



Dabigatran use and cerebrovascular event risk across body mass index in atrial fibrillation: a real-world nested case–control study

Karim M. Mahawish^{1,2} · Valery Feigin² · P. Alan Barber³ · Derrick A. Bennett⁴ · Rita Krishnamurthi² · Harvey D. White⁵

Received: 3 April 2026 / Accepted: 25 August 2026
© The Author(s) 2026

Abstract

Dabigatran is widely used for stroke prevention in atrial fibrillation (AF), but concerns remain regarding its effectiveness in patients with Class III obesity (BMI ≥ 40 kg/m²). We evaluated the association between dabigatran use in patients with AF and ischaemic stroke (IS) or transient ischaemic attack (TIA) across body mass index (BMI) categories in a multiethnic New Zealand population. In this retrospective nested case–control study, cases with incident IS/TIA were identified from the fifth Auckland Regional Community Stroke Study (1st September 2020–31st August 2021), and event-free controls were randomly selected from the National Minimum Dataset. Multivariable logistic regression was used to estimate adjusted odds ratios (aORs) for IS/TIA, and effect modification by BMI category (<30, 30–39.9, ≥ 40 kg/m²) was assessed using an interaction term. Among 1,854 patients with AF (295 cases, 1,559 controls), dabigatran use was associated with lower odds of IS/TIA (adjusted odds ratio [aOR] 0.50, 95% CI 0.38–0.68). After multivariable adjustment, BMI was not independently associated with IS/TIA risk. The association between dabigatran use and lower IS/TIA risk was similar in patients with BMI <30 and 30–39.9 kg/m², but the point estimate shifted towards the null in patients with BMI ≥ 40 kg/m² and was imprecise. There was no statistical evidence of effect modification by BMI (p-interaction=0.49), although clinically important attenuation in Class III obesity could not be excluded. In this real-world nested case–control study, there was no clear statistical evidence of BMI-related effect modification; however, the study had limited power in patients with BMI ≥ 40 kg/m², and clinically important attenuation, including the possibility of no reduction in IS/TIA odds with dabigatran use in Class III obesity cannot be excluded.

Graphical abstract

Dabigatran use and cerebrovascular event risk across body mass index in atrial fibrillation. Graphical summary of the study design and main findings. In this real-world nested case–control study of patients with atrial fibrillation, dabigatran use was associated with lower odds of ischaemic stroke/transient ischaemic attack. There was no clear statistical evidence that BMI modified the association between dabigatran use and IS/TIA, although clinically important attenuation in Class III obesity could not be excluded.

✉ Karim M. Mahawish
tyj9598@autuni.ac.nz

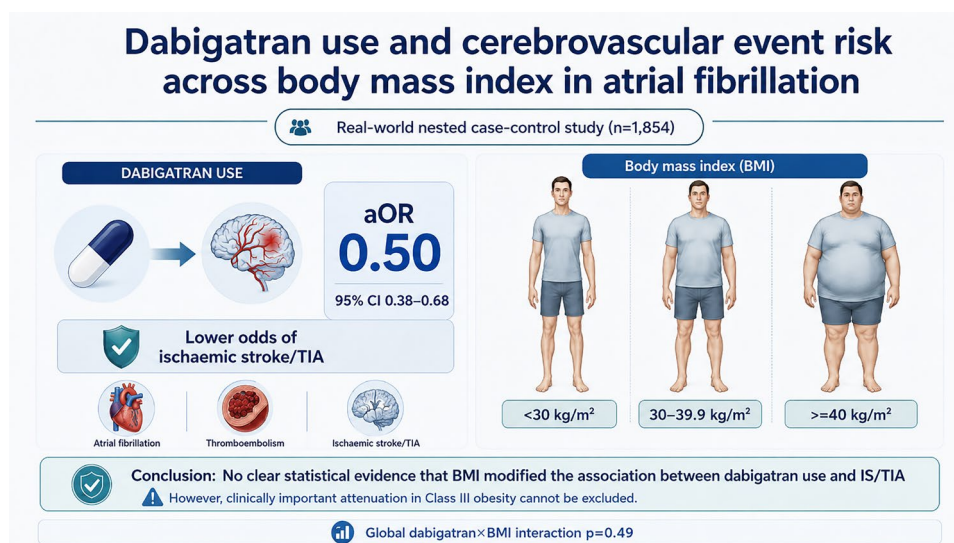
¹ Stroke Department, Adult Rehabilitation & Health of Older People, Health New Zealand - Te Whatu Ora Counties Manukau, 100 Hospital Road, Otahuhu, Auckland 2025, New Zealand

² National Institute for Stroke and Applied Neurosciences, School of Community & Public Health, Auckland University of Technology, 90 Akoranga Drive, Northcote, Auckland 0627, New Zealand

³ Department of Medicine, University of Auckland Faculty of Medical and Health Sciences, 85 Park Road, Grafton, Auckland 1023, New Zealand

⁴ Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, Big Data Institute, University of Oxford, Old Road Campus, Oxford, United Kingdom

⁵ Green Lane Cardiovascular Service, Health New Zealand - Te Whatu Ora, Te Toka Tumai, Auckland City Hospital, Park Road, Grafton, Auckland 1051, New Zealand



Key points

- Body mass index was not independently associated with IS/TIA risk after adjustment for clinical factors and anticoagulant use.
- The dabigatran-IS/TIA association was similar in patients with BMI <30 and 30–39.9 kg/m².
- There was no clear statistical evidence that BMI modified the association between dabigatran use and IS/TIA; however the point estimate shifted towards the null in Class III obesity and was imprecise.
- Larger real-world studies with greater representation of patients with Class III obesity are needed to more precisely evaluate potential effect modification and inform anticoagulant selection in this group.

