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# Cryptogenic ischemic stroke

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# Cryptogenic ischemic stroke

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# Editorial: Cryptogenic ischemic stroke

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KEYWORDS

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Editorial on the Research Topic
Cryptogenic ischemic stroke

Cryptogenic ischemic stroke, an imaging-confirmed ischemic event with no identifiable etiology despite a comprehensive workup (1), and its subtype, embolic stroke of undetermined source (ESUS) (2), remains a challenging diagnosis for vascular neurologists. The Research Topic featured in *Frontiers in Neurology* includes several articles about cryptogenic stroke, they describe uncommon etiologies and guide the selection of optimal therapeutic strategies in the absence of a definitive cause.

Potential causes of cryptogenic stroke can be classified according to the system involved. Cardioembolic sources include left atrial pathology (e.g., covert atrial fibrillation, atrial cardiomyopathy), left ventricular disease, patent foramen ovale (PFO), and valvular disease (3). In this context Zhang et al. describes the use of dual stent retrievers in mechanical thrombectomy for infective endocarditis-associated large vessel occlusion, a strategy that is particularly useful in cases of bifurcation occlusions.

In this Research Topic Saito et al. present findings of a prospective multicenter substudy in Japan, they included 241 patients with recent ischemic stroke, and evaluated a non-invasive, wireless patch ECG during seven days to detect atrial fibrillation (AF). This arrhythmia was detected in 8.7% of patients. Although this rate is lower than in other cohorts (4), the simplicity and accessibility of this diagnostic method are noteworthy.

Three contributions address the relationship between PFO and stroke. Two narrative reviews delve into pathophysiological mechanisms such as *in-situ* thrombosis, paradoxical embolism, atrial cardiopathy, arrhythmias, circulating biomarkers, and genetic predisposition (Li et al.; Amini). Shah et al., proposes a novel diagnostic approach employing transcranial Doppler (TCD) supported by an AI-assisted robotic system. Using transesophageal echocardiography (TEE) as the reference standard for PFO detection, TCD achieved 92% sensitivity and 87.5% specificity in detecting large right-to-left shunts; by contrast, TTE yielded 78.6% and 71.4%, respectively. Discordance between TCD and echocardiographic findings is not uncommon, potentially due to differences in shunt origin or Valsalva maneuver efficacy during TEE (5). These results support the use of TCD a screening tool for PFO detection.

Esnaola Barriola et al. report a case series of 10 patients with mobile aortic arch thrombi associated with atherosclerotic plaques, identified via suprasternal echocardiography performed by neurologists. The patients received anticoagulation, although optimal

management strategies remain unclear (6). Follow-up imaging was also included in this study.

Non-stenotic carotid atherosclerosis is an underrecognized etiology of ischemic stroke, warranting a multimodal diagnostic approach. High-resolution MRI can assess plaque vulnerability and therapeutic response, as demonstrated in a case series by Yang et al.. Additionally, Zhou and Hui conducted a systematic review on contrast-enhanced ultrasound (CEUS) for detecting unstable plaques. Although CEUS demonstrated moderate sensitivity and limited specificity (61%), it remains a cost-effective and accessible alternative compared to advanced imaging modalities.

Acquired hypercoagulability, especially cancer, represents another relevant category in cryptogenic strokes. Nearly 15% of oncology patients experience stroke, and 2–10% are diagnosed with stroke annually. Carneado-Ruiz's narrative review emphasizes diagnostic biomarkers, particularly D-dimer, and treatment considerations in oncologic patients with ischemic stroke. Although anticoagulation is often selected, its superiority over antiplatelet therapy remains unproven, except in specific contexts such as venous thromboembolism with PFO, nonbacterial thrombotic endocarditis, and markedly elevated D-dimer (7). Moreover anticoagulants, including direct oral agents, may increase bleeding risk in this population (8). Diagnostic strategies for cancer-related stroke, including optimal timing and modality, are yet to be standardized.

Biomarker research continues to expand. Beyond D-dimer, cardiac biomarkers such as B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are proposed as markers for ESUS of cardioembolic origin (9). Hang et al. applied Mendelian randomization and genome-wide association studies (GWAS) to assess causal relationships between metabolites and ESUS. Their findings suggest a protective association with O-methylascorbate (X-11593) and implicate various lipid-related metabolites. However, generalizability is limited to European populations, and further research is warranted.

Finally, Ruiz-Franco et al. examined neurological manifestations in a cohort of Fabry disease patients, assessing the prevalence of cryptogenic stroke as a potential early manifestation (10). No association was found, likely due to regional genetic differences or enzyme replacement therapy effects.

In summary, the contributions in this Research Topic provide valuable insights into the multifactorial nature of cryptogenic ischemic stroke and underscore the need for continued multidisciplinary research to refine diagnostic and therapeutic strategies.

## Author contributions

AA-P: Conceptualization, Writing – review & editing, Software, Writing – original draft. LA-P: Writing – review & editing, Writing – original draft. EM: Writing – review & editing, Writing – original draft. PM: Writing – review & editing.

## Conflict of interest

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# Causal relationship between metabolites and embolic stroke: based on Mendelian randomization and metabolomics

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**Purpose:** This research employed Mendelian randomization (MR) methods to explore whether metabolites are causally associated with embolic stroke of undetermined source (ESUS).

**Methods:** Genome-Wide Association Study (GWAS) data regarding metabolites and ESUS were downloaded from the database. Metabolites were employed as exposure factors, ESUS served as the outcome variable, and single nucleotide polymorphisms (SNPs) exhibiting significant association with ESUS were chosen as instrumental variables. The causal association between exposure factor metabolites and the outcome variable ESUS was assessed using two methods: MR-Egger regression and inverse variance-weighted (IVW) analysis.

**Results:** A causal relationship was observed between X-11593--O-methylascorbate* and ESUS, indicating a protective factor. Moreover, a causal relationship was identified between cholesterol esters in large very-low-density lipoprotein (VLDL), cholesterol esters in medium low-density lipoprotein (LDL), concentration of medium LDL particles, phospholipids in medium LDL, phenylalanine, total cholesterol in small LDL, total lipids in medium LDL and ESUS, representing risk factor. Funnel plots exhibited a symmetrical distribution of SNPs, while pleiotropic tests ($p > 0.05$) and leave-one-out tests indicated that the results were relatively stable.

**Conclusion:** Metabolites are causally associated with ESUS. LDL and VLDL-related metabolites are identified as risk factors for ESUS.

KEYWORDS

**metabolite, Mendelian randomization, embolic stroke of undetermined source, genome-wide association study, inverse variance-weighted**

## 1 Introduction

Stroke is a serious disease marked by high morbidity, recurrence, disability, and mortality rates. It poses significant health risks and economic burdens. The main pathological types are ischemic and hemorrhagic stroke, with embolic stroke of undetermined source (ESUS) accounting for about 17% of ischemic stroke patients (1). ESUS refers to non-lacunar

ischemic stroke where intracranial or extracranial vascular stenosis and cardiogenic emboli are excluded (2). Currently, effective treatment options for ESUS remain limited. Therefore, understanding the etiology and risk factors of ESUS and identifying potential diagnostic treatments are crucial for public health (3).

Metabolites are intermediates or end products of metabolic reactions and their levels can be impacted by numerous factors, including diet, genetics, gut microbiota, lifestyle, and disease (4). Through metabolite analysis, the mechanisms of disease development can be understood, targets for disease intervention can be sought, disease risk can be mitigated, and stratified prevention and management can be achieved (5). Currently, the causal function of metabolites in disease etiology has been demonstrated, providing new ideas for diagnosis and treatment. Additionally, many metabolites exhibit high heritability, making human genetics a method for assessing the impact of metabolites on disease outcomes.

Building on this understanding, Mendelian Randomization (MR), a causal inference method, has recently gained widespread usage in the field of epidemiology. This approach relies on genome-wide association study (GWAS) data, utilizing genetic variants as instrumental variables (IVs) in order to examine the impact of exposure on disease outcomes (6). Due to the random assignment of genetic variation at conception, this approach can break the confounding of most risk factors and reduce the tendency of confounding to bias the results, thus achieving the effect of simulating randomized controlled trials. In this research, MR analysis methods utilizing GWAS data were employed for the investigation of the causal association between metabolites and ESUS. The aim was to present novel ideas and directions for the future diagnosis and treatment of ESUS.

# 2 Methodology

## 2.1 Data selection

In this study, metabolite-related GWAS data were used as exposure factors. Single nucleotide polymorphisms (SNPs) exhibiting significant association with ESUS were employed as IVs, while ESUS-associated data were used as outcome variables.

## 2.2 Data sources

Metabolite-related data and GWAS data for ESUS in this study were derived from databases encompassing https://gwas.mrcieu.ac.uk/, https://www.ebi.ac.uk/gwas/, and https://www.finngen.fi/en. Metabolite-related GWAS data utilized in this research mainly included met-a-536, met-c-881, met-c-905, met-c-906, met-c-907, met-c-908, met-c-919, and met-c-924. GWAS data for ESUS was I9_STR_EMBOLIC. As this study relied on publicly available data, ethical approval or consent was not required.

## 2.3 Relevance analysis

MR Assay meets the following three hypothetical premiums:

① Relevance hypothesis: significant association between IVs and metabolites (exposure factors);

② Independence hypothesis: lack of association between IVs and ESUS (outcome variable) and other confounding factors;

③ Exclusivity hypothesis: IVs can only influence ESUS (outcome variable) by affecting metabolites (exposure factors) and cannot influence ESUS through other pathways (7).

SNPs strongly associated with exposure factors were selected as IVs and filtered at the condition of $p < 5e\text{-}08$.

## 2.4 Linkage disequilibrium

Linkage disequilibrium (LD) is the phenomenon where genetic variants located close to each other on a chromosome tend to be inherited together more often than would be expected by chance. This means that the likelihood of specific alleles (gene variants) from two or more loci appearing together on a single chromosome is greater than if the alleles were distributed randomly (8). To mitigate potential bias from LD, the screening criteria for single nucleotide polymorphisms (SNPs) are outlined below:

(1) Kb > 10,000;
(2) $r^2 < 0.001$.

Here, Kb refers to the range of regions in LD. $r^2$ is evaluated between 0 and 1, where $r^2 = 1$ denotes a complete LD relationship between two SNPs, while $r^2 = 0$ suggests a complete linkage equilibrium relationship between two SNPs, indicating the random assignment of these two SNPs (9).

## 2.5 Removing weak tool variables

To avoid bias for weak IVs, the F-statistic was utilized to determine their strength. An IV with an *F*-value <10 was defined as weak, while an F-value >10 was considered a non-weak IV (10). The strength of selected individual tool variables was evaluated by formula ($F = \frac{N-K-1}{K} \times \frac{R^2}{1-R^2}$), with N representing the total sample size of GWAS data exposed, K representing the number of screened IVs, and $R^2$ representing the proportion of exposures explained by IV. $R^2$ is calculated as $R^2 = 2 \times (1\text{-MAF}) \times \text{MAF} \times (\beta/\text{SD})^2$, where MAF represents the minor allele frequency, β indicates the effect size of the allele, and SD denotes the standard deviation (11).

## 2.6 Mendelian randomization analysis

MR-Egger regression and inverse variance-weighted (IVW) analysis were employed to reveal the causal association between exposure factor metabolites and outcome variable ESUS. IVW was utilized as the main method to evaluate the reliability of the findings, defining $p < 0.05$ as a positive result (12). The R package "TwoSampleMR" was utilized for the visualization of MR results, including forest plots, perceptual analysis plots, and scatter plots.

## 2.7 Sensitivity analyses

IVW and MR-Egger tests were employed to assess the heterogeneity. If the *p*-value was <0.05, it indicates heterogeneity in the study. IVs are considered pleiotropic if they influence outcome

occurrence through factors other than exposure factors (13). Pleiotropy can lead to independence and exclusivity assumptions that do not hold. The MR-Egger intercept test can detect the pleiotropy of the data and assess the robustness of the results (14). Data were considered pleiotropic on $p$-value <0.05. Sensitivity analysis was conducted using the "leave-one-out method," a systematic process that involves the step-by-step removal of individual SNP results. This method evaluates the combined effect of the remaining SNPs, aiming to examine whether a single SNP impacts the causal effect. Funnel plots were drawn using R language to observe whether SNPs were symmetrical and thereby determine the reliability of the findings.

## 2.8 Statistical methods and software

In this study, R 4.3.1 software[1] and strawberry-perl 5.32.1.1 software[2] were utilized to conduct the relationship analysis of MR. Statistical significance was determined at $p < 0.05$.

# 3 Results

## 3.1 Screening instrumental variables

The selection of SNPs strongly associated with exposure and outcome factors was carried out by utilizing the R packages, including "dplyr," "gwasglue," "tidyr," and "VariantAnnotation". The filtration condition was set at $p < 5e\text{-}08$. A total of 8 SNP datasets strongly linked with metabolites were identified:

met-a-536 (X-11593--O-methylascorbate*),

met-c-881 (Cholesterol esters in large very-low-density lipoprotein (VLDL)),

met-c-906 (Total lipids in medium LDL),

met-c-907 (Concentration of medium LDL particles),

met-c-908 (Phospholipids in medium LDL),

met-c-919 (Phenylalanine), and.

met-c-924 (Total cholesterol in small LDL) (Figure 1; Table 1).

## 3.2 Screening instrumental variables

SNPs strongly associated with exposure and outcome factors were selected employing the R packages, such as "dplyr," "gwasglue," "tidyr," and "VariantAnnotation" with filtration condition of $p < 5e\text{-}08$. Among them, 6 SNPs in met-a-536 were strongly associated with ESUS; 25 SNPs in met-c-881 were strongly associated with ESUS; 25 SNPs in met-c-905 were strongly associated with ESUS; 23 SNPs in met-c-906 were strongly associated with ESUS; 23 SNPs in met-c-907 were strongly associated with ESUS; 20 SNPs in met-c-908 were strongly associated with ESUS; 4 SNPs in met-c-919 were strongly associated with ESUS; and 21 SNPs in met-c-924 were strongly associated with ESUS. $F$-value calculations and removal of confounding factors were performed for the selected SNPs by employing the R package MR. As a result, no weak IVs and confounding factors were identified (Table 2).

## 3.3 Findings of Mendelian randomization analysis

The causal association between exposure factors and outcomes was assessed by employing MR-Egger regression and IVW analysis. Visualization of MR results was performed by utilizing the R package "TwoSampleMR," including forest plots and scatter plots. The findings exhibited a causal relationship between X-11593--O-methylascorbate ($p = 0.029$, OR = 0.222, 95% CI: 0.058 ~ 0.858) and ESUS, indicating a protective factor. Cholesterol esters in large VLDL ($p = 0.046$, OR = 1.184, 95% CI: 1.003 ~ 1.398), cholesterol esters in medium LDL ($p = 0.030$, OR = 1.205, 95% CI: 1.018 ~ 1.426), total lipids in medium LDL ($p = 0.041$, OR = 1.204, 95% CI: 1.008 ~ 1.438), the concentration of medium LDL particles ($p = 0.042$, OR = 1.203, 95% CI: 1.006 ~ 1.437), phospholipids in medium LDL ($p = 0.022$, OR = 1.239, 95% CI: 1.031 ~ 1.489), phenylalanine ($p = 0.046$, OR = 1.749, 95% CI: 1.009 ~ 3.032), and total cholesterol in small LDL ($p = 0.024$, OR = 1.225, 95% CI: 1.028 ~ 1.461) were causally related to ESUS and were identified as risk factors (Figures 2A–G).

## 3.4 Sensitivity analyses

IVW methods and MR-Egger regression were used for analyzing the heterogeneity. The results revealed that all datasets had $p > 0.05$, and no heterogeneity was observed. Egger regression orientation analysis was further used to analyze whether there was orientation level multidirectionality. The results showed that all datasets had $p > 0.05$, and no orientation-level multidirectionality was observed (Table 3). The funnel plot showed that SNPs were symmetrically distributed and the results obtained were relatively stable (Figure 3). The leave-one-out method was used to eliminate SNPs one by one and observe any changes in the effect values. The results indicated that no strong influential SNP loci were identified (Figure 4).

# 4 Discussion

In this study, public large-sample GWAS data were employed for analyzing the potential causal association between metabolites and ESUS using R language. X-11593--O-methylascorbate* (IWV, $p = 0.029$, OR = 0.222, 95% CI: 0.058 ~ 0.858) exhibited a causal relation with ESUS and was identified as a protective factor. Cholesterol esters in large VLDL (IWV, $p = 0.046$, OR = 1.184, 95% CI: 1.003 ~ 1.398), cholesterol esters in medium LDL (IWV, $p = 0.030$, OR = 1.205, 95% CI: 1.018 ~ 1.426), total lipids in medium LDL (IWV, $p = 0.041$, OR = 1.204, 95% CI: 1.008 ~ 1.438), concentration of medium LDL (IWV, $p = 0.042$, OR = 1.203, 95% CI: 1.006 ~ 1.437), phospholipids in medium LDL (IWV, $p = 0.022$, OR = 1.239, OR = 1.239, 95% CI: 1.031 ~ 1.489), phenylalanine (IWV, $p = 0.046$, OR = 1.749, 95% CI: 1.009 ~ 3.032), and total cholesterol in small LDL (IWV, $p = 0.024$, OR = 1.225, 95% CI: 1.028 ~ 1.461) were causally associated with ESUS and were identified as risk factors.

1 https://cloud.r-project.org/

2 https://strawberryperl.com/

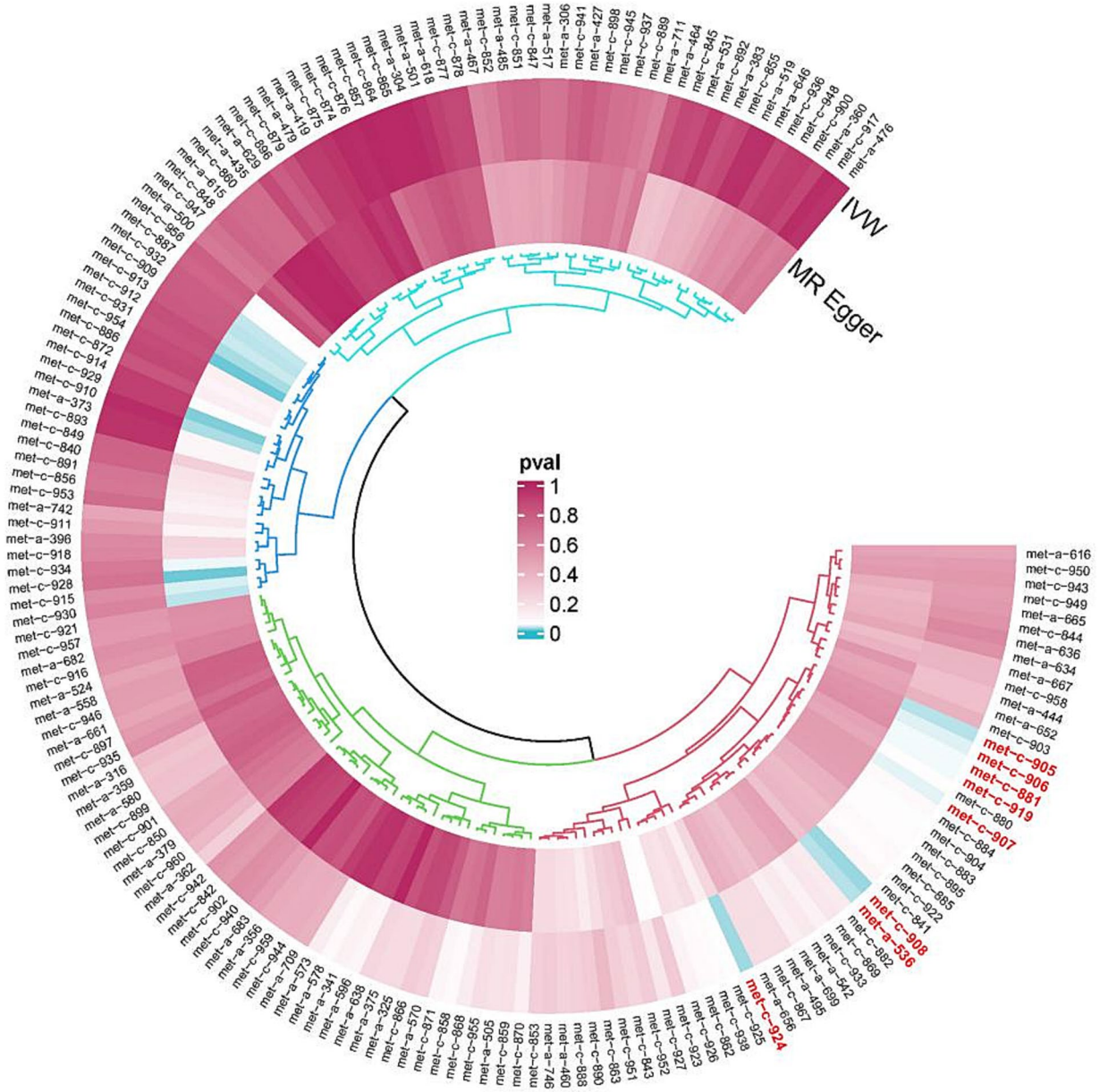


FIGURE 1
GWAS dataset of SNPs strongly associated with metabolites and ESUS.

Stroke represents a serious condition that is categorized into ischemic and hemorrhagic strokes. Among them, ischemic stroke without a clear cause is called cryptogenic stroke, with ESUS being one of its subtypes (15, 16). Alterations in metabolite levels are regarded as the primary response of biological systems to various biological events. They can amplify small changes in genes and proteins and, more directly, precisely, and sensitively, reflect the physiological and pathological conditions of the body. Consequently, metabolites are associated with numerous human diseases (17). Recent studies indicate that metabolites are related to stroke and play crucial roles in its onset and progression. Inhibition of metabolite levels has been shown to delay the occurrence and development of ESUS.

This study presents several advantages. Firstly, it utilized large sample GWAS data, ensuring the reliability of the results. Secondly, SNPs were carefully screened through association analysis, LD analysis, and the removal of weak instrumental variables and confounders, effectively mitigating potential bias (18, 19). Thirdly, the symmetrical distribution of SNPs was confirmed by funnel plots, and the relatively stable results were supported by pleiotropy and leave-one-out tests. Lastly, the exploration of the molecular mechanisms by investigating the causal association between metabolites and ESUS, with metabolites as exposure factors, holds significant clinical relevance (20).

This study has several limitations. Although MR-Egger regression and IVW methods indicated no significant heterogeneity between the analyses ($p > 0.05$), potential sources of heterogeneity may arise from variations in instrumental variables (IVs), including differences in analytical platforms, experimental designs, and population characteristics, necessitating a more detailed exploration of these

TABLE 1 Metabolites related GWAS data information.

| GWAS-ID | NAME | Sample | SNPs |
|---|---|---|---|
| met-a-536 | X-11593--O-methylascorbate* | 7,788 | 2,545,561 |
| met-c-881 | Cholesterol esters in large VLDL | 19,273 | 11,820,655 |
| met-c-905 | Cholesterol esters in medium LDL | 19,273 | 11,820,631 |
| met-c-906 | Total lipids in medium LDL | 19,273 | 11,818,458 |
| met-c-907 | Concentration of medium LDL particles | 19,273 | 11,818,918 |
| met-c-908 | Phospholipids in medium LDL | 21,558 | 11,871,461 |
| met-c-919 | Phenylalanine | 22,663 | 12,042,964 |
| met-c-924 | Total cholesterol in small LDL | 21,556 | 11,871,461 |

TABLE 2 Mitochondrial dataset tool variation scale.

| GWAS-ID | Type | SNPs |
|---|---|---|
| met-a-536 | ESUS | 6 |
| met-c-881 | ESUS | 25 |
| met-c-905 | ESUS | 25 |
| met-c-906 | ESUS | 23 |
| met-c-907 | ESUS | 23 |
| met-c-908 | ESUS | 20 |
| met-c-919 | ESUS | 4 |
| met-c-924 | ESUS | 21 |

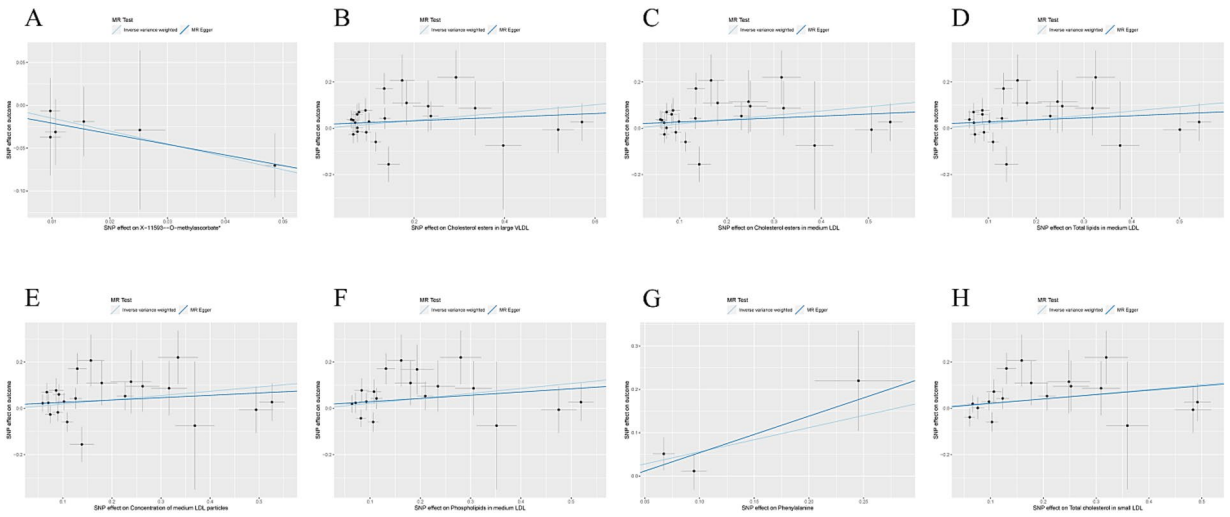


FIGURE 2
**(A)** Scatter plot of the causal relationship between X-11593--O-methylascorbate* and ESUS, mainly evaluated by IVW method; **(B)** Scatter plot of the causal relationship between Cholesterol esters in large VLDL and ESUS, mainly evaluated by IVW method; **(C)** Scatter plot of the causal relationship between Cholesterol esters in medium LDL and ESUS, mainly evaluated by IVW method; **(D)** Scatter plot of the causal relationship between Total lipids in medium LDL and ESUS, mainly evaluated by IVW method; **(E)** Scatter plot of the causal relationship between Concentration of medium LDL particles and ESUS, mainly evaluated by IVW method; **(F)** Scatter plot of the causal relationship between Phospholipids in medium LDL and ESUS, mainly evaluated by IVW method; **(G)** Scatter plot of the causal relationship between Phenylalanine and ESUS, mainly evaluated by IVW method; **(H)** Scatter plot of the causal relationship between Total cholesterol in small LDL and ESUS, mainly evaluated by IVW method.

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TABLE 3 Heterogeneity analysis.

| GWAS-ID | Type | Heterogeneity tests | | Directional horizontal pleiotropy tests |
|---|---|---|---|---|
| | | MR Egger | IVW | |
| met-a-536 | ESUS | 0.983 | 0.993 | 0.780 |
| met-c-881 | ESUS | 0.146 | 0.151 | 0.401 |
| met-c-905 | ESUS | 0.158 | 0.160 | 0.365 |
| met-c-906 | ESUS | 0.105 | 0.110 | 0.419 |
| met-c-907 | ESUS | 0.109 | 0.122 | 0.499 |
| met-c-908 | ESUS | 0.181 | 0.209 | 0.560 |
| met-c-919 | ESUS | 0.240 | 0.450 | 0.762 |
| met-c-924 | ESUS | 0.277 | 0.337 | 0.904 |

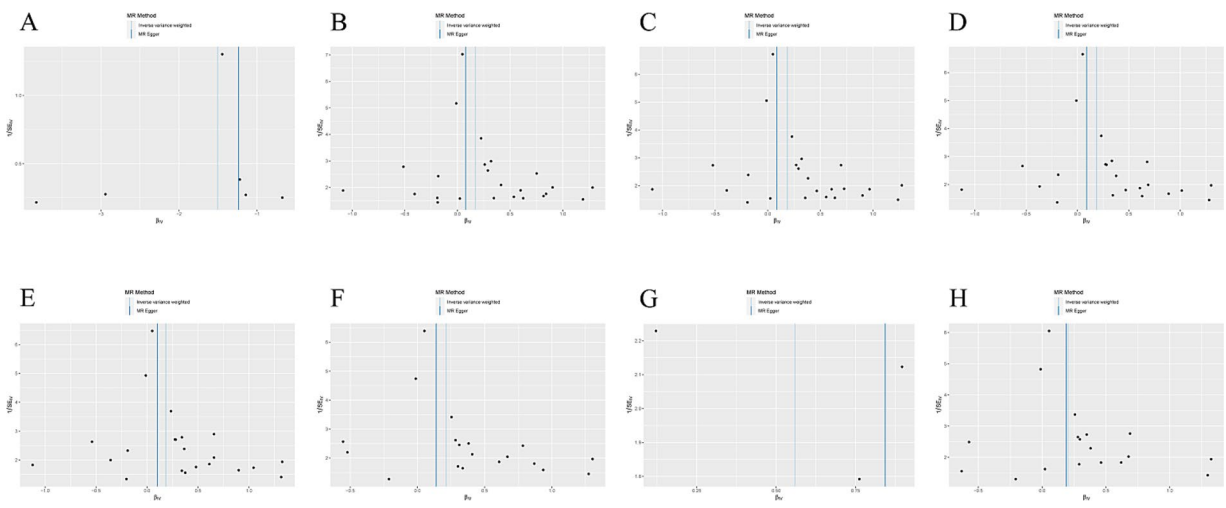


FIGURE 3
**(A)** Funnel plot of the causal relationship between X-11593--O-methylascorbate* and ESUS, mainly evaluated by IVW method; **(B)** Funnel plot of the causal relationship between Cholesterol esters in large VLDL and ESUS, mainly evaluated by IVW method; **(C)** Funnel plot of the causal relationship between Cholesterol esters in medium LDL and ESUS, mainly evaluated by IVW method; **(D)** Funnel plot of the causal relationship between Total lipids in medium LDL and ESUS, mainly evaluated by IVW method; **(E)** Funnel plot of the causal relationship between Concentration of medium LDL particles and ESUS, mainly evaluated by IVW method; **(F)** Funnel plot of the causal relationship between Phospholipids in medium LDL and ESUS, mainly evaluated by IVW method; **(G)** Funnel plot of the causal relationship between Phenylalanine and ESUS, mainly evaluated by IVW method; **(H)** Funnel plot of the causal relationship between Total cholesterol in small LDL and ESUS, mainly evaluated by IVW method.

sources to enhance the validity of the findings. Additionally, the GWAS data are predominantly derived from European populations, resulting in a lack of representation from African and Asian cohorts; thus, future research should include diverse populations for a more comprehensive understanding of the associations examined. The number of IVs for SNPs within each dataset is relatively limited, indicating a need for larger sample sizes to identify additional SNPs as IVs. While this research utilized Mendelian Randomization (MR) to analyze the causal relationship between metabolites and ESUS, no mechanistic studies were conducted to elucidate the underlying biological processes, which could provide valuable insights. Furthermore, the findings may be influenced by residual confounding factors not fully accounted for in the analyses, and it is essential to consider these impacts in future investigations. Lastly, the analytical methods employed may have limitations in detecting all possible causal relationships, warranting the exploration of alternative methodologies, such as sensitivity analyses or different statistical approaches, to validate the robustness of the results.

## 5 Conclusion

This research evaluated the potential causal effect of metabolites on embolic stroke of undetermined source (ESUS) through Mendelian Randomization (MR) analysis. The findings revealed that X-11593-O-methylascorbate is causally related to ESUS, functioning as a protective factor. Conversely, several metabolites, including cholesterol esters in large very-low-density lipoprotein (VLDL), cholesterol esters in medium low-density lipoprotein (LDL), total lipids in medium LDL, concentration of medium LDL particles, phospholipids in medium LDL, phenylalanine, and total cholesterol in small LDL, were identified as risk factors associated with ESUS.

While these outcomes provide a theoretical basis for further investigations into the dynamics of metabolite levels during ESUS, it is crucial to explore the underlying biological mechanisms connecting these metabolites to ESUS (21). Future studies should incorporate experimental approaches to better understand how specific

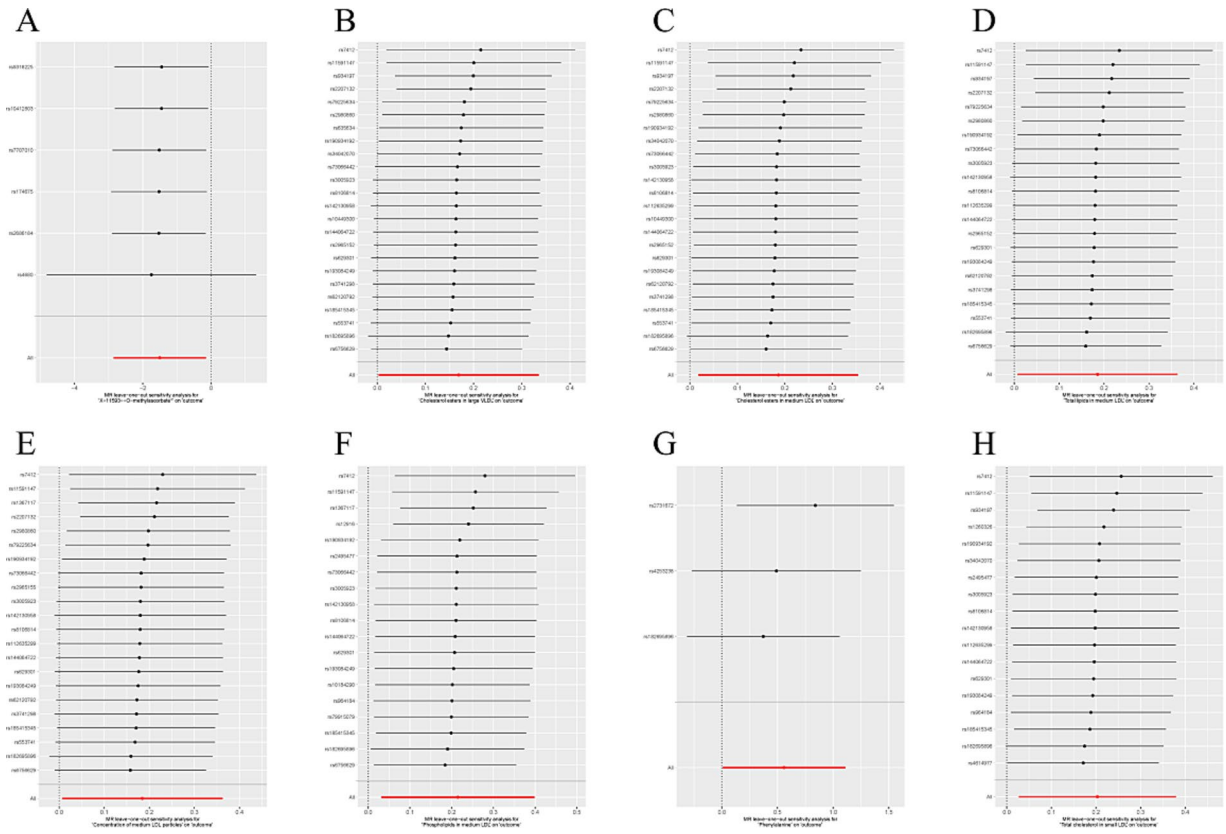


FIGURE 4
**(A)** "Leave one method" forest map of the causal relationship between X-11593--O-methylascorbate* and ESUS, mainly evaluated by IVW method; **(B)** "Leave one method" forest map of the causal relationship between Cholesterol esters in large VLDL and ESUS, mainly evaluated by IVW method; **(C)** "Leave one method" forest map of the causal relationship between Cholesterol esters in medium LDL and ESUS, mainly evaluated by IVW method; **(D)** "Leave one method" forest map of the causal relationship between Total lipids in medium LDL and ESUS, mainly evaluated by IVW method; **(E)** "Leave one method" forest map of the causal relationship between Concentration of medium LDL particles and ESUS, mainly evaluated by IVW method; **(F)** "Leave one method" forest map of the causal relationship between Phospholipids in medium LDL and ESUS, mainly evaluated by IVW method; **(G)** "Leave one method" forest map of the causal relationship between Phenylalanine and ESUS, mainly evaluated by IVW method; **(H)** "Leave one method" forest map of the causal relationship between Total cholesterol in small LDL and ESUS, mainly evaluated by IVW method.

metabolites influence the pathophysiology of ESUS (22, 23). For example, *in vitro* studies could be conducted to investigate the effects of these metabolites on endothelial function, coagulation pathways, and inflammatory responses, which are critical in the development of ESUS. Understanding these mechanisms would not only clarify the causal relationships identified but also inform clinical interventions aimed at modifying metabolite levels to reduce the risk of ESUS. In addition to exploring biological mechanisms, it is essential to strengthen the clinical application prospects of the findings (24, 25). The study suggests that managing metabolite levels may help reduce the incidence of ESUS; however, the discussion lacks a thorough exploration of how these findings can be translated into clinical practice. Specifically, there is a need to elaborate on potential directions for drug development and personalized treatment strategies based on the identified metabolites (26).

In summary, while this study lays a solid foundation for understanding the causal relationships between metabolites and ESUS, future research should prioritize elucidating the underlying biological mechanisms and translating these findings into actionable clinical strategies. By doing so, it may be possible to not only mitigate the risk of ESUS but also pave the way for innovative therapeutic approaches that harness the power of metabolite modulation in clinical practice.

## Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

## Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of

kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

## Author contributions

YH: Writing – original draft, Writing – review & editing. ZC: Conceptualization, Data curation, Formal analysis, Writing – original draft. JR: Data curation, Formal analysis, Investigation, Supervision, Writing – review & editing. YW: Writing – review & editing. KZ: Project administration, Resources, Visualization, Writing – original draft. QZ: Writing – original draft, Writing – review & editing.

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## Conflict of interest

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.

## Publisher's note



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# Dual-stent thrombectomy for recanalization of cerebral embolism caused by infective endocarditis: a case report

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**Methods:** In this case report, we present an in-depth narrative of a patient who was subjected to mechanical thrombectomy (MT) for an obstruction in the main trunk and bifurcation of the left middle cerebral artery subsequent to Infective Endocarditis (IE). Initial intervention using a solitary-stent technique proved to be ineffective; thus, we shifted to a dual-stent strategy, which successfully recanalized the compromised blood vessel.

**Results:** The dual-stent retriever method can be especially advantageous for treating persistent clots that occur at arterial bifurcations resisting the efforts of a single-stent retriever during the MT process.

**Conclusion:** Dual-stent thrombectomy increases the likelihood of clot extraction due to its ability to encompass a larger area of the thrombus within the stent's framework, potentially improving the clinical outcomes.

KEYWORDS

**dual-stent thrombectomy, infective endocarditis, large-vessel occlusion, valve replacement surgery, clinical outcomes**

## Background

Cerebral embolic events (CEEs) are common complications of IE. Embolism of the middle cerebral artery is the most prevalent type of CEE, presenting with large emboli in a significant proportion of cases. MT is the standard care for acute ischemic stroke (AIS) due to large vessel occlusion (LVO); however, MT fails to achieve adequate recanalization in nearly one-third of these cases. Especially, LVO involving bifurcation is usually resistant and has a high clot burden, reducing the possibility of successful recanalization (Figure 1B). Rescue therapy using dual-stentrievers yields good results for clots refractory to single-stentriever treatment (Figure 1C).

A 56-year-old female patient presented with symptoms of right-sided limb weakness and dysarthria. She was admitted to the hospital 5 h after the onset of symptoms. A brain computed tomography (CT) scan was performed, which ruled out the presence of intracerebral hemorrhage. The patient reported intermittent low-grade fevers 2 months before hospitalization, peaking at a body temperature of 37.7°C. Her medical history was unremarkable for other conditions, such as hypertension, diabetes mellitus, coronary artery disease, or arrhythmia.

On admission, she was conscious and her vital signs were as follows: blood pressure 159/92 mmHg; pulse rate 76 beats/min; temperature 37.2°C, and respiration rate 19 per

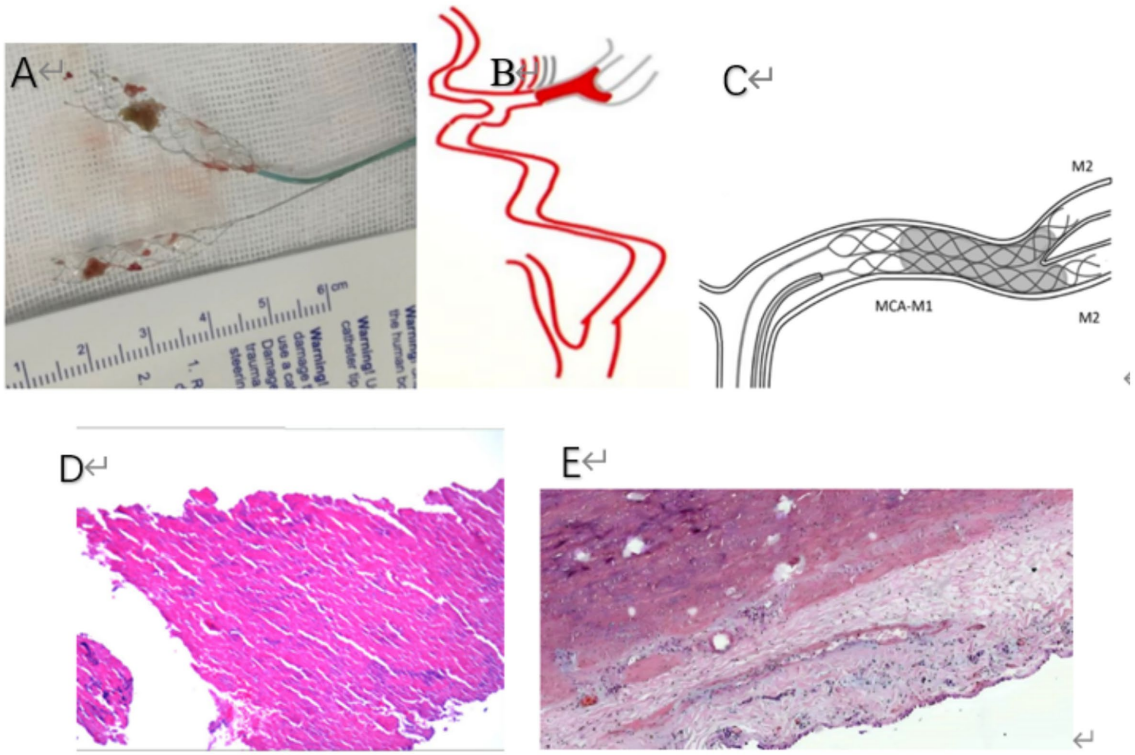


FIGURE 1
**(A)** The clot was successfully extracted by using a dual-stent technique. **(B)** A schematic representation depicts a thrombus obstructing the middle cerebral artery and extending to its bifurcation site. **(C)** A schematic illustration demonstrates the concurrent deployment of dual-stent retrievers within a clot lodged in the M1 segment of the middle cerebral artery (MCA-M1). The distal ends of these retrievers are shown reaching into both branches of the MCA bifurcation, corresponding to the M2 segments. **(D)** The pathological examination following stent thrombectomy revealed a mass of gray-white tissue that was visually observed to have a fleshy and solid texture. The dimensions of the tissue were measured to be 0.4 cm in length, 0.3 cm in width, and 0.3 cm in height. Upon microscopic analysis, it was determined that the specimen consists predominantly of red blood cells, accounting for about 70% of the sample. The remaining 30% is made up of white blood cells, fibrin, and platelets. The examination was conducted at a magnification of 10 times using hematoxylin and eosin (HE) staining. **(E)** Pathological results after heart valve resection surgery, under the microscope, there was proliferation of fibrous tissue in the valve leaflets, hyaline degeneration, calcium salt deposition, small vessel proliferation, lymphocyte infiltration, and local thrombosis. Pathological diagnosis: (Aortic Valve) Chronic valvulitis. (HE × 10).

minute. Neurological objective assessment on admission showed that the patient was conscious, her head and eyeballs were deviated to the left, with mixed aphasia, right hemiplegia, and shallow nasolabial fold on the right side. She exhibited uncooperative tongue extension on examination. Her Right Babinski sign and Chaddock's sign were positive. A grade 3/6 systolic ejection murmur was heard in the auscultation area of the aortic valve.

She was admitted with an NIHSS score of 16, and the electrocardiogram demonstrated normal sinus rhythm and normal axis without any ischemic changes or pathological Q waves. Routine blood tests, bleeding and clotting times, blood glucose levels, and kidney function were all within normal limits. Magnetic resonance imaging (MRI) of the brain revealed hyperintense signals on T1-weighted and T2-weighted images in the left basal ganglia and caudate nucleus (Figure 2A). Magnetic resonance angiography (MRA) confirmed an occlusion in the left middle cerebral artery (Figure 2B). Further evaluation indicated a distal thrombus in the left middle cerebral artery (MCA), which extended to both the superior and inferior divisions.

Consequently, the diagnosis of acute cerebral infarction was confirmed. Additionally, the patient presented with an unexplained fever.

Beyond the time window of intravenous thrombolysis upon her admission, the patient was transferred to the angiosuite. With the consent of the patient's family, an emergency cerebral angiography was performed, followed by endovascular thrombectomy. The occlusion of the left middle cerebral artery was identified (Figure 3A). Following an unsuccessful attempt with a single-stent thrombectomy, a dual-stent thrombectomy strategy was adopted, and the blood clot was successfully removed (Figure 1A). This intervention led to successful recanalization of the affected artery, achieving a modified thrombolysis in cerebral infarction (mTICI) score of 3 (Figure 3G).

