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Practice patterns of vascular neurologists in timing anticoagulation for high risk stroke mechanisms versus atrial fibrillation

Farhan Khan[1,3]✉, Vivien Lu[2], Shadi Yaghi[1] & Shyam Prabhakaran[2]

The optimal timing for initiating anticoagulation following an ischemic stroke remains a debated issue. While several professional societies offer guidelines derived from observational studies and randomized clinical trials in patients with atrial fibrillation, these studies often exclude patients with high-risk embolic sources and hemorrhagic transformation. To address this gap, we conducted a nationwide survey to determine current practice patterns among vascular neurologists. We used the REDCap platform at the University of Chicago to distribute a survey to board-certified vascular neurologists identified through the American Board of Psychiatry and Neurology and the American Academy of Neurology databases. Statistical analyses, including t-tests, chi-squared tests, Mann-Whitney-Wilcoxon tests, and Kruskal-Wallis tests, were performed to evaluate continuous and categorical variables as applicable. Out of 1,556 invited participants, 201 (approximately 13%) responded, with 62% identifying as academic neurologists. Early anticoagulation is defined as within 24 h for ischemic stroke < 1.5 cm, 5 days for one third of MCA territory with hemorrhagic transformation type 1, and 7 days with parenchymal hemorrhage type 2. When compared to atrial fibrillation, vascular neurologists are more likely to initiate early anticoagulation in ischemic stroke with hemorrhagic transformation type 1 when it is caused by LV thrombus (69% vs. 21%, $p < 0.001$), antiphospholipid syndrome (87% v 21%, $p < 0.001$), and non-occlusive thrombus (83% vs. 21%, $p < 0.001$). A similar trend of early anticoagulation was noted in cases of ischemic stroke with parenchymal hemorrhage type 2 caused by LV thrombus (63% vs. 13%, $p < 0.001$), antiphospholipid syndrome (73% vs. 13%, $p < 0.001$), and non-occlusive thrombus (71% vs. 13%, $p < 0.001$) when compared to atrial fibrillation as the underlying cause. This study suggests that vascular neurologists prefer early anticoagulation in high-risk stroke mechanisms as compared to atrial fibrillation.

Keywords Timing of anticoagulation, Ischemic stroke, Embolism, Hemorrhagic transformation, High risk stroke mechanisms

Anticoagulation following an ischemic stroke from a known embolic source is known to reduce the risk of recurrent stroke[1–3]. However, determining the optimal timing for initiating anticoagulation presents a challenge. Early initiation can reduce the risk of recurrent stroke but may also increase the risk of hemorrhagic transformation[4]. The American Heart Association (AHA) guidelines suggest that anticoagulation should generally be started within 4–14 days post-stroke, though initiation may be deferred in cases involving hemorrhagic transformation[5]. The 1-3-6-12-day and 1-2-3-4 rules were developed by consensus opinion with graded increase in delay of anticoagulation after TIA and ischemic stroke based on stroke severity[2,6,7].

Recent randomized studies, including ELAN, TIMING, and OPTIMAS, have investigated the safety and efficacy of early initiation of anticoagulation after ischemic stroke in patients with atrial fibrillation. These studies suggest a potential benefit of early anticoagulation, with no significant increase in hemorrhagic complications. However, the results were either not statistically significant or showed modest clinical effects, and they primarily focused on patients with atrial fibrillation. Importantly, these trials did not address real-world scenarios involving

[1]Department of Neurology, Brown University, Providence, RI, USA. [2]Department of Neurology, University of Chicago, Chicago, IL, USA. [3]593 Eddy Street, Providence, RI 02903, USA. ✉email: farhankhan.md@outlook.com

patients with other high-risk stroke mechanisms, such as left ventricular (LV) thrombus or antiphospholipid syndrome[8]. In the setting of reduced ejection fraction or myocardial wall motion abnormalities, the presence of LV thrombus significantly increases the risk of thromboembolism. Moreover, non-occlusive clots in the extracranial or intracerebral arteries also pose a high embolic risk, where anticoagulation is often preferred over antiplatelet therapy to prevent recurrent events. Moreover, it remains uncertain how these findings have influenced clinical practice[9,10]. Given these limitations, we aim to conduct a nationwide survey to better understand the practice patterns of vascular neurologists regarding the timing of anticoagulation in patients with ischemic stroke and known embolic sources. This survey will help to clarify how current practices align with existing guidelines and identify areas for potential improvement.

Methods

The study was approved by the University of Chicago Institutional Review Board (IRB), and a waiver of written informed consent was granted. In accordance with IRB guidelines, language was included in the survey invitation informing participants that their completion and submission of the survey would imply their consent to participate. This approach was deemed appropriate given the anonymous and voluntary nature of the survey, as well as the minimal risk to participants. Vascular neurologists were identified through the American Board of Psychiatry and Neurology verifyCert database, and email addresses were confirmed by cross referencing physician names with the American Academy of Neurology member database. The survey was administered to 1,556 vascular neurologists practicing in the United States in July 2023, followed by three weekly reminders.