Keywords Obesity · Dabigatran · Atrial fibrillation · Ischaemic stroke · Transient ischaemic attack

Introduction

Atrial fibrillation (AF) is a major cause of ischaemic stroke (IS) in New Zealand and worldwide [1, 2]. Obesity is an important and potentially modifiable risk factor for AF [3]. New Zealand has the third-highest adult obesity prevalence among the Organisation for Economic Co-operation and Development countries, with a marked ethnic gradient [4]. According to World Health Organization criteria, obesity is classified as Class I (body mass index [BMI] 30.0–34.9 kg/m²), Class II (35.0–39.9 kg/m²), and Class III (≥40 kg/m²) [5]. In 2024/25, Class III obesity affected 5.8% of the total New Zealand population, but was more prevalent among Māori (10.9%) and Pacific peoples (22.7%) than among Europeans/others (4.9%) or Asians (1.4%) [6].

Pivotal trials of direct oral anticoagulants (DOACs) under-represented patients with Class III obesity. In the Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET-AF) trial, median BMI was 28.3 kg/m² (IQR 25.2–32.1), while in the Dabigatran versus Warfarin in Patients with Atrial Fibrillation (RE-LY) trial, the mean body weight in the dabigatran arm was 82.5 kg (SD ±19.4);

13.2% and 10% of participants had Class II and III obesity respectively [7–9]. This has raised concern regarding the generalisability of trial findings to patients with Class III obesity.

Pharmacokinetic studies have further suggested that dabigatran, but not the factor Xa inhibitors rivaroxaban and apixaban, may be associated with subtherapeutic peak and trough plasma concentrations in patients with Class III obesity and AF [10]. In 2021, the International Society on Thrombosis and Haemostasis (ISTH) updated its 2016 guidance to support the use of the factor Xa inhibitors apixaban and rivaroxaban in patients with a BMI ≥40 kg/m² for the prevention of venous thromboembolism, while advising caution with dabigatran because of limited data [10].

Observational evidence evaluating DOAC effectiveness in obesity has been mixed. Several studies suggest preserved effectiveness of DOACs across BMI strata, including Class III obesity, although agent-specific inference for dabigatran has been limited [11, 12]. In contrast, a meta-analysis of DOAC trial data suggested higher vascular mortality among participants with Class III obesity treated with dabigatran compared with those of normal BMI (OR 2.4 [1.42–4.05], although this finding was based primarily on the RE-LY trial

and limited numbers of patients with Class III obesity [13]. Collectively, these findings highlight persistent uncertainty regarding dabigatran effectiveness in Class III obesity.

Dabigatran is the most commonly prescribed DOAC in New Zealand, yet real-world data on its clinical performance across the BMI spectrum are limited [14]. We therefore evaluated the association between dabigatran use and IS/TIA risk in patients with AF in Auckland, New Zealand, and examined whether this association varied according to BMI, with particular focus on Class III obesity (BMI ≥ 40 kg/m²).

Methods

Study design and population

We conducted a retrospective nested case–control study of adult patients with AF residing in greater Auckland. Cases were patients who experienced IS/TIA during the fifth Auckland Regional Community Stroke Study (ARCOS V), surveillance period 1st September 2020 to 31st August 2021. ARCOS is a population-based stroke/TIA registry that prospectively identifies all incident IS/TIA events across the Auckland region once every decade. ARCOS V employs multiple overlapping sources for case ascertainment, and all diagnoses undergo independent clinical adjudication using standardised criteria [1].

Controls were randomly selected from the New Zealand Ministry of Health National Minimum Dataset (NMDS), which captures all publicly funded hospital admissions nationwide. Because almost all ARCOS V cases had hospital contact, both cases and controls represent patients receiving secondary care within the three major Auckland hospital networks [15, 16]. Since controls were sampled from the same underlying population during the ARCOS V surveillance period, and exposure status was ascertained prior to the index date, odds ratios from logistic regression approximate the relative odds of IS/TIA associated with anticoagulant exposure in this population. We excluded patients with moderate-to-severe mitral stenosis or mechanical heart valves.

Exposure: dabigatran use

Dabigatran exposure was specified a priori as the primary exposure of interest, given pharmacokinetic data suggesting lower dabigatran plasma concentrations in obese patients, and was ascertained using dispensing records before the index/reference date: For cases, the index date was the date of incident IS/TIA. For controls, a reference date was randomly assigned within the ARCOS V surveillance period,

from 1 September 2020 to 31 August 2021. Exposure status for controls was therefore assessed before this randomly assigned reference date, rather than across the entire surveillance period.

Anticoagulant exposure was not assessed after the index event, as post-event prescribing does not inform pre-event exposure and would introduce reverse causation. Similarly, for controls, exposure was not assessed after the randomly assigned reference date. Warfarin and rivaroxaban use were included as separate covariates due to different pharmacokinetic profiles and potentially different prescribing patterns. Patients with no anticoagulant dispensing during the pre-index/reference exposure-assessment window served as the reference group.

Anticoagulant adherence was assessed using the proportion of days covered (PDC) for DOACs (dabigatran, rivaroxaban) and time in therapeutic range (TTR) for warfarin. During the study period, apixaban was not publicly funded in New Zealand and was therefore not included. PDC was calculated as the proportion of days covered by dispensed medication over the relevant dispensing period, with $\geq 80\%$ indicating good control [17]. TTR was calculated using Rosendaal's linear interpolation method, with $\geq 70\%$ defining good control in accordance with European Society of Cardiology guidelines [18].

