



Proton Pump Inhibitor Co-prescription, Dabigatran Use, and Ischaemic Stroke or Transient Ischaemic Attack in Atrial Fibrillation: A Population-Based Case-Control Study

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Received: 22 May 2026 / Accepted: 22 September 2026
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Abstract

Background and Objectives Proton pump inhibitors (PPIs) reduce gastric acidity and lower dabigatran plasma concentrations, raising concern about a clinically relevant drug–drug interaction. We examined whether PPI co-prescription modified the association between dabigatran use and atrial fibrillation (AF)-associated ischaemic stroke (IS) or transient ischaemic attack (TIA).

Methods We conducted a population-based case-control study of adults with AF in Auckland, New Zealand. Cases were patients with adjudicated IS/TIA between September 2020 and August 2021 identified from the fifth Auckland Regional Community Stroke Study, which uses multiple overlapping ascertainment sources and independent clinical adjudication. Controls were patients with AF from the same source population who remained free of IS/TIA during the surveillance period, sampled from the Ministry of Health National Minimum Dataset. Individual-level demographics, comorbidities and medication exposures were obtained from electronic clinical records and dispensing data. Multivariable logistic regression included dabigatran use, PPI use and their interaction term, with adjustment for pre-specified clinical covariates.

Results The analytic sample comprised 300 IS/TIA cases and 1,608 controls. Dabigatran use was associated with lower odds of IS/TIA (adjusted odds ratio [aOR] 0.36 [95%CI 0.24–0.53]). PPI use was associated with higher odds of IS/TIA (aOR 1.55 [95%CI 1.08–2.24]), but this association is likely subject to residual confounding and should not be interpreted as causal. The dabigatran × PPI interaction was not statistically significant (aOR 0.98 [95%CI 0.57–1.69]; $p = 0.94$).

Conclusion We found no evidence of a large dabigatran-specific interaction with PPI co-prescription. These findings do not support a major clinically important attenuation of dabigatran's association with lower odds of AF-associated IS/TIA, although modest effect modification cannot be excluded. Generalisability to lower-risk primary-care AF populations and healthcare systems with different patient characteristics may be limited.

Key Points

PPIs can lower dabigatran levels, but it is uncertain whether this increases stroke risk.

We found no evidence that taking a PPI with dabigatran causes a large reduction in dabigatran's ability to prevent stroke.

Smaller effects cannot be ruled out, and the higher stroke rate seen in PPI users should not be interpreted as evidence that PPIs cause stroke.

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1 Introduction

Direct oral anticoagulants reduce the risk of thromboembolism in atrial fibrillation (AF) but increase the risk of systemic and gastrointestinal bleeding [1]. Dabigatran etexilate is an orally administered prodrug that is converted to dabigatran, a direct and reversible thrombin inhibitor [2]. Proton pump inhibitors (PPI) are commonly co-prescribed to mitigate the risk of upper gastrointestinal bleeding, although the magnitude of their benefit remains uncertain [3]. Existing guidelines recommend the use of PPI in patients on ≥ 2 antithrombotic agents [4]. Unlike factor Xa inhibitors (e.g. rivaroxaban, apixaban), dabigatran etexilate requires an acidic gastric environment for optimal conversion and absorption [5]. Concomitant PPI therapy increases gastric pH and has consistently been shown to lower both peak and trough dabigatran plasma concentrations [6–9]. PPI also have mild P-glycoprotein inhibitory effect, which in theory might increase dabigatran levels, but this appears to be outweighed by the reduction in gastric acidity and consequent impaired absorption [10].

Despite this plausible pharmacokinetic interaction, the clinical relevance remains unclear. In the Dabigatran versus Warfarin in Patients with Atrial Fibrillation (RE-LY) trial of 18,113 patients, 2491 (14%) were on PPI at baseline. Subgroup analysis did not demonstrate an increased risk of ischaemic stroke with PPI co-prescription ($p = 0.33$), but this analysis was not powered for interaction effects [11]. In contrast, isolated case reports have suggested the possibility of reduced dabigatran effectiveness in PPI users [5]. Large real-world studies directly evaluating whether PPI use attenuates dabigatran's stroke-preventive effect remain limited. In particular, it remains uncertain whether the observed reduction in dabigatran concentrations with PPI therapy translates into reduced effectiveness against clinically adjudicated thromboembolic events in routine practice.

The aim of this study was to determine whether PPI co-prescription modifies the association between dabigatran use and AF-associated IS/TIA in a population-based case-control study. The study protocol has been published previously [12].