Survey data were collected and managed using Redcap electronic data capture tools hosted at the University of Chicago. The survey contained 9 questions. Multiple choice questions addressed the years of experience, geographic location, type of clinical setting, academic vs. nonacademic, and factors for consideration of heparinization before transitioning to oral anticoagulation. Clinical vignettes isolated key variables of interest and used a slider scale depicting days since stroke to assess vascular neurologists' preference towards starting anticoagulation after ischemic stroke (supplemental materials 1). ECASS III definition was used for quantification of hemorrhage[11].

Statistical analysis

Continuous variables were summarized by means (SD) when normally distributed or median when not normally distributed. Categorical variables were summarized by proportions. For clinical purposes, the sliding scale was also converted into a binary variable (early vs. late). Early anticoagulation is defined as within 24 h for small ischemic stroke (< 1.5 cm), 5 days for one third of MCA territory with hemorrhagic transformation type 1, and 7 days for 1/3 of MCA territory with parenchymal hemorrhage type 2. Late anticoagulation is defined as > 24 h for small stroke, > 5 days for stroke with PH1 and > 7 days. Shapiro wilk test was performed to assess the assumption of normality. Parametric (t-test) and non-parametric (Mann-Whitney U and Kruskal Willis) tests were performed to assess continuous variables where applicable. The primary analysis was stratified by stroke size and hemorrhagic transformation subtype across high-risk stroke mechanisms—including left ventricular (LV) thrombus, antiphospholipid syndrome (APS), and non-occlusive internal carotid artery clot—using atrial fibrillation as the reference group. This comparison was chosen because, although atrial fibrillation is associated with an increased risk of systemic thromboembolism, the day-to-day risk remains relatively lower compared to other high-risk stroke mechanisms, making it a suitable baseline for evaluating the urgency of anticoagulation in these conditions. Chi-square tests and Fisher's exact tests were performed for comparison of categorical variables where applicable. To detect a 10% variation among vascular neurologists with 90% power, a survey of 200 vascular neurologists was needed. The statistical analysis was performed using Stata 18 LLC, College Station, TX.

Results

Among the 1556 participants, 201 (~ 13%) responded, with 62% identifying as academic neurologists. Over three quarters were at a thrombectomy-capable or comprehensive stroke center. In terms of experience, 27 (14%) participants had less than 5 years, 54 (27%) had 5 to 10 years, 47 (24%) had 10 to 15 years, and 73 (36%) had greater than 15 years of experience. A similar geographic representation was noted in the survey (68 in Northeast vs. 43 in Midwest vs. 49 in South vs. 41 in West = 201) (Table 1).

More experienced vascular neurologists (> 15 years of experience) were less likely to initiate heparin bridge in scenarios involving hemorrhagic transformation type 1 (21% vs. 49%, $p < 0.01$), parenchymal hemorrhage type 2 (25% vs. 56%, $p < 0.01$), and non-occlusive thrombi (36% vs. 74%, $p < 0.01$) compared to their less experienced counterparts (less than 5 years of experience). In cases of underlying mechanism due to atrial fibrillation, vascular neurologists working at comprehensive stroke center/thrombectomy capable center preferred early anticoagulation with hemorrhagic transformation type 1 (8 days vs. 11 days, $p = 0.03$) and parenchymal hemorrhage type 2 (15 vs. 21 days, $p = 0.001$) compared to vascular neurologists practicing at primary stroke center. A similar trend of early anticoagulation was noted in cases of LV thrombus with hemorrhagic transformation type 1 (PH1) (4 days vs. 7 days, $p = 0.006$) and parenchymal hemorrhage type 2 (PH2) (8 days vs. 12 days, $p = 0.006$).

Small ischemic stroke < 1.5 cm without HT

In cases of small ischemic stroke (< 1.5 cm) without hemorrhagic transformation, vascular neurologists were more likely to initiate anticoagulation therapy earlier in patients with left ventricular (LV) thrombus (1.4 days vs. 2.4 days, $p < 0.001$), non-occlusive internal carotid artery (ICA) thrombus (< 1 day vs. 2.4 days, $p < 0.001$), and antiphospholipid syndrome (1.7 days vs. 2.4 days, $p = 0.47$, Fig. 1) compared to those with atrial fibrillation.

Characteristics	*N*(%)
Academic	125 (62.2)
Community	76 (37.8)
Primary	40 (19.90)
Comprehensive/Thrombectomy capable	151 (75.1)
Teleneurology	10 (5.0)
Practice years	
< 5 yrs	27 (13.4)
5–10 yrs	54 (26.9)
10–15 yrs	47 (23.4)
> 15 yrs	73 (36.3)
Geographic	
Northeast	68 (33.9)
Midwest	43 (21.4)
South	49 (24.4)
West	41 (20.4)

Table 1. Baseline characteristics of vascular neurologists.