In New Zealand, prescription medicines are typically dispensed in 30-day supplies. Up to five sequential dispensings prior to the index/reference date were identified, and the PDC was calculated based on the cumulative days supplied between dispensings, truncated at the index/reference date. Thus, patients were not classified as exposed on the basis of any historical use before the index/reference date; classification was based on dispensing during the defined pre-index/reference exposure-assessment window; the median duration of which was 155 days (IQR 138–204). Variation in this observation length reflects differences in prescription dispensing frequency rather than differences in follow-up duration.

For warfarin, TTR was calculated using Rosendaal's linear interpolation method from INR values and corresponding test dates entered into a standard Rosendaal-method spreadsheet template. INR measurements from approximately 12 months before the index/reference date were used. The resulting TTR was categorised as good control versus not good control, using TTR $\geq 70\%$ as the threshold. The individual INR dates and values, completed TTR templates, and continuous TTR values were not retained in the analytic dataset. Therefore, the number and spacing of INR measurements used for each patient's TTR calculation could not be summarised. Although the duration of observation differed between DOAC and warfarin exposure metrics, both were

intended to reflect usual anticoagulant exposure and control before the index/reference date.

Historical anticoagulant dispensing before the pre-index/reference exposure-assessment window was not collected. Therefore, patients classified as anticoagulated may have included both new and prevalent users, and patients classified as non-anticoagulated may have included both never-users and past users who discontinued anticoagulation before the exposure-assessment window. The study therefore estimates the association between anticoagulant dispensing during the pre-index/reference exposure-assessment window and IS/TIA, rather than the effect of anticoagulant initiation.

Individual renal function values (e.g. creatinine clearance) were not available; however, dabigatran dose, which is selected clinically based on renal function and age, was recorded and examined in sensitivity analyses.

Body mass index categorisation

BMI was extracted from electronic clinical records using the most recent documented measurement in relation to the surveillance period. BMI was obtained either from a recorded BMI value or calculated from recorded height and weight. Data sources included primary care referral documents, inpatient clinical observations, and measurements recorded in investigation reports, including echocardiography and spirometry. For analysis, BMI was categorised as <30 kg/m², 30.0–39.9 kg/m² (Class I–II obesity), and ≥ 40 kg/m² (Class III obesity) to ensure stable estimation of effect modification and to reflect the clinically relevant threshold highlighted in ISTH guidance, which supports factor Xa inhibitor use but advises caution with dabigatran in patients with BMI ≥ 40 kg/m² because of limited data [10, 19].

Covariates

Covariates were specified a priori based on established associations with IS/TIA risk in AF. These included age, self-identified prioritised ethnicity (Māori, Pacific peoples, European and Others (e.g., East/South Asians, Middle Eastern, Latin American and African), in accordance with national standards), and comorbidities (left ventricular failure, hypertension, diabetes mellitus, vascular disease, and prior IS/TIA) [20]. Sex was coded as female or male, consistent with the CHA₂DS₂ VASc risk score definition.

Baseline comorbidities, including prior IS/TIA, were ascertained from electronic clinical records up to and including 31st August 2020, before the start of the ARCOS V surveillance period. The ARCOS V index event for cases was therefore distinct from any prior IS/TIA recorded as a

baseline comorbidity. Prior IS/TIA included documented ischaemic stroke or transient ischaemic attack before the surveillance period.

Individual level clinical data on AF diagnosis, and comorbidities, were obtained through systematic review of electronic clinical records, including clinician-documented diagnoses in discharge/clinic letters, electrocardiograms, echocardiograms, Holter monitors, etc. BMI was extracted from documented clinical measurements rather than administrative registry fields, as described above. Anticoagulant exposure was ascertained separately from dispensing records, as described above. Administrative diagnostic codes and laboratory values were not used as sole criteria for comorbidity ascertainment. This was intended to minimise misclassification and ensure consistent ascertainment of exposures and covariates.

This study has been approved by the Health and Disability Ethics Committee (HDEC) (ref: 2023 AM 9094) and Auckland University of Technology Ethics Committee (24/4), and granted an exemption from obtaining informed consent by Auckland University of Technology Ethics Committee (AUTEC) (24/4).

Statistical analysis

Continuous variables were visually assessed using histograms and were non-normally distributed; they are therefore presented as median (interquartile range) and compared using the Wilcoxon rank-sum test. Categorical variables are presented as counts and percentages and compared using the chi-squared test or Fisher's exact test, as appropriate.

Multivariable logistic regression was used to estimate adjusted odds ratios (aOR) and 95% confidence intervals (CIs) for the association between anticoagulant use and IS/TIA. Ethnicity was included as an adjustment variable because the risk of IS is higher among Māori and Pacific peoples than among Europeans in New Zealand cohorts [21].

Effect modification of dabigatran by BMI was assessed by including a BMI $\times$ dabigatran category interaction term in multivariable models adjusted for all prespecified covariates, including warfarin and rivaroxaban use. Sensitivity analyses were performed to assess the robustness of the BMI $\times$ dabigatran interaction. First, BMI was modelled dichotomously as <40 versus ≥ 40 kg/m². Second, the analysis was restricted to patients receiving dabigatran or no anticoagulant, excluding warfarin and rivaroxaban users. This analysis was undertaken as a sensitivity analysis to address potential confounding associated with the untreated comparator; comparative effectiveness between individual anticoagulants was not the prespecified primary objective. Third, because dabigatran dosing is influenced by renal

function and age, the analysis was restricted to standard-dose dabigatran users, defined as 150 mg twice daily, and non-anticoagulated patients. Fourth, because non-anticoagulated patients may differ systematically from anticoagulated patients, an active-comparator analysis was performed among anticoagulated patients only, using rivaroxaban as the reference anticoagulant. This active-comparator model was repeated with additional adjustment for good anticoagulant control, defined as PDC $\geq 80\%$ for DOAC users or TTR $\geq 70\%$ for warfarin users.

