

**REVIEW**

Patent Foramen Ovale in Cryptogenic Stroke: A 20-Year Systematic Review of Evolving Interventional and Antithrombotic Strategies

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ABSTRACT: Background: Patent foramen ovale (PFO) is the most prevalent congenital cardiac anomaly and a key structural heart disease enabling paradoxical embolism, a leading mechanism of cryptogenic stroke. Over the past two decades, the management of PFO-associated stroke has evolved substantially from antithrombotic therapy alone to include percutaneous PFO closure. This systematic review aims to delineate the evolution of therapeutic strategies and clinical evidence in PFO-related stroke research, with particular emphasis on interventional and antithrombotic approaches. **Methods:** We performed a preferred reporting items for systematic reviews and meta-Analyses (PRISMA)-informed bibliometric systematic review of literature published from 2004 to 2024. The primary bibliometric dataset was retrieved from the Web of Science Core Collection, and PubMed was used as a sensitivity source to evaluate retrieval coverage. Using CiteSpace, VOSviewer, and Microsoft Excel, we analyzed 1178 articles and reviews to map research trends, identify key contributors, and synthesize major clinical findings in structural and congenital heart disease. **Results:** The United States emerged as the most productive country (367 publications; 12,342 citations), while European nations—Germany, Switzerland, and Italy—formed a strong collaborative network. PubMed sensitivity retrieval identified 3497 potentially relevant records, confirming that database selection materially affects retrieval sensitivity. Analysis revealed a paradigm shift from early diagnostic approaches to therapeutic comparisons between PFO closure and medical therapy. Landmark randomized controlled trials (RESPECT, REDUCE, DEFENSE-PFO) demonstrated that percutaneous PFO closure combined with antiplatelet therapy significantly reduces recurrent ischemic stroke compared with medical therapy alone in appropriately selected patients aged 18–60 years. Current guidelines recommend PFO closure for PFO-attributable cryptogenic stroke, often identified using the RoPE score and high-risk anatomical features. Key remaining challenges include management of post-procedural atrial fibrillation, older patients, primary prevention, and integrated risk stratification. **Conclusions:** This systematic bibliometric review documents the maturation of PFO-stroke research from mechanistic exploration to evidence-based interventional management within the field of structural and congenital heart disease. Optimal secondary prevention requires a personalized approach balancing closure efficacy against procedural risks. As structural heart interventions continue to evolve, ongoing interdisciplinary collaboration between cardiologists and neurologists remains essential for advancing PFO-related stroke care.

KEYWORDS: Bibliometrics; patent foramen ovale; cryptogenic stroke; research trends; PFO closure; therapeutic intervention

1 Introduction

The foramen ovale is a crucial physiological shunt in the fetal circulatory system, located within the interatrial septum, which facilitates the direct flow of oxygenated blood from the right to the left atrium. Postnatally, physiological changes in pulmonary and systemic vascular resistance elevate left atrial pressure above that of the right atrium, leading to the functional and eventual anatomical fusion of the septum primum and secundum, thereby closing the foramen ovale. Persistence of this opening beyond three years of age is defined as a patent foramen ovale (PFO), the most prevalent congenital cardiac anomaly, affecting approximately 25% of the adult population globally [1–4]. A growing body of clinical and epidemiological evidence has established significant associations between PFO and a spectrum of clinical disorders, primarily attributable to paradoxical embolism, in which venous thrombi bypass the pulmonary circulation by shunting directly through the PFO into the systemic arterial circulation. This mechanism has been implicated in cryptogenic stroke (CS), migraine with aura, and other neurovascular and systemic conditions [5–9].

Cryptogenic stroke, an ischemic stroke for which no definitive etiology is identified after a comprehensive diagnostic workup [10,11], has been a major focus of PFO-related research. Paradoxical embolism via a PFO is now considered a leading mechanism underlying a substantial proportion of CS cases, particularly in younger patients [12,13]. Consequently, critical questions regarding risk stratification for PFO-attributable stroke recurrence and the optimal secondary prevention strategies have become central challenges in cardiology and neurology. The clinical discourse is dominated by debates over the comparative efficacy of antiplatelet therapy, systemic anticoagulation, and percutaneous PFO closure [14,15]. These ongoing discussions underscore the necessity for continued research to refine patient selection criteria and tailor long-term management strategies. High-risk PFO generally refers to anatomical or functional features that increase the probability of paradoxical embolism, including a large right-to-left shunt, atrial septal aneurysm, long PFO tunnel, prominent Eustachian valve or Chiari network, substantial shunt at rest or during Valsalva maneuver, and the absence of an alternative stroke mechanism after standardized neurological evaluation [16,17].

Bibliometrics offers a quantitative and objective methodology to analyze the scholarly landscape of a research field [18–20]. By employing mathematical and statistical techniques, this approach can systematically map the evolution of scientific knowledge, identify key contributors, and reveal emerging trends, thus overcoming the potential biases inherent in traditional narrative reviews. Despite the extensive volume of clinical and basic research on PFO-mediated paradoxical embolism, a comprehensive bibliometric analysis of this specific domain is lacking. This study aims to fill that gap by systematically analyzing literature published over the past two decades. Through co-occurrence analysis of keywords, co-citation analysis, and mapping of collaborative networks among authors, institutions, and countries, we seek to delineate the primary research themes, influential stakeholders, and geographical distribution of research activities. Furthermore, this analysis will identify the foundational knowledge base and pinpoint the research frontiers, providing a valuable reference to guide future investigative efforts in this clinically significant field. The 20-year evolution of PFO-related stroke research, shifting from diagnostic exploration to evidence-based therapeutic interventions, is summarized in the Central Illustration.

2 Materials and Methods

2.1 Data Source and Search Strategy

The review was planned and reported in accordance with the preferred reporting items for systematic reviews and meta-Analyses (PRISMA) 2020 statement, where applicable, for bibliometric systematic reviews [21]. The primary bibliographic dataset for quantitative bibliometric mapping was retrieved from the Web of Science Core Collection (WoSCC), specifically the Science Citation Index Expanded (SCIE), because WoSCC provides standardized cited-reference fields required for co-citation and burst analyses. To address retrieval sensitivity, we also performed a PubMed sensitivity search using title/abstract terms for PFO and stroke-related embolic events. The PubMed strategy was: ((patent foramen ovale[Title/Abstract] OR PFO[Title/Abstract]) AND (stroke[Title/Abstract] OR embol*[Title/Abstract] OR thromboembol*[Title/Abstract] OR transient ischemic attack[Title/Abstract] OR TIA[Title/Abstract])) AND (2004:2024[pdat]). PubMed retrieved 3497 records before bibliometric field harmonization. Because PubMed does not provide the same cited-reference structure required for CiteSpace co-citation and burst detection, PubMed results were used for sensitivity assessment and clinical interpretation rather than merged into the WoSCC bibliometric dataset. The WoSCC search was conducted on 15 December 2024, and encompassed literature published from January 1, 2004, to the search date. The search strategy targeted records where key terms appeared in the title (TI) or author-supplied keywords (AK). The following advanced search query was executed:

(TI = (Embol*) OR TI = (Thromboembol*) OR TI = (stroke) OR TI = (Transient Ischemic Attack) OR TI = (TIA) OR AK = (Embol*) OR AK = (Thromboembol*) OR AK = (stroke) OR AK = (Transient Ischemic Attack) OR AK = (TIA)) AND (TI = (patent Foramen Ovale) OR TI = ("PFO") OR AK = (patent foramen ovale) OR AK = ("PFO")).

