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ORIGINAL RESEARCH

Bibliometric Analysis of Non-Vitamin K Antagonist Oral Anticoagulants (NOACS) in the Prevention of Venous Thrombosis and Pulmonary Embolism

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Introduction: Venous thromboembolism (VTE) is a leading cause of cardiovascular-related deaths. Non-vitamin K antagonist oral anticoagulants (NOACs) offer effective therapy without injections or blood monitoring. This bibliometric analysis explores the research on NOACs for preventing VTE and pulmonary embolism.

Methods: Literature up to July 20, 2024, was searched in Web of Science Core Collection. Citespace software was used for screening and analysis.

Results: In this study, we analyzed 2124 articles and 767 reviews from 11,282 institutions across 528 countries and regions, encompassing 830 publications and 60 research directions. The USA led in publication count, followed by Germany and Canada. Cardiovascular System Cardiology, Hematology, and General Internal Medicine were the top research areas, while THROMBOSIS AND HAEMOSTASIS was the leading journal. From 2004 to 2024, we observed accelerated publication growth, particularly from 2008, highlighting the emergence of NOACs as a major research focus. Key contributors, including Bengt I. Eriksson, and major institutions like Harvard Medical School and University of Amsterdam, played pivotal roles in advancing anticoagulant research. Co-citation and keyword clustering analyses revealed research hotspots in NOACs, cancer-associated venous thromboembolism, stroke prevention, and COVID-19-related thrombotic events, reflecting a shift towards individualized anticoagulation therapy and the growing importance of NOACs in various clinical contexts.

Conclusion: The development of NOACs has progressed rapidly, with an increasing number of publications, indicating the lead research in the United States and other Western nations. Comparative studies on the safety and efficacy of NOACs have become a significant focus, shifting from traditional anticoagulants. Pharmacogenetics-guided use of NOACS shows new hope of precision medicine.

Keywords: bibliometric analysis, non-vitamin K antagonist oral anticoagulants (NOACS), venous thrombosis, pulmonary embolism, oral anticoagulants, thromboembolism

Introduction

Venous term thromboembolism (VTE) includes both pulmonary embolism (PE) and deep vein thrombosis (DVT). VTE is a major cause of morbidity and mortality, ranking as the third leading cause of cardiovascular-related deaths, after

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myocardial infarction and stroke.[1] The recurrence risk of VTE after the initial event is noteworthy. About 10% of patients experience a recurrence within the first year[2,3] and 30% within ten years after stopping anticoagulant therapy.[3,4] The successful management of VTE requires a careful balance between preventing recurrence and minimizing bleeding complications. Clinical guidelines suggest initiating VTE treatment with subcutaneous low-molecular-weight heparin (LMWH) or fondaparinux,[5–7] followed using a vitamin K antagonist (VKA).[7] Yet, both LMWH and VKAs have associated risks of severe bleeding events.[8,9] LMWH is exclusively administered through subcutaneous injection, making it less convenient. VKAs need regular blood monitoring to ensure the correct dosage and can have potential drug interactions.

Non-vitamin K antagonist oral anticoagulants (NOACs) offer effective anticoagulation, eliminating the need for subcutaneous injections and routine blood monitoring. The four primary NOACs used for VTE treatment are rivaroxabanc,[10,11] edoxaban,[12,13] apixaban,[14,15] and dabigatran.[16,17] Compared to VKAs, NOACs exhibit a more rapid onset of action, possess fixed dosages, do not have known food-related effects, have fewer drug interactions, obviate the need for routine monitoring for dosage adjustment, and display shorter half-lives.[18]

Bibliometrics is a research field that employs statistical methods to investigate academic publications, aiming to identify delineating publication patterns and elucidating interconnections among them.[19,20] Similar to epidemiology, bibliometrics researchers analyze data on publication aspects like authors, topics, and funding sources to answer domain-specific questions, much like epidemiologists study patient data to understand population health trends. The primary focus of bibliometrics lies in the examination and exploration of characteristics and relationships inherent within academic publications.[19,20]

The present study utilizes citespace for bibliometric visualization statistics to investigate the current research focal points and future development trends, taking into account the diverse advantages of NOACs in the prevention and treatment of VTE. This bibliometric analysis addresses the gap in understanding global research trends on NOACs for VTE prevention.

Bibliometric analysis of VTE aims to uncover research trends, key topics, and future directions in the field, thereby supporting the advancement of evidence-based medicine and clinical practice. By examining publication growth patterns, research hotspots, and international collaboration networks, this approach evaluates the developmental trajectory of the field, identifies emerging themes, and highlights research gaps. Additionally, bibliometric analysis optimizes resource allocation, prevents redundant research, and fosters international cooperation, facilitating progress in precision medicine and personalized therapy. Particularly in addressing emerging challenges, bibliometric analysis provides critical insights for understanding and improving the management of VTE.

Methods

Data Extraction

The literature search was conducted in the Web of Science Core Collection (WoSCC) to retrieve literature published up to July 20, 2024. The search strategy incorporated terms [(TS=(NOACs OR Non-vitamin K antagonist oral anticoagulants OR Rivaroxaban OR Pradaxa OR dabigatran OR Apixaban OR edoxaban)) AND TS=(deep venous thrombosis or pulmonary embolism or thromboprophylaxis)] with a language filter applied for English articles. This search yielded a total of 2988 articles from 832 journals, authored by 13580 contributors, affiliated with 11282 institutions across 528 countries/regions. After removing duplicates and considering only articles and reviews, 2124 articles and 767 reviews remained. This process is illustrated in Figure 1. For creating statistical charts and performing linear regression and polynomial regression calculations, we use Microsoft's Excel software.

Data Analysis

We employed CiteSpace software (version 6.4.R1) to perform bibliometric analysis, explore research collaboration networks, investigate co-citation patterns in the literature, and examine keyword co-occurrence networks. This analysis aimed to explore the current research hotspots in the field of NOACs globally, elucidating their evolutionary trajectory and development trends.

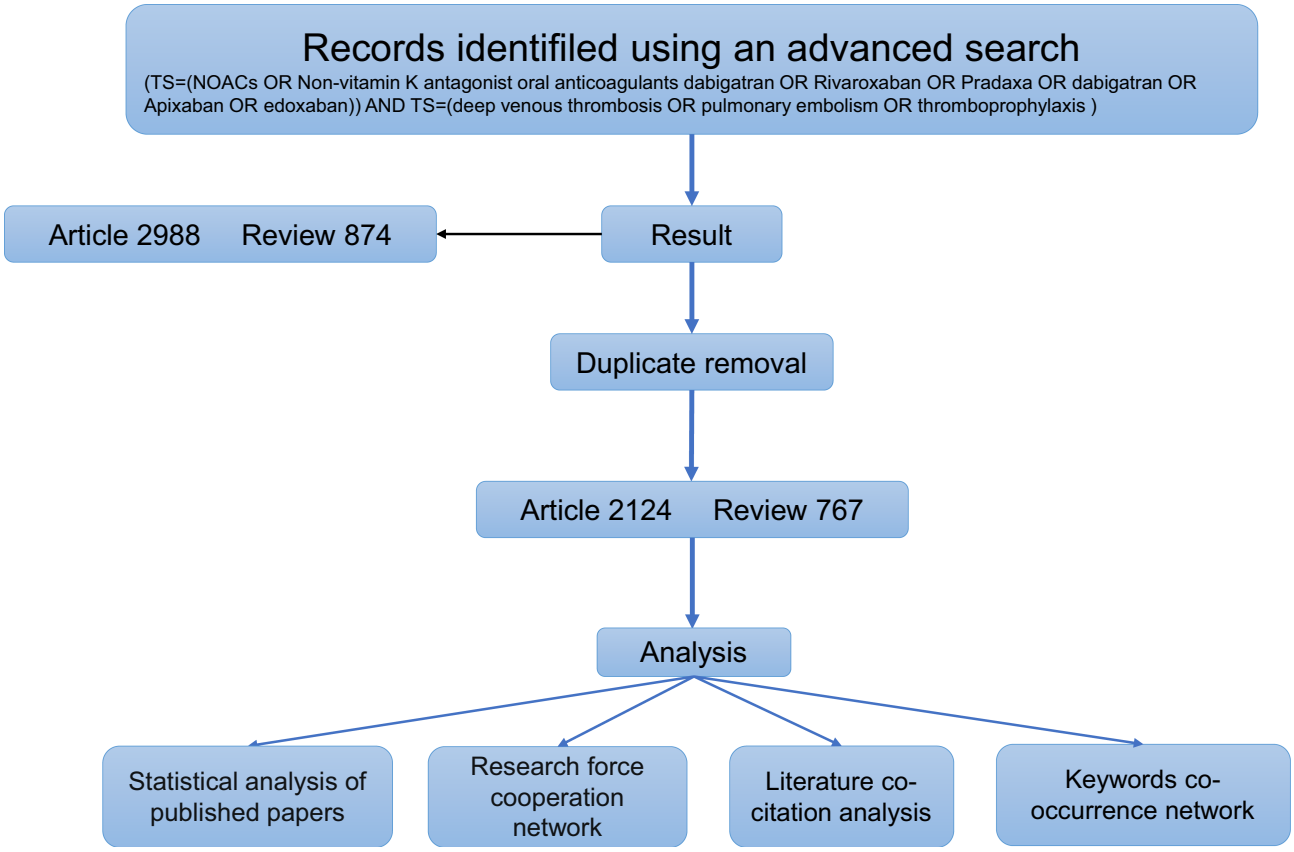

Figure 1 Flow chart of data collection and extraction of articles.

The Cite Space software offers two metrics, namely Modularity (Q value)[21] and Weighted Mean Silhouette (S value),[22] which are derived from the network structure and clustering clarity. These metrics can serve as a foundation for evaluating the efficacy of graphical visualization. Generally, the Q value ranges between 0 and 1, with $Q > 0.3$ indicating significant community structure.

A clustering efficiency is considered convincing when the S value reaches 0.7; if it exceeds 0.5, the clustering is typically regarded as reasonable. We assess the importance of nodes in a network by measuring their centrality, burstness, and Sigma value.[22] Centrality indicates a node's role as a bridge between unrelated nodes, emphasizing its structural significance. Bursts signify the emergence of new areas that can provide insights into topic development direction, and employing burst detection algorithms enables identification of temporal trends in topics. The Sigma value is a composite used to identify innovative literature and evaluate the level of topic innovation.

