Stroke

CLINICAL AND POPULATION SCIENCES

Recurrent Ischemic Stroke and Bleeding in Patients With Atrial Fibrillation Who Suffered an Acute Stroke While on Treatment With Nonvitamin K Antagonist Oral Anticoagulants: The RENO-EXTEND Study

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BACKGROUND: In patients with atrial fibrillation who suffered an ischemic stroke while on treatment with nonvitamin K antagonist oral anticoagulants, rates and determinants of recurrent ischemic events and major bleedings remain uncertain.

METHODS: This prospective multicenter observational study aimed to estimate the rates of ischemic and bleeding events and their determinants in the follow-up of consecutive patients with atrial fibrillation who suffered an acute cerebrovascular

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ischemic event while on nonvitamin K antagonist oral anticoagulant treatment. Afterwards, we compared the estimated risks of ischemic and bleeding events between the patients in whom anticoagulant therapy was changed to those who continued the original treatment.

RESULTS: After a mean follow-up time of 15.0±10.9 months, 192 out of 1240 patients (15.5%) had 207 ischemic or bleeding events corresponding to an annual rate of 13.4%. Among the events, 111 were ischemic strokes, 15 systemic embolisms, 24 intracranial bleedings, and 57 major extracranial bleedings. Predictive factors of recurrent ischemic events (strokes and systemic embolisms) included CHA_2DS_2-VASc score after the index event (odds ratio [OR], 1.2 [95% CI, 1.0–1.3] for each point increase; P=0.05) and hypertension (OR, 2.3 [95% CI, 1.0–5.1]; P=0.04). Predictive factors of bleeding events (intracranial and major extracranial bleedings) included age (OR, 1.1 [95% CI, 1.0–1.2] for each year increase; P=0.002), history of major bleeding (OR, 6.9 [95% CI, 3.4–14.2]; P=0.0001) and the concomitant administration of an antiplatelet agent (OR, 2.8 [95% CI, 1.4–5.5]; P=0.003). Rates of ischemic and bleeding events were no different in patients who changed or not changed the original nonvitamin K antagonist oral anticoagulants treatment (OR, 1.2 [95% CI, 0.8–1.7]).

CONCLUSIONS: Patients suffering a stroke despite being on nonvitamin K antagonist oral anticoagulant therapy are at high risk of recurrent ischemic stroke and bleeding. In these patients, further research is needed to improve secondary prevention by investigating the mechanisms of recurrent ischemic stroke and bleeding.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: anticoagulants ■ atrial fibrillation ■ hypertension ■ ischemic stroke ■ recurrence

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
A-S-C-O-D	atherosclerosis, small vessel disease, cardiac pathology, other causes, and dissection
NOAC	nonvitamin K antagonist oral anticoagulant
OR	odds ratio
PSM	propensity score matching
RENO	Causes and Risk Factors of Cerebral Ischemic Events in Patients With Nonvalvular AF Treated With NOACs for Stroke Prevention

In patients with atrial fibrillation (AF), oral anticoagulation reduces the risks of ischemic stroke and systemic embolism in patients with AF by 60% to 70%.[1] Nonvitamin K antagonist oral anticoagulants (NOACs) are currently the gold standard for this clinical indication.[2,3] In a meta-analysis of randomized controlled trials, the residual risk of ischemic stroke in patients treated with NOACs was estimated at 1.4% per year[4]; observational studies have reported an annual risk of 8.9% (7.3–10.8) in patients with AF on anticoagulant treatment.[5–7] Several possible mechanisms for this residual risk of stroke have been suggested, including an absent or reduced adherence to anticoagulation, noncardioembolic stroke causes, or cardioembolic mechanisms different from AF. Identifying one or more of these mechanisms could allow for a more targeted and individualized approach for secondary prevention.[8,9] To this regard, the results of the recent RENO study (Causes and Risk Factors of Cerebral Ischemic Events in Patients With Nonvalvular AF Treated With NOACs for Stroke Prevention) suggested that the prescription of reduced off-label dose of NOACs, atrial enlargement, hyperlipidemia, and CHA_2DS_2-VASc were independently associated with high ischemic stroke rates.[10] Currently, guidelines on managing stroke recurrences under NOACs are lacking as no specific randomized controlled trials have addressed the issue of changing or not the NOAC administered at the time of stroke.

