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Brief Communication

Characteristics of Ischemic Stroke Despite Oral Anticoagulant Use For Atrial Fibrillation

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ABSTRACT: Oral anticoagulation (OAC) prevents stroke in atrial fibrillation, yet a residual stroke risk remains. In this single-center retrospective analysis of acute ischemic stroke patients despite OAC, suboptimal OAC treatment is common (30%: inappropriate dosing (17%); patient non-adherence (13%)). Other causes of stroke included OAC interruption (14.5%), a competing stroke mechanism (11.0%), and undetermined breakthrough stroke in 44.5%. Overall, easily modifiable causes of ischemic stroke despite OAC are common. Accordingly, strategies to improve treatment compliance, including appropriate dosing along with guideline-based risk factor and periprocedural OAC management, should be emphasized to improve secondary stroke prevention in this patient population.

RÉSUMÉ : Les accidents vasculaires cérébraux ischémiques et leurs caractéristiques, dans la fibrillation auriculaire, malgré l'anticoagulothérapie orale. Les anticoagulants oraux (AO) visent à prévenir la survenue d'accidents vasculaires cérébraux (AVC) dans le contexte de la fibrillation auriculaire, mais il persiste un risque résiduel. Ainsi, dans une analyse rétrospective de dossiers de patients ayant subi un AVC ischémique aigu, malgré les AO, réalisée dans un centre de traitement, l'application sous-optimale de traitement par les AO s'est révélée chose courante (30 %; posologie inappropriée [17 %], non-observance thérapeutique [13 %]). Par ailleurs, il existe d'autres causes possibles d'AVC, notamment l'interruption de l'anticoagulothérapie orale (14,5 %), la présence concomitante de mécanismes d'AVC (11,0 %) et la survenue d'AVC d'origine inconnue (44,5 %). Pourtant, plusieurs causes d'AVC ischémique, malgré les AO, sont facilement modifiables. Aussi faudrait-il mettre l'accent sur des stratégies permettant d'améliorer l'observance thérapeutique, la prescription de régimes posologiques appropriés ainsi que la prise en charge de facteurs de risque et de l'anticoagulothérapie orale en phase péri-interventionnelle, fondée sur des lignes directrices, dans le but rendre plus efficace la prévention secondaire des AVC dans ce groupe particulier de patients.

Keywords: Acute stroke; anticoagulation; treatment failure

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Atrial fibrillation (AF), an independent predictor for ischemic stroke, increases the risk by three to five fold.[1] Oral anticoagulation (OAC) is an effective treatment to prevent ischemic stroke when compared to placebo or antiplatelet therapy.[2,3] Nonetheless, a residual stroke risk despite OAC remains, estimated at 1.4% per year with direct oral anticoagulants (DOAC) use and 1.7% per year with vitamin-K antagonists (VKA).[2] A recent pooled analysis showed that patients with ischemic stroke despite OAC are at higher risk of recurrent events, thereby highlighting the need to optimize stroke prevention strategies in this patient population.[4] Mechanisms underlying ischemic stroke despite therapeutic OAC remain however largely elusive.

Modifiable causes of ischemic stroke despite OAC include pharmacological inefficacy due to either patient noncompliance, inappropriate dosing, drug or food interactions or periprocedural interruption.[5] Furthermore, the presence of other stroke mechanisms (such large or small-vessel disease) may contribute to ischemic stroke risk.[6,7] Beyond easily-identifiable stroke mechanisms, however, a significant proportion of ischemic strokes despite OAC remain unexplained and portend worse clinical outcomes.[4] Due to a lack of available evidence to guide management, specific recommendations can not be made regarding optimal management in these patients.[5,8] The aim of this study was to describe the characteristics of patients presenting with an ischemic stroke despite OAC use in a single high-volume Canadian comprehensive stroke center (CSC).