To further address measured confounding associated with the untreated comparator, an inverse-probability-weighted sensitivity analysis was performed after excluding warfarin and rivaroxaban users. Inverse sampling weights were first applied to account for the known sampling fractions of cases and controls. Within each BMI category, the propensity for dabigatran use was estimated using sampling-weighted logistic regression including age, sex, ethnicity, cardiac failure, hypertension, diabetes, vascular disease, and prior IS/TIA. Stabilised inverse-probability-of-treatment weights were calculated and truncated at the 1st and 99th percentiles, then combined with the sampling weights. Covariate balance was assessed using standardised mean differences. The weighted BMI $\times$ dabigatran model additionally adjusted for the prespecified covariates and used robust standard errors.

Finally, because prior IS/TIA is a strong predictor of recurrent cerebrovascular events, the primary analysis was repeated after excluding individuals with prior IS/TIA recorded before 31st August 2020. Detailed results of sensitivity analyses are presented in the Supplementary Material.

Model diagnostics included assessment of leverage (hat) values and deviance residuals to identify influential observations, and evaluation of the linearity assumption for BMI in the logit using a Box-Tidwell test.

This manuscript was written in accordance with strengthening the reporting of observational studies in epidemiology (STROBE) recommendations for case-control studies [22]. All analyses were performed using Stata version 17BE (StataCorp, College Station, TX). The study protocol has been published previously [23].

Results

Patient demographics

A total of 1,908 patients with AF were identified. BMI data were missing in 54 patients; the proportion with missing BMI did not differ significantly between cases and controls (1.7% vs 3.4%, $p=0.15$) and were excluded. No missing data were present for other variables included in the study.

Hence, 1,854 patients with AF were included in this analysis [295 cases and 1,559 controls]. Dabigatran dose varied across BMI strata, with Class III obesity patients more frequently receiving standard-dose (150 mg twice daily [BD]) therapy and patients with normal/overweight BMI receiving the lower (110 mg BD) dose. Differences in comorbidities stratified by BMI category are demonstrated in Supplementary file, Table 1.

Baseline characteristics are shown in Table 1. Cases were older than controls (median 77 vs 69 years) and had higher rates of prior IS/TIA. The ethnic distribution differed modestly between cases and controls, with a higher proportion of European patients among cases and a lower proportion of Māori and Pacific peoples compared with controls. Median BMI was lower in cases than controls. Overall, two-thirds (69.6%) of participants were prescribed an anticoagulant, with dabigatran being most frequently used (63.5%).

Multivariable analysis of factors associated with IS/TIA

Table 2 presents the crude and multivariable logistic regression analyses. After adjustment for demographics, comorbidities, ethnicity, and anticoagulant use, BMI was not independently associated with IS/TIA risk. Compared with BMI <30 kg/m², neither BMI 30–39.9 kg/m² nor ≥ 40 kg/m² was associated with IS/TIA.

Among controls, anticoagulated and non-anticoagulated patients differed in several baseline characteristics (Supplementary file, Table 2). Anticoagulated controls were older than non-anticoagulated controls (median age 70 years [IQR 62–78] vs 65 years [IQR 56–75]) and had higher median CHA₂DS₂ VASc scores (3 [IQR 2–4] vs 2 [IQR 1–3]). Anticoagulated controls also had higher prevalences of heart failure, diabetes, hypertension, prior IS/TIA, and vascular disease. BMI differed modestly between groups, while sex and ethnicity distributions were similar. These differences indicate that anticoagulated and non-anticoagulated controls were not exchangeable at baseline.

In the primary model, dabigatran use was associated with lower odds of IS/TIA compared with no anticoagulant use (aOR 0.50, 95% CI 0.38–0.68); estimates for the other anticoagulants as shown in Table 2. Increasing age remained strongly associated with IS/TIA risk (aOR per year 1.04, 95% CI 1.03–1.05). There was no statistical evidence of differences in IS/TIA risk between ethnic groups after adjustment.

Anticoagulant control was not included in this primary model, as individuals not receiving anticoagulation formed the reference group. Model diagnostics did not identify influential observations based on inspection of leverage and deviance residuals.

Table 1 Baseline characteristics of patients with atrial fibrillation, stratified by incident IS/TIA status

Variable	Controls: AF without IS/TIA N=1,559	Cases: AF with incident IS/TIA N=295	p-value
Median age (IQR) years	69 (60–77)	77 (66–84)	<0.001
Female n (%)	722 (46.3)	142 (48.1)	0.565
Ethnicity n (%)			0.033
European	588 (37.7)	124 (42.0)	
Māori	336 (21.6)	61 (20.7)	
Pacific peoples	471 (30.2)	68 (23.1)	
Others	164 (10.5)	42 (14.2)	
Median BMI, (IQR) kg/m ²	31.4 (26.6–37.6)	29.2 (25.0–35.6)	<0.001
BMI categories kg/m² n (%)			<0.001
<30 (low/normal/overweight)	651 (41.7)	159 (53.9)	
30–34.9 (Class I obesity)	385 (24.6)	54 (18.3)	
35–39.9 (Class II obesity)	238 (15.2)	46 (15.6)	
≥40 (Class III obesity)	289 (18.5)	36 (12.2)	
Comorbidities n (%)			
Left ventricular failure	292 (18.7)	47 (15.9)	0.254
Hypertension	986 (63.3)	204 (69.2)	0.052
Diabetes	460 (29.5)	91 (30.9)	0.644
Vascular disease	462 (29.6)	94 (31.9)	0.443
Prior IS/TIA	247 (15.8)	85 (28.8)	<0.001
Anticoagulation n (%)			
Any oral anticoagulant use	1114 (71.5)	176 (59.7)	<0.001
Among anticoagulated patients			
Warfarin	182 (16.3)	30 (17.1)	0.814
Rivaroxaban	225 (20.2)	34 (19.3)	0.787
Dabigatran	707 (63.5)	112 (63.6)	0.965
Good control among anticoagulated patients n (%)			
DOAC	916/1114 (82.2)	119/176 (67.6)	<0.001
Warfarin	773/932 (82.9)	107/146 (73.3)	0.005
	143/182 (78.6)	12/30 (40.0)	<0.001