In the context of CiteSpace, several key parameters play crucial roles in analyzing and visualizing scientific literature. The g-index, proposed by Leo Egghe in 2006, measures the academic impact of literature, authors, or topics, and improves upon the h-index by giving more weight to highly cited works.[23] The Look Forward Rate (LRF) is used in burst detection algorithms to determine the time span for analyzing changes in hot literature, with higher values suited for long-term trends and lower values for short-term hotspots.[24] The L/N (Logarithm/Normalization) parameter involves logarithmic and normalization processing of edge weights in the network, enhancing balance and preventing dominance by high-weight nodes.[25] The Latest Boundary Year (LBY) defines the temporal scope of the analysis, allowing researchers to focus on recent developments or long-term trends.[26] Finally, the edge threshold (e) controls the strength of connections in the literature network, filtering out weak connections to highlight strong associationsThese parameters, when adjusted appropriately, optimize the analysis results and provide deeper insights into scientific research trends.[27]

In CiteSpace, the selection of parameters for bibliometric analysis should be comprehensively considered based on research objectives, data characteristics, and domain-specific features. The g-index emphasizes the weight of highly cited

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documents, with the k-value typically ranging from 10 to 25, determined by the distribution characteristics of highly cited references. The LRF sets the depth of the temporal retrospection, with common values of 2.0 or 3.0, which can be adjusted according to the research span. The L/N controls network density, with a standard value of 10, and can be modified if the network is overly complex or sparse. The LBY determines the retrospective years within a time slice, usually set to 5 or 10 years, and can be extended for long-term trend studies. The e parameter, which controls weighted centrality in the network, has a default value of 1.0 and can be adjusted based on the importance of nodes. These parameters are optimized through iterative testing and adjustments based on data size and research needs to generate high-quality analytical networks tailored to specific research objectives. In this study, the optimal parameter settings were determined through multiple adjustments and tests, considering the research direction and data characteristics. These parameters will be referenced in detail for each subsequent research direction.

Result

General Information

After the A total of 2124 articles and 767 reviews were included in our study. A comprehensive analysis was conducted, revealing the presence of 11282 institutions, spanning across 528 countries and regions. The findings also encompassed data from 830 publications and identified 60 distinct research directions. Notably, Figure 2 highlights the top ten entities within each category. In Figure 2A, Cardiovascular System Cardiology takes first place, Hematology ranks second, and General Internal Medicine occupies third position. As illustrated in Figure 2B, McMaster University is in the top position and Harvard University follows closely in second place, while Bayer AG claims third place. In Figure 2C, with the USA leading at 1064 publications. Germany secures second place with 388 publications, while Canada ranks third with 387 publications. Regarding the Author, Ageno W securing the top position, followed by Lip GYH in second place, and Cohen AT in third place (Figure 2D).

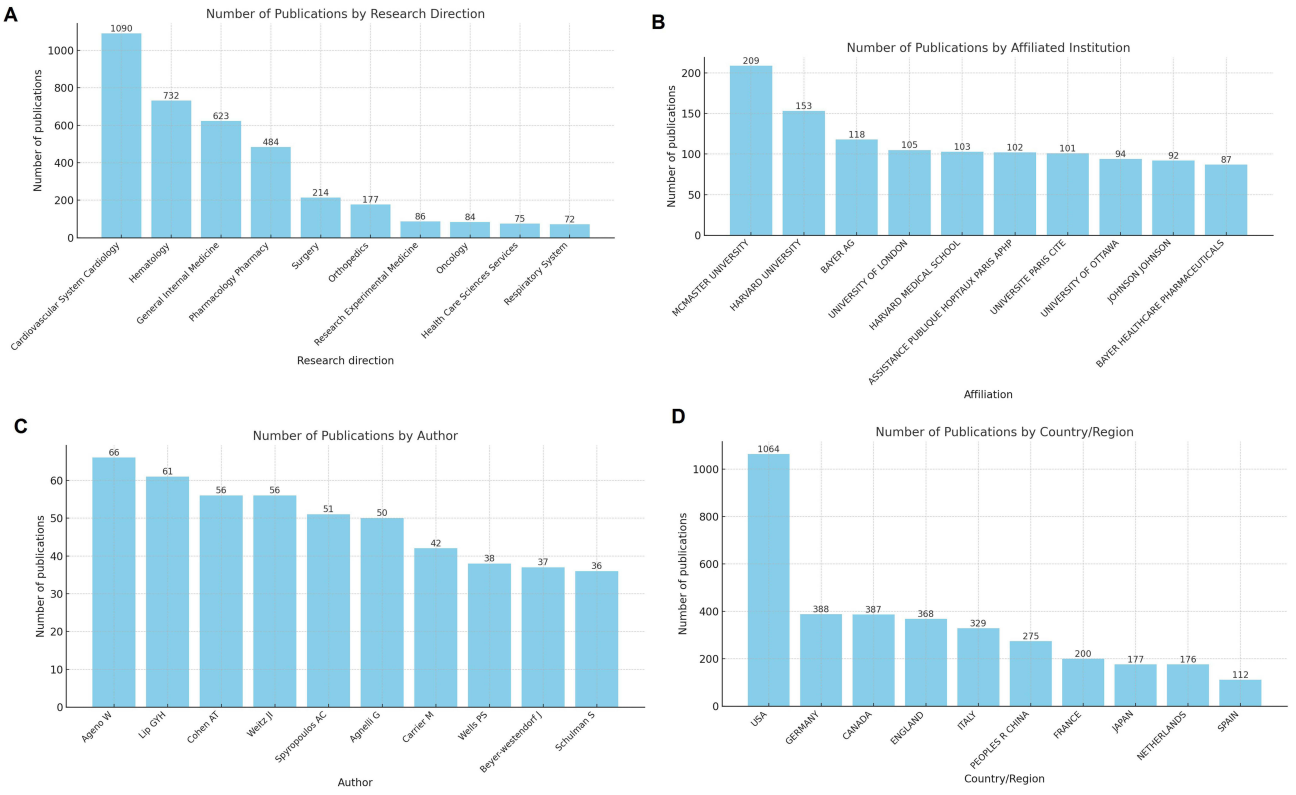

Figure 2 General information of non-vitamin K antagonist oral anticoagulants (NOACS) in the prevention of venous thrombosis and pulmonary embolism. (**A**). The rank of research by the number of publications. (**B**). The rank of affiliated institution based on publication count. (**C**). The rank of author by publications. (**D**). The rank of countries/regions on publications.

Publication Statistic

We conducted a comprehensive analysis of publication trends spanning from 2004 to 2024, revealing an accelerated growth rate in publications starting from 2008. This indicates the emergence of NOACs as a prominent research area around 2007. Figure 3 illustrates the annual and cumulative publication trends related to non-vitamin K antagonist oral anticoagulants (NOACs) from 2004 to 2024. Specifically, Figure 3A depicts the annual publication counts, showing the number of research articles published each year. Utilizing linear regression analysis (blue dashed line) with the equation $y=15.62x-31314.32$ ($R^2=0.9333$), it reveals that the annual publication volume of NOACs research has exhibited an overall upward trend during this period. Particularly, after 2010, there is a notable increase in the annual publication counts.

Conversely, Figure 3B presents the cumulative publication counts of NOACs literature and their temporal trends. The light blue bar chart indicates the cumulative publication counts for each year, while the red dashed line represents a fitted curve based on quadratic polynomial regression with the equation $y=7.46x^2-29890.69x+29940466.85$ ($R^2=0.9991$). This demonstrates that the cumulative publication volume exhibits an accelerating growth trend over time. Consequently, this implies that NOACs have gradually gained widespread attention in research and clinical applications. The volume of literature published has increased rapidly over the past two decades, especially exhibiting a significant upward trend in the past ten years, which reflects the continuously increasing importance and research value of this field in the management of cardiovascular diseases.

Collaborative Networks

Contribution of Authors and Co-Cited Authors

We achieved the result depicted in Figure 4A by adjusting the parameters as follows: g-index (k=15), LRF=3.0, L/N=10, LBY=5, and e=1.0. The Modularity Q is 0.8683 and the Weighted Mean Silhouette S is 0.9533. The network consists of 9 clusters, with Cluster #1 denoted as registry, Cluster #2 denoted as coagulation, and Cluster #3 denoted as rivaroxaban being the three largest clusters identified through our analysis approach. Among these clusters, Cluster #1 comprises of 38 nodes with a silhouette value of 0.959 and it is annotated as registry by LLR analysis results; Cluster #2 consists of 36 nodes with a silhouette value of 0.926.

