Mechanisms of ischaemic strokes and transient ischaemic attacks despite oral anticoagulation in patients with atrial fibrillation

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ABSTRACT

AIMS: The aim of this article was to characterise the mechanisms underlying "breakthrough" ischaemic stroke (IS) or transient ischaemic attack (TIA) despite oral anticoagulation in patients with atrial fibrillation (AF).

METHODS: We conducted a cross-sectional analysis of adults with non-valvular AF who experienced IS/TIA in the fifth Auckland Regional Community Stroke Study (ARCOS V: September 2020 to August 2021). Using clinical records, we collected data on demographics, comorbidities and peri-event anticoagulant dosing and intake. Anticoagulant adherence in the months preceding IS/TIA was categorised as good control if proportion of days covered (PDC) ≥80% for direct oral anticoagulant users or time in therapeutic range (TTR) ≥70% for warfarin users. IS/TIA mechanism was adjudicated using standardised criteria and classified as cardioembolic or non-cardioembolic, and patient characteristics were compared.

RESULTS: Among 179 patients (76/179 [43%] female), 138/179 events (77%) were adjudicated as cardioembolic, while the remainder were attributed to competing mechanisms. Compared with non-cardioembolic events, cardioembolic aetiology was associated with younger median age (72 vs 81 years), lower proportions with good anticoagulant control (87/138 [63%] vs 34/41 [83%], p=0.017) and higher rates of peri-event missed or under-dosing (90/138 [65%] vs 18/41 [44%], p=0.014). In multivariable analysis, good control was independently associated with higher odds of a non-cardioembolic mechanism (adjusted odds ratio 3.67 [95% confidence interval 1.35–9.99], p=0.011).

CONCLUSION: Most breakthrough IS/TIA events on oral anticoagulation were either associated with anticoagulant under-exposure (in patients with a cardioembolic aetiology) or a competing mechanism rather than anticoagulant failure. These findings highlight the importance of careful assessment to inform appropriate secondary prevention strategies.

Oral anticoagulants substantially reduce stroke risk due to atrial fibrillation (AF). However, a residual risk of ischaemic stroke (IS) or transient ischaemic attack (TIA) persists. Such events are often labelled "breakthrough" strokes or treatment failure. Increasingly, however, evidence suggests that many of these events arise from competing stroke mechanisms unrelated to AF or from potentially preventable medication-related factors, such as non-adherence or sub-therapeutic anticoagulant exposure.[1,2] For New Zealand, the relative contribution of competing stroke mechanisms and potentially preventable anticoagulant-related factors to IS/TIA occurring despite oral anticoagulation remains poorly characterised.

The Auckland Regional Community Stroke (ARCOS) study is a long-running, population-based registry that prospectively captures all stroke and TIA events occurring over a 12-month period once every decade within a well-defined geographical region. The registry includes comprehensive data on patient demographics, comorbidities and outcomes, with near-complete case ascertainment achieved through multiple overlapping sources.[3]

In this study, we identified patients with non-valvular AF receiving oral anticoagulation with IS/TIA in ARCOS V (fifth iteration of study). Events were adjudicated and classified as cardioembolic or non-cardioembolic based on clinical characteristics and investigation findings.

The aims of this study were:

- to characterise the mechanisms underlying IS/TIA occurring despite oral anticoagulation in patients with AF;
- to compare clinical characteristics and anticoagulant exposure between cardioembolic and non-cardioembolic events; and

- to explore factors associated with non-cardioembolic mechanisms.

This approach directly addresses the real-world clinical challenge of interpreting and managing IS/TIA occurring despite anticoagulation in a New Zealand health system with a high burden of AF and an ethnically diverse population.[4]

Methods

Data on IS/TIA cases were sampled from ARCOS V (1 September 2020 to 31 August 2021). Demographic data, including self-identified ethnicity, were collected using a simplified prioritised ethnicity framework (Māori, Pacific peoples, European and Others), consistent with standard New Zealand reporting practices.[5] Clinical records were reviewed to extract vascular comorbidities (left ventricular failure, hypertension, diabetes, prior IS/TIA, vascular disease) to calculate CHA_2DS_2–VASc stroke risk score (congestive heart failure, hypertension, age ≥75 [doubled], diabetes, prior TIA/IS [doubled], vascular disease, age 65 to 74 and female sex).