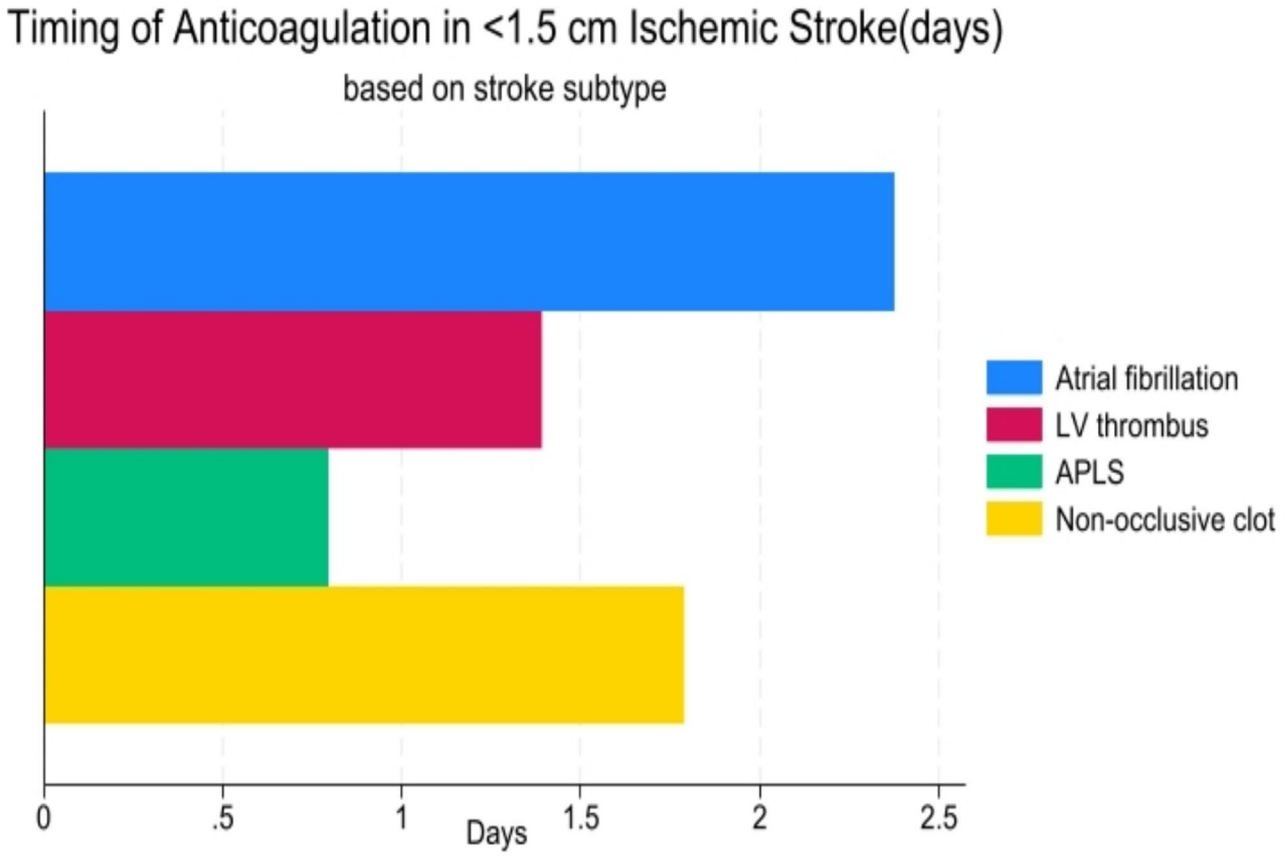

Fig. 1. Mena Timing of anticoagulation initiation in patients with small ischemic stroke (< 1.5 cm) without hemorrhagic transformation. Mean timing of anticoagulation earlier in patients with left ventricular thrombus (1.4 days vs. 2.4 days, $p < 0.001$), non-occlusive internal carotid artery thrombus (< 1 day vs. 2.4 days, $p < 0.001$), and antiphospholipid syndrome (1.7 days vs. 2.4 days, $p = 0.47$) compared to those with atrial fibrillation.

Early versus late

In terms of early anticoagulation for small embolic-appearing ischemic stroke (< 1.5 cm) with no hemorrhagic transformation, most vascular neurologists preferred anticoagulation within 24 h when the underlying mechanism was LV thrombus (69% vs. 36%, $p < 0.001$), APS with concurrent PE (90% vs. 36%, $p < 0.001$), and non-occlusive clot (87% vs. 36%, $p < 0.001$, Fig. 2) when compared to atrial fibrillation.

Ischemic stroke involving 1/3 of middle cerebral artery with HT1

When compared to atrial fibrillation in cases of ischemic stroke with hemorrhagic transformation type 1, they demonstrated a preference for early initiation when left ventricular thrombus (5 days vs. 9 days, $p < 0.001$), antiphospholipid syndrome (3 days vs. 9 days, $p < 0.001$), and non-occlusive internal carotid artery clot (3 days vs. 9 days, $p < 0.001$; Fig. 3) were considered the underlying causes.