2 Methods

2.1 Study Design and Data Sources

We conducted a population-based case-control study within the Auckland regional population of adults with

known AF. Cases were patients with adjudicated ischaemic stroke or transient ischaemic attack (IS/TIA) identified from the fifth Auckland Regional Community Stroke Study (ARCOS V) during the surveillance period from 1 September 2020 to 31 August 2021. ARCOS is a population-based stroke/TIA registry that prospectively identifies incident cerebrovascular events across the Auckland region at approximately decennial intervals. ARCOS V used multiple overlapping sources for case ascertainment, and all diagnoses underwent independent clinical adjudication using standardised criteria. IS and TIA were adjudicated using the World Health Organization time-based criteria [12]. Uncertain or discordant cases were reviewed at scheduled diagnostic review meetings and resolved by specialist consensus. Potential events were identified from public and private hospital records, emergency department and outpatient neurology records, general practice and other community health-care records, residential and rehabilitation facilities and mortality and coronial data.

Controls were patients with AF identified from the New Zealand Ministry of Health National Minimum Dataset (NMDS) up to 31 August 2020 who remained free of IS/TIA during the surveillance period; individuals subsequently identified by ARCOS V as having an IS/TIA were excluded. The NMDS captures all publicly funded hospital admissions nationwide. Controls were sampled in an approximately 4:1 ratio to cases, with sampling stratified by ethnicity to preserve representation of major population groups. Control selection was independent of dabigatran and PPI exposure status.

Almost all ARCOS V cases had hospital contact during the surveillance period (98.9%); therefore, cases and controls were drawn from patients receiving secondary care within the three major Auckland hospital networks (Health New Zealand - Auckland City Hospital, Counties Manukau and Waitematā) [13, 14]. Individual-level clinical information, including AF phenotype, comorbidities, laboratory findings, radiology reports, medication exposure, and antithrombotic therapy, was obtained through detailed review of electronic clinical records and hospital/community dispensing systems. For both cases and controls, pre-existing AF was confirmed by individual clinical-record review. Evidence included a documented clinical diagnosis of AF and available cardiac investigations demonstrating AF, including electrocardiograms; echocardiography reports documenting AF were also reviewed where available.

2.2 Study Population

The source population comprised Auckland-resident adults with AF recorded in hospital records, on or before 31 August 2020—before the ARCOS V surveillance period; similarly, cases were eligible if they had known AF by 31

August 2020. Patients with incident AF first diagnosed at presentation with the index IS/TIA were excluded. Controls were selected from the AF source population and were eligible if they survived and remained free of IS/TIA during the surveillance period.

We excluded patients with valvular AF, defined as moderate-to-severe mitral stenosis or mechanical heart valves, and patients with brief AF during cardiac procedures (e.g. coronary artery bypass graft) and resolving before discharge.

Eligibility was confirmed by individual clinical-record review, including verification of AF and relevant exclusion criteria, because diagnostic coding in the source datasets did not always correspond to the clinical diagnosis.

2.3 Exposure Ascertainment

The primary exposures were current dabigatran use and any PPI use. The exposure analysis focused on dabigatran because it is the oral anticoagulant for which a clinically plausible interaction with PPI therapy has been proposed. Factor Xa inhibitors were not included in the primary exposure definition because their absorption characteristics differ from dabigatran and their inclusion would obscure the specific dabigatran $\times$ PPI interaction under investigation.

Medication exposure was determined from electronic prescribing and dispensing records. For cases, dabigatran, PPI, and other antithrombotic exposures were ascertained before the index adjudicated IS/TIA date. For controls, medication exposure was ascertained during the ARCOS V surveillance period. Participants were classified into four mutually exclusive exposure groups: no dabigatran/no PPI, no dabigatran/PPI, dabigatran/no PPI, and dabigatran/PPI.

PPI exposure required evidence of regular prescribing/dispensing during the surveillance period; a single short-term prescription, such as a 1-month course, was insufficient for classification as PPI use. PPI type and prescribed dose were recorded, but dispensing frequency, cumulative duration of use and adherence could not be quantified. For dabigatran users, prescribed dose, dose appropriateness and documented reasons for reduced-dose prescribing were extracted from clinical records. Dose appropriateness was assessed using clinically relevant prescribing criteria from the dabigatran datasheet, including older age, bleeding risk and moderate renal impairment. Given these multiple indications for dose reduction, appropriateness was analysed as a pragmatic binary measure rather than modelling each determinant of dose selection separately. Renal function results were reviewed as part of this assessment, but numerical creatinine clearance or eGFR values were not systematically extracted into the analytic dataset and therefore could not be included as covariates in the multivariable model.

2.4 Covariates

Covariates were selected a priori based on clinical relevance and established associations with anticoagulant prescribing and thromboembolic risk. Baseline comorbidities were defined on or before 31 August 2020. Covariates included age, sex, hypertension, diabetes mellitus, congestive cardiac failure, arterial disease, previous IS/TIA and AF phenotype, classified as paroxysmal or persistent/permanent. Arterial disease included peripheral vascular disease and coronary artery disease.

