi. 2023; 40: 1053–1061. (In Chinese)
[89] Wang B, Zhou S, Jiang S, Qin S, Gao B. Personalized Medical Devices Connect Monitoring and Assistance: Emerging Wearable Soft Robotics. Analytical Chemistry. 2023; 95: 8395–8410.
[90] Jin DY, Chen X, Liu Y, Williams CM, Pedersen LC, Stafford DW, *et al*. A genome-wide CRISPR-Cas9 knockout screen identifies FSP1 as the warfarin-resistant vitamin K reductase. Nature Communications. 2023; 14: 828.