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Adverse Events Associated with Anticoagulation Therapy: A Scoping Review

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Abstract **Review Article**

Anticoagulation therapy is used to prevent thromboembolic events in different clinical scenarios. Yet the utilization of anticoagulants can lead to adverse events (ADEs) that can affect patient outcomes. This scoping review aimed to provide an overview of ADEs associated with anticoagulation therapy by identifying commonly reported examples, types of ADEs, risk factors, and areas of clinical controversy. The study included a mix of study designs, including longitudinal and randomized controlled trials. Warfarin, direct oral anticoagulants (DOACs), and heparin were among the frequently mentioned anticoagulants. Bleeding-related events, thromboembolic complications, as well as other ADE such as over-anticoagulation and allergy were identified. Various risk factors contributing to these ADEs were recognized; they encompassed patient characteristics, comorbidities, concomitant medications and laboratory parameters. The review emphasizes individualized risk assessment through close monitoring and educating patients to minimize potential adverse drug effects (ADE). Gaps and controversies in the literature underscore the need for further research to elucidate mechanisms underlying ADEs, identify new biomarkers for risk stratification, minimizing adverse events while maximizing therapeutic benefits.

Keywords: *Review, Anticoagulation, Adverse Events, Thromboembolism*.

INTRODUCTION

Anticoagulation therapy (Potpara & Lip, 2020) can manage many medical conditions to inhibit the clotting cascade and prevent thromboembolic events that could cause blood clots (Clark *et al*., 2014). Nonetheless, like any other medication intervention, anticoagulation therapy presents many actual or potential Adverse Drug Events (ADEs) with clinical implications. Studies on ADEs associated with anticoagulation therapy corroborate many key discoveries. Clark *et al*., (2007) surveyed patients receiving stable therapeutic anticoagulation. They found that those whose International Normalized Ratio (INR) had become significantly sub-therapeutic were at an increased risk of anticoagulation-related adverse events within three months of therapy initiation. This reaffirms the importance of maintaining therapeutic INR levels to minimize ADE occurrences. In another study, Dabigatran *et al*., (Clark *et al*., 2014) reported that the simultaneous use of warfarin and some antibiotics raised the risk of excessive anticoagulation significantly when antibiotics impeded warfarin metabolism.

Various factors may increase the likelihood of ADEs occurring in patients on anticoagulation therapy. Such risks include age, comorbidities such as renal impairment or liver disease, concurrent medications such as antiplatelet agents, genetic variability in drug metabolism, and fluctuations in the INR for patients receiving warfarin therapy (Lechat *et al*., 2001; Clark *et al*., 2014).

A scoping review was conducted to understand ADEs associated with anticoagulation therapy comprehensively. While previous studies have explored various aspects of these ADEs (Clark *et al*., 2007; Clark *et al*., 2014; Johnson, 2008; Lechat *et al*., 2001; Houston *et al*., 2020; Lee *et al*., 2021), a systematic synthesis of this literature is lacking.

This review aims to 1) identify commonly reported anticoagulation therapies, 2) define associated ADEs, 3) assess risk factors, including patient characteristics, medication interactions, and comorbidities, and 4) identify gaps and controversies in the existing research. By synthesizing available evidence, this review will contribute to a more comprehensive understanding of anticoagulation-related ADEs and inform strategies for prevention and management.

METHODOLOGY

We employed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method to identify relevant studies. We formulated inclusion criteria using the *Population, Intervention, Comparison, and Outcome* (PICO) framework. The population of interest was adult patients receiving anticoagulation therapy; the intervention was any anticoagulant drug, and the outcome was adverse events associated with this therapy.

We included English-language studies published between 2000 and 2023 investigating adverse events related to anticoagulation therapy in adult patients. We excluded studies involving pediatric patients, pregnant women, non-English publications, and those that did not discuss adverse events or complications associated with anticoagulation therapy.