Concomitant antiplatelet therapy, including aspirin and clopidogrel, and use of other oral anticoagulants, including warfarin and rivaroxaban, were also recorded. Aspirin was included in the multivariable model as a potential confounder because its use may prompt PPI co-prescription for gastroprotection and is associated with underlying vascular risk. Clopidogrel was not included because concomitant monotherapy use with anticoagulation was uncommon ($n = 24$). Apixaban is available in New Zealand but was not publicly funded during the study period and was therefore not included as an exposure category. Body mass index (BMI) was recorded for descriptive purposes but was not included in the multivariable model because data were missing for 54 participants.

Anticoagulant adherence or control was assessed using proportion of days covered (PDC) for direct oral anticoagulants and time in therapeutic range (TTR) for warfarin. PDC was calculated as the proportion of days covered by dispensed medication over the relevant dispensing period, with $PDC \geq 80\%$ defining good control [15]. TTR was calculated using Rosendaal's linear interpolation method, with $TTR \geq 70\%$ defining good control [16].

2.5 Outcome

The outcome was AF-associated IS/TIA, defined as an adjudicated IS/TIA event during the ARCOS V surveillance period in an individual with known AF before the event. Subclinical or incidentally detected cerebral infarctions without a corresponding clinically recognised IS/TIA event were not included in the outcome definition.

2.6 Statistical Analysis

Baseline characteristics were summarised across the four dabigatran-PPI exposure groups. Continuous variables were summarised using the mean and standard deviation when approximately normally distributed and the median and interquartile range otherwise. Categorical variables were summarised as frequencies and proportions.

The primary analysis assessed whether PPI co-prescription modified the association between dabigatran use and

AF-associated IS/TIA. We fitted an unconditional multi-variable logistic regression model including dabigatran use, PPI use, and their interaction term, dabigatran $\times$ PPI. The model adjusted for pre-specified covariates relevant to anticoagulant prescribing and thromboembolic risk, including age, sex, AF phenotype, hypertension, diabetes mellitus, congestive cardiac failure, arterial disease, previous IS/TIA, aspirin therapy and non-dabigatran oral anticoagulant use. Dabigatran, warfarin and rivaroxaban were mutually exclusive exposure categories, with patients receiving no oral anticoagulant forming the reference category. Warfarin and rivaroxaban were included as adjustment variables; the pre-specified interaction analysis was restricted to dabigatran $\times$ PPI. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were reported.

To describe model-based differences across the four exposure groups, we used marginal standardisation with the “margins” command in Stata 19 to derive adjusted predicted probabilities of case status within the analytic case-control sample. These estimates were interpreted as model-based predicted case probabilities, not population absolute risks.

All analyses were performed using Stata 19 (StataCorp, College Station, Texas). This manuscript was prepared in accordance with STROBE reporting guidance for observational studies [17].

2.7 Sample Size

No formal a priori sample size calculation was performed because the analysis used an existing case-control dataset derived from the ARCOS V surveillance period and the NMDS control sampling frame. To contextualise the null dabigatran $\times$ PPI interaction finding, we performed a simulation-based power analysis using the observed exposure-group distribution and model-based event probabilities in the analytic sample. Simulated datasets were generated under a range of assumed dabigatran $\times$ PPI interaction odds ratios. Power was estimated as the proportion of 1000 simulations in which the interaction term was statistically significant at $\alpha = 0.05$.

2.8 Sensitivity Analysis

Several sensitivity analyses were performed. First, because a pharmacokinetic interaction would be most apparent in patients with reliable dabigatran exposure, we repeated the analysis restricted to dabigatran users with good adherence, defined as PDC $\geq 80\%$. This model assessed the association between PPI use and IS/TIA amongst adherent dabigatran users, using the same pre-specified clinical covariates as the primary model but without the dabigatran term or dabigatran $\times$ PPI interaction.

Second, to address potential outcome misclassification, we repeated the primary interaction model using a restricted outcome definition that included only adjudicated IS and excluded TIA.

Third, because controls were sampled within prioritised ethnicity strata, we repeated the primary model with additional adjustment for ethnicity. An additional complete-case analysis included BMI as a covariate.

Finally, an additional sensitivity analysis categorised PPI exposure as none, lower dose (omeprazole 20 mg, pantoprazole 20 mg or lansoprazole 15 mg daily), or higher dose (omeprazole ≥ 40 mg, pantoprazole ≥ 40 mg or lansoprazole ≥ 30 mg daily) and assessed its interaction with dabigatran use.

3 Results

3.1 Baseline Characteristics

Baseline characteristics of the 1908 individuals included, stratified by the four dabigatran-PPI exposure groups, are presented in Table 1. PPI type and prescribed total daily dose are shown in Supplementary Table 1. Omeprazole was the most commonly prescribed PPI (529/631, 83.8%).

