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Recurrent ischemic stroke in atrial fibrillation patients despite NOAC therapy: Recent advances and their therapeutic implications

Short title: Recurrent stroke in atrial fibrillation patients despite NOAC therapy

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ABSTRACT

Non-vitamin K oral anticoagulants (NOACs) are currently the preferred anticoagulant therapy for patients with non-valvular atrial fibrillation. Nevertheless, for patients receiving oral anticoagulants, clinical trials have reported a residual annual risk of recurrent ischemic events ranging from 0.7% to 2.3%, in both primary and secondary prevention settings. Furthermore, in the non-randomized RENO-EXTEND study, patients who had an ischemic stroke while on NOAC therapy, also had a recorded combined rate of thromboembolic and bleeding events of 16.7%, corresponding to an annual incidence of 13.4%. For those patients who experience an ischemic stroke while receiving NOAC therapy, reliable evidence on how to proceed with management is limited. This patient setting need to take into consideration the following strategies: 1) Exclude poor adherence to treatment; 2) Assess potential drug–drug interactions; 3) Ensure the prescription of the most appropriate NOAC dose; 4) Confirm the underlying mechanism of the recurrent ischemic event; 5) Continue the same NOAC after a cardioembolic event occurring during NOAC therapy, when appropriate; 6) Consider switching to a different NOAC so to improve adherence; 7) Evaluate, on a case-by-case basis and for the shortest feasible duration, the possible addition of an antiplatelet agent to NOAC therapy; 8) Consider left atrial appendage occlusion combined with indefinite NOAC therapy in selected patients

with recurrent events despite anticoagulation; 9) Increment stricter risk factor controls. Moreover, results from randomized controlled trials investigating for more effective management strategies are needed to better treat patients in this setting.

Key words: atrial fibrillation, breakthrough ischemic stroke, direct oral anticoagulants, recurrent stroke, secondary prevention

INTRODUCTION

To date, evidence from registries and clinical trials has shown that non-vitamin K oral anticoagulants (NOACs) have a more favorable risk-benefit profile than warfarin, for both primary and secondary stroke prevention in patients with non-valvular atrial fibrillation (NVAF). Owing to their significant impact on reducing hemorrhagic stroke (risk ratio [RR], 0.43; 95% confidence interval [CI], 0.29–0.64) and all-cause mortality (RR, 0.87; 95% CI, 0.80–0.95). Even when compared with warfarin which achieves a high time in therapeutic range (>70%), NOACs are currently considered the preferred anticoagulant therapy for patients with NVAF [1, 2]. Nevertheless, for patients receiving oral anticoagulants, clinical trials have consistently reported a residual annual risk of recurrent ischemic events, ranging from 0.7% to 2.3%, in both primary and secondary prevention settings [3]. Furthermore, the non-randomized RENO-EXTEND study observed that those patients who experienced an ischemic stroke while on NOAC therapy also had on average a combined rate of thromboembolic and bleeding events of 16.7%, corresponding to an annual incidence of 13.4% [4]. A meta-analysis including 78 733 patients, reported that in patients with stroke despite oral anticoagulants, the risk was 7.20% per year (95% CI, 5.05%–9.34%) for ischemic stroke and 1.40% per year (95% CI, 0.40%–2.40%) for intracerebral hemorrhage [5]. In light of the above findings, randomized controlled trials (RCTs) are needed to investigate for better define more effective management strategies for patients on NOACs who experience stroke recurrence.

The aim of this review was to provide practical guidance on how to best address this clinical challenge.

POSSIBLE CAUSES OF ISCHEMIC STROKE RECURRENCE WHILE ON NOACS

Stroke recurrence during NOAC therapy may be related to several factors including: 1) Poor adherence to the prescribed anticoagulant regimen; 2) Drug–drug interactions; 3) An alternative, non-cardioembolic mechanism underlying the recurrent event; 4) Inappropriate

dosing of NOACs; 5) Cardioembolism occurring despite adequate anticoagulation due to residual risk, and 6) Pharmacological failure of NOAC therapy.

Non-adherence and non-persistence to prescribed therapy

Non-vitamin K oral anticoagulants are administered in fixed dosing regimens without the need for coagulation monitoring, which may result in less overall medical follow-up. Consequently, concerns of lower adherence (i.e., taking medication as prescribed) and persistence (i.e., continuation of treatment) to NOACs have been raised, especially since treatment non-adherence and discontinuation have been reported to be associated with higher thromboembolic and mortality risks [6]. In a randomized study that investigated 277 782 AF patients, 69.6% NOAC and 37.2% vitamin-K antagonist (VKA) users were recorded as persistent after 1 year, whereas 44.3% and 18.9% after 5 years, respectively. Among subjects having discontinued either NOAC or VKA treatment, 75.4% and 46.1% reinitiated any OAC within 5 years, respectively [7].