After completing the active therapeutic intervention, the patient exhibited a noticeable improvement in her condition. Physical examination revealed a minor reduction in the fluency of her speech, while the muscle strength of her right limbs was rated at grade 5 on the medical scale. The patient was deemed fit for discharge after recovery (Figure 3H). Upon discharge, her National Institutes of Health Stroke Scale (NIHSS) score and her Modified Rankin Scale (MRS) score were both 2 (Figure 3H).

Endovascular treatment was as follows: All procedures were conducted by an experienced neurointerventionist using a monoplane angiography system. A 6F guiding support catheter (ev3, Plymouth, MN) was introduced into the Petrous segment of the left internal carotid

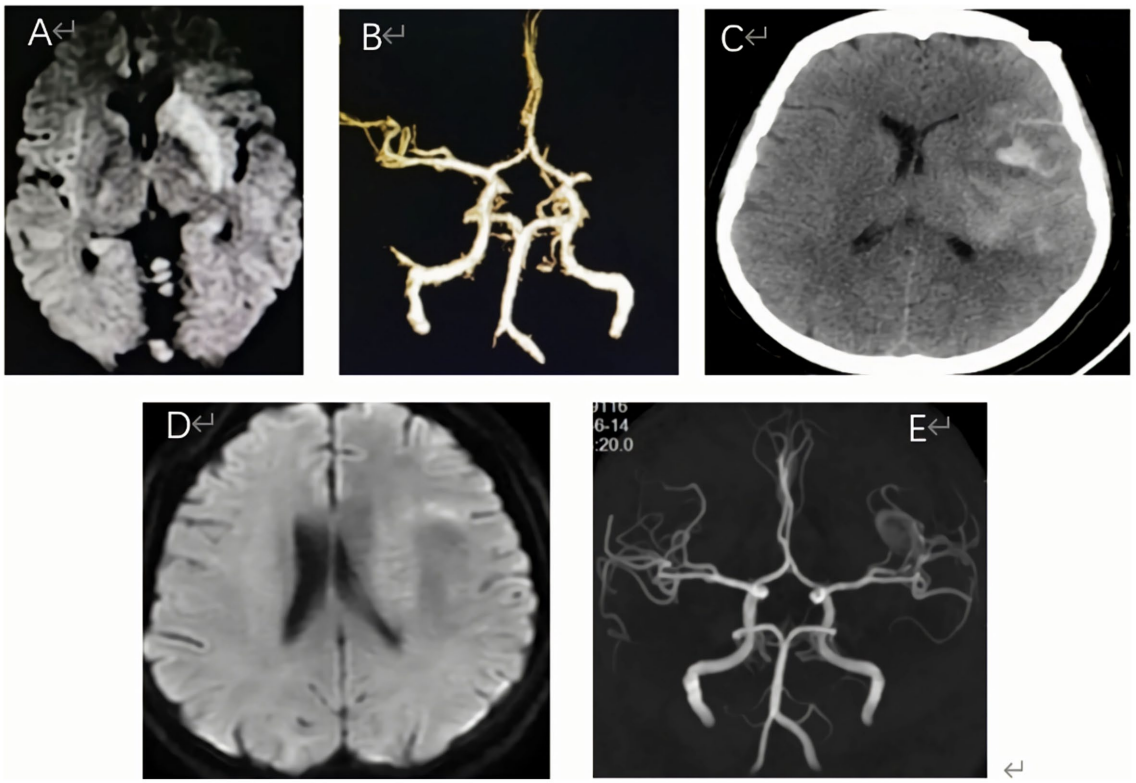


FIGURE 2
**(A)** Diffusion-weighted imaging (DWI) demonstrated prominent hyperintense signals within the basal ganglia and caudate nucleus, indicating potential acute ischemic changes. **(B)** Magnetic resonance angiography (MRA) confirmed the presence of an occlusion in the left middle cerebral artery. **(C)** A non-contrast CT head scan found contrast extravasation, and no intracranial hemorrhage or hyperperfusion. **(D)** Three days after oneset, brain MRI showed significant improvement in the high signal on the basal ganglia, but no significant increase of infarcted tissue. **(E)** Brain MRA indicated complete recanalization of the left MCA on the third day after operation.

artery. Then, a Rebar 18 microcatheter (ev3, Plymouth, MN) was navigated over the 300 cm long 0.014-in ASAHI guidewire (Asahi Intecc Medical, Japan), beyond the distal end of the occlusive clot under roadmap guidance. After withdrawing the micro-guidewire, the length of the occlusion and the distal lumen of the lesion was confirmed through microcatheter angiography (Figure 3B). After the complete release of the stent (Solitaire-FR, 4 mm × 20 mm, Medtronic), we observed the partial recanalization of the left middle cerebral artery (Figure 3C). Thrombectomy with three passes of the Solitaire-FR device 4 mm × 20 mm in the inferior MCA trunk was unsuccessful, and a left MCA bifurcation clot was observed (Figure 3D). At this point, we decided to employ a novel strategy for MT incorporating two Solitaire FR devices. A 6F guiding catheter could not be placed at the same time at two Rebar-18 microcatheters. Therefore, the Rebar-18 microcatheter was first placed in the M2 segment of the left MCA through the superior MCA trunk, while a Solitaire-FR 4 mm × 20 mm was placed such that the proximal end of the stent did not cover the bifurcation. Subsequently, the microcatheter was completely removed from the 6F guiding, leaving a bare Solitaire-FR inside the 6F guiding. Then, the inferior MCA trunk was catheterized with the same microcatheter and the Solitaire-AB 6 mm × 30 mm was unfolded by withdrawing the microcatheter (Figures 3E,F). When the microcatheter tip was nearly aligned with the bifurcation, we pulled the first Solitaire-FR to engage the clot. We continued to withdraw the microcatheter to position the second Solitaire FR in parallel (Figure 1C). Then, both stents were slowly pulled together into the 6F guiding under continuous aspiration. As resistance was felt while retracting the stent retriever, the entire assembly was slowly withdrawn under continuous aspiration. Subsequent follow-up angiograms showed the mTICI 3 reperfusion of MCA (Figure 3G). The interval between groin puncture and final revascularization was 98 min. After endovascular treatment, a CT scan confirmed no intracranial hemorrhage or hyperperfusion (Figure 2C). Brain MRI showed significant improvement in the high T1/T2 signal on the left basal ganglia (Figure 2D). MRA indicated complete recanalization of the left MCA on the third postoperative day (Figure 2E).

Further diagnostic assessments were conducted during the hospital stay. The blood culture test yielded a positive result for group streptococcus. Additionally, the level of antistreptolysin O was notably increased, reaching a titer of 263.72 IU/mL. In histopathological examinations, microscopic examination revealed that red blood cells constituted approximately 70%, while white blood cells, fibrin, and platelets collectively comprised 30%. The results were consistent with the study conducted by Thiene G et al. (1). A transesophageal echocardiogram (TEE) indicated the presence of thickened aortic valve leaflets accompanied by unusual growth, suggesting a high likelihood of vegetation. Consistently, we observed aortic regurgitation. Notably, a 9 by 10-mm mass was detected at the aortic valve's base (See Supplementary Video). The patient continued to experience intermittent, mild fevers, with temperatures fluctuating between 37.5 and 37.9°C.

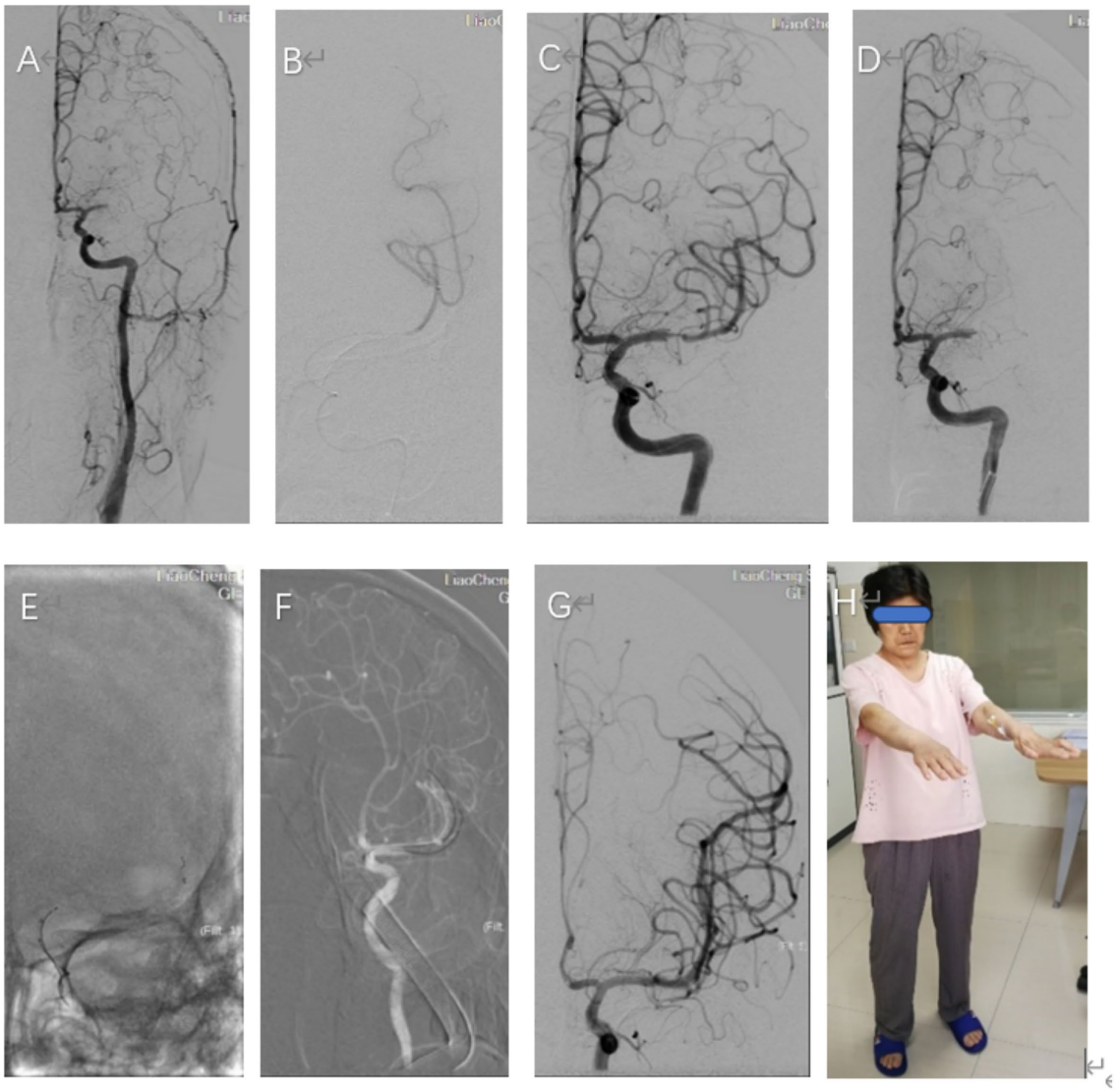


FIGURE 3
**(A)** A frontal angiogram showing, Left carotid angiogram confirmed occlusion of the left middle cerebral artery (MCA, M1 segment). **(B)** The presence of the distal true lumen was verified through the administration of contrast media via a microcatheter, successfully visualizing the lumen's continuity. **(C)** Upon the full deployment of the stent, a partial restoration of blood flow was achieved in the left middle cerebral artery. The stent used was a 4 mm × 20 mm SOLITAIRE-FR stent. **(D)** Persistent occlusion of the left MCA after three passes with the single-stent retriever, and observed in the angiographic images. **(E,F)** The deployment of two stents within the M2 trunk's superior and inferior branches was visualized through a fluoroscopic anteroposterior projection, which revealed the positioning of the stent retrievers in the left middle cerebral artery (MCA). Post-deployment, a contrast agent was injected to assess the stentriever positioning and vascular patency. **(G)** A frontal angiographic image demonstrates the full restoration of blood flow in the left middle cerebral artery (MCA), resulting in a modified Thrombolysis in Cerebral Infarction (mTICI) score of 3, indicating optimal reperfusion. **(H)** At the time of discharge, the patient's neurological status was assessed using the National Institutes of Health Stroke Scale (NIHSS), which resulted in a score of 2, indicating mild stroke severity. Additionally, her functional outcome was evaluated with the Modified Rankin Scale (MRS), yielding a score of 2, suggesting slight disability affecting daily activities.

The patient was diagnosed with a cerebral embolism, which was attributed to subacute bacterial endocarditis. Consequently, the patient underwent aortic valve replacement. We scheduled a heart valve replacement surgery. The pathological results can be seen in Figure 1E. Postoperatively, the patient was consistently administered warfarin and underwent regular follow-up assessments for 2 years. To date, the patient's health status has been favorable.

## Discussion

The incidence rate of IE embolism is 22–50%. It can affect all arteries, with cerebral artery embolism being the most common type (2). This type presents mostly with large embolus, manifesting as single or multiple lesions on imaging. The prognosis of most patients remains poor. MT has shown a significant benefit for patients with AIS of large intracerebral vessels (3). Rescue therapy using two

simultaneous stentrievers yields good results for patients with clots refractory to MT with a single stentriever (4–6); During the actual operation, left internal carotid arteriography in the frontal projection showed left middle cerebral artery occlusion in this study, extending to both divisions. After the failure of single-stent thrombectomy, we combined the strategy adopted by Li et al. (5) and Cabral et al. (6) and used dual-stentriever thrombectomy as a rescue therapy for bifurcation occlusion. Consequently, we selected an alternative approach, employing a dual-stent technique to accomplish thrombectomy. Simultaneously, the excised vegetation was immediately removed and subjected to histopathological studies (see Figure 1A).

The presence of a high-density sign in a portion of the left cerebral hemisphere on postoperative CT images was attributed to the extravasation of the contrast agent. No severe complications were observed after the procedure. This patient's TEE showed that the vegetation size was 9 mm × 10 mm. Based on the results of Mohananey et al. (7) and Papadimitriou et al. (8), there is an increased risk of re-embolization and mortality during hospitalization if the size exceeds 10 mm. We scheduled the patient for elective open-chest heart valve replacement surgery. The pathological results can be seen in Figure 1E. Under the microscope, we observed the proliferation of fibrous tissue in the valve leaflets, hyaline degeneration, calcium salt deposition, small vessel proliferation, lymphocyte infiltration, and local thrombosis. The pathological diagnosis was chronic valvulitis of the aortic valve (Figure 1D, HE×10).

Positive blood culture results of IE patients are risk factors for cerebrovascular diseases (9). Early valve replacement significantly reduces the risk of recurrence and death. The results of this case report showed Streptococcus spp. as the causative microbe, consistent with the findings of Misfeld et al. (10) Therefore, we performed early valve replacement surgery to prevent related adverse complications.

Therefore, as a rescue technique to MT technique, dual-stent thrombectomy has a high recanalization rate in selected cases and has many advantages. First, it acts as a temporary bypass by allowing the immediate restoration of flow through the clot by expanding the stent within the clot (11). Second, the dual-stent increases the degree of stent expansion, which may reflect the ability of the dual-stent thrombectomy technique to facilitate the device-clot interaction (12). Third, the dual-stent thrombectomy technique results in a longer device surface, which can enhance the device purchase distal to the clot, increasing the chances of removing the clot (13) (Figure 1C). Vega P et al. (14) found that dual-stentriever thrombectomy yields high rates of successful recanalization after the first pass with a low rate of complications, suggesting that it can be an effective and safe first-line treatment for M1 and TICA occlusions. Nevertheless, larger prospective studies are needed to validate the feasibility and safety of this strategy and determine its ability to improve clinical outcomes.

Our search did not find any randomized trials investigating the efficacy and safety of thrombectomy in IE associated with AIS. Moreover, there are few reported cases of thrombolysis or MT in this setting. Therefore, we can only draw conclusions based on some retrospective studies. Our conclusions may not be comprehensive, but they are reasonable inferences based on existing data and experience. This case study demonstrated that the dual-stent MT could be a viable and relatively safe strategy for LVO strokes subsequent to IE. These findings underscore the importance of prompt diagnosis, proactive intervention, and the necessity of an experienced multidisciplinary team to ensure optimal management and outcomes.

## Data availability statement

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

## Ethics statement

This study was approved by the Institutional Review Committee of the Second People's Hospital of Liaocheng City (Liaocheng City). Approval number: 2023 (39). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

HZ: Conceptualization, Data curation, Investigation, Methodology, Project administration, Software, Resources, Visualization, Writing – original draft, Writing – review & editing. JC: Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. WC: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft. FL: Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft. JY: Conceptualization, Funding acquisition, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing.

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## Conflict of interest

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.

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## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1484492/full#supplementary-material

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# Suprasternal aortic arch echocardioscopy as a potential tool in detection and follow-up of mobile thrombi in patients with ischemic stroke

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**Introduction:** Severe or complicated atheromatosis of the aortic arch represents an important and often underdiagnosed embolic source in patients with ischemic stroke. The presence of a floating thrombus has significant clinical relevance, as it is associated with a high risk of early recurrence. The aim of this study was to analyze the potential of echocardiographic examination through the suprasternal window in both the detection of embolic sources and the monitoring of the response to anticoagulant treatment in patients with mobile thrombi.

**Methods:** This case series study included ten consecutive patients with a mobile floating aortic arch thrombus associated with an atheromatous plaque, detected by focused echocardiography and confirmed by Computed Tomography Angiography (CTA). Epidemiological, clinical, radiological, and ultrasound characteristics were analyzed. Clinical and ultrasound follow-up was performed after initiation of anticoagulation as secondary prevention to assess the efficacy and safety of this treatment.

**Results:** Ten patients (seven female) with a mean age of 76 years were identified. After anticoagulation, a complete resolution of the mobile thrombus was observed in eight of them during ultrasound follow-up. One patient suffered an ischemic recurrence. Two patients receiving associated antiplatelet therapy presented severe hemorrhagic complications, one of which was fatal. Once the disappearance of the mobile thrombus was detected, anticoagulation was discontinued, and no further ischemic recurrences were observed.

**Discussion:** Floating thrombus of the aortic arch is an underdiagnosed but clinically relevant condition. The study of the aortic arch with echocardiography through the suprasternal window is a highly available and harmless technique, that may be highly useful for the detection and monitoring of response to treatment of this pathology. Furthermore, early anticoagulation could be an effective and safe treatment in these patients.

KEYWORDS

**aortic arch, mobile thrombus, suprasternal, echocardioscopy, ischemic stroke, anticoagulation**

## Introduction

Ischemic stroke can arise from various distinct mechanisms and understanding the underlying cause is crucial, as this knowledge guides evidence based treatment strategies to prevent future strokes (1).

Approximately 25% of ischemic strokes are classified as cryptogenic (2), and about one sixth fit the criteria for Embolic Stroke of Undetermined Source (ESUS), defined as a stroke that appears non-lacunar on neuroimaging without an identifiable source after a comprehensive evaluation to exclude known stroke etiologies (3). The challenge lies in identifying effective secondary prevention strategies when the specific mechanism of the stroke is unknown.

Different studies have highlighted a correlation between Aortic Arch Atherosclerosis (AAA) and cerebral infarction, particularly in those cases where no obvious etiology is identified (4, 5). Nevertheless, the aortic arch presents a challenging area for the diagnostic techniques typically employed in clinical practice. Consequently, there is a growing recognition of this vascular territory as a 'missing link' in many cerebral infarctions of undetermined origin, especially evident in patients experiencing recurrent ischemic events despite receiving appropriate general treatment (5).

While transesophageal echocardiography (TEE) has classically been considered the gold standard for detecting AAA and their mobile components, transthoracic echocardiography (TTE) offers valuable visualization of thoracic aorta, including the aortic arch through the suprasternal window, a place where aortic atheroma is common. It is precisely in this area that there is often a blind zone for TEE due to the overlapping of the trachea and the right main bronchus, which does not allow the transesophageal probe to provide images of sufficient resolution (6). Therefore, suprasternal window TTE (sTTE) can effectively visualize protruding atheromas and even mobile components, serving as an excellent screening tool and providing complementary views to TEE examination. Although it is not always possible to obtain an image with sufficient resolution, the available studies obtain images in up to 84% of patients (6, 7), which makes it ideal as a screening technique.

The wide use of CT angiography in potential candidates for thrombectomy (8) has placed this technique in a preferential position in the study of AAA. Its main strengths are short acquisition times and high reproducibility. It also provides information on plaque composition and even on the presence of intraluminal thrombi. However, this modality has limitations, including reduced availability, exposure to ionizing radiation, and the necessity for contrast administration, so it is not an ideal technique for serial studies.

Given the paucity of literature on this subject and the hypothesis that it may be a valuable tool for identifying embolic sources in the aortic arch causing stroke, the objective of this study is to evaluate the potential of sTTE as a promising technique in the diagnosis and monitoring of mobile aortic thrombi in patients with ischemic stroke.

Abbreviations: CTA, Computed Tomography Angiography; AAA, Aortic Arch Atherosclerosis; TEE, Transesophageal echocardiography; TTE, Transthoracic echocardiography; sTTE, Suprasternal window TTE; ESVS, European Society for Vascular Surgery.

## Materials and methods

We describe a consecutive series of ten patients with mobile floating aortic arch thrombi associated with atheromatous plaques, visualized by sTTE. Data collection was conducted between 2017 and 2024 at a Spanish tertiary referral center (Navarre University Hospital).

The sTTE studies were performed by an experienced vascular neurologist (RMA) certified in focused stroke echocardiography according to the Spanish Certification Consensus (9). Patients who underwent an echocardiographic study, as part of the etiological evaluation of the stroke, that detected a mobile thrombus in the suprasternal window, and whose findings were subsequently confirmed by CT angiography, were included in the study. Patients who did not meet all these criteria were excluded.

Echocardiographic data were acquired using Philips Affinity CV and Philips CX50 equipment (Philips Ultrasound Systems, Bothell, WA) with a 2–5 MHz sector array ultrasound transducer probe. Patients were positioned supine, and the window was deemed satisfactory when the aortic arch image was captured in its long axis, encompassing the origins of the innominate, left common carotid, and left subclavian arteries. The study was complemented with parasternal, apical, and subcostal views. Additionally, each study was supplemented with CTA, providing information about thrombus number, localization, morphology, and mobility.

Data collected from hospital records included patient demographics, personal and family medical history, cardiovascular and thrombotic risk factors, iatrogenic causes, proinflammatory states, other embolic events, atherosclerotic burden, functional status, clinical presentation, diagnostic method, stroke pattern, and treatment. Patient follow-up comprised regular outpatient clinic visits and ultrasound monitoring to assess evolution and response to treatment. Individual patient consent was obtained, and the study was conducted in accordance with the requirements of the local ethics committee.

## Results

### Patient characteristics

Over a period of eight years, a total of ten patients with aortic arch thrombus were identified. Patient characteristics and risk factors are presented in Table 1.

Seven patients were female, with a mean age of 76 years (range, 53–87 years). All patients presented with an ischemic vascular event and underwent TTE through the in the acute phase, which detected the presence of a mobile thrombus associated with an atheromatous plaque, in the absence of another embolic source.

In all patients, a review was made of factors that could favor the presence of aortic atheromatosis, including: the presence of vascular risk factors, a high atherosclerotic burden at other levels, underlying procoagulant states, or relevant family history.

Regarding vascular risk factors, the majority of patients ($n = 8$) presented with at least one vascular risk factor: hypertension ($n = 4$), dyslipidemia ($n = 7$), smoking ($n = 4$), diabetes mellitus ($n = 2$) and COPD ($n = 1$). Seven patients had at least two vascular risk factors, and three had three or more.

In relation to the presence of systematic atheromatosis, all patients had atherosclerotic plaques at other levels. Two patients had

TABLE 1 Patient characteristics and risk factors.

| *n* | Age | Sex | Cardiovascular risk factors | Procoagulant abnormalities or Proinflamatory states | Iatrogenic causes | Atherosclerotic load |
|---|---|---|---|---|---|---|
| 1 | 83 | F | HT, DL | Normal | - | Severe abdominal<br>Mild carotid |
| 2 | 79 | F | HT, DL | Normal | Cardiac catheterization | Moderate coronary |
| 3 | 81 | F | - | anti-B2GP1 antibodies | - | Mild carotid |
| 4 | 84 | F | - | Not tested | - | Mild carotid |
| 5 | 75 | F | Smoking, DL | Not tested | Cardiac catheterization | Moderate coronary<br>Severe carotid<br>Severe aortic |
| 6 | 87 | F | DM, DL | Normal | - | Mild carotid<br>Severe intracraneal |
| 7 | 70 | M | HT, DL, Smoking | Normal | - | Severe carotid<br>Mild intracraneal |
| 8 | 79 | F | DL | Not tested<br>Giant cell arteritis | Corticosteroid therapy | Mild carotid<br>Mild intracraneal |
| 9 | 67 | M | DM, Smoking | Normal | - | Moderate peripheric<br>Severe aortic<br>Severe coronary<br>Severe carotid |
| 10 | 53 | M | HT, DL, Smoking | Factor V Leiden | - | Mild carotid<br>Mild intracraneal |

F, Female; M, Male; HT, Hypertension; DL, Dyslipedemia; DM, Diabetes Mellitus.

atheromatous lesions with stability criteria and no signs of severe stenosis and the rest had atheromatosis with severity data. Eight of the patients had atheromatosis in other localization. Three had coronary artery disease, two of them with a previous history of acute myocardial infarction with multivessel disease. One patient had an occlusion of the superior mesenteric artery by atherosclerotic plaque. Six had carotid stenosis >70% or stenosis in intracranial arteries. There was no evidence of systemic embolism in any of the patients.

For the study of procoagulant conditions, thrombophilia testing was performed in 6 patients, including tests for lupus anticoagulant, protein C activation resistance, functional protein C and protein S, functional antithrombin, factor VIII, anti-cardiolipin antibodies (IgG and IgM), anti-β2 glycoprotein 1 antibodies (IgG and IgM), and molecular genetic studies for Factor V Leiden and Prothrombin. One patient was found to have a heterozygous pathogenic polymorphism of Factor V Leiden.

On addition, yartogenic causes that could have mediated an embolic mechanism of stroke due to the detachment of plaques or mobile elements were also reviewed. In two patients, the stroke occurred following cardiac catheterization: one via radial approach and another requiring the implantation of an intra-aortic balloon counterpulsation device. One patient was on low-dose corticosteroid treatment due to a Giant Cell Arteritis.

## Clinical presentation and neuroimaging

All patients presented with an ischemic vascular event as the primary reason for vascular study that revealed the presence of the thrombus. The clinical presentation included a persistent neurological focality in 8 patients and a transient neurological focality in two patients. However, in all patients the presence of an ischemic lesion was confirmed on MRI in diffusion sequences.

Regarding the morphology of the ischemic lesion observed on MRI diffusion sequences, more than half of them showed a pattern of small scattered multiterritory infarcts ($n = 6$). The remaining cases showed territorial lesions ($n = 3$) and a punctate lesion in the posterior territory ($n = 1$) (Figure 1).

## Diagnostic method and thrombus characteristics

The presence of thrombi was initially identified through sTTE in six patients, with subsequent confirmation by CTA. In the remaining four patients, thrombi were first detected by CTA and subsequently visualized and monitored using sTTE (Figure 2).

In six patients, a pedunculated mobile thrombus was observed. This term describes a blood clot attached to the vascular surface, often at the site of an atheroma or even on an apparently healthy endothelium, via a narrow stalk or pedicle. The designation "mobile" indicates that the thrombus moves or swings freely within the lumen due to blood flow, thereby posing a significant risk of embolization (Supplementary Video S1). The localization was as follows (Figure 3): origin of the brachiocephalic trunk ($n = 4$), medial wall of the distal portion of the ascending aorta ($n = 1$) and origin of the left common carotid artery ($n = 1$).

In four patients, complicated atheromatosis of the aortic arch was identified, with ulcerative lesions and multiple mobile elements

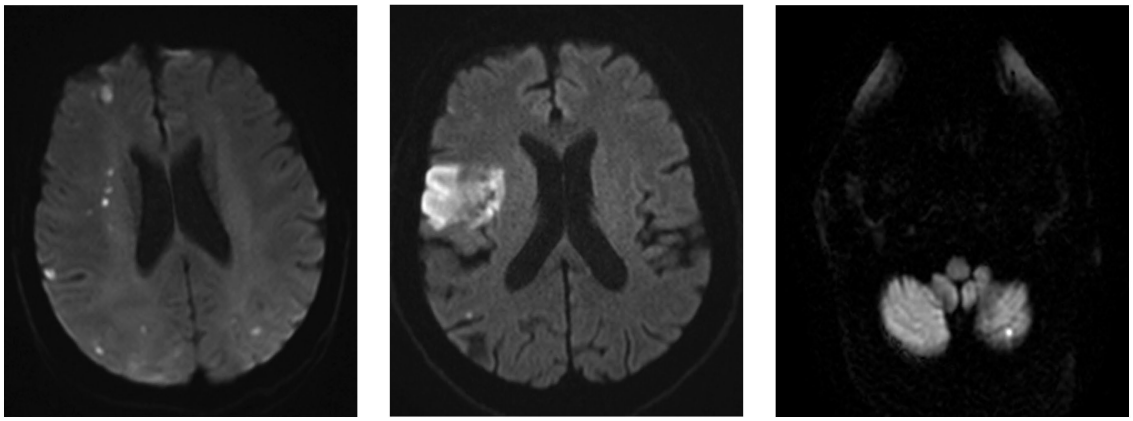

FIGURE 1
Left: Multiple small scattered pattern in patient 2. Middle: Big isolated infarct in patient 9. Right: Isolated small cerebellar infarct in patient 4.

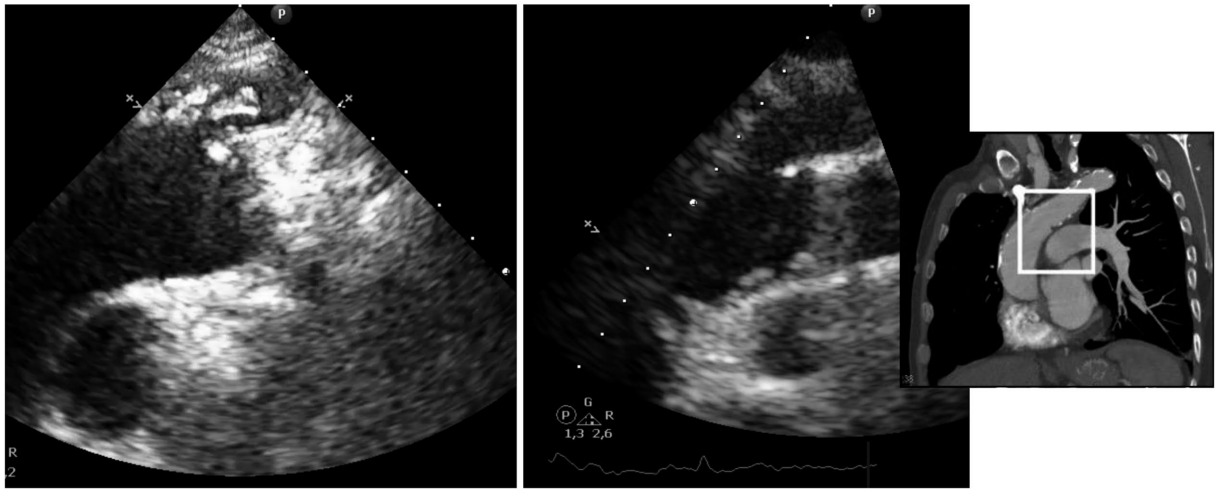

FIGURE 2
Different morphology of mobile thrombi in the aortic arch, identified using sTTE. Left: unique thrombus attached by a pedunculated portion to an atheroma plaque. Right: Multiple mobile elements suggestive of thrombi and/or plaque fragments compatible con shaggy aorta.

suggestive of thrombi and/or plaque fragments, consistent with the "shaggy aorta" pattern (Figure 4; Supplementary Video S2). This term describes the presence of spiculated images visualized through various diagnostic tools, representing an extreme manifestation of aortic atherosclerosis. This condition is characterized by extensive and severe atheromatous disease, featuring scattered ulcers, loosely held debris, a weakened medial arterial layer, and a propensity for thrombus formation (Figure 5) (10).

## Treatment and follow-up

All patients received only medical treatment. Monitoring of all patients was carried out, but three of them died during follow-up. Disappearance of the floating thrombus was observed in 8 patients.

Seven patients were treated solely with an antivitamin K (acenocoumarol). Of them, five exhibited complete thrombus resolution, while two died from renal failure two months post-treatment initiation. One of these patients had a long-standing history of chronic kidney disease stage V, complicated by multiple episodes of acute tubulointerstitial nephritis. The other patient was admitted with acute respiratory failure and developed acute pre-renal failure due to multifactorial causes, including iron-deficiency anemia and a state of dehydration.

One patient maintained treatment with antivitamin K and single antiplatelet therapy (acetylsalicylic acid) concomitantly, showing complete thrombus resolution.

Two patients received triple therapy (anticoagulation plus dual antiplatelet therapy): one with a direct-acting anticoagulant (apixaban) and the other with acenocoumarol, both in combination with acetylsalicylic acid and clopidogrel. Both demonstrated thrombus resolution, but one experienced gastrointestinal hemorrhage, and the other died from hemorrhagic stroke.

During follow-up, stroke recurrences were observed in two of the ten patients. One patient presented with ischemic lesions in both anterior and posterior territories, while the other experienced an

anterior hemispheric territorial infarction. Upon confirmation of thrombus resolution with anticoagulant therapy, all patients were transitioned to single antiplatelet therapy and none of them experienced recurrent ischemic stroke.

The clinical presentation, stroke characteristics, treatment and evolution are summarized in Tables 2, 3.

## Discussion

The present study suggests that sTTE may be a valuable diagnostic and monitoring tool for stroke patients with mobile thrombi in the aortic arch. In addition, oral anticoagulant treatment with acenocoumarol appears to be safe and effective in preventing recurrence of stroke, and the disappearance of the mobile thrombus is achieved.

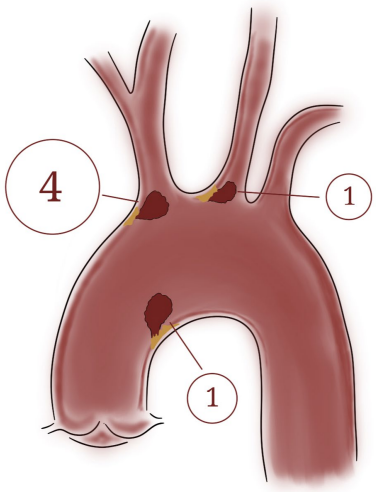


FIGURE 3
Localization of the six mobile thrombi attached by a pedunculated portion to an atheroma plaque: Origin of the brachiocephalic trunk ($n$ = 4), medial wall of the distal portion of the ascending aorta ($n$ = 1) and origin of the left common carotid artery ($n$ = 1).

AAA has been recognized as a significant causal factor in the etiology of stroke (11, 12). Its incidence and severity increase with age, smoking, hypercholesterolemia, hypertension, diabetes mellitus, male sex, hyperhomocysteinemia, or hyperfibrinogenemia. This is a slow and dynamic process with varying degrees of severity, which can progress, regress, or remain stable. The most severe plaques, with the highest embolic risk, are those that are ≥4 mm thick, have mobile components, ulcerated lesions, and hypoechogenic elements (5, 12). In some series, AAA has been detected in up to 29% of patients with embolic strokes of undetermined source (ESUS) and severe AAA in up to 8% (4). However, these numbers might even underestimate the role of AAA as a causal factor, since by considering only patients with ESUS, those with a potentially more severe atherosclerotic profile classified directly as having strokes of atherosclerotic origin are excluded. Additionally, it is possible that a thrombus adhered to the atherosclerotic plaque may have migrated and caused the stroke before being detected.

We recruited 10 patients with mobile aortic arch thrombi associated to AAA. The study is comparable to the series presented by Weiss et al. in 2016, which is, to our knowledge, the only study to date that provides detailed narrative data including risk factors, clinical presentation, and treatment response for this uncommon condition (13). There was a predominance of female patients, consistent with findings from other reported series (14), and exhibited a higher mean age compared to other studies (15). A high prevalence of cardiovascular risk factors was observed, with 70% of patients having at least two recognized factors. Only one patient exhibited a procoagulant abnormality, and in two cases, the stroke occurred following cardiac catheterization. A high embolic risk associated with these types of lesions has been described following procedures such as surgeries or catheterizations, underscoring the importance of characterizing the aorta prior to such interventions (10).

In our series, we identified two distinct types of mobile thrombi: 60% of patients had a pedunculated mural thrombus attached to an isolated atheroma plaque, while the remaining 40% exhibited multiple small thrombi or plaque debris in the context of

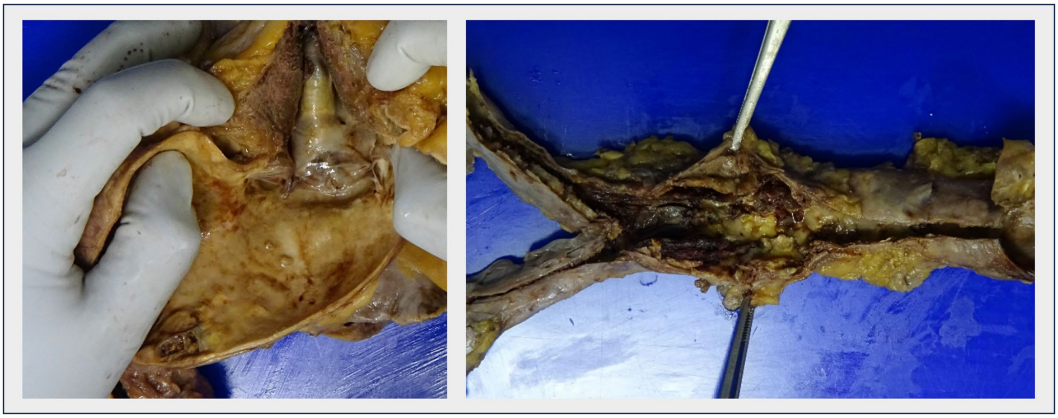

FIGURE 4
"Shaggy aorta" Severe aortic degeneration, with ulcerated plaques and attached small thrombi. Left: Aortic arch. Right: Abdominal aorta in the same patient.

severe aortic surface degeneration, also referred to as aortic debris or shaggy aorta. The concept of "Shaggy aorta" has been described referring to severe degeneration of the aortic surface, which is extremely friable and can cause systemic embolisms (16). This condition is predominantly observed in elderly patients with severe atherosclerotic disease (10). Aortic atherosclerosis could represent a spectrum of disease, ranging from pure atherosclerotic debris floating in the aorta—most prevalent in elderly patients—to nearly pure clot formations, which are often found in younger patients (17). This hypothesis is supported by pathological examinations of the aortic wall, where the thrombus insertion site consistently involves an atheromatous plaque, even though it may not be visibly calcified (13, 17). However, 'cryptogenic' thrombi in the aortic arch have also been described, occurring in the absence of atherosclerotic or aneurysmal disease. These infrequent thrombi have been primarily associated with malignant diseases (infiltration of the aortic wall, paraneoplastic syndrome), prothrombotic conditions such as primary polycythemia vera, antiphospholipid antibody syndrome, hypercoagulable states, primary endothelial disorders, or even iatrogenic causes (18).

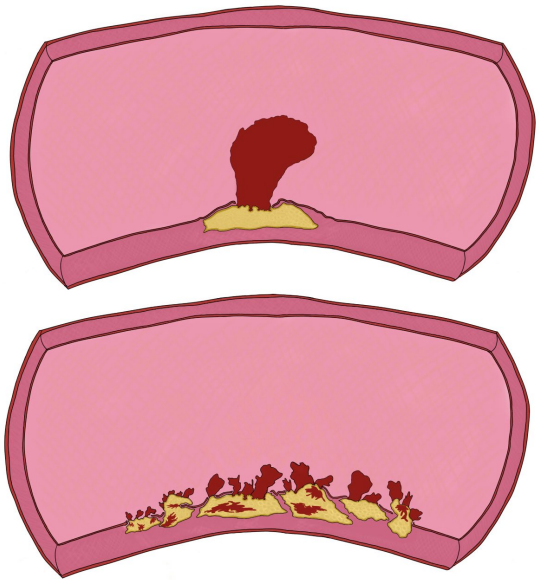

FIGURE 5
Illustration of the two types of mobile thrombi described in this study. Top: Pedunculated mobile thrombus; Bottom: Shaggy aorta.

Regarding the predominant neuroimaging pattern, as described in recent studies, a small scattered lesion pattern in multiple territories is highly suggestive of AAA (19, 20). This pattern has also been observed in patients with associated cancer (the three territories sign) in various studies, highlighting the importance of investigating this possibility (21). During the follow-up period, none of the patients in our series exhibited this underlying etiology.

The progression of atheromatous plaques and thrombus formation in the aortic arch is a dynamic and evolving process, therefore real-time dynamic imaging techniques can be very valuable for studying these changes. Focused echocardiography allows a rapid approach to the etiological diagnosis of stroke. Its

TABLE 2 Diagnosis, thrombus/stroke characteristics and treatment.

| *n* | Clinical presentation | Diagnostic method | Thrombus localization | Thrombus morphology | Radiological pattern of the stroke |
|---|---|---|---|---|---|
| 1 | Posterior territory ischemic stroke (POCI) | TTE | Origin of the brachiocephalic trunk | Pedunculated movile thrombus | Small scattered multiterritory |
| 2 | Posterior territory ischemic stroke (POCI) | CTA | Origin of the brachiocephalic trunk | Pedunculated mobile thrombus | Small scattered multiterritory |
| 3 | Left hemispheric ischemic stroke (PACI) | TTE | Origin of the brachiocephalic trunk | Pedunculated mobile thrombus | Small scattered multiterritory |
| 4 | Right hemispheric ischemic stroke (TACI) | CTA | Origin of the brachiocephalic trunk | Pedunculated mobile thrombus | Puntiform |
| 5 | Left hemispheric ischemic stroke (PACI) | TTE | Inferior portion of the aortic arch | Pedunculated mobile thrombus | Small scattered multiterritory |
| 6 | Left hemispheric ischemic stroke (PACI) | TTE | Origin of the left common carotid artery | Pedunculated mobile thrombus | Small scattered multiterritory |
| 7 | Left hemispheric ischemic stroke (TACI) | CTA | Exit of the supraaortic trunks, subclavian arteries, and both carotid arteries | Shaggy aorta | Small scattered multiterritory |
| 8 | Right hemispheric ischemic stroke (PACI) | TTE | Aortic arch and descending thoracic aorta, distal to the exit of the supraaortic trunks | Shaggy aorta | Territorial |
| 9 | Right hemispheric ischemic stroke (PACI) | CTA | Aortic arch and descending thoracic aorta, distal to the exit of the supraaortic trunks | Shaggy aorta | Territorial |
| 10 | Right hemispheric ischemic stroke (PACI) | TTE | Inner wall of the ascending aorta, aortic arch, and descending aorta | Shaggy aorta | Small scattered multiterritory |

CTA, Computed Tomography Angiography; TTE, Transthoracic echocardiography.

TABLE 3 Treatment, response, and recurrence.

| *n* | Treatment | Treatment response | Stroke recurrence and recurrence pattern | Follow up period (months) |
|---|---|---|---|---|
| 1 | Acenocumarol | Resolution | No | 7 |
| 2 | Acenocumarol | Resolution | No | 16 |
| 3 | Acenocumarol | Resolution | No | 12 |
| 4 | Acenocumarol | Resolution | No | 84 |
| 5 | Apixaban<br>Acetylsalicylic acid Clopidogrel | Resolution<br>Digestive hemorrhage | No | 7 |
| 6 | Acenocumarol | Resolution | No | 36 |
| 7 | Acenocumarol | Death due to renal failure | No | 2 |
| 8 | Acenocumarol | Death due to renal failure | Yes, multiterritory | 2 |
| 9 | Acenocumarol<br>Acetylsalicylic acid | Resolution | No | 36 |
| 10 | Acenocumarol<br>Acetylsalicylic acid Clopidogrel | Resolution<br>Death due to hemorrhagic stroke | Yes, territory | 8 |

accessibility, bedside applicability, and safety make it an ideal technique for both screening and patient follow-up. Studies have demonstrated that the performance of this technique by appropriately trained neurologists is at least as effective as when conducted in cardiology units (22). Moreover, as previously mentioned, the sTTE plays a significant role in the evaluation of the aortic arch. This view primarily depicts the aortic arch and the three major supra-aortic vessels (innominate, left carotid, and left subclavian arteries), providing a good visualization of the distal ascending aorta, which is a blind spot for TEE (23). So, the most significant advantage over TEE is its higher resolution in the initial portion of the aortic arch, an area where complicated plaques are frequently detected. Furthermore, earlier identification of cardioembolic sources can lead to more timely diagnosis and management of stroke, potentially reducing both the risk of recurrence and the duration of hospitalization, consequently mitigating the economic burden of stroke (22).

The optimal management strategy for aortic arch thrombi remains unclear. A variety of approaches are currently employed, including conservative treatments with anticoagulation or thrombolysis, interventional modalities such as thromboaspiration or balloon-catheter thrombectomy, and open surgical procedures such as thrombectomy, thromboendarterectomy, and aortic prosthetic replacement (24). While oral anticoagulation is generally considered the initial treatment, early surgical intervention has shown promising results. Both endovascular and open surgical techniques have demonstrated safety, suggesting that definitive treatment should be tailored to individual patient characteristics (25). Some authors have even suggested that symptomatic individuals should be classified as high-risk for recurrent embolism and consequently, they should undergo surgical removal, reserving conservative treatment for selected cases such as high-risk and elderly patients with contraindications for surgery, as well as asymptomatic individuals (13).