Vascular disease: peripheral vascular disease or coronary artery disease. IQR: interquartile range. BMI: body mass index. IS: ischaemic stroke. TIA: transient ischaemic attack. Good control was defined as PDC ≥80% for DOAC users and TTR ≥70% for warfarin users. DOAC users included dabigatran and rivaroxaban users. PDC: proportion of days covered; TTR: time in therapeutic range.

A prespecified interaction model found no statistical evidence that BMI modified the association between dabigatran use and IS/TIA (global interaction $p=0.49$). Dabigatran use was associated with lower odds of IS/TIA in patients with BMI <30 kg/m² (aOR 0.48, 95% CI 0.32–0.72) and BMI 30–39.9 kg/m² (aOR 0.46, 95% CI 0.29–0.74). In patients with BMI ≥40 kg/m², the association was not statistically significant and the confidence interval was wide (aOR 0.75, 95% CI 0.36–1.55). This subgroup included only 36 IS/TIA cases, of whom 19 were treated with dabigatran. Therefore, clinically important attenuation in Class III obesity cannot be excluded, and these findings should not be interpreted as evidence of equivalence across BMI categories (Table 3; Fig. 1).

Sensitivity analyses

Sensitivity analyses are shown in Supplementary file, Table 3. There was no clear statistical evidence of BMI-related effect modification when BMI was modelled dichotomously as <40 versus ≥40 kg/m², when the analysis was restricted to patients receiving dabigatran or no

anticoagulant, or when the analysis was restricted to standard-dose dabigatran users and non-anticoagulated patients. Across these analyses, estimates for the BMI ≥40 kg/m² subgroup remained imprecise.

In an active-comparator sensitivity analysis restricted to anticoagulated patients, with rivaroxaban as the reference anticoagulant, there was no statistical evidence that the relative association of dabigatran versus rivaroxaban with IS/TIA varied according to BMI (global interaction $p=0.58$). Adjusted odds ratios for dabigatran versus rivaroxaban were 0.88 (95% CI 0.50–1.56) at BMI <30 kg/m², 1.30 (0.62–2.73) at BMI 30–39.9 kg/m², and 1.61 (0.45–5.79) at BMI ≥40 kg/m². Estimates were imprecise, particularly in Class III obesity, and this analysis was not powered to establish comparative effectiveness between individual anticoagulants. Findings were similar after additional adjustment for good anticoagulant control.

In a further analysis excluding patients with prior IS/TIA before ARCOS V, dabigatran remained associated with lower odds of IS/TIA in the BMI <30 kg/m² reference group (OR 0.45, 95% CI 0.28–0.72; $p=0.001$), with no clear

Table 2 Multivariable logistic regression model for ischaemic stroke or transient ischaemic attack

Variable	IS/TIA n/N	Crude OR (95% CI)	aOR (95% CI)	p-value
Age per year	-	1.04 (1.03–1.05)	1.04 (1.03–1.05)	<0.001
Female sex	142/864	1.08 (0.84–1.38)	0.94 (0.71–1.23)	0.63
Ethnicity				
European	124/712	Ref	Ref	0.225
Māori	61/397	0.86 (0.62–1.20)	1.32 (0.90–1.94)	
Pacific peoples	68/539	0.69 (0.50–0.94)	0.96 (0.66–1.39)	
Others	42/206	1.21 (0.82–1.79)	1.32 (0.87–1.99)	
BMI per kg/m ²	-	0.97 (0.95–0.98)	0.99 (0.97–1.01)	0.315
BMI categories kg/m²				
< 30 (normal/overweight)	159/810	Ref	Ref	0.572
30–39.9 (Class I/II obesity)	100/719	0.66 (0.50–0.87)	0.85 (0.62–1.16)	
≥40 (Class III obesity)	36/325	0.51 (0.35–0.75)	0.85 (0.54–1.35)	
Comorbidities				
Left ventricular failure	47/339	0.82 (0.59–1.15)	1.15 (0.80–1.67)	0.455
Hypertension	204/1190	1.30 (1.0–1.70)	1.27 (0.95–1.69)	0.113
Diabetes	91/551	1.07 (0.81–1.40)	1.13 (0.83–1.52)	0.446
Vascular disease	94/556	1.11 (0.85–1.45)	0.94 (0.71–1.26)	0.689
Prior IS/TIA	85/332	2.15 (1.62–2.86)	2.21 (1.63–3.0)	<0.001
Anticoagulant type				
No oral anticoagulant	119/564	Ref	Ref	<0.001
Warfarin	30/212	0.62 (0.40–0.95)	0.40 (0.25–0.64)	<0.001
Rivaroxaban	34/259	0.57 (0.37–0.85)	0.44 (0.28–0.68)	<0.001
Dabigatran	112/819	0.59 (0.46–0.79)	0.50 (0.37–0.68)	

Model adjusted for age, sex, ethnicity, BMI (examined as a continuous variable and as a categorical variable in separate otherwise identical models), anticoagulant type, and comorbidities. BMI: body mass index. IS: ischaemic stroke. TIA: transient ischaemic attack. aOR: adjusted odds ratio.