This query yielded an initial 2926 WoSCC records. The results were refined by applying inclusion criteria: (1) document type limited to "Article" or "Review Article"; (2) language restricted to English; and (3) publication years from 2004 to 2024. After database-scope, language, and document-type restrictions, a final dataset of 1178 publications was exported in plain text format for analysis. The literature screening and selection process is detailed in Supplementary Fig. S1, and a completed PRISMA 2020 checklist is provided as Supplementary Material. The exported records and database filters were manually verified by the author team, and discrepancies in record eligibility or term standardization were resolved through discussion with a senior author. No automation tools beyond database filters and bibliometric software were used for eligibility screening.

2.2 Data Analysis and Visualization

The bibliometric analysis and visualization were performed using CiteSpace (version 6.1.R6; Chaomei Chen, Drexel University, Philadelphia, PA, USA; <https://citespace.podia.com>), VOSviewer (version 1.6.18; Centre for Science and Technology Studies, Leiden University, Leiden, the Netherlands; <https://www.vosviewer.com>), and Microsoft Excel 2021 (Microsoft Corporation, Redmond, WA, USA). The raw data exported from WoSCC, comprising titles, authors, keywords, institutions, countries, citations, journals, and publication dates, were first processed and standardized in Excel.

VOSviewer, developed by van Eck and Waltman [22,23], was employed to construct and visualize static network maps based on co-occurrence data. The counting method was set to full counting. For country/region, institution, author, and keyword networks, the minimum occurrence thresholds were selected to retain the most informative connected items while avoiding over-fragmented networks; the top

25 keywords and references were displayed for burst analyses. In these maps, nodes represent individual items, node size corresponds to frequency, and connecting lines signify total link strength.

CiteSpace, developed by Dr. Chaomei Chen [24,25], was used to analyze temporal dynamics and intellectual structure. The time slicing was set from 2004 to 2024 with one year per slice; the node types included keywords, cited references, authors, institutions, and countries; selection criteria used the top N strategy (N = 50 per slice) with pruning by Pathfinder and pruning sliced networks. Burst detection was performed using Kleinberg’s algorithm. For the polynomial publication-growth model, leave-one-out cross-validation was used to evaluate overfitting; the mean absolute prediction error was 3.6 publications per year, and the root mean square error was 4.9 publications per year, indicating that the model was used descriptively rather than for prospective forecasting. The principal methodological parameters and sensitivity checks are summarized in Table 1.

Table 1: Methodological parameters and sensitivity checks.

Item	Setting or Result
PRISMA reporting	PRISMA 2020 statement followed where applicable; checklist prepared as Supplementary Material.
Primary bibliometric source	WoSCC/SCIE; 2926 initial records and 1178 final articles/reviews.
PubMed sensitivity search	3497 records retrieved using PFO and stroke/embolism title-abstract terms, used to assess retrieval sensitivity.
CiteSpace parameters	Version 6.1.R6; 2004–2024; one-year slices; top N = 50 per slice; pathfinder pruning; burst detection by Kleinberg algorithm.
VOSviewer parameters	Version 1.6.18; full counting; country, institution, author, journal, reference, and keyword networks.
Cross-validation of publication-growth model	Leave-one-out mean absolute prediction error 3.6 publications/year; root mean square error 4.9 publications/year.

PFO, patent foramen ovale; PRISMA, preferred reporting items for systematic reviews and meta-Analyses; WoSCC, web of science core collection; SCIE, science citation index expanded.

By integrating the analytical capabilities of these tools, we conducted a multi-dimensional analysis of the research landscape. Excel was used for descriptive statistics, such as tracking annual publication trends. VOSviewer provided clear visualizations of collaborative structures, while CiteSpace offered a dynamic perspective on the evolution of research frontiers and foundational knowledge.

No separate protocol was prospectively registered or publicly posted before this bibliometric analysis.

3 Results

3.1 Publication and Citation Trends

The temporal dynamics of scholarly output in PFO-related stroke research from 2004 to 2024 are depicted in Fig. 1A,B. Fig. 1A illustrates that while the annual volume of publications has demonstrated a fluctuating yet gradually declining trend since peaking in 2018 (n = 89), the annual citation count has followed a distinct, fluctuating upward trajectory. A notable peak in citation frequency occurred in 2024, with 2592 citations, suggesting that recent high-impact research has significantly influenced the field. Fig. 1B shows the cumulative growth in publications, which has continued to rise, although the rate of growth has moderated in recent years. A polynomial regression analysis was applied to the cumulative publication data to describe the historical growth pattern ($R^2 = 0.9999$). This high coefficient of determination indicates

that the regression model closely fits the historical data, describing a sustained, albeit maturing, growth trajectory for the field (Fig. 1B).