Anticoagulant adherence was assessed using the proportion of days covered (PDC) for direct oral anticoagulants (DOACs; dabigatran, rivaroxaban) and time in therapeutic range (TTR) for warfarin for the period leading up to the index event. PDC was calculated using dispensed medication over the relevant observation period, with ≥80% indicating good control.[6] TTR was calculated using the Rosendaal linear interpolation method, with ≥70% defining good control in accordance with the European Society of Cardiology guidelines.[7,8] Adherence was assessed using patient-specific look-back windows aligned to prescription refill cycles.

IS/TIA admission records were reviewed for documented missed anticoagulant doses in the peri-event period. Where available, laboratory coagulation tests were also reviewed to assess anticoagulant exposure. Dilute thrombin clotting time (dTCT) was used as a sensitive indicator of dabigatran exposure, recognising that values reported as >80 seconds may still reflect subtherapeutic anticoagulation.[9] The international normalised ratio (INR) was used to assess warfarin exposure. Routine coagulation assays (prothrombin time [PT] and activated partial thromboplastin time [aPTT]) were not used to assess rivaroxaban exposure due to known limitations in sensitivity and specificity.[10] DOAC levels were infrequently measured but were recorded when available. Anticoagulant exposure was categorised into standard- and under-exposure; the latter was defined as the composite of documented missed doses, subtherapeutic dosing or low laboratory markers of exposure (dTCT <80 seconds for dabigatran or INR <2.0 for warfarin).

All IS/TIA events were independently adjudicated by stroke physicians within the ARCOS Stroke Adjudication Committee using standardised criteria, as previously described.[11] The mechanism was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) system following review of clinical information, neuroimaging, vascular imaging and cardiac investigations.[12] Discrepancies were resolved by consensus at monthly adjudication meetings.

Statistical analysis

Continuous variables are presented as means (standard deviation) if normally distributed, or medians (interquartile range) if non-normally distributed, based on visual inspection of histograms. Group comparisons were performed using Student's *t*-tests for normally distributed variables and Wilcoxon Rank-Sum Tests for non-normally distributed variables. Categorical variables are presented as frequencies (%) and compared using Chi-squared or Fisher's exact tests. A two-sided p-value <0.05 was considered statistically significant. A complete-case approach was used.

In addition, we performed a multivariable logistic regression analysis to explore factors associated with non-cardioembolic mechanisms of IS/TIA, adjusting for age, sex, body mass index (BMI), vascular comorbidities and anticoagulant control. A pre-specified sensitivity analysis was also performed restricting the cohort to patients with IS only, excluding TIA, to assess the robustness of findings to outcome definition.

The study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[13] Analyses were conducted using Stata BE version 17 (StataCorp, College Station, Texas, United States of America).

Ethical approval: The study was approved by the Health and Disability Ethics Committee (HDEC) (ref: 2023 AM 9094) and the Auckland University of Technology Ethics Committee (AUTEC) (ref: 24/4), with a waiver of informed consent.

Data availability statement: Anonymised data are available from the corresponding author on reasonable request, subject to institutional and

ethical approval.

Results

We identified 179 patients, (76/179 [43%] female) with AF receiving oral anticoagulants who presented with IS (130/179 [73%]) or TIA (49/179 [27%]). Following independent adjudication, 138/179 (77%) patients were categorised as having cardioembolic IS/TIA. Table 1 demonstrates the breakdown by TOAST categorisation.

Patients with non-cardioembolic events were older than those with cardioembolic events (median age 81 [interquartile range (IQR) 73–85] vs 72 [63–81] years; p=0.0013) (Table 2). Because prescription refill intervals and patient adherence patterns varied, the adherence assessment window differed between individuals; the median observation period was 149 days (IQR 139–165). Good anticoagulant control during this period was more common among non-cardioembolic than cardioembolic events (34/41 [83%] vs 87/138 [63%]; p=0.017). Conversely, cardioembolic events were more often associated with anticoagulant under-exposure in the immediate pre-event period, including missed doses or subtherapeutic dosing (90/138 [65%] vs 18/41 [44%]; p=0.014).