Table 3 Adjusted association between dabigatran use and ischaemic stroke or transient ischaemic attack by body mass index category

BMI category (kg/m ²)	Dabigatran vs no oral anticoagulant, aOR (95% CI)*	p-value
< 30 (normal/overweight)	0.48 (0.32–0.72)	<0.001
30–39.9 (Class I/II obesity)	0.46 (0.29–0.74)	0.001
≥40 (Class III obesity)	0.75 (0.36–1.55)	0.442

Adjusted for age, sex, ethnicity, left ventricular failure, hypertension, diabetes, vascular disease, prior IS/TIA, and use of warfarin or rivaroxaban. The global BMI × dabigatran interaction p-value was 0.49. BMI: body mass index. aOR: adjusted odds ratio.

evidence of BMI-related effect modification (global interaction p=0.621).

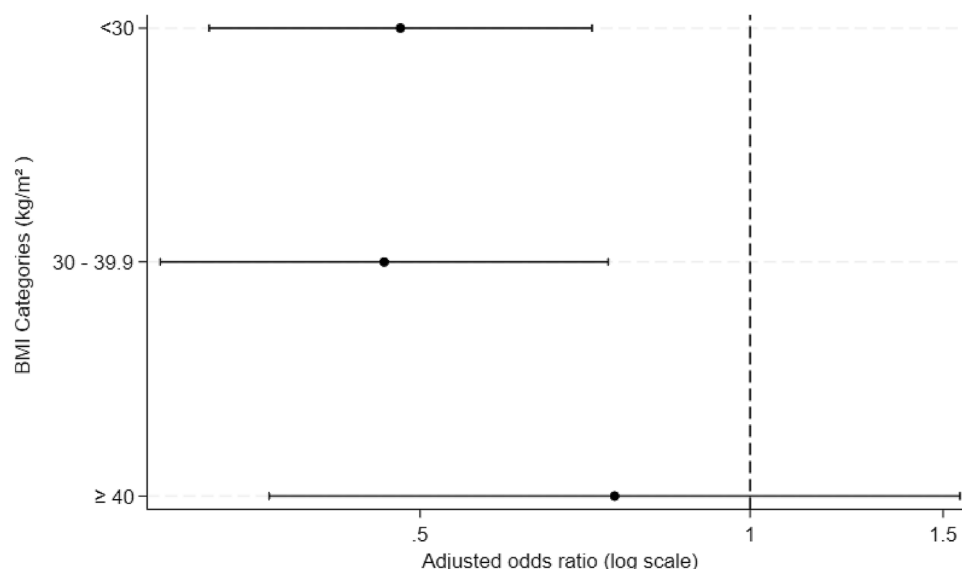
Inverse-probability weighting substantially improved covariate balance between dabigatran users and patients receiving no anticoagulant within BMI strata (Supplementary Table 4). In the weighted and covariate-adjusted analysis, there remained no statistical evidence of BMI-related effect modification (global interaction p=0.45). The ORs for dabigatran use were 0.37 (95% CI 0.24–0.57) for BMI <30 kg/m², 0.54 (0.30–0.98) for BMI 30–39.9 kg/m², and 0.60 (0.25–1.44) for BMI ≥40 kg/m² (Supplementary Table 5).

Discussion

In this nested case–control study, there was no clear statistical evidence that BMI modified the association between dabigatran use and IS/TIA (global interaction p=0.49). Dabigatran estimates were similar in patients with BMI <30 and 30–39.9 kg/m², but the point estimate shifted towards the null in patients with BMI ≥40 kg/m². Only 36 IS/TIA cases had BMI ≥40 kg/m², and the estimate in this subgroup was imprecise. The study therefore cannot exclude clinically important attenuation, including the possibility of no reduction in IS/TIA odds with dabigatran use in patients with Class III obesity.

Sensitivity analyses did not provide clear statistical evidence of BMI-related effect modification, although several estimates in Class III obesity remained imprecise. Inverse-probability weighting substantially improved measured covariate balance between dabigatran users and patients receiving no anticoagulant within BMI strata, with no statistical evidence of effect modification in the weighted analysis (global interaction p=0.45). These findings align with prior observational studies suggesting broadly similar DOAC effectiveness across BMI strata, despite pharmacokinetic concerns regarding reduced dabigatran exposure in severe obesity. BMI itself was not independently associated with IS/TIA risk after multivariable adjustment (aOR 0.99, 95% CI 0.97–1.01).

Fig. 1 Association between dabigatran use and ischaemic stroke or transient ischaemic attack across body mass index categories. Adjusted odds ratios (95% CI) were 0.48 (0.32–0.72) for BMI <30 kg/m², 0.46 (0.29–0.74) for BMI 30–39.9 kg/m², and 0.75 (0.36–1.55) for BMI ≥40 kg/m²



Dabigatran is predominantly renally cleared, and reduced renal function increases systemic drug exposure. Although individual renal function data were not available, impaired renal function was cited as the indication for dose reduction in similar proportions across BMI strata, while patients with Class III obesity were more frequently prescribed standard-dose (150 mg BD) therapy (Supplementary file, Table 1). This may partially offset concerns regarding reduced drug exposure in obesity. Conversely, pharmacokinetic studies suggest lower peak and trough concentrations in individuals with higher body weight due to increased volume of distribution [24]. In this context, the shift of the dabigatran point estimate towards the null in Class III obesity could represent attenuation of the association; however, the wide confidence interval and non-significant interaction test prevent this from being distinguished reliably from sampling variability.

This study has several strengths. We used detailed individual-level data on anticoagulant type, medication coverage, comorbidities, BMI, and ethnicity, allowing adjustment for key clinical factors associated with both anticoagulant prescribing and IS/TIA risk. Anticoagulant exposure was ascertained from dispensing records before the index/reference date, reducing reliance on self-report or clinician documentation alone. IS/TIA events were independently adjudicated by the ARCOS adjudication committee, enhancing outcome validity. BMI was extracted from clinical records rather than administrative registry fields, allowing classification across clinically relevant BMI categories, including Class III obesity. Multivariable models were prespecified and incorporated major vascular risk factors, allowing adjustment for important measured confounders.