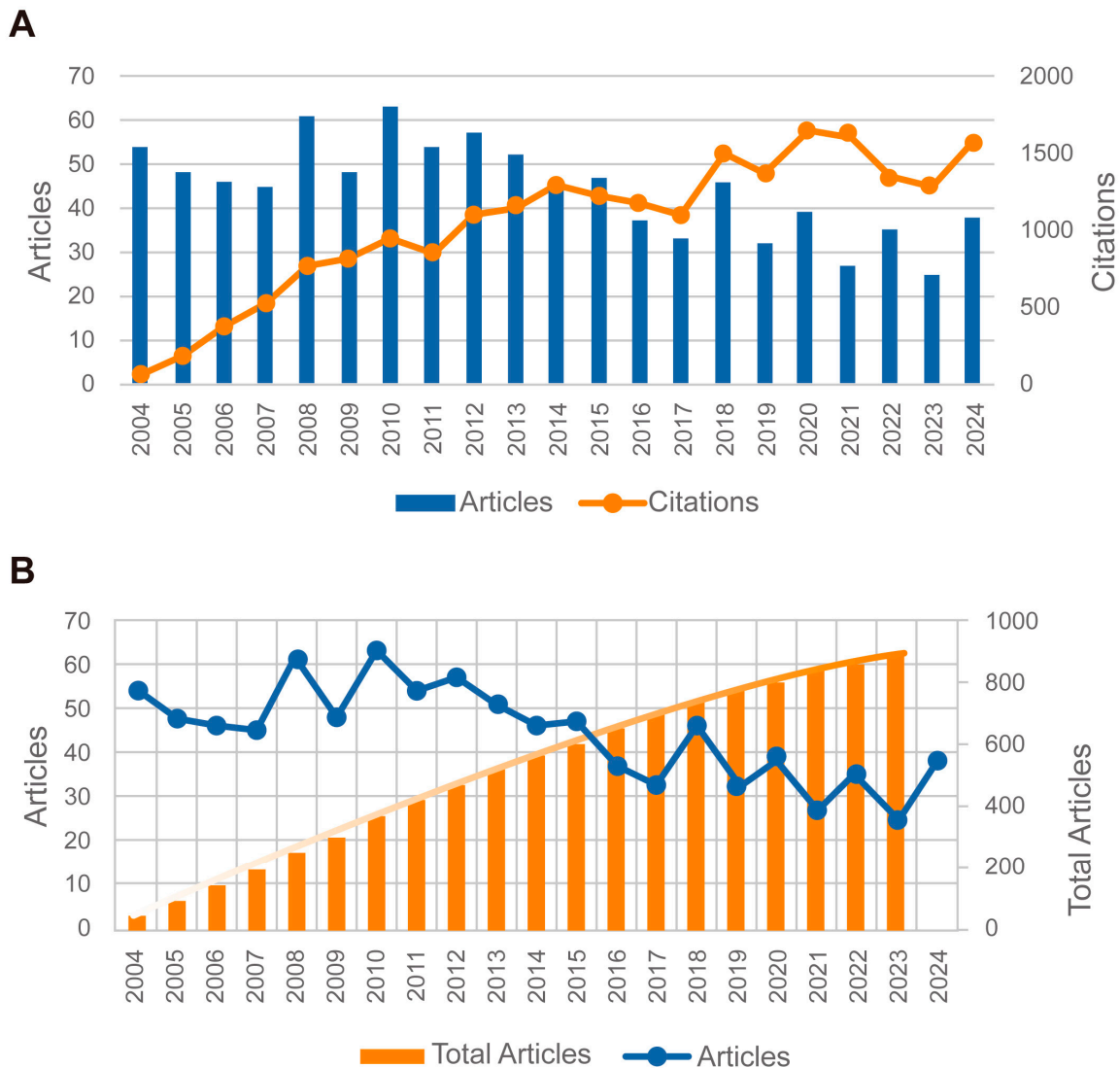


Figure 1: Temporal trends in PFO-stroke research. (A) Annual publication volume and citation frequency from 2004 to 2024. (B) Cumulative publication growth with the polynomial trend line ($R^2 = 0.9999$).

3.2 Analysis of Countries/Regions

Table 2 presents the top five most productive and influential countries/regions in PFO-stroke research. The United States holds a commanding lead, ranking first in both publication volume (367 documents) and total citations (12,342), establishing it as the global epicenter of research in this domain. European nations also demonstrate substantial contributions, with Germany, Italy, and Switzerland being major research hubs. The country collaboration map is shown in Fig. 2, confirming that the United States acts as the central hub with extensive collaborative links to Germany, China, and Italy. A strong European collaborative cluster is also evident, with Germany, the United Kingdom, and France forming a tightly interconnected network. This dense web of international partnerships underscores the global and collaborative nature of contemporary research in this field.

Table 2: Overview of the top 5 contributors in PFO-stroke research (2004–2024) based on publication volume.

Rank	Country (Documents)	Institution (Documents)	Author (Documents)	Journal (Documents)
1	USA (367)	University Hospital Bern (34)	Meier B. (43)	Catheter Cardiovasc Interv (71)
2	Italy (166)	Columbia University (29)	Mattle H.P. (28)	Stroke (49)
3	Germany (128)	University of Pennsylvania (29)	Thaler D.E. (27)	J Stroke Cerebrovasc Dis (41)
4	China (101)	Mayo Clinic (28)	Rigatelli G. (23)	Echocardiography (28)
5	Switzerland (91)	Tufts University (28)	Kent D.M. (22)	Neurological Sciences (25)

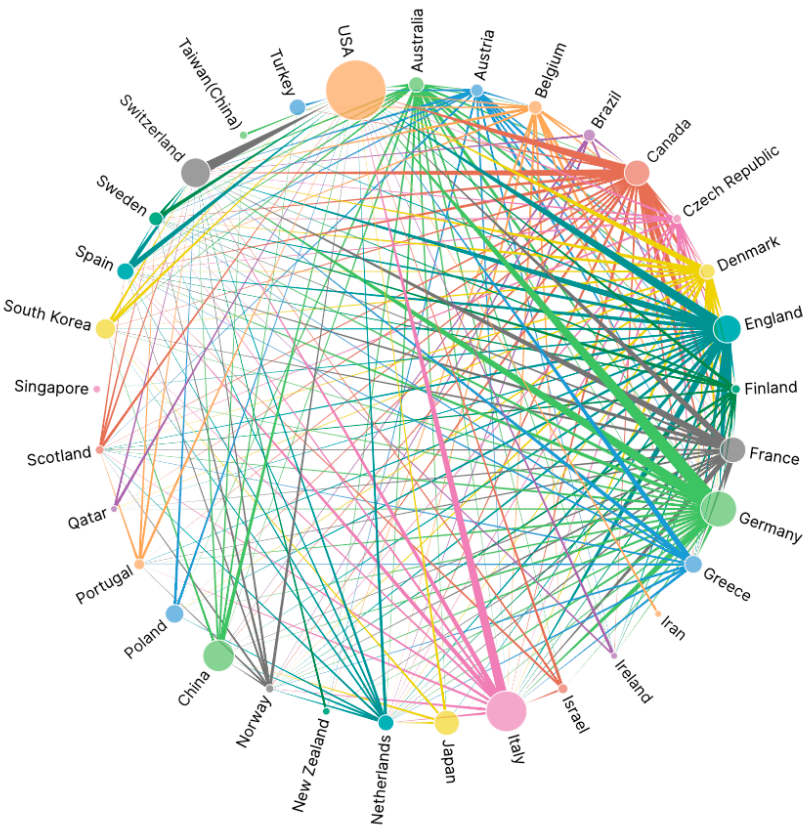


Figure 2: Country/region collaboration network in PFO-stroke research. Node size indicates publication volume, and link thickness indicates collaboration strength.

3.3 Analysis of Authors

Table 2 also provides an overview of the most prolific authors. Bernhard Meier (University of Bern, Switzerland) is the most prolific author with 43 publications, followed by Heinrich P. Mattle (University of Bern, Switzerland) with 28 and David E. Thaler (Tufts Medical Center, USA) with 27. The author co-citation analysis reveals a different set of leaders. Jean-Louis Mas (Université de Paris, France) is the most co-cited author (788 citations), followed by Shunichi Homma (Columbia University, USA; 607 citations) and David M. Kent (Tufts University, USA; 506 citations). Network mapping of co-authorship and co-citations is provided in Fig. 3, showing distinct collaborative clusters organized by geographical and institutional proximity.