The study's comparison group included patients receiving other treatments such as antiplatelet agents or placebo. The primary outcomes of interest were bleeding events, thromboembolism recurrence following stroke, and mortality. To initiate the scoping review process, we developed a preliminary search strategy using relevant Medical Subject Headings (MeSH) and keywords aligned with our study objectives. PubMed was used as the electronic database for searching."

The study employs the PRISMA method for identifying and obtaining data. The PICO (Population, Intervention, Comparison, and Outcome) framework was also used to formulate the inclusion criteria to ensure that relevant studies have been selected. In this case, the population includes patients on anticoagulant therapy; the intervention is anticoagulation therapy, while the outcome is adverse events associated with this therapy. The inclusion criteria include studies investigating adverse events related to anticoagulation therapy, English language-only studies, 2000 - 2023 research period, random control or longitudinal designs, human participants, and full-text articles published in peer-reviewed journals. The exclusion criteria are Studies involving pediatric patients (under 18 years of age) or pregnant women. These studies do not discuss adverse events or complications associated with anticoagulation therapy, and non-English studies. The search strategy is as shown below:

(Anticoagulation OR anticoagulant OR warfarin OR apixaban OR dabigatran OR edoxaban OR rivaroxaban OR heparin) AND (adverse events OR complications OR bleeding OR thromboembolism OR stroke recurrence OR mortality) AND (clinical trial OR comparative study or placebo). Additional relevant studies were identified by manually searching the reference lists to avoid omitting studies. The PRISMA flowchart is shown below.

The study selection process was conducted in two stages:

1. Title and Abstract Screening: Two independent reviewers assessed titles and abstracts against the inclusion and exclusion criteria. Only studies that met the criteria or were uncertain about eligibility proceeded to full-text review.
2. Two independent reviewers assessed the full text of eligible studies. Any disagreements were resolved through consensus or by a third party.

The quality of the included studies was evaluated using the Cochrane Risk of Bias tool, which was tailored to the study design. To synthesize the data and achieve the review's objectives, a thematic analysis was conducted. This involved identifying and collating relevant data from selected studies, mapping them into themes related to our research objectives, and interpreting the results.

RESULTS

Summary of Study Methodology

The studies included in the review were either longitudinal studies or randomized controlled trials (RCTs). Of the 30 analyzed articles, 10 were longitudinal (observational), and 20 were RCTs (experimental). Longitudinal studies tracked participants over time to assess the long-term effects of anticoagulation therapy, while RCTs randomly assigned participants to treatment groups for a rigorous evaluation of efficacy and safety.