The publication with the highest number of citations in Cluster #6 is "Ageno, Walter" which has accumulated a total of 61 citations. Following closely behind is "Lip, Gregory Y H" in Cluster #7 with a count of 50 citations. In third place within this cluster is "Agnelli, Giancarlo" which has been cited 45 times. In terms of bursts, "Eriksson, Bengt I"in Cluster #2 exhibits bursts measuring at a rate of approximately 8.86 burst-making it the item ranked highest for bursts across all clusters analyzed. In terms of bursts, a term used to indicate a sudden increase in the attention a publication receives over a specific period, "Eriksson, Bengt I" in Cluster #2 exhibits bursts measuring at a rate of approximately 8.86, making it the item ranked

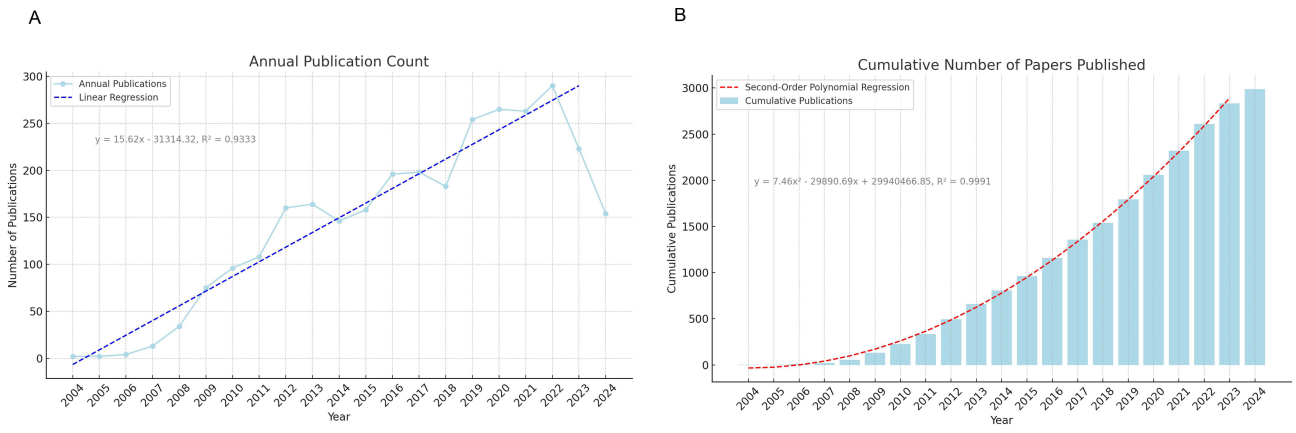

Figure 3 Cumulative publication counts of NOACs. (**A**). The line graph depicted illustrates the annual publication count. A linear regression analysis yielded the equation $y = 15.62x-31314.32$, $R^2 = 0.9333$. (**B**). The bar graph presents the cumulative number of papers published each year. A second-order polynomial regression equation was employed to ascertain that the yearly growth rate of papers adheres to $y=7.46x^2-29890.69x+29940466.85$, $R^2 = 0.9991$.

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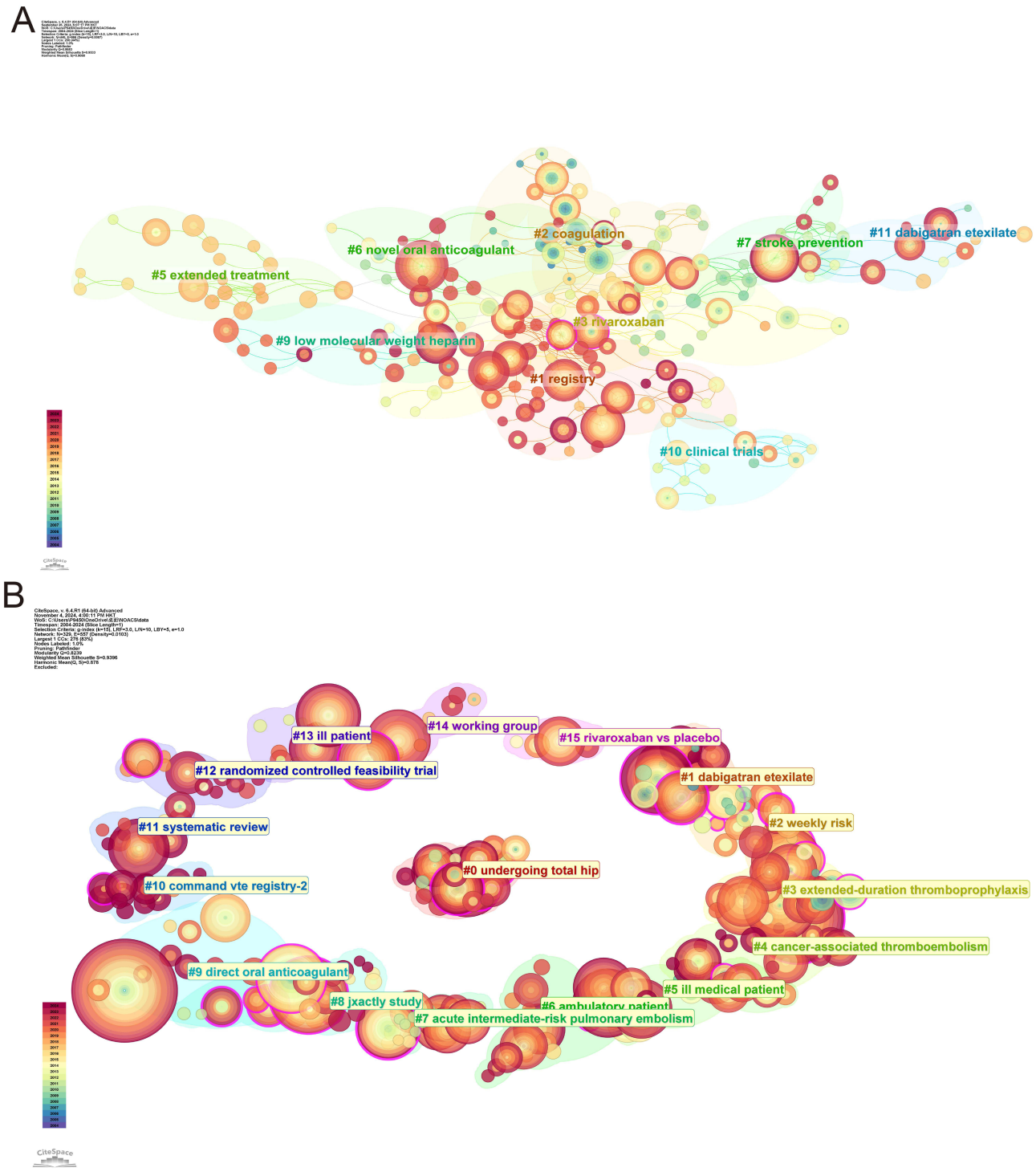

Figure 4 Collaborative networks of authors and institutional cooperation. (**A**). The Author Collaboration Network comprises 11 distinct clusters, which were generated through keyword-based clustering analysis. Cluster #1 REGISTRY represents the largest cluster in terms of size, followed by Cluster #2 UNDERGOING TOTAL Hip REPLACEMENT as the second largest, and so forth. Among these clusters, the top five are identified as follows: Cluster #1 REGISTRY; Cluster #2 UNDERGOING TOTAL HIP REPLACEMENT; Cluster #3 EXTENDED THROMBOPROPHYLAXIS; Cluster #5 SHORTENED HOSPITAL LENGTH; and Cluster #6 FIRST UNPROVOKED VENOUS THROMBOEMBOLISM. (**B**). The network diagram illustrates the clustering of institutional cooperation based on keywords. Cluster #0 emerges as the largest cluster, followed by Cluster #1 as the second largest, and so forth. Amongst these clusters, the top five are identified as follows: Cluster #0 represents "UNDERGOING TOTAL HIP" Cluster #1 signifies "DABIGATRAN ETEXILATE" Cluster #2 denotes "WEEKLY RISK" Cluster #3 refers to "EXTENDED-DURATION THROMBOPROPHYLAXIS", and finally, Cluster #4 is labeled as "CANCER-ASSOCIATED THROMBOEMBOLISM".

highest for bursts across all clusters analyzed. This indicates that the publication by Eriksson experienced a significant surge in interest and citations during a particular time window, highlighting its pivotal role in influencing research directions at that time. The second-highest burst rate belongs to Misselwitz, Frank in Cluster #2 at approximately 8.38 burst. Lastly, Crivera, Concetta in Cluster #5 displays bursts occurring at an approximate rate of about 7.60 burst.

In the analysis of co-authors as shown in Figure 4B, Eriksson, Bengt I demonstrated significant contributions, with notable scores in Sigma, CENTRALITY, and BURSTS metrics. Therefore, we have summarized some of his research. In the article "Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty", the efficacy of rivaroxaban and enoxaparin in preventing VTE after hip arthroplasty was compared, revealing that rivaroxaban has a greater advantage in reducing the incidence of VTE.[28] Consequently, this study laid the foundation for the use of rivaroxaban in postoperative anticoagulation therapy. Moreover, the double-blind study "Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial" demonstrated that dabigatran is equivalent to enoxaparin in VTE prevention, and as an oral medication, dabigatran offers greater convenience.[29] Additionally, the study "Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery" demonstrated the advantages of fondaparinux in hip fracture surgery, showing significant efficacy with a lower risk of bleeding, making it suitable for high-risk postoperative VTE patients.[30] Furthermore, the study "Oral, direct Factor Xa inhibition with BAY 59–7939 for the prevention of venous thromboembolism after total hip replacement" validated the effectiveness of BAY 59–7939 (ie, rivaroxaban) as a novel oral Factor Xa inhibitor for the prevention of thrombosis after hip replacement, offering a new option for anticoagulation therapy.[31]

Eriksson, Bengt I has made numerous significant contributions in the field of anticoagulation and antithrombotic therapy, particularly impacting the clinical practice of preventing VTE following hip and knee surgeries. His research primarily focuses on the pharmacodynamics and safety of novel oral direct thrombin and Factor Xa inhibitors (such as rivaroxaban, dabigatran, and fondaparinux), providing effective anticoagulation options for postoperative patients and reducing the risk of complications.

Distributions of Institutions

We employed the g-index parameters (k=15), LRF=3.0, L/N=10, LBY=5, and e=1.0 to compute clustering scores. The resulting Modularity Q is 0.8239 and Weighted Mean Silhouette S is 0.9396. The network consists of 16 clusters as illustrated in Figure 4B. Clustering labels were generated using the LLR algorithm. In Cluster #0 UNDERGOING TOTAL HIP, a significant collaboration exists by Harvard Medical School. Cluster #1 DABIGATRAN ETEXILATE represents the second largest cluster where Assistance Publique Hopitaux Paris (APHP), Universite Paris Cite, and University of Amsterdam exhibit strong collaboration. For Cluster #2 weekLY RISK, Johnson & Johnson stands out with the highest citation count at 136 citations. The noteworthy fact that Bayer Healthcare Pharmaceuticals has achieved a burst value of 21.14 highlights their active pursuit of innovative research and significant contribution to the advancement of this specific field of study. The centrality score reveals that the Imperial College London, situated in cluster #2, exhibits a value of 0.26, with a corresponding sigma value of 2.31. This institution can be deemed to play a pivotal bridging role and contributing significantly to innovation.