A retrospective observational study was performed of consecutive patients evaluated for acute stroke at the Centre Hospitalier de l'Université de Montreal, with clinical data

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prospectively collected in the Montreal Neurovascular and STrokE Repository. A large proportion of suspected acute stroke patients arrive at our center after redirection from primary stroke centers (PSC) by paramedics in the case of severe suspected stroke. As such, redirected patients are repatriated to PSC the next day to continue medical management, including stroke workup. All consecutive adults diagnosed with acute ischemic stroke and preexisting use of OAC for known AF between 12/01/2017 and 03/31/2021 were included in the study. Data were analyzed separately as: 1) the *whole cohort* (all stroke patients evaluated at the CSC) and 2) *local* cohort (patients subsequently hospitalized at our institution), on account of missing data, and in particular in-hospital stroke workup, in the subgroup of patients subsequently repatriated to PSC. Data collection and analyses was approved by the local institutional review boards with waiver of patient consent given the retrospective nature of the study (local REB project number: 2021-9429, 20.337). Statistical analyses included chi-square test of independence or Fisher's exact tests for categorical variables and the Mann–Whitney *U*-test for continuous variables to test differences between groups. Outcomes were dichotomized into favorable (mRS ≤ 2) and poor outcome (mRS 3–6). Data were analyzed using SPSS software (IBM SPSS Statistics Version 26.0.0.1). Statistical level of significance was set at $p < 0.05$.

During the study period, 2,700 patients were evaluated for a suspected acute stroke, of which 173 (0.64%) were diagnosed with an ischemic stroke despite OAC and were included in the study (*whole* cohort). Among these, 65 patients were subsequently hospitalized at the CSC (*local* cohort). Baseline characteristics including prior antithrombotic use for the whole cohort are shown in Table 1. Regarding OAC at the time of stroke, 27 (15.6%) patients were on VKA, while 146 (84.4%) were prescribed DOACs. Suboptimal OAC treatment was found in 52 (30%) patients, due to inappropriate dosing (17%), and patient non-adherence (13%). A concomitant stroke mechanism was found in 19 (11.0%) patients, and stroke etiology was classified as undetermined other than AF in 77 (44.5%) patients. An interruption of the OAC treatment was present in 25 (14.5%) patients, on account of bleeding complications in 3, recent stroke in 2, and invasive procedures in 20 patients including gastrointestinal investigations, dental procedures, cardiac pacemaker change, skin biopsy, and ENT surgery). Data regarding timing and duration of periprocedural OAC interruption were unavailable.

Baseline characteristics of the local cohort were similar to the whole cohort, except for fewer LVO and lower baseline NIHSS (Table 1). Transthoracic echocardiography (TTE) was performed in 38 (59%) patients. Of these, left atrial volumes were found to have severely enlarged in 15 and moderately enlarged in 3 based on Lang's criteria.[9] Among surviving patients at discharge ($n = 44$), OAC management was highly heterogeneous (Figure 1). The outcome at 3 months was available for 57 (88%) patients, with median (IQR) 90-day mRS 4 [2–6]. Nineteen (33.3%) patients had a favorable outcome (mRS 0–2) and 21 (32.3%) patients died.

In our study, modifiable and preventable causes of ischemic stroke were identified in 30% of patients; results that are in line with previous findings,[10] albeit in contrast to other studies suggesting that patients on DOACs typically achieve high rates of adherence.[11] Off-label inappropriate under-dosing of DOAC remains an important cause of ischemic stroke despite DOAC therapy,[12] with rates reaching 17% in our study.