Patients not receiving dabigatran and co-prescribed a PPI were the oldest group (median age 74 years), whereas the two dabigatran groups were younger (median age 68–71 years). Persistent/permanent AF was more prevalent amongst PPI users (56–65%) than non-users (45–61%). Comorbid conditions associated with stroke risk, including hypertension, diabetes, congestive cardiac failure, vascular disease and previous IS/TIA were markedly more common amongst PPI users than non-users.

Amongst dabigatran users, 479 received 150 mg twice daily, 351 received 110 mg twice daily and 6 received 75 mg twice daily. Dabigatran dosing was documented as clinically appropriate in 785 patients (93.9%). Documented reasons for reduced-dose prescribing included older age (62.7%), renal impairment (43.0%) and bleeding risk (10.8%).

Mean CHA₂DS₂ VASc scores were higher amongst PPI users than non-users, both in patients not prescribed dabigatran (3.8 versus 2.9) and in those prescribed dabigatran (3.7 versus 3.1), consistent with greater baseline thromboembolic risk amongst PPI users. As expected, use of warfarin and rivaroxaban was confined to the non-dabigatran groups. Aspirin and clopidogrel use was more frequent among PPI users. Baseline characteristics varied substantially across the four joint exposure groups, reflecting differences in comorbidity and treatment selection and supporting the need for multivariable adjustment.

Table 1 Baseline characteristics of patients included in the case-control study

Variable	No dabigatran/no PPI <i>N</i> = 771	No dabigatran/PPI <i>N</i> = 301	Dabigatran/no PPI <i>N</i> = 506	Dabigatran + PPI <i>N</i> = 330
AF-associated IS/TIA (%)	115 (14.9)	71 (23.6)	56 (11.1)	58 (17.6)
Median age (IQR)	68 (19)	74 (17)	68 (15)	71 (16)
Female (%)	372 (48.3)	146 (48.5)	221 (43.7)	153 (46.4)
Persistent/permanent AF (%)	347 (45.0)	169 (56.2)	310 (61.3)	213 (64.6)
Cardiac failure (%)	106 (13.8)	52 (17.3)	114 (22.5)	72 (21.8)
Diabetes (%)	194 (25.2)	103 (34.2)	144 (28.5)	115 (34.9)
Previous IS/TIA (%)	100 (13.0)	69 (22.9)	91 (18.0)	78 (23.6)
Hypertension (%)	450 (58.4)	209 (69.4)	326 (64.4)	230 (69.7)
Arterial disease (%)	175 (22.7)	125 (41.5)	125 (24.7)	140 (42.4)
Mean CHA ₂ DS ₂ VASc (SD)	2.9 (1.8)	3.8 (1.6)	3.1 (1.5)	3.7 (1.5)
Aspirin (%)	139 (18.0)	72 (23.9)	16 (3.2)	19 (5.8)
Clopidogrel (%)	11 (1.4)	13 (4.3)	4 (0.8)	13 (3.9)
Warfarin (%)	142 (18.4)	72 (23.9)	0	0
Rivaroxaban (%)	165 (21.4)	100 (33.2)	0	0
Median BMI (IQR)	31.2 (10.8)	29.7 (9.4)	31.8 (11)	31.6 (12.1)
Ethnicity				
European (%)	307 (39.8)	123 (40.9)	190 (37.5)	127 (38.5)
Māori (%)	162 (21.0)	57 (18.9)	118 (23.3)	66 (20.0)
Pacific (%)	223 (28.9)	71 (23.6)	158 (31.2)	95 (28.8)
Other (%)	79 (10.2)	50 (16.6)	40 (7.9)	42 (12.7)

Arterial disease (peripheral vascular or coronary artery disease). CHA₂DS₂ VASc: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, previous IS/TIA, vascular disease, age 65–74 years, and sex category [female]

AF, atrial fibrillation; BMI, body mass index (kg/m²); IQR, interquartile range; IS, ischaemic stroke; PPI, proton pump inhibitor; SD, standard deviation; TIA, transient ischaemic attack

3.2 Primary Analysis: Association of Dabigatran, PPI Use, and Their Interaction with AF-Associated IS/TIA

Results of the multivariable logistic regression model are presented in Table 2. After adjustment for age, sex, comorbidities (cardiac failure, hypertension, diabetes, arterial disease, previous IS/TIA), AF phenotype and concomitant antithrombotic therapy, dabigatran use was strongly associated with lower odds of AF-associated IS/TIA, (aOR 0.36, [95% CI 0.24–0.53]). In contrast, PPI use was associated with higher odds of IS/TIA (aOR 1.55 [95% CI 1.08–2.24]), most likely reflecting confounding by indication and greater comorbidity amongst PPI users.

The dabigatran $\times$ PPI interaction term was not statistically significant (aOR 0.98 [95% CI 0.57–1.69], $p = 0.94$), providing no evidence of a large dabigatran-specific interaction with PPI co-prescription.