The research themes of the first three clusters focus on VTE and the application and management of anticoagulants in various clinical settings. Specifically, the studies address the prevention and treatment of VTE using anticoagulants, such as Rivaroxaban and Dabigatran, in patients undergoing hip arthroplasty, patients with atrial fibrillation, and hospitalized patients with heart failure. The primary focus is on evaluating the efficacy and safety of these anticoagulants, thereby aiming to mitigate the risk of venous thromboembolism in these populations. Collectively, these internationally renowned universities and healthcare institutions have made significant scholarly contributions in the fields of cardiovascular disease and venous thromboembolism management.

Distributions of Countries

The clustering score was calculated using the g-index parameters (k=15), LRF=3.0, UN=10, LBY=5, and e=1.0, resulting in a Modularity Q of 0.504 and Weighted Mean Silhouette S of 0.9227. The graphical representation of these results can be seen in Figure 5A. This analysis identified seven distinct clusters, with Cluster #0 being characterized as SURGRY

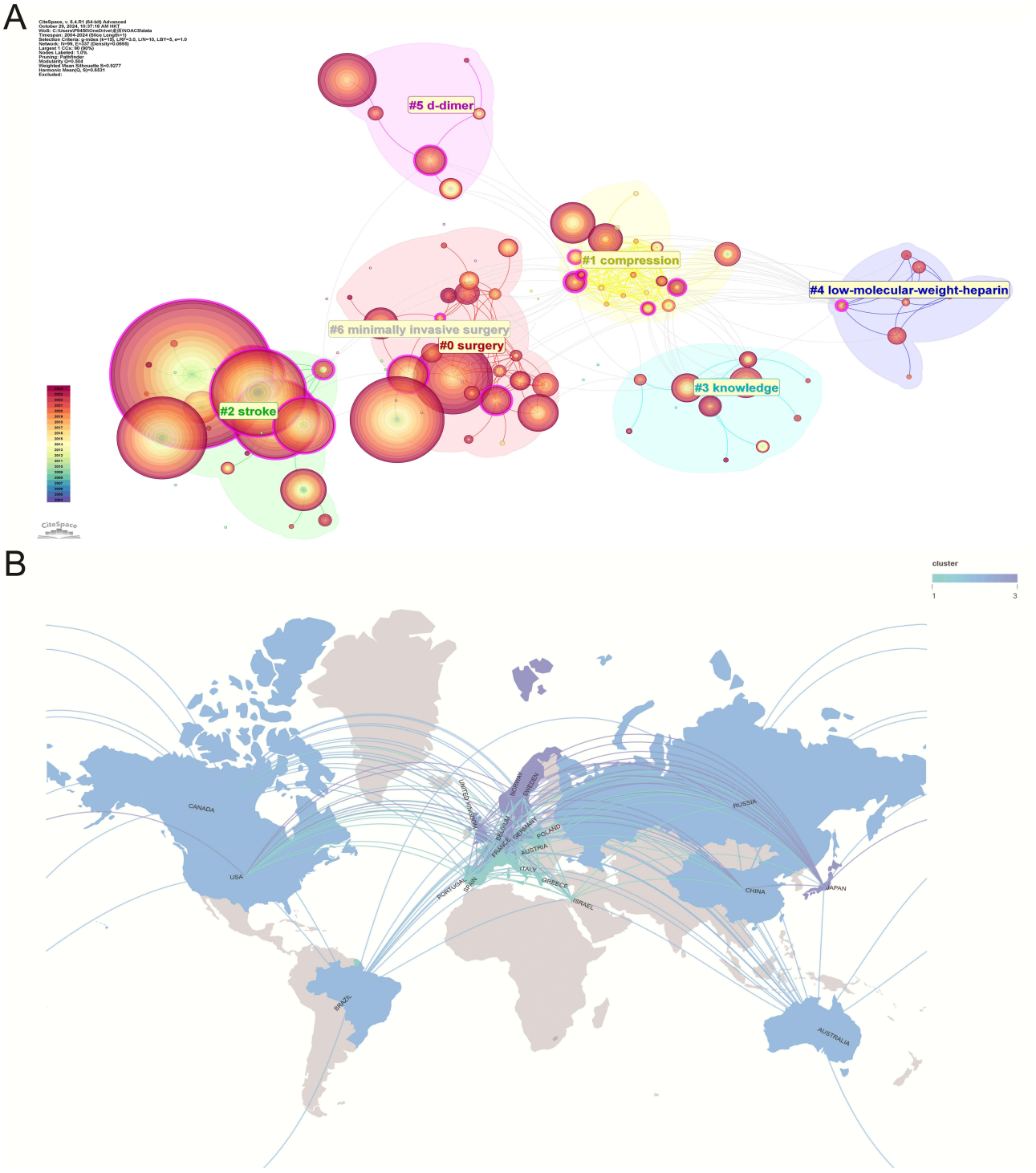

Figure 5 Graphs of national distributions and cooperation networks. (**A**). Graphs of national cooperation networks were clustered by key words. The network consists of 7 clusters. Cluster #0 surgery is the largest Cluster, Cluster #1 compression is the second largest cluster, and so on. China, the country in Cluster #0 CASE REPORT, has the largest bursts Counts. USA has the most Citation Counts in Cluster #2 stroke. (**B**). A geographical visualization map illustrates the patterns of national cooperation, with interconnecting lines symbolizing their cooperative relationships.

where China shows a strong association with Russia, receiving 275 citations. Notably, Cluster #2 STROKE primarily consists of European and American countries engaged in collaborative research efforts. Among them, the United States has received 1064 citations, Germany has obtained 388 citations, and Canada has garnered 385 citations. The geographic visualization of the National Collaborative Network is displayed in Figure 5B.

In summary, the network analysis reveals distinct collaboration patterns in the research of VTE and its related treatments. The seven identified clusters demonstrate regional research priorities and the extent of international cooperation. Notably, China's strong association with Russia and the prominence of European and American collaborations in Cluster #2 highlight the global nature of VTE research efforts. The citation metrics further emphasize the pivotal role of institutions in the United States, Germany, and Canada in advancing the field. These insights not only enhance our understanding of the current landscape of VTE research but also underscore the importance of fostering international collaborations to address global health challenges. Future research could benefit from expanding the collaborative network to include more diverse geographic regions, thereby enriching the collective knowledge and enhancing the overall impact of VTE-related studies.

Co-Citation Analysis

The visualization parameters used in the literature co-citation study were as follows: g-index (k=10), LRF=3.0, L/N=10, LBY=5, and e=1.0. Furthermore, Modularity Q was calculated to be 0.7421 and Weighted Mean Silhouette S was found to be 0.8996. The clustering results are presented in Figure 6A. Eriksson BI, 2008, NEW ENGL J MED, V358, P2765 in Cluster #3, with citation counts of 347. The article presents an introduction to Rivaroxaban, an oral direct factor Xa inhibitor used for thromboprophylaxis after total hip replacement surgery.[32]

Currently available anticoagulant drugs typically require injection administration (eg, low molecular weight heparin) or pose challenges due to their unpredictable pharmacological characteristics (eg, warfarin). Rivaroxaban, as an orally administered direct factor Xa inhibitor widely employed in clinical practice, is shown in this study to be comparable in efficacy to enoxaparin at a once-daily dose and exhibits similar rates of major bleeding (primary safety endpoint) at the 5 mg and 10 mg once-daily dose groups. Considering both efficacy and safety aspects, these findings suggest that further investigation should focus on the 10 mg once-daily dose of Rivaroxaban. The ongoing Phase III RECORD study currently investigates this dosing regimen. Additionally, Rivaroxaban is undergoing Phase III development for the treatment of venous thromboembolism and stroke prevention in patients with atrial fibrillation. In comparison with currently available anticoagulant drugs, Rivaroxaban offers advantages such as predictable pharmacological properties and eliminates the need for coagulation monitoring, making it appealing for short-term and long-term anticoagulant therapy.

One of the most cited articles in Cluster #3 is the study by Lassen et al (2008) published in the New England Journal of Medicine.[33] In this multicenter, randomized, double-blind, non-inferiority trial (RE-MODEL), 2,076 adult patients undergoing elective total knee replacement were assigned to receive either oral dabigatran etexilate (150 mg or 220 mg once daily) starting postoperatively or subcutaneous enoxaparin (40 mg once daily) starting preoperatively, with treatment lasting 6 to 10 days. The results showed that both doses of dabigatran etexilate met the non-inferiority criteria, with venous thromboembolism (VTE) and all-cause mortality rates of 31.1% and 34.6% in the 220 mg and 150 mg groups, respectively, compared to 33.7% in the enoxaparin group. The incidence of major bleeding events was similar across all groups, indicating comparable safety profiles. The study concluded that oral dabigatran etexilate is as effective and safe as enoxaparin for VTE prevention after total knee replacement surgery, offering a convenient oral anticoagulant option without the need for subcutaneous injections or routine coagulation monitoring, which may enhance patient compliance and comfort.