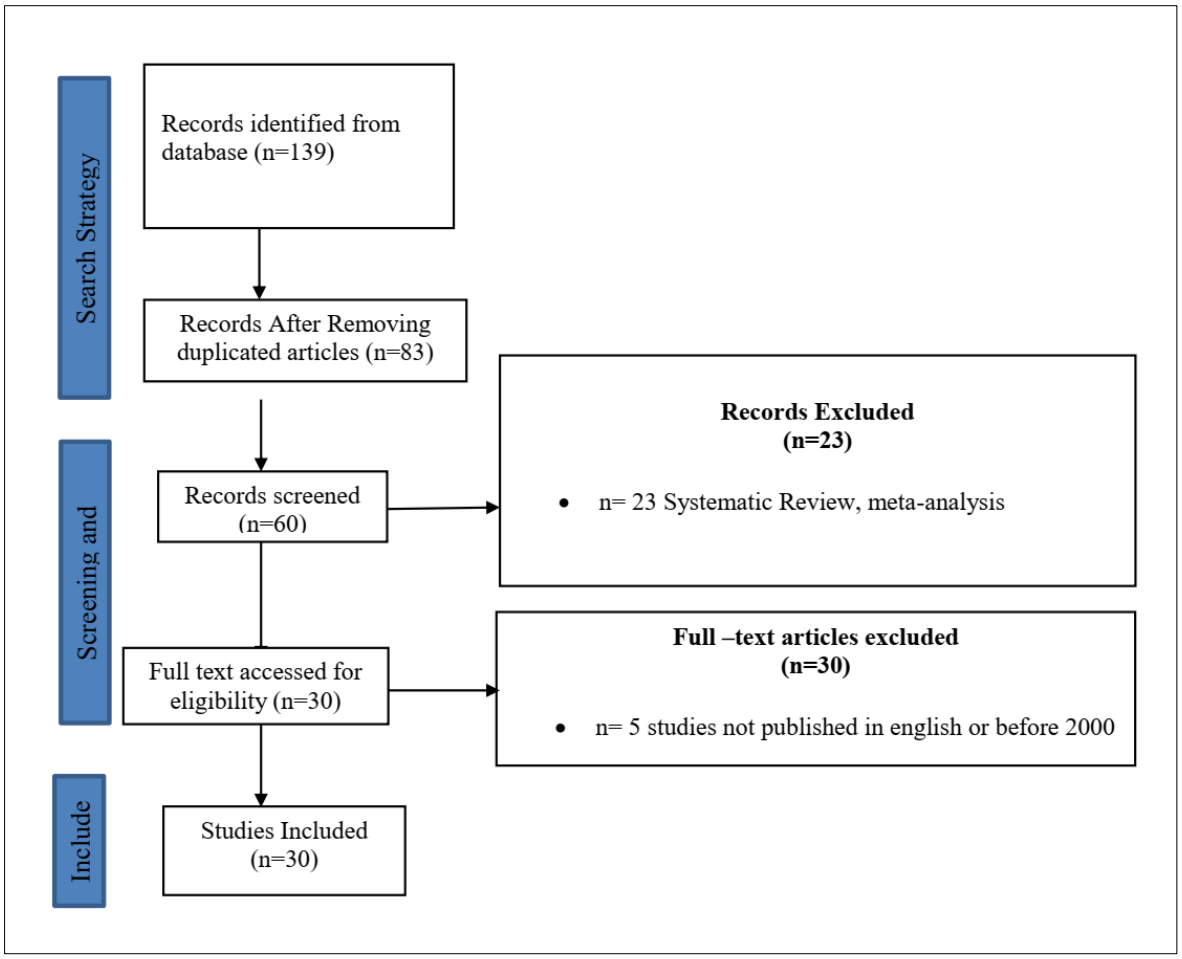

Figure 1: PRISMA Diagram of the Study

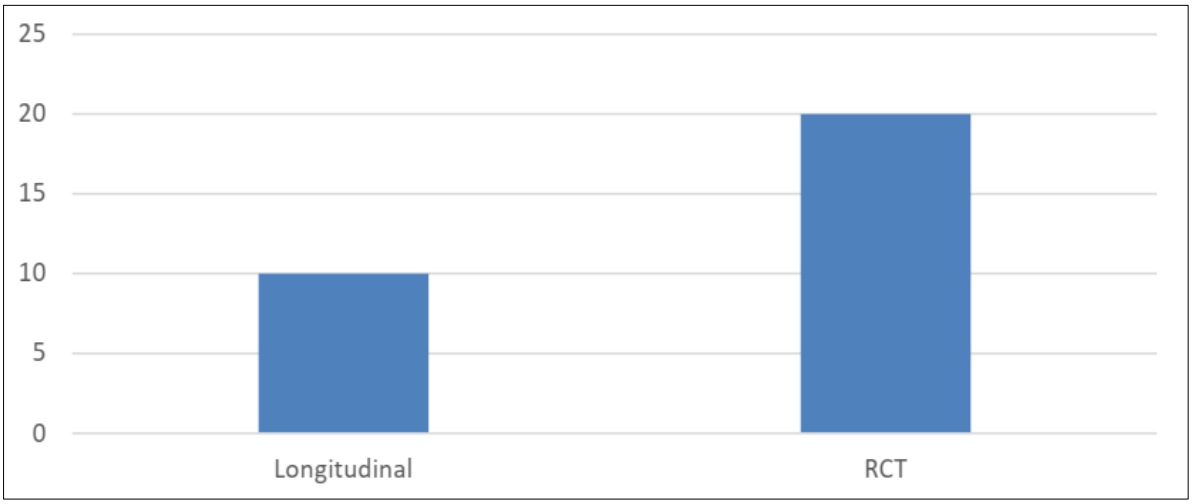

Figure 1: Methodological Trend

Figure 2 shows a trend of increasing publications on anticoagulation therapy over time, with a significant rise in 2020 and 2021. This suggests growing research interest in this area.

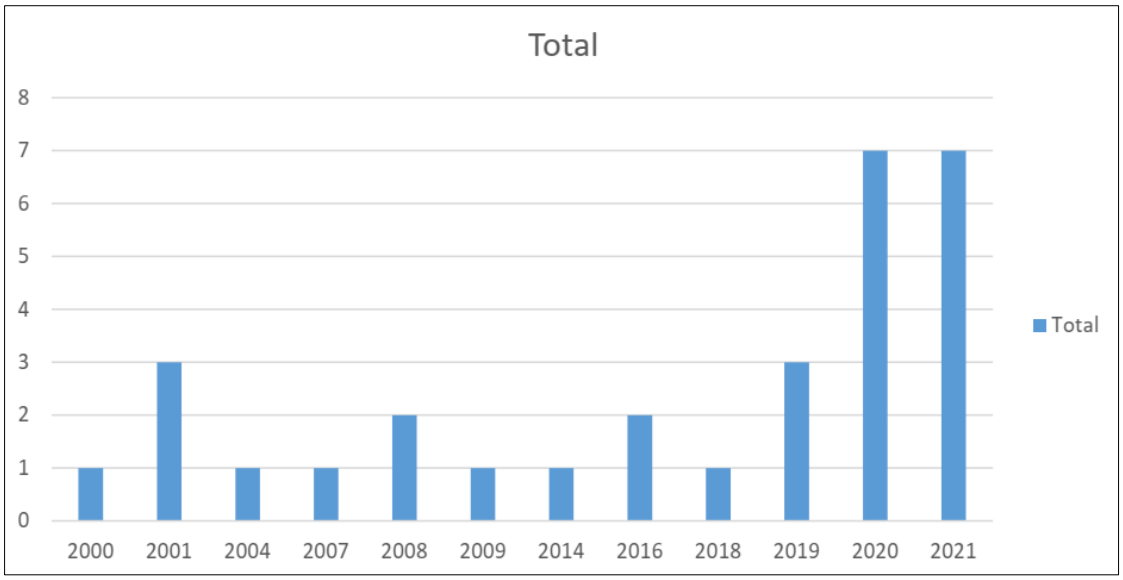

Figure 2: Trends in Publications

Commonly Reported Anticoagulation Therapy

In the scoping review, the analysis revealed a variety of anticoagulant therapies that were commonly reported across the included studies (Figure 3). These anticoagulants encompassed Warfarin, heparin, rivaroxaban, and fluindione. Some other studies use multiple of them (Stingl *et al*., 2016).