Early versus late

In patients with HT1, a similar pattern of early anticoagulation was noted when underlying mechanism is embolism due to LV thrombus (69% vs. 22%, $p < 0.001$), antiphospholipid syndrome(87% vs. 22%, $p < 0.001$) and in the presence of non-occlusive thrombus (83% vs. 22%, $p < 0.001$, Fig. 4).

Ischemic stroke involving 1/3 of middle cerebral artery with PH2

For ischemic strokes with parenchymal hemorrhage type 2, anticoagulation initiation was significantly delayed in atrial fibrillation compared to non-occlusive internal carotid artery clot (17 days vs. 8 days, $p < 0.001$), antiphospholipid syndrome (17 days vs. 8 days, $p < 0.001$), and left ventricular thrombus (17 days vs. 9 days, $p < 0.001$; Fig. 5).

Early versus late

A similar preference for early anticoagulation was observed among vascular neurologists when comparing atrial fibrillation with PH2 to other conditions: LV thrombus (63% vs. 13%, $p < 0.001$), antiphospholipid syndrome (73% vs. 13%, $p < 0.001$), and non-occlusive thrombus (71% vs. 13%, $p < 0.001$, Fig. 6). Other results were statistically non-significant (see supplemental Table 1).

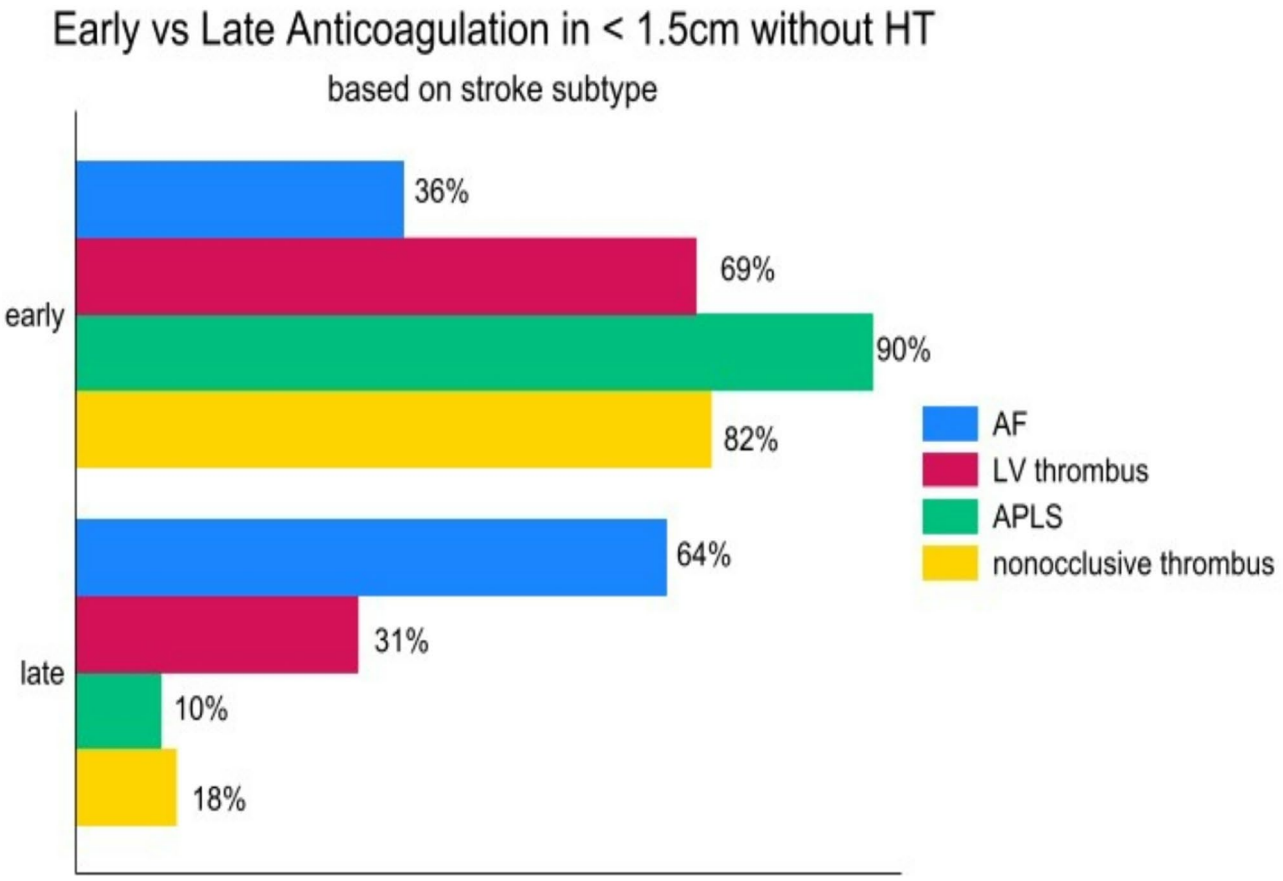

Fig. 2. Early anticoagulation was more frequently preferred for left ventricular thrombus (69% vs. 35%, $p < 0.001$), antiphospholipid syndrome (90% vs. 35%, $p < 0.001$), and non-occlusive clot (87% vs. 35%, $p < 0.001$) compared to atrial fibrillation. Note: The comparison group is atrial fibrillation.