The top ranked item by bursts is Kearon C, 2016, CHEST, V149, P315 in Cluster #0, with bursts of 147.33.[34] This highly influential guideline provides comprehensive evidence-based recommendations for anticoagulant therapy in VTE disease, significantly impacting clinical practice. The guideline emphasizes that patients with proximal DVT or PE should receive at least three months of anticoagulant therapy, recommending DOACs over VKAs in non-cancer patients due to their convenience and better risk-benefit profile. It also advises against the routine use of inferior vena cava filters and compression stockings to prevent post-thrombotic syndrome, emphasizing individualized treatment based on patient risk

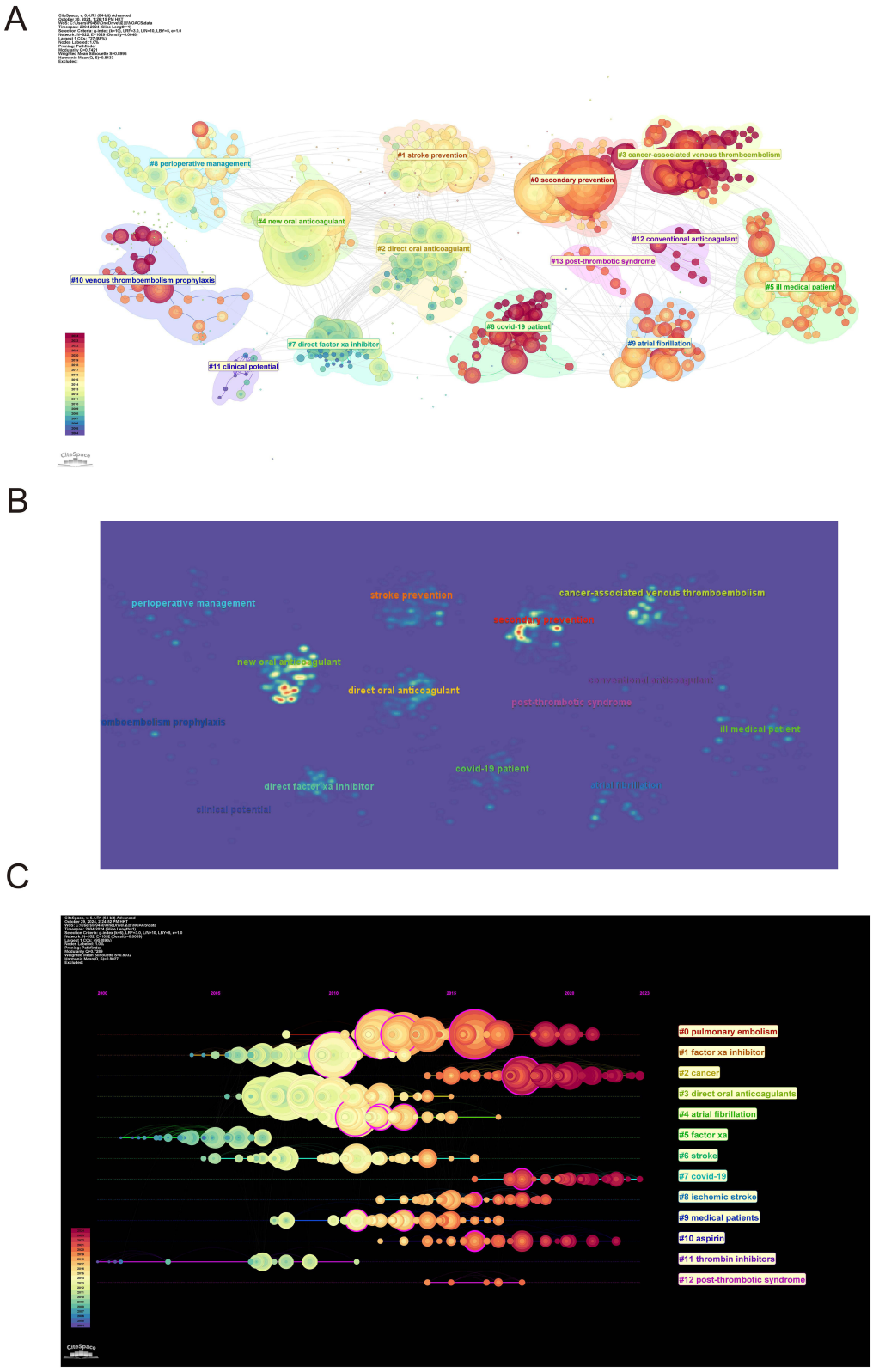

Figure 6 The literature co-citation network. (**A**) The literature co-citation network diagram was constructed and clustered based on key words. The network comprised 13 clusters, with Cluster #0 secONDARY PREVENTION being the largest cluster consisting of 66 members. Following that, Cluster #1 RECURRENT VENOUS THROMBOEMBOLISM had 64 members, while Cluster #2 CANCER-ASSOCIATED VENOUS THROMBOEMBOLISM had 64 members. (**B**) is a density view of (A), using color intensity to represent the concentration and co-citation frequency of references. Highlighted areas indicate references that are frequently co-cited in literature, usually representing core research contributions in this field. Warmer color areas indicate strong associations between references, showing that these references are frequently cited together, thus reflecting the density and focus of related research. (**C**) presents a timeline evolution map of co-cited references, depicting the changes in research hotspots in the NOACs field from 2004 to 2024. Each circle represents a group of co-cited references, with the size reflecting the number of citations, while the color gradually changes from cool (earlier) to warm (recent), illustrating the rise and decline of various research topics over time.

assessment. By covering various clinical scenarios in VTE management, including recurrent events and special populations, this article provides key references for clinicians, shaping current VTE treatment strategies.

The top ranked item by centrality is Cohen AT, 2016, NEW ENGL J MED, V375, P534 in Cluster #10, with centrality of 0.29. In our bibliometric analysis, we found that the article by Cohen et al (2016) published in the New England Journal of Medicine has significant impact.[35] This study is a randomized, double-blind, phase III clinical trial evaluating the efficacy and safety of extended prophylaxis with betrixaban in acutely ill hospitalized medical patients for the prevention of VTE. The results showed that extended use of betrixaban significantly reduced the incidence of VTE events compared to the standard course of enoxaparin, without significantly increasing the risk of major bleeding. This study fills the gap in long-term thrombosis prevention for acutely ill medical patients, supporting betrixaban as an effective option for extended VTE prophylaxis, and provides important guidance for the clinical management of high-risk patients.

The heat map generated by CiteSpace software reveals the research hotspots and keyword distribution in the field of anticoagulant drugs (Figure 6B). In the figure, keywords such as "new oral anticoagulant", "cancer-associated venous thromboembolism", "stroke prevention", and "direct oral anticoagulant" form high-density areas, indicating that these topics appear frequently in the literature and represent the core research hotspots in this field. These high-intensity areas demonstrate that research on anticoagulant drugs in applications such as cancer prevention, stroke management, and oral administration methods is extensive and in-depth. Additionally, keywords like "perioperative management", "atrial fibrillation", and "COVID-19 patients" also show a certain level of attention, reflecting that with the development of the pandemic and changes in surgical management needs in recent years, these topics are gradually becoming emerging directions in anticoagulant drug research. The color variations in the figure visually display the differences in keyword popularity, providing researchers with reference points to identify hot topics and explore potential research gaps, thereby aiding in grasping development trends and future research directions in the field.

The co-citation timeline map (Figure 6C) shows the temporal evolution trends of research hotspots in anticoagulant drugs. Since the year 2000, research focus has gradually shifted from early aspirin and thrombin inhibitors to DOACs and factor Xa inhibitors. After 2010, research on new oral anticoagulant drugs became increasingly active, drawing widespread attention especially in anticoagulant therapy for pulmonary embolism, cancer-associated thrombosis, and COVID-19. Recent hotspots focus on the prevention and treatment of thrombosis related to pulmonary embolism, cancer, and COVID-19, indicating that research in this field has expanded from traditional drugs to new application scenarios, providing important directions for future studies.

Through co-citation analysis, we can identify the main clusters of NOACs research and their development trends, revealing their applications in different clinical contexts. Current studies focus on the prevention and treatment of venous thromboembolism, especially in high-risk populations such as cancer patients, atrial fibrillation patients, and those with COVID-19. In these areas, NOACs have gradually replaced traditional vitamin K antagonists (like warfarin) due to their convenient use and good safety profile, becoming the first-line treatment choice. The application of direct oral anticoagulants in preventing recurrent venous thromboembolism, cancer-associated venous thromboembolism, and postoperative thrombosis prevention demonstrates the significant value and wide applicability of NOACs. Furthermore, the management of COVID-19 patients in Cluster #7 specifically highlights that the use of NOACs in COVID-19-related thrombotic events has become a research hotspot, indicating a sharp increase in the demand for anticoagulant therapy amid the pandemic. Burst analysis of the literature shows that in recent years, research on the application of NOACs in the COVID-19 pandemic, cancer-associated thrombosis treatment, and atrial fibrillation has received significant attention, becoming the main trend in this field. Additionally, literature with high betweenness centrality indicates the bridging role of these studies in cross-disciplinary applications, further emphasizing the importance of NOACs in multidisciplinary collaboration. The close connections between clusters not only demonstrate the wide application of NOACs in venous thromboembolism, cardiovascular diseases, and cancer management but also highlight their importance as a comprehensive anticoagulation strategy. High silhouette scores also attest to the focus and consistency of these clusters in research, further showcasing the in-depth exploration and refined development of NOACs in the field of anticoagulant therapy, providing clear directions and foundations for future clinical and basic research.

Keyword

Regarding the occurrence of keywords, we implemented the g-index (k=5) approach with LRF=3.0, LIN=10, LBY=5 e=1.0. The evaluation of clustering yielded a Modularity Q score of 0.8378 and a Weighted Mean Silhouette S value of 0.9604. We identified a total of 16 clusters (Figure 7A). The largest cluster (#0) comprises 26 members and exhibits a value of 0.953; it has been labeled as DABIGATRAN ETEXILATE by LLR algorithms. The second largest cluster (#1) also consists of 26 members but possesses a value of 0.979; this cluster is designated as CARDIOVASCULAR EVENT by the LLR algorithm. Moving on to the third largest cluster (#2), it encompasses 24 members with a silhouette value of 1 and is recognized as ATRIAL FIBRILLATION according to the LLR algorithm.

Analyzing the clusters, we find that clusters #0 to #4 all revolve around venous thromboembolism (VTE), but each has a different focus. For example, cluster #0 involves "dabigatran etexilate", with 26 members and an average year of 2010, reflecting the application of dabigatran etexilate as a NOAC in VTE prevention. In contrast, cluster #2 focuses on "atrial fibrillation", showcasing the important role of NOACs in cardiovascular diseases, especially in patients with atrial fibrillation. Additionally, cluster #3 is related to "colorectal cancer", indicating a growing research interest in the application of NOACs among cancer patients. The silhouette scores of these clusters are mostly above 0.9, demonstrating internal consistency and data stability, with cluster #4 reaching a silhouette score of 0.994, indicating very high thematic consistency in research on "dabigatran etexilate". Moreover, "knee replacement" in cluster #8 highlights the application of NOACs in postoperative thrombosis prevention, which complements cluster #15's focus on "knee replacement surgery", both reflecting the efficacy and safety of NOACs in orthopedic surgical patients.

From the perspectives of burst detection and centrality analysis, NOACs exhibit high citation bursts and centrality values in multiple areas such as cardiovascular diseases, cancer-associated thrombosis, and postoperative thrombosis prevention. For instance, research on "cancer-associated venous thromboembolism" in cluster #14 shows significant literature bursts, highlighting the important role of NOACs in thrombosis management among cancer patients. Cluster #6's "case reports" reflect the exploration of NOACs in individual cases under different clinical contexts, providing important references for clinicians when selecting anticoagulant treatment plans.