This study has several limitations. The case-control design precludes causal inference, and residual confounding cannot be excluded. Adherence was derived from dispensing

data and may not fully reflect actual medication use. This analysis was conducted within an existing clinically adjudicated AF case-control cohort and was not prospectively powered specifically for BMI × dabigatran interaction testing. Although Class III obesity is relatively common in New Zealand, only 36 IS/TIA cases had BMI ≥40 kg/m². As a result, estimates in this subgroup were imprecise, and clinically important attenuation, or even absence, of the protective association between dabigatran use and IS/TIA cannot be excluded. These findings should not be interpreted as evidence of equivalence across BMI categories.

Cases and controls were sampled predominantly from secondary care settings, which may limit generalisability to community AF populations, although internal validity is unlikely to be affected. BMI does not fully capture adiposity or fat distribution and may misclassify risk across ethnic groups, with higher lean mass at a given BMI in Pacific populations and greater metabolic risk at lower BMI in Asian populations [25, 26]. More informative measures of central adiposity, such as waist-hip ratio, were not available. BMI was derived from clinically recorded height and weight or documented BMI rather than standardised research measurements. Measurement source and timing varied between patients, which may have introduced some BMI misclassification.

Use of non-anticoagulated patients as the reference group may introduce confounding by indication and healthy-user or frailty-related bias. Among controls, anticoagulated patients were older and had higher CHA₂DS₂ VASc scores and greater comorbidity burden than non-anticoagulated patients, indicating that these groups were not exchangeable at baseline. Although we adjusted for measured demographic and clinical covariates and performed an inverse-probability-weighted and active-comparator sensitivity analysis

residual confounding remains possible. The degree of attenuation in Class III obesity was less marked in the weighted analysis, indicating that the point estimate was sensitive to the analytic approach. The active-comparator analysis reduced reliance on the untreated comparator but was limited by small numbers within treatment-by-BMI strata and was not powered for comparative-effectiveness inference between dabigatran and rivaroxaban.

For warfarin users, TTR was calculated and then categorised as good control versus not good control using a threshold of TTR $\geq 70\%$. The individual INR dates and values, completed Rosendaal templates, and continuous TTR values were not retained in the analytic dataset. We therefore could not summarise the number or spacing of INR measurements contributing to each patient's TTR calculation, nor the distribution of TTR values.

The study also included prevalent anticoagulant users. Historical anticoagulant dispensing before the pre-index/reference exposure-assessment window was not collected; therefore, we could not distinguish new users from prevalent users, nor could we distinguish never-users from past users among patients classified as non-anticoagulated. This may introduce prevalent-user bias and exposure misclassification, and it prevented a new-user sensitivity analysis. Accordingly, the findings should be interpreted as associations with recent pre-index/reference anticoagulant dispensing rather than causal estimates of anticoagulant initiation. An active-comparator new-user design would be preferable for causal inference.

Finally, generalisability may be influenced by local prescribing patterns, given the high use of dabigatran in New Zealand.

Conclusion

In summary, we found no clear statistical evidence that BMI modified the association between dabigatran use and risk of IS/TIA in patients with AF. Overall, dabigatran use was associated with lower odds of IS/TIA. The BMI $\times$ dabigatran interaction was not statistically significant, but the point estimate shifted towards the null in patients with Class III obesity and the confidence interval was wide. Therefore, these findings should not be interpreted as evidence of equivalence across BMI categories, and clinically important attenuation or absence of the protective association in patients with Class III obesity cannot be excluded. Further real-world studies or pooled analyses with larger numbers of patients with Class III obesity are warranted.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11239-026-03394-1>.

Acknowledgements We thank the ARCOS Subcommittee for reviewing the manuscript and providing helpful comments and feedback.

Author contribution KMM designed the study and drafted the manuscript. VF, HW, PAB, DB and RK reviewed and contributed to the manuscript. RK assisted with obtaining approvals and funding for this study.

Funding Open Access funding enabled and organized by CAUL and its Member Institutions. Health Research Council of New Zealand, 20-680

Data availability Anonymised data are available from the corresponding author on reasonable request, subject to institutional and ethical approval.

Declarations

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.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Feigin VL, Krishnamurthi R, Nair B, Rautalin I, Parag V, Anderson CS et al (2025) Trends in stroke incidence, death, and disability outcomes in a multi-ethnic population: Auckland regional community stroke studies (1981–2022). *Lancet Reg Health - West Pac* 56:101508. <https://doi.org/10.1016/j.lanwpc.2025.101508>
2. Mukherjee K, Kamal KM (2019) Impact of atrial fibrillation on inpatient cost for ischemic stroke in the USA. *Int J Stroke* 14(2):159–166. <https://doi.org/10.1177/1747493018765491>
3. Grundvold I, Bodegard J, Nilsson PM, Svennblad B, Johansson G, Östgren C et al (2015) Body weight and risk of atrial fibrillation in 7,169 patients with newly diagnosed type 2 diabetes; an observational study. *Cardiovasc Diabetol* 14(1):5. <https://doi.org/10.1186/s12933-014-0170-3>
4. Obesity | Ministry of Health NZ [Internet]. 2025 [cited 2025 Feb 19]. Available from: <https://www.health.govt.nz/strategies-initiatives/programmes-and-initiatives/obesity>
5. Patel SM, Braunwald E, Steffel J, Boriani G, Palazzolo MG, Antman EM et al (2024) Efficacy and safety of non-vitamin-K antagonist oral anticoagulants versus warfarin across the spectrum of body mass index and body weight: an individual patient data meta-analysis of 4 randomized clinical trials of patients with atrial fibrillation. *Circulation* 149(12):932–943. <https://doi.org/10.1161/CIRCULATIONAHA.123.066279>