A cross-sectional study [8] reported a substantial prevalence of insufficient or absent anticoagulation among patients with NVAF who had survived a stroke. Specifically, among 396 patients receiving oral anticoagulants and enrolled in prospective stroke registries, approximately 50% were found to have poor adherence, with no significant difference between NOAC and vitamin VKA users (56% vs. 44%). Factors independently associated with low adherence included educational level, absence of heart failure (HF), smoking history, prior VKA use prior to the index stroke, and previous ischemic stroke. These findings underscore the clinical relevance of properly assessing and addressing treatment adherence [9, 10].

Drug–drug interactions

It has been well established that medications inducing P-glycoprotein or CYP3A4 may lower NOAC plasma concentrations, whereas inhibitors of P-glycoprotein or CYP3A4 can increase their levels. In fact, both types of interactions — particularly those involving certain antiepileptic agents (e.g., phenytoin, carbamazepine, phenobarbital) — may significantly contribute to stroke recurrence risk during NOAC therapy [9]. In spite of this, a systematic review [11] evaluating real-world risks of drug interactions in patients treated with NOACs was able to identify only a limited number of case reports and retrospective observational studies.

Alternative stroke etiology of recurrence (non-cardioembolic)

Regarding the possibility of alternative etiologies, non-cardioembolic causes should be excluded first (e.g., intracranial or extracranial atherosclerosis and small vessel disease), as these conditions generally require different therapeutic approaches [12]. Indeed, the RENO study [13] showed that approximately 30% of cerebrovascular events occurring during NOAC therapy had been classified as strokes due to non-cardioembolic mechanisms. Similarly, another observational study identified large artery atherosclerosis as the most frequent competing cause [3].

Inappropriate NOAC dosing

Currently, among NOAC users, nearly 40% receive reduced doses; particularly patients older than 65 years, having low body weight, or with renal impairment [9, 13, 14]. It has been reported that in real-world clinical practice, between 16% and 45% of patients are prescribed low-dose NOACs [10]. The RENO study [13] reported that, 317 cases (44.5%) and 207 controls (29.6%) had been treated with reduced NOAC doses; among these, 111 cases (35.0%) and 53 controls (27.5%) had received an inappropriately low dose. Both the RENO [13] and RENO-ICH [15] studies reported that inappropriate low-dose NOAC use was inversely associated with the risk of intracranial hemorrhage (odds ratio [OR], 0.61; 95% CI, 0.38–0.98). However, inappropriate dosing was linked to an observed threefold increase in the risk of ischemic cerebral events (OR, 3.18; 95% CI, 1.95–5.85) [16].

A meta-analysis [17], including 23 RCTs and observational studies including a total of 175 801 patients, evaluated the efficacy and safety of inappropriate vs. recommended NOAC doses in patients with NVAF. Inappropriate low dosing was associated with a higher risk of the composite outcome of ischemic stroke, transient ischemic attack, and systemic embolism (OR, 1.21; 95% CI, 1.05–1.39), as well as all-cause mortality (OR, 1.66; 95% CI, 1.18–2.35), but not major bleeding (OR, 1.01; 95% CI, 0.83–1.22). In the subgroup analysis, Asian patients were associated with a non-significant increase in the composite outcome (OR, 1.17; 95% CI, 0.89–1.54), whereas non-Asian populations exhibited a significant increase (OR, 1.21; 95% CI, 1.07–1.36). This difference may have in part reflected the lower average creatinine clearance and body weight common among Asian patients, as well as differences in their prescribed therapeutic regimens, such as less frequent use of gastric antiacid and antiplatelet drugs. Nevertheless, in this meta-analysis, non-Asian patients receiving inappropriate low-dose NOACs had a significantly higher risk of ischemic events.

In conclusion, strict adherence to recommended NOAC dosing regimens appears to be essential for optimizing therapeutic benefit in patients with NVAF.

Cardioembolism despite adequate anticoagulation due to residual risk

Several studies have shown that NVAF-related cardioembolism, despite adequate anticoagulation seems to be the most frequent mechanism underlying stroke recurrence, with rates ranging from 44.1% [3] to 74.2% [4]. This phenomenon may have reflected the persistence of a substantial residual stroke risks in specific patient subgroups who are known to have poor outcomes within 3 months [18, 19].