Obesity was more prevalent among patients with cardioembolic events, with a higher proportion of patients in the BMI ≥40kg/m² category compared with non-cardioembolic events (23/138 [17%] vs 2/41 [5%]; p=0.001). Further, there were significant ethnicity-based differences, with a higher proportion of Pacific peoples and fewer Europeans with cardioembolic strokes.

To explore factors associated with IS/TIA mechanism among patients with breakthrough events, we constructed a multivariable logistic regression model with non-cardioembolic IS/TIA as the outcome (Table 3). Good anticoagulant control was independently associated with higher odds of a non-cardioembolic mechanism (adjusted odds ratio [aOR] 3.67 [95%CI 1.35-9.99], p=0.011). BMI was inversely associated with non-cardioembolic IS/TIA (aOR 0.94 [95%CI 0.88-0.99], p=0.037). Age, sex, and comorbidities were not significantly associated with IS/TIA mechanism.

In a sensitivity analysis restricted to IS events (excluding TIA), results were broadly similar to the primary analysis, with good anticoagulant control remaining associated with a higher likelihood of a non-cardioembolic mechanism (aOR 3.13 [95% CI 1.0–9.84], p=0.05).

Discussion

In this real-world cohort of patients presenting with IS/TIA despite oral anticoagulation, we observed two distinct patterns. Approximately two-thirds of cardioembolic events were associated with reduced anticoagulant exposure, including missed doses, under-dosing or low laboratory markers of anticoagulant effect. In contrast, non-cardioembolic events accounted for nearly one-quarter of presentations and occurred predominantly in patients with good anticoagulant control in the period leading up to the index event and better anticoagulant exposure in the peri-event period. Together, these findings suggest that many so-called "breakthrough" events reflect either potentially preventable under-exposure or competing stroke mechanisms rather than intrinsic failure of anticoagulation, emphasising the importance of careful aetiologic evaluation rather than reflex escalation of antithrombotic therapy.

In the multivariable analysis, patients with good anticoagulant control were more likely to have a non-cardioembolic mechanism. Findings were unchanged in sensitivity analyses restricted to patients with IS.

Higher BMI was more common among cardioembolic breakthrough events, consistent with

Table 1: Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification of ischaemic stroke/transient ischaemic attack mechanism in patients with atrial fibrillation receiving oral anticoagulation.

Mechanism	N/N (%)
Cardioembolism	138/179 (77)
Large artery atherosclerosis	9/179 (5)
Small vessel occlusion	15/179 (8)
Other determined aetiology	2/179 (1)
Undetermined aetiology	15/179 (8)

Table 2: Clinical characteristics and anticoagulant exposure in patients with IS/TIA on oral anticoagulation, stratified by adjudicated mechanism.

	All cases	Non-cardioembolic	Cardioembolic	p-value
Continuous data	**Mean (SD)** **Median (IQR)** **Range**	**Mean (SD)** **Median (IQR)** **Range**	**Mean (SD)** **Median (IQR)** **Range**	
Age (years)	73 (12) 75 (64–82) 27–95	78 (11) 81 (73–85) 50–95	71 (13) 72 (63–81) 27–94	0.0013
CHA_2DS_2–VASc score	3.9 (1.6) 4 (3–5) 0–9	4.2 (1.2) 4 (4–5) 2–7	3.8 (1.7) 4 (3–5) 0–9	0.107
Admission NIHSS score	11 (8) 7 (4–17) 0–30	8 (7) 6 (4–12) 2–25	11 (8) 9 (4.5–17.5) 0–30	0.276
HbA1c (mmol/mol)	47 (21) 42 (37–51) 29–148	42 (15) 40 (36–47) 31–91	49 (22) 43 (38–53) 29–148	0.142
LDL mmol/L	2.2 (1.0) 2.1 (1.6–2.6) 0.5–7.2	2.4 (1.1) 2.2 (1.7–2.6) 0.8–7.2	2.1 (0.9) 2.0 (1.5–2.6) 0.5–5.7	0.279
Categorical data	**N/N (%)**	**N/N (%)**	**N/N (%)**	
Female	76/179 (43)	17/41 (42)	59/138 (43)	0.883
Ethnicity European Māori Pacific peoples Others	 77/179 (43) 34/179 (19) 44/179 (25) 24/179 (13)	 25/41 (61) 7/41 (17) 4/41 (10) 5/41 (12)	 52/138 (38) 27/138 (20) 40/138 (29) 19/138 (14)	 0.026
BMI category (kg/m^2) <30 30–<40 ≥40	 89/179 (51) 62/179 (35) 25/179 (14)	 31/41 (76) 8/41 (20) 2/41 (5)	 58/138 (43) 54/138 (40) 23/138 (17)	 0.001
Current/ex-smoker n (%)	78/179 (44)	14/41 (34)	64/138 (46)	0.166
Persistent/permanent AF	136/179 (76)	32/41 (78)	104/138 (75)	0.724