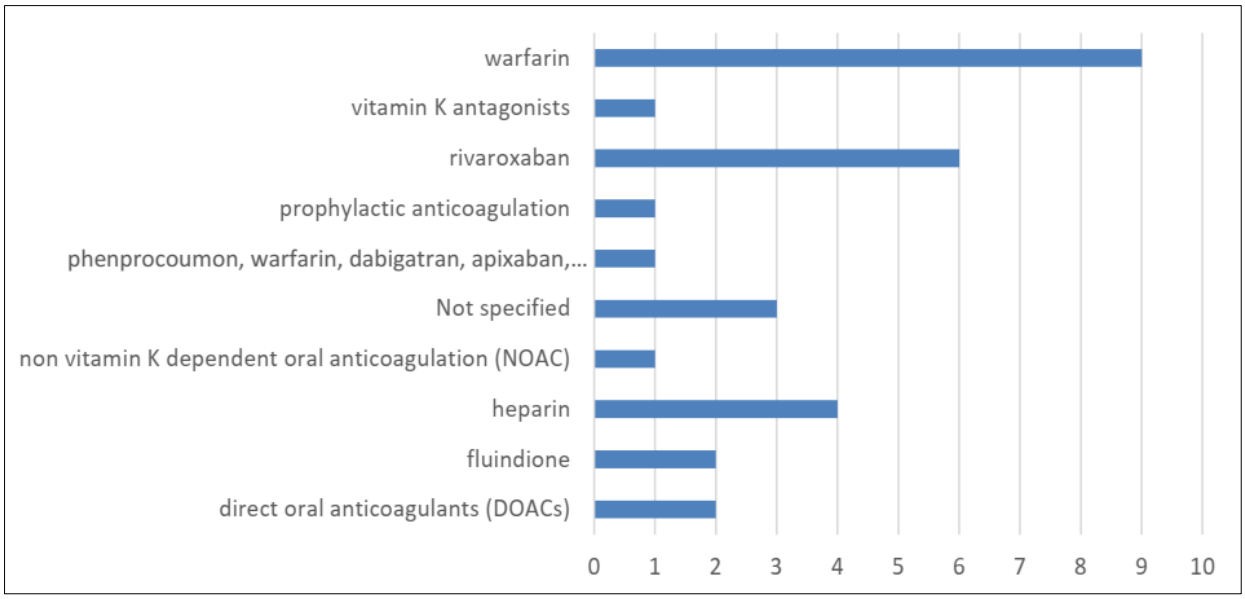

Figure 3: Type of Anticoagulant

Warfarin was the most frequently reported anticoagulant, used in nine studies (Clark *et al*., 2007; Clark *et al*., 2014; Johnson, 2008; Chan *et al*., 2009; Johnson *et al*., 2008; Puskas *et al*., 2018; Maria Suarez *et al*., 2019; Galatro *et al*., 2004; Huynh *et al*., 2001). This reflects its widespread use as a vitamin K antagonist. Rivaroxaban, a direct oral anticoagulant (DOAC), was reported in six studies (Lopes *et al*., 2021; Potpara & Lip, 2020; Feitosa-Filho *et al*., 2021; Dangas *et al*., 2019; Stojkovic *et al*., 2020; Rodilla *et al*., 2021). DOACs have gained popularity due to their convenience and predictable pharmacokinetics. Heparin, a parenteral anticoagulant, was mentioned in four studies (Houston *et al*., 2020; Bikdeli *et al*., 2021; Lawler *et al*., 2021; Verheugt *et al*., 2016). It is commonly used for rapid anticoagulation.

Other anticoagulants mentioned included fluindione, non-vitamin K-dependent oral anticoagulation (NOAC), prophylactic anticoagulation, vitamin K antagonists, phenprocoumon, dabigatran, and apixaban (Stingl *et al*., 2016). Some studies did not specify the type of anticoagulant used (Yusuf *et al*., 2001; Rosati *et al*., 2020; Diep & Garcia, 2021).

Types of ADEs Associated with Anticoagulation Therapy

This review identified various types of adverse drug events (ADEs) associated with anticoagulation therapy. These ADEs can be categorized into sub-themes based on their nature and clinical impact.

Bleeding-Related ADEs

Bleeding-related ADEs are among the most reported in the literature. Different studies use different terminologies, which essentially mean the same thing. These include hemorrhage (Johnson, 2008; Johnson *et al*., 2008; Huynh *et al*., 2001), hemorrhagic complications (Lechat *et al*., 2001; Lechat *et al*., 2000), major bleeding (Houston *et al*., 2020; Potpara & Lip, 2020; Nordbeck & Hu, 2020; Feitosa-Filho *et al*., 2021; Lawler *et al*., 2021; Stingl *et al*., 2016; Stojkovic *et al*., 2020), bleeding complications (Galatro *et al*., 2004), and general bleeding (Diep & Garcia, 2021; Rodilla *et al*., 2021; Huynh *et al*., 2001).