An analysis of 7 prospective cohort studies including 5413 patients with NVAF and recent cerebral ischemia demonstrated a higher risk of acute ischemic stroke (hazard ratio [HR], 1.6; 95% CI, 1.2–2.3; $P = 0.005$) among patients who had already been receiving anticoagulant therapy at baseline [18]. In fact, the annualized rate of recurrent ischemic stroke was reported to be more than double in patients whose index stroke had occurred while on anticoagulation (8.9%; 95% CI, 7.3%–10.8%), compared to previously untreated patients (3.9%; 95% CI, 3.3%–4.4%).

In the RENO-EXTEND study [4], the CHA_2DS_2-VASc score assessed after the index event was significantly associated with the risk of recurrent ischemic events (OR, 1.2; 95% CI, 1.0–1.3 for each 1-point increase; $P = 0.05$). Within the CHA_2DS_2-VASc score, the factors most strongly associated with recurrence among patients treated with NOACs were advanced age, male sex, prior stroke, diabetes mellitus, and congestive HF — most of which are non-modifiable risk factors.

NOAC treatment failure

Suboptimal anticoagulant effects, potentially related to high inter-individual variability, might contribute to thromboembolic complications during NOAC therapy [3, 20]. Indeed, thromboembolic events occurring during NOAC treatment have frequently been reported in patients with plasma drug levels in the lowest range of anticoagulation at the time of the event, particularly among those patients with high cardiovascular risk profiles [20]. However, given the substantial inter-individual variability and as well as the absence of a clearly defined therapeutic cutoff for anticoagulant activity, measuring NOAC plasma levels after a thromboembolic event is unlikely to meaningfully influence any important decisions regarding clinical management [6, 20].

CLINICAL APPROACH

Currently, for those patients who have experienced an ischemic stroke while receiving NOAC therapy, the availability of published robust evidence to guide their clinical management is limited; consequently, international guidelines are unable to provide clear recommendations. In this context, however, several potential strategies can be still be considered as suggested also by the World Stroke Organization (WSO) guidelines [21]:

1. Correcting inappropriate low NOAC doses.
2. Continuation of the same NOAC.
3. Switching to another NOAC.
4. Switching to a NOAC with a different dosing frequency.
5. Switching to a NOAC with a different mechanism of action.
6. Switching to warfarin.
7. Adding an antiplatelet agent to the NOAC.
8. Performing left atrial appendage occlusion (LAAO) while continuing NOAC therapy.

With regard to switching therapy, to date, no randomized trials have specifically addressed its possible influence. In the international observational study RENO-EXTEND [4], which included 1240 patients with acute stroke while on NOAC treatment, the composite rate of ischemic and bleeding events did not differ significantly between patients who had their original NOAC changed and those who had not (OR, 1.2; 95% CI, 0.8–1.7). Similarly, another large observational study [3] enrolled 5314 patients who had experienced ischemic events while on oral anticoagulation. Among those patients taking NOACs at the time of stroke, switching to another NOAC — whether with a different agent, dosing frequency, or mechanism of action — was not associated with lower odds of the composite outcome (recurrent ischemic stroke, intracerebral hemorrhage, and all-cause death within 3 months) or recurrent stroke alone, compared with the no switch group. In patients with cardioembolism, despite anticoagulation, twice-daily NOAC regimens were associated with a lower occurrence of the composite outcome, though not of recurrent stroke alone.

In RENO-EXTEND, among the included 920 patients whose index event was cardioembolic stroke, 401 had their NOAC switched after the event and 351 had not. A combined outcome occurred in 58 patients (14.5%) in the switch group and in 44 patients (12.5%) in the no-switch group ($P = 0.4$). Ischemic events were occurred in 34 patients (8.6%) who had their NOAC changed vs. 27 patients (7.7%) who had not ($P = 0.7$).

A meta-analysis of 8 observational studies including 14 307 patients, (mean age 75 years, 48% female) reported that switching to warfarin was associated with a higher risk of ischemic stroke when compared with keeping the original NOAC (RR, 1.80; 95% CI, 1.42–2.29) or

changing NOAC dosage (RR, 1.72; 95% CI, 1.20–2.45). Switching to warfarin was also associated with higher ICH rates compared with keeping the same NOAC (RR, 2.90; 95% CI, 2.01–4.18) and NOAC-to-NOAC switch (RR, 3.25; 95% CI, 2.13–4.96). Keeping the same NOAC and switching to another NOAC, independently from mechanism, lead to similar rates for primary and secondary outcomes [22].