Periprocedural management of anticoagulation in patients undergoing invasive procedures is another major cause of ischemic stroke despite OAC use. In our study, 14.5% of patients presented with an ischemic stroke due to OAC interruption, of which 80% were on account of an invasive procedure. Interrupting anticoagulation for an invasive procedure transiently increases the risk of thromboembolism.[13] Despite published literature and clinical practice recommendations,[14] periprocedural anticoagulation managements remains heterogeneous, with inappropriately prolonged

Table 1: Baseline characteristics of the whole study cohort ($n = 173$) and the hospitalized (local) subgroup ($n = 65$) with acute ischemic stroke despite therapeutic anticoagulation. Values are presented as *n* (%), mean ± SD or median [IQR]

Characteristic	Whole cohort *N* = 173	Local cohort *N* = 65
Age	79.0 ± 10.0	78.6 ± 10.5
Female sex	90 (52.0)	26 (40.0)
Medical history		
Hypertension	128 (74.0)	48 (73.8)
Dyslipidemia	100 (57.8)	36 (55.4)
Type 2 diabetes	48 (27.7)	17 (26.2)
Active cigarette smoking	15 (8.7)	7 (10.8)
Coronary artery disease	36 (20.8)	15 (23.1)
Valvulopathy	29 (16.8)	16 (24.6)
Congestive heart failure	23 (13.3)	11 (16.9)
CHADS-VASC	4 [3–5]	4 [3–5]
Prior antithrombotic use		
Warfarin	27 (15.6)	5 (7.7)
DOACs	146 (84.4)	60 (92.3)
Apixaban	79 (54.1)	31 (51.7)
Rivaroxaban	49 (33.6)	20 (33.3)
Dabigatran	15 (10.3)	6 (10.0)
Edoxaban	3 (2.1)	3 (5.0)
Combined antiplatelet use	12 (6.9)	6 (9.2)
Index stroke event		
Baseline NIHSS	15 [7–22]	8 [5–20.25]
Large vessel occlusion*	88 (50.9)	21 (32.3)
IV thrombolysis	20 (11.6)	6 (9.2)
Endovascular thrombectomy	101 (58.4)	20 (30.8)
Discharge NIHSS	8 [3–19]	5 [1–13.5]
Identified stroke mechanism		
OAC non-adherence	23 (13.3)	11 (16.9)
OAC interruption**	25 (14.5)	7 (10.8)
Inappropriate OAC dose	29 (16.8)	6 (9.2)
Undetermined breakthrough stroke	77 (44.5)	28 (43.1)
Other competing mechanism***	19 (11.0)	13 (20.0)

*CTA was not performed at presentation in 26 patients (whole cohort) and 15 patients (local cohort) due to an absence of indication for EVT or allergy to contrast product. For the patients in the local cohort without a CTA at presentation: six patients had a recent vascular imaging of the neck or a carotid doppler during the hospitalization, four patients died before performing vascular imaging and five patients did not receive vascular imaging since they were not considered candidates for vascular surgery and another stroke mechanism seemed more likely.
**Because of invasive procedure, bleeding, recent stroke.
***Atherosclerosis, dissection, endovascular intervention, small-vessel disease, prothrombotic state, dural fistula, zoster vasculitis.

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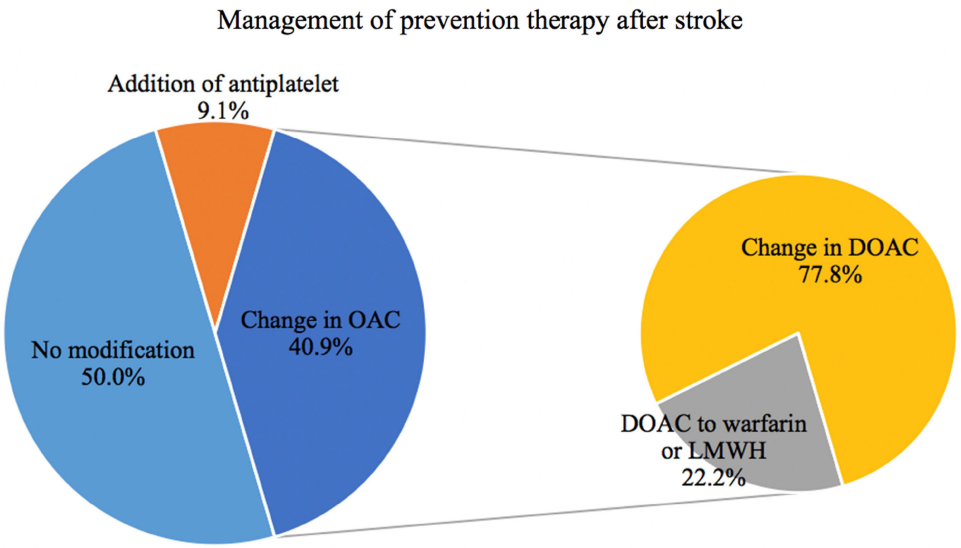