Overall, the co-citation relationships among these clusters reveal a strong coherence in the research themes of NOACs. The strong link between "venous thromboembolism" and "oral anticoagulants" indicates the widespread application of NOACs in VTE management, while comparative studies of different drugs (such as dabigatran, rivaroxaban, etc). in various clinical settings have gradually become research hotspots. This analysis demonstrates the diverse applications of NOACs in the prevention and treatment of thrombosis, with extensive and in-depth research in specific populations such as cancer patients, elderly patients, and postoperative orthopedic patients. Future research may focus more on the application of NOACs in comorbidities, drug interactions, and personalized therapy; these areas are likely to promote the further popularization and optimization of NOACs in clinical practice.

The keyword timeline map reveals the temporal evolution characteristics and dynamic changes of research hotspots in the field of NOACs (Figure 7B). By analyzing the evolution of keywords over different time periods and their academic impact, we can better understand the research trends and development trajectory in this field. From 2004 to 2024, the research field of NOACs has undergone a transition from traditional anticoagulants to dabigatran etexilate. Initial research primarily focused on the mechanisms of action and indications of traditional anticoagulants, but with the emergence of novel agents, research directions have gradually shifted towards exploring the efficacy, safety, and application of NOACs in specific populations. For instance, the use of NOACs like dabigatran etexilate in patients with atrial fibrillation has received extensive attention, aiming to reduce the risk of stroke. Additionally, the management of cancer-associated venous thromboembolism has become a research hotspot in recent years, highlighting the potential application value of these agents in oncology patients. Moreover, systematic reviews and the formulation of clinical practice guidelines for NOACs in recent years have further promoted the standardization and regulation of this field. By integrating and analyzing extensive clinical trial data, researchers have strived to clarify the therapeutic advantages and risks of NOACs in specific indications, providing more scientifically grounded medication guidance for clinicians. Collectively, this information outlines the process of gradual deepening and diversification in the field of NOACs research, not only demonstrating its potential applications across different clinical scenarios but also reflecting the academic community's ongoing interest and exploration of its clinical uses. These dynamic research hotspots and

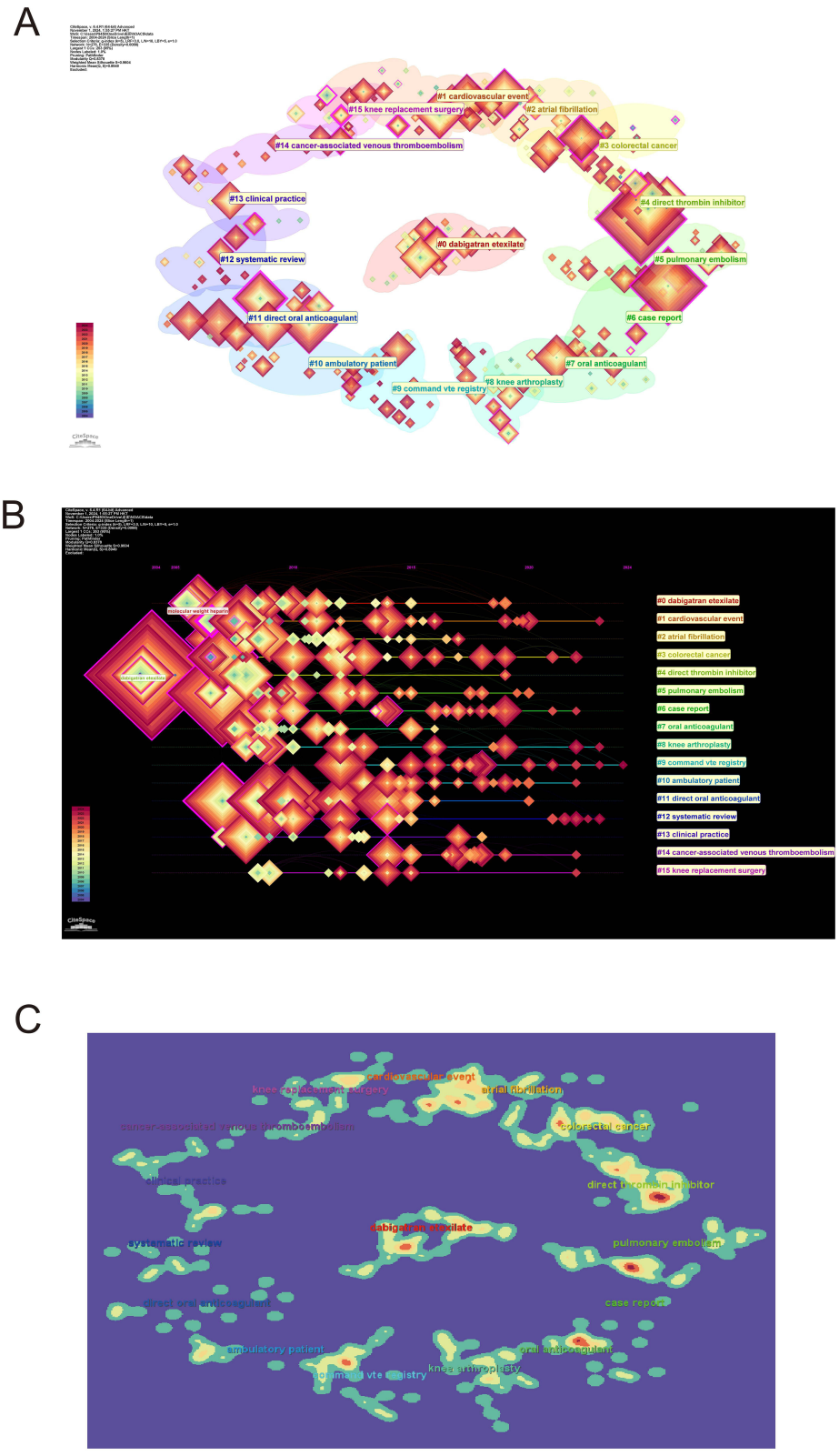

Figure 7 Graphs of keywords co-occurrence. (**A**). Keyword Clustering shows keyword clusters in NOACs research. Each bubble represents a keyword, with size indicating academic influence and color representing different time periods. These clusters highlight major themes such as "perioperative management", "stroke prevention", and "cancer-associated venous thromboembolism". (**B**). Keyword Timeline Evolution presents a timeline of keywords from 2004 to 2024, showing the rise of research topics. Each diamond represents a keyword, with size indicating publication volume. Topics like "dabigatran etexilate" and "pulmonary embolism" have gained prominence in recent years. (**C**). Keyword Density View is a density view of (**A**), using color intensity to show the concentration of frequently co-occurring keywords. Warmer areas indicate higher concentrations, reflecting core research areas. (**D**). Keyword Burst Detection shows keyword burst analysis, indicating the strength and duration of research focus from 2004 to 2024. Keywords like "dabigatran etexilate" and "factor Xa inhibitor" have shown significant bursts, indicating intense academic interest.

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development trends provide direction for the future research and application of NOACs, holding significant academic value and clinical relevance.

The heat map of keywords displays the hotspot distribution of anticoagulant drug research (Figure 7C), revealing the main focus areas in this field in recent years. High-frequency areas such as "dabigatran etexilate", "direct thrombin inhibitor", "pulmonary embolism", and "cardiovascular event" indicate that research on the application of new oral anticoagulant drugs in cardiovascular diseases and pulmonary embolism prevention is particularly active. Meanwhile, keywords like "atrial fibrillation" and "cancer-associated venous thromboembolism" highlight the importance of anticoagulant drugs in the treatment of cancer patients and high-risk cardiovascular patients. Additionally, the emergence of keywords such as "systematic review" and "case report" also reflects the emphasis on clinical evidence in this field. These hotspots provide clear directions for future research on anticoagulant drugs.

In summary, research on anticoagulant drugs has evolved from an early focus on postoperative thrombosis prevention and new drug development to individualized anticoagulant therapy targeting different pathophysiological conditions. This research trend not only reflects advancements in drug technology but also represents the transition from laboratory research to clinical application, providing important directions and guidance for future personalized and precision therapy.

Citation Bursts in Anticoagulation Research

This series of charts focuses on the field of anticoagulation research, highlighting different entities (authors, journals, institutions), research priorities (keywords), and citation bursts of key literature. It reflects the research trajectory and evolving hotspots in this field since 2004. Overall, anticoagulation therapy has undergone significant phase transitions over the past two decades, from the clinical trials of NOACs to their broader application and multicenter studies, providing valuable academic references for the medical and pharmaceutical fields.

Firstly, the Top 25 citation bursts of highly cited authors (Supplementary Figure 1), indicate that multiple scholars have led the development of anticoagulation research at different periods. In the early years (2004–2012), Eriksson BI, Geerts WH, and Ansell J exhibited significant citation bursts, highlighting the widespread attention on clinical trials of novel anticoagulants at that time. After 2019, researchers such as Young AM and Key NS have emerged, suggesting a growing academic focus on the continuous exploration of new treatment regimens and the implementation of multicenter randomized clinical trials. The timing and intensity of these citation bursts not only reflect the academic influence of individual researchers but also mirror the research trends of corresponding periods. Secondly, the Top 25 citation bursts of highly cited journals (Supplementary Figure 2) reveal a surge in pharmacology and clinical research citations between 2006 and 2015, with journals such as *Clin Pharmacol Ther* and *Eur J Clin Pharmacol* experiencing high citation activity. In recent years, journals like *Blood Advances* and *Lancet Haematol* have shown strong citation growth, further indicating that hematology research, particularly in anticoagulation therapy, is currently undergoing rapid development. The citation bursts of journals also serve as a directional reference for researchers in selecting publication platforms. In the Top 25 citation bursts of highly cited institutions (Supplementary Figure 3), both pharmaceutical companies and academic institutions have contributed to the advancement of anticoagulation research. Bayer Healthcare Pharmaceuticals and Bayer AG experienced high citation bursts between 2006 and 2016, reflecting the significant academic and clinical focus on the development of new-generation anticoagulants such as rivaroxaban. Meanwhile, academic institutions like Kyoto University and the University of Bern have demonstrated increasing influence in recent years, suggesting that clinical and fundamental research on anticoagulation therapy is progressively expanding to more regions and institutions. Regarding the Top 25 citation bursts of highly cited keywords (Supplementary Figure 4), early research hotspots included *Dabigatran etexilate* (2005–2013) and *Factor Xa inhibitor* (2006–2012). In recent years, keywords such as *Direct oral anticoagulants* (2018–2024) and *Multicenter* (2022–2024) have gained prominence, indicating that anticoagulant drug development has transitioned from initial molecular design and pharmacodynamic studies to large-scale, multicenter clinical validation. The increasing focus on the safety and efficacy of direct oral anticoagulants in clinical practice highlights the dynamic interaction between clinical needs and pharmaceutical innovation.Finally, the Top 25 citation bursts of highly cited references (Supplementary Figure 5) clearly identify pivotal studies that have driven advancements in the field at different times. Early key publications, such as Eriksson BI (2008, *NEJM*)

and Kakkar AK (2008, *Lancet*), led the research on the clinical applications of novel oral anticoagulants like rivaroxaban and dabigatran. Subsequent studies, such as Raskob GE (2018, *NEJM*), continued to gain influence post-2018, providing academic support for the expanded use of new drugs across more indications and patient populations. The "burst" of these references not only reflects their scientific value but also lays a crucial foundation for future research.