Overall, these findings suggest that changing the NOAC type does not confer additional benefit. However, findings suggest that switching therapy to improve adherence might be a reasonable individualized strategy.

When concomitant etiologies are present, optimal risk factor controls and combination therapy (e.g., statins or antiplatelet agents) are often considered. However, antiplatelet addition has been associated with an increased risk of major bleeding [1, 3, 4]. Accordingly, in RENO-EXTEND, the addition of an antiplatelet agent to a NOAC after the index event was linked to a significantly higher rate of hemorrhagic complications (intracranial and major extracranial bleeding; OR, 2.8; 95% CI, 1.4–5.5; P = 0.003). Therefore, combination therapy should be evaluated on a case-by-case basis, particularly in patients with recent ischemic heart disease or coronary angioplasty and stenting. However, as emphasized by the WSO guidelines, evidence is missing for short-term addition of antiplatelet agents in patients with a competing large-artery stroke mechanism [21].

According to the 2024 European Society of Cardiology and 2025 WSO guidelines on AF, percutaneous LAAO may be considered for stroke prevention in patients with AF who have contraindications to long-term oral anticoagulation [23]. To date, 4 RCTs have evaluated this strategy: the PROTECT AF trial, the PREVAIL trial, the PRAGUE-17 study and the CLOSURE-AF study [24–26]. In PROTECT AF, at a mean follow-up of 3.8 years, 39 primary endpoint events (8.4%) occurred in the device group compared with 34 events (13.9%) in the warfarin group (rate ratio 0.60; 95% credible interval 0.41–1.05), therein, meeting predefined criteria for both noninferiority and superiority. The primary endpoint included stroke, systemic embolism, and cardiovascular or unexplained death. Additionally, cardiovascular mortality (HR, 0.40; 95% CI, 0.21–0.75; P = 0.005) and all-cause mortality (HR, 0.66; 95% CI, 0.45–0.98; P = 0.04) were both lower in the device group. The PREVAIL trial evidenced the noninferiority of LAAO compared with warfarin for stroke or systemic embolism occurring more than 7 days after randomization (risk difference 0.0053; 95% CI, −0.0190 to 0.0273). Notably, both trials excluded patients with contraindications to long-term oral anticoagulation. Finally, PRAGUE-17 was a randomized noninferiority trial that compared percutaneous LAAC (Watchman or Amulet) with NOACs (95% apixaban) in patients with nonvalvular AF and a

history of cardioembolism, clinically-relevant bleeding, or both CHA_2DS_2-VASc ≥3 and HASBLED ≥2. The primary endpoint was a composite of cardioembolic events (stroke, transient ischemic attack, or systemic embolism), cardiovascular death, clinically relevant bleeding, or procedure-/device-related complications (LAAO group only). The primary analysis was modified intention-to-treat. The study randomized 402 patients with AF (201 per group, mean age 73.3 ± 7.0 years, 65.7% male, CHA_2DS_2-VASc 4.7 ±1.5, HASBLED 3.1 ± 0.9). After 3.5 years median follow-up (1354 patient-years), LAAO was noninferior to NOACs for the primary endpoint by modified intention-to-treat (subdistribution HR [sHR]: 0.81; 95% CI, 0.56–1.18; *P* = 0.27; *P* for noninferiority = 0.006). For the components of the composite endpoint, the corresponding sHRs were: 0.68 (95% CI, 0.39–1.20; *P* = 0.19) for cardiovascular death, 1.14 (95% CI, 0.56–2.30; *P* = 0.72) for all-stroke/transient ischemic attack, 0.75 (95% CI, 0.44–1.27; *P* = 0.28) for clinically relevant bleeding, and 0.55 (95% CI, 0.31–0.97; *P* = 0.039) for nonprocedural clinically relevant bleeding. The primary endpoint outcomes resulted being similar in the per-protocol (sHR, 0.80; 95% CI, 0.54–1.18; *P* = 0.25) and on-treatment (sHR, 0.82; 95% CI, 0.56–1.20; *P* = 0.30) analyses.