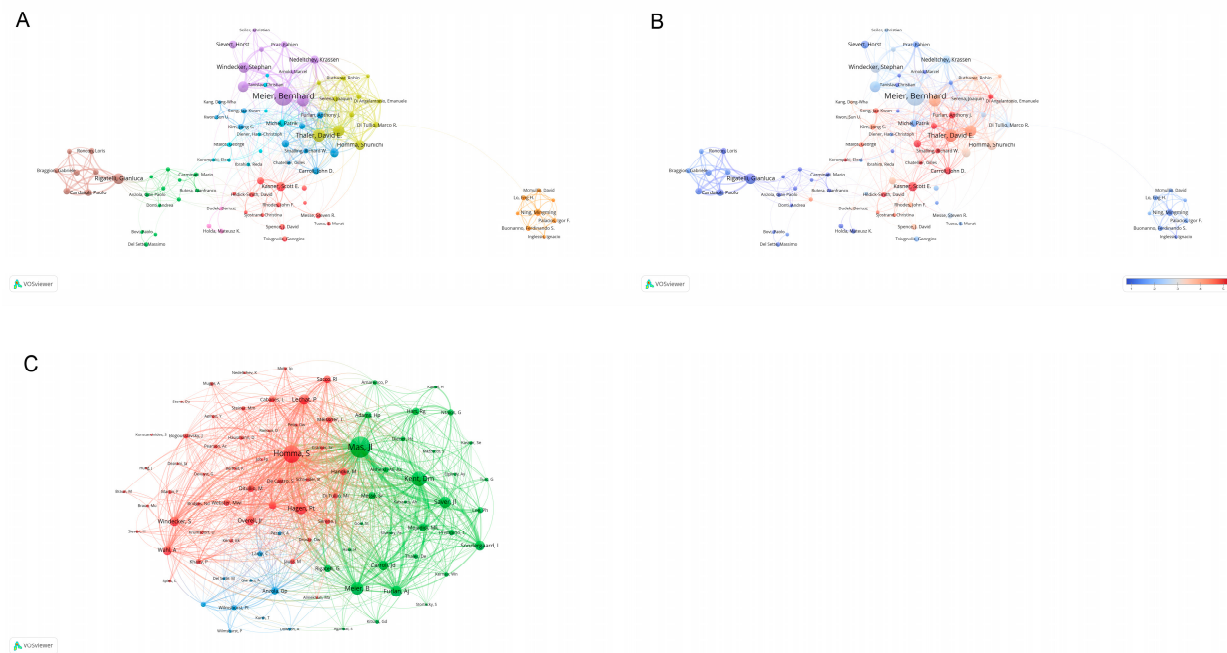


Figure 3: Author collaboration and co-citation structure. (A) Author co-authorship network. (B) Temporal overlay of the author co-authorship network according to average publication year. (C) Author co-citation network.

3.4 Analysis of Institutions

The analysis of institutional productivity is summarized in Table 2. The University Hospital Bern (Switzerland) is the most productive institution with 34 publications. American institutions dominate the top list, including Columbia University, the University of Pennsylvania, and the Mayo Clinic, all demonstrating high productivity and citation impact. Institutional collaboration networks are shown in Fig. 4, highlighting a strong European network centered around the University Hospital Bern and a prominent North American cluster centered in Boston, USA.

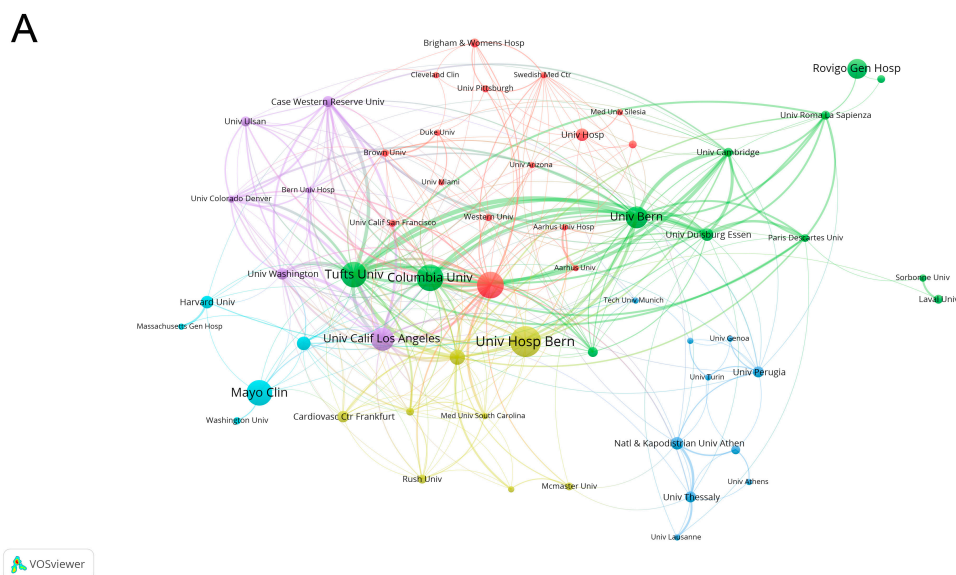


Figure 4: Cont.

B

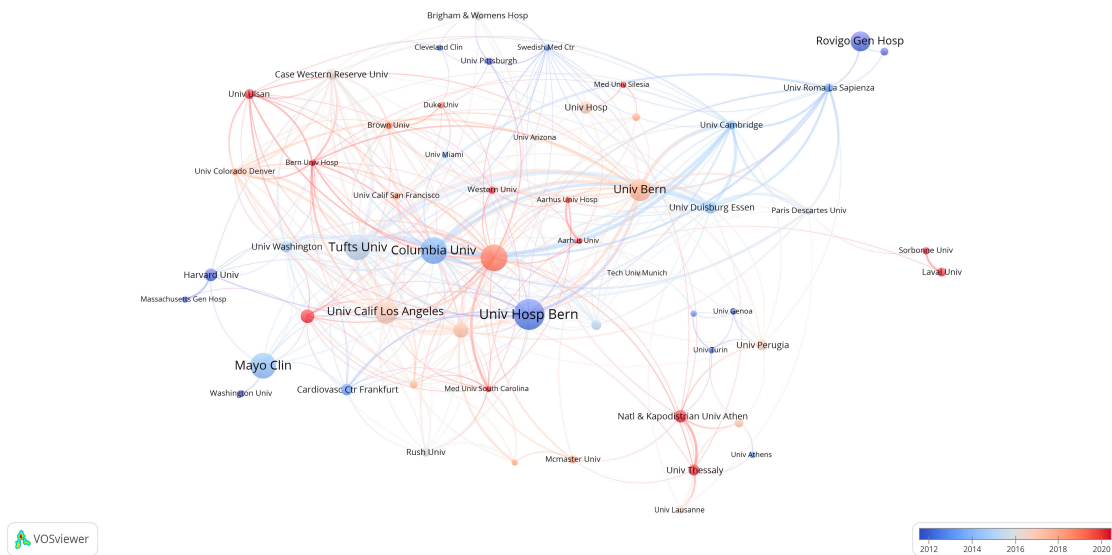
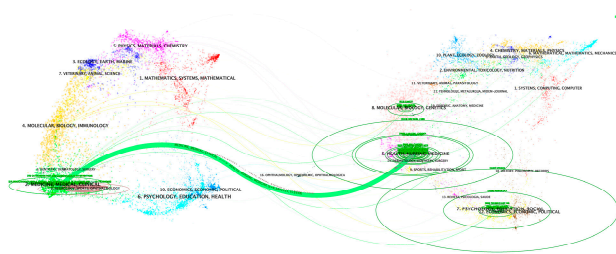


Figure 4: Institutional collaboration and temporal structure. (A) Institutional collaboration network. (B) Temporal overlay of the institutional collaboration network according to average publication year.