The recently published 2023 European Society for Vascular Surgery (ESVS) Guidelines (26) have attempted to provide guidance on the management of mobile carotid thrombi, strongly recommending anticoagulation (Class I, Level C). Given the lack of evidence on the optimal management of floating thrombi in the aortic arch, and based on the analogy with carotid floating thrombi, we decided to initiate empirical treatment with anticoagulation once the presence of a floating thrombus was confirmed.

It was observed a positive response to anticoagulation therapy in the majority of patients, with most achieving complete thrombus resolution. Notably, vitamin K antagonists, both as monotherapy and in combination with antiplatelet agents when previously prescribed, proved effective in resolving thrombi. However, the efficacy of these treatments must be weighed against potential risks. Hemorrhagic complications were observed in two patients. Of particular concern was the occurrence of a fatal hemorrhagic stroke in one patient receiving triple therapy, while another patient on the same regimen experienced non-fatal gastrointestinal bleeding. These observations underscore the delicate balance between achieving therapeutic anticoagulation and minimizing bleeding risks, especially in complex treatment regimens.

Upon confirmation of mobile thrombus resolution, anticoagulation was discontinued in all cases, with no subsequent ischemic recurrences observed. Notably, the three patients who died during follow-up (two from renal failure and one from cerebral hemorrhage) and the two who experienced stroke recurrence prior to thrombus resolution presented with aortic debris, a phenotype associated with advanced age and an increased burden of cardiovascular risk factors (16). Interestingly, in our series, patients with this type of aortic involvement had a lower mean age than those with a single pedunculated thrombus (67.2 vs. 81.5 years), although they exhibited a higher prevalence of cardiovascular risk factors (particularly a greater incidence of dyslipidemia and smoking).

It is important to note that this study is limited by its observational design and the absence of a control group. Patients were included consecutively as they were identified with mobile thrombi following an initial ischemic event. Although some studies have implemented methodological procedures to mitigate selection bias, most aortic plaque studies only include patients who are symptomatic and subsequently referred for diagnostic evaluations. Consequently, these studies, including the present one, are not entirely free from such

biases. Furthermore, a direct comparison between transthoracic echocardiography through the suprasternal window and the angioCT was not conducted. As a result, no conclusions can be drawn in this regard, as this is beyond the scope of the study. Regarding treatment, there are no universal recommendations in the literature for selecting the most appropriate therapeutic modality for each patient. The limited sample size of this study precludes drawing generalizable conclusions about treatment modalities. Additionally, there are currently no established guidelines for the follow-up of these patients, and significant variability exists in the study. Patients were included prospectively as they met the selection criteria, resulting in some patients being studied for several months while others had shorter follow-up periods.

## Conclusion

In conclusion, our findings suggest that sTTE may serve as a valuable technique for the detection and monitoring of mobile thrombi in the aortic arch, as it is an accessible and less invasive method compared to current reference tests. Therefore, it is essential to conduct diagnostic and therapeutic utility studies specifically designed for this purpose, in order to confirm this hypothesis and recommend its implementation. Nevertheless, given its accessibility and safety for patients, we propose the implementation of this technique in clinical practice as a screening method to identify potential embolic sources in patients presenting with embolic stroke, particularly when a pattern of multiple scattered cortical lesions in different areas is observed. Finally, until additional studies provide adequate evidence, early anticoagulation may be an effective and safe treatment option for some patients. However, further research is warranted to optimize treatment protocols and identify patient factors that may predispose to complications, thereby improving overall outcomes in this high-risk population.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by Comité ético de investigación médica del Hospital Universitario de Navarra (CEIM). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

## Author contributions

IE: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. EE: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. PM: Supervision, Writing – review & editing. EM: Supervision, Writing – review & editing. MM: Supervision, Writing – review & editing. FC: Supervision, Writing – review & editing. AJ: Supervision, Writing – review & editing. RM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

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## Conflict of interest

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.

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1528325/full#supplementary-material

SUPPLEMENTARY VIDEO S1
Suprasternal window, axial view at the level of brachiocephalic trunk, showing a mobile thrombus attached to an hyperechogenic atherosclerotic plaque.

SUPPLEMENTARY VIDEO S2
Suprasternal window, longitudinal view, showing an aortic arch with irregular surface at inferior wall, produced by multiple small atherosclerotic plaques with several mobile components attached.

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# Cryptogenic stroke and patent foramen ovale: endeavoring for clarity

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This review aims to summarize current knowledge and highlight recent findings on the association between cryptogenic stroke (CS) and patent foramen ovale (PFO). By presenting sometimes conflicting data, the review underscores the necessity for further research to clarify the complex mechanisms behind PFO-related CS and optimize its management. Results from research identifies specific conditions and scores, such as the risk of paradoxical embolism (RoPE) score, that help assess the likelihood of PFO-related cryptogenic stroke and guide treatment decisions. PFO closure has demonstrated substantial benefits in select cases, especially those with high-risk PFO features, though complications such as atrial fibrillation were frequently documented. Biomarker measurements, such as reduced total homocysteine (tHcy) level after PFO closure or high D-dimer levels indicating a higher risk of stroke recurrence, represent newer areas of study with a promising future in medical practice. Cryptogenic stroke (CS) remains a diagnostic challenge. This article reviews the current understanding of PFO-related CS, focusing on the interplay of concomitant pathological conditions, PFO closure, stroke recurrence, and some of the related biomarkers.

KEYWORDS

**cryptogenic stroke (CS), PFO (patent foramen ovale), PFO closure, stroke recurrence, biomarkers, perioperative stroke, RoPE score and PASCAL classification, PFO detection**

## Introduction

The TOAST trial classifies ischemic strokes into five subtypes, (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-vessel occlusion, (4) stroke of other determined etiology, and (5) stroke of undetermined etiology also known as cryptogenic stroke (CS) (1).

The incidence of CS associated with patent foramen ovale (PFO) varies across studies. Some reports suggest PFO is found in approximately 40–50% of CS cases, while in the general population, its prevalence is about 20–25% (2). However, PFO can also be incidental and present in other pathological conditions, including migraine, stroke or transient ischemic attack (TIA), hypoxia-induced events, obstructive sleep apnea, high-altitude pulmonary edema, and platypnea-orthodeoxia syndrome (3). Notably, the older the individual, the larger the right-to-left shunt (3). PFO can also allow venous gas bubbles to enter the arterial system, leading to arterial gas embolism (AGE), a clinical feature of decompression illness (4).

The enigmatic nature of cryptogenic stroke highlights the challenges physicians face in identifying its primary causes. With high prevalence of PFO in CS, understanding the risks associated with PFO is crucial to improving insights into CS and its underlying pathological mechanisms.

## Patent foramen ovale and cryptogenic stroke

In embryonic development, the pulmonary circulation is bypassed since gas exchange does not occur in the lungs. During this stage, the right atrium, which has higher pressure, shunts blood to the left atrium, where pressure is lower, through the foramen ovale. However, after birth, the closure of this shunt is critical. Failure of the foramen ovale to close properly leads to a condition known as patent foramen ovale (PFO) (5).

PFO is estimated to exist in approximately 25% of the general population (6). Clinical trials suggest that PFO is present in about 50% of cryptogenic stroke cases which makes it one of the most common etiologies associated with CS or embolic stroke of undetermined source (ESUS) (7).

In the SAFAS study, which examined the prevalence of PFO in strokes, 10% (23 out of 229 cases) were found to be PFO-linked. However, the study suggests that this finding may be due to its focus on patients with large PFOs. The study also highlighted that PFO-associated strokes occur at younger ages compared to non-PFO strokes (58 vs. 69 years, $p < 0.001$). Additionally, the left atrial volume index (LAVI) was lower in PFO-linked cases (25 vs. 32, $p = 0.023$) (8). Another study by Park et al. (9) found that age was not a significant factor in differentiating PFO-positive and PFO-negative CS cases (56.0 vs. 53.6 years; $p = 0.087$).

## Scoring system

High risk PFOs are more likely to be causative factors in cryptogenic strokes (10). In the DEFENSE-PFO trial, a high-risk PFO was characterized as either a defect larger than 3 mm or a PFO associated with atrial septal aneurysm (ASA) demonstrating hypermobility of the septum during the Valsalva maneuver, leading to a significant increase in PFO size (11).

The risk of paradoxical embolism (RoPE) score and the PASCAL classification are key tools in evaluating the relationship between patent foramen ovale (PFO) and cryptogenic stroke (CS). The RoPE score predicts the probability that a PFO is responsible for a cryptogenic stroke by assessing clinical and imaging factors. These factors include patient age, history of stroke risk factors, and imaging findings. A higher RoPE score suggests a stronger association between the PFO and stroke which aids in determining whether the PFO might be a causal factor (Table 1) (12).

On the other hand, the PASCAL classification evaluates the anatomical and physiological characteristics of the PFO, such as the size of the defect and the shunt type. This classification is particularly useful for assessing the embolic potential of a PFO and identifying patients at higher risk of adverse events. Being used together, these tools provide a framework and a general idea for diagnosis and management decisions regarding PFO-related cryptogenic strokes (Table 2) (12). The case report by Patel et al. (13) was analyzed using the RoPE score and PASCAL classification.

For the 14-year-old male patient who was presented with cryptogenic stroke:

1 Age: The patient is 14 years old, which falls into the RoPE score age bracket of 18–29 years, earning the maximum 5 points.

TABLE 1 RoPE score components by Kent et al. (12).

| RoPE score components | |
|---|---|
| No history of hypertension | +1 |
| No history of diabetes | +1 |
| No history of stroke/TIA | +1 |
| Nonsmoker | +1 |
| Cortical infarct, on imaging | +1 |
| Age | |
| 18–29 | +5 |
| 30–39 | +4 |
| 40–49 | +3 |
| 50–59 | +2 |
| 60–69 | +1 |
| ≥70 | 0 |

TABLE 2 PASCAL classification system by Kent et al. (12).

| High RoPE score (≥7) | High risk PFO feature (LS and/or ASA) | PFO-related stroke |
|---|---|---|
| Absent | Absent | Unlikely |
| Absent | Present | Possible |
| Present | Absent | Possible |
| Present | Present | Probable |

RoPE, risk of paradoxical embolism; LS, large shunt; ASA, atrial septal aneurysm; PASCAL, PFO-associated stroke causal likelihood; PFO, patent foramen ovale.

2 Absence of hypertension: No history of hypertension (+1 point).
3 Absence of diabetes: No history of diabetes (+1 point).
4 No history of stroke/TIA: The patient had no prior neurological events (+1 point).
5 Non-smoker: The patient is a nonsmoker (+1 point).
6 Cortical infarct on imaging: Neuroimaging revealed an acute ischemic infarct in the middle cerebral artery (MCA) territory, which qualifies as a cortical infarct (+1 point).

### Total RoPE score: 10/10

A RoPE score of 10 strongly suggests that the PFO is pathogenic rather than incidental (estimated probability of 88–92% that the PFO is related to the stroke).

### PASCAL classification

The PASCAL classification incorporates the RoPE score and evaluates the anatomical and physiological characteristics of the PFO:

1 High RoPE score (≥7): This patient scores 10 on the RoPE scale which fulfills this criteria.
2 High-risk PFO Features: TEE revealed a marked right-to-left shunt through the PFO. This anatomical characteristic is classified as high-risk.

### PASCAL classification: "probable" PFO-related stroke

The PASCAL classification indicates a strong likelihood that the PFO contributed to the stroke.

## PFO detection techniques

Transesophageal echocardiography (TEE) is considered the gold standard for the diagnosis of PFO due to its superior accuracy and versatility (Figure 1) (14). However, performing the Valsalva maneuver during TEE can be technically challenging because of the sedative effects used during the procedure. A study by Yamashita et al. (15) demonstrated that inferior vena cava (IVC) compression is an effective and non-inferior alternative to the conventional Valsalva maneuver for PFO detection ($p < 0.05$). This technique avoids the challenges faced after sedation and has improved diagnostic accuracy. Additionally, injecting contrast medium through femoral veins has been shown to significantly enhance detection rates compared to antecubital injections (16). The number of injections also positively correlates with TEE sensitivity, providing a reliable approach for increasing detection (17).

Transcranial Doppler ultrasound, is another technique with the advantage of being non-invasive. Although it does not provide the same anatomical detail as TEE, its non-invasive method, makes it a good choice for initial screening and for patients where TEE is contraindicated (17).

## Paradoxical embolism

Paradoxical embolism is a significant complication associated with PFO. The presence of a right-to-left shunt through the PFO increases the risk of embolic events by allowing thrombi to bypass the lungs and enter the systemic circulation (18). A systematic review reported that the overall 30-day incidence of adverse events following an impending paradoxical embolism (IPDE) was approximately 18% (19).

It is worth mentioning that Catastrophic antiphospholipid syndrome (APS), which is a sever form of antiphospholipid syndrome (APS) resulting in multiple blood clots, can predispose to paradoxical embolism with a concomitant PFO (20).

## Concomitant pathological conditions

Underlying thromboembolic conditions can exacerbate the risk of embolic strokes, especially in the presence of a PFO. The interaction between PFO and hypercoagulability in stroke patients was explored in a study that found no significant association between them (21). The prevalence of hypercoagulability was similar among stroke patients with and without PFO (21).

May–Thurner syndrome (MTS) is characterized by the compression of the iliac vein by an overlying artery, typically in the pelvic region. This venous compression can lead to deep vein thrombosis (DVT) and, in combination with a PFO, increases the risk of ischemic stroke (22). Compression of left common iliac vein by the right common iliac artery is typical of this syndrome (23).

Additionally, the co-occurrence of atrial fibrillation (AF) and PFO has been frequently documented. A right-to-left shunt in patients with

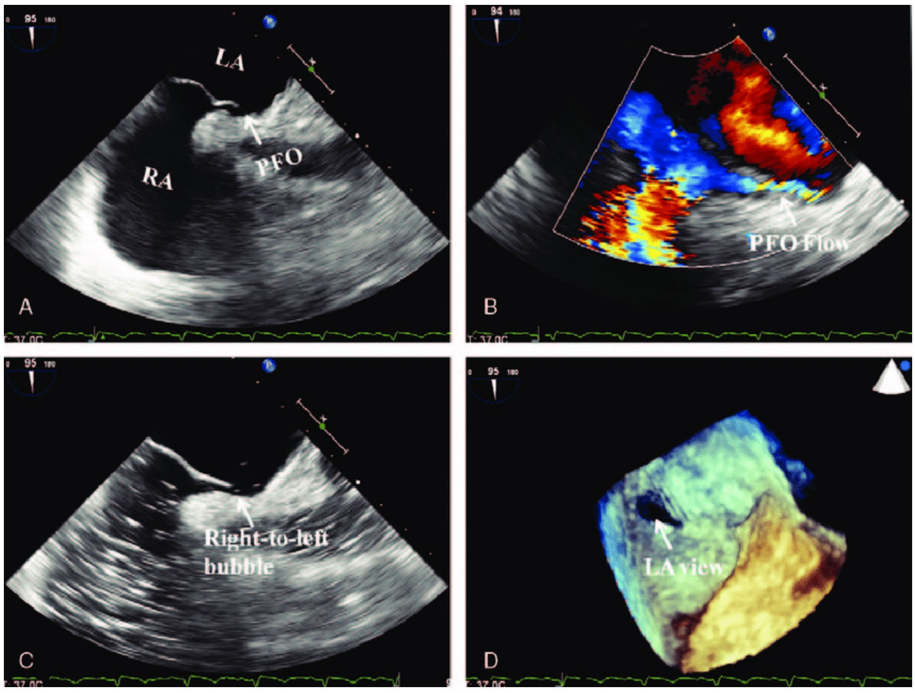



FIGURE 1
"Transesophageal echocardiography (TEE) confirming the PFO (arrow) (43). **(A)** The two-dimensional TEE in the biatrial view detected a separation between the primum and secundum atrial septum. **(B)** Color Doppler demonstrated bilateral but mainly right-to-left flow by decreasing the color gain and wall filtration. **(C)** Contrast TEE revealed right-to-left shunt after the contrast agent (6 mL of 1% injection vitamin B6 and equal volume of 5% sodium bicarbonate solution) was administered through the dorsal vein of right hand. **(D)** Real-time three-dimensional TEE confirmed the PFO. LA, left atrium; PFO, patent foramen ovale; RA, right atrium" by (Source Publication) is licensed under the Creative Commons Attribution-ShareAlike 4.0 International License.

PFO and AF significantly raises ischemic stroke risk, while a left-to-right shunt is associated with reduced stroke risk (24).

## Stroke recurrence

Stroke recurrence is a major concern in ischemic stroke management, both in the short and long term. A cohort study from Haukeland University Hospital reported a total recurrence rate of 14.2% over 9 years, associated with higher mortality (HR = 2.25, 95% CI = 2.04–3.18) (25).

A meta-analysis found no association between PFO and increased risk of recurrent stroke or transient ischemic attack (TIA), with a risk ratio of 1.18 (95% CI = 0.78–1.79, $p = 0.43$) for the combined outcome of recurrent stroke/TIA and a risk ratio of 0.85 (95% CI = 0.59–1.22, $p = 0.37$) for recurrent strokes (26).

D-dimer levels, which indicate clot breakdown, are crucial for assessing stroke risk. Elevated D-dimer levels (>1.0 mg/L) are associated with significantly higher rates of recurrent ischemic events following cryptogenic stroke. This was especially pronounced in patients with PFO, with an adjusted hazard ratio (aHR) of over 4.0 (95% CI = 1.63–10.2) compared to D-dimer levels <0.5 mg/L. In contrast, PFO-negative patients with D-dimer >1.0 mg/L had a lower aHR of 1.34 (95% CI = 0.63–2.86) (27). Elevated D-dimer levels were found to increase the risk of all-cause mortality in patients without PFO. Additionally, patients with high D-dimer levels exhibited a heightened risk of pulmonary thromboembolism, regardless of the presence of PFO (28).

Regarding the stroke recurrence in young patients (aged 18–45 years), a study by Arauz et al. (29) showed no evidence of escalated risk for stroke recurrence in presence of PFO among young patients.

## Perioperative stroke

Strokes occurring during surgery or within 30 days postoperatively are classified as perioperative strokes (30). An analysis of the National Readmission Database (NRD) found an increased risk of perioperative stroke and mortality in patients with atrial septal defect (ASD) or PFO. For example, skin and burn surgeries showed a 30-day stroke rate of 0.80% in ASD/PFO patients compared to 0.02% in non-ASD/PFO patients, with an adjusted odds ratio (aOR) of 27.94 ($p = 0.001$) (31).

A meta-analysis by Hobbes et al. (32) supported the increased perioperative stroke risk associated with PFO but found no evidence that PFO directly increased long-term adverse outcomes in perioperative strokes.

# Patent foramen ovale closure

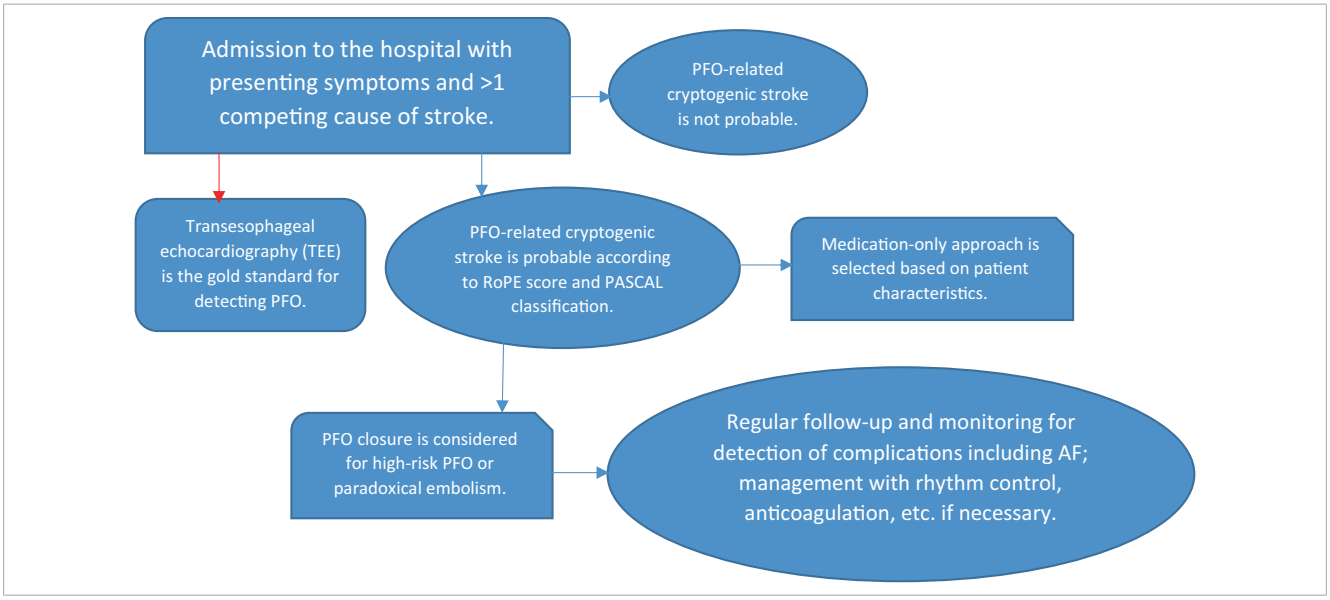
PFO closure has been shown to reduce the recurrence of strokes in appropriately selected patients. High-risk PFO is a primary factor for recommending percutaneous closure. In patients aged ≤60 years, percutaneous closure may be indicated in cases of paradoxical embolism or a history of antithrombotic therapy. For patients older than 60 years, a history of thromboembolic disease is an important consideration in deciding whether to proceed with percutaneous closure (33).

- In a study, 143 patients (29.3%) aged ≤60 years underwent PFO closure. The key indications included detection of high-risk PFO, criteria for paradoxical embolism, and prior use of antithrombotics.
- In the >60 years group, 24 patients (19%) underwent PFO closure, with indications including a history of pulmonary thromboembolism, predisposition to thromboembolic disease, criteria for paradoxical embolism, and high-risk PFO.
- The study also noted a low recurrence rate of stroke following PFO closure, though older individuals exhibited a slightly higher recurrence rate (33).

A meta-analysis revealed a 41% decrease in recurrent stroke rates following closure, particularly in patients with high-risk PFOs (34). The CLOSE trial demonstrated that PFO closure combined with antiplatelet therapy was superior to antiplatelet therapy alone in preventing stroke recurrence aneurysm [with a hazard ratio of 0.03 (95% CI, 0 to 0.26; $p < 0.001$)]. This benefit was most pronounced in patients with high-risk PFO features such as large shunts or atrial septal. The secondary composite outcome of stroke, transient ischemic attack (TIA), or systemic embolism was significantly lower in the PFO closure group compared to the antiplatelet-only group (3.4% vs. 8.9%; hazard ratio = 0.39, 95% CI = 0.16–0.82, $p = 0.01$) (35).

However, complications such as atrial fibrillation were reported in 4.6% of cases following PFO closure, a rate significantly higher than in patients managed with antiplatelet therapy alone ($p = 0.02$); the impact of AF secondary to PFO closure on stroke risk remains unclear (36). In another study the incidence of atrial fibrillation (AF) after PFO closure was reported at <5%, peaking around day 14 post-closure and declining after day 45 (37). The pathophysiological mechanisms behind post-PFO closure AF are not well understood but may include local irritation, device-related interference, tissue stretch, and nickel hypersensitivity. Management strategies focus on rhythm control, with flecainide showing promise, and anticoagulation tailored to individual risk profiles. Post-closure AF is generally benign and resolves within 45 days, minimizing thromboembolic risks (37). Preexisting AF may also be uncovered through intensive diagnostic strategies (7).

The CLOSURE 1 trial, which evaluated the efficacy of the STARFlex septal closure system, found no significant advantage of PFO closure over medical therapy (38). Furthermore the periprocedural major vascular complications occurred in 3.2% of patients in the closure group. The Kaplan–Meier estimates of 2-year rates of stroke were 2.9% in the closure group and 3.1% in the medical-therapy group, and respective rates of 3.1 and 4.1% for TIA. The key findings of the study were that there was no significant difference between the two treatment groups in the rate of recurrent stroke or TIA (38). Conversely, the REDUCE trial supported the efficacy of PFO closure, reporting a significantly lower risk of recurrent stroke compared to antiplatelet-only therapy (39). The study found that clinical ischemic stroke occurred in 1.4% of patients in the PFO closure group and in 5.4% of patients in the antiplatelet-only group. Also the incidence of new brain infarctions was significantly lower in the PFO closure group than in the antiplatelet-only group [18 patients (4.7%) vs. 19 patients (10.7%)] (relative risk = 0.44, 95%, CI = 0.24 to 0.81, $p = 0.02$), but the incidence of silent brain infarction did not differ significantly




between the study groups ($p = 0.75$). Atrial fibrillation or flutter occurred in significantly more patients in the PFO closure group than in the antiplatelet-only group (6.6% vs. 0.4%, $p < 0.001$); 83% of the cases of atrial fibrillation or flutter were detected within 45 days after the procedure, with 59% of them being resolved within 2 weeks after onset (39). Recurrent stroke rates after PFO closure was slightly higher in patients aged 18–45 compared to those aged 46–59 (1.5% vs. 1.3%, respectively). Contrary to that, in a meta-analysis by Xu et al. (40) younger patients had fewer outcomes of recurrent neurological episodes after PFO closure. Noteworthy is that in diagnosed AF concomitant with PFO, PFO closure is not the best option since there is no clear way to rule out the PFO as being merely an incidental factor (36).

## Biomarkers

Biomarkers hold significant promise as tools for evaluating PFO-related strokes. Evidence indicates that total homocysteine (tHcy) levels are markedly reduced following PFO closure, particularly in cases of complete closure (41). In contrast, medical therapy alone does not appear to influence tHcy levels. Advanced analytical techniques such as metabolite profiling, orthogonal partial least squares discriminant analysis (OPLS-DA), and two-way repeated-measures ANOVA have been employed to identify metabolites associated with PFO closure. Furthermore, mixed-effects model repeated measures analysis was used to assess the impact of residual shunting and PFO treatment on tHcy levels. The findings revealed that PFO closure significantly reduces peripheral blood tHcy levels, while residual shunting is independently associated with elevated tHcy levels (41).

Additional findings suggest improvements in dynamic cerebral autoregulation and reductions in platelet-derived growth factor-BB, a marker often elevated in PFO populations (42, 44). Concept of stroke-related biomarkers provide avenues for further research.

## Multidisciplinary approach

Effective management of cryptogenic stroke with PFO requires a collaborative approach. Neurologists are essential for assessing stroke symptoms, interpreting neuroimaging, and ruling out other etiologies. Collaboration with cardiologists and radiologists is crucial for making appropriate management decisions. Below is a flowchart summarizing the decision-making process for cryptogenic stroke with suspected PFO:

## Discussion

While PFO is strongly associated with cryptogenic stroke, but its presence does not confirm causality, since it may also be an incidental finding. Biomarkers provide additional data about stroke risk and the proper intervention. However, challenges such as accurately selecting patients for PFO closure and evaluating the true likelihood of PFO being the causative factor in cryptogenic stroke remain areas of uncertainty. Multidisciplinary collaboration and ongoing research, particularly longitudinal studies and randomized controlled trials, are essential to guide us in the endeavor of understanding the mechanisms linking PFO and cryptogenic stroke and addressing the enigmatic nature of these events.

## Author contributions

TA: Writing – original draft, Writing – review & editing.

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## Conflict of interest

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

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The authors declare that no Gen AI was used in the creation of this manuscript.

## Publisher's note



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# Enhancing the diagnostic efficacy of right-to-left shunt using robot-assisted transcranial Doppler: a quality improvement project

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**Background:** Stroke is the leading cause of adult disability worldwide, with approximately 30% of strokes remaining cryptogenic. One potential important etiology is a patent foramen ovale (PFO), which may contribute to stroke through paradoxical thromboembolism or *in situ* thromboembolus formation. Recent advancements in robot-assisted transcranial Doppler (raTCD) have shown increased sensitivity in detecting right-to-left shunt (RLS) compared to transthoracic echocardiography (TTE), particularly in detecting the large shunts which are associated with higher stroke risk.

**Methods:** We conducted a retrospective quality improvement project at our regional stroke center to compare the performance of TTE and raTCD in identifying RLS in ischemic stroke patients. The study involved 148 patients admitted between February 2021 and February 2023. All patients underwent TTE and raTCD with agitated saline bubble contrast, with additional transesophageal echocardiography (TEE) at the treatment team's discretion. The primary metrics analyzed included differences in overall RLS detection and large RLS detection rates for raTCD, TTE and TEE.

**Results:** raTCD detected RLS in 60.1% of patients compared to 37.2% with TTE ($p < 0.001$), with a 42.6% detection rate for large shunts on raTCD versus 23.0% on TTE ($p < 0.001$). The sensitivity and specificity of raTCD were 92 and 87.5%, respectively, compared to 78.57 and 71.43% for TTE, using TEE as the gold standard. Nine patients underwent PFO closure, all correctly identified with large shunts by raTCD, while TTE missed or underestimated the PFO size in 44% of the cases.

**Conclusion:** raTCD significantly outperforms TTE in detecting RLS and large shunts, suggesting its integration into standard PFO workup protocols may enhance secondary stroke prevention. These findings support the adoption of raTCD as a complementary diagnostic tool alongside TTE and TEE for more accurate PFO detection and risk stratification.

KEYWORDS

**cryptogenic stroke, transcranial Doppler ultrasound (TCD), patent foramen ovale, patent foramen closure, robotic**

# 1 Introduction

A significant advancement in the field of patent foramen (PFO) detection occurred with the development of robot-assisted transcranial Doppler (raTCD). The potential importance of this technology stems from the fact that a large percentage of stroke remains cryptogenic (approximately 30%), representing an ongoing serious health care problem (1, 2). Our inability to properly diagnose stroke etiology significantly jeopardizes secondary stroke preventive measures (3–6). PFO has a reported prevalence of approximately 25% in the general population and up to 40% in patients with acute ischemic stroke (3). It is well recognized that PFO can facilitate the passage of paradoxical thromboembolus from the venous to the arterial circulation or serve as a site for *in situ* thromboembolus formation. While PFO closure is now considered the gold standard in younger patients with PFO-related stroke (<60-year-old), increasing evidence is emerging of a potential benefit of PFO closure in selected older patients (7–10). Based on the results of multiple positive PFO closure trials conducted over the past 8 years, multiple American and European medical societies have published PFO diagnostic and management guidelines including indication for PFO closure (2, 3, 5, 6, 11–13). The methodology for optimal PFO detection has been a topic of extensive investigation. The results of the recently published RoBotic TCD Ultrasound BubbLe Study Compared to Transthoracic Echocardiography for Detection of Right to Left Shunt (BUBL Study—NCT04604015) reported an approximately three times higher right to left shunt rate (RLS) compared to transthoracic echocardiography (TTE) (14, 15). Furthermore, TTE completely missed or significantly downsized two thirds of large shunts detected by raTCD. These findings were deemed highly clinically relevant as PFO size is known to be a predictor of stroke risk and of central importance in calculating the risk/benefit ratio for PFO closure. Based on these results, numerous commentators have touted raTCD to be a significant medical advancement and have called for further independent "real-world" data (4, 8, 11–17). To that end, we executed an independent hospital-based quality improvement project to compare the performance of TTE versus raTCD in identifying RLS in a real-world setting at a regional stroke center and assess how increased detection may translate into improved secondary stroke prevention by PFO closure.

# 2 Methods

This study was a single-center quality improvement project conducted at CHI Memorial Hospital in Chattanooga, TN. The study involved a retrospective chart review, with data collection occurring between February 2021 and February 2023, and chart review conducted by clinical staff from February to July 2023. The project aimed to evaluate the impact of incorporating automated transcranial Doppler (raTCD) into the stroke workflow compared to standard transthoracic echocardiography (TTE) for the diagnosis of right-to-left shunts (RLS) and patent foramen ovale (PFO). It also sought to quantitate the effect of raTCD utilization on the rate of PFO closures. The data dictionary for the study included patient demographics, raTCD results, TTE results, TEE results, and PFO closure. Local IRB waived the need for patient consent and all data was collected as part of standard clinical practice. Independent statistical analysis was funded by the non-profit NeuroScience Innovation Foundation.

## 2.1 Data collection protocol

All imaging was collected as standard of care on patients who underwent hospitalization for an acute neurovascular episode, including ischemic stroke or transient ischemic attack. All patients underwent TTE with agitated saline bubble contrast as part of routine clinical care. Based on increasing evidence of the importance of TCD in the workup of cryptogenic stroke, raTCD was performed on all patients as part of standard cryptogenic stroke workup. All patients underwent TCD with agitated saline bubble contrast using an automated TCD platform (raTCD - NovaGuide Intelligent Ultrasound, NeuraSignal, Inc., Los Angeles, CA, United States). Additional testing, such as TEE, was left to the discretion of the neurology treatment team.

The raTCD is a five degree-of-freedom robotic unit supported by artificial intelligence (AI) algorithms for the identification of the acoustic window and signal optimization using a traditional diagnostic TCD. The contrast for the TCD bubble studies was delivered by injecting agitated saline contrast at both rest and with calibrated Valsalva, with the patient in the supine or near supine position. All raTCDs studies were performed by ultrasonographers following completion of raTCD training and demonstrated technical proficiency. The raTCD bubble studies were read by a blinded fellowship trained certified vascular neurologist and graded using the Spencer Logarithmic Scale (SLS) criteria (18). We adopted the same definitions for a "large" RLS/PFO by raTCD as was used in the BUBL study (SLS $\geq$ Grade 3) and TTE RLS/PFO grading was categorized as small, moderate, or large, with reads of moderate or large being classified as large for secondary analysis (14). All TTE bubble studies were performed by certified ultrasonographers and were read by blinded level III echocardiography board-certified cardiologists.

## 2.2 Outcome measures

The primary outcomes paralleled those within the BUBL study including: (a) rate of RLS detection with TTE and raTCD; (b) rate of large RLS for TTE and raTCD; (c) RLS detection rate of raTCD vs. TEE; (d) RLS detection rate of TTE vs. TEE; (e) sensitivity and specificity of raTCD and TTE using TEE as the gold standard; and (f) comparison of patients who received closure between raTCD and TTE for identification of RLS/PFO[14].

## 2.3 Statistical methods

The statistical methods were performed in parallel to that performed in the original BUBL study described in detail by Rubin et al. (14). We retrospectively analyzed data from 148 ischemic stroke patients who underwent both raTCD and TTE over a 25-month period starting February 2021. Continuous variables were reported as means with standard deviations (SD) or medians with interquartile ranges (IQR), appropriately determined by normality of the data assessed using the Shapiro–Wilk test. Categorical variables were presented as frequency counts and percentages (n, %). For comparisons between categorical variables, we used chi-square tests or Fisher's exact tests, as appropriate, to assess statistical significance. These were summarized in 2×2 tables. Two-sample proportion tests were conducted, with 95% confidence intervals and *p*-values reported to determine the statistical significance of the differences in detection rate of RLS/PFO between different detection tools. The exact

confidence intervals were calculated using the Clopper-Pearson method for binomial proportions. Sensitivity and specificity analyses were performed using TEE as the reference standard, with corresponding confidence intervals computed using the Wilson score method without continuity correction. All statistical analyses were performed using the statistical package R (version 4.3.1). Significance was determined at a two-tailed $p$-value <0.05.

## 3 Results

We retrospectively analyzed data from 148 ischemic stroke patients who underwent both raTCD and TTE collected over a 25-month period starting February 2021. Patient demographics are presented in Table 1. Of the total population, 60.1% were male with a mean age (±S.D.) of 58.0 ± 14.1. TTE and raTCD were performed in 100% of patients of which 14.9% ($n$ = 22) underwent TEE, TTE, and raTCD. Table 2A summarizes the overall RLS detection rate for raTCD versus TTE. Analysis revealed a 22.9% higher RLS shunt detection rate for raTCD (1.6 x higher) with a RLS shunt detection rate of 60.1% ($n$ = 89 positives) for raTCD vs. 37.2% ($n$ = 55 positives) for TTE ($p$ < 0.001; CI: 11.2, 34.7%). Table 2B summarizes the large RLS detection rate for raTCD versus TTE. Among the total 148 cases studied, 42.6% ($n$ = 63 positives) were identified by raTCD to have large shunts (classified as RLS Grade ≥ 3), representing 70% (63/89) of all positive shunts identified on raTCD. In comparison, among the total 148 cases studied, 23.0% ($n$ = 34 positives) were identified by TTE as large shunts (classified as moderate or large size on TTE), representing 61.8% ($n$ = 34/55) of all positive shunts identified by TTE. Thus, raTCD detected 19.6% more large PFOs (1.9 x higher) than TTE ($p$ < 0.001; CI 8.5, 30.7%). The agreement matrix presented in Table 3A demonstrates that of the total 9 patients in our study that underwent PFO closure 11.1% ($n$ = 1) had no PFO detected on TTE at all while no PFO that underwent closure was missed by raTCD. The agreement matrix presented in Table 3B demonstrates that all the PFOs in this study that underwent closure were designated large by raTCD; however, of those nine large/closed PFO cases, 44.4% ($n$ = 4) were misdiagnosed as being of small PFO size on TTE. The agreement matrix presented in Table 4A compares raTCD with TEE ($n$ = 33) with raTCD detecting 72.7% (24/33) and TEE 72.7% (24/33) ($p$ = 1.0; CI: −21.5, 21.1%). Table 4B shows the agreement matrix between TTE and TEE 177 ($n$ = 22) with TTE 59.1% (13/22) and TEE detecting 63.6% (14/22) ($p$ = 1.0; CI: −37.8, 28.7%). Using TEE for comparison, we calculated the sensitivity and specificity of raTCD vs. TTE. Our results showed raTCD sensitivity and specificity of 95.8 and 88.9%, vs. TTE sensitivity and specificity of 78.6 and 75.0%, respectively (Table 4C). Of the 148 cases studied, 6.1% ($n$ = 9) had no bone window using raTCD.

TABLE 1 Patient demographics and testing performed.

| | |
|---|---|
| Total patients N | 148 |
| Gender, n(%) | |
| Female | 59 (39.9%) |
| Male | 89 (60.1%) |
| Age | |
| Mean (SD) | 58.0 ± 14.1 |
| Median (IQR) | 59.0 (48.8, 68.2) |
| Patient Cohort | |
| TCD performed n (%) | 148 (100.0%) |
| TTE performed n (%) | 148 (100.0%) |
| TEE performed n (%) | 22 (14.9%) |

## 4 Discussion

PFO is associated with right-to-left cardiac shunt and is a well-documented cause of embolic stroke (19). Accurate PFO detection, sizing, and anatomic characterization are essential when assessing PFO as a potential etiology for stroke and when calculating risk/benefit ratio for PFO closure (3). Given the multiple randomized trials showing the benefit of symptomatic PFO closure in properly selected

TABLE 2 Agreement matrix—comparison between raTCD and TTE for the detection of All RLS and large RLS.

| (A) All RLS detection rate raTCD vs. TTE. | | | |
|---|---|---|---|
| ($n$ = 148) | TTE Positive | TTE Negative | Total |
| raTCD positive | 50 (33.8%) | 39 (26.4%) | 89 (60.1%) |
| raTCD negative | 5 (3.4%) | 54 (36.5%) | 59 (39.9%) |
| Total | 55 (37.2%) | 93 (62.8%) | 148 (100%) |
| Diference: 22.9%<br>(1.6 × higher for raTCD) | 95% CI: [11.2, 34.7%] | | $p$ < 0.001 |

| (B) Large RLS detection rate raTCD vs. TTE. | | | |
|---|---|---|---|
| ($n$ = 148) | TTE large positive | TTE large negative | Total |
| raTCD large positive | 33 (22.3%) | 30 (20.3%) | 63 (42.6%) |
| raTCD large negative | 1 (0.7%) | 84 (56.8%) | 85 (57.4%) |
| Total | 34 (23%) | 114 (77%) | 148 (100%) |
| Diference: 19.6%<br>(1.9 × higher for raTCD) | 95% CI: [8.5, 30.7%] | | $p$ < 0.001 |

TABLE 3 Agreement matrix—comparison between raTCD and TTE for cases with PFO closure.

| (A) All RLS detection rate raTCD vs. TTE for cases with PFO closure. | | | |
|---|---|---|---|
| (*n* = 9) | TTE positive | TTE negative | Total |
| raTCD positive | 8 (88.9%) | 1 (11.1%) | 9 (100%) |
| raTCD negative | 0 (0%) | 0 (0%) | 0 (0%) |
| Total | 8 (88.9%) | 1 (11.1%) | 9 (100%) |

| (B) Large RLS detection rate raTCD vs. TTE for cases with PFO closure. | | | |
|---|---|---|---|
| (*n* = 9) | TTE large positive | TTE large negative | Total |
| raTCD large positive | 5 (55.6%) | 4 (44.4%) | 9 (100%) |
| raTCD large negative | 0 (0%) | 0 (0%) | 0 (0%) |
| Total | 5 (55.6%) | 4 (44.4%) | 9 (100%) |

TABLE 4 Agreement matrix between raTCD vs. TEE and TTE vs. TEE.

| (A) Detection rate of RLS between raTCD vs. TEE for patients with TEE performed. | | | |
|---|---|---|---|
| (*n* = 33) | TEE positive | TEE negative | Total |
| raTCD positive | 23 (69.7%) | 1 (3.0%) | 24 (72.7%) |
| raTCD negative | 1 (3.0%) | 8 (24.2%) | 9 (27.3%) |
| Total | 24 (72.7%) | 9 (27.3%) | 33 (100%) |
| Difference: 0.0% | 95% CI: [−21.5, 21.1%] | $p = 1.0$ | |

| (B) Detection rate of RLS between TTE and TEE for patients with TEE performed. | | | |
|---|---|---|---|
| (*n* = 22) | TEE positive | TEE negative | Total |
| raTCD positive | 11 (50.0%) | 2 (9.1%) | 13 (59.1%) |
| raTCD negative | 3 (13.6%) | 6 (27.3%) | 9 (40.9%) |
| Total | 14 (63.6%) | 8 (36.4%) | 22 (100%) |
| Difference: −4.5% | 95% CI: [−37.8, 28.7%] | $p = 1.0$ | |

| (C) Sensitivity and specificity of detecting PFO (TEE as the gold standard). | | |
|---|---|---|
| | Sensitivity | Specificity |
| raTCD | 95.8% | 88.9% |
| TTE | 78.6% | 75.0% |

patients, highly accurate PFO characterization is an essential step in secondary stroke prevention (3, 6, 13). In this independent investigation of raTCD, reported here, we performed a retrospective review of 148 acute ischemic stroke patients admitted over a two-year period to our regional stroke center. We compared RLS detection rates and PFO size estimates based on number of bubbles detected, using raTCD and TTE in all patients and compared the findings to TEE when performed. Both the raTCD and TTE procedures followed established protocols for bubble studies, ensuring consistency and reliability in the diagnostic process. Our results corroborate the findings of Rubin et al. (14) as we found a significantly higher rate (delta = 22.9%, 1.6 x higher) of overall RLS with raTCD versus TTE (60.1% vs. 37.2%, $p < 0.001$) and a significantly higher rate (delta = 19.6%, 1.9 x higher) of large RLS with raTCD versus TTE (42.6% vs. 23.0%, $p < 0.001$). Unlike Rubin et al. who did not document PFO closures, we documented that at the time of our analysis nine patients in our data set had undergone PFO closure. Despite the lack of statistical significance in our PFO closure patient population between PFO detection on raTCD vs. TTE, likely due to low patient number, our results do raise significant clinical concern as 11.1% ($n = 1$) of patients who underwent closure had their PFO missed entirely on TTE. Furthermore, 44.4% ($n = 4$) of the patients who underwent PFO closure had their shunts size significantly underestimated or not detected at all on TTE (all of which demonstrated large shunts on raTCD). It was owing to the performance of the raTCD that the large size of each of these cases was identified which raised the heightened alert for the need for further characterization by TEE and possible closure. The clinical importance of our findings was further underscored by the fact that 26.4% ($n = 39$) of our study population were negative on TTE but positive on raTCD (Table 2A), while only 3.4% ($n = 5$) were detected on TTE but missed on raTCD. Similarly, we found it highly clinically concerning that 20.3% ($n = 30$) of large RLS were missed on TTE but detected on raTCD, while only 0.7% ($n = 1$) were missed on raTCD but detected

on TTE (Table 2B). Of the five subjects with a positive TTE and negative TCD, three had no windows which was known prior to the bubble contrast injection and the remaining two were negative on TEE. As TEE is often not routinely performed during the initial screen for PFO (and itself may underdiagnose PFO), the highly statistically significant improvement in our data for RLS shunt detection by raTCD over TTE suggests that many patients would be in jeopardy of having their PFO totally undiagnosed if TTE alone is used for screening. Similarly important, the highly significant difference that we report for large shunt detection rate by raTCD over TTE points to the inadequacy of TTE alone in the assessment of PFO size. Initial detection of a PFO on screening imaging may steer clinicians either toward or away from performing TEE and, as discussed below, accurate PFO sizing may be critical in calculating the risk/benefit ratio of PFO closure the ultimate driver in the close/no close decision. Therefore, reliance on TTE alone for PFO screening may lead to incorrect clinical decision making, missed opportunities for proper secondary stroke prevention by PFO closure, and increased subsequent stroke risk for patients. Finally, our study was able to expand on Rubin et al. by reporting sensitivity and specificity for both raTCD and TTE compared to TEE (sensitivity of 95.8% and specificity of 88.9% for raTCD and sensitivity of 78.6% and specificity of 75.0% for TTE). While our overall total RLS detection rate by raTCD (60.1%) was almost identical to that reported by Rubin et al. (64%), our overall rate of positive RLS detected by TTE was higher (37.2% vs. 20%). When compared to the report by Rubin et al., we found a substantially higher rate of large RLS on raTCD (42.6% vs. 27.0%) and on TTE (23.0% vs. 10%). The reason for our higher detection rates of RLS on raTCD for larger PFOs and for all PFOs on TTE is uncertain. This variability between our single center results and the multi-center trial reported by Rubin may have involved multiple factors discussed in detail below.