Amongst covariates, older age (aOR 1.03 [95% CI 1.02–1.05]), persistent/permanent AF (aOR 2.85 [95% CI 2.10–3.86]) and previous IS/TIA (aOR 2.13 [95% CI 1.56–2.90]) were independently associated with higher odds of IS/TIA.

3.3 Adjusted Predicted Probabilities

Adjusted predicted probabilities derived from the interaction model are presented in Table 3 and shown in Fig. 1. These estimates represent model-based predicted probabilities of case status within the analytic case-control sample. Dabigatran use was associated with similar reductions in predicted case probability amongst non-PPI users and PPI users, consistent with the absence of a large dabigatran $\times$ PPI interaction.

Points represent adjusted model-predicted probabilities of IS/TIA case status derived from the multivariable logistic regression model; lines connect estimates within PPI strata. The analytic sample comprised 1908 participants: no dabigatran/no PPI, $n = 771$; no dabigatran/PPI, $n = 301$; dabigatran/no PPI, $n = 506$; dabigatran/PPI, $n = 330$. Confidence intervals are not displayed in the figure and are reported in Table 3. Predicted probabilities refer to case status within the analytic case-control sample and should not be interpreted as population absolute risks. IS, ischaemic stroke; PPI, proton pump inhibitor; TIA, transient ischaemic attack

The similar reduction in predicted case probability across PPI strata was consistent with the non-significant dabigatran

Table 2 Crude and adjusted odds ratios for IS/TIA from the dabigatran $\times$ PPI interaction model

Variable	<i>n</i> (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	<i>p</i> -value
Dabigatran	836 (43.8)	0.75 (0.58–0.97)	0.36 (0.24–0.53)	< 0.001
PPI	631 (33.1)	1.66 (1.29–2.14)	1.55 (1.08–2.24)	0.018
Dabigatran $\times$ PPI interaction	330 (17.3)	0.97 (0.58–1.63)	0.98 (0.57–1.69)	0.94
Age		1.04 (1.03–1.05)	1.03 (1.02–1.05)	< 0.001
Female	892 (46.8)	1.08 (0.94–1.40)	1.02 (0.78–1.34)	0.88
Persistent/permanent AF	1039 (54.5)	2.55 (1.94–3.35)	2.85 (2.10–3.86)	< 0.001
Cardiac failure	344 (18.0)	0.84 (0.61–1.18)	1.04 (0.72–1.50)	0.83
Hypertension	1215 (63.7)	1.32 (1.02–1.73)	1.16 (0.87–1.54)	0.33
Diabetes	556 (29.1)	1.09 (0.83–1.43)	1.04 (0.78–1.40)	0.79
Previous IS/TIA	338 (17.7)	2.21 (1.66–2.93)	2.13 (1.56–2.90)	< 0.001
Arterial disease*	565 (29.6)	1.19 (0.91–1.54)	1.0 (0.74–1.34)	0.99
Aspirin	246 (12.9)	1.48 (1.06–2.08)	0.95 (0.64–1.41)	0.79
Warfarin	214 (11.2)	0.86 (0.57–1.29)	0.28 (0.17–0.46)	< 0.001
Rivaroxaban	265 (13.9)	0.79 (0.54–1.16)	0.31 (0.20–0.50)	< 0.001

Arterial disease (peripheral vascular or coronary artery disease). Warfarin and rivaroxaban were included as adjustment variables and were not evaluated as primary exposures of interest

AF, atrial fibrillation; CI, confidence interval; IS, ischaemic stroke; OR, odds ratio; PPI, proton pump inhibitor; TIA, transient ischaemic attack

Table 3 Model-predicted probability of ischaemic stroke/TIA case status by exposure group

Exposure group	Number	Model-predicted probability of case status	(95% CI)
No dabigatran/no PPI	771	0.20	(0.17–0.23)
No dabigatran/PPI	301	0.27	(0.21–0.33)
Dabigatran/no PPI	506	0.09	(0.07–0.11)
Dabigatran/PPI	330	0.13	(0.09–0.16)

Model-predicted probabilities of IS/TIA case status within the analytic case-control sample, obtained from the multivariable logistic regression model including dabigatran, PPI, their interaction term, and other model covariates. These estimates should not be interpreted as population absolute risks. CI, confidence interval; PPI, proton pump inhibitor

dabigatran users, the association between PPI use and IS/TIA was elevated but imprecisely estimated (aOR 1.63 [95% CI 1.00–2.64], $p = 0.050$).

There was no evidence that the association with dabigatran differed according to PPI dose: interaction aORs were 1.01 (95% CI 0.56–1.80) for lower-dose PPI and 0.89 (95% CI 0.31–2.50) for higher-dose PPI (global interaction $p = 0.97$). Additional adjustment for BMI did not materially alter the dabigatran $\times$ PPI interaction (aOR 0.94 [95% CI 0.54–1.62], $p = 0.82$).