3.5 Analysis of Journals

Table 2 also lists the top five journals by publication volume. Catheterization and Cardiovascular Interventions published the most articles (71), followed by Stroke (49). In terms of co-citations, Stroke leads decisively with 4058 citations. High-impact general medical and cardiology journals, including the New England Journal of Medicine, the Journal of the American College of Cardiology, and Circulation, also feature prominently in the co-citation rankings. Journal network mapping and dual-map overlay results are shown in Fig. 5, demonstrating strong citation pathways between general medicine, interventional cardiology, neurology, and clinical research.

A



B

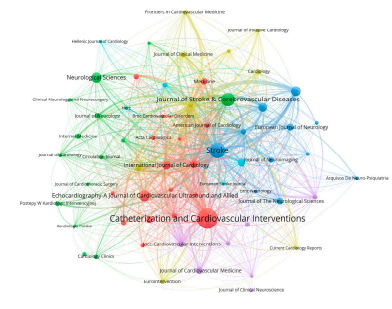


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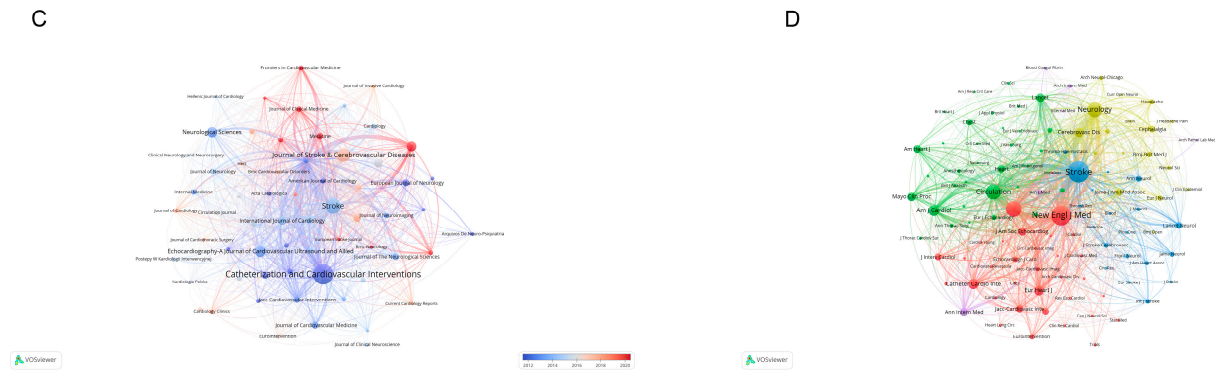


Figure 5: Journal distribution and interdisciplinary citation structure. (A) Dual-map overlay showing citation pathways between source and citing disciplines. (B) Network visualization of journals publishing PFO-stroke research. (C) Temporal overlay of the journal network according to average publication year. (D) Journal co-citation network.

3.6 Analysis of Keywords

A co-occurrence analysis of author keywords provides insight into the core topics and evolving themes of the research field. As shown in Table 3, “patent foramen ovale” (898 occurrences), “stroke” (344), and “cryptogenic stroke” (249) are the most frequent keywords, confirming the central focus of the domain. “Paradoxical embolism” (151) is also a core concept.

Table 3: Top 20 author keywords by occurrence frequency in PFO-stroke research.

Rank	Keyword	Occurrences	Rank	Keyword	Occurrences
1	Patent Foramen Ovale	898	11	Right-To-Left Shunt	53
2	Stroke	344	12	Transient Ischemic Attack	50
3	Cryptogenic Stroke	249	13	Pulmonary Embolism	43
4	Paradoxical Embolism	151	14	Transcatheter Closure	42
5	Ischemic Stroke	84	15	Atrial Fibrillation	41
6	Migraine	79	16	Atrial Septal Aneurysm	41
7	PFO Closure	71	17	Percutaneous Closure	39
8	Echocardiography	65	18	Transcranial Doppler	33
9	Transesophageal Echocardiography	63	19	Embolic Stroke Of Undetermined Source	32
10	Embolism	53	20	Secondary Prevention	31

PFO, patent foramen ovale.

The keyword co-occurrence network (Fig. 6A) visualizes primary thematic clusters. These clusters represent different facets of the field: cardiovascular disease aspects, structural heart defects and closure, diagnostic imaging, associated neurological symptoms such as migraine, stroke mechanisms, antithrombotic therapy, and other embolic complications. The normalized-citation overlay (Fig. 6B) highlights keywords with comparatively high citation impact, while the temporal overlay (Fig. 6C) shows the progression from earlier diagnostic and mechanistic terms to more recent treatment- and outcome-oriented topics. The keyword-cluster timeline (Fig. 6D) further demonstrates the longitudinal persistence and interaction of themes including interatrial septum, recurrent stroke, atrial cardiopathy, pulmonary embolism, right-to-left shunt, and cryptogenic stroke. The keyword citation burst analysis (Fig. 7) identifies keywords with a sharp increase in frequency over time. Early bursts (2004–2010) included diagnostic terms such as “transesophageal echocardiography” and anatomical features such as “atrial septal aneurysm.” A subsequent wave (2014–2020) focused on evidence synthesis (“meta-analysis”) and long-term management (“secondary

prevention”). The most recent bursts (2018–2024 onward) are dominated by treatment-related terms such as “PFO closure,” “antiplatelet therapy,” and “outcome,” alongside “embolic stroke of undetermined source,” reflecting the current emphasis on optimizing therapeutic interventions and patient outcomes based on evidence from major clinical trials.