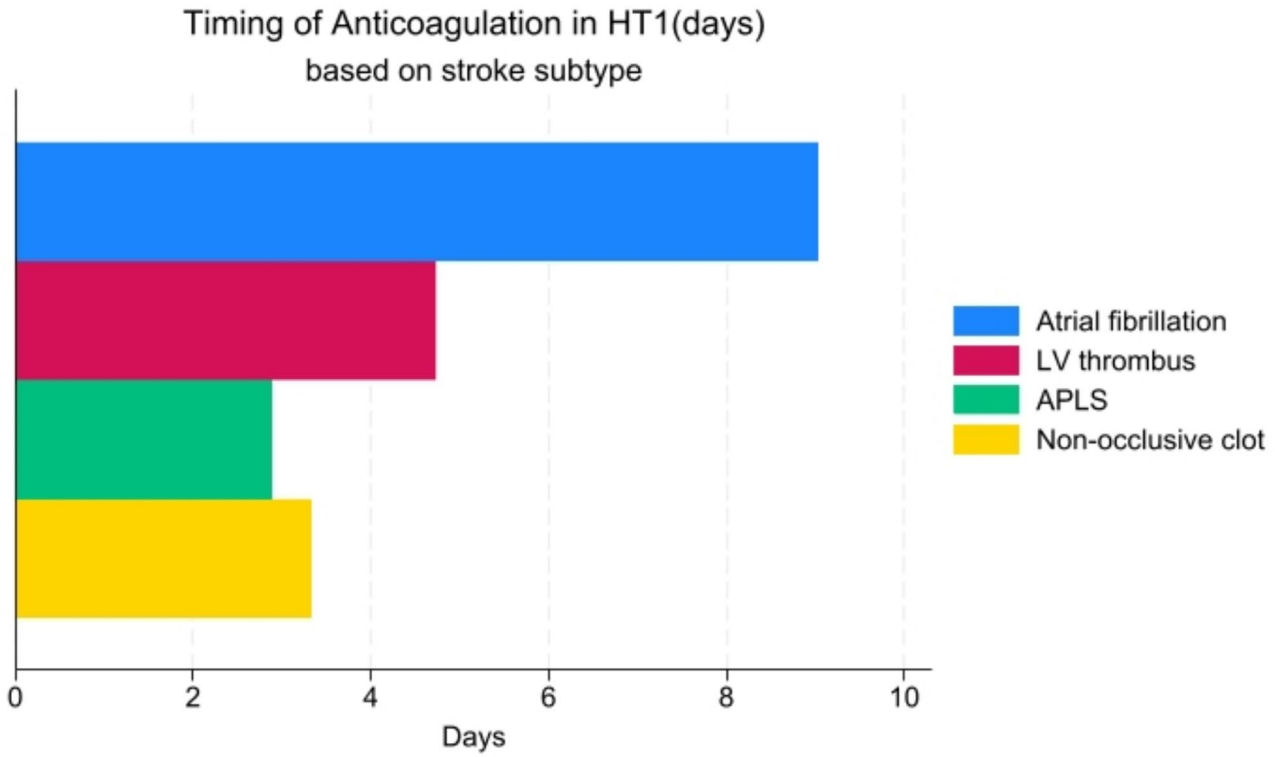

Fig. 3. Mean timing of anticoagulation (in days) after ischemic stroke for patients with a 1/3 MCA ischemic stroke with HT1. The mean timing of anticoagulation for underlying mechanisms includes non-occlusive thrombus (3 days vs. 9 days, $p < 0.001$), antiphospholipid syndrome (3 days vs. 9 days, $p < 0.001$), and non-occlusive internal carotid artery thrombus (5 days vs. 9 days, $p < 0.001$).

Discussion

Our study noted that vascular neurologists prefer early initiation of anticoagulation in high-risk stroke mechanisms even in the presence of hemorrhagic transformation.

For patients with high-risk stroke mechanisms, such as left ventricular thrombus, antiphospholipid syndrome, and non-occlusive thrombi, vascular neurologists were more likely to initiate early anticoagulation. This pattern of early anticoagulation is consistent with early recurrence of ischemic stroke and systemic thromboembolism associated with these mechanisms[8,12]. Our findings differ from those observed with the 1-3-6-12 rule and the 1-2-3-4-day rule[6,7]. This discrepancy could be explained because these studies used stroke severity based on NIHSS stroke, lack of inclusion of patients with hemorrhagic transformation. These results are unique from large observational studies and randomized clinical trials that excluded patients with hemorrhagic transformation and high-risk stroke mechanisms (LV thrombus, APS etc.)[1,2].