In conclusion, the citation data presented in these charts offer a comprehensive overview of the shifting research hotspots and deepening exploration within the field of anticoagulation. From early investigations into the mechanisms and clinical trials of novel anticoagulants to recent research on multicenter studies, direct oral anticoagulants, and drug safety in complex patient populations, this analysis of citation bursts among authors, journals, institutions, keywords, and references provides valuable directional insights for future researchers and a strong academic basis for ongoing improvements in clinical practice.

Discussion

Research Trends

Our bibliometric analysis reveals a consistent increase in achievements within the field of NOACs and DVT since 2004. The top 10 cited articles exhibit impact factors exceeding 150, with the majority published in The New England Journal of Medicine, indicating that this journal has been instrumental in driving significant contributions to this field. In terms of research paper publications, the United States leads with a substantial count of 1064, surpassing other countries by a significant margin. Our data analysis demonstrates a Modularity Q score of 0.504 and Weighted Mean Silhouette S score of 0.9277, providing evidence for substantial collaboration between countries and enabling inference of clear country relationships across different fields through clustering results. McMaster University located in Canada emerges as the institution with the highest number of publications, followed by Harvard University in the United States. Notably, Bayer AG ranks third among institutions—a result aligned with its involvement as a pharmaceutical company specializing in NOACs research.

Among authors, Eriksson Bengt I stands out with an impressive in this field; furthermore, "Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty" garners significant citations as the most influential article.[32] This study compared Rivaroxaban and Enoxaparin in hip arthroplasty patients for thromboprophylaxis. Results showed lower incidence of major efficacy outcomes with Rivaroxaban (1.1% vs 3.7%) and lower severe venous thromboembolism rate (0.2% vs 2.0%) compared to Enoxaparin. No significant difference in major bleeding rates was observed. Extended use of Rivaroxaban for thromboprophylaxis can effectively reduce blood clot occurrence with similar safety to Enoxaparin.

The article titled "Dabigatran etexilate versus enoxaparin for VTE prevention after total hip replacement: a randomized, double-blind, non-inferiority trial". It compares NOACs with enoxaparin for preventing VTE after hip arthroplasty.[29] The study shows that both Dabigatran etexilate and enoxaparin are equally effective in reducing overall VTE events and all-cause mortality after hip replacement. Dabigatran etexilate further reduces the risk of major VTE and associated mortality. Author Eriksson Bengt I contributed to the clinical safety comparisons of NOACs and traditional anticoagulants, advancing the field of NOACs.

Research Concentration

According to the publication ranking of keywords, it is evident that rivaroxaban, apixaban, and dabigatran typically exhibit thromboprophylaxis effects in venous thromboembolism, pulmonary embolism, and deep vein thrombosis. These drugs are often compared with traditional medications such as warfarin, enoxaparin, and molecular weight heparin for risk assessment and safety evaluation. Among the Strongest Citation Bursts identified in this study, the keyword "dabigatran etexilate" first appeared in 2004 with a Strength value of 85.26. This keyword was associated with total hip replacement procedures. Dabigatran etexilate belongs to a novel class of non-peptide direct thrombin inhibitors. In two large randomized double-blind clinical trials conducted on this drug, it has demonstrated comparable efficacy to enoxaparin in preventing venous thromboembolism. Dabigatran etexilate exhibits distinct characteristics when compared to conventional oral anticoagulants. Firstly, it functions as a direct thrombin inhibitor (DTI), whereas traditional oral

anticoagulants like warfarin target clotting factors within the vitamin K cycle pathway. Secondly, the anticoagulant effect of dabigatran etexilate can be promptly reversed using a specific antidote (Idarucizumab), while traditional oral anticoagulants require discontinuation or waiting for drug metabolism to reverse their effects.[36,37] To summarize, there are significant differences between dabigatran etexilate and traditional oral anticoagulants in terms of their mechanism of action and reversibility. Relevant studies have extensively examined the comparative efficacy of NOACs in relation to conventional anticoagulants.

Research Hotspots

Research Hotspots Shift

The transfer of research hotspots can be observed through Supplementary Figure 4 which presents the Top 25 Keywords with the Strongest Citation Bursts. Since 2004, there has been a shift in research focus from dabigatran etexilate to bay597939and subsequently to edoxaban. A substantial amount of research has been conducted on comparing the efficacy and safety profiles of these novel medications against conventional therapies.

Dabigatran Etexilate

Dabigatran etexilate is a low molecular weight prodrug that converts into an effective inhibitor of thrombin. Upon oral administration, Dabigatran etexilate undergoes rapid and complete hydrolysis by esterases, resulting in the formation of its active component dabigatran.[4,38–40] The biotransformation process commences in the intestines, where a combination of Dabigitan etexilate and Dabigitan enters the portal vein. The kidneys play a crucial role in eliminating dabigatran, as it is primarily excreted through renal excretion. Approximately 80% of the circulating dabigatran and minimal quantities of dabigatran glucuronides are eliminated via the urinary system.[41] Compared to Warfarin, Dabigatran does not require blood monitoring and has a faster onset time between 0.5 to 2 hours, much shorter than Warfarin's 36 to 72 hours. It possesses stable and predictable pharmacokinetic characteristics. Compared to Enoxaparin, Dabigatran does not require injection and has twice the duration of action compared to Enoxaparin. Dabigatran is equivalent or superior in anticoagulant effect compared to Warfarin and Enoxaparin while having comparable or lower safety profile than both drugs. Dabigatran etexilate was frequently mentioned in the findings of this study, particularly in comparative trials with enoxaparin for the prevention of VTE following total knee or hip arthroplasty, where it demonstrated notable efficacy. Citation analysis of the literature indicates that in large-scale clinical trials such as RE-MODEL, dabigatran etexilate exhibited comparable efficacy and safety to enoxaparin. Additionally, its oral administration and lack of requirement for routine monitoring confer advantages in improving patient adherence.

Keyword clustering analysis further suggests that the cluster containing "dabigatran etexilate" (eg, Cluster #0 or #4) represents a research hotspot, highlighting its extensive application across various indications, including knee and hip arthroplasty and atrial fibrillation. Its convenience and relatively favorable safety profile have contributed to its emergence as a key member of the novel oral anticoagulants (NOACs), garnering significant attention and research interest in postoperative thromboprophylaxis, stroke prevention in non-valvular atrial fibrillation, and cancer-associated thrombosis.

In summary, based on citation network analysis, burst term detection, and timeline mapping, it is evident that dabigatran etexilate has attracted substantial research attention in recent years due to its predictable pharmacokinetic properties and favorable risk-benefit profile. The growing body of evidence-based medicine supports its role as a crucial agent in advancing individualized and precision anticoagulation therapy.

Rivaroxaban

Rivaroxaban is an anticoagulant medication that selectively inhibits activated coagulation factor X (FXa), demonstrating notable attributes like high oral bioavailability and rapid onset of action.[42] It has a systemic clearance of approximately 10 L/h. The absorption of rivaroxaban in healthy individuals occurs rapidly, with peak concentrations observed within 2 to 4 hours after tablet ingestion.[43,44] In younger subjects, terminal half-life of rivaroxaban can reach 5–9 hours, while in elderly patients with 11–13 hours. Although the elderly have higher plasma concentration, the average AUC increased about 1.5 times, mainly due to reduced total clearance and renal clearance, thus no dose adjustment is necessary.[45]

Rivaroxaban exhibits a rapid onset of action and possesses favorable pharmacokinetic and pharmacodynamic properties, making it suitable for a diverse range of individuals with minimal drug interactions. Moreover, rivaroxaban shows potential advantages across multiple therapeutic indications.[46,47] In contrast to subcutaneous injections required by low molecular weight heparin and fondaparinux, as well as the regular monitoring of international normalized ratio (INR) necessitated by vitamin K antagonists, rivaroxaban offers a highly convenient administration method.[42] This convenience has contributed to its popularity in the field of anticoagulant therapy. The likelihood of oral factor Xa inhibitors, such as rivaroxaban, emerging as a feasible substitute for vitamin K antagonists in patients susceptible to thromboembolism is bolstered.

The findings of this study indicate that rivaroxaban also holds a significant position in the literature on NOACs, particularly due to its exceptional efficacy in the prevention of VTE following major orthopedic surgeries, such as hip and knee arthroplasty, as well as its widespread use in patients with atrial fibrillation.

Citation analysis highlights that the study "Eriksson BI, 2008, NEW ENGL J MED, V358, P2765" has been cited 347 times within Cluster #3, underscoring the research significance of rivaroxaban in thromboprophylaxis after hip replacement surgery. Compared to enoxaparin, rivaroxaban, as an oral direct Factor Xa inhibitor, eliminates the need for injection and routine hematologic monitoring. Studies have demonstrated that it effectively reduces thrombotic events while maintaining a relatively manageable bleeding risk, confirming a favorable risk-benefit profile in multiple clinical trials.