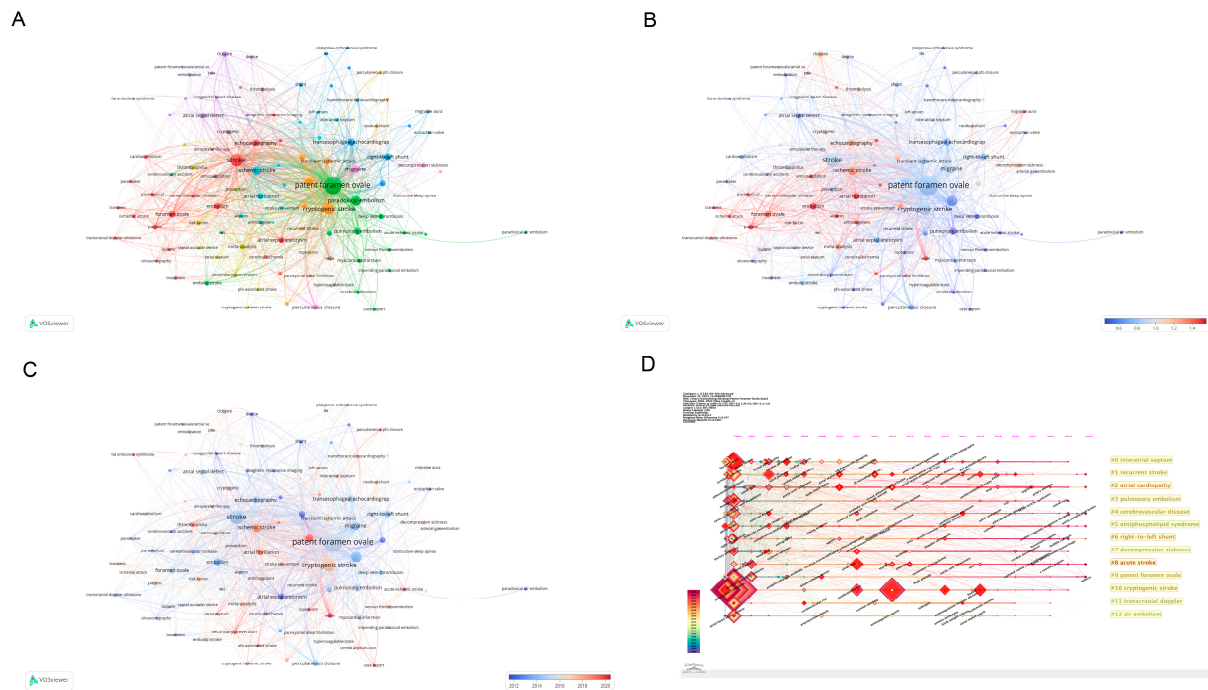


Figure 6: Keyword knowledge maps and temporal evolution. (A) Keyword co-occurrence network. (B) Overlay visualization according to normalized citation impact. (C) Temporal overlay according to average publication year. (D) CiteSpace keyword-cluster timeline view.

3.7 Analysis of Highly Cited References

Fig. 8A provides a temporal network visualization of influential cited references, with nodes representing individual articles. Key publications, identified by their high centrality and citation counts, include landmark clinical trials published by Saver et al. (2017) [26], Carroll et al. (2013) [27], and Meier et al. (2013) [28]. The reference co-citation cluster analysis shown in Fig. 8B reveals the major research streams within the literature. The largest cluster, “#0 ESUS” (embolic stroke of undetermined source), demonstrates the centrality of this clinical entity to the field. It is closely linked to clusters on secondary stroke prevention and atrial septal aneurysm, indicating that research on PFO is deeply embedded within the broader context of stroke prevention.

Finally, Fig. 8C displays the top 25 references with the strongest citation bursts. The article by Furlan et al. (2012) on the CLOSURE I trial [29] exhibited the highest burst strength (59.1), reflecting its profound, though initially negative, impact on the field. Subsequent positive trials, such as those reported by Wahl et al. (2012) [30], Carroll et al. (2013) [27], Meier et al. (2013) [28], and Lee et al. (2018) [31], also show strong citation bursts. These papers collectively shifted the clinical paradigm by providing robust evidence from randomized controlled trials that PFO closure is superior to medical therapy for secondary stroke prevention in appropriately selected patients.

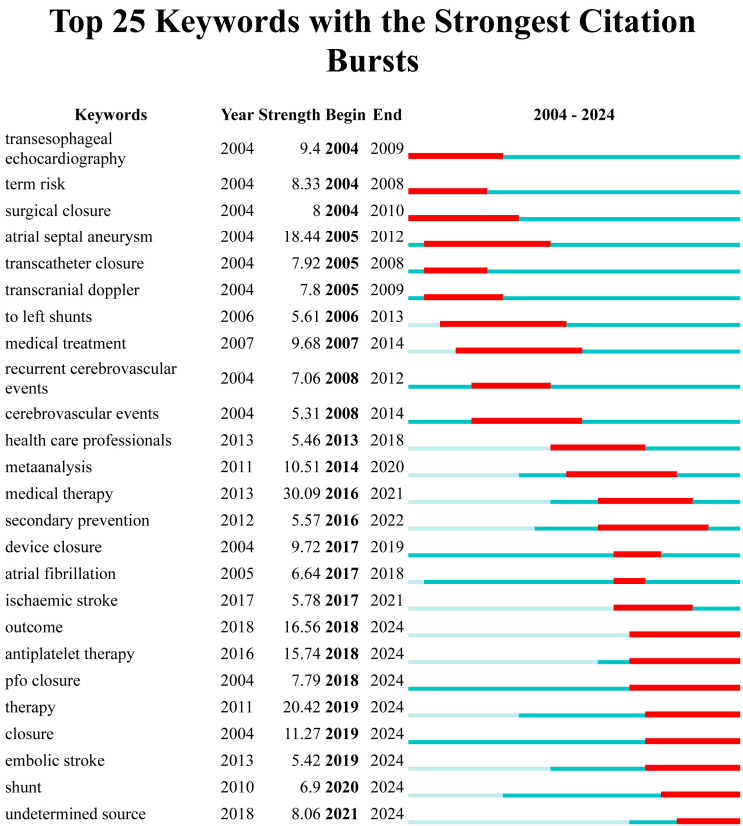


Figure 7: Top 25 keywords with the strongest citation bursts in PFO-stroke research.

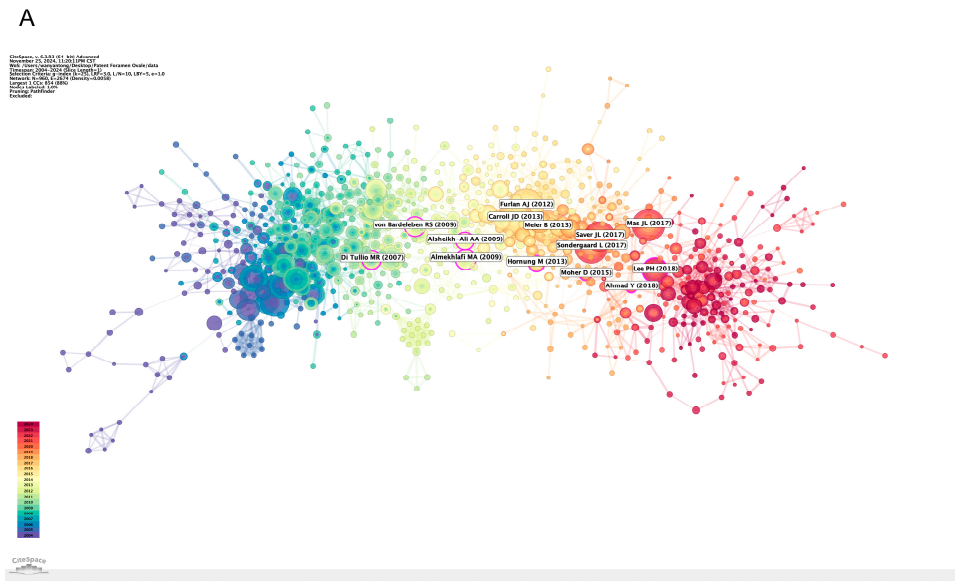


Figure 8: Cont.