## 4.1 Concordance of studies supporting a central role for TCD in RLS detection

Numerous investigations have compared various methodology for PFO detection including TTE, TEE, and TCD (4, 17, 20–25). The development of raTCD has emerged as a potentially important advancement in the field of PFO detection. The recent muti-center investigation comparing raTCD versus TTE by Rubin et al. reported a 41.4% overall higher rate of RLS detection in stroke patients and a 17.4% higher detection of large RLS by raTCD over TTE (14). The accompanying editorial underscored the potential significance of Rubin's findings and called for additional investigations comparing raTCD to TTE and TEE (15). Similarly, Rubin's findings led to a direct call for further investigation of raTCD by the Roundtable of Academia and Industry for Stroke Prevention (RAISE) (3). Based on the current literature, RAISE endorsed raTCD being considered in the current workup for PFO[3]. In a recent commentary by Dr. Braydon Dymm titled "Could Robot-Assisted Transcranial Dopler Replace Transthoracic Echocardiography as Screening for Right to Left Shunt After Cryptogenic Stroke" they challenged the current standard of TTE per se as the initial screening tool for PFO detection in patients with cryptogenic stroke (26).

Our results are consistent with previous reports comparing TTE, TCD, and TEE for the detection of PFO. Mojadidi et al. in 2014 published a meta-analysis of 27 studies and 1,968 patients with the aim of determining the accuracy of TCD using TEE as a reference. Their meta-analysis showed that TCD had a sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR-) of 97, 93%, 14, and 0.04, respectively. These authors concluded that TCD is the preferred test for detecting RLS in patients with cryptogenic stroke or migraine (27). A more recent meta-analysis (35 studies, 3,067 patients) reported a sensitivity, specificity, and area-under-curve for PFO diagnosis by TCD of 96.1, 92.4%, and 0.98 versus 45.1, 99.6%, and 0.86 for TTE. The analysis also reported LR+ and LR-for the TCD (12.62, 0.04) and TTE (106.61, 0.55) respectively leading to their conclusion of the diagnostic superiority of TCD in comparison to TTE for RLS detection (4). A more recent study (775 patients with TCD and TTE) reported significant test superiority (dominance) of TCD over TTE for RLS/PFO detection and concluded with the recommendation for TCD as the preferred screening method for RLS despite the limitations of differentiating between intracardiac and extracardiac shunts (28). Similar results were also reported in a 2018 investigation suggesting the need for TCD within the PFO work up (29). This recent widespread interest in TCD is in line with the joint European position paper involving nine separate national societies which in 2019 called for TCD to be incorporated as an essential part of PFO workup (12). Similarly, the European Stroke Organization (ESO) in their 2024 published expert consensus report stated "as there is no technique that can be considered as a gold standard, we advise locally agreed diagnostic algorithms using the available techniques (TCD, TTE and TOE) to diagnose an RLS." In that statement they cited the recent Rubin et al. study as support (30). These various publications are summarized in Table 5 comparing the overall performance of TCD, TTE, and TEE.

## 4.2 Unique aspects of raTCD that may lead to increased accuracy of raTCD

The major limitation of TCD is the inability to distinguish between non-cardiac and cardiac RLS. Despite the fact that PFO is the most likely diagnosis in RLS if bubbles are detected within 3–5 cardiac cycles of injection, current guidelines recommend that all possible PFO's detected by TCD be evaluated by TEE prior to attempted closure (3). This is critical to confirm the absence of an extracardiac shunt and for anatomic PFO characterization. Despite this limitation, TCD has specific advantages in the assessment of RLS/PFO including: (1) a high bubble detection rate through the intracranial circulation in the very narrow diameter middle cerebral artery whose directionality of bubbles are all aligned with the angle of insonation; (2) the ability to quantify and confirm an adequate Valsalva maneuver by measuring a $\geq$ 25% drop in MCA flow velocities; and (3) unlike TTE and TEE, TCD is typically performed with the patient in a semi-upright position which has been demonstrated to be associated with higher rates of PFO detection. Furthermore, there appear to be additional technical advantages of raTCD that increase its ability to detect RLS. These include: (1) bilateral simultaneous automated insonation with vessel imaging optimization (alleviating the need or a trained vascular technologist) addressing the known limitation of manual TCD, TTE, and TEE; (2) raTCD incorporates advanced software to aid the user in identification of the regions of interest for the study as well as full audio and video playback to aid distinguishing

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TABLE 5 Comparison of detection rate of raTCD/TCD vs. TTE and TEE between various other published studies.

| Variable | Study (year) | Total enrollment (n) | Age (years) | Lack of bone window (%) | raTCD/ TCD detection rate (%) | TTE detection rate (%) | Diff (%) | 95% CI of diff (%) | *P*-value | TEE (n) | raTCD/ TCD detection rate (%) | TEE detection rate (%) | *P*-value | Neg on TEE/ Pos on TCD (n) | Neg on TCD/ Pos on TEE (n) | Sensitivity (%) | Specificity (%) | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall RLS detection rate | Current study* | 148 | 58.0 ± 14.1 | 6.1% | 59.9% | 36.7% | 23.2% | [11.3, 34.9%] | 0.00012 | 33 | 72.7% | 72.7% | 1.0 | 1 | 1 | 92.0 | 87.5 | 78.6 | 71.4 |
| | Rubin et al. (34)* | 129 | 59.7 ± 14.6 | 5.8% | 63.6% | 20.2% | 43.4% | [35.2,52.0%] | <0.001 | 14 | 85.7% | 57.1% | 0.221 | 5 | 1 | n/a | n/a | n/a | n/a |
| | Pirabanchi et al. (20)* | 212 | 55.8 ± 11.3 | 7.6% | 61.1% | 33.3% | 27.8% | n/a | n/a | 32 | 78.1% | 50.0% | n/a | 9 | 0 | 100.0*** | 58.0*** | n/a | n/a |
| | Tian et al. (38) | 775 | 43.0 ± 16.3 | n/a | 94.8% | 84.5% | 10.3% | n/a | <0.001 | 46 | 97.8% | 47.8% | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| | Mullet et al. (29) | 101 | 51.0 ± 15.8 | 5.6% | 52.4% | 45.7% | 6.7% | n/a | n/a | 51 | 52.4% | 68.6% | n/a | 4 | 0 | n/a | n/a | n/a | n/a |
| | Liu et al. (35) | 161 | 42.0 ± 15.6 | n/a | 92.8% | 93.3% | −0.6% | n/a | >0.5 | 130 | 92.8% | 86.9% | 0.04 | n/a | n/a | 92.8 | n/a | 93.3 | n/a |
| | Katsanos et al. (4)** | 3,067 | 50.0 | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | 96.1 | 92.4 | 45.1 | 99.6 |
| | Mojadidi et al. (27)** | 1,968 | 47.8 ± 5.7 | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | 97.0 | 93.0 | n/a | n/a |
| Large RLS detection rate | Current study* | 148 | 58.0 ± 14.1 | 6.1% | 42.6% | 23.0% | 19.6% | [8.5, 30.7%] | 0.00053 | | | | | | | | | | |
| | Rubin et al. (14)* | 129 | 59.7 ± 14.6 | 5.8% | 27.1% | 10.1% | 17.0% | [11.5, 24.5%] | <0.001 | | | | | | | | | | |
| | Pirabanchi et al. (20)* | 212 | 55.8 ± 11.3 | 7.6% | 25.9% | n/a | n/a | n/a | n/a | | | | | | | | | | |
| | Liu et al. (35) | 161 | 42.0 ± 15.6 | n/a | 46.4% | 49.6% | −3.2% | n/a | >0.5 | | | | | | | | | | |

*Used raTCD (NeuraSignal, Inc.). **Meta-analysis. ***Used TTE as the Gold Standard compared to other studies which used TEE. "Diff" means difference in detection rates. n/a, Not applicable or not reported in study.

bubbles injected peripherally from artifact; (3) unlike TTE (in which atrial images are partially obscured by the ribs) and manual TCD (which has a higher rate of unsuccessful insonation due to poor bone windows), raTCD offers excellent visualization of the unobstructed intracranial vasculature for bubble detection (31) including "no window" rates of 6.1% in the current study, 5.8% in BUBL study by Rubin et al. (14) and 3.5% in a group of healthy volunteers (32); and (4) utilization of Power M-Mode TCD which has been shown to be more sensitive for RLS detection compared to single gated manual TCD (18).

## 4.3 Impact of study protocol on RLS screening test accuracy

In addition to technological differences between imaging modalities, the specifics of different scanning protocols can have a dramatic impact on the accuracy of tests. Valsalva maneuver appears to play a major role in the ability to detect a positive bubble study on TEE or TTE. Caputi et al. reported an overall PFO detection rate by TEE of 63% with a general concordance between manual TCD and TEE of approximately 90% with a sensitivity and specificity for cTCD of 96.8 and 78.4%, respectively (17). Without Valsalva, TCD was far superior at overall RLS detection (75%) over TEE (48%) ($p < 0.001$). Furthermore, of the patients that demonstrated a "shower-curtain" pattern on TCD at rest (indicating very large RLS), only 71% of those patients exhibited RLS at all on TEE at rest. Of patients that exhibited a smaller, "non-curtain effect," RLS at rest on TCD, only 22% of those were noted to have any RLS on TEE at rest. These findings indicate the highly operator dependent nature of TEE and the critical aspect of Valsalva when performing TEE and TCD. Based on their results and the individual benefits of both TEE and TCD, Caputi et al. proposed that "the combination of TEE and TCD could be considered the real gold standard for PFO" (17). The critical importance of Valsalva also applies to TTE where the maneuver has been reported to increase specificity from 40 to 60% (33). While adequate Valsalva can be easily confirmed quantitatively on raTCD by a drop in the MCA flow velocity of approximately 25%, adequate Valsalva on TTE or TEE is much harder to confirm and in the case of TEE harder to elicit due to patient sedation. Difficulty with patient tolerability of the TEE probe, variations in cardiac anatomy and operator experience all may contribute to reducing the sensitivity of TTE and TEE in PFO detection. Patient positioning also appears to be an additional potentially important factor in PFO detection. Lucreziotti et al. reported increased RLS on TCD and TTE with patients in the sitting position compared to the supine position (31). Regarding raTCD, Rubin et al. reported similar results in their secondary analysis of the BUBL study showing that both Valsalva and bed positioning (HOB angle 0°–45°) had a significant impact on RLS grade whereas IV location did not (34). As TTE is typically performed with the patient semi-prone, this may be a driver to lower performance. In our study however (where raTCD was performed at or below 45° incline) it is unlikely that this factor is a major contributing factor to our results. Given the known positional effects on PFO detection it would be theoretically ideal to compare raTCD and TTE simultaneously in identical positions. Practically speaking, however, optimal imaging windows on TTE are highly positional dependent based on body habitus and are often suboptimal in the semi-erect position.

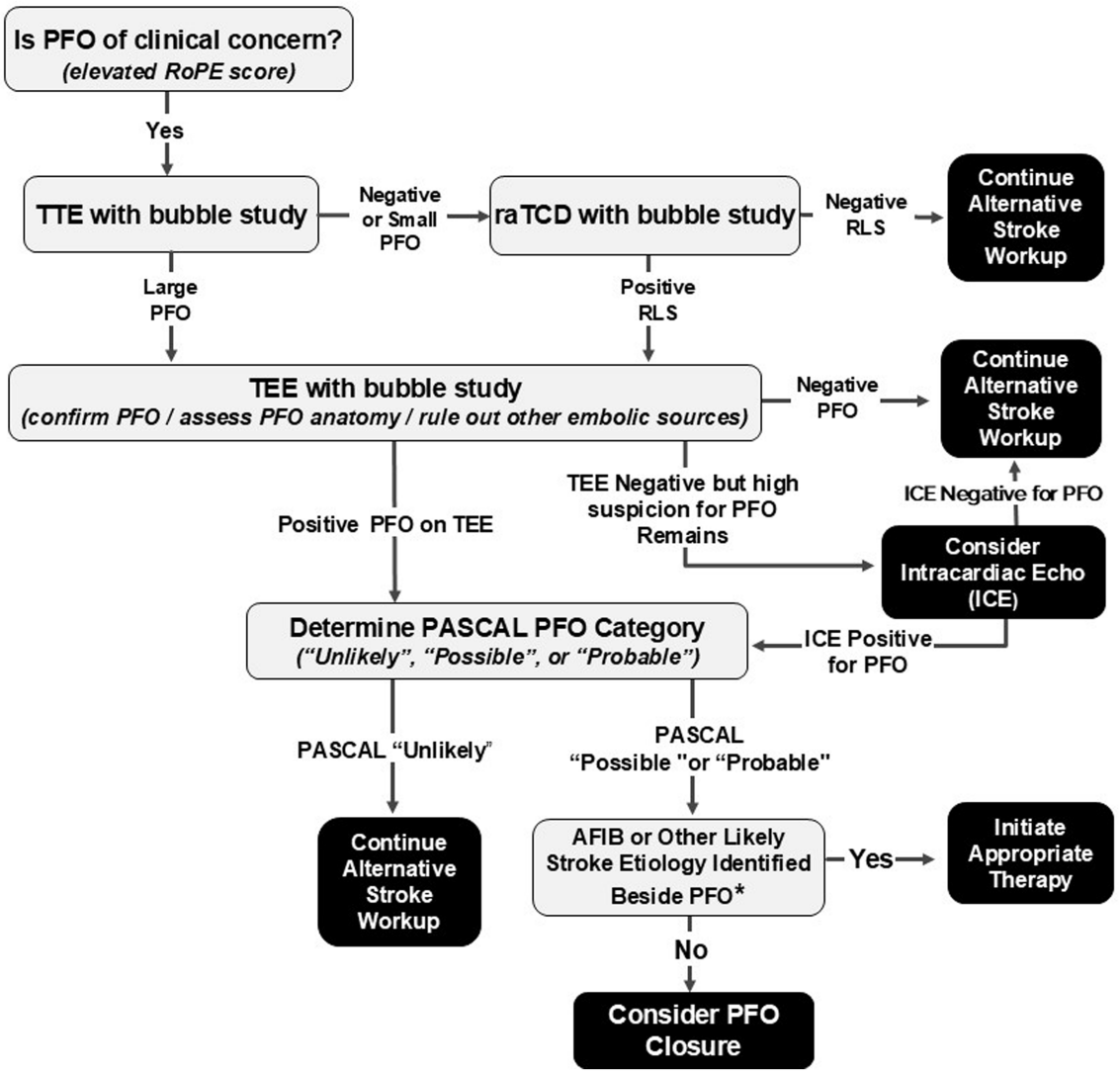


FIGURE 1
Recommended diagnostic algorithm for PFO diagnosis and patient selection for PFO closure. *Perform long-term cardiac monitoring (approx. 3–6 months) and rule out hypercoagulable state, connective tissue disease, autoimmune process, or other stroke etiologies as clinically indicated.

Despite strong support in the literature for the role of TCD when performed in conjunction to TTE for RLS detection, variability does exist in the reported specificity of TTE for RLS detection (see Table 5). A paper published in Echocardiography in 2020 (161 patients with various neurological disorders) utilizing right heart catheterization as the gold standard reported a sensitivity of 92.75% for TCD and 93.33% for TTE, but specificity was not reported (35). TTE image quality is known to be highly dependent on BMI (36). Therefore, well-established regional differences in BMI nationally (highest in our region of the south) may contribute to the variability in published RLS detection rates using TTE (37). In addition to a multitude of other variables (ex., ultasonographer experience, degree of patient hydration, hardware and software variability, etc.), Valsalva technique is a critical determinant of RLS detection rates on TTE (38). As most centers, including ours, do not use calibrated Valsalva during standard TTE bubble studies, variation in Valsalva may contribute significantly to the variability in reported rates of RLS on TTE. The ability of raTCD to mitigate the magnitude of the influence of many of these variables appears advantageous (4, 17, 23, 33).

## 4.4 Rational for the new protocol for PFO workup incorporating raTCD

Recommendations are emerging in numerous review articles and society guidelines in the United States and from Europe, that the concept of TEE as a "gold standard" be replaced by the concept that TEE, TCD, and TTE each have their own unique strengths and limitations and that proper PFO screening requires a coordinated protocol that often involves all three. Based on our results and the numerous other investigations discussed above, we now propose the following protocol as shown schematically in Figure 1. This protocol builds upon that presented in the muti-society European guidelines published in 2019 and the recent ESO guidelines on the diagnosis and management of PFO (12, 30). TTE with agitated saline injection is the logical initial diagnostic test to be performed to screen for PFO. Given its non-invasive nature and the need to assess for other causes of embolic source (mural wall thrombus, low ejection fraction, wall motion abnormalities, or significant valvular

abnormalities), TTE with bubble study is the obvious best initial screening tool. Next, if no PFO or a small PFO is detected on TTE, TCD should then be performed. We favor raTCD based on its advantages listed above and it significant increased RLS detection rate compared with manual TCD (14). The benefit of raTCD stems from its increased sensitivity for overall RLS detection and its superior ability to identify a larger number of bubbles leading to a more accurate estimate of shunt size. While numerous scales, such as the ROPE score, have been employed to assess likelihood of PFO as a causative factor for stroke, more refined scales (ex., PASCAL) now incorporate PFO size and the presence of high-risk structural features (atrial septal aneurysm (ASA)) (39, 40). PASCAL allows for an easy and highly clinically useful validated calculation of the risk/benefit ratio of PFO closure (3). When calculating a PASCAL score to determine risk/benefit ratio for potential PFO closure on a patient with cryptogenic stroke, the clinician must go through a 4-step process of: (1) accurately identifying that a PFO is present; (2) calculating the ROPE score based on the patients history; (3) estimating the size of the PFO (if PFO is absent or small on TTE, raTCD should be performed); and (4) utilization of TEE to rule out a non-cardiac cause of RLS and determining the presence or absence of an associated ASA. With this data in hand, the PASCAL score can then be calculated (3). Based on PASCAL, if the PFO is determined to be the "possible" or "probable" stroke etiology, the risk/benefit ratio may favor PFO closure in properly selected patients. If PASCAL determines that the PFO is an "unlikely" etiology of stroke, PFO closure may be associated with increased harm. Even in the absence of an ASA, the identification of a larger PFO (which may be detected on raTCD but undersized or missed on TTE or TEE) in the setting of a high ROPE scale score may result in a moderate risk PASCAL PFO score qualifying for closure (3). Therefore, missing a PFO completely or mislabeling a PFO as small based on erroneous TTE/TEE information may lead to loss of opportunity for proper secondary stroke prevention by PFO closure. Similarly, the presence of ASA, even in the presence of a small PFO, combined with high ROPE score may qualify as a "possible" risk PFO on PASCAL thereby justifying PFO closure. For these reasons, a stepwise protocol utilizing TTE, raTCD, and TEE appears to be the best approach for PFO detection and rigorous adjudication to properly determine the risk/benefit ratio for PFO closure.

The preponderance of evidence discussed above now indicates that by utilizing a combination of TTE, TEE, and raTCD, as outlined in Figure 1, we can significantly reduce the likelihood of missed PFO diagnoses that could otherwise occur with the exclusive use of TTE and/or TEE. Recent publications also suggest that in rare cases in which a high index of suspicion for PFO remains (ex., positive raTCD but negative TTE/TEE), intracardiac echocardiography (ICE) or other invasive intracardiac imaging can be considered (41–43). Ongoing large-scale comparisons of TCD, TTE and TEE performance and studies on how best to optimize each should continue to be reported. The cumulative literature to date does suggest that the etiology of stroke for many patients has likely been shrouded in mystery for years due to lack of proper PFO detection. It is now time to adopt a new standard of care approach for PFO screening based on a composite assessment with TTE, raTCD, and TEE. In that way we can best fulfill our commitment to our patients to provide them with the highest-level of secondary stroke prevention.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by CommonSpirit Research Institute Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this is a retrospective study.

## Author contributions

RS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. CD: Conceptualization, Data curation, Writing – review & editing. LG: Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing. SL: Conceptualization, Supervision, Validation, Writing – review & editing, Data curation, Methodology. VR: Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing, Investigation. VM: Data curation, Investigation, Methodology, Writing – review & editing. JP: Data curation, Investigation, Writing – review & editing, Conceptualization, Project administration. LD: Data curation, Investigation, Project administration, Writing – review & editing. TD: Investigation, Project administration, Writing – review & editing, Conceptualization, Formal analysis, Funding acquisition, Supervision, Validation, Writing – original draft.

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## Conflict of interest

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.

## Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

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# Cryptogenic strokes and neurological symptoms of Fabry disease

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**Introduction:** Fabry disease (FD) is the second most common lysosomal storage disorder. It mainly affects young people. FD can be characterized by neurological symptoms that can occur in both the central and peripheral nervous systems. Cerebrovascular involvement is common in FD and is considered an important cause of cryptogenic strokes. This study aimed to describe the neurological symptoms in patients with FD in general and, specifically, to determine the frequency of association between this disease and cerebrovascular manifestations in our environment.

**Materials and methods:** This retrospective, observational, cross-sectional study included all patients in the FD registry of the nephrology and cardiology Departments of our center. A descriptive analysis of demographic, neurological, clinical, and neuroimaging variables was performed, with a particular focus on their association with stroke or other cerebrovascular events prior to diagnosis.

**Results:** A total of 25 patients were included, with 14 (68%) of them being women. The median age of the patients was 52 years (relative intensity of collaboration [RIC] = 24.5). The patients belonged to five families with specific galactosidase alpha gene (GLA) mutations. Neuroimaging was performed in 13 (52%) patients, most of whom did not have neurological symptoms but had normal imaging results. Only 2 (8%) patients had nonspecific white matter hyperintensities. Among the 11 (44%) patients with neurological involvement, the most common symptom was pain in the extremities (32%). Stroke was identified in only one patient (4%), which occurred prior to the diagnosis of FD and was determined to be of cardioembolic etiology.

**Discussion:** FD is found to be associated with several neurological symptoms. In our study, the most common neurological symptom was limb pain, which had varied characteristics. On the other hand, the incidence of stroke was significantly lower than that expected.

KEYWORDS

**stroke, Fabry disease (FD), Fabry disease – complications, cryptogenic stroke (CS), cryptogenic stroke**

# 1 Introduction

Fabry disease (FD) is the second most common lysosomal storage disorder, following Gaucher disease. This disease is an X-linked inherited disorder of sphingolipid metabolism caused by decreased or absent activity of the lysosomal enzyme $\alpha$-galactosidase. This enzyme typically affects the heart (cardiomyopathy and arrhythmias), kidneys (resulting in proteinuria and renal failure), nervous system (causing neuropathic pain and stroke), and skin (manifesting as angiokeratomas) (1, 2). The prevalence of FD is estimated to be between 1/117000 and 1/476000. However, a comprehensive international database would be necessary to determine the true prevalence (3–6).

Peripheral neuropathy is the most common form of presentation, affecting approximately 80% of patients with FD (7). Cerebrovascular involvement is also frequently observed. FD is considered to be a significant cause of stroke, with ischemic strokes/transient ischemic attacks (TIAs) occurring in up to 25% of patients with FD (7). The pathology of FD increases the risk of stroke across all age groups, particularly in young individuals. It raises the risk of ischemic stroke up to 12 times in men aged 25–44 years and 10 times in women (8). Additionally, FD is also associated with hemorrhagic stroke and other less frequent cerebrovascular manifestations (vascular dementia, cervical artery dissection, etc.).

Magnetic resonance imaging (MRI) is considered the gold standard for imaging. In patients with FD, certain findings that have been described as more frequent (7), such as the pulvinar sign (9), extensive white matter lesions (10), or ectasia and elongation of the basilar artery (11), can be found. However, these findings are not specific to this pathology and must be interpreted in a clinical context. The pulvinar sign is now understood to occur with a significantly lower incidence in Fabry disease than previously described, and selective involvement of the pulvinar is recognized as a rare neuroradiological sign of the disease (12).

This study aims to describe the neurological symptoms in patients with FD in general and, specifically, to assess the frequency of association between this disease and cerebrovascular manifestations in our environment.

# 2 Materials and methods

This retrospective, observational, and cross-sectional study included patients from the Fabry disease registry in the Nephrology and Cardiology Services of Torrecárdenas University Hospital in Almeria. The clinical history (Diraya and Single Health Record) was reviewed to identify neurological symptoms assessed in the emergency department, primary care, or hospital. This review included assessments by the Neurology Service (through consultations or hospital admissions) and complementary tests that were performed (neurophysiology and neuroimaging). To obtain this information, an independent reviewer retrieved the reports containing the necessary data from the patient's electronic medical records, anonymized these reports, and sent them to the study authors for the collection of variables into the databases. For report selection, the reviewer searched the records of emergency, neurology, nephrology, cardiology, neurophysiology, and imaging studies.

The inclusion criteria for this study were as follows: patients aged 18 years and those with a genetic or biochemical diagnosis of Fabry disease, specifically with pathogenic mutations, in the province of Almería. The exclusion criteria had patients with mutations of uncertain significance or nonpathogenic mutations and those without documented follow-up.

## 2.1 Variables

The study considered several variables, including demographic, clinical, and neuroimaging data. Demographic variables included sex, current age, age at diagnosis of Fabry disease, and disease duration. Clinical variables encompassed ischemic stroke (categorized by large vessel, lacunar, anterior territory, and posterior territory), hemorrhagic stroke (deep territory and lobar), and stroke etiology (atherothrombotic, cardioembolic, arterial dissection, cryptogenic). Other clinical symptoms assessed included vascular dementia, neuropathy (sensory, motor, or mixed), distal extremity pain, acroparesthesia, palmoplantar hypesthesia, dysautonomia (manifested by hypohidrosis, reduced salivation, reduced lacrimation, intestinal motility disorders, and cardiac arrhythmias), as well as other diagnoses such as multiple sclerosis, aseptic meningitis, and dolichoectasia. Cardiac involvement was assessed in terms of cardiomyopathy and arrhythmias, whereas renal involvement was evaluated through proteinuria and renal insufficiency. Cutaneous and ocular involvement was determined by the presence of angiokeratomas and cornea verticillate, respectively. Additional neurological symptoms, such as headache and vertigo, were also recorded. Neuroimaging data included the presence of white matter lesions (classified as periventricular, subcortical, or generalized), the pulvinar sign, and ectasia or elongation of the basilar artery.

## 2.2 Statistical analysis

A descriptive analysis of the variables was performed. Quantitative variables were expressed as means ± standard deviations (SD) or medians (interquartile ranges). Qualitative variables were expressed as total numbers and percentages (%). Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS), Windows version 27.0 (IBM, Armonk, New York).

# 3 Results

A total of 28 patients were obtained from the records under follow-up by the nephrology and cardiology services, of which three were excluded due to age below 18 years, resulting in a final sample of 25 patients, of whom 14 (68%) were women with a median age of 52 years (RIC = 24.5). The median age at disease diagnosis was 38 years (RIC = 26.5), and the median time of evolution at the time of analysis (May 2024) was 10 years (RIC = 6).

The patients belonged to five families, each with a specific genetic GLA mutation: Family A with the mutation p.Pro205Ser consisted of 16 members (62.5% female), Family B with the mutation p.Val199Gly comprised 2 members (100% female), Family C with the mutation p.Trp626Tre included 4 members (75% female), Family D with the

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mutation p.Gly80Asp contained 2 members (100% female), and Family E with the mutation p.Cys202Arg consisted of 4 members (75% female).

Of the 25 patients, 13 (52%) had renal involvement, 16 (64%) had cardiac involvement, 6 (24%) had skin involvement, 2 (8%) had ocular involvement, and 11 (44%) had neurological involvement. Neuroimaging studies were performed in 13 patients (52%), most of whom did not have neurological symptoms, and the results were normal in the majority (44%) with non-specific white matter lesions in two patients (one with subcortical predominance and one with periventricular predominance) (Table 1).

Among the 11 patients with neurological involvement, the majority (63.6%) presented with neurological involvement as the disease progressed. The most frequent symptom was pain in the extremities, with variable characteristics, sometimes in the form of burning and sometimes with radicular distribution, which did not always correlate with pathological findings in neurophysiological studies. The second most frequent symptom was acroparesthesia (36.4%) and dysautonomia, which also appeared in 4 patients (36.4), in the form of hyposweating in 2 of them and in the form of intestinal hypomotility in the other two. Neuropathy confirmed by neurophysiological study was observed in 3 patients (27.3), all of whom had mixed characteristics and were sometimes related to other comorbidities. Vascular dementia was observed in one patient. Another patient had a stroke before diagnosis, which was associated with the presence of *de novo* non-valvular atrial fibrillation. Other neurological symptoms were common among these patients, with headache being the most frequent (20%), typically meeting the migraine criteria. Occipital neuralgia was diagnosed in one patient; headache was diagnosed before the FD diagnosis. Two patients reported vertigo and one with non-specific visual disturbance and dysgeusia (Figure 1).

Of the total sample, 14 (56%) received enzyme replacement therapy (ERT). When the patients were categorized based on the presence or absence of neurological involvement, 5 (45.5%) of the patients with neurological involvement received ERT, whereas the percentage was higher in the group of patients without neurological involvement, 8 (57.1%); however, this difference was not statistically significant.

Furthermore, we analyzed the various neurological and non-neurological clinical manifestations by family and, consequently, by genetic mutation.

First, we defined the system-specific involvement in relation to each genetic mutation, and in the following paragraph, we provided a detailed description of the neurological involvement, also according to the specific genetic mutation. In Family A (mutation GLA p.Pro205Ser), 11 members (68.75%) exhibited cardiac involvement, 9 members (56.25%) presented renal involvement in the form of proteinuria, 3 members (18.75%) had cutaneous involvement, and 5 members (31.25%) displayed neurological involvement. In Family B (mutation GLA p.Val199Gly), 100% of the patients exhibited cutaneous, renal, and ocular involvement, and 1 member (50%) exhibited cardiac and renal involvement. In Family C (mutation nonsense GLA p.Trp626Tre), cardiac and renal involvement was observed in 25% of the patients, 100% had neurological involvement, and none exhibited cutaneous or ocular involvement. In Family D (mutation missense GLA p.Gly80Asp), 1 member (50%) exhibited proteinuria, and no patients presented with involvement in other systems. Finally, in Family E (mutation GLA Cys202Asp), all patients (100%) demonstrated cardiac involvement, 25% had renal and cutaneous involvement, and 50% presented neurological involvement, with no ocular involvement observed in any of them (Table 2).

In the total sample, 14(%) patients were treated with migalastat, alpha-galactosidase, beta-galactosidase, or a combination of these medications (Table 2). When divided by family, of the 16 members of Family A, one was treated with migalastat for 26 months without changes, one received alpha-galactosidase for 138 months without changes, and two were treated with beta-galactosidase for 86 and 160 months, respectively, without changes. The remaining four patients from this family underwent treatment modifications over time: one started with alpha-galactosidase for 120 months and later switched to beta-galactosidase for 26 months; another started with alpha-galactosidase for 108 months, followed by beta-galactosidase for 84 months, and finally migalastat for 24 months. The last member of this family had been administered with beta-galactosidase for 48 months and later switched to migalastat, which was administered for 42 months. In Family B, one of the two patients received treatment with beta-galactosidase for 36 months. In Family C, four patients

TABLE 1 The results for all variables included in the study.

| | Total ($n$ = 25) |
|---|---|
| Women, n (%) | 17 (68) |
| Actual Age, median (RIC) | 52 (24.5) |
| Age at diagnosis, median (RIC) | 38 (26.5) |
| Evolution time, median (RIC) | 10 (6) |
| Cardiological involvement, n (%) | 16 (64) |
| Kidney involvement, n (%) | 13 (52) |
| Skin involvement, n (%) | 6 (24) |
| Eye involvement, n (%) | 2 (8) |
| Neurological involvement, n (%) | 11 (44) |
| Neurological assessment | 14 (56) |
| Debut, n (%) | 4 (16) |
| Evolution, n (%) | 7 (28) |
| Stroke, n (%) | 1 (4) |
| Vascular dementia, n (%) | 1 (4) |
| Neuropathy, n (%) | 3 (12) |
| Limb pain, n (%) | 8 (32) |
| Acroparesthesia, n (%) | 4 (16) |
| Dysautonomia, n (%) | 4 (16) |
| Previous neurological diagnosis, n (%) | 2 (8) |
| Other neurological symptoms, n (%) | 7 (28) |
| Neuroimaging, n (%) | 13 (52) |
| Normal, n (%) | 11 (44) |
| Periventricular white matter hyperintensities | 1 (4) |
| Deep white matter hyperintensities | 1 (4) |
| Pulvinar sign | 0 (0) |
| Elongation of the basilar artery | 0 (0) |

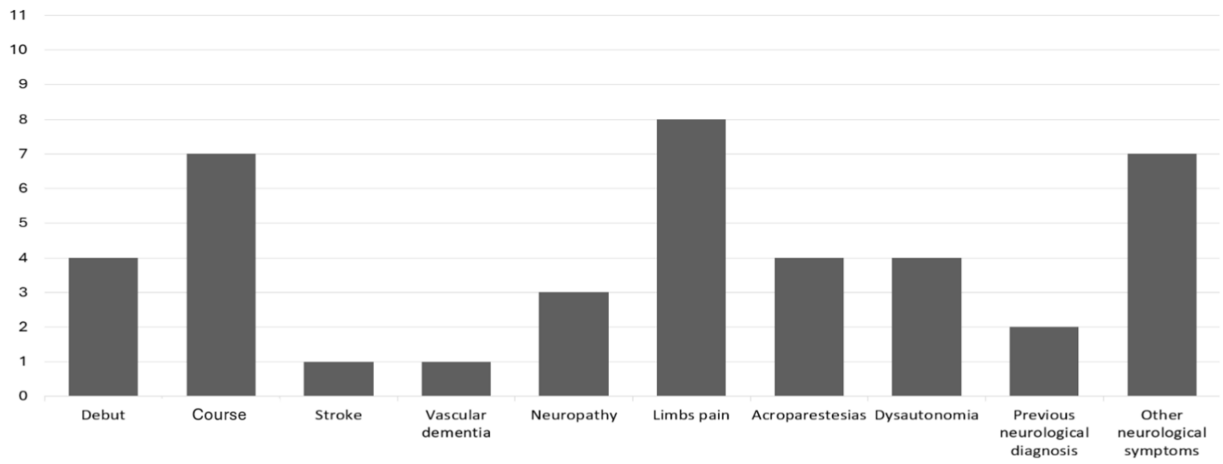


FIGURE 1
Neurological involvement (n = 11). This graph represents the 11 patients who exhibited neurological involvement, indicating whether it appeared at disease onset (4/11) or during the disease course (7/11), along with the specific type of neurological involvement.

TABLE 2 Phenotypes and treatment characteristics by families and mutations.

| | Family A (Pro205Ser) *n* = 16 | Family B (Val199Gly) *n* = 2 | Family C (Trp262Tre) *n* = 4 | Family D (Gly262Asp) *n* = 2 | Family E (Cys202Arg) *n* = 4 |
|---|---|---|---|---|---|
| **System involvement** | | | | | |
| Heart | 11 (68.75%) | 1 (50%) | 1 (25%) | 0 (0%) | 4 (100%) |
| Renal | 9 (56.25%) | 1 (50%) | 1 (25%) | 1 (50%) | 1 (25%) |
| Cutaneous | 3 (18.75%) | 2 (100%) | 0 (0%) | 0 (0%) | 1 (25%) |
| Ocular | 0 (0%) | 2 (100%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Neurological | 5 (31.25%) | 2 (100%) | 2 (50%) | 0 (0%) | 1 (25%) |
| **Treatment** | | | | | |
| No treatment | 9 | 1 (50%) | 0 (0%) | 0 (0%) | 2 (50%) |
| Migalastat | 3 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Fabrazyme | 4 | 1 (50%) | 4 (100%) | 0 (0%) | 1 (25%) |
| Replagal | 3 | 0 (0%) | 0 (0%) | 0 (0%) | 1 (25%) |
| Mean duration of therapy (months) | 123 | 36 | 56 | - | 10 |

received beta-galactosidase treatment for 103, 24, 48, and 48 months, respectively. Finally, in Family E, one patient received beta-galactosidase for 14 months, and another received alpha-galactosidase for 6 months. No patient in Family D received treatment.

Finally, we analyzed the neurological involvement of the members of each family (Figure 2).

- Family A: Among the five members with neurological symptoms, four exhibited these symptoms during the course of the disease. One patient presented with sensory neuropathy characterized by pain in the extremities, two experienced headaches, and the last had vertiginous symptoms. The patient with sensory neuropathy showed periventricular white matter hyperintensities on MRI and developed vascular dementia, whereas the others had no significant findings on neuroimaging. The fifth patient in Family A exhibited neurological symptoms at disease onset, presenting with pain in the extremities and acroparesthesia. The patient had been evaluated by a neurologist several years previously and was discharged with a diagnosis of headache. MRI revealed the following bifrontal deep white matter hyperintensities:

- Family B: Both members (100%) experienced neurological symptoms throughout the course of the disease, both in the form of neuropathy: one sensory and the other mixed, with the latter being more symptomatic, presenting not only paresthesias but also hypo-anhidrosis and abdominal pain crises. Neuroimaging in both patients was normal.

- Family C: Two of the four patients presented with neurological symptoms. They consisted of one man and one woman, both with extremity pain. No imaging studies were available for either of them.

- Family D: No patient exhibited neurological symptoms.

- Family E: Of the total, 50% (2 out of 4) presented with neurological symptoms. One patient experienced headaches and vertigo throughout the course of the disease and had a prior diagnosis

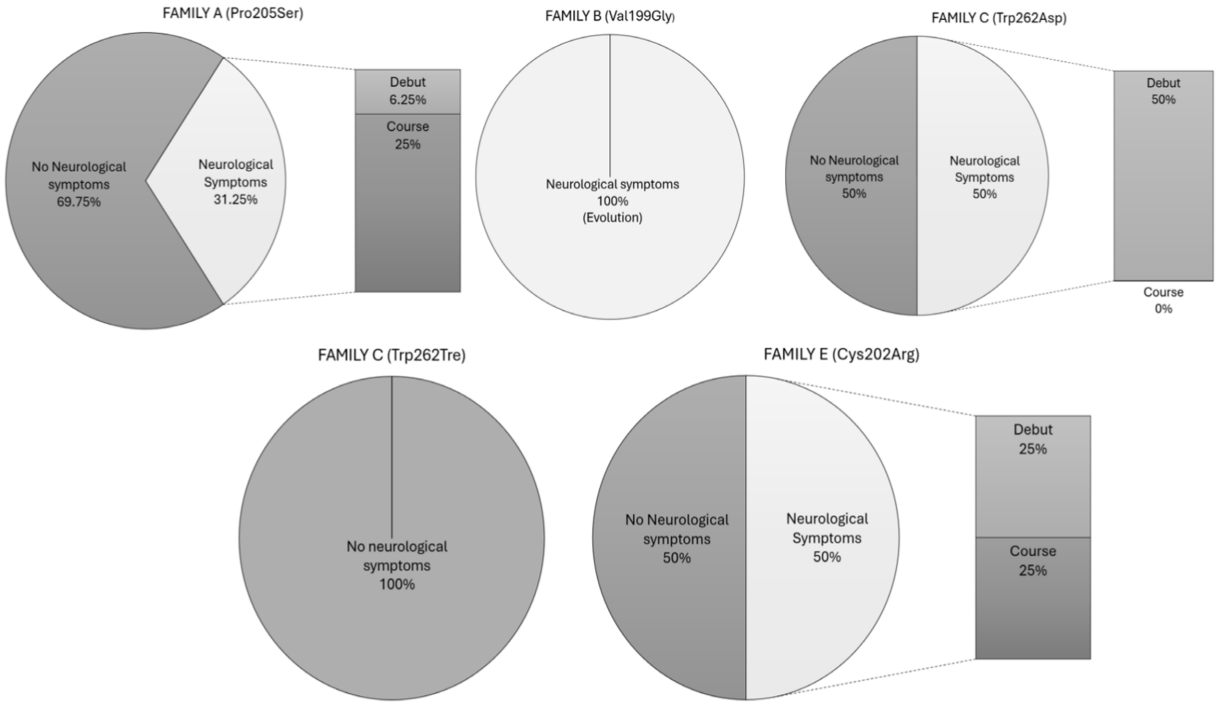


FIGURE 2
Neurological symptoms by families. This graph shows the percentage of neurological and non-neurological involvement per genetic mutation, indicating the proportion of neurological symptoms that appeared at disease onset or during the course of the disease.

of occipital neuralgia before Fabry's disease was detected. The second patient in the sample was the only one to have a stroke. He had experienced a transient ischemic attack (TIA) 4 years previously and ultimately suffered a large vessel ischemic stroke in the posterior circulation, also in the context of non-valvular atrial fibrillation. During the etiological study of this stroke, ventricular hypertrophy was found on echocardiography, prompting further investigation. He was diagnosed with Fabry disease 1 year later (Table 2).

## 4 Discussion

FD is associated with several neurological symptoms. In the current study, the most frequent neurological symptom was limb pain with varied characteristics, with a lower prevalence of cryptogenic stroke than expected. These results suggest that the prevalence of stroke among patients with Fabry disease may be overestimated, in contrast to the majority of previous studies reporting a high prevalence of this complication.

The most frequent neurological symptom among our sample was limb pain. This is congruent with the available literature: peripheral neuropathy is the most common presentation (80%) in the form of fine fiber sensory neuropathy in which distal pain is the most frequent presentation (60–80%), followed by acroparesthesia and hypoaesthesia in the hands and soles of the feet. When it appears in childhood, this symptomatology should prompt us to consider this entity (7).

On the other hand, the low frequency of debuts with strokes was higher than expected. According to available evidence, the frequency of vascular events in patients with FD is >25% (7). Studies analyzing this relationship vary depending on the population: some analyze "cryptogenic stroke patients" and look for FD, and others analyze "patients with FD" and look for stroke as a manifestation.

The most frequent analyses are the cryptogenic stroke populations and the frequency of FD among them. We identified 14 studies with these characteristics (13–24). The majority of these studies are retrospective, and the frequency of FD varies between 0 and 6.49%. Some studies found a notable presence of FD, such as Rolfs et al. (13) with 3.88% of cases, while others reported very low prevalence, such as Kinoshita et al. (23) and Reinsin et al. (24), who found rates of 0.3 and 0.16%, respectively. The highest observed prevalence was reported by Wolkiak et al. (6.49%) (15) and Gündoğdu et al. (3.7%) (19). Romani et al. (25) recently analyzed the largest sample size (1906 patients) in a multicenter study involving 33 Italian neurological stroke units and found a prevalence of FD of 3 (0.16%).

In our center, we analyzed the frequency of FD in 99 young individuals with stroke, without identifying any positive cases during a 19-month observation period (26). As a result, our diagnostic protocol currently includes FD screening only in the presence of other suspicious manifestations (non-hypertensive hypertrophic cardiomyopathy, proteinuria, renal failure, neuropathic pain, angiokeratomas, megadolichobasilar, pulvinar sign, white matter hyperintensities of undetermined etiology, angiokeratomas, cornea verticillata) and not as a standard procedure.

Two systematic reviews analyzed studies about FD among cryptogenic stroke patients. The first study from 2013 included 9 studies and found that FD may explain 1% of strokes among young people and between 3 and 5% of cryptogenic strokes (27). The second systematic review, which was more recent from 2021, included 11 studies (28). In their pooled analysis, the prevalence of FD was

0–3.88%, and the results suggested that this prevalence is higher in patients with stroke recurrence.

On the other hand, we found 4 studies about the neurological manifestations of FD, similar to our study (29–32). First, Buechner et al. (29) studied the central nervous system involvement in a group of FRD Italian patients and described stroke in 25.6%. In the second study, Sims et al. (30) analyzed the Fabry Registry data to identify patients who suffered during the natural history period and found a prevalence of 5.6%. Afterward, Schelleckes et al. (31) detected 5 vascular events (2 strokes and 3 transient ischemic attacks) among 15 patients with FD. More recently, a multicenter study with a larger sample size (54 patients) described 5 strokes (9.25%) among them (32). This is consistent with our study, in which the prevalence (4%) was even lower than the lowest figure reported in the cited articles. Since ERT has been shown to ameliorate endothelial dysfunction in Fabry patients (7), we hypothesize that the difference in stroke frequency between studies may be influenced by whether or not patients initiated treatment: in the study with the highest prevalence of stroke detected (33), no patient had received enzyme replacement therapy (ERT), while 14 (56%) of our sample were undergoing ERT. However, in the studies by Sims and Nampoothiri, none of the patients received ERT (34).

Regarding genetics, understanding the phenotypic correlations of all known GLA gene variants and elucidating the pathophysiological mechanisms that link genetic mutations to their clinical manifestations are crucial for all stakeholders involved in providing healthcare to patients with Fabry disease and their families (34). The Human Gene Mutation Database (35) reports more than 900 GLA gene variants, of which nearly 75% are point mutations, most of which are pathogenic. The disease exhibits an X-linked recessive inheritance pattern. It is associated with mutations in the GLA gene (locus Xq22.11) in nearly 100% of the affected males, accompanied by a reduction in the enzymatic activity of Alpha-Galactosidase A. The clinical presentation encompasses a broad spectrum, ranging from mild in heterozygous females to severe in hemizygous males affected by the classic form, characterized by absent residual alpha-galactosidase activity.