In light of the aforementioned, the RENO-EXTEND study sought to estimate the rates of ischemic and bleeding events after an acute ischemic stroke in patients with AF while on treatment with NOACs and investigate for predictive factors of these events. Subsequently, we compared the estimated risks for ischemic and bleeding events between those who had or not their anticoagulant therapy changed.

METHODS

The data that supported the findings of this study are available from the corresponding author upon reasonable request.

In this multicenter observational cohort study performed between January 2018 and December 2020, consecutive acute cerebrovascular ischemic patients with AF who were taking NOAC treatment at the time of the event were prospectively collected. Patients were enrolled from 43 Stroke Units across Europe and United States (25 from academic hospitals and 18 from nonacademic hospitals) all with high expertise about the management of patients with stroke.

Patients who had suspended anticoagulant therapy at least 24 hours before the cerebrovascular event for any reason and patients who did not guarantee adherence to treatment were excluded. To verify compliance, the patients and family members were asked how the prescribed anticoagulant was taken. Each research center was free to change or not the NOAC treatments.

The study was approved by the pertinent institutional review boards if required. Informed consent was obtained according to local requirements.

This study was designed following recommendation of the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology; Supplemental Material).

Clinical, Radiological, and Laboratory Risk Factors

Data on known risk factors for stroke were collected as previously described[11,12] (Supplemental Material).

The doses of NOACs were recorded, and any reasons for prescribing reduced doses were also collected. Reduced doses of NOACs were considered off-label in the absence of the recommended clinical and laboratory criteria for dose reduction.[13–16]

Both the CHA_2DS_2-VASc score and the HAS-BLED score (hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol) before and after the index event were also calculated[17] (Supplemental Material).

Lead investigators were required to report on the type and dosage of prescribed NOACs and the vascular management. Moreover, physicians were also required to perform neuroradiological examinations: cerebral computed tomography or cerebral magnetic resonance imaging. Any recurrent ischemic stroke, symptomatic systemic embolism, intracranial bleeding, and death were recorded during this period.

Cause of the Index Stroke

For the causes of stroke, the atherosclerosis, small vessel disease, cardiac pathology, other causes, and dissection (A-S-C-O-D) classification was adopted.[18] A-S-C-O-D phenotyping assigns a degree of likelihood of causal relationship to every potential disease (1 for potentially causal, 2 for causality is uncertain, 3 for unlikely causal but the disease is present, 0 for the absence of disease, and 9 for an insufficient workup to rule out the disease). The cause of the index event was considered cardioembolic in the case of (A[0,2,3]-S[0,2,3]-C1-O[0,2,3]) according to the A-S-C-O-D classification.

Outcome Evaluation

Patients were followed-up prospectively by face-to-face or telephone interviews. The duration of follow-up was at least 12 months. Patient follow-ups started at the moment of index events. The initiation of oral anticoagulation followed international guideline recommendations.[2]

The primary outcome measure was the composite of ischemic stroke, systemic embolism, intracranial bleeding, and major extracranial bleeding. Recurrent stroke was defined as the sudden onset of a new focal neurological deficit of vascular origin in a site consistent with the territory of a major cerebral artery and was categorized as ischemic or hemorrhagic. Intracranial bleeding was defined as a spontaneous hemorrhagic stroke (intraparenchymal bleeding), subdural, or subarachnoid hemorrhage. Traumatic intracranial bleeding was not considered as an outcome event. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ confirmed by imaging at either surgery or autopsy.

Death data were recorded; functional recovery was assessed by the modified Rankin Scale, dichotomizing between functional independence (modified Rankin Scale score 0–2) and disability (modified Rankin Scale score ≥3).

Major extracranial bleeding was defined as a reduction in the hemoglobin level of 2 g per deciliter or more, the requirement of a blood transfusion of at least 2 units, or symptomatic bleeding in either a critical area or organ.