Simulation-based analyses indicated limited power to detect modest interaction effects, with estimated power of 31.8% for an interaction OR of 1.50 and 55.8% for an OR of 1.75. Power increased to 77.3% for an OR of 2.00 and > 95% for ORs ≥ 2.50 .

$\times$ PPI interaction term, although modest effect modification cannot be excluded (Fig. 2).

3.4 Sensitivity Analyses

Sensitivity analyses were consistent with the primary finding of no statistically significant dabigatran $\times$ PPI interaction. The interaction remained non-significant when the outcome was restricted to adjudicated IS ($n = 236$; aOR 1.23 [95% CI 0.67–2.25], $p = 0.51$). Additional adjustment for ethnicity did not materially alter the estimates for dabigatran (aOR 0.36 [95% CI 0.24–0.54]), PPI use (aOR 1.53 [95% CI 1.07–2.21]) or dabigatran $\times$ PPI interaction (aOR 0.99 [95% CI 0.57–1.70], $p = 0.96$). Amongst 668 adherent

4 Discussion

The aim of this study was to determine whether PPI co-prescription modified the association between dabigatran use and AF-associated IS/TIA. In this population-based case-control study of adults with AF, we found no statistically significant dabigatran $\times$ PPI interaction for AF-associated IS/TIA. The interaction estimate was centred close to the null, and model-based predicted case probabilities showed a similar pattern of lower IS/TIA probability with dabigatran use amongst PPI users and non-users. These findings do not support a large dabigatran-specific reduction in clinical effectiveness associated with PPI co-prescription. However, modest effect modification cannot be excluded.

Fig. 1 Model-predicted IS/TIA case status by dabigatran and PPI use

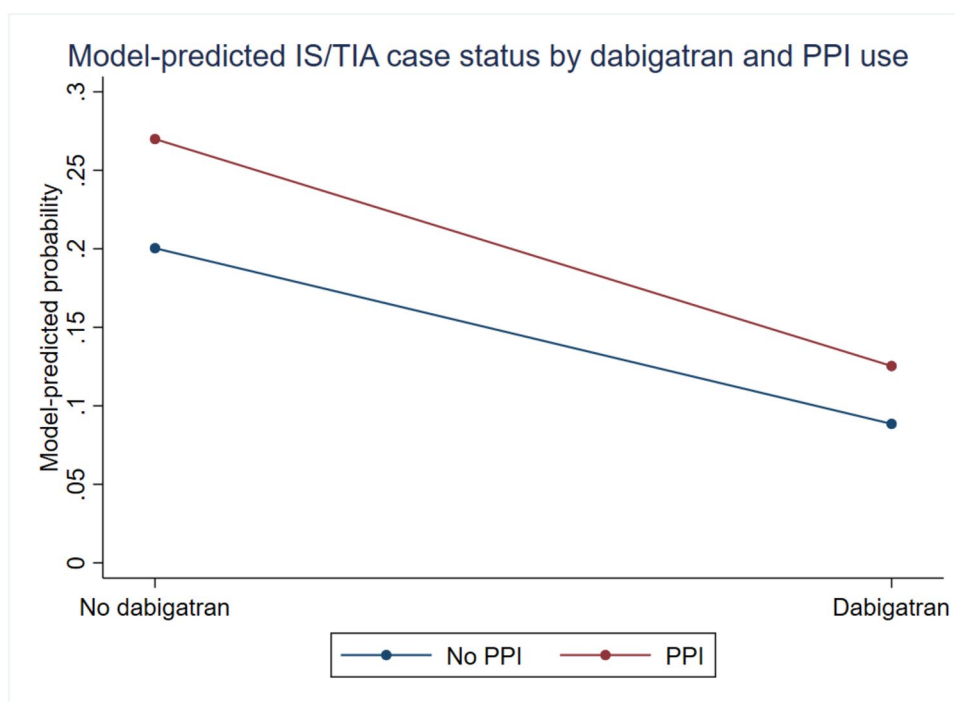
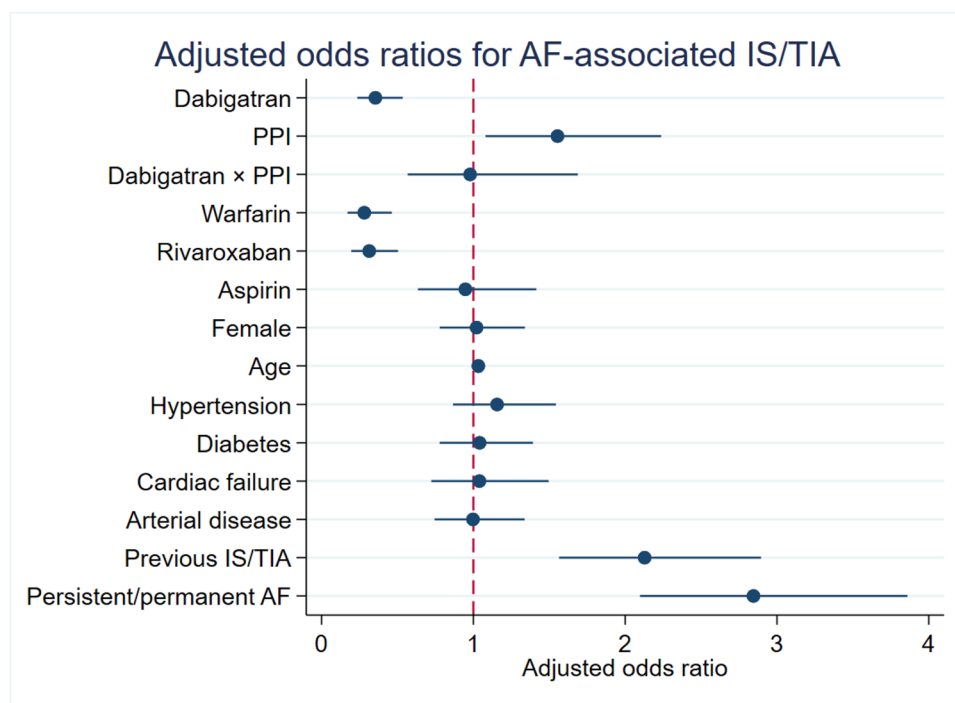