6. Annual Update of Key Results 2024/25: New Zealand Health Survey | Ministry of Health NZ [Internet]. 2025 [cited 2026 Jan 9]. Available from: <https://www.health.govt.nz/publications/annual-update-of-key-results-202425-new-zealand-health-survey>
7. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W et al (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 365(10):883–891. <https://doi.org/10.1056/NEJMoa1009638>
8. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A et al (2009) Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 361(12):1139–1151. <https://doi.org/10.1056/NEJMoa0905561>
9. Ezekowitz ME, Parise H, Connolly SJ, Brueckmann M, Kleins E, Clemens A et al (2014) The use of dabigatran according to body mass index: the RE-LY experience [abstract P6257]. *Eur Heart J* 35(Suppl 1):1111
10. Martin KA, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S (2021) Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. *J Thromb Haemost* 19(8):1874–1882. <https://doi.org/10.1111/jth.15358>
11. Kaplan RM, Tanaka Y, Passman RS, Fine M, Rasmussen-Torvik LJ, Vupputuri S et al (2020) Efficacy and safety of direct oral anticoagulants for atrial fibrillation across body mass index categories. *J Am Heart Assoc* 9(24):e017383. <https://doi.org/10.1161/JAHA.120.017383>
12. Elad B, Maman N, Ayalon S, Goldstein LH (2023) Effectiveness and safety of direct oral anticoagulants for stroke prevention in atrial fibrillation patients with extreme obesity. *Am J Cardiol* 202:223–228. <https://doi.org/10.1016/j.amjcard.2023.06.079>
13. Shaikh F, Wynne R, Castelino RL, Inglis SC, Ferguson C (2021) Effectiveness of direct oral anticoagulants in obese adults with atrial fibrillation: a systematic review of systematic reviews and meta-analysis. *Front Cardiovasc Med* 8:732828. <https://doi.org/10.3389/fcvm.2021.732828>
14. Harper P, Chang A, Stephens M (2022) The changing use of anticoagulants in New Zealand. *N Z Med J* 135(1554):35–43
15. Mahawish K, White H, Feigin V, Krishnamurthi R (2025) Refining predictive risk models for stroke in atrial fibrillation: a scoping review and meta-analysis for Aotearoa New Zealand, Māori and Pacific peoples. *N Z Med J* 138(1611):102–113. <https://doi.org/10.26635/6965.6846>
16. Barber PA, Krishnamurthi R, Parag V, Anderson NE, Ranta A, Kilfoyle D et al (2011) Incidence of transient ischemic attack in Auckland, New Zealand, in 2011 to 2012. *Stroke* 42(9):2183–2188. <https://doi.org/10.1161/STROKEAHA.116.014010>
17. Ozaki AF, Choi AS, Le QT, Ko DT, Han JK, Park SS et al (2020) Real-world adherence and persistence to direct oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 13(3):e005969. <https://doi.org/10.1161/CIRCOUTCOMES.119.005969>
18. Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns HJGM et al (2024) 2024 ESC guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 45(36):3314–3414. <https://doi.org/10.1093/eurheartj/ehae176>
19. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S (2016) Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. *J Thromb Haemost* 14(6):1308–1313. <https://doi.org/10.1111/jth.13323>
20. webcoordinator@msd.govt.nz. Improving how we report ethnicity [Internet]. MSD; [cited 2023 Feb 20]. Available from: <https://www.msd.govt.nz/about-msd-and-our-work/tools/how-we-report-ethnicity.html>
21. Mahawish KM, Krishnamurthi R, Davis A, Zagreanu C, Zeng I, White HD et al (2012) Declining incidence of atrial fibrillation-associated ischemic stroke in Auckland, New Zealand (2012 versus 2021). *J Am Heart Assoc* 15(5):e045260. <https://doi.org/10.1161/JAHA.125.045260>
22. Vandenbroucke JP, Pocock SJ, Poole C, Schlesselman JJ, Egger M (2007) Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Ann Intern Med* 147(8):W163–W194. <https://doi.org/10.7326/0003-4819-147-8-200710160-00010-w1>
23. Mahawish KM, Zeng I, White H, Feigin V, Krishnamurthi R (2026) Methods article for a study protocol: refining stroke prediction in atrial fibrillation patients in an ethnically diverse population – a study protocol. *Neuroepidemiology* 60(3):413–421. <https://doi.org/10.1159/000546212>
24. Menichelli D, Pannunzio A, Baldacci E, Cammisotto V, Castellani V, Mormile R et al (2025) Plasma concentrations of direct oral anticoagulants in patients with nonvalvular atrial fibrillation and different degrees of obesity. *Clin Pharmacokinet*. <https://doi.org/10.1007/s40262-025-01474-8>
25. Frayon S, Cherrier S, Cavaloc Y, Watelez G, Lerrant Y, Galy O (2018) Relationship of body fat and body mass index in young Pacific Islanders: a cross-sectional study in European, Melanesian and Polynesian groups. *Pediatr Obes* 13(6):357–364. <https://doi.org/10.1111/ijpo.12229>
26. Kapoor N, Lotfaliany M, Sathish T, Thankappan KR, Thomas N, Furler J et al (2020) Prevalence of normal weight obesity and its associated cardio-metabolic risk factors – results from the baseline data of the Kerala Diabetes Prevention Program (KDPP). *PLoS ONE* 15(8):e0237974. <https://doi.org/10.1371/journal.pone.0237974>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.