Follow-up visits and outcome adjudication were performed by local investigators, not in a blinded fashion.

Statistical Analysis

For patients with or without outcome events, differences in clinical characteristics and risk factors were calculated using the χ^2 test of proportions (with a 2-sided α level of 5%). Ninety-five percent CIs were calculated for odds ratio (OR). A second step analysis aimed to identify predictors of outcome events among baseline characteristics. Univariate tests were performed to compare clinical characteristics and risk factors associated with stroke on admission in patients with and without outcome events. Multivariable logistic regression analysis was performed to identify independent predictors for outcome events. The variables included in this analysis were the following: CHA_2DS_2-VASc score after admission for the index stroke (separately as a continuous variable or including the risk factors within the score excluding the CHA_2DS_2-VASc score), hyperlipidemia, current alcohol abuse, current smoking habit, paroxysmal AF, presence of malignancy, antiplatelet therapy in addition to NOACs after the index stroke, cardioembolic index stroke, history of previous major bleeding and changes in the type of anticoagulant therapy after the index stroke.

To compare the risk of outcome events in those patients who did not have their anticoagulant therapy changed after the index event and those who changed their anticoagulant therapy, the relation between the survival function and the set of explanatory variables were calculated by Cox proportional hazard models. These models provide an estimate of the treatment effect on survival after an adjustment for other explanatory variables. The same Cox proportional hazard analyses were performed in patients diagnosed with a cardioembolic ischemic index stroke to compare the risk of outcome events in those patients who had had their anticoagulant therapy changed after the index event and those who had not had their anticoagulant therapy modified. The results of these analyses were reported as hazard ratios.

Using propensity score matching (PSM), a further analysis was performed to compare the overall risk of outcome events in those patients who did not have their anticoagulant therapy modified after their index events versus those who underwent modifications of anticoagulant therapy. In this PSM, survival function and empirical cumulative hazard function were estimated via the Kaplan-Meier estimator for the 2 groups; any differences between survival functions were tested using the log-rank statistic (or Mantel-Haenszel test), that in the case of large samples has an asymptotic χ^2 distribution.[19] Patients were censored at the time of an outcome event, death, or if they had been lost to follow-up. Data were analyzed using the SPSS/PC Win package 25.0.

Sample Size Calculation

To perform a logistic regression analysis, we needed at least 10 patients with outcome for each variable included in the model.[20] The expected outcome event rate at 12 months was estimated to be 11%.[9] In light of the above, to evaluate the predictors of the primary outcome events, it was calculated that 910 patients would have been needed; meaning that at least 10 variables were required for inclusion in the model to address a sufficient level of confounding.

RESULTS

Characteristics of the Patients

Overall, 1300 consecutive patients who suffered an acute ischemic stroke while on treatment with NOACs were included in the study. Of these, 1240 patients were included in the analysis (10 patients were excluded due to incomplete data, and 50 were lost to follow-up, and there were no data for them; Figure S1). Of these 50 patients, 16 patients had their NOACs changed, whereas 15 did not and 19 did not receive NOACs. The characteristics of the included patients are reported in Table S1. Out of 1240 patients, 491 (39.6%) were appropriately treated with low-dose NOACs before the index event, and 149 of these (30.3%) were treated with a nonlabel low dose.

Concerning the causes of the index events, 920 (74.2%) were diagnosed as cardioembolic strokes, according to the A-S-C-O-D classification.

After the index event, 490 patients treated with an appropriate dose of NOAC (39.5%) had their NOACs changed (68 switched from dabigatran to factor Xa inhibitor, 139 from factor Xa inhibitor to dabigatran and 283 switched to another Xa inhibitor). In contrast, 527 treated with appropriate dose (42.5%) continued with the same NOAC at the same dose, 83 (6.7%) continued with the same NOAC but had the dose increased, 58 (4.7%) were shifted to warfarin and 82 (6.6%) were shifted to low molecular weight heparin and never prescribed oral anticoagulants for the following reasons: early ischemic stroke recurrence, early hemorrhagic transformation, early death or severe index stroke. The characteristics of the patients subdivided by the types of treatment received after the index event are summarized in Table S2 while patterns of switch are revealed by Sankey diagram in Figure S2.