Thromboembolic ADEs

Thromboembolic events have also been identified as ADEs linked to anticoagulation therapy. These include thromboembolism (Clark *et al*., 2007), venous thromboembolism (Bikdeli *et al*., 2021), and cerebral thromboembolic events (Puskas *et al*., 2018). Additionally, thrombotic events were reported in one study (Maria Suarez *et al*., 2019).

Excessive Anticoagulation and Adverse Cardiac Events

Excessive anticoagulation was noted as an ADE in one study (Clark *et al*., 2014), while major adverse cardiac events (MACEs) were highlighted as ADEs in another study (Rosati *et al*., 2020).

Other ADEs

Other ADEs associated with anticoagulation therapy include laboratory-confirmed heparin-induced thrombocytopenia (Houston *et al*., 2020), faster decline in mean eGFR (estimated glomerular filtration rate) (Gutiérrez, 2019), mortality (Chan *et al*., 2009), mild transient sensations of warmth during or shortly after infusion (Ansell *et al*., 2020), and severe allergic reactions (Verheugt *et al*., 2016).

Risk Factors of ADEs Associated with Anticoagulation Therapy

Patient-Related Risk Factors

Several studies have identified specific patient characteristics that increase the risk of ADEs. These include older age (over 65 years), history of hypertension, recent heart failure, and decreased left ventricular function (Lechat *et al*., 2001; Lechat *et al*., 2000). Conditions typically requiring anticoagulation, such as deep venous thrombosis and atrial fibrillation, are also associated with a higher risk of ADEs, particularly major bleeding (Gutiérrez, 2019). Additionally, unstable angina has been identified as a risk factor (Yusuf *et al*., 2001).

Coexisting Medical Conditions and Comorbidities

Certain medical conditions and comorbidities are significant risk factors for ADEs. Cardiovascular comorbidities, including atherosclerosis and coronary artery disease, increase the risk (Nordbeck & Hu, 2020). Cancer diagnosis, hypercoagulability, thrombosis, and hyperinflammation were also identified as risk factors (Clark *et al*., 2014; Houston *et al*., 2020). Cushing syndrome (CS) was explicitly noted in one study (Maria Suarez *et al*., 2019).

Medication-Related Risk Factors

The use of specific medications can contribute to ADEs. For example, warfarin therapy combined with antiplatelet therapy increases the risk of hemorrhages (Johnson *et al*., 2008). The use of warfarin, clopidogrel, and/or aspirin is also associated with a higher risk of ADEs (Chan *et al*., 2009). Additionally, anticoagulation induced by direct oral anticoagulant (DOAC) therapies has been linked to ADEs (Ansell *et al*., 2020).

Laboratory and Clinical Factors

Elevated D-dimer concentration, a clot formation and breakdown biomarker, has consistently been identified as a risk factor for ADEs (Lopes *et al*., 2021; Feitosa-Filho *et al*., 2021; Diep & Garcia, 2021). D-dimer levels were also associated with thromboembolic events (Lawler *et al*., 2021; Puskas *et al*., 2018). Other factors contributing to ADEs include impaired renal function, polypharmacy, and the intake of drugs with high-risk potential (Stingl *et al*., 2016).

Procedural and External Factors

Specific procedures and external factors have been mentioned as risk factors for ADEs. Violent sneezing, carrying heavy loads, sports/recreational activities, chiropractic manipulation, abrupt/prolonged head rotation, and prolonged phone use have all been identified as triggers for major adverse cardiac events (MACEs) (Rosati *et al*., 2020). The presence of epidural, spinal, or pericardial catheters, major surgery within 14 days before enrollment, and the coexistence of severe obesity with severe renal insufficiency were also associated with ADEs (Bikdeli *et al*., 2020).