Table 2 (continued): Clinical characteristics and anticoagulant exposure in patients with IS/TIA on oral anticoagulation, stratified by adjudicated mechanism.

	All cases	Non-cardioembolic	Cardioembolic	p-value
Comorbidities				
Left ventricular failure	30/179 (17)	7/41 (17)	23/138 (17)	>0.99
Hypertension	124/179 (69)	30/41 (73)	94/138 (68)	0.076
Diabetes	55/179 (31)	8/41 (20)	47/138 (34)	0.085
Previous IS/TIA	62/179 (35)	16/41 (39)	46/138 (33)	0.501
Coronary artery disease	52/179 (29)	11/41 (27)	41/138 (30)	0.721
Anticoagulants				
Warfarin	30/179 (17)	9/41 (22)	21/138 (15)	0.468
Rivaroxaban	35/179 (20)	9/41 (22)	26/138 (19)	
Dabigatran	114/179 (64)	23/41 (56)	91/138 (66)	
Good anticoagulant control	121/179 (68)	34/41 (83)	87/138 (63)	0.017
Peri-event anticoagulant under-exposure	108/179 (60)	18/41 (44)	90/138 (65)	0.014

AF = atrial fibrillation. IS = ischaemic stroke. TIA = transient ischaemic attack. BMI = body mass index. NIHSS = National Institutes of Health Stroke Scale. Good anticoagulant control = PDC≥80% or TTR≥70%. CHA_2DS_2–VASc = AF stroke risk score (congestive heart failure, hypertension, age ≥75 [doubled], diabetes, prior IS/TIA [doubled], vascular disease, age 65 to 74 and female sex). LDL = low-density lipoprotein. SD = standard deviation. IQR = interquartile range.

Table 3: Multivariable logistic regression analysis of factors associated with a non-cardioembolic mechanism among patients with breakthrough IS/TIA while receiving anticoagulation.

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
Age	1.05 (1.02–1.09)	1.04 (0.99–1.08)	0.119
Female	0.95 (0.47–1.92)	0.73 (0.33–1.61)	0.439
Comorbidities			
Left ventricular failure	1.03 (0.41–2.61)	2.19 (0.76–6.37)	0.149
Hypertension	1.28 (0.59–2.80)	1.77 (0.73–4.31)	0.208
Diabetes	0.47 (0.20–1.10)	0.74 (0.28–1.97)	0.548
Prior IS/TIA	1.28 (0.62–2.63)	1.24 (0.56–2.76)	0.590
Vascular disease	1.07 (0.51–2.24)	0.68 (0.29–1.57)	0.364
Good anticoagulant control	2.85 (1.18–6.89)	3.67 (1.35–9.99)	0.011
BMI kg/m²	0.93 (0.88–0.97)	0.94 (0.88–0.99)	0.037

BMI = body mass index. IS = ischaemic stroke. TIA = transient ischaemic attack. OR = odds ratio. CI = confidence interval.

obesity as a marker of AF substrate rather than differential anticoagulant effectiveness.[14,15] Ethnic variation should be interpreted cautiously and likely reflects clustering of underlying differences in AF burden, cardiometabolic risk factors, socioeconomic factors and residual confounding by structural factors rather than intrinsic biological differences. In New Zealand, Māori and Pacific peoples experience AF at younger ages and have a higher burden of cardioembolic stroke.[16,17] Detailed examination of the interrelationships between ethnicity, obesity and TIA/IS risk is beyond the scope of the present analysis and will be addressed in separate future studies.