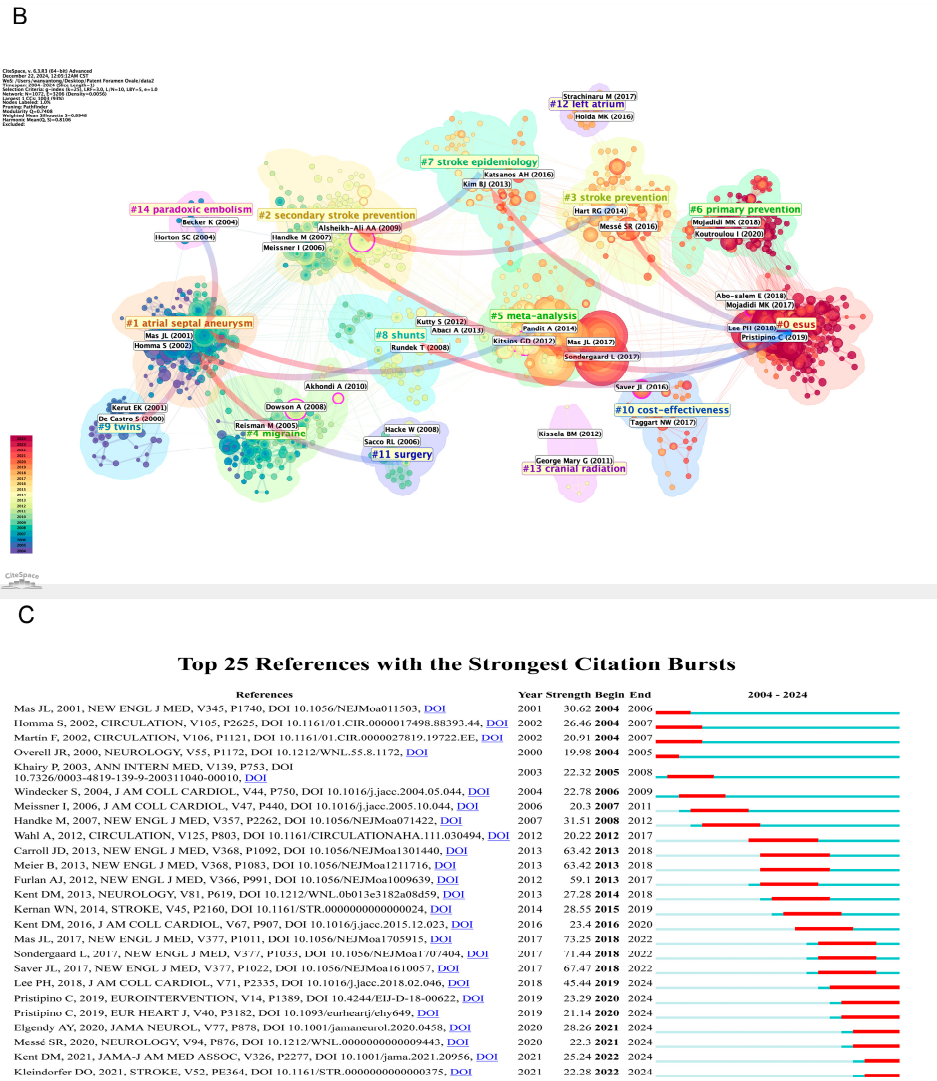


Figure 8: Intellectual structure and landmark references. (A) Temporal network of influential cited references. (B) Reference co-citation cluster map, including ESUS and secondary stroke prevention. (C) Top 25 references with the strongest citation bursts.

4 Discussion

4.1 General Distribution and Key Contributors

This bibliometric analysis provides a comprehensive overview of the global research landscape of PFO-associated stroke from 2004 to 2024. Our findings reveal a maturing field characterized by a shift from exploratory and diagnostic research to a focus on evidence-based therapeutic interventions. The trend of decreasing annual publication volume alongside increasing citation frequency suggests a consolidation of research efforts. As foundational questions about the PFO-stroke link were addressed, the field has likely pivoted towards higher-impact, methodologically rigorous studies, such as large-scale clinical trials and meta-analyses, which garner more citations and have a greater influence on clinical guidelines. Important unresolved questions remain, particularly whether evidence from younger randomized-trial populations can be generalized to older patients. Current guidelines primarily support closure in patients younger than 60 years with PFO-attributable ischemic stroke, whereas randomized data in older patients remain

limited. Recent evidence indicates that PFO closure in selected older patients may be safe and may reduce recurrence compared with antithrombotic therapy alone, but prospective randomized trials are still required before routine expansion of indications [32]. Evidence for PFO closure as primary stroke prevention is even more limited and should not be extrapolated from secondary-prevention trials [33].

Geographically, the United States is the undisputed leader in both productivity and research impact, a finding consistent with its substantial investment in medical research and the presence of world-leading academic institutions. European countries, particularly Germany, Switzerland, and Italy, also form a powerful research consortium. The author analysis identified Bernhard Meier as the most prolific author and Jean-Louis Mas as the most influential in terms of co-citations. The co-citation prominence of Mas and colleagues underscores the field's focus on carefully selected patients. More broadly, the long-term RESPECT results reported by Saver et al. in 2017 (750 citations in our dataset) were pivotal in shaping current clinical practice by demonstrating the superiority of closure for secondary stroke prevention in selected patients [26]. This highlights the critical role of key opinion leaders and their high-impact research in driving the field forward. Similarly, the institutional analysis confirms the dominance of major academic medical centers in the USA and Europe, with University Hospital Bern and Tufts University emerging as key hubs of productivity and influence, respectively.

The journal analysis underscores the field's dual focus on cardiology and neurology. While interventional cardiology journals like *Catheterization and Cardiovascular Interventions* are primary venues for procedural research, leading neurology journals like *Stroke* serve as the intellectual core, as indicated by their high co-citation scores. The publication of seminal trials in premier journals such as the *New England Journal of Medicine* signifies the clinical importance and broad academic interest in this topic.

4.2 Research Hotspots and Evolving Frontiers

The keyword analysis effectively traces the intellectual evolution of the field. The persistent high frequency of “patent foramen ovale,” “stroke,” “cryptogenic stroke,” and “paradoxical embolism” confirms their status as foundational concepts. The citation burst analysis reveals a clear chronological progression of research themes, moving from diagnosis to therapy. The current and ongoing bursts for “PFO closure,” “antiplatelet therapy,” and “therapy” (burst strength 20.42) confirm that optimizing treatment strategies remains the foremost research frontier.

4.2.1 Advancements in Diagnostic Imaging

The diagnosis and risk stratification of PFO remain heavily reliant on imaging. While transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are standard modalities, research continues to refine their application. Studies have confirmed TTE as a valuable initial screening tool, particularly for detecting large right-to-left shunts (RLS) [34,35], while TEE provides superior anatomical detail and specificity [35,36]. The importance of a properly performed Valsalva maneuver during contrast studies has been emphasized to minimize false-negative results [36]. Recent work has also highlighted the enhanced diagnostic yield of combining contrast-TTE with TEE [37]. Moreover, advanced techniques are emerging. Intracardiac echocardiography (ICE) has shown superiority over TTE/TEE in identifying high-risk PFO features [38], and transcranial Doppler (TCD), including robotic automated TCD (raTCD), has proven to be a highly sensitive and specific non-invasive method for detecting RLS [39–41], offering a viable alternative, especially in stroke unit settings. TCD is highly sensitive for detecting right-to-left shunt but does not define PFO anatomy; therefore, combining TCD with TTE or TEE can improve the overall diagnostic pathway by pairing sensitive shunt screening with anatomical confirmation and risk-

feature assessment. Peri-interventional TEE remains important for defining septal anatomy, guiding device selection, and identifying residual shunts. Inferior vena cava compression during TEE can enhance PFO detection when the Valsalva maneuver is suboptimal [42], and TEE under moderate-to-deep sedation has been reported as feasible when maneuvers are carefully performed [43]. Three-dimensional TEE further improves visualization of PFO morphology, tunnel length, adjacent septal aneurysm, and relationships with surrounding atrial structures [44].