On multivariable analysis, predictive factors associated with change of NOACs included CHA_2DS_2-VASc score (OR, 1.4 [95% CI, 1.1–1.8] for each point increase; *P*=0.001) and index event of cardioembolic origin (OR, 2.4 [95% CI, 1.4–4.1]; *P*=0.001), while adding an antiplatelet to a NOAC was associated with retaining the preexisting NOAC regimen (OR, 0.5 [95% CI, 0.3–1.0]; *P*=0.05).

When including in the model the different research centers, similar results were obtained for CHA_2DS_2-VASc score (OR, 1.3 [95% CI, 1.1–1.6] for each point increase; *P*=0.001) and for index event of cardioembolic origin (OR, 2.9 [95% CI, 1.8–4.7]; *P*=0.001).

Rates and Predictive Factors of Ischemic and Bleeding Events

After a mean follow-up time of 15.0±10.9 months (1550 patient-years; median 12 months, interquartile range, 12–15), 192 patients (15.5%) had 207 outcome events corresponding to an annual rate of 13.4%. The following events were observed: 111 ischemic strokes, 15 systemic embolisms, 24 intracranial bleedings, and 57 were major extracranial bleedings. The ischemic and bleeding events according to the type of treatment are summarized in Table S3.

On multivariable analysis, predictive factors for thromboembolic and bleeding events were history of major bleeding (OR, 4.1 [95% CI, 2.2–7.6]; *P*=0.0001), the addition of an antiplatelet to NOACs (OR, 1.7 [95% CI, 1.1–2.9]; *P*=0.03), age (OR, 1.0 [95% CI, 1.0–1.0] for each year increase or OR, 1.2 [1.0–1.4] for each decade increase; *P*=0.045), male sex (OR, 1.5 [95% CI, 1.0–2.2]; *P*=0.04) and hypertension (OR, 2.2 [95% CI, 1.1–4.2]; *P*=0.02).

Predictive factors of ischemic events (ischemic stroke and systemic embolism) included CHA_2DS_2-VASc score after the index event (OR, 1.2 [95% CI, 1.0–1.3] for each point increase; *P*=0.05) and hypertension (OR, 2.3 [95% CI, 1.0–5.1]; *P*=0.04).

Predictive factors of hemorrhagic events (intracranial and major extracranial bleedings) included age (OR, 1.1 [95% CI, 1.0–1.2] for each year increase; *P*=0.002), history of major bleeding (OR, 6.9 [95% CI, 3.4–14.2]; *P*=0.0001) and the addition of an antiplatelet to a NOAC (OR, 2.8 [95% CI, 1.4–5.5]; *P*=0.003). Figure 1 and Table S4 describe the events in those patients who had or not antiplatelet therapy associated with NOAC after index event.

In patients with a history of stroke or transient ischemic attack, the rate of the combination of thromboembolic and bleeding events was 16.8% (79/471) compared with 14.7% (113/769) of the patients without a history of stroke or transient ischemic attack (*P*=0.1).

Outcome Events in Patients Who Continued Anticoagulant Therapy Unchanged After the Index Event Compared With Those Who Changed the Type of NOAC

The Cox regression curve analyses comparing the overall outcome events in patients who did not have their NOAC changed after the index event (n=527) with those who changed the type of their NOACs (n=490) are reported in Figure 2. There was no difference in the rate of the primary outcome (hazard ratio of 1.1 [95% CI, 0.8–1.4]), or of ischemic outcome events (hazard ratio of 1.1 [95% CI, 0.7–1.4]) or bleeding outcome events (hazard ratio of 1.4 [95% CI, 0.7–2.5]). Comparing strategies of anticoagulation after the index event, it resulted