Underdosing has been reported in 7–40% of anticoagulated patients with AF in retrospective studies and is associated with increased mortality without a reduction in bleeding risk.[20,21] In our cohort, underdosing was identified in 21/179 (12%) of patients, a frequency consistent with prior reports and supporting the generalisability of our findings.

For patients with true breakthrough cardioembolic IS/TIA despite adequate anticoagulation, guidance from the literature is less clear. One study demonstrated a reduction in stroke recurrence with switching from warfarin to a DOAC; however, switching DOACs was not beneficial.[1] Since many thrombi originate in the left atrial appendage, some authors advocate for appendage occlusion; however, the benefit for this is uncertain.[22]

Key strengths of this study include the use of a well-established, population-based stroke registry and independent adjudication of IS and TIA events. Detailed individual-level clinical data were available, including antithrombotic prescriptions, laboratory tests of coagulation and documented clinical assessments, allowing classification of anticoagulant exposure and identification of medication-related factors at the time of presentation. Although conducted within a New Zealand health system, this study included a diverse ethnic population and demonstrated patterns of breakthrough stroke mechanisms and anticoagulant underexposure consistent with prior international reports, suggesting potential relevance beyond the local setting.

There are several limitations to this study. This *post hoc* analysis of registry data relied on retrospective assessment of anticoagulant exposure, and residual confounding is possible. The absence of a contemporaneous control group limits inference to descriptive comparisons within patients experiencing breakthrough events. In addition, laboratory assessment of DOAC exposure is imperfect, particularly for factor Xa inhibitors, and some misclassification cannot be excluded. Adjusted analyses were exploratory and should be interpreted as supportive rather than causal. Finally, our statistical analysis included the potential for type I error inflation due to multiple statistical testing, meaning that significant findings may be spurious. Further, the modest sample size may mean non-significant findings may represent type II error.

Despite these limitations, our findings suggest that many IS/TIA in anticoagulated patients may reflect suboptimal anticoagulation or competing mechanisms rather than true pharmacological failure. This distinction is important. As anticoagulant uptake improves, the residual prevention challenge shifts from whether patients are prescribed therapy to how effectively it is delivered. Health-system strategies such as improved monitoring of DOAC dispensing continuity, support for treatment persistence and optimisation of TTR in warfarin users represent plausible, testable approaches to reducing risk. Crucially, these efforts must address inequities, particularly among Māori and Pacific peoples, who face greater barriers to optimal treatment. Future work should evaluate whether such service-level interventions translate into fewer breakthrough events.

COMPETING INTERESTS
KMM received a Health Research Council of New Zealand grant as part of his doctoral studies for this research. The other authors did not receive any financial support for the research, authorship and/or publication of this article.
Outside of this work, HDW has received grant support from Sanofi-Aventis, DalCor Pharma UK Inc, CSL Behring, National Health Institutes, Sanofi Aventis Australia Pty Ltd, Janssen Research and Development LLC and Merck Sharp & Dohme (New Zealand) Ltd. HW has received consulting fees from DalCor Pharma UK Inc, CSL Behring, Sanofi Aventis Australia Pty Ltd, Esperion Therapeutics, Janssen Research and Development LLC and Merck Sharp & Dohme (New Zealand) Ltd. HW has had travel and accommodation paid for attendance at Investigator meetings (2025) by Merck Sharp & Dohme (New Zealand) Ltd. HW has participated on the CSL Behring advisory board and the VEVRE advisory board 2024.

ACKNOWLEDGEMENTS
We would like to thank Dr Irene Zeng, biostatistician at Auckland University of Technology, for reviewing the manuscript and providing feedback. ChatGPT was used to assist with language editing; the authors take full responsibility for the content.

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URL
https://nzmj.org.nz/journal/vol-139-no-1636/mechanisms-of-ischaemic-strokes-and-transient-ischaemic-attacks-despite-oral-anticoagulation-in-patients-with-atrial-fibrillatio

CITATION
Mahawish KM, Feigin V, Krishnamurthi R, White HD. Mechanisms of ischaemic stroke and transient ischaemic attack despite oral anticoagulation in patients with atrial fibrillation. 2026 Jun 12;139(1636):44-51. doi: 10.26635/6965.7380.

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