For atrial fibrillation, vascular neurologists generally prefer delayed anticoagulation. However, recent clinical trials, OPTIMAS and ELAN, have demonstrated that early anticoagulation is safe, with no significant differences in outcomes between patients with NIHSS scores < 10 and those with scores > 10[1,2]. They also noted no difference in mortality, symptomatic intracerebral hemorrhage in early and late anticoagulation groups in these trials. Additionally, early initiation of DOACs may offer the practical advantage of enabling a higher proportion of patients to start secondary prevention treatment before hospital discharge. This data may influence vascular neurologists' approach to early anticoagulation in cases of ischemic stroke caused by atrial fibrillation and could be studied in the future.

In contrast to the Berlin Atrial Fibrillation Registry[13]which focused on the overall timing of OAC (re) initiation following ischemic stroke or TIA and adherence to the '1–3–6–12 days rule', our study provides a more granular view by examining how stroke mechanism and imaging features influence decision-making among vascular neurologists. We found that clinicians were significantly more likely to initiate early anticoagulation in patients with small ischemic strokes (< 1.5 cm) without hemorrhagic transformation when the underlying mechanism was a left ventricular thrombus, non-occlusive internal carotid artery thrombus, or antiphospholipid syndrome, compared to atrial fibrillation. Even in cases of hemorrhagic transformation type 1 or parenchymal hematoma type 2, earlier anticoagulation was more commonly favored for non-AF embolic mechanisms. These results suggest that vascular neurologists weigh embolic source and hemorrhagic risk dynamically rather than strictly adhering to a time-based rule. While the Berlin Registry concluded that adherence to the '1–3–6–12 days rule' was not associated with differences in clinical outcomes, our findings indicate that individualized decision-making, based on mechanism and radiologic features, may drive early anticoagulation and reflect current real-world practice trends not fully captured in prior observational cohorts or RCTs.

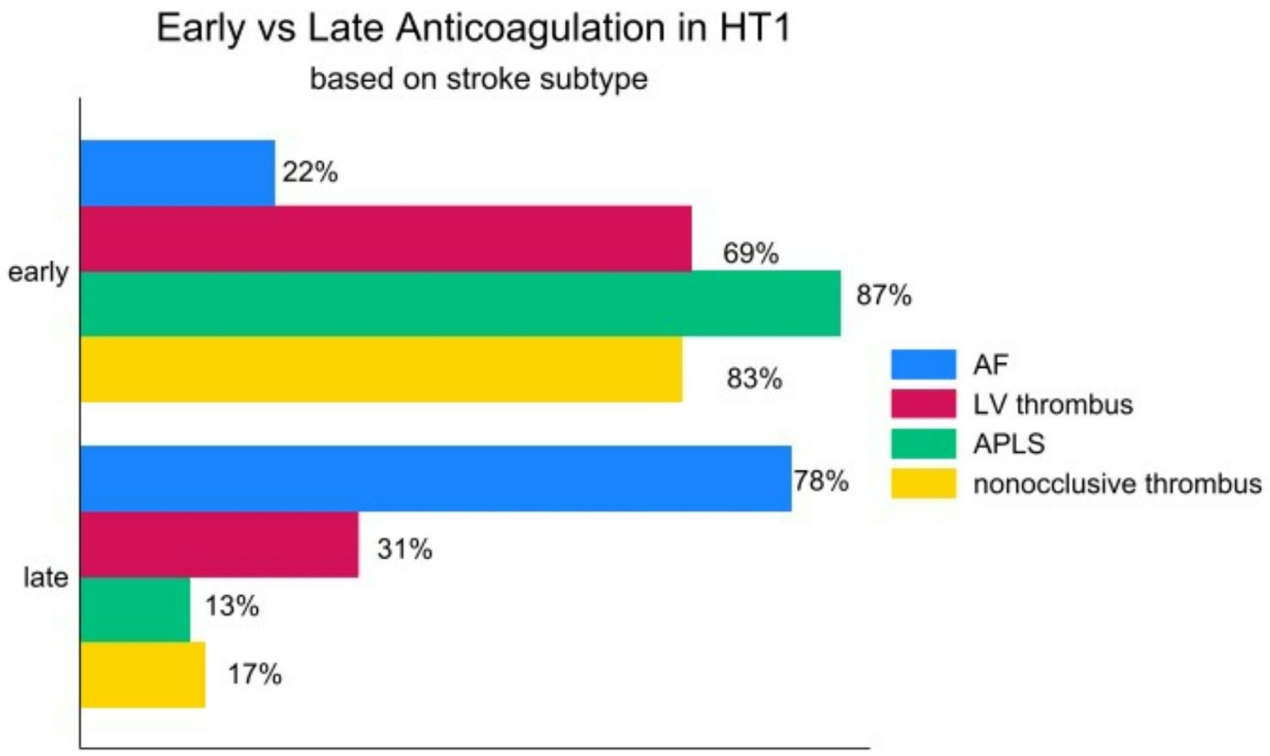

Fig. 4. Timing of anticoagulation involving 1/3 of MCA territory with HT1. Early initiation of anticoagulation noted in groups of LV thrombus (21% vs. 69%, $p < 0.001$), APS(21% vs. 69%, $p < 0.001$) and non-occlusive clot in the internal carotid artery(21% vs. 83%). LV indicates left ventricular; APS indicates antiphospholipid syndrome. Note: The comparison group is atrial fibrillation.