Fig. 2 Adjusted odds ratio for AF-associated ischaemic stroke/TIA from the multivariable logistic regression model. Points represent adjusted odds ratios and horizontal lines represent 95% confidence intervals. The dashed vertical line indicates the null value (OR = 1). The analytic sample comprised 1908 participants. AF, atrial fibrillation; IS, ischaemic stroke; OR, odds ratio; PPI, proton pump inhibitor; TIA, transient ischaemic attack



PPI use was associated with higher odds of IS/TIA in the adjusted model. This association should not be interpreted as evidence that PPI therapy causes thromboembolism or specifically attenuates dabigatran effectiveness. PPI co-prescription likely identifies patients with greater comorbidity, frailty, polypharmacy, gastrointestinal disease, renal dysfunction or other unmeasured risk factors.

Residual confounding by indication is therefore likely despite multivariable adjustment, and the observed association between PPI use and IS/TIA should not be interpreted causally. A recent large meta-analysis reported that the association between PPI use and stroke risk was modest and influenced by underlying cardiovascular

comorbidity, supporting the likelihood of residual confounding in observational studies of PPI exposure [18].

The biological rationale for a dabigatran $\times$ PPI interaction remains plausible. Dabigatran etexilate requires an acidic gastric environment for absorption, and pharmacokinetic studies have shown that PPI therapy can reduce dabigatran peak and trough concentrations [12]. This has raised concern that PPI co-prescription may lead to under-anticoagulation. Clinical evidence, however, remains limited. Subgroup analyses from major trials were not designed primarily to evaluate interaction effects, whilst observational studies and case reports have been limited by small sample sizes, confounding, or absence of clinical endpoints [3, 5, 11]. In a large Korean cohort of patients receiving concomitant OAC and PPI therapy, ischaemic stroke risk did not differ significantly between individual anticoagulants, although the study did not compare dabigatran users with and without PPI therapy [19]. More recently, a population-based cohort of older DOAC users found substantial evidence of residual confounding in comparisons of DOAC-PPI co-therapy with DOAC therapy alone; a secondary analysis found no increase in thrombotic events during PPI co-therapy. However, this analysis pooled different DOACs and used a broad composite thrombotic outcome rather than specifically examining adjudicated cerebrovascular events [20]. Our study adds clinically relevant evidence by directly testing the dabigatran $\times$ PPI interaction for adjudicated cerebrovascular outcomes using detailed individual-level clinical and medication data.

Sensitivity analyses were broadly consistent with the primary finding of no statistically significant dabigatran $\times$ PPI interaction. The interaction remained non-significant when the outcome was restricted to adjudicated ischaemic stroke and after additional adjustment for ethnicity. Amongst adherent dabigatran users, the association with PPI use was elevated but imprecisely estimated. Simulation-based analyses indicated limited power to detect modest interaction effects but reasonable power to detect larger effects. Therefore, the null interaction finding should be interpreted as evidence against a large clinically important dabigatran-specific interaction, rather than as proof of absence of any interaction. The study was insufficiently powered to exclude more modest attenuation of dabigatran effectiveness that could nevertheless be clinically important.

The high proportion of clinically appropriate dabigatran dosing provides some reassurance that the findings were not primarily driven by obvious dosing misclassification, although dose appropriateness does not replace direct measurement of dabigatran exposure.