Our study included five missense/nonsense mutations, one per family: GLA p.P205S, GLA p.V199G, GLA p.W626X, GLA p.G80D, and GLA C202A; we found a bibliography about all of them (36–40).

In Family A (GLA p.P205S), two patients exhibited periventricular white matter hyperintensities on MRI. A Chinese study aimed to evaluate the genotype–phenotype correlation in patients with Fabry disease, including the nonsense mutation Pro205Ser (37). This mutation was associated with an atypical presentation predominantly affecting the kidneys without white matter hyperintensities.

The only patient in the sample who presented with a stroke belonged to Family E. This mutation (Cys202Arg) is listed in ClinVar (633244), HGMD (CM1826087), and dbSNP (rs1569303843) as a pathogenic mutation causing Fabry disease. It was first described in the literature in a case report of cardiac involvement (41). These findings are consistent with the clinical presentation of our patient with cardioembolic stroke who exhibited this mutation and ventricular hypertrophy.

In neuroimaging studies, although characteristic findings are observed in Fabry disease (FD) patients, most of these are nonspecific, such as the pulvinar sign (12). The identification of corpus callosum lesions is particularly valuable for differentiating between multiple sclerosis (MS) and FD, given that patients with FD demonstrate a significantly lower incidence of corpus callosum involvement. This approach may help clinicians to promptly establish an accurate diagnosis and develop appropriate management strategies (42). The limitations of our study stem from its retrospective nature and low prevalence of vascular manifestation.

The neurological manifestations of FD are variable. The most common symptom in our population was limb pain, according to the literature. On the other hand, in our environment, the low frequency of ischemic stroke before and after diagnosis is important compared to the expected frequency. Nevertheless, the prevalence varies among studies because of the selected population and may be overestimated in some of them. FD is a possibly treatable because of cryptogenic stroke that should be considered, particularly in young patients with cardiopathy or proteinuria. The actual prevalence of FD among cryptogenic stroke patients can vary geographically according to genetic mutations and should be analyzed in future studies to determine if the prevalence is overestimated.

In conclusion, FD is associated with several neurological symptoms. In our study, the most frequent neurological symptom was limb pain with varied characteristics. On the other hand, the low frequency of stroke was important compared to that expected.

## Data availability statement

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

## Ethics statement

The studies involving humans were approved by the Institutional Ethics Committee (Comite Provincial de Almería, HU Torrecárdenas) (Protocol code: CEIC1, Internal study code: 40/2024, Protocol version and date: V.2.0 de 06 de mayo de 2024). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants in accordance with the national legislation and the institutional requirements.

## Author contributions

MR-F: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. BV-G: Conceptualization, Visualization, Writing – review & editing. PM-S: Conceptualization, Methodology, Supervision, Visualization, Writing – review & editing. RG-L: Conceptualization, Visualization, Writing – review & editing. CG-N: Conceptualization, Visualization,

Writing – review & editing. AA-P: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

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## Conflict of interest

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.

## Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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# Evaluation of the effect of statin treatment on intracranial atherosclerotic plaques using magnetic resonance vessel wall imaging: a case series

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**Introduction:** Intracranial artery stenosis highly increases the recurrence risk of transient ischemic attack and ischemic stroke, especially in Chinese patients. Patients with intracranial atherrotic disease (ICAD) should be actively treated with risk factor control, such as lipid management. This report discusses vessel wall MRI (VW-MRI) to evaluate plaque in-situ changes in four patients with ICAD after anti-lipid therapy of statins.

**Case report:** Four patients with ischemic stroke and ICAD were prospectively enrolled. VW-MRI and serum low-density lipoprotein cholesterol (LDL-C) were assessed at baseline and follow-up (at least 11–12 months). All patients received statins throughout the study. Compared with baseline, the LDL-C decreased in one case, the length of basilar artery plaque and the overall plaque enhancement segment were shortened, and the plaque thickness was reduced, indicating that the plaque tended to regress. In the second case, LDL-C increased after one year compared with baseline, along with upgraded plaque enhancement and new intraplaque hemorrhage, indicating plaque progression. After 2.5 years, LDL-C decreased significantly, while VW-MRI changes were minimal. LDL-C increased in the third case, but VW-MRI indicated plaque regression. In the fourth case, LDL-C decreased significantly, and the degree of basilar artery plaque stenosis was reduced. However, plaque enhancement upgraded, and intraplaque hemorrhage increased, indicating plaque progression.

**Conclusion:** VW-MRI can monitor the in-situ changes of plaques after lipid-lowering therapy with statins, provide key information that is difficult to reflect in systemic serological lipid indices like LDL-C, and help identify cases that are not responsive to current anti-lipid therapy.

KEYWORDS

**MRI, vessel wall imaging, intracranial atherosclerosis, statins, efficacy assessment, case reports**

# 1 Introduction

Cerebral ischemic stroke causes a heavy burden on society due to its high recurrence rate and disability rate (1). Approximately 46% of ischemic stroke patients in China are caused by intracranial atherosclerotic disease (ICAD) (2). Decreased hemodynamic perfusion induced by ICAD and unstable rupture of responsible plaques are associated with ischemic stroke events. Therefore, in addition to using traditional assessment to evaluate arterial narrowing, it is particularly important to evaluate the characteristics of ICAD plaques.

Magnetic resonance vessel wall imaging (vessel wall MRI, VW-MRI) is a non-invasive vascular imaging method that has been widely used in clinical intracranial vessels since the publication of the expert consensus by the American Society of Neuroradiology in 2017 (3). The technical core of VW-MRI is the black blood technology, which suppresses the intravascular blood signal to allow for good signal contrast between the arterial wall and the blood, allowing for high-resolution visual observation of the intracranial arterial wall structure, clarifying the distribution of atherosclerotic plaques relative to the lumen, judging the characteristics of plaques, determining the degree of vessel remodeling, etc.

Both the Chinese Guidelines for Secondary Prevention of Ischemic Stroke and Transient Ischemic Attack 2022 and the Chinese Scientific Statement on the Long-term Management of Blood Lipids in Patients with Ischemic Stroke and transient ischemic attacks recommend that ICAD patients should actively adopt risk factor control therapy, including lipid management (4, 5).

Some studies have shown that statins can lower low-density lipoprotein cholesterol (LDL-C) and enhance the stability of coronary and carotid plaques, preventing plaque rupture (6, 7). However, the effect of LDL-C control on ICAD could be different due to the thick inner elastic lamina and lack of outer elastic lamina in the intracranial artery (8), and there are fewer related reports (9–14)， in contrast with the internal carotid artery. This study prospectively collected and reported 4 cases of ICAD-induced ischemic stroke and conducted a long-term statin therapy based on the Guidelines 2022 to explore the clinical value of using VW-MRI to evaluate the efficacy of statin anti-lipid treatment on ICAD plaques (4).

# 2 Case report

## 2.1 Case 1

A 64-year-old male patient presented to the hospital with a 3-h history of sudden left-sided limb and facial numbness. He had a history of diabetes and had been receiving long-term insulin therapy with good glycemic control. He had a clinical diagnosis of ICAD. The brain MRI showed a fresh infarction lesion on the right side of the pons. MRA suggested severe stenosis of the basilar artery near the middle segment. Intracranial VW-MRI showed multiple atherosclerotic plaque formation with obvious stenosis of the middle segment of the basilar artery. The plaque length was 11.3 mm, the plaque thickness was 2.4 mm, the degree of luminal stenosis [luminal stenosis degree = (1-luminal area at stenosis / normal luminal area) × 100%] was about 80%, and the plaque burden [plaque burden = (1− luminal area at stenosis / total vascular area)], was about 0.94. The plaque enhancement was grade 2 (Grade 0 means no enhancement, with plaque signal intensity ≤ adjacent normal intracranial artery wall signal intensity. Grade 1 means mild to moderate enhancement, pituitary infundibulum enhancement > plaque signal intensity > normal artery wall signal intensity. Grade 2 means obvious enhancement, with plaque signal intensity ≥ pituitary infundibulum enhancement) (15), suggesting plaque instability (Figures 1A–C). Following the neurologist's instructions, the patient took a long-term high-intensive rosuvastatin (20 mg/d) treatment. After 12 months, follow-up VW-MRI showed the plaque length was 7 mm, the plaque thickness was 1.6 mm, the luminal stenosis was about 80%, the plaque burden was about 0.93, the plaque enhancement degree was still grade 2, and the overall plaque enhancement segment was shortened (Figures 1D–F), indicating that the plaque tended to be stable. LDL-C decreased from 1.22 mmol/L at baseline to 1.07 mmol/L at follow-up, consistent with the change of image of image findings. There was no recurrence of stroke or TIA in the following time.

## 2.2 Case 2

A 67-year-old female patient presented with dizziness for 1 month. MRA revealed left vertebral artery stenosis. She had a history of diabetes, with poor glycemic control, and a clinical diagnosis of ICAD. Intracranial VW-MRI showed atherosclerotic plaque formation in the intracranial segment of the left vertebral artery with significant luminal stenosis, with a plaque length of 15 mm, a plaque thickness of 2.4 mm, a luminal stenosis of about 86%, a plaque burden of about 0.94, and the plaque enhancement was grade 1, indicating some instability (Figures 2A–C). During the follow-up period, the patient took a moderate-intensity to high-intensity rosuvastatin (10–20 mg/d) treatment intermittently as poor complicance. A follow-up VW-MRI was performed 11 months later. Compared with the baseline examination, the plaque length was 15 mm, the plaque thickness was 2.7 mm, the luminal stenosis was about 92%, the plaque burden was about 0.95, the fresh intraplaque hemorrhage (The presence of fresh IPH was identified as >150% signal relative to nearby medial pterygoid muscles on precontrast T1-weighted images) (16) was detected and the plaque enhancement was elevated to grade 2 (Figures 2D–F), suggesting a trend of plaque progression, indicating that the anti-lipid therapy was not effective. The LDL-C increased from 1.68 mmol/L at baseline to 3.64 mmol/L at the point of follow-up, consistent with the image findings. A third intracranial VM-MRI at 30 months follow-up was performed. Compared with the second scan, there were no significant changes in plaque length, plaque thickness (15 mm and 2.7 mm, respectively), luminal stenosis and plaque burden (about 91% and 0.95, respectively), intraplaque hemorrhage and plaque enhancement (Figures 2G–I), indicating no significant change in plaque characteristics. The LDL-C decreased from 3.64 mmol/L at the second time to 1.58 mmol/L at the third time.

## 2.3 Case 3

A 37-year-old male patient presented with a transient left-hand numbness and slurred speech for 4 h. He had a history of hypertension. The clinical diagnosis was ICAD. MRI and MRA at an outside hospital showed multiple infarctions in the right frontal,

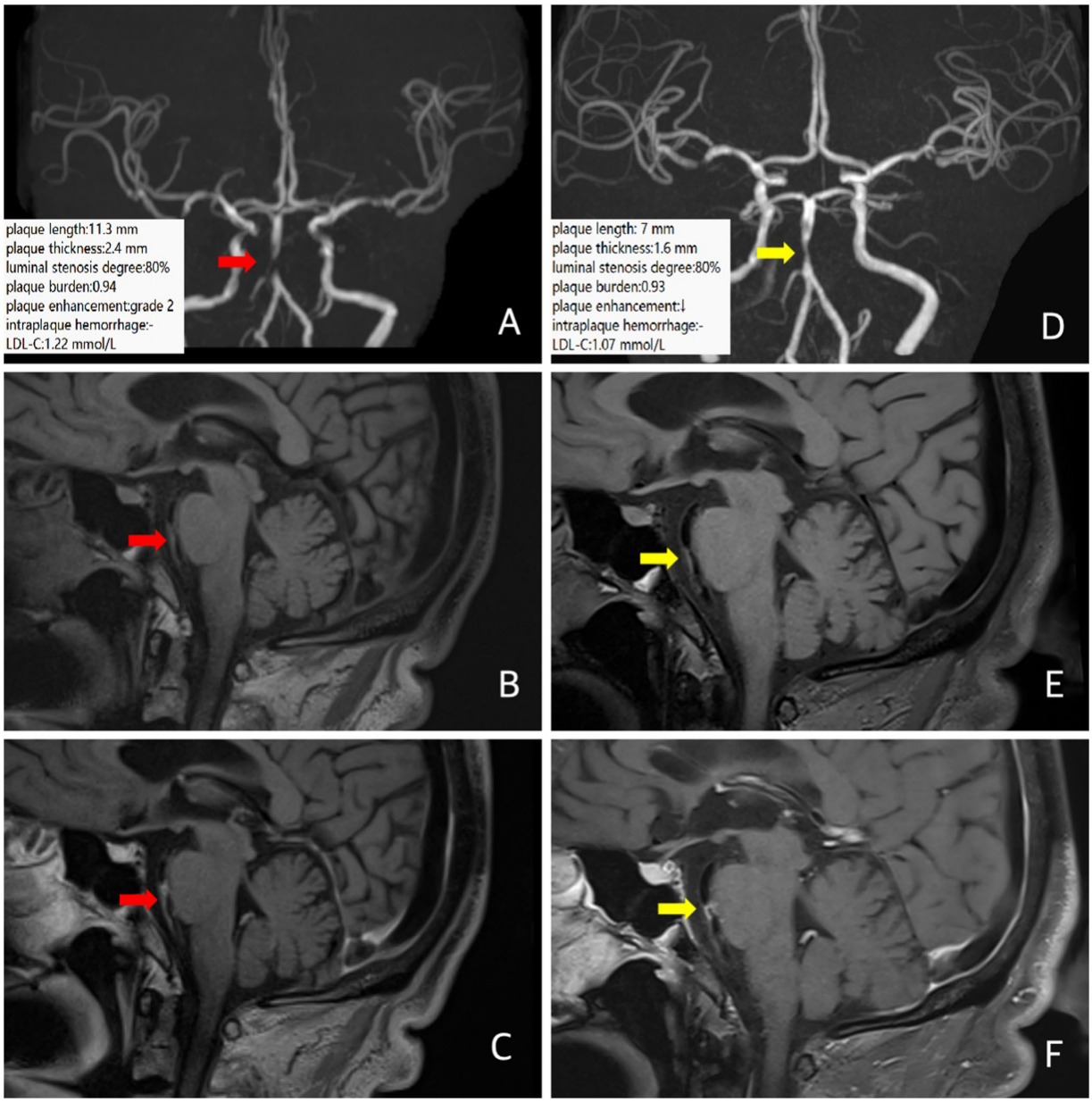


FIGURE 1
In case 1, patient at baseline (red arrow) and follow-up images 12 months later (yellow arrow). Three-dimensional time-of-flight cerebral magnetic resonance angiography showed significant stenosis in the middle segment of the basilar artery **(A,D)**. Coronal T1 plain scan weighted imaging **(B,E)** and enhanced imaging **(C,F)** in whole brain magnetic resonance imaging using different inversion angles to optimize contrast showed multiple atherosclerotic plaque formation in the basilar artery with obvious stenosis in the middle lumen and obvious plaque enhancement. Follow-up intracranial VW-MRI showed that compared with baseline, the length of the plaques was shortened, the plaque thickness was attenuated and there was no significant change in luminal stenosis, plaque burden, or plaque enhancement. Still, the overall enhancement segment was shortened, suggesting that the plaque tended to be stable. The LDL-C levels decreased.

parietal, temporal, and occipital lobes, as well as severe stenosis of the right internal carotid artery communicating segment. Baseline intracranial VW-MRI showed atherosclerotic plaque formation in the right internal carotid artery communicating segment with severe focal stenosis, the plaque length was 5.2 mm, the plaque thickness was 2.0 mm, the degree of luminal stenosis was about 78%, the plaque burden was about 0.86, with possible intraplaque hemorrhage, and the plaque enhancement was grade 1 (Figures 3A–C), suggesting plaque instability. The patient took a high-intensity rosuvastatin (20 mg/d) treatment. A follow-up VW-MRI was performed 11 months later. VW-MRI showed that the plaque length was 3.4 mm, the plaque thickness was 0.9 mm, the luminal stenosis was about 73%, the plaque burden was about 0.80, and the intraplaque hemorrhage seemed weakened, indicating that the plaque tended to be stabilized and regress (Figures 3D–F). On the contrary, the LDL-C elevated from 1.52 mmol/L at baseline to 1.79 mmol/L at follow-up, indicating a clinical mismatch.

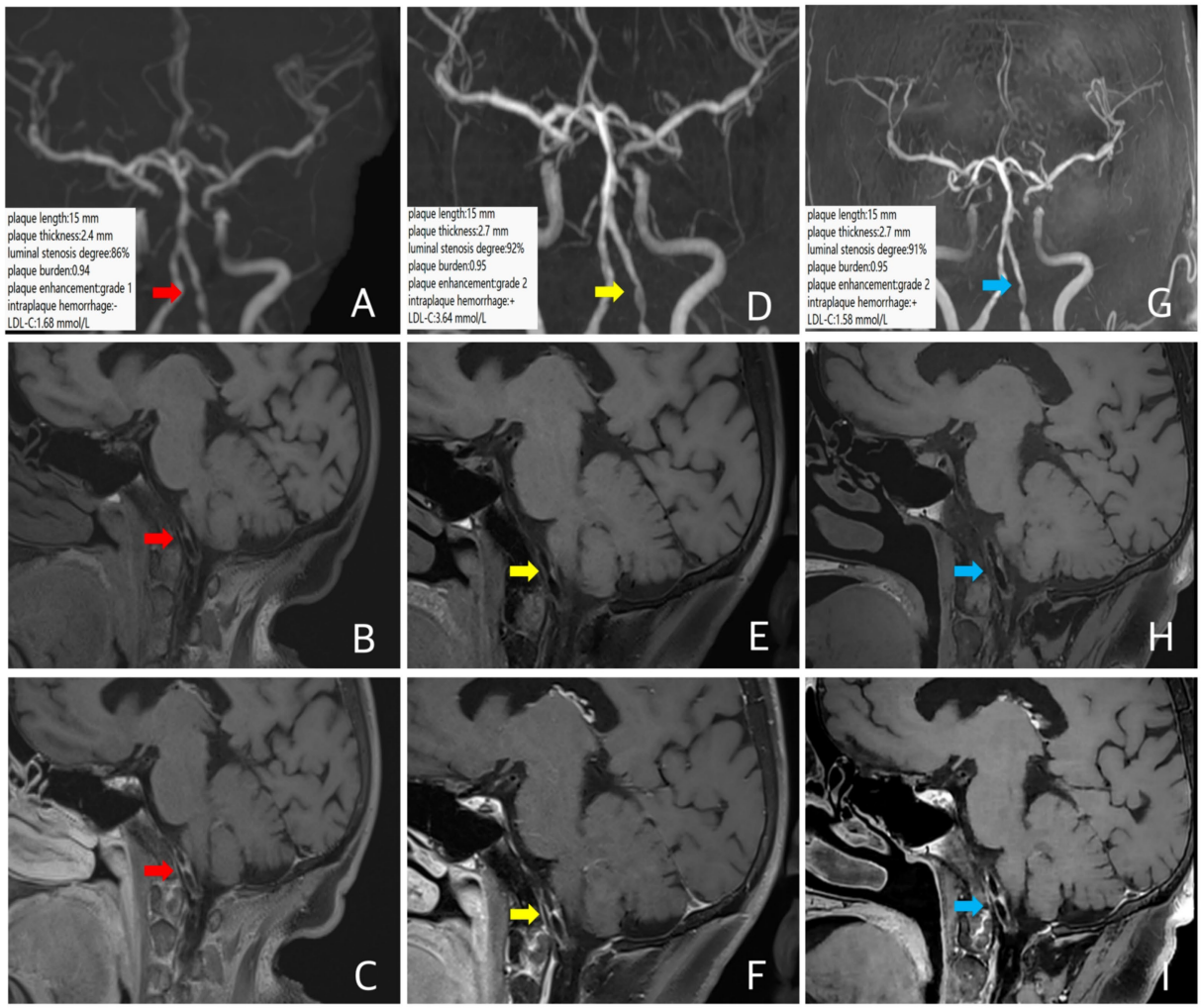


FIGURE 2
In case 2, patient at baseline (red arrow), follow-up images 11 months later (yellow arrow), and follow-up images 30 months later (blue arrow). Three-dimensional time-of-flight cerebral magnetic resonance angiography showed significant stenosis of the intracranial segment of the left vertebral artery **(A,D,G)**. Coronal T1 plain scan weighted imaging **(B,E,H)** and enhanced imaging **(C,F,I)** in whole brain magnetic resonance imaging using different inversion angles to optimize contrast showed multiple atherosclerotic plaque formation in the left vertebral artery plaque with obvious stenosis and obvious plaque enhancement. The 11-month follow-up intracranial VW-MRI showed no significant changes in plaque length and plaque thickness compared with baseline, a slight increase in the luminal stenosis and the plaque burden, a new intraplaque hemorrhage occurred, and the plaque enhancement upgrades **(D–F)**, indicating a progressive tendency in the plaque. Which LDL-C level is elevated. At 30 months, intracranial VW-MRI showed no significant changes in plaque compared with the second examination **(G–I)**, in which LDL-C levels decreased.

## 2.4 Case 4

A 57-year-old male patient was admitted to the hospital with sudden right limb weakness and was clinically diagnosed with ICAD. MRI and MRA showed acute infarction in the left anterior part of the pon and severe stenosis of the middle segment of the basilar artery. He had a history of hypertension for more than 20 years, a history of diabetes mellitus for 15 years, and poor glycemic control. Baseline intracranial VW-MRI showed atherosclerotic plaque formation in the basilar artery wall with severe focal luminal stenosis. The plaque length was 15.8 mm, the plaque thickness was 3.1 mm, the degree of luminal stenosis was about 85%, the plaque burden was about 0.92, and the plaque enhancement was grade 0, with possible intraplaque hemorrhage, suggesting some instability (Figure 4). The patient took a long-term high-intensity rosuvastatin (20 mg/d) treatment, and received a subcutaneous injection of the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (evolocumab) 140 mg, once every two weeks. Follow-up VW-MRI after 12 months showed that the plaque length was 15.8 mm, the plaque thickness was 3.2 mm, the degree of luminal stenosis was about 67%, the plaque burden was about 0.89, the intraplaque hemorrhage seemed increased, and the plaque enhancement elevated to grade 1, indicating plaque progression (Figure 4). However, the LDL-C decreased from 2.33 mmol/L at baseline to 0.13 mmol/L at the end point of follow-up, indicating a clinical mismatch.

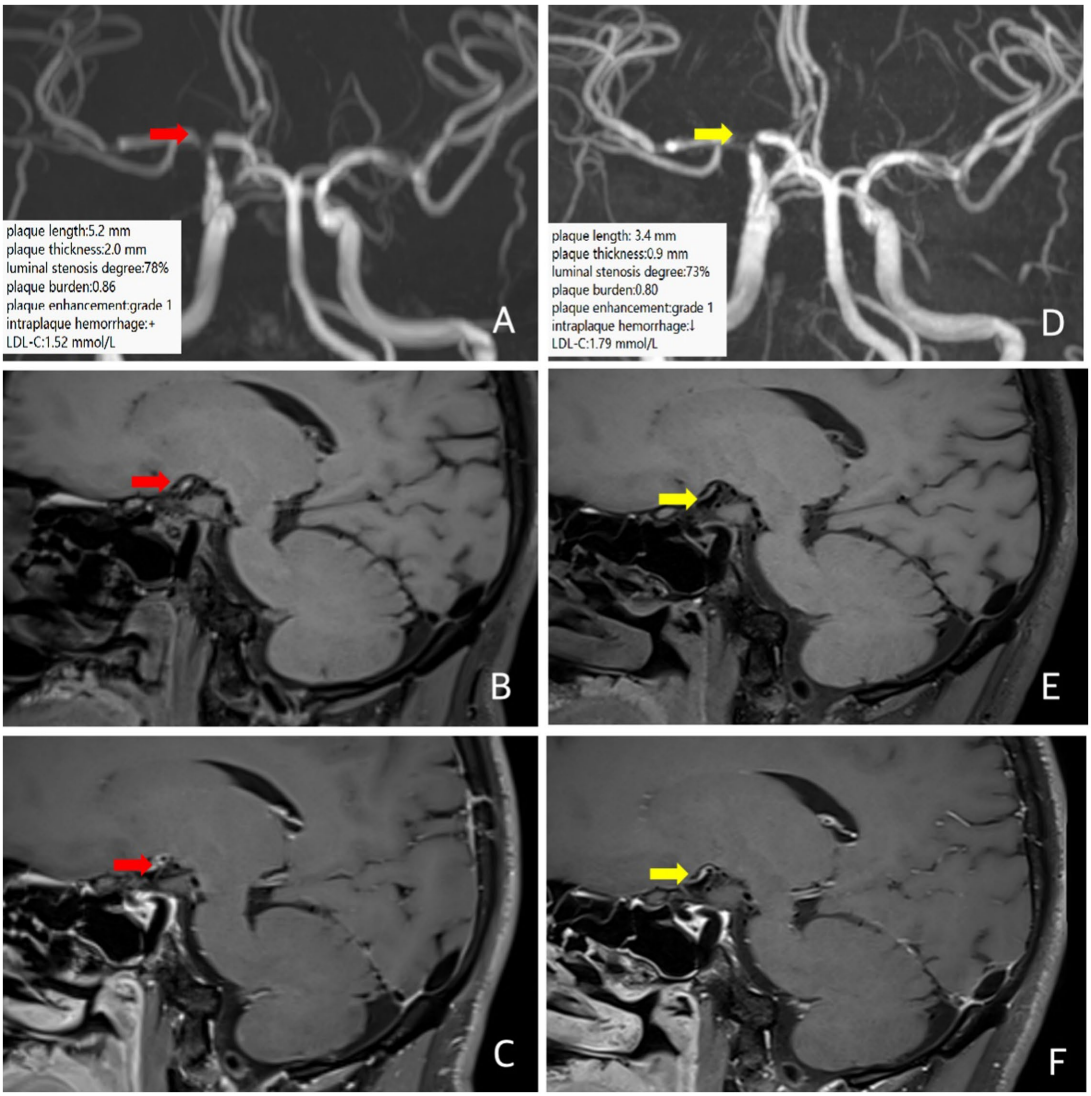


FIGURE 3
In case 3, the patient is at baseline (red arrow) and follow-up images 12 months later (yellow arrow). Three-dimensional time-of-flight cerebral magnetic resonance angiography showed significant stenosis of the right internal carotid artery communicating segment **(A,D)**. Coronal T1 plain scan weighted imaging **(B,E)** and enhanced imaging **(C,F)** in whole brain magnetic resonance imaging using different inversion angles to optimize contrast showed atherosclerotic plaque was formed in the right internal carotid artery communicating segment, with obvious stenosis of the lumen, intraplaque hemorrhage (T1 signal significantly higher than the surrounding muscle signal) and obvious plaque enhancement. Follow-up intracranial VW-MRI showed a shorter plaque length and a lower plaque thickness than the baseline, a slight reduction in luminal stenosis and plaque burden, and a weakening of signals in intraplaque hemorrhage, suggesting that the plaque is receding and stabilizing. The LDL-C level is elevated.

## 3 Discussion

Compared with traditional luminal imaging techniques, VW-MRI can directly show the structural characteristics and some pathophysiological changes of plaques while assessing the degree of vascular luminal stenosis (17–19). Studies of carotid plaques have shown that lowering LDL-C can stabilize plaques by removing cholesterol from plaques, decreasing lipid core content, inducing plaque shrinkage, and even increasing plaque calcification content (6, 20). VW-MRI showed good agreement between the composition of intracranial plaques and histology and the observer (21), which provides a theoretical basis for evaluating intracranial plaque efficacy using this imaging technique.

Statins remain the first-line treatment for controlling serum cholesterol levels and lowering LDL-C. A meta-analysis of randomized clinical trials of statins showed that a 1 mmol/L reduction in LDL-C was associated with a 22% reduction in the incidence of major vascular events. Reducing LDL-C to <1.8 mmol/L (normal reference value is 1.0 to 3.3 mmol/L) or less than 50 percent of baseline may be more effective in preventing ischemic stroke recurrence and improving clinical outcomes (22). LDL-C levels have also been found to be associated with plaque changes. Although LDL-C seems a good serologic marker reflecting the efficacy of statins, a study (23) showed that the burden of ischemic stroke attributable to either elevated apolipoprotein B (apoB) or non-high-density lipoprotein (non-HDL) cholesterol is higher than that attributable to elevated low-density

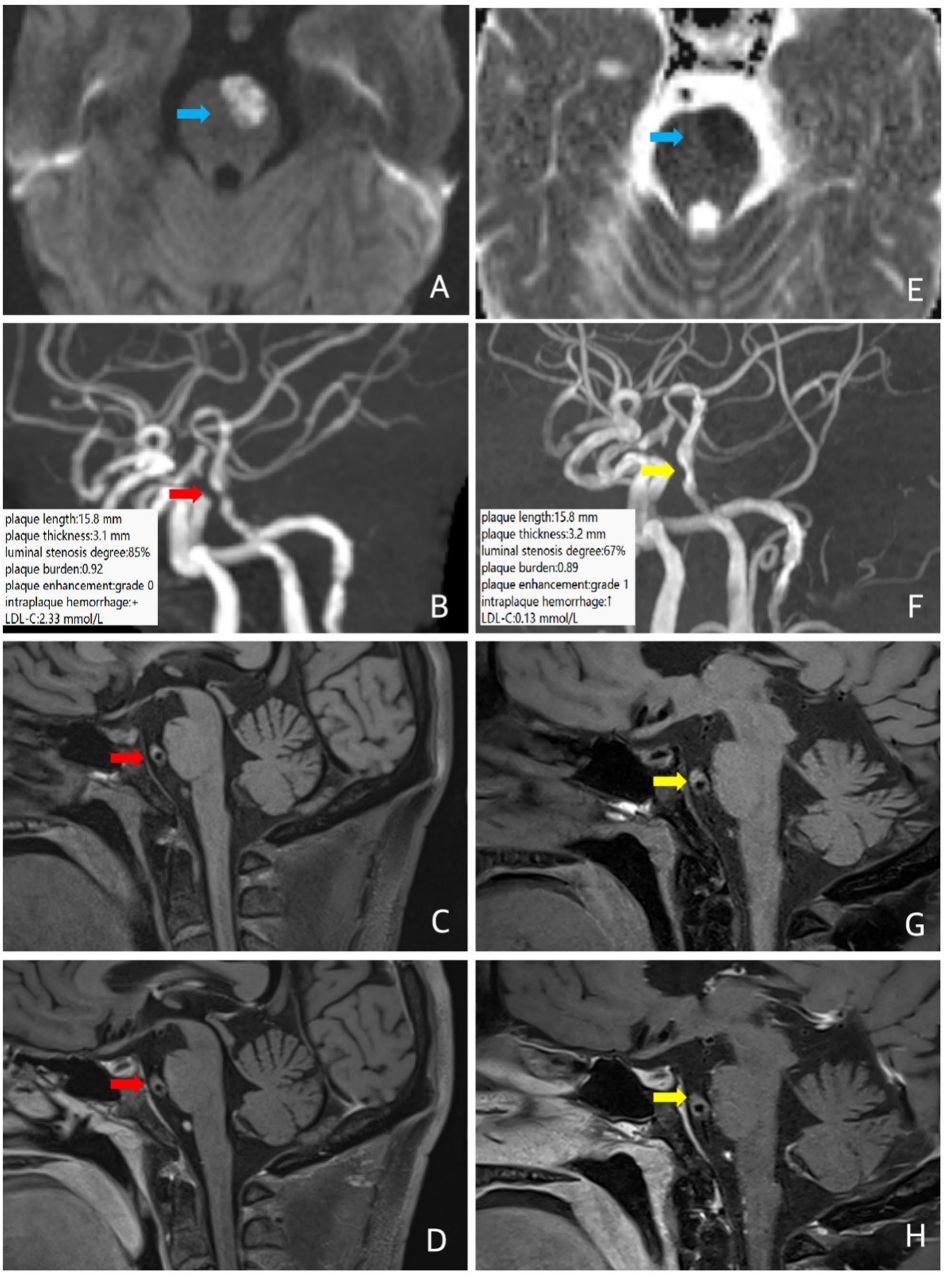


FIGURE 4
In case 4, patient at baseline (red arrow) and follow-up images 12 months later (yellow arrow). Three-dimensional time-of-flight cerebral magnetic resonance angiography showed the basal artery is tortuous and long, and the middle part is narrow. Coronal T1 plain scan weighted imaging **(C,G)** and enhanced imaging **(D,H)** in whole brain magnetic resonance imaging using different inversion angles to optimize contrast showed multiple atherosclerotic plaques were found in the basilar artery, especially in the middle segment, obvious stenosis of the lumen, eccentric thickening of the left wall of the basilar artery, and suspected intraplaque hemorrhage (T1 signal was higher than that of the temporal muscle nearby). There was no obvious enhancement of the plaque. The follow-up intracranial VW-MRI showed no significant changes in plaque length, plaque thickness, and plaque burden compared to baseline, a slight increase in luminal stenosis, plaque enhancement upgrades, and increased TI high signal **(C,G)**, suggesting plaque progression. Which LDL-C level decreased significantly. In case 4, diffusion sequence (blue arrow) showed limited diffusion in the left anterior portion of the pons, increased signal on DWI **(A)** and decreased signal on ADC **(E)**, suggesting a fresh infarct.

lipoprotein (LDL) cholesterol. Cases of worsening plaques during follow-up despite the decrease of LDL-C have been reported, indicating the importance of evaluating the in-situ changes of plaques (24).

The meta-analysis of Zhou et al. (25) showed that the optimal re-evaluating time of VWI for the carotid artery was more than 12 months, and the intracranial plaque changes were shown as early as 11–12 months. We found that the length and thickness of plaque were still good indicators, which was consistent with the study of Huang et al. (26) showed that in patients treated with statins for >6 months ($n$ = 31), plaque length, wall thickness, plaque burden, luminal stenosis, and plaque enhancement were significantly reduced. Moreover, we found that plaque enhancement and intraplaque hemorrhage may be more readily

observable than other plaque information, suggesting that they could be sensitive indicators of plaque changes. For example, after taking the booster dose of statin antilipid for a long time, the LDL-C level of case 1 decreased by about 13%, within 1.8 mmol/L, and there was no significant change in the degree of luminal stenosis and the plaque burden, while the plaque enhancement segment was shortened, indicating that the plaque tended to be stable. In case 4, PCSK9 evolocumab was added to the booster-dose statin anti-lipid, and the LDL-C level decreased significantly. Although the degree of luminal stenosis and the plaque burden was reduced, the intraplaque hemorrhage increased and the plaque enhancement escalated, suggesting plaque progression. Further research is needed to increase the sample size and validate the results with consideration of individual differences.

It is worth noting that a clinical mismatch between LDL-C changes and plaque changes occurred in some cases. In case 2, after intermittent anti-lipid therapy with standard to intensive doses of statins, the second follow-up showed that although the LDL-C level decreased significantly, the plaque changes were not obvious on VW-MRI. In case 3, although the LDL-C level remained within 1.8 mmol/L (but tended to increase) after long-term intensive dose statin anti-lipid therapy, VW-MRI showed that the plaque had a tendency to regress or had already regressed, which preceded the decline in LDL-C level. In addition, case 4 added PCSK9 evolocumab to intensification-dose statin-based antilipid therapy, and there was also a mismatch between LDL-C changes and VW-MRI reflecting plaque progression. In recent years, some scholars have reported a mismatch similar to case 4. In a long-term follow-up of a 47-year-old man with acute occipital lobe infarction caused by ICAD, Xiao et al. (24) found that despite the decrease in LDL-C levels, one of the plaques had an increase in stenosis and enhancement rate from baseline at a 3-month VW-MRI follow-up, suggesting early identification of patients who did not respond well to medications. Chung et al. (13) also found a similar situation in the follow-up study. They used VW-MRI to examine 77 patients with ICAD-induced acute ischemic stroke found that after 6 months of treatment with an intensive dose of statin (atorvastatin 40–80 mg/d or rosuvastatin 20 mg/d), 35 percent of patients still had no change in the volume and degree of ICAD plaque enhancement (defined as less than 25% change, non-responders) even increased (defined as an increase of more than 25%, progression). The decrease in LDL-C was smaller in nonresponders and progressors ($-47.3 \pm 38.2$ versus $-74.8 \pm 34.1$, $p = 0.002$) compared with good responders, suggesting that nonresponders and progressors may be insensitive to statins.

The study (27) showed that the role of elevated serum LDL-C in the progression of plaque enhancement in offenders was not linear, LDL was independently associated with ischemic events in Grade-1 enhancement plaques (OR 6.778, 95%CI 2.122–21.649, $p = 0.001$). In patients with Grade-2 enhancement plaques, however, LDL was not associated with ischemic events; in contrast, Neutrophil/Lymphocyte ratio was independently associated with ischemic events caused by Grade-2 enhancement plaques (OR 2.188, 95%CI 1.209–3.961, $p = 0.010$).In addition, a study (26) has shown that the efficacy of statins may be influenced by some factors, including individual age, BMI, high blood pressure, blood glucose, and duration of statin therapy. The research (28) indicates there are differences in the characteristics of plaque enhancement and stroke patterns between atherosclerosis in the anterior and posterior circulation. This may be one of the potential mechanisms explaining the differing effects of lipid-lowering therapy. The factors responsible for the phenomenon of mismatch between LDL-C changes and plaque changes are worth further investigation.

Randomized clinical trials in recent years have demonstrated that the addition of newer lipid-lowering agents such as the selective enteric cholesterol absorption inhibitors ezetimibe or PCSK9 evolocumab to statin therapy can further reduce LDL-C levels and reduce the risk of ischemic stroke recurrence, providing new treatment options for patients who are allergic to statins or are insensitive to response (29, 30). Based on the clinical mismatch between LDL-C changes and plaque changes, doctors can monitor the changes in ICAD plaques through VW-MRI, especially by the plaque enhancement and intraplaque hemorrhage, which is consistent with the results of Lou et al. (31), early identification of patients who are not sensitive to the efficacy of current drugs and help to formulate new treatment options or evaluate participation in clinical trials of other endovascular treatments to reduce the risk of stroke recurrence.

## 4 Conclusion

As indicated in these four cases of ICAD, VW-MRI could directly monitor the in-situ changes of intracranial vessel wall plaques after anti-lipid treatment of statins, provide key information that would be otherwise difficult to be timely reflected by serum marker LDL-C, and help tailor the treatment strategy by identifying cases that are not sensitive to current anti-lipid regimen by the time of one year. The mismatch between the plaque changes on intracranial VM-MRI and the LDL-C changes is worthy of further cohort studies.

## Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author/s.

## Ethics statement

The studies involving humans were approved by the Sichuan Provincial People's Hospital, Chengdu, China. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

KY: Writing – original draft. PZ: Writing – original draft. YW: Writing – review & editing. BH: Writing – review & editing.

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## Conflict of interest

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.

## Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

## Publisher's note



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# Clinical research progress on pathogenesis and treatment of Patent Foramen Ovale-associated stroke

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Patent Foramen Ovale (PFO), a common cardiac abnormality, has been established as the most prevalent cause of Cryptogenic Stroke (CS). In 2022, the American Society of Cardiovascular Angiography and Interventions (SCAI) officially defined PFO-induced CS as PFO-Associated Stroke (PFO-AS), whose onset characteristics and treatment methods are currently the focus of pertinent clinical research. Previously, the pathogenesis of PFO-AS was commonly believed to be related to Paradoxical Embolism (PDE) or *in situ* thrombosis. Recently, atrial heart disease, which could lead to abnormal cardiac structure and circulating biomarker accumulation, potentially causing vascular endothelial injury and promoting thrombosis, has also been associated with the pathogenesis of PFO-AS. Therefore, PFO-AS could be the outcome of multiple pathogenesis mechanisms. Furthermore, significant research progress has been made in elucidating the pathogenic PFO gene. Nonetheless, additional in-depth research is still required to better elucidate the precise mechanisms underlying PFO-AS. Notably, the clinical and imaging characteristics of PFO-related Ischemic Stroke (IS) are slightly different from those of other IS causes. Furthermore, the assessment of the correlation between PFO and stroke mostly relies on The Risk of Paradoxical Embolism Score (RoPE) and PFO-Associated Stroke Causal Likelihood classification (PASCAL) system, which could be a limitation. Additionally, PFO examinations mainly relied on cardiac anatomy evaluation in the past, highlighting another potential gap. Moreover, recent research suggests that PFO closure may increase the risk of Heart Failure (HF) with preserved Ejection Fraction (HFpEF). Conversely, after 2017, four Randomized Controlled Trials (RCTs): CLOSE, RESPECT, REDUCE, and DEFENSE-PFO, demonstrated that transcatheter PFO closure is more effective in preventing various risk events than conventional pharmacotherapy. This review comprehensively summarizes the latest research progress on PFO-AS pathogenesis, treatment, prevention, and management decisions, providing a valuable clinical reference.

KEYWORDS

**PFO-Associated Stroke, pathogenesis, acute phase treatment, secondary prevention, plugging therapy**

# 1 Introduction

Cryptogenic Stroke (CS) is a type stroke that cannot be linked to a definitive cause after evaluating all known possible causes or has an unknown cause despite examinations. Notably, CS accounts for 25% of all Ischemic Stroke (IS) cases, and its severe nature increases the risk of death, disability, and recurrence, placing a huge burden on medical care systems and society as a whole. The most common causes of CS include Patent Foramen Ovale (PFO), Paroxysmal Atrial Fibrillation (PAF), latent arrhythmia, latent malignant tumor, and so on. As delineated within the confines of a literature about "NeuroVISION study" (1), individuals harboring a PFO, when contrasted with those perioperative stroke patients devoid of such an anomaly, exhibit an elevated risk of stroke, augmented National Institutes of Health Stroke Scale (NIHSS) scores, and a higher incidence of in-hospital mortality. This corroborates the assertion that the PFO constitutes a significant risk factor for stroke. In CS patients, the PFO detection rate is 40–56%, significantly higher than that in healthy individuals (4–18%) and other stroke patients with clear causes, potentially leading to serious complications (2). Given its significant prevalence, in 2022, the American Society for Cardiovascular Angiography and Interventions (SCAI) officially defined PFO-induced CS as PFO-Associated Stroke (PFO-AS) (3). Significant advancements in PFO-AS research have also been recently realized, especially from 2017, when the New England Journal of Medicine (NEJM) published the research results of CLOSE (4), REDUCE (5), and RESPECT (6). These studies reported that PFO closure surgery can reduce the risk of stroke recurrence more effectively than conventional drug therapy, greatly informing PFO-AS treatment and secondary prevention. Nonetheless, more insights into the prevention and treatment of PFO-AS are still required, making PFO-related research highly relevant contemporary research topic. There is also a need to further explore the pathophysiological mechanisms underlying PFO-AS. This review will focus on PFO-AS pathogenesis, diagnosis, treatment, and prevention, providing a valuable reference for other related studies and clinical management.

# 2 Pathogenesis

The foramen ovale is a physiological channel in the heart's atrial septum that develops in the embryonic stage. Normally, this channel closes between 5 and 7 months post-birth. Notably, this channel would be referred to as PFO if it remains open after 3 years of age. Recently, increasing research has closely linked PFO with CS, implying the potential involvement of Paradoxical Embolism (PDE), which increases the risk of other related diseases, thus threatening patients' lives (Figure 1).

## 2.1 Paradoxical embolism

The PDE concept was first proposed by Julius Cohenheim, a German pathologist, in 1877 (7). It occurs when patients with Venous Thromboembolism (VTE) have a right-to-left Shunt (RLS) channel. In such situations, emboli in the systemic venous system or right heart pass to the left or systemic arterial system via other arteriovenous pathways, such as the open foramen ovale, causing embolism, which, in turn, leads to ischemic infarction at the corresponding site or organ. This phenomenon is currently considered the primary etiological mechanism of PFO-AS (8).

Ohanna Härtl et al. (9) performed mechanical thrombectomy on 58 CS patients and then histologically examined the retrieved thrombi to further elucidate the pathophysiological mechanisms underlying PFO-AS. According to the results, PFO-AS patients had a higher proportion of Red Blood Cells (RBCs) and a lower fibrin/platelet ratio in the thrombus component compared to patients with CS alone, implying that PFO-related thrombi may originate in the venous system, resulting in IS via PDE. However, they could only detect deep vein thrombus in 1.1 to 27% of PFO-AS patients and could still not identify the source of the emboli in 80 to 90% of PFO-AS patients (10). These findings suggest the involvement of other mechanisms in PFO-associated thrombus besides PDE.