The study also revealed differences based on the type of clinical setting, with neurologists at comprehensive stroke centers/thrombectomy capable stroke centers being more likely to initiate early anticoagulation with large ischemic strokes and high-grade hemorrhagic transformation (PH1 and PH2) compared to those at primary stroke centers. This may reflect differing institutional protocols, access to neurosurgery, neuro-critical care, advanced imaging, and monitoring capabilities, as well as the greater experience of vascular neurologists at comprehensive stroke centers[14].

The difference in the use of bridging anticoagulation between more experienced neurologists (with over 15 years of experience) and their less experienced counterparts (with fewer than 5 years of experience) may stem from their deeper understanding of studies indicating that bridging with low molecular weight heparin is associated with increased rates of recurrent stroke and higher incidence of symptomatic intracranial hemorrhage[15]. Additionally, more experienced clinicians are likely to adopt a more cautious approach to anticoagulation in patients who have a higher risk of bleeding, influenced by their accumulated clinical experience.

Overall, these results suggest variability in practice among vascular neurologists based on hospital setting, years of experience, and stroke subtype. This underscores the necessity for more precise guidelines and protocols tailored to the specific stroke mechanisms and patient profiles.

Limitations

Our study has several limitations. The overall response rate was low (13%) and majority of the participants identified themselves as academic. Due to the nature of the study, we could not assess the impact of these decisions on patient outcomes. This study reflects the practices of vascular neurologists within the U.S. only; therefore, its generalizability to general neurologists and international practices (Asia, Europe) is limited.

Conclusion

In conclusion, our study reveals substantial variability in the timing of anticoagulation among vascular neurologists, influenced by clinical experience, stroke etiology, and hospital setting. Future research should aim to include more diverse patient populations and explore the outcomes of different anticoagulation strategies in high-risk groups.