The main clinical implication is that apparent excess thromboembolic risk amongst patients co-prescribed dabigatran and PPI should be interpreted cautiously. PPI use identifies a higher-risk clinical phenotype and may be confounded by factors incompletely captured in routine

clinical data. These findings do not support withholding clinically indicated PPI therapy solely because of concern about a large reduction in dabigatran effectiveness. However, because modest attenuation of dabigatran effectiveness cannot be excluded, clinicians should avoid unnecessary long-term PPI therapy and ensure appropriate dabigatran dosing and adherence, renal function assessment and review of potential interacting medications, particularly in patients at high thromboembolic risk. Measurement of dabigatran concentration or anticoagulant activity may be considered in selected high-risk patients where available, although routine monitoring is not supported by data.

This study has several strengths. ARCOS V provided adjudicated IS/TIA outcome data from a population-based surveillance study using multiple overlapping ascertainment sources. Medication exposure, AF phenotype, comorbidities and antithrombotic therapy were obtained through individual-level review of clinical records and dispensing data. The analysis directly tested the pharmacological interaction of interest using an interaction term and contextualised the null finding using model-based predicted probabilities and simulation-based power analysis.

Several limitations should be acknowledged. First, residual confounding by indication remains likely, because PPI users had greater cardiovascular comorbidity and higher baseline thromboembolic risk than non-users. Medication exposure was based on prescribing and dispensing records, rather than confirmed ingestion; although regular PPI use was required, treatment duration, dispensing frequency, and adherence could not be quantified. Dabigatran plasma concentrations were unavailable, and other potential P-glycoprotein-modifying medications were not systematically collected, limiting assessment of individual variation in dabigatran exposure. The study was underpowered to exclude modest effect modification or differences between individual PPI subtypes; findings were unchanged when PPI exposure was stratified by dose, although the higher-dose estimate was imprecise. Renal function was reviewed when assessing dose appropriateness, but quantitative creatinine clearance or eGFR was not available for adjustment, leaving potential residual confounding by renal function. Sub-clinical or incidentally detected cerebral infarctions were not assessed. Because controls were required to survive and remain free of IS/TIA throughout the surveillance period, survivor selection cannot be excluded if medication exposure was associated with mortality during follow-up. Finally, NMDS-derived controls may have had a greater comorbidity burden than AF patients managed exclusively in the community. This may have introduced selection bias of uncertain direction and magnitude and could also limit generalisability to lower-risk primary-care AF populations.

Larger real-world studies with sufficient power to detect modest interactions should incorporate other determinants of

dabigatran exposure and effectiveness, including concomitant P-glycoprotein-modifying medications and extremes of body weight, to assess whether combinations of these factors increase susceptibility to clinically relevant reductions in dabigatran effectiveness.

5 Conclusions

PPI co-prescription was not associated with a statistically significant modification of dabigatran's association with AF-associated IS/TIA. The findings do not support a large clinically important dabigatran-specific PPI interaction, but modest effect modification cannot be excluded. PPI use was associated with higher baseline thromboembolic risk, most likely reflecting residual confounding and greater comorbidity amongst PPI users.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40261-026-01600-9>.

Declarations

Author contributions KMM conceptualised and designed the study, applied for ethics approval, collected the data, performed the statistical analysis, interpreted the results, and drafted the manuscript. RK contributed to study design, assisted with ethics approval and provided critical revision of the manuscript. VF contributed critical revision of the manuscript. HW contributed to clinical interpretation of the pharmacological and cardiovascular aspects of the study and critically revised the manuscript. All authors read and approved the final version and agree to be accountable for the work.

Funding Open Access funding enabled and organized by CAUL and its Member Institutions. This work was supported by the Health Research Council, New Zealand. The funder had no role in the design, data collection, data analysis, and reporting of this study. (HRC grant number 20-680).

Data Sharing and Data Availability The data that support the findings of this study are not publicly available due to patient privacy and institutional data governance restrictions. Anonymised data may be made available from the corresponding author following a request outlining the proposed research purpose, subject to institutional data-governance and ethical approval. Requests should be directed to Dr Karim Mahawish (tyj9598@autuni.ac.nz). All methods used in the analysis are described in the manuscript.

Ethics Approval This study was performed in line with the principles of the Declaration of Helsinki. 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).

Consent to Participate The requirement for written informed consent was waived by the Auckland University of Technology Ethics Committee (24/4) because this was a low-risk observational study using routinely collected clinical data.

Competing Interests KMM received a Health Research Council of New Zealand grant as part of his doctoral studies for this research. HW reports grant support paid to the institution and fees for serv-

ing on Steering Committees of the ODYSSEY trial from Sanofi and Regeneron Pharmaceuticals, the ISCHAEMIA and MINT study from the National Institutes of Health, the Librexia and AF and ACS studies from Janssen Research and Development LLC and the MK0616 Study from Merck Sharp & Dolme Ltd. The other authors declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

Consent for Publication

Not applicable.

Code availability Not applicable.

AI USE ChatGPT was used to improve manuscript readability.

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