Figure 1: Management of secondary stroke treatment in patients with an ischemic stroke despite current anticoagulation in the local cohort. (21 patients died before restarting anticoagulation treatment, results shown for 44 patients total). LMWH = low molecular weight heparin

OAC interruption and subsequent embolic risk.[15] Details regarding OAC interruption were not systematically captured and as a result, we were unable to decipher whether OAC management followed guideline recommendations. Evidently, systemic capture of these data is necessary to optimize periprocedural antithrombotic management.

In previous studies, 30% of patients with ischemic stroke despite OAC had a non-cardio-embolic cause of stroke,[12] as supported by our local cohort, in which a competing cause of stroke was found in approximately 20% of patients. Whether cardiovascular risk factor management was optimal in our patients is not known, but the presence of other cardiovascular risk factors in patients taking OAC for AF increases the risk of recurrent stroke.[4,12]

Of patients who underwent TTE, severe left atrial enlargement was found in a significant proportion of patients. Indeed, several studies suggest that left atrial enlargement severity, a marker of atrial cardiopathy, is associated with increased stroke risk, particularly in those with ischemic stroke despite OAC.[16–19] Left appendage morphology was not described in TTE reports, although this has been shown to be associated with the risk of stroke.[20] It is currently unknown whether the presence of left atrial enlargement or left appendage morphology should modify anticoagulation regimens or periprocedural anticoagulation interruption in patients with AF.

Regarding post-stroke antithrombotic management, our findings show that practice patterns were heterogeneous, reflecting the lack of evidence to guide clinicians in this context.[8] In 50% of patients, physicians chose to continue prior anticoagulation, while in the other half, the anticoagulant agent was either changed or complemented with the addition of an antiplatelet agent. A recent survey found similar practice patterns.[21] Nevertheless, changing the type of anticoagulant may not help to reduce the risk of future ischemic strokes.[4]

Our study has several limitations. Although all patient data was collected prospectively as part of clinical care, as a retrospective study, information regarding, stroke workup and follow-up data were not available after CSC discharge for the majority of our population given PSC repatriation protocols. Furthermore, information was not available to discern whether periprocedural management and OAC interruption was appropriate and guideline-based in most patients due to the retrospective nature of the analyses. Lastly, since this is a retrospective observational study with relatively small sample size in a single CSC, we were limited in detecting significance differences in our results, and our findings may not be generalizable. Furthermore, the possibility of selection bias exists, particularly regarding more severe strokes seen at our institution, potentially skewing the results. Finally, the relatively short follow-up period limits the ability to assess the risk of recurrent stroke in this high-risk population.

Overall, one-third of stroke despite therapeutic OAC was identified to be secondary to preventable causes such as inappropriate OAC dosing and a lack of treatment compliance. Patient and physician education regarding the importance of adequate OAC dosing, treatment compliance and guideline-based periprocedural OAC management should be emphasized to reduce ischemic stroke risk while prospective studies are warranted to improve secondary stroke prevention in this patient population.

Author contributions. Study conception and design, data collection, statistical analysis, manuscript writing: MCD, CD, LG.

Gathering and inclusion of patients in the prospective registry, manuscript revision: ND, YD, GJ, CO, CS, AYP, LG.

Cardiology expertise and manuscript revision: GR.

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