## 2.2 *In situ* thrombus

Generally, the left atrial pressure is often higher than the right atrial pressure, hence, the PFO is often closed and accompanied with no significant RLS production. When patients perform the Valsalva maneuver (breath-holding and forced expiration maneuver following deep inspiration), cough, or sneeze, because the pressure gradient may not be large enough, the blood flow in the PFO tunnel is low-velocity or even stasis, allowing platelets to easily adhere, aggregate, and activate, resulting in thrombus formation *in situ*. In this regard, some scholars have questioned whether the foramen ovale is the source or channel for thrombus formation. For instance, in a preliminary study on PFO *in situ* thrombus formation involving stroke patients with PFO and non-stroke patients, researchers at Fuwai Hospital first assessed the microstructure of the foramen ovale via high-resolution Optical Coherence Tomography (OCT) (11). According to the results, 11 stroke patients and one non-stroke patient with a migraine exhibited thrombus *in situ* within the PFO. Furthermore, all 12 patients presented with irregular or discontinuous endocardial surfaces, implying that endocardial abnormalities at the PFO could be the pathological basis for PFO-associated *in situ* thrombus. Although this study's sample size was small, the *in situ* thrombus detection rate was as high as 100%, and all patients exhibited abnormal endocardial alterations. These findings are consistent with those of Kasner SE et al., which suggested that endocardial abnormalities could be responsible for thrombus *in situ* (12). Furthermore, in Yan et al.'s cross-sectional study that was published in Strokein 2023 (13), 131 PFO patients with unknown risk factors were divided into three groups: stroke, migraine, and asymptomatic. Subsequently, OCT was used to assess the incidence and size of primary thrombus in the groups of PFO patients. According to the results, compared to the asymptomatic group (which showed no *in situ* thrombus), the stroke and migraine groups showed a significantly higher incidence of *in situ* thrombus. This study further confirms that *in situ* thrombus could be a characteristic feature of PFO-AS patients and migraine patients, there are important implications for guiding treatment. Overall, endocardium abnormalities at the foramen ovale are common in patients with *in situ* thrombus; thus, thrombus attached at these irregular and discontinuous surfaces of the endocardium is highly likely to be associated with *in situ* thrombus formation.

Although the above-mentioned studies on *in situ* thrombus had small sample sizes and OCT technology could be vulnerable to visual

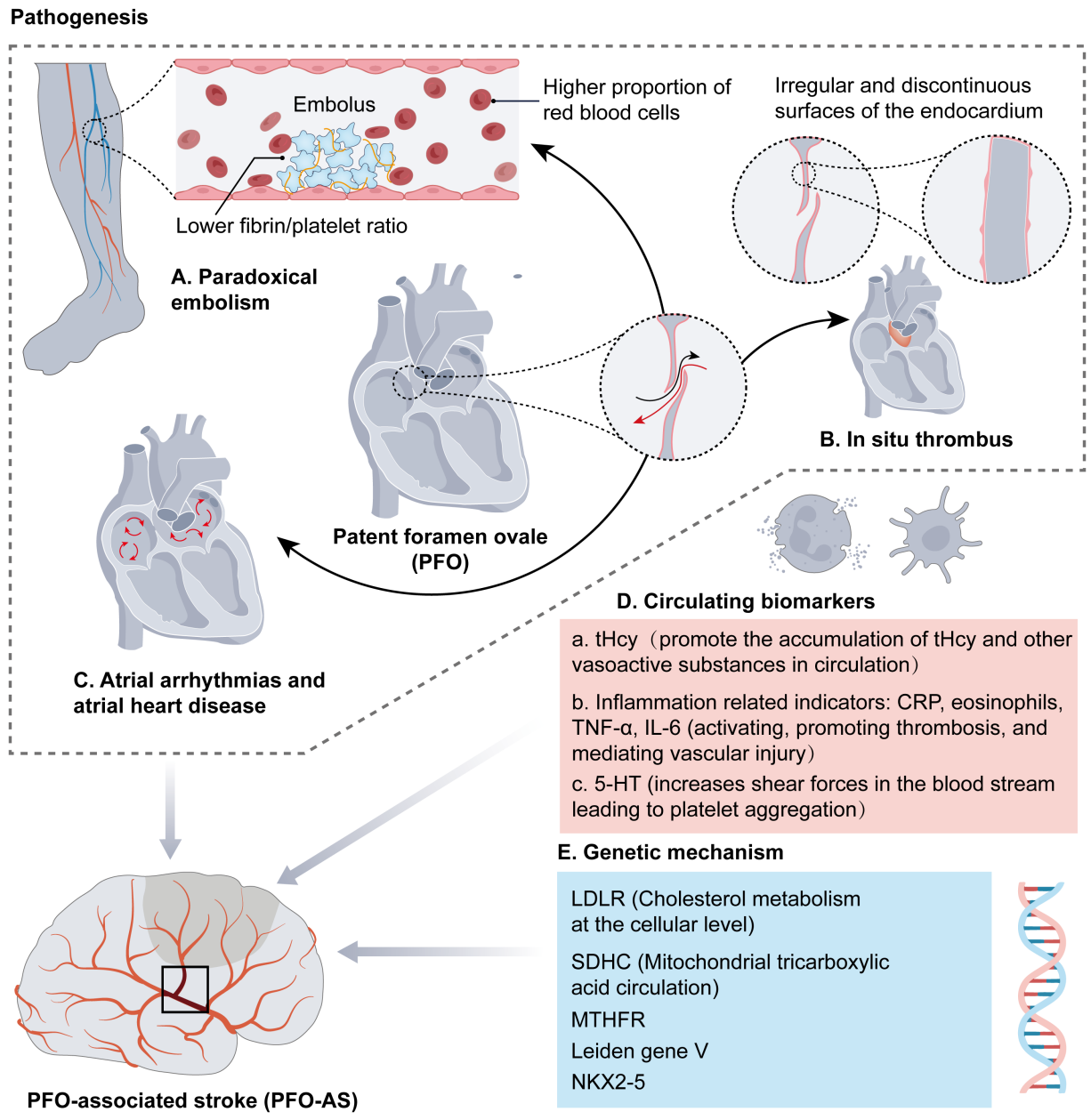


FIGURE 1
Pathogenesis of PFO-AS.

field, it is noteworthy that *in situ* thrombus, as a mechanism, may represent a novel potential therapeutic target for antithrombotic treatment or prophylactic PFO closure in PFO-AS patients.

## 2.3 Atrial arrhythmias and atrial heart disease

Atrial heart disease denotes a condition where alterations in the structure, systolic function, or electrophysiological properties of the atrium result in clinical manifestations like atrial remodeling and conduction abnormalities. It is often suspected to be an underlying cause of unexplained embolic stroke, independent of atrial fibrillation (14). Atrial arrhythmias refer to abnormal electrical activity originating from the atrium, leading to irregular heart beat frequency or rhythm.

PFO, a physiological opening in the atrial septum, typically bears no direct causal relationship with atrial arrhythmias. However, in cases of certain structural heart diseases, such as atrial septal aneurysms (ASA), both PFO and atrial arrhythmias may coexist. Studies indicate (15) that when blood flow within the atrium enters the ASA, the velocity slows down, creating eddies. This can not only lead to blood stasis and subsequent thrombosis but also continuously stimulate the atrial electrophysiological conduction system, ultimately triggering atrial arrhythmias. In addition, if PFO patients exhibit a significant number of RLS, on the one hand, the abnormal blood flow

may stimulate the atrial electrophysiological system, subsequently triggering ectopic atrial electrical activity, increasing the likelihood of atrial arrhythmias. On the other hand, hemodynamic changes can elevate atrial pressure or volume load and ultimately progressing to atrial heart disease. Under such circumstances, blood flow tends to stagnate, increasing the risk of thrombosis, which in turn heightens the occurrence of adverse cardiovascular events, including stroke (16, 17). Recent studies have further corroborated the mechanism behind blood stasis and thrombosis in PFO patients. In 2023, researchers conducted a specific 3D computational fluid dynamics analysis to compare the differences in blood retention time within the left atrium among patients with PFO, atrial fibrillation, and those with normal heart rhythm. This comparison aimed to assess the extent of left atrial blood stasis. The findings revealed that patients with PFO and those suffering from atrial fibrillation exhibit analogous blood flow patterns, as well as structural and functional abnormalities in the left atrium. These abnormalities heighten the incidence of atrial electrophysiological abnormalities, thereby increasing the risk of stroke (18).

## 2.4 Circulating biomarkers

Research has shown that small molecule metabolites are also involved in the pathogenesis of cardiovascular and cerebrovascular illnesses (19).

### 2.4.1 Homocysteine (Hcy)

Whether by administering exogenous homocysteine *in vitro* or through ex vivo blood tests and animal models involving patients with elevated homocysteine levels, current research findings suggest that Hcy can induce oxidative stress, triggering platelet activation, hypercoagulable state formation, endothelial dysfunction, and influencing the degree and speed of blood clot contraction during the thrombosis process, ultimately promoting thrombus formation (20).

Deng et al. (17) prospectively examined PFO-AS patients and continuously performed the serial sampling of cardiac, atrial, and venous blood before and after PFO closure using Mass Spectrometry (MS) analysis. Specifically, they aimed to explore the effect of occlusion on circulation in PFO patients. According to the results, Hcy was the most significantly downregulated factor in intracardiac plasma after PFO closure, correlating positively with the number of PFO shunts. Furthermore, during the four-year follow-up period, Hcy levels in venous blood were lower following complete PFO closure compared to cases intervened with medical treatment alone (including antiplatelet agents and anticoagulants). Notably, Hcy levels did not change in patients who received medical treatment alone. These findings offer a major reference for molecular clinical research, demonstrating that PFO-induced shunting, especially large-sized shunting, could promote the accumulation of Hcy and other vasoactive substances in circulation. Overall, besides being a channel through which blood clots pass, PFO could also lay the structural foundation for thrombus formation, causing damage to the nervous and blood systems.

### 2.4.2 Inflammation-related indicators

According to research (21), C-Reactive Protein (CRP) upregulation is an independent risk factor for IS events. In addition, proinflammatory cytokines such as Tumor Necrosis Factor-$\alpha$ (TNF-α) and Interleukin-6 (IL-6), besides being involved in the inflammatory response of IS, can activate endothelial cells' normal anticoagulant and fibrinolytic properties, promoting thrombus formation, which could, in turn, lead to venous thrombosis and stroke (22). Moreover, retrospective studies reported that eosinophils could activate and promote thrombus formation, as well as mediate vascular injuries. Specifically, patients with RLS exhibited a higher proportion of eosinophils in whole blood than those without RLS. Additionally, the proportion of eosinophils correlated positively with shunt volume, indicating an association between a greater shunt volume and an increased presence of eosinophils (23). Based on these findings, we deduced that eosinophils may be involved in the development of stroke via vascular injury mediation and thrombus activation and induction, leading to venous microthrombi entering the left atrium through the foramen ovale.

### 2.4.3 Serotonin (5-Hydroxy tryptamine, 5-HT)

5-HT is a vasoactive prothrombotic substance that induces Oxidative Stress (OS) within the heart. Generally, 5-HT is released from aggregated platelets, remains in venous blood, and is metabolically inactivated by pulmonary Monoamine Oxidase (MAO) in RLS absence. Notably, PFO presence increases shear forces in the bloodstream leading to platelet aggregation, thus facilitating the release of significant amounts of 5-HT. At the same time, 5-HT free in blood could further promote platelet aggregation, damage vascular endothelial cells, promote thrombus, and increase the risk of stroke (21).

Overall, PFO presence directly or indirectly lays the pathophysiological foundation for thrombus formation, and the accumulation of circulating small molecule metabolites could alter the status of normal endothelial cells, not only increasing the risk of PDE in PFO patients but also directly promoting thrombus formation, mediating vascular injury, and increasing the risk of stroke.

## 2.5 Genetic mechanism

Genetic factors have been established to significantly influence CS as a severe PFO outcome. According to research (24), coagulation-associated genetic variants, genetic susceptibility to cardio-structural abnormalities, and genetic variants associated with arterial wall elasticity and stability highlight the significance of genetic factors in PFO-AS. Xinyi Li et al. (25), in their 2024 study, employed Whole-Exome Sequencing (WES), a gene sequencing technology, to identify the potentially mutated genes and gene mutation spots in PFO patients before analyzing the PFO-associated mutated genes using ClinVar and OMIM databases. According to the results, stroke occurred in 3 of the 25 PFO patients enrolled in the study, with a suspected causative genetic variant (LDLRNM 00527.5c947A > G) detected in one patient. Notably, this causative genetic variant has been associated with familial hypercholesterolemia and could increase the risk of cardiovascular and cerebrovascular diseases. After subjecting all 25 patients with clinical symptoms and undergoing PFO closure to WES, Xinyi Li et al. also discovered mutations in 48 related genes, of which LDLR and SDHC were suspected to be pathogenic genes. The LDLR and SDHC genes are primarily involved in cholesterol metabolism at the cellular level and mitochondrial

Tricarboxylic Acid circulation (TCA), respectively. Through the detection of enrolled cases and database analysis, the researcher s also discovered that the NKX 2–5 gene was involved in PFO pathogenesis through other mutation sites and signaling pathways. This finding is consistent with the 2016 study by Cao Y et al., which suggested that variations at the NKX 2–5 single nucleotide site could be associated with atrial septal defects (26). Moreover, two recently published case reports (27) found that mutations in the MTHFR gene or heterozygous mutations in the V Leiden gene correlated with morbidity in young PFO-AS patients. According to previous research (28), 33.3% of heterozygous mutation carriers of the Leiden gene V developed varying degrees of thrombus, suggesting that heterozygous mutation of the Leiden factor V correlates significantly with the prothrombotic state. This finding is consistent with the meta-analysis results of Alhazzani et al. (5, 29). Overall, identifying PFO-associated genetic variants via genetic testing enables the early detection of high-risk PFO patients, as well as timely reduction and intervention of complications, especially illnesses with a high risk of adverse outcomes such as CS. Moreover, the study of causative and mutated genes in PFO-AS patients could yield novel ideas for genetic counseling and gene therapy in PFO-AS patients.

As opposed to past clinical research that mainly focused on PDE regarding the pathogenesis of PFO-AS, *in situ* thrombus, atrial arrhythmias, atrial heart disease, circulating biomarkers, and causative genes, have recently gained significant research attention in the same context. In this regard, it is noteworthy that more scholars have attributed the pathogenesis of PFO-AS not to a single factor but to a myriad of clinical variables. Nonetheless, additional studies with larger samples will be required in the future to further explore the relevant biochemical parameters or even genomics to better elucidate the mechanisms underlying PFO-AS and facilitate its early diagnosis, thus guiding treatment and prognostic evaluation.

# 3 Criteria for diagnosis

## 3.1 General conditions

Although PFO-AS is generally comparable to CS, its incidence rate was found to be higher in males than females, potentially due to the influence of estrogen in women, which could increase the protective effects of cerebral blood flow on the nervous system via mechanisms such as antioxidant free radicals. Furthermore, a previous study that involved women aged ≥53 years found no significant gender difference among PFO-AS patients, potentially due to the fact that 90% of Chinese women reach menopause at the age of 53 (30). From an age distribution perspective, PFO-AS was more prevalent among young and middle-aged individuals (mean age = 46.59 ± 11.732 years), with a statistically significant difference compared to patients with CS without PFO. Previous research (31) has also identified younger age at onset as a significant risk factor in assessing PFO-AS, a phenomenon that was verified using The Risk of Paradoxical Embolism Score (RoPE) results. In other words, the younger the age, the higher the score, and the more likely it was to diagnose PFO-AS. Regarding neurological impairment, PFO-AS patients had median NIHSS and Modified Rankin Scale (mRS) scores of 2 (1,4) and 1 (1,2), respectively. These values were comparable to those of CS patients without PFO. Furthermore, there was no statistically significant difference between the two groups in terms of PFO size. The average PFO diameter among the patients was 4.9 mm (1–19 mm), which could allow thrombi to pass through, although it was less likely to completely block the main blood flow. Additionally, although brain tissue damage accumulated in PFO-AS patients, the extent of neurological impairment was relatively mild. Regarding pre-admission Blood Pressure (BP), for CS patients, it gradually rose from stroke onset, peaking upon admission. Regarding previous diseases, PFO-AS patients most likely had a smoking history and Hypertension (HTN).

## 3.2 Scores for assessing PFO-AS

The RoPE score and PFO-Associated Stroke Causal Likelihood classification (PASCAL) system are the most commonly used approaches for assessing the association between PFO and stroke. The higher the score, the greater the likelihood of PFO-AS (32), especially when considered alongside clinical manifestations and imaging results. PASCAL system uses the PASCAL score to assess the likelihood of PFO-related stroke (2). The likelihood of PFO causing stroke is evaluated based on the presence of high-risk PFO morphological features (large RLS or ASA) on TEE and whether the RoPE score is ≥7 points. The results can be classified as unlikely, possible, and probable. Currently, a RoPE score > 6 is defined as PFO-AS (or stroke of other causes). Notably, the RoPE score is a vital component of the PASCAL system, which helps with further classification (Tables 1, 2) (32).

## 3.3 Imaging features

For PFO-AS patients, cranial Magnetic Resonance Imaging (MRI) could yield relevant and specific outcomes. First, imaging often reveals multiple infarcts in various vascularized areas, with a predominance

TABLE 1 RoPE score.

| Characteristic | Points |
|---|---|
| RoPE score calculation | |
| No history of | |
| Hypertension | 1 |
| Diabetes | 1 |
| Stroke or transient ischemic attack | 1 |
| Nonsmoker | 1 |
| Cortical infarct on imaging | 1 |
| Age, y | 5 |
| 18–29 | 4 |
| 30–39 | 3 |
| 40–49 | 2 |
| 50–59 | 1 |
| 60–69 | 0 |
| >79 | |
| Total Rope Score (sum of individual points)= | |

TABLE 2 PASCAL system.

| High rope score (≥7) | High-risk PFO feature (LS and/or ASA) | PFO-related stroke |
|---|---|---|
| Absent | Absent | Unlikely |
| Absent | Present | Possible |
| Present | Absent | |
| Present | Present | Probable |

of posterior circulation infarcts. Furthermore, posterior cerebral artery territory infarcts are independent predictors of PFO presence in CS patients. These phenomena are generally consistent with those of Kim et al. (33) who earlier proposed that PFO strokes often manifest as multiple small ischemic lesions in the vertebrobasilar circulation without any visible vessel occlusion on angiography. Second, on T2W or DWI imaging, more infarcts often present as multiple cortical lesions, with fewer lesions in the subcortical and cortico-subcortical regions. Furthermore, it was previously established that small and medium-sized lesions were more frequent and highly likely to affect posterior circulation during acute or recurrent stroke (34). These phenomena could be attributed to the fact that epinephrine weakly regulates the vertebrobasilar artery, and blood flow increases when performing the Valsalva maneuver, thus increasing the probability of thrombus entering the posterior circulation. Therefore, when the above-mentioned characteristic imaging findings appear in cranial MRIs, a PFO should be highly considered, and the underlying cause could be established based on the imaging findings.

## 3.4 PFO-associated tests

As per the relevant guidelines (35), PFO-related tests encompass a variety of procedures, including Transthoracic Echocardiography (TTE), Enhanced Transcranial Doppler Ultrasound (c-TCD), Transcatheter Echocardiography (TEE), Transductal Sonography (c-TEE), cardiac ultrasonography, and intracardiac echocardiography. Notably, c-TEE and intracavitary ultrasound are often used to diagnose and treat special cases.

Presently, TTE and TEE are the commonly used approaches for diagnosing PFO, with both methods having the capability of evaluating the anatomy of the interatrial septum and the interatrial septal shunt. More specifically, TTE could be used to directly observe the atrial septal discontinuity signal and blood flow signal by placing the probe on patients' chest walls. Previous research (36) showed a sensitivity of 50% for TTE. On the other hand, Mojadidi et al. (37) found a 93% specificity in CS patients using harmonic imaging. Although TTE offers high specificity, it is noteworthy that obesity and emphysema, among other risk factors, could affect its performance in adults, potentially resulting in a relatively low sensitivity. Moreover, since TEE can more directly observe the internal structures of the heart through the esophagus and display the fusion of primary and secondary septa, as well as detect fine shunts and classify PFO, it could offer higher sensitivity and specificity compared to TTE (38, 39).

The c-TCD test is a standard method for detecting the presence or absence of RLS. Using the c-TCD test, RLS could be quantified by observing the number of bubbles at rest and after the Valsalva maneuver. For RLS, the c-TCD test has sensitivity and specificity values of 65–100% and 97–100%, respectively. According to related research (40), c-TCD could also confirm the presence of smaller PFOs by monitoring blood flow patterns during a stronger Valsalva maneuver. Consequently, c-TCD can detect 90–100% of PFOs identified by TEE and even find small PFOs that TEE misses in some cases. Based on these insights, c-TCD is a useful tool for clinically screening PFO and is the most convenient and highly accepted noninvasive test for patients. However, it is difficult to determine the source of RLS using c-TCD.

Overall, improving the detection rate of PFO-AS based on patients' general conditions, clinical manifestations, RoPE score, PASCAL system, and imaging findings could yield a more accurate treatment plan for future interventions.

# 4 Treatment

In treating definite IS, it is noteworthy that PFO-AS has the same therapeutic principles as acute IS. Acute IS treatment primarily involves monitoring patients' vital signs, opening the infarcted vessel as soon as possible, restoring intracranial perfusion, protecting brain tissue nerve function, and promptly addressing complications. While monitoring patients' basic vital signs, recanalization therapy is the key intervention during the acute phase, and it mainly includes intravenous thrombolytic therapy, Endovascular Treatment (EVT), and antithrombotic therapy.

## 4.1 Acute phase treatment

### 4.1.1 Thrombolytic therapy

In consonance with the directives of the American Heart Association/American Stroke Association (AHA/ASA) (41), the enhancement of cerebral circulation constitutes a critical therapeutic modality. It is imperative for patients who have undergone brain imaging diagnostics and present with an onset time of 4.5 h or less to receive intravenous thrombolytic therapy expeditiously. It is underscored that the administration of intravenous alteplase is associated with significant therapeutic benefits. According to research, PFO-AS patients treated with alteplase within the intravenous thrombolysis window may exhibit a better prognosis than stroke patients of other etiologies (42). On the one hand, rt-PA could exert a notable dissolution effect if the primary underlying cause of PFO-AS is PDE, where the emboli originate from the venous system. In such cases, the detached emboli often consist primarily of fibrin and RBCs and are loose in texture, thus resulting in a high recanalization rate. On the other hand, patients who receive rt-PA intravenous thrombolysis and are younger at the onset of stroke tend to have a better prognosis. These deductions are consistent with the previous conclusion proposed by Gaffney PJ (43), Schwartz ML (44), and other scholars that in acute stroke patients with RLS, since the emboli originate from a fibrin-rich thrombus in the deep venous system, symptoms may improve more after rt-PA thrombolysis. It is also noteworthy that the use of third-generation thrombolytic drugs such as Tenecteplase in PFO-AS was recently explored further (45). Furthermore, in 2024, Ruixian Wang published an article in Neurologist (46), reporting that applying recombinant human urinary

kininogen following intravenous thrombolysis greatly improved neurological function and reduced stroke recurrence in acute IS patients. In another study, Haiqing Song et al. (47) discovered no increase in the mortality rate or risk of symptomatic intracerebral hemorrhage in >60% of patients over a time window of 4.5–6 h, implying that intravenous recombinant human prourokinase was effective and safe in patients within 4.5–6 h after stroke onset. Given that multiple studies have confirmed that the use of recombinant human prourokinase after intravenous thrombolysis could effectively improve the safety of thrombolysis and late neurological recovery, then the therapeutic results for PFO-AS patients are equally promising.

### 4.1.2 Mechanical thrombectomy

Some of the common EVT interventions include mechanical thrombectomy, intra-arterial thrombolysis, and angioplasty. In recent years, EVT, especially mechanical thrombectomy, has become a vital treatment for IS patients, particularly those with a large vessel occlusive stroke, who are beyond the thrombolysis time window and with contraindications to thrombolysis. According to relevant research (48), compared to pharmacotherapy, mechanical thrombectomy resulted in a higher recanalization rate and a better neurological prognosis in stroke patients with large vessel occlusion of anterior circulation within 6 h post-onset. Consequently, many centers have extended EVT to large vessel occlusions in the posterior circulation, particularly basilar artery embolization (49). Previous research has also revealed that imaging is characterized by multiple infarcts in poly vascularized areas and posterior circulation infarcts, as well as posterior cerebral artery territory infarcts, which are independent predictors of PFO presence in CS patients. Moreover, recent RCTs (50, 51) and meta-analyses (52–55) on acute IS patients demonstrated that concomitant medical therapy with EVT is more effective than medical therapy alone in obtaining good functional outcomes. At the same time, some studies with small sample sizes posited that combined EVT for basilar artery occlusion could yield better outcomes (56–58). Consequently, we hypothesized that PFO-AS patients, especially those with lesions accumulated in the posterior circulation, may benefit more from EVT, a deduction that certainly requires further validation through prospective RCTs (59). Nonetheless, it is noteworthy that vascular injury (perforation, dissection, or pseudo aneurysm) could complicate EVT, and a more professional and precise assessment would be required for the risk of vasospasm (60).

### 4.1.3 Drug therapy

Current medical interventions for acute IS mainly include antiplatelet and anticoagulant therapies. Furthermore, aspirin or clopidogrel treatment should be initiated as early as possible for patients who do not satisfy the criteria for intravenous thrombolysis or do not require EVT. For patients with mild stroke, dual antiplatelet therapy (DAPT), consisting of aspirin and clopidogrel, is recommended within 24 h of stroke onset and should be continued for 21 days (61). On the other hand, for mild stroke patients carrying CYP2C19 loss-of-function alleles, aspirin combined with ticagrelor is recommended and should be continued for 21 days (62).

A recent ARAMIS trial published in JAMA found (63) that aspirin plus clopidogrel was no less effective compared with intravenous thrombolysis in the management of non-disabling minor stroke. Clinically, PFO-AS is prevalence in young adults (64) and is associated with relatively low disability (31, 65–67). The classification of PFO-AS as a non-disabling minor stroke warrants further investigation. Moreover, DAPT may serve as an alternative to thrombolytic therapy if appropriate assessment criteria are established for PFO-AS. Compared to thrombolytic therapy, patients treated with dual antibodies exhibited lower rates of bleeding and other complications. Zi W et al. (68) subsequently conducted a randomized controlled study at 117 centers in China to investigate the effect of tirofiban, a class of glycoprotein (GP) IIb/IIIa receptor antagonist, in patients with moderate to severe disability and no macrovascular occlusive stroke. The study showed that 29.1 and 22.2% of patients in the tirofiban and aspirin groups, respectively, achieved good functional prognosis; Moreover, the incidence of symptomatic cerebral hemorrhage in the tirofiban group was slightly higher than that in the aspirin group (1.0, 0%), and there was no significant difference in mortality between the two groups (3.8, 2.6%). In recent years, clinical studies have demonstrated that only about 10% of patients can achieve early recanalization of occluded vessels following intravenous thrombolysis. Therefore, adjuvant drug therapy should be administered to improve the efficacy of intravenous thrombolysis (69). Another RESCUE-BT2 study by Zi W et al. (68) showed that the proportion of patients treated with tirofiban who achieved good prognosis was significantly higher compared with those who received aspirin in the subgroup of patients without neurological improvement after intravenous thrombolysis. However, given the small sample size of this study, larger randomized controlled studies are needed to validate the safety and efficacy of intravenous thrombolysis combined with tirofiban treatment. Elsewhere, a trial named, (Multi-arm Optimization of Stroke Thrombolysis; ClinicalTrials.gov number, NCT03735979) randomized controlled study investigated the efficacy and safety of eptifibatide, a glycoprotein IIb/IIIa receptor antagonist, and argatroban, an anticoagulant, combined with alteplase thrombolysis in patients with ischemic stroke.

In patients with acute ischemic stroke, emergency thrombolytic therapy administered within 0–3 h can improve the symptoms of neurological deficits, promote motor function recovery and self-care ability, and reduce adverse reactions compared with administration between 3 and 5 h. In clinical practice, few patients can achieve thrombolysis within 3 h, especially the aged groups. Thrombolysis is not only affected by objective factors such as detection time, transport time, and examination time, as well as the cognitive understanding of the patient and his family about the condition.

## 4.2 Secondary prevention

### 4.2.1 Drug therapy

Secondary prevention of PFO-AS is increasingly being studied worldwide. All PFO-AS patients, regardless of whether they receive thrombolysis or intervention, should be administered antithrombotic therapy. The PICSS (CS with PFO) study found no significant reduction in stroke recurrence or death 2 years after treatment with warfarin compared with aspirin (70). In the PFO subgroup of the rivaroxaban Secondary Prevention for Unexplained Embolic Stroke Study (NAVIGATE ESUS) (71), the annual stroke risk was 2.6 and 4.8% in the rivaroxaban and aspirin groups, respectively, and rivaroxaban was slightly superior to aspirin in decreasing the risk of recurrent ischemic stroke. Diener et al. (72) performed a meta-analysis of patients who developed PFO-AS in four trials, PICSS (70),

CLOSE (4), NAVIGATE ESUS (71), and RESPECT (6), and reported that the risk of recurrent ischemic stroke was similar between anticoagulant and antiplatelet therapy groups. Given the predominantly venous origin of thrombi in PFO-AS and the associated risk of bleeding with anticoagulation, antiplatelet therapy is often considered a more appropriate secondary preventive measure. However, anticoagulation is recommended for PFO-AS patients with pulmonary embolism, deep vein thrombosis, or underlying hypercoagulable states (73).

## 4.2.2 Plugging therapy

### 4.2.2.1 Applicable conditions for PFO closure

In accordance with the 2022 SCAI Guidelines for Management of Patent Foramen Ovale (3), for individuals aged between 18 and 60 years, who lack anticoagulation indications, possess high-risk anatomic configurations, and have a RoPE score of 7 or higher, and have a history of PFO-related stroke, PFO occlusion may be considered feasible subsequent to professional assessment. Patients categorized as possible and probable to benefit from PFO closure surgery by PASCAL system experience a reduced risk of postoperative late-onset atrial fibrillation (>45 days) and stroke recurrence (2).

After 2017, four randomized controlled; CLOSE (4), RESPECT (74), REDUCE (5), DEFENSE-PFO (75) uncovered that transcatheter closure of PFO was more effective than medical therapy alone. Another meta-analysis found that the annualized risk of recurrent stroke was approximately 1% in patients treated with medical therapy alone, whereas that of recurrent stroke was decreased by approximately 60% in patients undergoing transcatheter PFO closure (32). Considering the available evidence regarding the effectiveness of transcatheter PFO closure, the 2022 SCAI Guidelines for Management of Patent Foramen Ovale strongly recommend the use of transcatheter PFO closure in patients aged between 18 and 60 years with previous PFO-AS. PFO closure can effectively reduce the risk of stroke recurrence, regardless of the degree of PFO anatomical complexity. This suggests that the benefits of PFO closure extend to both high-risk and low-risk PFO patients. It's important to note that most patients included in current studies are under the age of 60, limiting the generalizability of the findings to all age groups. It has been shown (76) that transcatheter closure of PFO may be as safe and effective in patients >60 years of age as in patients <60 years of age. A recent study in 2024 found (77) 143 patients with PFO closure and 199 patients with drug-only stroke aged >60 years, with a mean follow-up of 5.6 ± 1.5 years. All patients who did not undergo PFO closure exhibited persistent shunts. In contrast, only seven of 134 patients who received PFO closure had residual shunts. Additionally, the rates of new-onset atrial fibrillation, recurrent stroke, unexplained death, and neurological death were 5, 6%, 1, and 2, respectively, in the group without closure, compared to 3, 3%, 0, and 0 in the closure group. This study suggests that closure therapy should be adopted in patients older than 60 years as in younger patients. However, elderly patients have a higher incidence of postoperative complications such as stroke, TIA, peripheral embolism, and postoperative atrial fibrillation (78). Additional prospective studies are necessary to evaluate the safety and efficacy of transcatheter PFO closure in patients younger than 18 and older than 60 years of age.

However, Park J et al. (79) performed a retrospective study in JASE comprising 4,804 patients with a history of HF, of whom 981 patients with PFO, 161 underwent PFO occlusion. During the 3.5-year follow-up, the incidence of HF in patients with PFO was lower than that in patients without PFO, and the rate of HF in patients who received PFO occlusion was higher. Moreover, recent research also suggests that PFO closure may increase the risk of Heart Failure (HF) with preserved Ejection Fraction (HFpEF) (80). On the one hand, before performing occlusion surgery, PFO may act as a "pressure reducing valve" for high-risk populations (patients with concomitant structural heart disease, left atrial enlargement, left ventricular hypertrophy, etc.), allowing left to right shunting during exercise or elevated left atrial pressure, reducing the risk of pulmonary congestion; On the other hand, it may be due to the reduced left atrial compliance after occlusion surgery, which weakens the protective effect of natural shunting. Although this study does not alter the indications for PFO occlusion, clinicians must consider the hemodynamic implications of the procedure. Ideal candidates for PFO occlusion are likely true PFO-Associated Stroke patients without underlying structural or functional heart disease. Preclinical studies suggest that these patients have a lower risk of developing heart failure following PFO closure. In patients with structural or functional heart diseases, PFO closure can reduce the incidence of stroke, but it will also increase the risk of HF. Therefore, a large-scale prospective study is needed to explain the relationship between PFO and HF, so that for patients with PFO-AS, we can more fully confirm the indications of PFO occlusion and increase long-term prognosis benefits.

In summary, the effectiveness of PFO occlusion in reducing the risk of recurrent stroke has been confirmed in randomized controlled trials, approved by guidelines and recommended at this level (3, 73, 81) (Table 3). The subset of patients show may optimally benefit from transcatheter PFO closure is currently not fully understood, and the 2022 SCAI still recommend a RoPE score $\geq 7$ (3). Future research should focus on a multi-dimensional approach, considering PFO anatomical and morphological characteristics, patient history (particularly the presence of structural and functional heart diseases), various diagnostic techniques, and scoring systems. This comprehensive approach will enable the identification of specific patient subgroups who may benefit most from PFO closure and facilitate personalized diagnosis and treatment.

There are two methods of transcatheter PFO occlusion and transcatheter PFO suture before occlusion.

### 4.2.2.2 Transcatheter closure of PFO

Currently, two types of occluders are available, one is metal occluders related to nitinol, and the other is biodegradable occluders.

The ever-increasing clinical demand and technological progress have resulted in the widespread use of Amplatzer and IrisFIT occluders in clinical practice as polyester fibers to facilitate the positioning of the occluders toward the interatrial septum so that it is unaffected by the spatial orientation of the interatrial septum itself. However, nickel-titanium occluders are associated with long-term heart problems: such as nickel ion precipitation and nickel allergy, mechanical complications of long-term wear (such as erosion, perforation, cardiac tamponade), displacement, embolism and serious postoperative residual shunt problems (82). To determine the most suitable occluders for patients, the commonly used reference indicators include: (1) Age: in principle, 18 mm occluders should be selected for ages below 18 years; (2) Combined ASA: the occluders should be covered (pay attention to the activity of atrial septum); (3)

TABLE 3 Guidelines for transcatheter PFO closure therapy.

| | 2020AAN guidelines | 2021AHA/ASA guidelines | 2022SCAI guidelines |
|---|---|---|---|
| Suggestions | For patients under 60 years of age who have no other mechanism of stroke and have no embolic embolism and PFO, the clinician can weigh the potential benefits and risks before performing PFO closure surgery | In patients aged 18 to 60 years with non-lacunar ischemic stroke, where the cause is unknown despite thorough evaluation and PFO has high-risk anatomical features, transcatheter device closure of PFO+ long-term antiplatelet therapy is more reasonable than antiplatelet therapy alone to prevent stroke recurrence | For patients aged 18 to 60 years with prior PFO-related stroke, transcatheter PFO closure is recommended compared with antiplatelet therapy, which is superior to antiplatelet therapy alone, regardless of the patient's anatomy; In patients with AF with a history of ischemic stroke, PFO is closed by a compensation cabinet |
| Recommendation, level of evidence | C | 2a | Strong recommendation |

Select the appropriate size occluders with reference to the PFO size and the distance between the upper and lower cavities in combination with TEE results (Table 4).

Biodegradable occluders include partially biodegradable occluders and fully biodegradable occluders. Biodegradable occluders are more technically demanding to fabricate, require many material and specific PFO sizes and location. Therefore, when performing PFO closure, clinicians should accurately measure and display the location, size, tunnel length and distance from the surrounding tissue of the PFO, and then select the appropriate size of the occluders. Currently, few degradable occluders products are available in the market, and their clinical effects need to further investigated.

#### 4.2.2.3 Transcatheter PFO suture

The PFO stapler is currently under development, and the Noble Stitch stapler consists of three dedicated catheters, two of which suture delivery catheters capture and suture the secondary septum and the primary septum, respectively, and then secure and trim the excess suture using another Kwik not catheter. Compared to the PFO occluders, the PFO stapler lacks a permanent prosthesis, minimizes the incidence of atrial fibrillation, and since it is metal-free, elicits no metal allergies, and does not require long-term antiplatelet therapy. Studies have shown that RLS ≥ Grade II, width > 5 mm, and length < 10 mm before PFO surgery are independent predictors of residual shunt ≥ Grade II after transcatheter closure of PFO (83). A multicenter, prospective Noble Stitch-based study of 186 PFO patients who had preoperative RLS ≥ grade II and were followed up for an average of (206 ± 130) days after surgery found that 75% of patients achieved complete closure (RLS grade 0) and 89% had RLS ≤ grade I without suture-related complications. A non-randomized, open-label NobleStitch EL STITCH trial with a larger sample size and longer follow-up is currently underway. The objective of the trial is to compare efficacy of the PFO closure and reduce the incidence of ischemic stroke events between NobleStitch and Amplatzer PFO. In 2025, The Shenzhen Hospital of Fuwai Hospital Chinese Academy of Medical Sciences will initiate a clinical trial on "A multicenter, randomized controlled, non-inferiority study to evaluate the safety and effectiveness of transcatheter PFO stapler system." The study will use the HaloStitch transcatheter PFO stapler system. Compared with metal occluders, HaloStitch also has no nickel ion precipitation, cardiac abrasion, postoperative atrial fibrillation and other complications, and does not lead to long-term anticoagulation.

TABLE 4 The results of TEE for PFO occluders size selection's reference.

| The shortest distance from the defect to the root of the aorta or from the defect to the superior vena cava orifice (mm) | Dimensions (mm) |
|---|---|
| <9 mm | Implant |
| 9–12.4 mm | 18 |
| 12.5–14.9 | 25 |
| 15–17.4 | 30 |
| ≥17.5 mm | 35 |

Both traditional transcatheter PFO closure and transcatheter PFO suture require a personalized approach tailored to the patient's individual circumstances, including their medical condition, economic factors, potential postoperative complications, residual shunts, and other relevant factors.

#### 4.2.2.4 Post closure drug-treatment

In consonance with pertinent guidelines (3), for individuals categorized as low-risk, the administration of DAPT, consisting of aspirin (75–100 mg/day) in conjunction with clopidogrel (75 mg/day), is advocated for a duration of 3–6 months. Subsequently, a transition to monotherapy, typically with aspirin, is recommended for long-term maintenance, with a minimum duration of 12–24 months subsequent to the surgical procedure. For patients who manifest concurrent atrial fibrillation or other indications for anticoagulation, or who exhibit anticoagulation status or a history of recurrent thrombotic events, anticoagulation therapy should be considered in light of individual circumstances and assessed bleeding risks, with the treatment course abbreviated to the greatest extent feasible. Moreover, in cases of significant postoperative occluders thrombosis or residual shunt, the duration of dual antiplatelet therapy may be prolonged or a switch to anticoagulant therapy may be warranted. For patients at high risk of bleeding, the duration of DAPT may be reduced to 1–3 months, or aspirin monotherapy may be employed.

#### 4.2.2.5 Post closure assessment

According to pertinent guidelines (3), echocardiography and ECG should be performed at 24 h, 1, 3, 6, 1 2 months and yearly after

PFO closure, and TTE right heart contrast echocardiography or c-TCD should be performed when necessary. Imaging assessments including occluders position, presence or absence of occluders thrombus, and changes in cardiac structure. TTE right heart contrast echocardiography or c-TCD should be performed 6 months after operation to determine whether there is still existing RLS. For patients with a significant number of RLS, regular follow-up was continued, with repeat TTE right heart contrast echocardiography or c-TCD performed after one year. If RLS persisted, a TEE was recommended. If any clinical symptoms are detected during the entire process, timely ECG and echocardiography are recommended to identify new complications, such as arrhythmia and new thrombus. Moreover, the prognoses of the patients need to be comprehensively assessed in combination with the relevant scoring scales such as clinical symptoms, postoperative NIHSS and mRS.

## 5 Conclusion and outlook

Current research has focused on investigating the pathogenesis, clinical characteristics, acute treatment and secondary prevention of PFO-AS.

Patients with PFO-AS require a treatment approach similar to that of CS during the acute phase. However, their younger age and milder symptoms necessitate a more targeted treatment strategy. PFO-AS patients often have fewer underlying comorbidities, allowing for greater flexibility in thrombolytic timing, drug selection, adjuvant therapies, mechanical thrombectomy, and bridging therapy prior to thrombectomy. Similarly, in terms of secondary prevention, the advantages of occlusion therapy have been documented. However, clinicians should consider the patient's history of heart disease and assess whether the patient presents a clear structural and functional heart disease as well as perform a comprehensive evaluation of the PFO structure (channel length and opening diameter), shunt volume, blood flow velocity and thrombus size, thrombus site, vascular occlusion and other clinical data in combination with the commonly used PFO screening methods and imaging related data, and select the appropriate treatment plan to prevent the occurrence and recurrence of various vascular events.

Unlike for stroke patients with known etiology, circulating biomarkers and genetic factors should be used to determine the etiology of PFO-AS patients. In future, researchers should explore PFO-associated circulating metabolites and causative genes, to identify new targets for the diagnosis and treatment of PFO-associated diseases.

## Author contributions

WL: Formal analysis, Writing – original draft, Writing – review & editing. JZ: Funding acquisition, Writing – review & editing. YZ: Writing – review & editing. WS: Writing – review & editing. SY: Writing – review & editing. QC: Writing – review & editing. SQ: Conceptualization, Project administration, Resources, Writing – review & editing. QK: Project administration, Writing – review & editing.

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## Conflict of interest

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The authors declare that no Gen AI was used in the creation of this manuscript.

## Publisher's note



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# Predictive value of contrast-enhanced carotid ultrasound features for stroke risk: a systematic review and meta-analysis

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**Objective:** To elucidate the contrast-enhanced ultrasound (CEUS) features of carotid artery plaques in patients who have experienced an ischemic stroke (IS).

**Methods:** A computerized search was conducted in databases such as PubMed, EMSCO, and Ovid to identify studies reporting CEUS findings of carotid artery plaques. Patients were categorized as IS and non-IS based on clinical and radiological diagnosis, and the quantitative and semi-quantitative CEUS data were analyzed for differences between the two groups.

**Results:** After the computerized search, a total of 13 eligible studies, comprising 3,092 participants (1,953 with stroke), were included for analysis. IS patients exhibited significantly higher plaque enhancement intensity versus control group (SMD = 0.71, 95% CI: 0.32, 1.11). The positive rate of plaque enhancement within the plaques was significantly higher in IS patients versus non-IS patients (OR = 3.25, 95% CI: 1.86, 5.68). The sensitivity of hyperintense lesion-based diagnosis of stroke was 0.68 (95% CI: 0.54, 0.80), and the specificity was 0.61 (95% CI: 0.47, 0.73), with an area under the curve (AUC) of 0.697.

**Conclusion:** There are significant differences in CEUS characteristics of carotid artery plaques between IS and non-IS patients. IS patients display markedly augmented plaque enhancement intensity and a higher rate of positive enhancement compared to non-stroke individuals. These noteworthy findings have critical implications in enhancing the accuracy of IS diagnosis and improving the stratification of stroke risk for patients.

**Systematic review registration:** This study is registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY), 202540006.

KEYWORDS

**carotid artery plaque, contrast-enhanced ultrasound, ischemic stroke, carotid stenosis, meta-analysis**

## 1 Introduction

Ischemic stroke (IS) stands as a prominent worldwide contributor to both mortality and disability, presenting a substantial risk to public health and welfare (1). Atherosclerosis, a persistent inflammatory, metabolic, and multifaceted condition impacting the inner lining of medium and large arteries, emerges as a primary causative factor of IS, with carotid artery

atherosclerotic plaque playing a significant role in its development (2). Traditionally, the assessment of stroke risk has focused on the degree of carotid stenosis. While severe carotid artery narrowing remains an important risk factor, emerging evidence suggests that patients with non-severe stenosis may also experience ischemic events (3, 4). Recent studies indicate that the stability of carotid artery atherosclerotic plaque, rather than just the degree of stenosis, is closely linked to the occurrence of ischemic stroke (IS). In fact, 25–50% of IS events are associated with the rupture of vulnerable plaques (5–7).

The distinctive features of unstable carotid artery plaques can be detected and measured using a range of non-invasive imaging techniques, including ultrasonography (US), computed tomography (CT), high-resolution magnetic resonance imaging (MRI), and nuclear imaging methods (8, 9). These advanced imaging modalities provide valuable information beyond just the degree of arterial narrowing, allowing for improved risk stratification and targeted management of patients at risk of ischemic stroke. Ultrasonography is an excellent screening tool for carotid artery atherosclerosis, as it is cost-effective, rapid, and widely accessible, enabling frequent follow-up examinations (10, 11). Contrast-enhanced ultrasound (CEUS) is a novel non-invasive technique that employs contrast agents containing gas microbubbles, which generate strong echo signals under ultrasound, enhancing image contrast and allowing for clearer visualization of tissue perfusion and structural features (12). As a "tracer" of the vascular system, CEUS can clearly delineate the contours of the vascular intima and carotid artery atherosclerotic plaques, including ulcerated plaques, enabling the assessment of plaque stability based on morphological characteristics (13, 14).

To date, however, there has been a paucity of multi-center, large-scale studies investigating the CEUS features of carotid artery plaques in the ischemic stroke population. To address this gap, we evaluate the CEUS characteristics of carotid artery plaques in patients with ischemic stroke.

# 2 Methodology

## 2.1 Literature search strategy

We conducted a literature search in the Embase, PubMed, and Ovid electronic databases to screen studies that reported the CEUS features of carotid artery plaques in patients with IS. The search terms used included "stroke," "carotid plaque," and "contrast-enhanced ultrasound." The search was limited to publications up to June 1, 2024, without any language restrictions. Next, we conducted a thorough manual search through the bibliographies of the chosen articles to uncover any supplementary studies that could bear relevance to the subject matter.