Furthermore, keyword clustering and timeline analysis in this study suggest that, like other NOACs such as dabigatran and apixaban, rivaroxaban has demonstrated substantial clinical value and research interest in stroke prevention for atrial fibrillation, cancer-associated thrombosis, and anticoagulation management in high-risk populations.

Apixaban

Apixaban, an oral direct inhibitor of factor Xa, is used to manage various thromboembolic disorders. These include reducing the risk of stroke in patients with non-valvular atrial fibrillation, thromboprophylaxis after hip or knee replacement surgery, treating and preventing DVT or pulmonary embolism. After oral administration, Apixaban reaches peak plasma concentration within 3–4 hours, primarily absorbed in the small intestine.[48,49] The elimination half-life of Apixaban is approximately 6 hours, but the apparent half-life extends to around 12 hours, achieving steady state after three days.[50–52] Apixaban offers several advantages over conventional therapies in the management and prevention of VTE. However, further extensive investigation is warranted to evaluate its efficacy and safety profile in special populations, including elderly patients aged 75 years or older, individuals with cancer, those who are underweight or overweight, as well as those with impaired renal function.[53]

Apixaban, as an oral direct Factor Xa inhibitor, holds a significant position in the literature and analysis results covered in this study. Its advantages, including the absence of a need for routine coagulation monitoring and high adherence to oral administration, contribute to its demonstrated efficacy and safety in the prevention and treatment of VTE and stroke associated with atrial fibrillation.

Large-scale randomized controlled trials and real-world data have confirmed that apixaban reduces bleeding risk and improves patient adherence in stroke prevention for non-valvular AF patients. Additionally, it has shown an excellent risk-benefit balance in thromboprophylaxis following major orthopedic surgeries (hip or knee arthroplasty) and in the management of cancer-associated thrombosis. Multiple authoritative guidelines, including the 2016 *CHEST* guideline by Kearon C et al, have recognized apixaban as an equally or preferentially recommended anticoagulant alongside other novel oral anticoagulants.

One of the key advantages of apixaban is its relatively lower potential for drug-drug interactions and its suitability for a broader patient population. However, its efficacy and safety in special populations, such as those with extreme obesity or severe renal impairment, require further evidence.

In conclusion, against the backdrop of the rapid development of NOACs, apixaban continues to receive considerable attention due to its safety, convenience, and broad applicability. Its growing body of evidence supports its role in future applications for special populations and the advancement of individualized anticoagulation therapy.

NOACs in Special Populations

NOACs have become a key treatment for stroke prevention in non-valvular atrial fibrillation (NVAF). They offer significant advantages over traditional VKAs, including a predictable pharmacokinetic profile, fixed dosing, and no need for routine monitoring, making them ideal[54] for patients with limited access to healthcare.[55–58] In patients with comorbidities, such as coronary artery disease, NOACs reduce thromboembolic risks with similar bleeding risks to warfarin.[56,59] However, potential drug-drug interactions should be monitored.[60,61] NOACs are generally safe for patients with mild to moderate renal impairment, though dose adjustments are necessary for severe renal dysfunction.[54,62] In procedural settings, such as atrial fibrillation catheter ablation, NOACs can be continued safely, reducing the risk of thromboembolic events compared to VKAs.[63,64] NOACs also benefit elderly and cancer patients, with low-dose regimens effective in minimizing bleeding risks while preventing stroke.[65] Despite their advantages, many eligible patients do not receive NOACs due to concerns about bleeding risks or lack of awareness among healthcare providers.[64] Education for both patients and healthcare providers is essential to ensure appropriate use. Meta-analysis of 35 studies (434,320 obese patients) showed DOACs are more effective and safer than warfarin for atrial fibrillation or blood clots in obesity, with lower risks of serious bleeding events and thrombotic complications.[66] In conclusion, NOACs offer a safer, more convenient alternative to VKAs for managing NVAF, especially in patients with comorbidities, renal impairment, and those undergoing specific procedures. However, individualized treatment and ongoing education are critical to optimizing their use.

Research Frontiers and Prospects

In recent decades, VKA have remained the predominant orally administered anticoagulants. While these medications have demonstrated high efficacy in treating and preventing VTE, they exhibit significant variability in dosage response among individuals and are susceptible to interactions with food and other drugs.[67] The concomitant use of LMWH with VKA allows for dose adjustments based on INR levels, addressing some challenges associated with VKA therapy. However, this approach necessitates subcutaneous injections which may be perceived as a drawback. On another front, NOACs can be classified into two groups-direct oral thrombin inhibitors such as dabigatran or direct oral factor Xa inhibitors. These medications offer advantages like ease of administration via the oral route and consistent interpatient dosage responses, NOACs represent an innovative advancement in anticoagulation therapy. Furthermore, their safety profile is further bolstered by recently introduced reversal agents. Future research will focus on gradually replacing traditional anticoagulant drugs in clinical practice and promoting the use of NOACs.[68]

Pharmacogenomic

There are still many unanswered questions regarding NOACs in pharmacogenomic studies, with research mainly focused on dabigatran, while genomic data for other NOACs are relatively scarce.[69] Since VKAs have a long and extensive history of use, they have become a focus of pharmacogenomic research. VKAs exhibit significant interindividual variability in therapeutic effects and have a narrow therapeutic window, making precise dose control particularly important in clinical applications. Through GWAS studies, several key genes related to VKAs drug response have been identified, such as VKORC1, CYP2C9, and CYP4F2.[70] The polymorphisms of these genes significantly affect drug metabolism, efficacy, and adverse reactions. Pharmacogenomic algorithms developed based on these gene polymorphisms can provide tailored individualized dosing for patients. Due to their unique pharmacokinetic properties, NOACs are more convenient to use than VKAs, as they do not require frequent INR monitoring.[71] Although NOACs have more stable pharmacokinetic characteristics, interpatient variability in clinical response to NOACs is still influenced by genetic polymorphisms. Existing studies suggest that the therapeutic effects and safety of NOACs could be further optimized through pharmacogenomics.[72] There are significant differences in the genetic polymorphism factors affecting drug response between VKAs and NOACs, and in the future, specific genetic analyses may be needed for each anticoagulant. A deeper understanding of the pharmacokinetic characteristics of drugs and their relationship with genetic polymorphisms is crucial for achieving personalized therapy.[69] Pharmacogenomics shows great potential in optimizing anticoagulant therapy, but there are still several bottlenecks to its widespread use in clinical practice. The main obstacles

include insufficient accumulation of pharmacogenomic data for NOACs, high costs of genetic testing, and lack of standardized guidelines.[73] In the future, more genomic research on NOACs is needed to promote the clinical application of genomics, overcome implementation barriers, reduce genetic testing costs, and establish unified clinical guidelines.

Future research on NOACs in pharmacogenomics will focus on the association between genetic polymorphisms and drug efficacy and adverse reactions, particularly variations in target genes, metabolic genes, and drug transporter genes. Personalized treatment will be a key focus, with studies on gene-drug interactions helping to optimize dosages and select the most suitable therapies. The integration of big data and artificial intelligence will advance precision medicine by improving the accuracy of drug response prediction through multi-omics data. Additionally, research on genetic differences across populations and epigenetics will support the global optimization of drug therapy.

Conclusion

After analyzing 2124 articles and 767 reviews, it is evident that the field of anticoagulation is witnessing a progressive surge in publications. The United States emerges as the leading contributor in terms of publication count. Extensive collaborations between nations and institutions have yielded remarkable achievements. NOACs are continuously evolving, with most authors drawing comparisons to traditional anticoagulants to demonstrate comparable or superior efficacy. Moreover, propelled by technological advancements and profound medical research, an increasing number of countries and institutions are reinforcing their collaborative efforts to foster the advancement of anticoagulant therapy. However, cautious utilization of NOACs remains imperative.

In the field of research on NOACs, researchers should focus on exploring the long-term efficacy and safety of NOACs in different patient populations, particularly those with comorbidities. This includes an in-depth investigation of their role in the prevention and treatment of VTE and PE. Furthermore, with the rapid advancements in pharmacogenomics, researchers should promote the integration of NOACs with genomics to explore personalized treatment strategies and provide theoretical support for the application of precision medicine. This direction not only has the potential to enhance the clinical efficacy of NOACs but also offers tailored treatment plans for patients.For clinicians, in light of the current importance of NOACs as a key option for the treatment of venous thromboembolism, they should consider NOACs as the drug of choice, especially in situations where traditional anticoagulants present poor efficacy or contraindications. Clinicians must pay greater attention to patient education, ensuring that patients understand the advantages of NOACs and fostering better medication adherence. NOACs have significant advantages over traditional anticoagulants, particularly in reducing the risk of bleeding and enhancing treatment safety. At the same time, clinicians should adjust treatment regimens flexibly, considering individual patient differences, to ensure optimal therapeutic outcomes for every patient. For policymakers, considering the rapid global development of NOACs, particularly the leadership in research from Western countries such as the United States, policymakers should take measures to improve the accessibility of NOACs in low-resource regions. Specific actions may include reducing the cost of NOACs, increasing insurance coverage, and strengthening the management of related drug imports. Furthermore, it is recommended that NOACs be included in national treatment guidelines, particularly for the prevention and treatment of venous thromboembolism and pulmonary embolism, ensuring that the use of these medications is widely and systematically available to patient populations.

In conclusion, this study underscores the dynamic evolution of anticoagulation research, propelled by multidisciplinary collaboration and innovative methodologies. Moving forward, sustained efforts in this field are essential to refine treatment strategies, ensure patient safety, and address unmet clinical needs in VTE management. These advancements hold significant promise for improving patient outcomes and enhancing quality of care globally.

Statements and Declarations

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

FXa, Coagulation factor X; DVT, Deep vein thrombosis; DTI, Direct thrombin inhibitor; INR, International normalized ratio; LMWH, Low-molecular-weight heparin; NOACs, Non-vitamin K antagonist oral anticoagulants; PTS, Prevent

post-thrombotic syndrome; PE, Pulmonary embolism; VTE, Venous thromboembolism; VKA, Vitamin K antagonist; WoSCC, Web of Science Core Collection.

Data Sharing Statement

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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