4.2.2 The Therapeutic Landscape: From Medical Management to Percutaneous Closure

The management of patients with PFO and a history of stroke has evolved significantly. Initial management relied on medical therapy, comprising antiplatelet agents (e.g., aspirin, clopidogrel) and anticoagulants [45]. While antiplatelet therapy remains a cornerstone for general secondary stroke prevention, studies exploring outcomes in PFO patients have yielded mixed results [46,47]. Direct oral anticoagulants (DOACs) have shown promise compared to aspirin in some observational studies [48], and a meta-analysis suggested that oral anticoagulation might be superior to antiplatelet therapy for preventing recurrence, although definitive randomized evidence is still needed [49]. However, whether DOACs are superior to antiplatelet therapy remains uncertain. The available data include prospective and observational evidence suggesting fewer recurrent events with dabigatran than aspirin in selected cryptogenic stroke patients with PFO [48], and meta-analytic evidence suggesting a possible advantage of oral anticoagulation over antiplatelet therapy [49]. Nevertheless, most closure trials were not designed to directly compare DOACs with antiplatelet therapy, and bleeding risk, occult atrial fibrillation, venous thrombosis risk, and patient preference must be considered. Thus, the current evidence supports DOACs as a reasonable individualized option in selected patients but not as universally superior therapy.

The most significant shift in the field has been the validation of PFO closure as a superior strategy for secondary prevention in carefully selected patients. Following several initially neutral or negative trials, landmark randomized controlled trials, including RESPECT, REDUCE, and DEFENSE-PFO, demonstrated that percutaneous PFO closure combined with antiplatelet therapy significantly reduces the risk of recurrent ischemic stroke compared with medical therapy alone [15,26,31]. This has led to updated clinical guidelines recommending closure for patients aged 18–60 years with a PFO-attributable cryptogenic stroke, often identified using tools like the RoPE score [16,17,50]. Subsequent meta-analyses and long-term follow-up studies have confirmed the sustained efficacy and safety of closure [51–54]. However, research frontiers remain, including the management of the small but significant risk of post-procedural atrial fibrillation [54–56] and the ongoing evaluation of newer-generation closure devices to optimize safety and efficacy [57,58]. The overarching trend is toward personalized medicine, using integrated risk stratification schemes like the PASCAL classification system to ensure that closure is offered to patients most likely to benefit [17,55]. Patient selection should integrate age, stroke phenotype, exclusion of alternative etiologies, RoPE score, PASCAL classification, and high-risk anatomy. Suitable candidates generally include patients aged 18–60 years with non-lacunar ischemic stroke or systemic embolism, no competing mechanism after standardized neurological and vascular workup, a moderate-to-large shunt or atrial septal aneurysm, and acceptable procedural risk. Patients with low RoPE scores, uncontrolled vascular risk factors, atrial fibrillation, or a plausible non-PFO stroke mechanism require more cautious individualized decision-making. In addition to device size and procedural factors, pre-closure atrial remodeling may contribute to post-procedural atrial fibrillation; speckle-tracking echocardiography has been proposed as a tool to detect left atrial structural and functional changes that may identify patients with latent arrhythmic vulnerability [59].

4.3 Strengths and Limitations

This study represents a comprehensive PRISMA-informed bibliometric analysis of the PFO-stroke literature over a 20-year period. By employing a multi-faceted analytical approach with validated software tools and by adding a PubMed sensitivity search, we provide an objective, data-driven overview of the field's structure, evolution, and key research trends. This quantitative perspective complements traditional narrative reviews by highlighting the intellectual connections and dynamic shifts within the scholarly landscape.

Nonetheless, certain limitations must be acknowledged. First, although the primary quantitative bibliometric dataset was restricted to English-language articles indexed in WoSCC to preserve cited-reference compatibility, this approach may introduce language and database-selection bias. The PubMed sensitivity search retrieved 3497 records and confirmed that broader biomedical searches identify additional potentially relevant literature; therefore, our findings should be interpreted as a WoSCC-based bibliometric map rather than an exhaustive clinical evidence synthesis. Second, the search strategy was limited to the title and author keyword fields to enhance specificity, which may have missed records where relevant terms appeared only in the abstract. Third, although we followed PRISMA reporting principles and provided a PRISMA flow diagram and checklist, this study is primarily bibliometric and did not conduct a formal ROBINS-I risk-of-bias assessment or meta-analysis of individual clinical outcomes. No separate protocol was prospectively registered or publicly posted before this bibliometric analysis. Finally, data collection was finalized on 15 December 2024, so late-indexed 2024 records and 2025–2026 publications are not included in the quantitative map. Future research should combine multi-database systematic review methods with risk-of-bias assessment and meta-analysis focused on specific clinical questions, such as PFO closure in older patients, primary prevention, DOAC-based strategies, and post-closure atrial fibrillation surveillance.

5 Conclusions

This bibliometric analysis maps the dynamic evolution of research on the association between PFO and stroke over the past two decades. The field has matured from establishing a causal link to focusing intensely on evidence-based strategies for secondary stroke prevention. The United States and key European nations, along with leading institutions such as Tufts University and the University Hospital Bern, have been instrumental in this progress. Research published in high-impact cardiology and neurology journals, such as *Stroke* and the *New England Journal of Medicine*, has shaped the current clinical landscape. The central research trend has been a decisive shift toward percutaneous PFO closure for selected patients with cryptogenic stroke, driven by landmark randomized trials (RESPECT, REDUCE, DEFENSE-PFO) and refined by risk stratification using RoPE and PASCAL frameworks. Future research should focus on older patients, primary prevention, DOAC-based individualized therapy, high-risk anatomical phenotypes, residual shunt surveillance, post-closure atrial fibrillation prediction, and continued interdisciplinary collaboration between cardiology and neurology.

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interpretation and visualization. Yanchun Zhi, Runyu Wang and Gairong Jin assisted with software analysis and manuscript drafting. Shunda Liu helped in processing the bibliographic data. Huilian Tan and Jun Liu designed the study, supervised the project, and critically revised the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials: The primary dataset analyzed during the current study is available from the Web of Science Core Collection (WoSCC) database using the search query provided in the manuscript. The PubMed sensitivity search strategy is also reported in the manuscript. Processed bibliometric data are available from the corresponding author on reasonable request.

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Abbreviation

PFO	Patent Foramen Ovale
CS	Cryptogenic Stroke
WoSCC	Web of Science Core Collection
SCIE	Science Citation Index Expanded
TTE	Transthoracic Echocardiography
TEE	Transesophageal Echocardiography
RLS	Right-to-Left Shunt
ICE	Intracardiac Echocardiography
TCD	Transcranial Doppler
DOACs	Direct Oral Anticoagulants
RoPE	Risk of Paradoxical Embolism
PASCAL	PFO-Associated Stroke Causal Likelihood
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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