## 2.2 Study selection criteria

The following predefined eligibility criteria were utilized for study inclusion: (1) Participants: Patients diagnosed with carotid artery atherosclerotic plaques were enrolled. All patients underwent CEUS prior to carotid endarterectomy. Based on the North American Symptomatic Endarterectomy Trial criteria (NASCET), the patients were categorized into two groups: those with asymptomatic and those with symptomatic internal carotid artery stenosis attributable to plaques. Symptomatic internal carotid artery stenosis was defined as the onset of neurological manifestations associated with the ipsilateral carotid artery within the preceding 120 - day period. Other potential etiologies of stroke, such as cardioembolism, were strictly excluded. Notably, none of the patients with asymptomatic internal carotid artery stenosis due to plaques had a history of ischemic events resulting from carotid artery stenosis. (2) Intervention: All participants underwent CEUS examination. (3) Outcome measures: Quantitative or semi-quantitative CEUS characteristics of carotid artery plaques, with clinical and imaging diagnoses of IS and non-ischemic stroke (non-IS). (4) Study design: No restrictions on study type. Research with fewer than 10 participants, along with individual case reports and case series, were omitted from consideration. Two separate evaluators screened the collected articles independently, with any disparities being reconciled by a third reviewer.

## 2.3 CEUS plaque enhancement

CEUS plaque enhancement, plaque enhanced intensity was calculated by subtracting baseline from peak intensities in the core, plaque shoulder, and vessel lumen.

## 2.4 Data extraction

A systematic data extraction process was carried out using an Excel spreadsheet to collect the following information from the included studies: publication year, first author, study design, participant count, and outcomes. Two reviewers independently extracted the data and verified the information, with any disagreements addressed with a third reviewer.

## 2.5 Heterogeneity assessment

The heterogeneity across the included studies was evaluated utilizing the corrected $p$-value and the I-squared ($I^2$) statistic. Studies were deemed to exhibit negligible heterogeneity when the $I^2$ statistic was below 50%, prompting the use of a fixed-effects meta-analytic model. Conversely, an $I^2$ value of 50% or greater was interpreted as indicative of substantial heterogeneity, leading the authors to employ a random-effects approach to provide a more conservative statistical description of the effect sizes.

## 2.6 Statistical analysis

The analysis of the data was conducted utilizing the meta package in the R programming language, and figures were generated accordingly. For quantitative data on plaque enhancement, the pooled effect size was reported as the standardized mean difference (SMD) with its 95% confidence interval (CI). For qualitative data, such as the presence or absence of plaque enhancement or intraplaque neovascularization (IPN), the pooled effect size was represented by the odds ratio (OR) with its 95% CI. Statistical significance was determined by whether the 95% CI of the SMD or OR contained 0 or 1, respectively. The diagnostic accuracy was analyzed using the R package meta4diag.

TABLE 1 Included studies characteristics.

| First author | Year | Enrollments | With stroke | Agent | Region of interest |
|---|---|---|---|---|---|
| Xiong (28) | 2009 | 71 | 35 | SonoVue | Entire plaque |
| Saito (29) | 2014 | 50 | 19 | Sonazoid | Entire plaque and shoulders |
| Luo (30) | 2019 | 116 | 62 | SonoVue | Entire plaque |
| Jain (31) | 2020 | 60 | 32 | SonoVue | Entire plaque and surface |
| Li (14) | 2023 | 660 | 349 | SonoVue | Entire plaque |
| Li (32) | 2024 | 61 | 32 | SonoVue | Entire plaque |
| Tan (33) | 2022 | 188 | 72 | SonoVue | Entire plaque and surface |
| Huang (34) | 2021 | 24 | 161 | Optison | Entire plaque |
| Li (35) | 2018 | 116 | 62 | SonoVue | Entire plaque |
| Cui (36) | 2023 | 321 | 162 | SonoVue | Entire plaque |
| Huang (37) | 2010 | 176 | 81 | SonoVue | Entire plaque |
| Zhao (38) | 2022 | 60 | 60 | SonoVue | Entire plaque |
| Cui (13) | 2022 | 50 | 12 | SonoVue | Entire plaque |

# 3 Results

## 3.1 Literature screening and selection

Initially, the literature search yielded 425 articles, and after eliminating duplicates, 141 articles remained. Subsequently, a screening of titles and abstracts produced the exclusion of 78 non-clinical studies, resulting in 63 full-text articles for further evaluation of their eligibility. Among these, 14 articles were excluded due to the inability to extract the specified data, 29 articles did not have a stroke control group, and 7 articles focused only on pediatric populations. Ultimately, 13 studies were included in the analysis.

## 3.2 Characteristics of included studies

The 13 included studies involved a total of 3,092 participants, of whom 1,953 had ischemic stroke (IS). The most commonly used contrast agents were SonoVue, Sonazoid, and Optison, with SonoVue being the most frequently employed. The regions of interest (ROI) included the plaque, plaque surface, and plaque shoulder (Table 1).

## 3.3 Meta-analysis of quantitative CEUS plaque enhancement

Three studies reported quantitative analysis of CEUS plaque enhancement, comprising 116 IS patients and 121 non-IS controls. Considerable diversity was evident across the studies, indicating substantial heterogeneity ($I^2 = 51\%$, $p = 0.13$), and a random-effects model was employed. The results demonstrated a higher plaque enhancement intensity in IS patients versus the control group (SMD = 0.71, 95% CI: 0.32, 1.11) (Figure 1).

## 3.4 Diagnostic value of semi-quantitative lesion analysis for stroke

For the stroke group, semi-quantitative positivity was considered as true positive (TP), and semi-quantitative negativity as false negative (FN). In the non-stroke group, semi-quantitative negativity was considered as true negative (TN), and semi-quantitative positivity as false positive (FP). A meta-analysis was performed to evaluate the diagnostic value of semi-quantitative positivity for stroke. The SROC scatter plot did not show a clear "shoulder-arm" pattern, and the Spearman correlation coefficient was 0.633 ($p = 0.076$), suggesting no threshold effect. The pooled sensitivity of semi-quantitative positivity for diagnosing stroke was 0.68 (95% CI: 0.54, 0.80), the pooled specificity was 0.61 (95% CI: 0.47, 0.73), and the AUC was 0.697 (Figures 2A,B).

## 3.5 Meta-analysis of semi-quantitative CEUS plaque enhancement

Ten research studies presented semi-quantitative evaluations of plaque enhancement. In this analysis, the absence of enhancement or localized enhancement restricted to the plaque's edge was deemed as negative, while linear and widespread enhancement were regarded as positive outcomes. The rate of positive plaque enhancement was notably higher in IS when compared to those without IS. Considerable variability was observed among the studies ($I^2 = 80\%$, $p < 0.001$), leading to the adoption of a random-effects model. The findings pointed towards a significantly elevated positive rate of CEUS plaque enhancement in IS versus non-IS patients (OR = 3.25, 95% CI: 1.86, 5.68) (Figure 3).

## 3.6 Publication bias assessment

Due to the limited number of studies available for each outcome, the feasibility of conducting Begg's test and Egger's test to assess potential publication bias was restricted. Nonetheless, upon visually

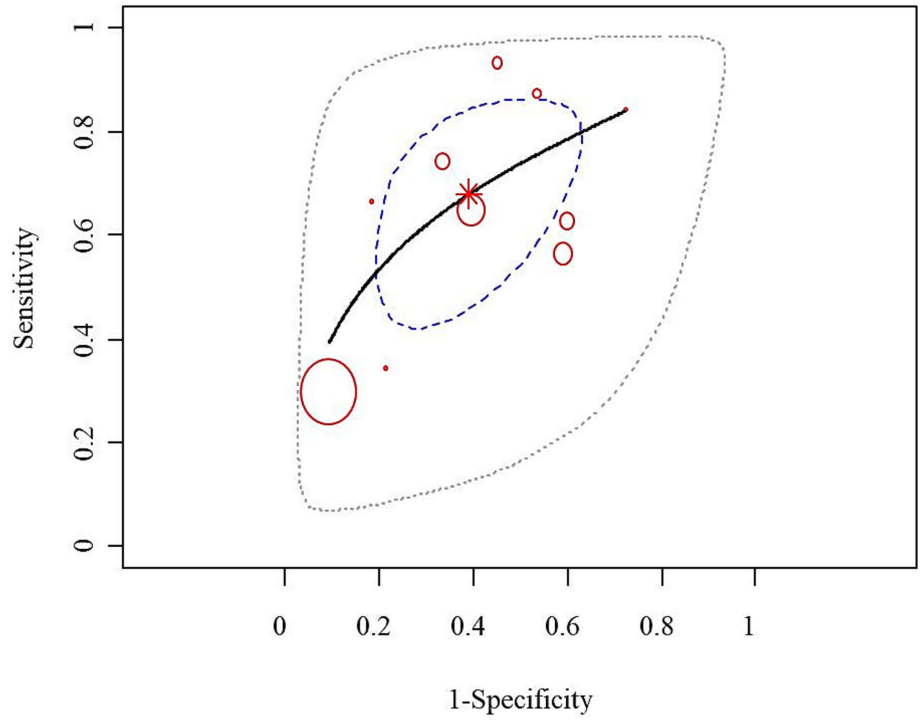


FIGURE 1
The flow chart for study retrieval and selection.

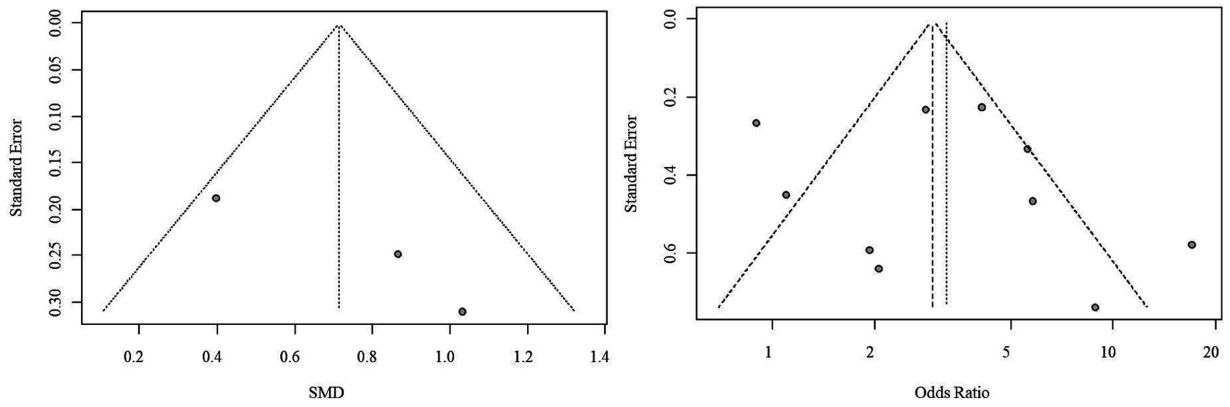


FIGURE 2
The forest plot of enhanced intensity in plaque by quantitative analysis. Significant variation was apparent among the studies, reflecting considerable heterogeneity ($I^2$ = 51%, $p$ = 0.13), prompting the application of a random-effects model. Findings revealed a notably elevated intensity of plaque enhancement in patients with ischemic stroke compared to the control group (SMD = 0.71, 95% CI: 0.32, 1.11).

inspecting the funnel plots, indications of potential publication bias for both outcome measures were noted (Figure 4).

## 4 Discussion

CEUS has gained popularity in its application for quantifying the structural characteristics of carotid atherosclerotic plaques, evaluating plaque stability, and assessing neovascularization. This analysis revealed that patients with a history of stroke exhibited significantly greater intensity of plaque enhancement versus the control group. This finding highlights the potential of CEUS as a valuable tool in distinguishing carotid plaques between stroke patients and non-stroke individuals. CEUS has the capability to detect neo-angiogenesis or enhanced inflammatory activity within the plaque of patients with IS. These processes are typically associated with increased plaque instability and rupture risk. Therefore, an increase in contrast enhancement intensity may serve as a potential biomarker of plaque vulnerability and tendency of stroke. Moreover, the rate of positive plaque enhancement was higher in IS patients versus non-stroke patients. The presence of enhanced contrast within the plaque, as detected by CEUS, further emphasizes the value of this modality in

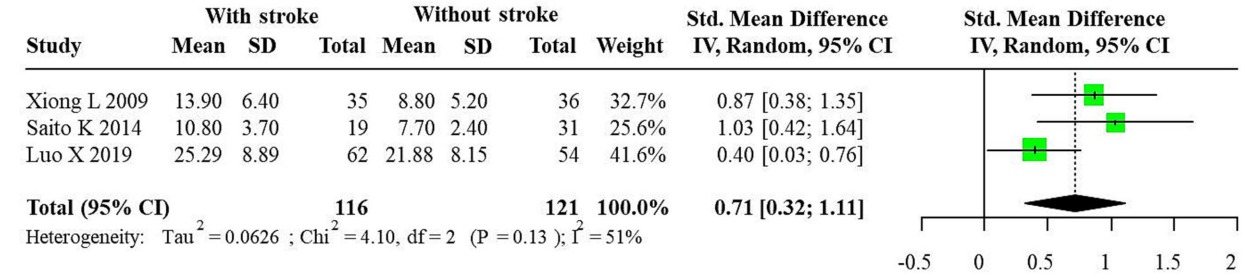


FIGURE 3
Forest plot of the sensitivity and specificity of semi-quantitative positivity for the diagnosis of stroke. The combined sensitivity of semi-quantitative positivity for stroke diagnosis was 0.68 (95% CI: 0.54, 0.80), while the combined specificity stood at 0.61 (95% CI: 0.47, 0.73), with an AUC of 0.697.

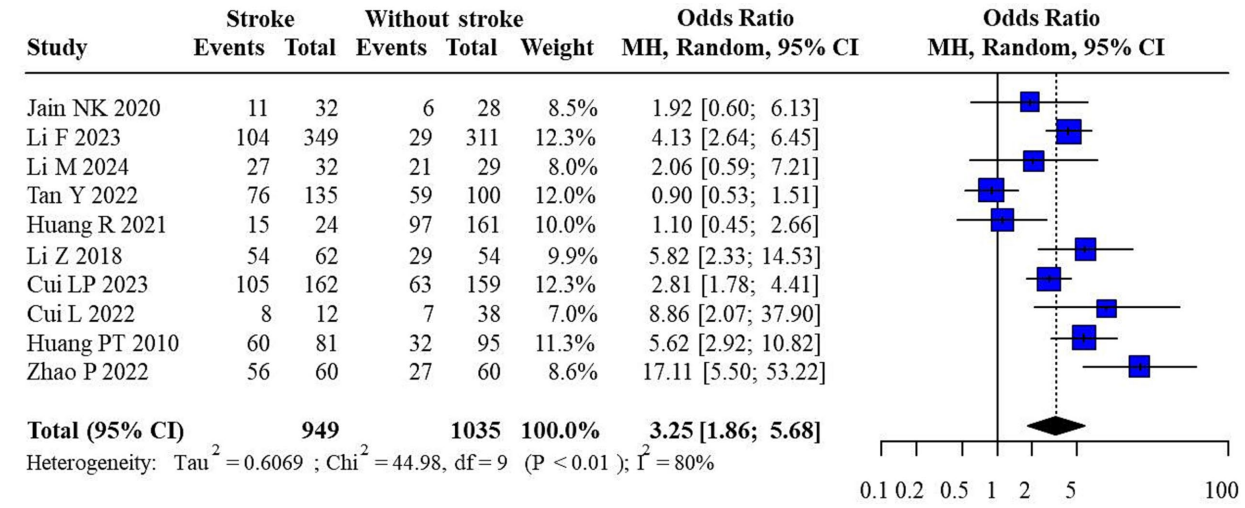


FIGURE 4
SROC curve of semi-quantitative positivity for the diagnosis of stroke. The scatter plot of the SROC did not exhibit a distinct "shoulder-arm" pattern, and the Spearman correlation coefficient was 0.633 ($p$ = 0.076), indicating the absence of a threshold effect.

identifying high-risk atherosclerotic plaques. The existence of intraplaque enhancement may indicate an active, unstable plaque state, which is associated with a higher risk of plaque rupture and consequently, an increased likelihood of stroke occurrence (Figure 5).

The sensitivity of CEUS in the diagnosis of IS indicates that it can correctly identify approximately 68% of patients who have experienced an IS event. While this value is not exceptionally high, it still maintains clinical utility, given the complex and multifactorial nature of stroke diagnosis. In non-IS patients, CEUS can correctly exclude approximately 61% of individuals. The relatively low specificity may reflect the limitations of CEUS in distinguishing plaque characteristics not associated with stroke, or the presence of similar plaque enhancement features in some non-stroke patients. The AUC was 0.697, indicating a moderate overall diagnostic performance of CEUS in differentiating IS patients from non-IS individuals. Although the AUC value did not reach a very high level, it still suggests the diagnostic potential of CEUS, particularly when combined with other clinical information and imaging modalities (Figure 6).

Vulnerable carotid plaques are a significant contributor to ischemic stroke, and the formation of new blood vessels (neovascularization) within the plaque plays a crucial role in increasing plaque vulnerability (15). The neomicrovasculature that develops within the plaque lacks the normal connective tissue support, making it prone to rupture and bleeding. This can lead to plaque instability and intraplaque hemorrhage (16). The presence of this neomicrovasculature within the carotid plaque serves as an independent risk factor for plaque rupture, hemorrhage, and a strong predictor of future cardiovascular and cerebrovascular events (17). The development of these delicate new blood vessels disrupts the structural integrity of the plaque, rendering it more unstable and prone to potentially devastating consequences, such as ischemic stroke.

CEUS, as a technique that reflects the microvascular system of the plaque, employs contrast agent microbubbles with similar characteristics to red blood cells, remaining within the vascular lumen (18). A number of studies have established a connection between the enhancement observed in CEUS and the histological vascular density of carotid plaques (19, 20). In patients undergoing carotid endarterectomy, pre-operative CEUS and CT examinations were conducted, followed by quantitative analysis of plaque enhancement and subsequent histopathological analysis. The results indicated a significantly higher CEUS plaque enhancement intensity in patients with CT-diagnosed IS compared to asymptomatic patients. Moreover,

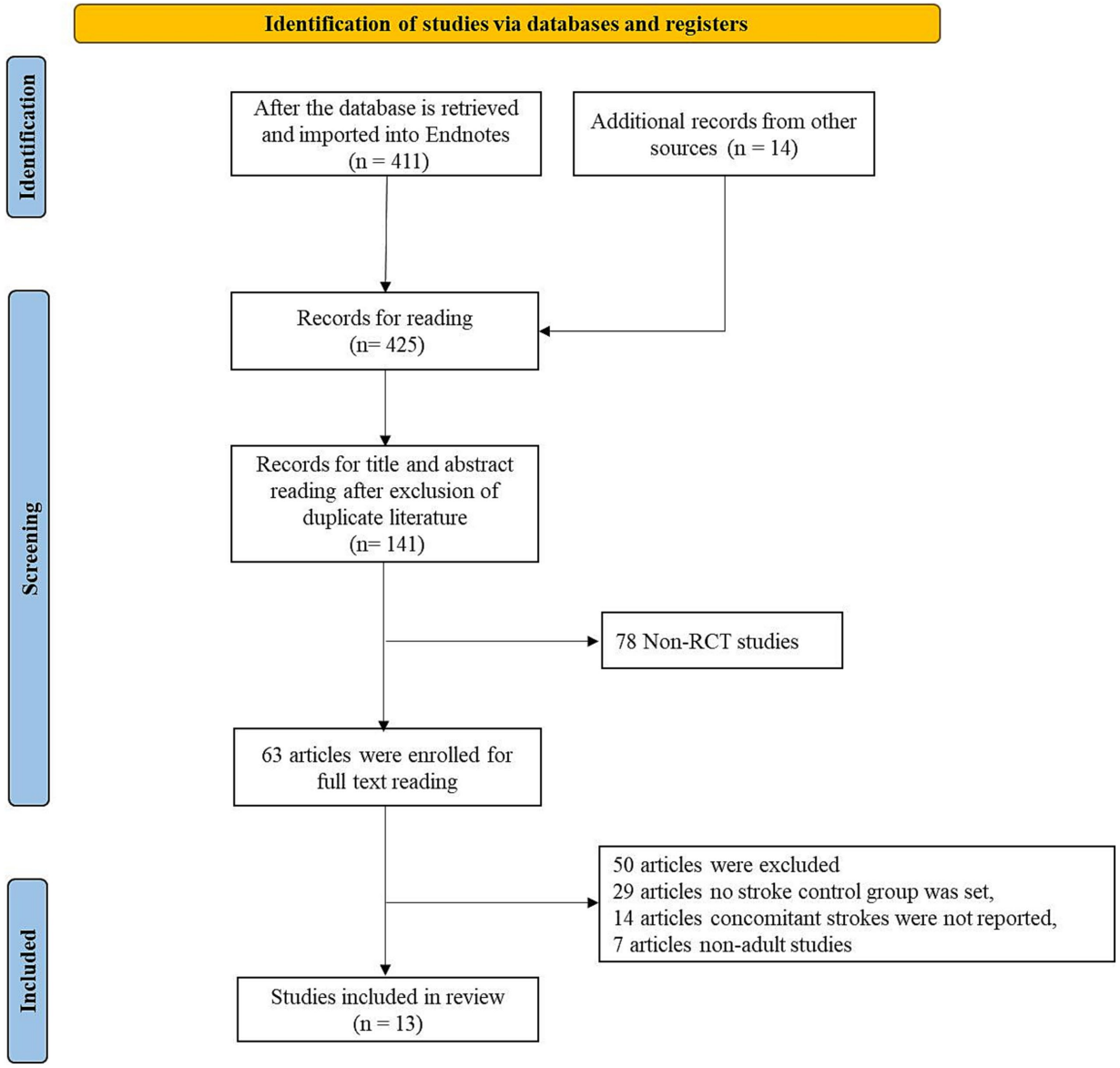


FIGURE 5
The forest plot of enhanced intensity in plaque by semi-quantitative analysis. Considerable heterogeneity was observed among the studies ($I^2$ = 80%, $p$ < 0.001), leading to the adoption of a random-effects model. The outcomes highlighted a significantly higher rate of positive CEUS plaque enhancement in ischemic stroke patients compared to non-ischemic stroke patients (OR = 3.25, 95% CI: 1.86, 5.68).

higher CEUS enhancement intensity correlated with a thinner fibrous cap and increased inflammatory infiltration on histopathology (21).

Quantitative analysis is an emerging trend in radiology, aiming to minimize subjectivity and enhance inter-observer consistency (22). The evaluation of neovascularization in atherosclerotic plaques using CEUS involves both semi-quantitative visual assessment and software-based quantitative assessment (23). The semi-quantitative assessment employs a scoring system proposed by Meng et al. (39), which categorizes plaque neovascularization into three levels: mild, with detectable microbubble flow only in the plaque's adventitia; moderate, with detectable microbubble flow in the plaque shoulders and within the plaque; and severe, with detectable microbubble flow throughout the entire plaque, including the plaque tip. Quantitative assessment utilizes dedicated analysis software to quantify the plaque enhancement intensity and neovascularization within the plaque on CEUS. The contrast quantification software adjusts the ROI frame-by-frame based on plaque size and shape, and establishes another ROI in the center of the carotid lumen near the plaque's proximal end as a reference (24). The software then automatically generates time-intensity curves for the plaque and lumen, calculating the enhancement intensity values and enhancement density (25). Schmidt et al. (26) confirmed a significant correlation between CEUS-detected neovascular quantity and histologically determined plaque vascular density, indicating good consistency between CEUS and histopathology in assessing plaque neovascularization. In patients scheduled for carotid endarterectomy, it is feasible to perform quantitative and volumetric imaging of the carotid artery and neovascularization within the plaque using CEUS (27). In this meta-analysis, both quantitative and semi-quantitative assessments

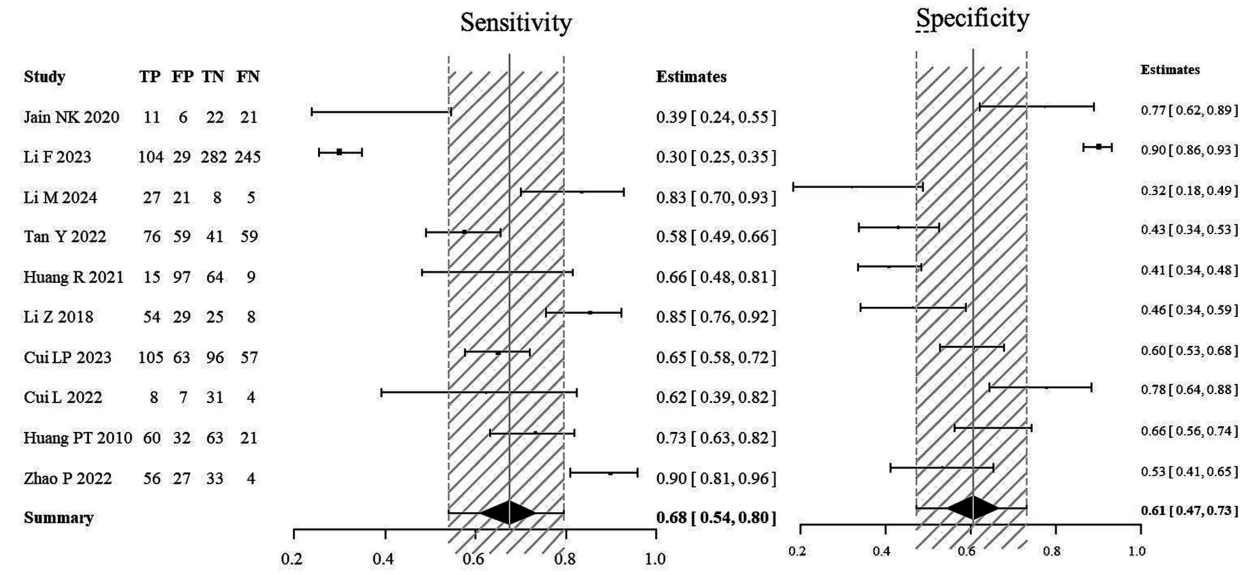


FIGURE 6
Funnel plot of publication bias. Observations from the funnel plots suggest the potential presence of publication bias for both outcome measures.

supported the value of CEUS in ischemic stroke. The results of this meta-analysis underscore the potential role of CEUS in the assessment of carotid plaque stability and stroke risk. However, to establish CEUS as a routine clinical examination tool, further research is needed to optimize its diagnostic performance, determine the optimal examination protocol, and delineate its applicability across different patient populations. Additionally, exploring the combined use of CEUS with other imaging modalities, such as CT and MRI, may improve the accuracy and reliability of stroke risk assessment. While this meta-analysis provides new insights and evidence to support the application of CEUS in stroke prevention and management, future studies will need to address the current challenges and drive the further development of this technology.

However, this study has certain limitations. The included studies were primarily observational or cross-sectional in design, resulting in lower methodological quality. Additionally, the criteria for semi-quantitative plaque enhancement grading were not completely consistent, leading to unavoidable heterogeneity. Furthermore, the dichotomization of semi-quantitative plaque enhancement data may have reduced the interpretability of the results.

## 5 Conclusion

The CEUS characteristics of carotid plaques in IS significantly differ from those in patients without stroke, demonstrating higher plaque enhancement intensity and positive enhancement rate. These findings emphasize the prominent role of CEUS in the diagnosis and risk stratification of IS.

## Data availability statement

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

## Ethics statement

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors, it does not require the approval of the independent ethics committee.

## Author contributions

SZ: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. PH: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing.

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## Conflict of interest

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.

## Publisher's note



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# Cryptogenic embolic stroke and cancer

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Oncologic and cerebrovascular diseases are among the diseases with the highest incidence rate and are leading causes of disability and mortality. The relationship between cancer and cerebrovascular disease has been studied for decades, yet it remains a challenge. Stroke, in relation to oncologic diseases, has particularities in its diagnosis and treatment. Cancer is an established risk factor for ischemic stroke. The highest risk of stroke occurs within the first 6 months after a cancer diagnosis and in patients with metastases. Between 2 and 10% of patients initially diagnosed with cryptogenic stroke are subsequently diagnosed with cancer within 1 year. The mechanism underlying cryptogenic ischemic stroke associated with oncologic disease is acquired hypercoagulability, which is the most frequent mechanism underlying stroke in patients with cancer. Sometimes, cancer presents itself as non-bacterial thrombotic endocarditis (NBTE) with cerebral infarction. Strokes are usually more severe, and their clinical presentation can be focal or multifocal. D-dimer levels are significantly elevated in patients with cancer-associated stroke. Magnetic resonance imaging (MRI) usually shows embolic lesions across several arterial territories, including both carotid territories and the vertebrobasilar territory. Patients with cancer-associated stroke face a higher risk of recurrence, recurrent thromboembolism, early neurological deterioration, and mortality. Patients with both stroke and cancer should be considered for thrombolysis (recombinant tissue plasminogen activator (rTPA) or tenecteplase) and endovascular treatment. Low-molecular-weight heparin is usually used empirically when a hypercoagulable state is suspected, and few studies have supported the use of direct oral anticoagulants as an option with similar efficacy. The objective of this review was to synthesize all relevant information available to date on neoplasia as a cause of cryptogenic embolic stroke and to provide useful insights for everyday clinical practice.

KEYWORDS

**cryptogenic embolic stroke, Cancer, MRI, d-dimer, review**

## 1 Introduction

Oncologic and cerebrovascular diseases have the highest incidence rate and are leading causes of disability and mortality. Approximately 40% of the population faces a lifetime risk of developing cancer (1, 2). The lifetime risk of stroke from the age of 25 years is 25% (3).

The connection between cancer and cerebrovascular disease has been a subject of study for decades. The first large series of autopsy studies in 1985 showed that 14.6% of patients with cancer had cerebrovascular disease and half of the cases were symptomatic. The main neurological complication associated with brain metastasis is cerebrovascular disease (ischemic and hemorrhagic) (4).

In the general population, most strokes are ischemic, and one-third of the cases remain cryptogenic with no recognized etiology (5). Cryptogenic ischemic strokes can be divided into subgroups, some of which have particularities in their diagnosis and treatment, such as stroke related to oncologic disease. This type of stroke occurs in patients with active cancer; less frequently, patients will have occult neoplasia, which, if diagnosed, will offer an enormous possibility for treatment and improvement in prognosis (6).

In recent years, a substantial body of scientific evidence has been generated that allows us to identify the specific characteristics of this association between stroke and cancer.

The objectives of this review were as follows: to synthesize all relevant information available to date on cancer as a cause of cryptogenic embolic stroke (CES-ONC) and to provide useful insights for everyday clinical practice that can help improve the management of patients with cancer and ischemic stroke.

## 2 Epidemiology

Of the population of patients with cancer, 15% have cerebrovascular disease (7, 8), and the frequencies of ischemic and hemorrhagic strokes are similar (8). Among patients with stroke, 10% have a history of cancer (7), and the prevalence of cancer in this group is higher than in the general population (9, 10). In the cryptogenic stroke subgroup, 10% of patients also have a history of cancer (7).

However, attributing the etiology of stroke to cancer presents two challenges:

1 Some of these associations might be coincidental.
2 A subgroup of patients with stroke may have occult neoplasms at the time of diagnosis, which could be the underlying cause.

The co-prevalence of stroke and cancer is expected to rise owing to an increase in the survival rate of patients with cancer. Registries of patients with oncologic diseases show an increase in survival in patients with lung, breast, and prostate cancers, the three types of cancer with the highest incidence rate (11).

Cancer is an established risk factor for ischemic stroke. Multiple studies, including prospective studies, have demonstrated an increased risk of ischemic stroke and other arterial thromboembolic events in patients with incident oncologic disease compared to controls (5, 12). The highest risk of stroke occurs within the first 6 months after a cancer diagnosis and in patients with metastases (12). The risk of stroke varies according to the type of stroke and is higher in cancers associated with pulmonary thromboembolism, particularly lung and pancreatic cancers (13, 14).

In patients with both stroke and cancer, 10% present with venous thromboembolism (10, 15, 16). In a population of patients with venous thrombosis of unknown etiology, the prospective randomized screening study Screening for Occult Malignancy in Patients With Idiopathic Venous Thromboembolism (SOME) found that only 3.9% of the patients were diagnosed with cancer within the following year.

Regarding the issue of occult neoplasia at the time of stroke diagnosis, between 2 and 10% of patients with cryptogenic stroke are diagnosed with cancer within a year of diagnosis (17–19).

The most frequently occurring neoplasms in patients with stroke are urogenital, breast, and gastrointestinal neoplasms. A higher incidence of stroke has been reported in patients diagnosed with lung, pancreatic, colorectal, breast, and prostate cancers (20).

## 3 Etiopathogenia

The type of tumor most commonly associated with embolic stroke of undetermined etiology is adenocarcinoma. However, all types of cancer, whether solid or hematologic, and at any stage, are associated with an increased risk of stroke.

The potential mechanisms through which cancer can cause stroke include cancer-related acquired hypercoagulability, direct invasion or compression of arteries, infection, and side effects of radiotherapy or chemotherapy.

The mechanism underlying CES-ONC is acquired hypercoagulability, which is the most frequently observed mechanism of stroke in patients with cancer. This state of hypercoagulability explains the high frequency of thrombotic events (both venous and arterial) in patients with cancer (21).

In the case of other mechanisms, there is a well-defined and identifiable etiology, and one could not speak of stroke without a known cause.

The pathobiology underlying a hypercoagulable state is complex and varies according to the type of cancer, its histology, and multiple interconnected factors. An increase in procoagulant factors, including tissue factors, mediated by both cancer cells and the systemic inflammatory response, is observed.

Stroke of unknown etiology in patients with a history of oncologic disease has a different molecular profile and peripheral blood gene expression (mRNA) compared to isolated cancer or isolated stroke (22, 23). There is an increase in the number of extracellular vesicles derived from cancer cells and platelets. These vesicles trigger a hypercoagulable state (24). In the OASIS-Cancer study, cancer cell-derived extracellular vesicles were found to correlate with D-dimer levels, which triggered hypercoagulability independently of tissue factor-dependent pathways. In patients with lung cancer, the subtype associated with vesicle elevation is adenocarcinoma (25).

Another factor is neutrophil extracellular trap formation, which is a part of the innate immune response and promotes platelet and coagulation factor activation. Patients with CES-ONC have increased levels of neutrophil extracellular trap formation, which are associated with thrombin–antithrombin complex, a marker of coagulation, and P-selectin, a marker of platelet activity (26).

In the OASIS-Cancer study, circulating plasma DNA and nucleosome levels, markers of neutrophil extracellular trap formation, were associated with high levels of D-dimer and were higher in patients with CES-ONC than in controls (22).

Another relevant factor is the presence of platelets with high activity and an increased tendency to aggregate. Extracellular vesicles derived from platelets and related to tissue factors are elevated in all

types of stroke, regardless of whether the etiopathogenetic mechanism is associated with neoplasia.

### 3.1 The etiopathogenetic mechanisms through which cancer causes embolic stroke of undetermined etiology are as follows

#### 3.1.1 Related to hypercoagulability

##### 3.1.1.1 Sterile vegetation on cardiac valves in the context of acquired hypercoagulability

In this case, cancer usually metastasizes and cerebral infarction is a late-stage complication (20). Occasionally, non-bacterial thrombotic endocarditis (NBTE) with cerebral infarction can be an initial manifestation of cancer (27). In a population of cancer patients, NBTE occurs in 9.3–19% of cases, while in patients diagnosed with NBTE, cancer can be found in 59% (28–31). Patients with emboli associated with NBTE have high platelet counts and low erythrocyte fractions (32).

##### 3.1.1.2 Through disseminated vascular coagulation

In this case, the condition meets the criteria for disseminated intravascular coagulation associated with thrombopenia and hypofibrinogenemia. Strictly speaking, it cannot be considered a stroke of undetermined etiology.

##### 3.1.1.3 Paradoxical embolism through a patent foramen ovale

In this case, 25% of the population has a patent foramen ovale as a remnant of fetal circulation. This is primarily due to hypercoagulability and the high risk of venous thrombosis.

#### 3.1.2 Other mechanisms not related to hypercoagulability or cryptogenic etiology

Cancer can cause stroke through other well-defined etiologies that are infrequent and, therefore, cannot be considered cryptogenic.

##### 3.1.2.1 Atherothrombosis may be associated with cancer risk factors, including obesity, carbohydrate intolerance, and smoking

Radiotherapy can cause arterial injury and destabilize atheroma plaques within months, especially when combined with the pro-inflammatory effects of cancer. Atheroma plaques in the aortic arch must also be considered because thoracic radiation is common in breast cancer or lymphoma. It can also damage the coronary arteries, cardiac valves, myocardium, and pericardium, leading to embolic stroke (33).

##### 3.1.2.2 Antineoplastic treatments

Generally, the risk of stroke associated with chemotherapy is low. However, this risk is higher with certain treatments, including methotrexate (MTX), 5-fluorouracil, cisplatin, and L-asparaginase (34, 35). Anthracycline chemotherapy can also lead to chronic cardiomyopathy. All agents with anti-estrogenic effects can increase the risk of stroke (36, 37). Immunotherapy, which is used in modern treatment regimens, can lead to vasculitis and myocarditis (38, 39).

Tumor embolism may be a mechanism of embolic stroke. This mechanism occurs when a tumor invades the pulmonary vein or cardiac cavity.

Embolic strokes can occur during tumor surgery due to tumor embolism, direct injury to the arteries, or cardiac arrhythmias associated with surgical intervention.

## 4 Clinical characteristics

The clinical characteristics of patients with CES-ONC can be defined as follows (20):

1- The traditional risk factors shared by cancer and stroke are obesity, carbohydrate intolerance, and smoking. In general, patients with an association between cancer and stroke have fewer traditional vascular risk factors than patients who have a stroke without cancer.
2- The oncologic antecedent most closely related to embolic stroke of undetermined etiology is adenocarcinoma, although all types of cancer, whether solid or hematologic, at any stage, are associated with an increased risk of stroke.
3- Strokes are usually more severe; therefore, we should consider the degree of previous disability due to oncologic disease as a possible confounding factor.
4- Its clinical presentation can be focal or multifocal. In 30–70% of cases, neuroimaging shows emboli lesions in several arterial territories, including both carotid territories and the vertebrobasilar territory (20, 25).
5- They face a higher risk of recurrence, recurrent thromboembolism, early neurological deterioration, and mortality.

## 5 Diagnostic considerations

In patients with a history of cancer and stroke of undetermined etiology, the diagnostic challenge lies in detecting and stratifying the importance of the relationship, ultimately establishing an etiopathogenetic link between ischemic stroke and acquired hypercoagulability associated with cancer. This condition not only increases the risk of venous thrombosis but also of arterial thrombosis (14).

Another diagnostic challenge in this context is that one of the causes of stroke of unknown etiology is the presence of occult neoplasia, which occurs in 2.8% of patients. However, the optimal screening strategy remains unclear. Moreover, biomarkers with adequate sensitivity and specificity to aid in early diagnosis are not yet available. This constitutes a relevant current diagnostic problem, without an adequate solution (6).

Approximately 50% of strokes in patients with oncologic disease are of undetermined etiology, a higher percentage compared to patients without cancer (8–11, 40, 41).

A high index of suspicion for acquired hypercoagulability associated with cancer should be maintained in patients with a history of oncologic disease and stroke of undetermined etiology (14). The condition is characterized by hypercoagulability rather than consumption coagulopathy.

In the case of venous thrombosis of unknown etiology, the prospective randomized screening study, SOME, found that only 3.9% of patients with venous thrombosis of unknown etiology were diagnosed with cancer within the following year. There were no diagnostic differences between the group of patients assigned to the computed tomography (CT) screening and the group of patients assigned to the basic evaluation, which included analysis, chest X-ray, and age- and sex-appropriate screening for breast, cervical, and prostate tumors.

Further studies with similar design are needed to be able to advise on the type of screening that is most appropriate for patients with cryptogenic embolic stroke and suspected occult neoplasia (12). Occult neoplasia is identified in 2–10% of embolic ischemic stroke cases; this diagnosis is made within a year after the stroke (17–19).

## 5.1 Biomarkers (42, 43)

D-dimer levels are significantly increased in patients with cancer-associated stroke of undetermined etiology compared to patients with stroke of conventional etiology (6.15 [standard deviation {SD}: 8.5] vs. 1.39 [SD: 1.9] in units of μg/mL) (10, 15). Most patients with CES have increased levels of inflammatory factors and D-dimer, although this profile occurs in cancer in general and in other stroke etiopathogenetic mechanisms (e.g., cardioembolic).

Other potential biomarkers suggesting neoplasia as the etiology of stroke are C-reactive protein (CRP) and fibrinogen. CRP levels of >20 mg/L have a sensitivity of 75% and specificity of 96%, whereas fibrinogen levels of >600 mg/dl have a sensitivity of 67% and specificity of 91% for ischemic stroke associated with neoplasia. Data from patients with lung cancer indicate that D-dimer, CA125, CA199, and CRP are biomarkers associated with this type of neoplasia.

Other possible factors that could be biomarkers (Table 1):

Related to adenocarcinomas: The production of mucin, a high molecular weight molecule that is glycosylated and secreted normally by endothelial cells, causes hypercoagulability. Adenocarcinomas: The pancreas, colon, breast, lung, prostate, and ovarian systems secrete this molecule into the bloodstream.

TABLE 1 Possible factors that could be biomarkers.

| Factors |
|---|
| Tissue factors. |
| Hematogenous extracellular vesicles derived from cancer cells and platelets (24). |
| MicroRNAs contained in cancer cell-derived extracellular vesicles (82). |
| Neutrophil extracellular trap formation (NETosis) (26). |
| Circulating plasma DNA and nucleosome levels, purported markers of NETosis (26). |
| Abnormal platelet activity with increased aggregation. |
| Increased von Willebrand factor levels. |
| Several endothelial markers (thrombomodulin, soluble intercellular adhesion molecule-1, vascular cell adhesion molecule-1). |
| Tumor expression of fibrinolysis inhibitors and inflammatory cytokines. |
| Factors related to adenocarcinomas: production of mucin. |
| Study of the thrombus extracted using the endovascular treatment technique (44, 45). |

Analysis of the thrombus extracted using endovascular treatment can provide information about the etiological subtype. In a histopathological study, patients with active cancer had higher platelet counts and lower erythrocyte fractions ("white clots") than those with inactive cancer and no cancer (44). Immunohistochemical assessments may offer more precise information for the diagnosis of cancer-associated stroke, and this type of analysis has achieved high diagnostic accuracy in identifying cancer-associated stroke, with areas under the curve ranging from 0.946 to 0.986. It has been demonstrated that it could predict occult cancer with probabilities ranging from 88.5 to 99.2% (45).

## 5.2 Neuroimaging markers: magnetic resonance imaging (MRI) and diffusion-weighted imaging (DWI)

In 30–70% of CES-ONC cases, embolic lesions are detected in several arterial territories, with the three-territory sign on MRI DWI commonly observed— characterized by multiple emboli in both carotid territories and the vertebrobasilar territory (46–51).

### 5.2.1 Biomarkers associated with MRI and DWI

Elevated CRP and D-dimer levels are associated with the neuroimaging patterns of multiple lesions (46). D-dimer levels greater than 0.55 mg/L, along with the presence of cerebral infarcts in multiple locations, have a specificity and positive predictive value of 99.7 and 92.9%, respectively, for cancer-related CES-ONC. When neuroimaging findings were not included, D-dimer levels of ≥5.5 mg/L had a high specificity of 99.6%, although the sensitivity level dropped considerably to 31.9% (47). We suspect occult neoplasia in patients with CES when abnormally elevated D-dimer levels or a combination of elevated D-dimer and MRI findings are present (47, 52).

## 5.3 Practical conclusion for diagnosis

Increased D-dimer levels are useful as a biomarker for CES-ONC. Other possible candidates of biomarkers include CRP and fibrinogen levels; however, these require further confirmatory studies.

More specific tumor markers have not proven to be useful as CES-ONC biomarkers (43).

The best results in terms of specificity and positive predictive value were obtained by combining elevated D-dimer levels and the presence of cerebral infarcts in multiple locations.

An optimal diagnostic study protocol for ischemic stroke should be followed, and evidence of cryptogenic embolic cerebral infarction (etiology not clarified) may be obtained after a comprehensive evaluation.

The study and treatment of patients should be conducted using a protocol that includes a detailed clinical history collected in a semi-structured manner, a detailed neurological examination, and a standardized clinical evaluation. We recommend assessing the severity of the neurological deficit using the National Institutes of Health Stroke Scale and the Rankin Scale at admission and discharge or at

7 days and 90 days. In the first diagnostic approach, we recommend describing each of the etiological phenotypes of cerebral infarction, classified according to the ASCOD criteria (53, 54).

Routine analysis should include a complete blood count, urea, creatinine, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride subfractions, glucose, electrolytes, ultrasensitive CRP, and liver enzymes. A 12-lead electrocardiogram should be performed and repeated periodically if there is suspicion of arrhythmia. In addition, postero-anterior chest radiography, cranial CT, cranial MRI, and transthoracic echocardiogram should be conducted. Cardiac monitoring with automatic 24-h rhythm detection or a 24-h Holter electrocardiogram is also recommended. Imaging evaluation of the extracranial and intracranial arteries should include cerebral arteriography, MRI angiography, CT angiography, or duplex imaging of the supra-aortic and transcranial trunks. Angio-CT should also be conducted as an imaging test to assess the proximal aortic arch. A thrombophilia, immunological, and serology study (syphilis, Lyme disease, and human immunodeficiency virus) should be conducted if deemed necessary by the neurologists in charge of the patient. Special thrombophilia studies should be conducted only in patients with a personal or family history of disease or signs of unusual thrombosis.