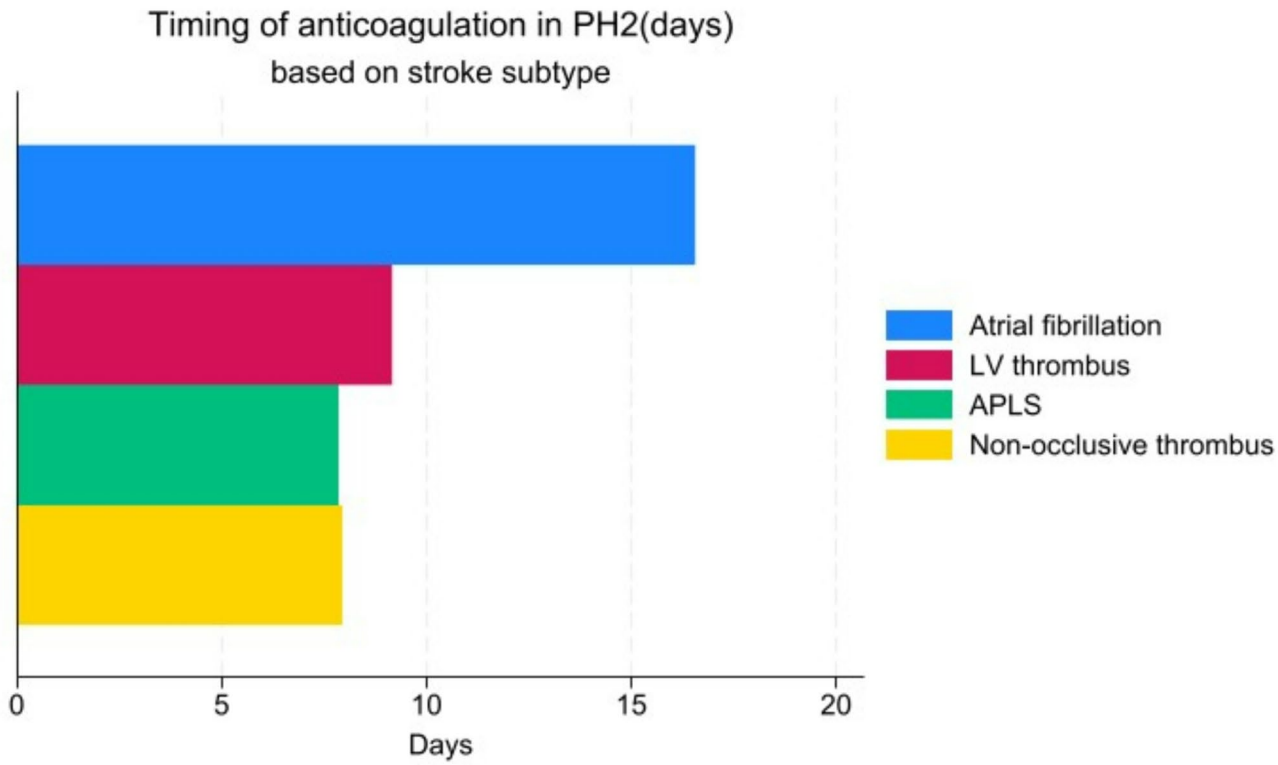

Fig. 5. Mean timing of anticoagulation (in days) after ischemic stroke for patients with a 1/3 MCA ischemic stroke with PH2. The mean timing of anticoagulation for atrial fibrillation is compared to non-occlusive clot (17 days vs. 8 days, $p < 0.001$), antiphospholipid syndrome (17 days vs. 8 days, $p < 0.001$), and left ventricular thrombus (17 days vs. 9 days, $p < 0.001$).

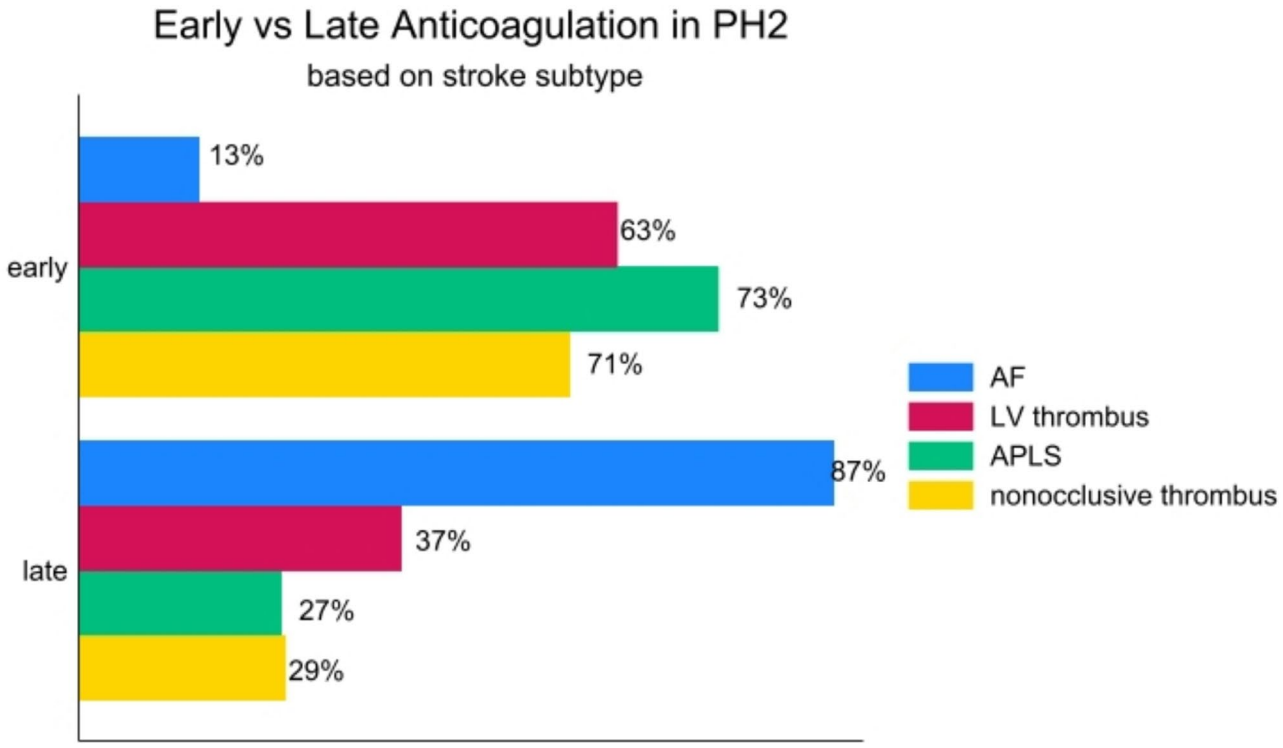

Fig. 6. Timing of anticoagulation involving 1/3 of MCA territory with parenchymal hemorrhage type 2. Early initiation of anticoagulation noted in groups of LV thrombus (13% vs. 63%, $p < 0.001$), APS (13% vs. 73%, $p < 0.001$) and non-occlusive clot in the internal carotid artery(13% vs. 71%, 0.001). LV indicates left ventricular; APS indicates antiphospholipid syndrome. Note: The comparison group is atrial fibrillation.

Data availability

The data supporting the findings of this study can be obtained from the corresponding author upon reasonable request.

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Author contributions
F.K conceptualized the idea, performed the analysis and wrote the main manuscript text. V.L helped with data collection and editing of the main manuscript. S.P and S.Y edited the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to F.K.

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