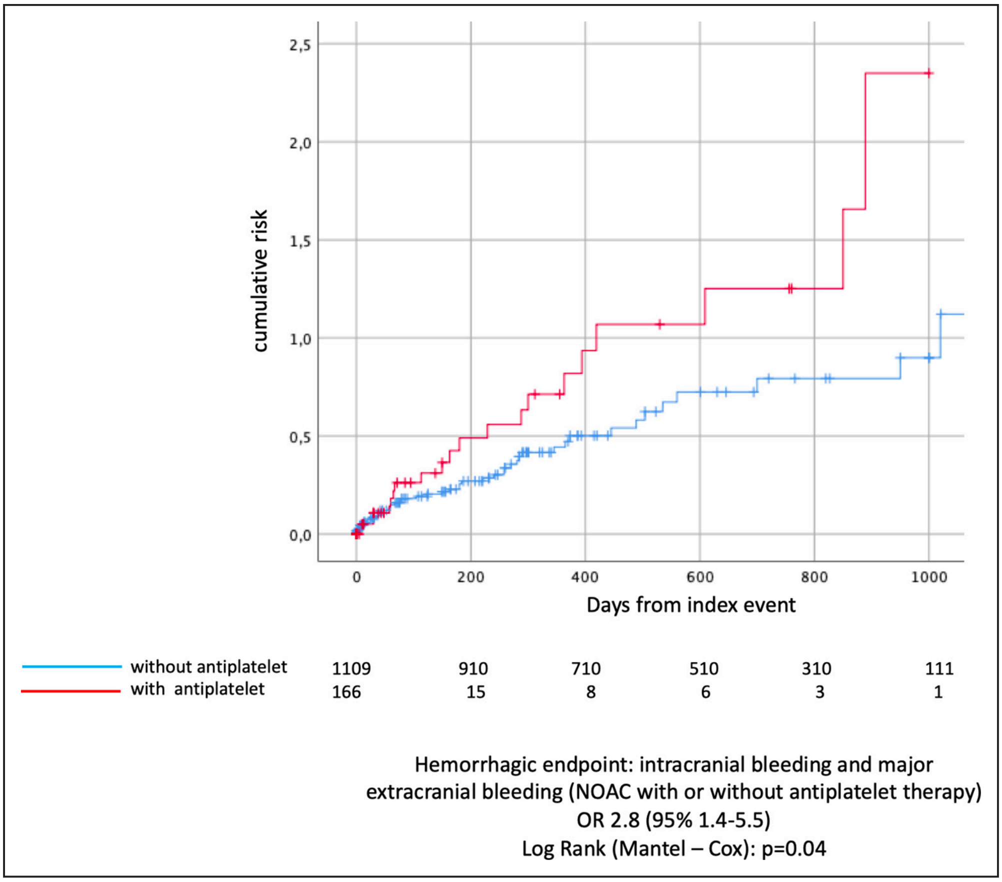

Figure 1. Hemorrhagic end point events (intracranial hemorrhage and major extracranial hemorrhage) in patients who had or not associated antiplatelet therapy to nonvitamin K antagonist oral anticoagulant (NOAC) in the overall population.

that, all the strategies were significantly less associated with the primary outcome, when comparing the results from a NOAC to the low molecular weight heparin switch (log rank–Mantel-Cox; *P*=0.01 versus NOAC-to-NOAC switch and NOAC dosage change; *P*=0.003 versus NOAC-to-warfarin switch, and *P*=0.005 versus no NOAC change; Figure S3). No observed differences emerged between NOAC-to-NOAC change strategies. The Cox regression curve analyses that compared the outcome events in patients with cardioembolic stroke as index event who did not have their type of NOAC changed after the index event, with those who underwent NOAC type changes are reported in Figure S4. Out of the 920 patients who had a cardioembolic stroke as an index event, 401 changed their type of NOAC after the index event, whereas 351 did not: 58 (14.5%) from the former group had a combined outcome event, compared with 44 (12.5%) from the latter group (*P*=0.4). Furthermore, 34 (8.6%) of the patients who had their NOAC type changed had an ischemic outcome event, compared with 27 (7.7%) of the patients who did not undergo such a change (*P*=0.7). About the bleeding outcome events, no differences were observed between the groups: 24 (5.9%) and 17 (4.8%), respectively (*P*=0.1).