In 2024 a meta-analysis was carried out including 7 trials and 73 199 patients where the risk of the primary end point was not statistically different between LAAO vs. VKAs (OR, 0.92; 95% CI, 0.62–1.50) and LAAO vs. NOACs (OR, 1.11; 95% CI, 0.71–1.73). LAAO and NOACs resulted in similar risks of major or minor (OR, 0.93; 95% CI, 0.61–1.42) and major bleeding (OR, 0.92; 95% CI, 0.58–1.46); however, after the exclusion of procedural bleeding, bleeding risk resulted being significantly lower in those patients undergoing LAAO. Here, both LAAO and NOACs were associated with reducing the risk of all-cause death compared with VKAs (LAAO vs. VKAs: OR, 0.70; 95% CI, 0.53–0.91; NOACs vs. VKAs: OR, 0.90; 95% CI, 0.85–0.95, respectively). NOACs ranked as the superior treatment for stroke or systemic embolism prevention (66.9%) and LAAO was ranked best for reducing major bleeding (63.9%) and death (96.4%) [27].

The CLOSURE-AF trial assigned patients with AF and a high risk of stroke and bleeding to undergo LAAO or receive physician-directed best medical care (NOAC, if eligible). The primary end point, which was tested for noninferiority, was a composite of stroke (ischemic or hemorrhagic), systemic embolism, major bleeding, or cardiovascular or unexplained death, assessed in a time-to-event analysis. A total of 912 adult patients underwent randomization. The primary end-point analysis included 446 patients who were assigned to undergo LAAO (device group) and 442 who were assigned to physician-directed best medical care (medical-therapy group). After a median follow-up of 3 years, a first primary end-point event had

occurred in 155 patients (incidence per 100 patient-years, 16.8) in the device group and in 127 patients (incidence per 100 patient-years, 13.3) in the medical-therapy group (difference in restricted mean survival time, −0.36 years; 95% CI, −0.70 to −0.01; $P = 0.44$ for noninferiority). Serious adverse events occurred in 368 patients (82.5%) in the device group and 342 (77.4%) in the medical-therapy group [28].

Conversely, the CHAMPION-AF trial which enrolled AF patients deemed to be suitable candidates for anticoagulation, randomly assigned patients to receive either device-based LAAO (device group) or NOAC therapy (anticoagulation group). The primary efficacy end point, a composite of death from cardiovascular causes, stroke, or systemic embolism, was tested for noninferiority after 3 years of follow-up. Of the 3000 patients who underwent randomization, 1499 were assigned to the device group and 1501 to the anticoagulation group. At 3 years, a primary efficacy end-point event had been recorded in 81 patients (Kaplan–Meier estimate, 5.7%) in the device group and in 65 patients (Kaplan–Meier estimate, 4.8%) in the anticoagulation group (difference, 0.9 percentage points; 95% CI, −0.8 to 2.6; $P <0.001$ for noninferiority). Non–procedure-related bleeding occurred in 154 patients (Kaplan–Meier estimate, 10.9%) in the device group and in 260 patients (Kaplan–Meier estimate, 19.0%) in the anticoagulation group (HR, 0.55; 95% CI, 0.45–0.67; $P <0.001$ for superiority) [29].

At present, there are no published robust data on the effectiveness of LAAO in patients with stroke recurrence while on NOAC therapy. Only results from small studies have suggested that combining indefinite oral anticoagulation with LAAO may be considered in selected high-risk patients to prevent further events [30–32].

Another important clinical strategy to implement is the correction of modifiable risk factors. To this regard, the RENO study highlighted that hyperlipidemia, history of HF, and diabetes were independent risk factors associated with recurrence in patients with ischemic stroke and AF, despite NOAC therapy. Whereas, the presence of paroxysmal AF was inversely correlated [10]. Therefore, careful cholesterol management, rhythm control, and the use of recent therapeutic strategies for HF and diabetes are treatment options that should be always considered for their proven effectiveness.

Finally, novel pharmacological and interventional approaches — such as factor XIa inhibitors and carotid filter devices — are currently being investigated with the aim of developing enhancers to stroke prevention with acceptable safety profile [33–35].

CONCLUSIONS

The clinical management of recurrent stroke in patients already receiving NOAC therapy should take into account the following key considerations:

1. Exclude poor adherence to treatment.
2. Assess potential drug–drug interactions.
3. Ensure prescription of the appropriate NOAC dose.
4. Determine the underlying mechanisms of the recurrent ischemic event.
5. Continue the same NOAC after a cardioembolic event occurring during NOAC therapy, when appropriate.
6. Consider switching to a different NOAC when the aim is to improve adherence.
7. Evaluate on a case-by-case basis the addition of an antiplatelet agent to NOAC therapy for the shortest duration possible.
8. Consider LAAO combined with indefinite NOAC therapy in selected patients with recurrent events despite any ongoing anticoagulation.
9. Adopt the most stringent control of modifiable risk factors.
10. Promote the realization of randomized clinical trials that aim to providing more definitive evidence in this clinical setting.

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