There must be evidence that the etiopathogenetic mechanism of cerebral infarction is embolic in nature:

Lacunar infarction must be ruled out on control brain MRI (including DWI diffusion sequence) performed between day 2 and day 5.

Lacunar infarction is defined as a subcortical cerebral infarct with a diameter of less than 1.5 cm (≤2.0 cm on skull MRI using DWI sequences) within the territory of the perforating arteries.

A specific diagnostic study in a patient with suspected CES-ONC must be added to the previous one:

A standard investigation, such as plasma D-dimer analysis, is a diagnostic and prognostic marker in these patients (55). A reduction in D-dimer levels after the initiation of antithrombotic therapy is associated with a lower risk of recurrence (56).

If the patient's conditions are favorable, transesophageal echocardiography should be performed after transthoracic echocardiography as transesophageal echocardiography is useful for identifying certain cardioembolic mechanisms, including NBTE and aortic atheroma.

If a patent foramen ovale with a significant right-to-left shunt is identified, the following evaluation should be conducted: bilateral lower extremity venous ultrasound, upper extremity venous ultrasound if a central venous catheter is present, and CT of the chest to evaluate venous thromboembolism. Pelvic magnetic resonance venography may be useful (57). If venous thrombosis with paradoxical embolism is diagnosed, long-term anticoagulation therapy is recommended. In patients with stroke and cancer, venous thromboembolism occurs in approximately 10% of cases, and the majority of these patients exhibit elevated D-dimer levels. The diagnosis of venous thrombosis in this patient type is relevant for diagnosis, treatment, and prognosis (58).

Finally, as discussed previously, histopathological analysis with immunohistochemical assessments of the thrombus extracted using endovascular treatment can be useful for providing information on the etiological subtype (45).

# 6 Treatment

For CES-ONC, we must continue to monitor the patient's vascular risk factors—smoking, high blood pressure, diabetes mellitus, hyperlipidemia, atrial fibrillation, and carotid stenosis.

It is recommended to not overlook possible coincidental etiologies that are susceptible to treatments other than those targeting hypercoagulability; recent data suggest that treatment with statins for vasculopathy due to radiotherapy may reduce the risk of stroke.

In relation to chemotherapy, treatments with an anti-androgen effect, such as most treatments for breast cancer, increase the risk of ischemic stroke.

## 6.1 Treating acquired hypercoagulable state in CES-ONC

There is uncertainty about the best way to treat an acquired hypercoagulable state, particularly regarding the most appropriate choice of antithrombotic agent.

Low-molecular-weight heparin is commonly used empirically when a hypercoagulable state is suspected, but the benefit is unclear, especially in patients with a high bleeding tendency.

A situation specific to these patients is the need for anticoagulation to prevent atrial fibrillation cardioembolism, extrapolated from the subgroup analysis of large randomized clinical trials on anticoagulation, recommending the use of direct-acting anticoagulants (DOACs) instead of antivitamin K.

Several small studies have compared different antithrombotic treatments; however, randomized trials are required.

The TEACH, a pilot trial, compared enoxaparin and aspirin in 20 patients with cancer and found no difference in the recurrence of thromboembolic events or survival rates. There was a problem of enrollment failure in the TEACH owing to patient reluctance to receive injections, and 40% of patients who were randomized to enoxaparin switched to aspirin because of discomfort with injections. This highlights a clear preference for the oral route in this patient group (58). The results of the Trial of Apixaban Versus Aspirin in Cancer Patients With Cryptogenic Ischemic Stroke (TEACH2) are still pending.

The Edoxaban for the Treatment of Coagulopathy in Patients With Active Cancer and Acute Ischemic Stroke (ENCHASE) pilot study (59) found that edoxaban and enoxaparin were comparable with respect to biomarkers of hypercoagulability and cerebral thromboembolism. Larger trials are warranted to compare the effects of edoxaban and enoxaparin on recurrent stroke and major bleeding events in patients with cancer-related ESUS.

A subanalysis of the NAVIGATE study showed that patients with embolic stroke of unknown etiology and a history of cancer experienced similar rates of ischemic stroke recurrence and mortality when treated with aspirin and rivaroxaban, which offers a better safety profile than rivaroxaban in terms of major bleeding (60).

The American Society of Clinical Oncology supports the use of DOACs for the treatment of cancer-associated venous thromboembolism, but it is not the same entity as stroke, and this guideline cautions that there are limited data on the risks and benefits of anticoagulation beyond 6 months.

Several randomized trials have shown that oral factor Xa inhibitors are comparable to sc low-molecular-weight heparin in

terms of efficacy and safety for the prevention of venous thromboembolism and major bleeding in patients with cancer, making them a compelling option for the treatment of CES-ONC (61–63). Low-molecular-weight heparin agents are commonly used empirically when a hypercoagulable state is suspected, but the benefit is unclear, especially in patients with a high bleeding tendency. The studies we have conducted so far suggest that oral factor Xa inhibitors are comparable to sc low-molecular-weight heparin in terms of safety and efficacy in patients with cancer and a hypercoagulable state.

## 6.2 Treatment during the acute phase of stroke

### 6.2.1 Treatment with intravenous thrombolysis

Cancer should not be considered a contraindication in itself for thrombolysis with recombinant tissue plasminogen activator (rTPA), as there is no evidence to suggest that the risk of complications is higher in cancer patients with this treatment.

However, there are no data on the results of tenecteplase in this patient type.

### 6.2.2 Endovascular treatment

The thrombus formed due to the state of hypercoagulability secondary to cancer has specific characteristics because of its nature, being rich in platelets and poor in erythrocytes, which makes its extraction difficult. Therefore, in CES-ONC, thrombi retrieved during endovascular procedures tend to fragment easily.

Thromboembolic phenomena occur under conditions of high flow and hypercoagulability (64).

In the SECRET study, in which a group of patients with CES-ONC was compared to another group of patients with conventional stroke (without cancer or with inactive cancer), there was no significant difference between the groups in terms of the National Institutes of Health Stroke Scale score 24 h after treatment (median change in the score of 2.5 in the active cancer group vs. 3 in both the no cancer and non-active cancer groups, $p = 0.844$). In addition, 45.5% of patients with active cancer had a Rankin Scale score $\leq 3$ at 3 months (65). Two recent studies involving large populations have shown no significant differences in the probability of discharge and cerebral hemorrhage after endovascular treatment in patients with stroke and cancer with metastasis versus those without cancer, although there were significant differences in in-hospital mortality (66, 67). Some studies have shown that endovascular treatment improves the quality of life in these patients (68–70).

Thus, decision-making must be a shared process between the patient and their family, preferably involving a team that includes a neurologist and oncologist, to accurately assess the risk–benefit balance of the different therapeutic measures (68).

Patients with stroke and cancer should be considered candidates for thrombolysis (rTPA or tenecteplase) and endovascular treatment.

After a stroke, the oncologist may have reservations about administering chemotherapy, concerned that the patient may be too weak to tolerate the possible side effects or that chemotherapy treatment could trigger another stroke (71). In this situation, a joint assessment by neurology and oncology is essential to assess treatment objectives, functional status, and overall risks and benefits.

# 7 Prognosis

The frequency of stroke recurrence in patients with CES-ONC ranges from 14 to 34%, and conventional ischemic stroke recurs in 15.7% of patients (72). D-dimer levels have traditionally been evaluated as a useful prognostic factor in these patients. Reductions in D-dimer levels after the initiation of antithrombotic treatment are associated with a better prognosis, including a lower risk of recurrence and improved survival (24).

Patients with CES-ONC have a poorer prognosis, long-term functional status, and survival than patients with cryptogenic stroke without cancer (71, 73).CES-ONC is associated with a poorer prognosis upon discharge and a tendency for longer stays in the Stroke Unit (74). In addition, the presence of both venous and arterial thromboembolisms was independently associated with poorer 1-year survival (58).

If patients present with NBTE, they have a significantly higher mortality rate of 80% and a stroke recurrence rate of 50% over a follow-up period of 6 months (70, 73).

However, in recent years, significant advances have been made in the field of cancer treatment. This has increased the survival and quality of life of many patients (74, 75). In the near future, genetic factors are expected to refine our prognosis. The driver gene KRAS aggravates cancer-associated stroke outcomes (76).

# 8 Discussion

To improve the management of these patients, we must maintain a high suspicion that the etiopathogenetic mechanisms described are present in patients in whom cancer and cryptogenic embolic ischemic stroke coexist.

The clinical presentation can be focal or multifocal, with elevated D-dimer levels. It is typical to find multifocal lesions in neuroimaging tests with the "three part sign."

The management of acute stroke does not differ between patients with and without cancer; the presence of neoplastic disease should not be considered an absolute contraindication for treatment with intravenous thrombolysis or endovascular treatment.

These patients tend to have a poorer prognosis when NBTE occurs, often indicating the presence of tumor-induced platelet aggregation and metastasis (70).

The complexity of treatment arises from the fact that there are several possible mechanisms that determine the relationship between stroke and cancer; therefore, not all patients respond optimally to anticoagulation.

Low-molecular-weight heparin is usually used empirically when a hypercoagulable state is suspected, and the limited studies available support the use of direct oral anticoagulants as an option with similar efficacy. However, ongoing clinical trials are needed before evidence-based recommendations can be made.

On the other hand, in this condition, both platelets and the coagulation cascade are activated, and a two-way antithrombotic treatment strategy (a combination of antiplatelet agents and anticoagulants) could be a more comprehensive approach for this patient population (77, 78).

To accurately assess the risk–benefit balance, we must consider that this population also has an increased risk of hemorrhage.

For embolic cryptogenic ischemic stroke with occult neoplasia, the best screening strategy is unclear and we do not have adequate biomarkers. A current challenge in the field of cerebrovascular disease is to obtain a biomarker with high sensitivity and specificity for occult neoplasia in stroke. In this sense, the detection of microvesicles released by cancer cells with a specific RNA content has the characteristics of an ideal biomarker, as it is one of the main pathways of hypercoagulability that occurs in this condition and causes embolic stroke.

We must advance our ability to precisely define CES-ONC (79).

This includes identifying the presence of predictive factors for occult neoplasia, such as clinical factors (age, risk factors, and severity) and biomarkers (CRP, D-dimer), as well as neuroimaging findings (RNMC DWI: "three parts") (80).

Regarding the impact of occult neoplasia on stroke, we can make an approximation based on data concerning its prevalence.

The percentage of patients with embolic stroke of undetermined origin (cryptogenic) was 13.5%, of which 2.8% had occult neoplasia.

The annual incidence of stroke is 187 per 100,000 inhabitants. The percentage of patients with occult neoplasia and embolic cryptogenic ischemic stroke among all strokes was 0.4%. Therefore, the incidence of stroke and occult neoplasia should be approximately three patients per year in a healthy area of 400,00 inhabitants.

A scale used to assess the risk of occult neoplasia in patients with cryptogenic embolic stroke is the OCCULT-5 score, which includes the following criteria: age $\geq$ 77 years, embolic stroke of undetermined source, multi-territorial infarcts, D-dimer levels $\geq$ 820 μg/L, and female sex. A score of $\geq$ 3 predicts occult neoplasia with a sensitivity of 64%, a specificity of 73%, a positive likelihood ratio of 2.35, and a negative likelihood ratio of 0.50 (81).

Having a biomarker with high sensitivity and specificity would enable the early diagnosis of cancer in this subgroup of patients, potentially improving survival outcomes due to the well-established benefits of early detection.

Stroke is a complication that must be considered in patients with cancer. Its diagnostic and therapeutic management have complexities that doctors who treat these patients must recognize to ensure appropriate and effective care.

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JC-R: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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# An efficient approach for detecting atrial fibrillation in ischemic stroke patients using a wearable device: a prospective multicenter substudy of the STABLED trial

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**Objective:** Stroke caused by atrial fibrillation (AF) is associated with high mortality and severe morbidity. Screening patients for AF may facilitate early initiation of anticoagulant therapy and prevent recurrent stroke; therefore, strategies to effectively detect AF in stroke patients are important.

**Methods:** This prospective multicenter study was conducted between April 27, 2020 and March 31, 2021 at seven sites in Japan, as a substudy of the STABLED trial, a multicenter prospective randomized study to evaluate the efficacy and safety of catheter ablation with anticoagulant therapy using edoxaban in patients with ischemic stroke and AF. This substudy included 241 patients who suffered ischemic stroke but had no diagnosis of AF. Patients were monitored with Duranta, a wearable non-invasive wireless patch ECG system. The primary outcome was the detection rate for AF while wearing Duranta.

**Results:** Of the 241 patients, 66.8% were men, and the mean age was 71.0 years. AF was detected in 21 of the 241 patients (8.7, 95% CI: 5.4–12.4) during follow-up using the Duranta wearable ECG system. ECG data were recorded for 7 days in all patients. The median number of days from stroke onset to Duranta placement was 2.0, but this duration varied considerably (median; IQR, 0–22.0). An adverse event of dermal pruritus was observed in 1 of the 241 patients (0.4%). Determinants for the detection of AF in patients with no previous history of AF were dyslipidemia and left atrial dimension.

**Conclusion:** Wearable wireless patch ECG systems such as Duranta are simple and efficient devices for detecting AF. In patients with ischemic stroke and no

diagnosis of AF, their use for detecting new AF may provide benefit through early initiation of anticoagulants and prevention of recurrent stroke.

KEYWORDS

atrial fibrillation, ischemic stroke, wearable device, multicenter study, prospective study

# 1 Introduction

Stroke is the fourth leading cause of death and long-term disability in Japan (1). Cardiogenic embolic stroke is mainly caused by atrial fibrillation (AF), which is a primary risk factor for ischemic stroke (2). AF-associated stroke is often severe, and is associated with high mortality and severe morbidity. In addition, because the risk of recurrent cardiogenic embolic stroke caused by AF can be significantly reduced by anticoagulants (3, 4), the detection of AF in patients with acute ischemic stroke is important. However, AF is often absent on admission, as well as being paroxysmal or asymptomatic, making it difficult to detect with symptom-driven monitoring strategies. Therefore, several methods have been used to detect AF. Standard methods include 12-lead electrocardiography (ECG), Holter ECG, and long-term monitoring. However, because AF often still goes undetected, subcutaneous electrocardiographs are sometimes implanted in the patient's chest, but these subcutaneous implantable devices are invasive, and there is a high demand for non-invasive methods that perform better in the detection of AF than the Holter-type ambulatory ECG. Currently, non-invasive devices, such as the ZIO patch (5), mobiCARE-MC100 TM (6), and AliveCor device (7), can effectively detect AF, although their use is not widespread. In addition, there are a number of non-regulatory consumer-based healthcare products that are capable of detecting AF, such as the Apple Watch series, although these are not certified for medical use, and their accuracy is insufficiently documented (8).

The STroke secondary prevention with catheter ABLation and EDoxaban (STABLED) trial in patients with non-valvular AF is a multicenter prospective randomized ongoing clinical trial to evaluate the efficacy and safety of catheter ablation with anticoagulant therapy using edoxaban in patients with AF and a history of recent ischemic stroke (9). In this substudy to the clinical trial, we took advantage of the data recorded from a particular cohort of patients who had recently suffered ischemic stroke (within 6 months) but had no history of non-valvular AF, and who were monitored for 7 days post-stroke using a relatively new device called Duranta, which is an iPhone-based single-lead electrocardiographic capture system (ZAIKEN, Co. Ltd., Tokyo, Japan). ECG data captured by the system are automatically transmitted to a cloud server via a dedicated iPhone. Duranta is non-invasive and can be easily attached and removed during hospitalization. The primary aim of this study was to evaluate the potential of a wearable ECG device for detecting AF in patients who had recently suffered ischemic stroke, and not to make direct comparisons between different devices.

In this companion study, we evaluated the detection rate of AF during hospitalization and the number of days when AF was most frequently detected by the Duranta system in the STABLED candidate stroke patients without a diagnosis of AF. Moreover, we made further analyses comparing clinical factors in the group in which AF was detected with those in the non-detection group.

# 2 Materials and methods

## 2.1 Study design

This multicenter prospective study was conducted between April 27, 2020 and March 31, 2021 at seven sites in Japan. A list of all participating institutions and their investigators is provided in Supplementary Table S1.

The protocol was approved by the Nippon Medical School Certified Clinical Research Review Board (approval no. CRB3180001) and prospectively registered with the Japan Registry of Clinical Trials (registration no. jRCT s032200054; https://jrct.niph.go.jp/latest-detail/jRCTs032200054). The study was conducted in accordance with the Declaration of Helsinki and the Clinical Trials Act in Japan. All study participants provided written informed consent before enrollment. The study design is summarized in Figure 1.

## 2.2 Study participants

The eligible patients were candidates for the STABLED trial. The study patients were required to satisfy all of the defined inclusion criteria and none of the exclusion criteria. Briefly, the inclusion criteria were: (1) age ≥20 and ≤85 years at the time of informed consent, (2) no history of non-valvular AF, (3) history of ischemic stroke in the previous 6 months, and (4) a modified Rankin Scale ≤3 or expected to improve to ≤3 with treatment. The major exclusion criteria were: (1) severe renal impairment (creatinine clearance rate <30 mL/min), (2) markedly reduced cardiac function (ejection fraction <35%), (3) atrial septal defect, (4) being unlikely to complete the study because of progressive malignancy, (5) participation or planning to participate in another interventional clinical trial, and (6) otherwise judged as not being suitable for the study by the investigators.

## 2.3 Duranta: single-lead ECG monitor

The Duranta wireless non-invasive patch ECG monitoring system (Medical Device Certificate Number 226AIBZX00055000) is a small and lightweight device (78.4 mm wide × 35.1 mm deep × 14.7 mm thick, 35 g) with two patch electrodes; the device is placed in a precordial position (Figure 2A). The battery lasts for up to 7 consecutive days without recharging. ECG data are automatically transmitted to a cloud server via a dedicated iPhone (Figure 2B).

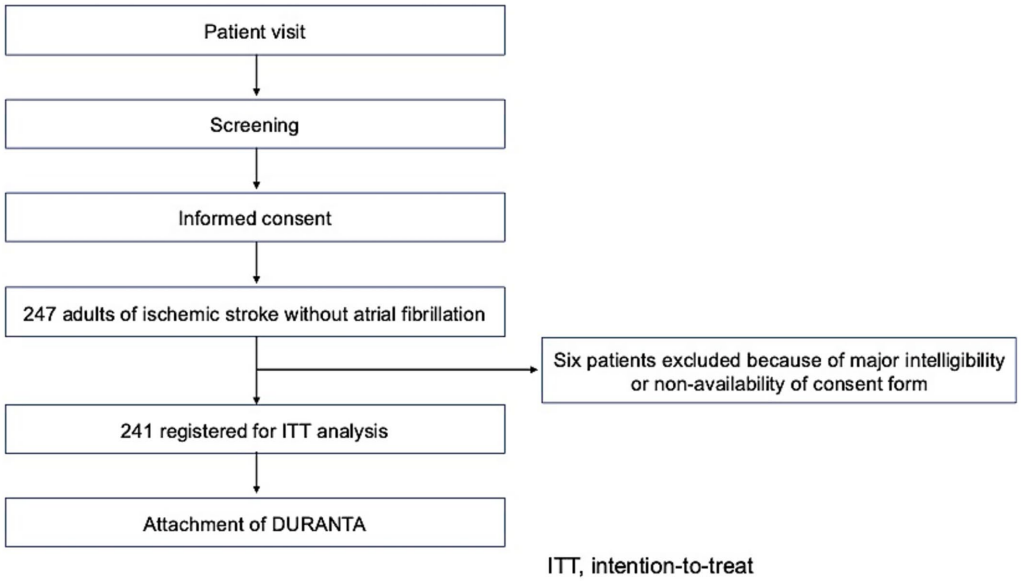


FIGURE 1
Flow chart of patient enrollment and screening.

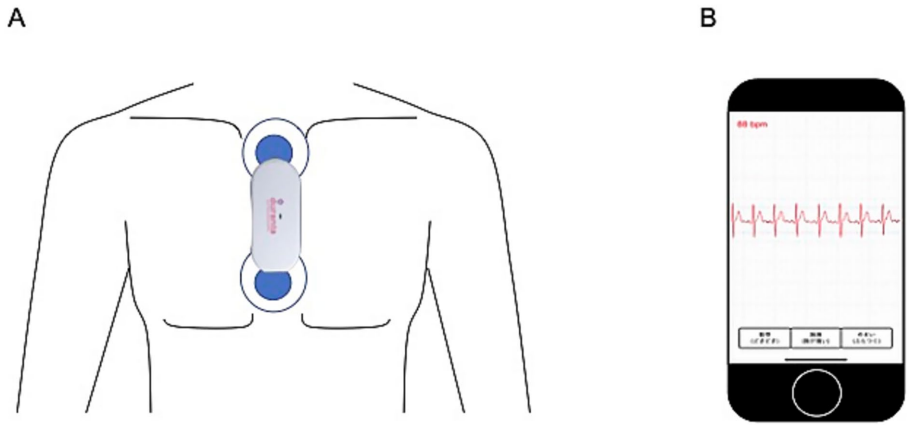


FIGURE 2
The Duranta wireless patch-type electrocardiographic monitoring system. The monitor is placed in a precordial position with a pair of electrode patches **(A)**. Recorded waveform data are sent to a bedside iPhone **(B)** via Bluetooth and then to a cloud server. Real-time ECG data can be checked on the iPhone. Physicians or medical staff can access the data on cloud server from PCs in the hospital for real-time observation.

Medical staff can access the cloud server with a personal ID and password, view the patient's ECG in real time on an iPad, and download the ECG data to a computer in the hospital. For this study, ECG recording was started immediately after the main switch was turned on, and the recorded waveform data were sent to a nearby iPhone via Bluetooth, and then further relayed to a cloud server via a 3G/4G/LTE/Wi-Fi network. The patients' personal information was not entered into the ECG devices, and there was therefore no risk of personal data leakage during the data delivery from the ECG devices.

## 2.4 Data collection

The following clinical information was obtained from the study data set: age, sex, ethnicity, body mass index, hypertension, dyslipidemia, diabetes, chronic kidney disease, congestive heart failure, and history of stroke or transient ischemic attack. In addition, current smoking, dementia, drinking habits, malignancy (active), modified Rankin Scale score, and National Institutes of Health Stroke Scale (NIHSS) score at baseline were assessed. The cardiothoracic ratio and brain natriuretic peptide (BNP) or N terminal (NT)-proBNP were also measured. Elevated BNP and NT-proBNP levels were defined as BNP > 100 pg./mL and NT-proBNP > 400 pg./mL (10). Transthoracic echocardiography measurements were performed at baseline by sonographers at each medical institution. The left ventricular ejection fraction and left atrial dimension (LAD) were evaluated. This study included patients with symptomatic ischemic stroke identified on magnetic resonance imaging (MRI) and diagnosed by Japanese stroke specialists. Diagnoses of hypertension, dyslipidemia, diabetes, renal dysfunction, and congestive heart failure

were made by the responsible physicians at each site based on the results of medications, blood tests, and chest X-rays.

## 2.5 Outcomes

The primary outcome was the AF detection rate while wearing Duranta. Exploratory outcomes included the number of days from Duranta placement to AF detection, number of days from stroke onset to AF detection, AF duration time, number of days from stroke onset to Duranta placement, number of AF events detected during Duranta placement, and duration of Duranta placement. Safety outcomes included any adverse events due to Duranta placement.

## 2.6 Statistical analyses

Continuous variables are expressed as median (interquartile range [IQR]), or number (%). Categorical data are expressed as the number of subjects (%). For comparisons of baseline characteristics, clinical characteristics, and examination-related factors between patients in whom Duranta detected AF and those in whom it did not, the chi-squared ($\chi^2$) test was used for categorical variables, and the Mann–Whitney test was used for continuous variables. Univariate analysis and multivariate logistic regression analysis were performed to identify factors (demographics, comorbidities, laboratory findings, physical examinations, age, and sex) associated with the detection of AF, with variables demonstrating $p < 0.05$ in the univariable test being entered into the multivariate logistic regression. Statistical significance was set at $p < 0.05$. All analyses were performed with SPSS version 27.0 (IBM, Armonk, NY), while the 95% confidence intervals for AF detection rates were calculated using Stata version 17 (StataCorp LLC, College Station, TX).

# 3 Results

## 3.1 Baseline characteristics of the patients

A total of 241 patients were enrolled in this study (161 men, 80 women). The median patient age was 71.0 years (IQR: 62.5–78.0) for all patients, 71.0 years (IQR: 62.0–78.0) for patients without AF (AF−), and 73.0 years (IQR: 67.0–79.0) for patients with AF (AF+). The clinical characteristics of the patients are summarized in Table 1. Dyslipidemia (AF−: 120 patients [54.5%], AF+: 17 patients, [81.0%], $p = 0.02$), cardiothoracic ratio (AF−: 51.0 [IQR 46.9–55.9], AF+: 56.0 [IQR 52.2–57.0], $p = 0.003$), and LAD (AF−: 34.1 [IQR 31.0–39.0], AF+: 36.1 [IQR 33.8–44.5.], $p = 0.032$) were significantly different between the groups (Table 1).

## 3.2 Primary and exploratory outcomes

AF, the primary outcome for this study, was detected in 21 of the 241 patients (8.7, 95% CI: 5.4–12.4) during follow-up using Duranta. The median number of days from Duranta placement to first AF detection was 2.0 (IQR: 1.0–3.5), the median AF duration time was 59 min (IQR: 7.5–397.5), the median number of AF detections in the AF + group was 2.0 (IQR: 1.0–3.5), the median number of days from stroke onset to AF detection was 4.0 (IQR: 3.0–6.0), and the duration of Duranta placement was 7 days in all patients (Table 2).

## 3.3 Adverse events

An adverse event occurred in only 1 (0.4%) of the 241 patients during Duranta placement. This was a case of dermal pruritus.

## 3.4 Time from stroke onset to Duranta placement in 21 patients with AF detected

Patients could be enrolled up to 6 months after stroke onset, and therefore Duranta was not always placed promptly after admission. Among the 21 patients in whom AF was detected, the median number of days from stroke onset to Duranta placement was 2.0 (IQR: 1.0–22.0), with 41.9% being equipped with Duranta 1 day after stroke onset, 47.6% between 2 and 4 days after stroke onset, and 9.5% 5 days or more after stroke onset (Figure 3).

## 3.5 Probability of new AF within the duration of Duranta placement

According to the Kaplan–Meier curve, the cumulative incidence rates for detection of AF were 0.029, 0.067, 0.084, and 0.88 at days 1, 3, 5, and 7 of Duranta placement, respectively (Figure 4).

## 3.6 Determinants of AF detection with Duranta

In the univariable analysis, dyslipidemia, NIHSS score at admission, cardiothoracic ratio, and LAD were identified as determinants of AF detection using Duranta. In the multivariable analysis, we adjusted for multiple potential confounders such as age, sex, dyslipidemia, NIHSS score at admission, cardiothoracic ratio, and LAD, and only dyslipidemia (adjusted odds ratio [aOR]: 3.92, 95% CI: 1.17–13.13, $p = 0.027$) and LAD (aOR: 1.10, 95% CI: 1.01–1.20, $p = 0.029$) were significantly associated with AF detection by Duranta (Table 3).

# 4 Discussion

This prospective multicenter study of patients with ischemic stroke in Japan investigated the detection of new atrial fibrillation with a non-invasive device, an iPhone-based single-lead electrocardiographic capture system.

When a patient with AF has a stroke, it is often severe (2) and the recurrence rate is high (11, 12), although anticoagulants are highly effective in preventing recurrence (3, 4). Therefore, when a patient without a history of AF has a stroke, tests to detect AF are routinely performed, usually ECG and Holter ECG (13). Compared with 24-h ECG recordings, 7-day Holter ECG recordings were shown to have better detection of AF (14, 15). Although implantable ECGs have been shown to provide a high level of evidence for the detection of AF after

TABLE 1 Baseline characteristics of the study subjects ($n$ = 241).

| | ALL | AF (–) | AF (+) | $p$ value |
|---|---|---|---|---|
| Subjects, *n* | 241 | 220 | 21 | |
| Age, median (IQR), years | 71.0 (62.5–78.0) | 71.0 (62.0–78.0) | 73.0 (67.0–79.0) | 0.114 |
| Sex | | | | |
| Male, *n* (%) | 161 (66.8) | 150 (68.2) | 11 (52.4) | 0.152 |
| Body-mass index, median (IQR), kg/m2 | 23.0 (21.0–25.5) | 23.0 (21.0–25.4) | 23.8 (22.1–27.0) | 0.126 |
| Comorbidities, *n* (%) | 241 | 220 | 21 | |
| Hypertension | 167 (69.3) | 153 (69.5) | 14 (66.7) | 0.786 |
| Diabetes | 63 (26.1) | 56 (25.5) | 7 (33.3) | 0.443 |
| Dyslipidemia | 137 (56.8) | 120 (54.5) | 17 (81.0) | 0.015 |
| Chronic kidney disease | 6 (2.5) | 5 (2.3) | 1 (4.8) | 0.425 |
| Congestive heart failure | 3 (1.2) | 3 (1.4) | 0 (0) | 1.000 |
| Previous stroke/TIA | 50 (20.8) | 46 (20.9) | 4 (19.0) | 0.839 |
| Malignant tumor | 9 (3.7) | 8 (3.6) | 1 (4.8) | 0.802 |
| Current smoker | 59 (24.5) | 55 (25.0) | 4 (19.0) | 0.577 |
| Drinking habit | 63 (26.1) | 58 (26.4) | 5 (23.8) | 0.797 |
| Clinical scores and labs, *n* | 241 | 220 | 21 | |
| mRS score at admission | 1 (1–3) | 1 (1–3) | 1.5 (1.0–3.0) | 0.867 |
| NIHSS score at admission | 2 (1–4) | 2 (1–4) | 3 (1–13) | 0.245 |
| CTR (%) | 51.5 (47.0–56.0) | 51.0 (47.0–55.8) | 56.0 (52.3–57.0) | 0.003 |
| LVEF (%) | 65.7 (61.0–71.0) | 66.0 (61.0–71.0) | 64.0 (61.6–68.0) | 0.649 |
| LAD (mm) | 34.8 (31.0–39.0) | 34.1 (31.0–39.0) | 36.1 (34.0–44.0) | 0.032 |
| BNP or NT-proBNP elevated | 40 (16.6) | 36 (16.4) | 4 (19.0) | 0.756 |
| Acute revascularization, *n* (%) | | | | |
| tPA | 26 (10.8) | 22 (10.0) | 4 (19.0) | 0.238 |
| MT | 31 (12.9) | 26 (11.8) | 5 (23.8) | 0.149 |
| Stroke etiology, *n* (%) | | | | |
| Small vessel disease | 57 (23.7) | 52 (23.6) | 5 (23.8) | 0.881 |
| Large-artery atherosclerosis | 31 (12.9) | 29 (13.2) | 2 (9.5) | |
| Others | 153 (63.5) | 139 (63.2) | 14 (66.7) | |

AF, atrial fibrillation; BNP, brain natriuretic peptide; CTR, cardiothoracic ratio; IQR, interquartile range; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; MT, mechanical thrombectomy; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; NT, N-terminal; tPA, tissue plasminogen activator; TIA, transient ischemic attack.

thorough evaluation (16, 17), insertable cardiac monitors are invasive to the patient and can cause adverse events, and early implantation after the onset of stroke is generally not performed. In addition, early rhythm control for AF improves the primary clinical outcome (18). Given the high rate of recurrent strokes in patients with AF, if a patient without a history of AF has a stroke and is subsequently found to have AF, prompt administration of anticoagulation to reduce the risk of recurrence and early intervention for rhythm control of AF are required. These require heart rate monitoring that is as simple and safe as possible for several days or longer, starting as early as possible after stroke onset.

This study enrolled patients without a known history of AF and without AF on the admission 12-lead ECG. If AF was observed on the admission ECG, the patient would have been diagnosed with cardioembolic stroke and excluded. Therefore, the study included patients with lacunar infarction, as well as those with cryptogenic stroke and embolic stroke of undetermined source (ESUS); however, at the time of admission, testing to determine the stroke etiology (e.g., transthoracic echocardiography, Holter ECG, transesophageal echocardiography, lower limb venous ultrasound, cerebral angiography, contrast-enhanced CT) was incomplete, so a definitive diagnosis of cryptogenic stroke or ESUS could not be made at that point. We can therefore only describe the patients as "ischemic stroke cases without AF on admission ECG." We believe the population likely includes cases that would eventually receive a diagnosis of cryptogenic stroke or ESUS after further testing.

According to the European Society of Cardiology 2020 guidelines (19), single-lead ECG recording using a wearable device can be used to confirm the diagnosis of AF (recommendation: Ia). In addition, a recent systematic review and meta-analysis suggests that non-invasive rhythm monitoring strategies should precede invasive monitoring (20). Detection of AF with wearable electrocardiographs, including patch ECG devices and wristwatch health products, has been reported. Studies such as the Apple Heart Study (21) and SCREEN-AF

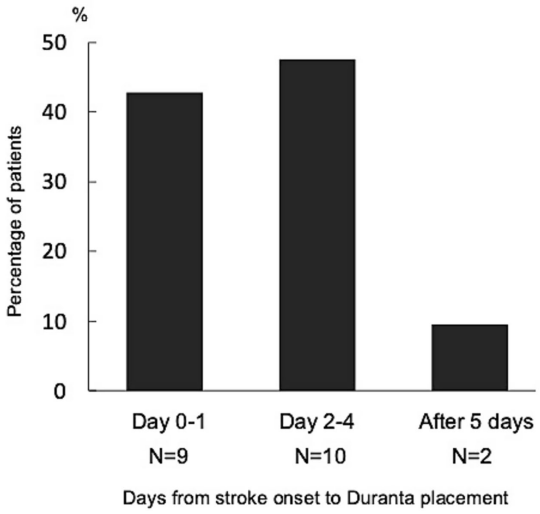


FIGURE 3
Time from stroke onset to Duranta was placed within 1 day after stroke onset in 9 patients (42.9%) of 21 patients with AF detected, between 2 and 4 days after stroke onset in 10 patients (47.6%), and 5 days or more after stroke onset in 2 patients (9.5%).

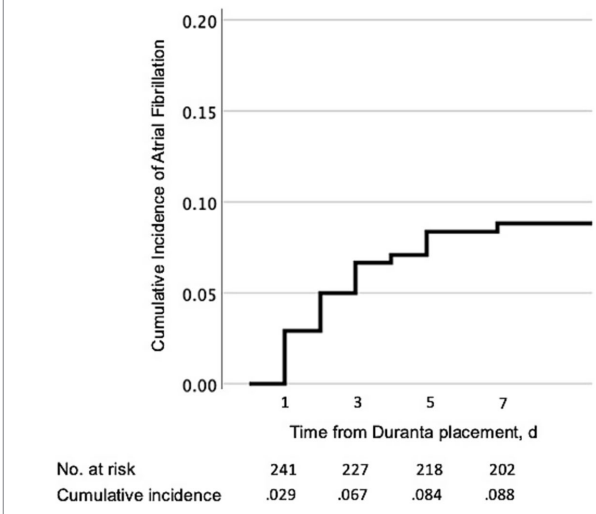


FIGURE 4
Kaplan–Meier curve for the cumulative incidence of detection of new atrial fibrillation with Duranta. The cumulative incidence rates at days 3 and 7 were 0.067 and 0.088, respectively. Most cases were detected within 3 days.

TABLE 2 Primary and exploratory outcomes.

| | |
|---|---|
| **Primary outcomes** | |
| Detection rate of AF while wearing Duranta, *n*, (%) | 21 (8.7, 5.4–12.4) |
| **Exploratory outcomes** | |
| Number of days from stroke onset to Duranta placement, median (IQR) | 2.0 (0–22.0) |
| Number of days of Duranta placement, median (IQR) | 7.0 (7.0–7.0) |
| Number of days from Duranta placement to first AF detection, median (IQR) | 2.0 (1.0–3.5) |
| Number of days from stroke onset to AF detection, median (IQR) | 4.0 (3.0–6.0) |
| AF duration time, median (IQR), minutes | 59 (7.5–397.5) |
| Number of AF events detected, median (IQR) | 2.0 (1.0–3.5) |

AF, atrial fibrillation; IQR, interquartile range.

(SCREENing for Atrial Fibrillation) (22) using a single-lead ECG have recently demonstrated the feasibility and effectiveness of single-lead ECG recorders for detecting AF after stroke. However, the results of these studies were based on data from the general population and were not specific to patients with ischemic stroke or transient ischemic attack (23). Wristwatch devices are simple and have the potential to screen many asymptomatic and symptomatic patients; however, these devices use a photoplethysmograph sensor to detect atrial fibrillation when checking heartbeats in the background (24), and they demonstrate variable sensitivity and specificity and do not have acceptable accuracy compared with prescribed ECG devices. In comparison, a patch ECG device usually uses a single channel of bipolar induction over the heart to record the ECG.

In this study, we used Duranta, a patch-type wireless real-time ECG monitor that is easy to attach to the patient. Duranta is iPhone-based, and one of the features of this system is that it is very easy to attach and remove if the patient has to go for other examinations such as CT, MRI, or echography, as well as to use the restroom or take a bath during their hospital stay.

The AF detection rate of the Duranta system was 8.7%, which is higher than the 4–5% (22, 25) reported in screening studies and the 5–7% (5, 26) in studies with a population of stroke patients. Furthermore, it is higher than the AF detection rate of 6.8% in a study using 7-day Holter monitoring in patients who suffered a recent embolic stroke of undetermined source (26). However, the data used in this study came from a subset of patients recruited to the STABLED trial who underwent monitoring with the Duranta system, and within the scope of this study, it is not possible to accurately compare the performance of the Duranta system in comparison with similar systems; other similar single-lead and patch portable ECG systems would likely provide similar results, with the evidence suggesting that the Duranta system is at least on a par with similar systems.

In this study, LAD and dyslipidemia were found to be associated with detection of AF after adjusting for confounding factors. Left atrial enlargement is well known to be an inducer of AF (27); the larger the left atrial size, the greater the risk of developing AF (28). Recently, prespecified analysis of the STROKE AF randomized clinical trials found that only congestive heart failure and left atrial enlargement were significant predictors of AF (29). Another study reported that not only left atrial enlargement, but also the left atrial volume index (LAVI), calculated by dividing the left atrial volume by the body surface area, was higher in an AF + group than in an AF− group (30). Unfortunately, because this was a multicenter registry study, echocardiography was not performed for all patients and LAVI was thus excluded from the statistical analysis. Therefore, LAD was used as a valuable clinical predictor for the detection of AF.

The finding of the association between dyslipidemia and AF appears to be complex and paradoxical. In a previous study, higher total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C)

TABLE 3 Determinants of atrial fibrillation detection with DURANTA.

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| | OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| Age | 1.04 (0.99–1.09) | 0.114 | 1.04 (0.96–1.07) | 0.604 |
| Sex | | | | |
| Female | Ref | | | |
| Male | 0.51 (0.21–1.27) | 0.147 | 0.72 (0.25–2.10) | 0.557 |
| Body-mass index | 1.12 (0.99–1.26) | 0.066 | | |
| Comorbidities | | | | |
| Hypertension | 0.88 (0.34–2.27) | 0.785 | | |
| Diabetes | 1.46 (0.56–3.81) | 0.435 | | |
| Dyslipidemia | 3.54 (1.15–10.87) | 0.027 | 3.92 (1.17–13.13) | 0.027 |
| Chronic kidney disease | 2.15 (0.24–19.31) | 0.494 | | |
| Congestive heart failure | NA* | | | |
| Previous stroke/TIA | 0.89 (0.29–2.77) | 0.841 | | |
| Malignant tumor | 1.33 (0.16–11.14) | 0.796 | | |
| Current smoker | 0.76 (0.42–1.35) | 0.348 | | |
| Drinking habit | 0.87 (0.31–2.49) | 0.799 | | |
| Clinical scores and laboratory analyses | | | | |
| mRS score at admission | 1.06 (0.74–1.51) | 0.763 | | |
| NIHSS score at admission | 1.06 (1.01–1.12) | 0.030 | 1.05 (0.99–1.12) | 0.107 |
| CTR | 1.11 (1.03–1.20) | 0.006 | 1.07 (0.97–1.18) | 0.173 |
| LVEF | 1.00 (0.95–1.06) | 0.969 | | |
| LAD | 1.11 (1.02–1.20) | 0.014 | 1.10 (1.01–1.20) | 0.029 |
| BNP or NT-proBNP elevated | 1.20 (0.38–3.78) | 0.752 | | |
| Acute revascularization | | | | |
| tPA | 2.12 (0.65–6.86) | 0.211 | | |
| MT | 2.33 (0.79–6.90) | 0.126 | | |

*Not used as an explanatory variable because neither outcome was observed.
Variables of age, sex, and those showing $p < 0.05$ in the univariable analysis were included in the final multivariable model. BNP, brain natriuretic peptide; CTR, cardiothoracic ratio; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; MT, mechanical thrombectomy; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; NT, N-terminal; OR, odds ratio; tPA, tissue plasminogen activator; TIA, transient ischemic attack.

levels were inversely associated with the incidence of AF over a mean follow-up period of 7.12 years (31). Low high-density lipoprotein (HDL) cholesterol was associated with an increased risk of new-onset AF in women, but not in men (32). Low HDL-C levels and high triglyceride (TG) levels, which are markers of metabolic syndrome, are associated with a higher risk of AF (33, 34). Reports of dyslipidemia and AF remain inconclusive, although low HDL-C and high TG levels may be associated with AF because metabolic syndrome is reported to be associated with the risk for AF (35). However, as dyslipidemia was diagnosed by the physicians in this study, it is unclear which lipid fraction was abnormal.

This study has some potential limitations. First, we cannot generalize our findings to non-hospitalized patients because our study included only in-hospital patients with ischemic stroke. Second, this study was conducted only at Japanese sites, and therefore, it is unclear whether the results can be extrapolated to patients from other countries. Third, the number of participants included in the current epidemiological study was small, which may have affected our findings through a lack of statistical power. Fourth, the enrolled patients without a known history of AF and without AF on the admission 12-lead ECG included patients with lacunar infarction, as well as those with cryptogenic stroke and ESUS; however, at the time of admission, testing to determine the stroke etiology was incomplete, so a definitive diagnosis of cryptogenic stroke or ESUS could not be made at that point. Finally, for hypertension, dyslipidemia, diabetes, chronic kidney disease, and medical history, the presence or absence of comorbidities was recorded according to the physician in charge, and therefore information on oral medications and laboratory values was not available.

## 5 Conclusion

In this prospective multicenter study performed in Japan, we found that a non-invasive wireless patch ECG system, the iPhone-based single-lead electrocardiographic capture system Duranta, found AF in 21 out of 241 ischemic stroke patients without a previous history of AF. The median time from Duranta placement

to first AF detection was 2 days. Determinants for AF detection in patients without a history of AF were dyslipidemia and LAD. In ischemic stroke patients with undiagnosed AF, the use of wireless patch ECG systems for detecting new AF may provide benefit in the form of early initiation of anticoagulant administration and prevention of recurrent stroke.

## Data availability statement

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

## Ethics statement

The studies involving humans were approved by the Institutional Review Board of Nippon Medical School (Approval number: CRB3180001). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

TS: Conceptualization, Data curation, Investigation, Methodology, Project administration, Validation, Writing – original draft. YN: Conceptualization, Formal analysis, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing. TO: Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. YS: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Validation, Writing – review & editing. SO: Data curation, Methodology, Project administration, Validation, Writing – review & editing. YI: Data curation, Methodology, Project administration, Validation, Writing – review & editing. KY: Data curation, Investigation, Methodology, Project administration, Writing – review & editing. YO: Data curation, Project administration, Validation, Writing – review & editing. HH: Data curation, Methodology, Validation, Writing – review & editing. TY: Data curation, Methodology, Validation, Writing – review & editing. MF: Conceptualization, Investigation, Supervision, Validation, Writing – review & editing. AT: Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Validation, Writing – review & editing. TK: Data curation, Funding acquisition, Validation, Writing – review & editing. KK: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

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## Conflict of interest

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## Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2025.1560495/full#supplementary-material

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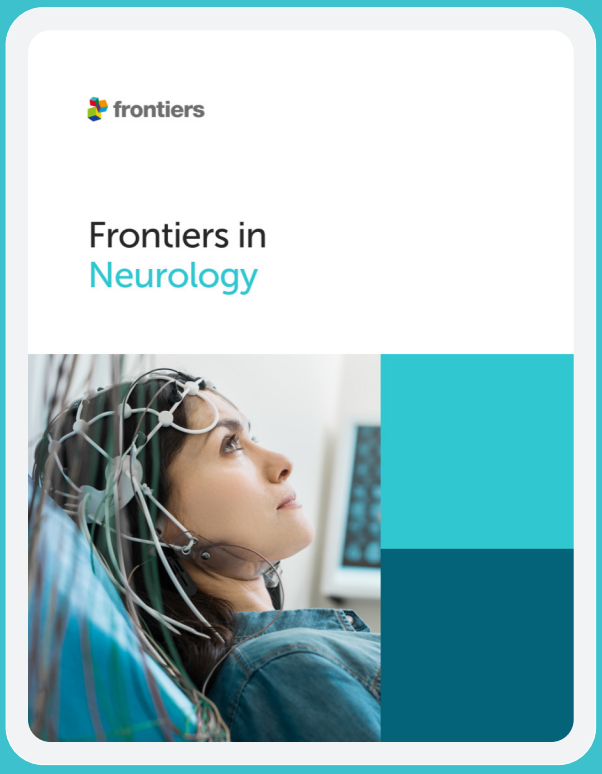


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