After PSM, 421 patients who did not have their type of NOAC changed were compared with 421 patients who did it. In Table S5, the characteristics of the patients after PSM are reported.

About outcome events, 67 (15.9%) of the patients who had their NOAC type changed had a combined outcome event, compared with 59 (14.1%) of those who did not (log rank–Mantel-Cox; *P*=0.4). Furthermore, 41 (9.7%) of the patients who had their NOAC type changed had an ischemic outcome event, compared with 37 (8.8%) of the patients who did not (log rank–Mantel-Cox; *P*=0.6). About bleeding outcome events, a difference between the groups: 26 (6.2%) and 22 (5.2%), respectively (log rank–Mantel-Cox; *P*=0.5) was not observed.

The Kaplan-Meier curve that compared the combined outcome events (ischemic stroke, systemic embolism, intracranial hemorrhage, and major extracranial bleeding) in patients who did not have their type NOAC changed with those who did not after PSM is reported in Figure S5.

DISCUSSION

The results of this study in patients with the previous stroke while on treatment with NOACs, showed a combined rate of thromboembolic and bleeding events of 16.7%, corresponding to an annual rate of 13.4%. These rates are higher than those observed in previous randomized controlled trials: 2.83% in the ENGAGE

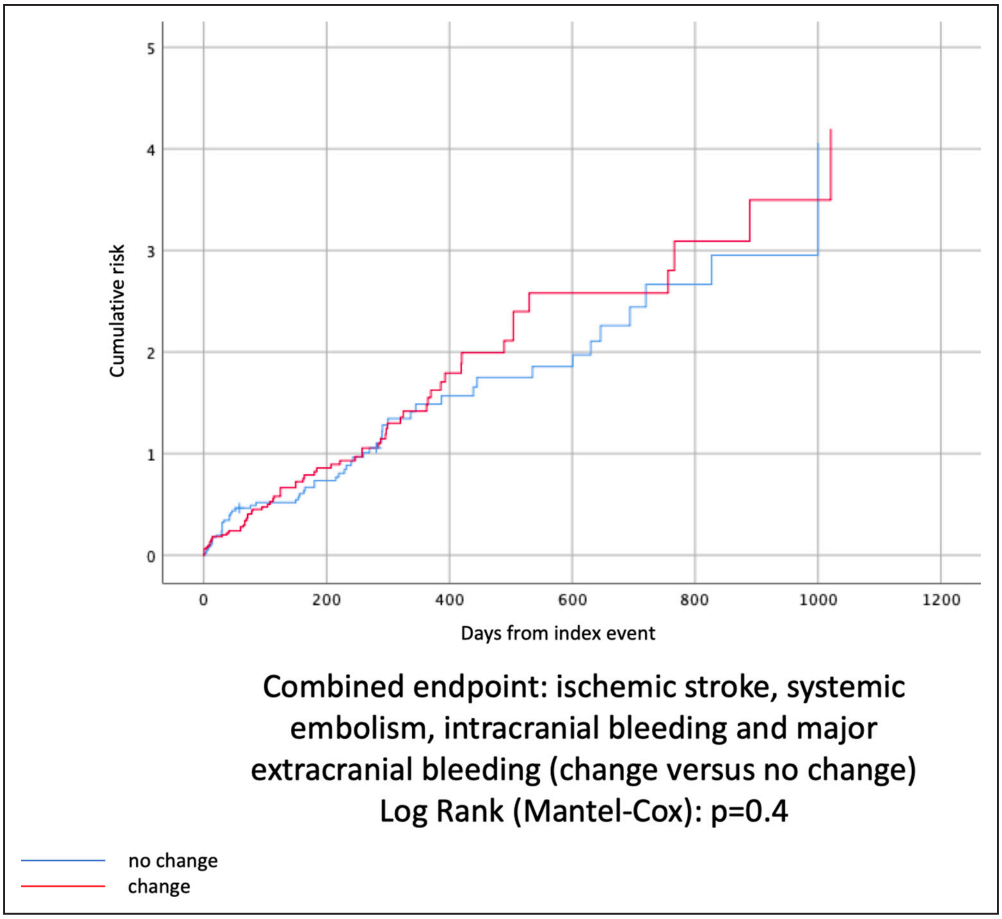

Figure 2. Cox regression curve analyses comparing the combined outcome events (ischemic stroke, systemic embolism, intracranial hemorrhage, and major extracranial hemorrhage) in patients who did not have their nonvitamin K antagonist oral anticoagulant (NOAC) changed after the index event with those who changed the type of their NOACs in the overall population.

AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation - Thrombolysis in Myocardial Infarction 48 Trial) for edoxaban[21]; 2.32% in RELY (Randomized Evaluation of Long-Term Anticoagulant Therapy Trial) for dabigatran 110 mg BID (relative risk, 0.84 [95% CI, 0.58–1.20]) and 2.07% for 150 mg BID[22]; 1.01% in ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Trial) for apixaban[15]; and 2.79% in ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) for rivaroxaban.[23] An individual patient data pooled analysis of 7 prospective real-world cohort studies on AF patients with recent cerebral ischemia, who had been on anticoagulation treatment, reported an annual risk for recurrent ischemic stroke and death of 4.7% and 10.2%, respectively, which is in line with our study.[5] This high residual stroke risk needs to be quantified for targeted treatment in these patients. The currently used CHA_2DS_2-VASc score may not be adequate to quantify the residual stroke risk as it weighs the history of previous strokes with a score of only 2. Furthermore, the CHA_2DS_2-VASc score does not acknowledge an added risk associated with every stroke recurrence in patients already under anticoagulation treatment.

The residual risk for stroke is often considered a treatment failure or related to causes other than cardioembolic. So, the first step in these patients is excluding noncardioembolic causes that would lead the physician to adjust to the original treatment strategy. In clinical practice, one of the options for patients with noncardioembolic recurrences and intracranial or extracranial atherosclerosis and small vessel disease may be to add antiplatelet therapy. However, this regimen was associated with an increase in the risk of major bleeding, with only a small stroke prevention benefit.[24] Likewise, our study found that add-on antiplatelets significantly increased the risk of bleeding in line with the AUGUSTUS trial (An Open-Label, 2x2 Factorial, Randomized Controlled Clinical Trial to Evaluate the Safety of Apixaban Versus Vitamin K Antagonist and Aspirin Versus Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention) and by Capodanno et al results on patients undergoing percutaneous coronary intervention, leading us to suggest the avoidance of prescribing the combination therapy including dual antiplatelet therapy and NOACs.[25,26]

In this study, we observed that changing the type of anticoagulant after the index event was not associated with a decreased risk of ischemic stroke recurrence, as reported by 2 observational studies.[5,6] These no responders to anticoagulant stroke therapy have an increased risk of ischemic events for each point increase of CHA_2DS_2-VASc score. Such high-risk patients might benefit from alternative preventive options, including left atrial appendage occlusion[27] even if there is a lack of data about the benefit of this procedure in patients on NOACs with a prior stroke, but only in those patients undergoing cardiac surgery.

The RENO-EXTEND study has several limitations: (1) it was observational, and neither individual NOAC type nor their doses were randomized; (2) other pharmacological treatments besides NOACs were not investigated. However, interactions between NOACs and other drugs are reported to be much lower than those of warfarin; (3) we have no information about the plasma level of NOACs; (4) the sample size was calculated to investigate for predictive factors associated with ischemic and bleeding events, but not to compare the risks of these events in patients who had and those did not have their anticoagulation molecule changed; (5) 50 patients were lost at follow-up; (6) as the reduced dose criteria are different in the label in Europe and United States, we adopted a single definition of the appropriate dose.

The strengths of our study include its large sample size and its prospective design. Additionally, our analyses reflect real-life experiences and thus may provide valuable information that could significantly reduce the incidence of ischemic events in patients with AF and stroke during NOAC therapy.

In conclusion, patients having a stroke despite being on therapy with NOACs are at high risk of recurrent ischemic stroke and bleeding. Further research is needed to investigate mechanisms of recurrent stroke and improve secondary prevention in these patients.

ARTICLE INFORMATION

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Supplemental Material

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