DISCUSSIONS

Discussion

This scoping review examined adverse drug events (ADEs) associated with anticoagulation therapy. The most frequently reported anticoagulant was warfarin (Clark *et al*., 2007; Clark *et al*., 2014; Johnson, 2008; Chan *et al*., 2009; Johnson *et al*., 2008; Puskas *et al*., 2018; Maria Suarez *et al*., 2019; Galatro *et al*., 2004; Huynh *et al*., 2001). However, the emergence of direct oral anticoagulants (DOACs), such as rivaroxaban, has gained prominence in recent years (Lopes *et al*., 2021;

Potpara & Lip, 2020; Feitosa-Filho *et al*., 2021; Dangas *et al*., 2019; Stojkovic *et al*., 2020; Rodilla *et al*., 2021).

The review identified a diverse range of ADEs associated with anticoagulation therapy. Bleeding-related events were most common, including hemorrhage (Johnson, 2008; Johnson *et al*., 2008; Huynh *et al*., 2001), hemorrhagic complications (Lechat *et al*., 2001; Lechat *et al*., 2000), major bleeding (Houston *et al*., 2020; Potpara & Lip, 2020; Nordbeck & Hu, 2020; Feitosa-Filho *et al*., 2021; Lawler *et al*., 2021; Stingl *et al*., 2016; Stojkovic *et al*., 2020), and bleeding complications (Galatro *et al*., 2004). Thromboembolic events, such as thromboembolism (Clark *et al*., 2007), venous thromboembolism (Bikdeli *et al*., 2021), and cerebral thromboembolic events (Puskas *et al*., 2018), were also reported.

Several risk factors for ADEs were identified. Patient-related factors included older age, hypertension, heart failure, and decreased left ventricular function (Lechat *et al*., 2001; Lechat *et al*., 2000). Coexisting medical conditions and comorbidities, such as cardiovascular diseases, cancer, hypercoagulability, and thrombosis, were also associated with increased risk (Nordbeck & Hu, 2020; Clark *et al*., 2014; Houston *et al*., 2020). Concomitant medication use, particularly antiplatelet agents, was linked to a higher risk of hemorrhages (Johnson *et al*., 2008; Chan *et al*., 2009). Laboratory and clinical factors, such as elevated D-dimer levels (Lopes *et al*., 2021; Feitosa-Filho *et al*., 2021; Diep & Garcia, 2021) and impaired renal function (Stingl *et al*., 2016), were additional contributing factors.

The findings have implications for clinical practice and future research. Identifying frequently reported anticoagulants and associated ADEs will inform healthcare professionals' decision-making. Recognizing risk factors highlights the importance of individualized risk assessment and personalized treatment plans. Future research should focus on elucidating mechanisms underlying ADEs, identifying novel biomarkers for risk stratification, and developing strategies to minimize adverse events while maximizing therapeutic benefits. Addressing gaps and controversies in the literature will help refine guidelines for anticoagulation therapy and improve patient outcomes.

CONCLUSION

This scoping review provides a comprehensive overview of adverse events (ADEs) associated with anticoagulation therapy. Common anticoagulants include heparin, warfarin, and rivaroxaban. Identified ADEs include bleeding, thromboembolism, excessive anticoagulation, and other events. Risk factors encompass patient characteristics, comorbidities, medications, and laboratory parameters. Personalized risk assessment, close monitoring, and patient education are essential to reduce ADE occurrence. Healthcare practitioners should consider these factors when selecting and dosing anticoagulants. Further research is needed to elucidate mechanisms, find novel biomarkers, and develop strategies to reduce harm and maximize therapeutic effects. This will help fill knowledge gaps and improve anticoagulation therapy guidelines for future research, ultimately enhancing patient outcomes and optimizing anticoagulant use in clinical practice.

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