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ORIGINAL RESEARCH

Trimetazidine Is Associated With Ameliorated Stroke Risk in Patients With Both Ischemic Heart Disease and Atrial Fibrillation

Yuen-Ting Cheng; Gregory Y. H. Lip, MD; Bernard M. Y. Cheung, PhD; Kai-Hang Yiu, MD, PhD; Hung-Fat Tse, MD, PhD; Yap-Hang Chan, MRCP

BACKGROUND: Myocardial ischemia is closely associated with arrhythmogenesis and prognostication in patients with atrial fibrillation (AF). Trimetazidine ameliorates myocardial ischemia through prioritizing cardiomyocyte metabolism to glucose oxidation. Whether trimetazidine clinically reduces stroke risk in patients with ischemic heart disease and AF was unknown.

METHODS: We recruited patients with ischemic heart disease from the Hong Kong Clinical Data Analysis and Reporting System between January 1, 1999 and December 31, 2020. Patients with comorbid AF were identified, and those with a history of prior stroke were excluded. Trimetazidine users and nonusers (with long-acting nitrates as the control) were compared for the primary end point of incident ischemic stroke using Cox proportional regression, with and without propensity matching.

RESULTS: The primary analysis included 12 527 patients with ischemic heart disease and preexisting AF (mean age, 77.5±10.3 years; 44.6% men), who were further categorized as trimetazidine users (n=960) versus nonusers (n=11 567). Over a follow-up period of 1133 (interquartile range, 442–2454) days, 2160 patients (17.2%) developed new-onset ischemic stroke. Trimetazidine use was independently associated with a lower risk of new-onset ischemic stroke (hazard ratio [HR], 0.55 [95% CI, 0.44–0.68]; *P*<0.001). Propensity score–matched analyses revealed similar findings (adjusted HR, 0.65 [95% CI, 0.52–0.80]; *P*<0.001). Furthermore, trimetazidine was also independently associated with a lower risk of recurrent ischemic stroke (HR, 0.51 [95% CI, 0.37–0.69]; *P*<0.001).

CONCLUSIONS: Treatment with trimetazidine is associated with a lower risk of incident and recurrent stroke in patients with both ischemic heart disease and AF. These findings will need to be confirmed in randomized controlled trials.

Key Words: atrial fibrillation ■ ischemia ■ metabolic reprogramming ■ stroke ■ trimetazidine

Persistently, stroke is the second leading cause of death worldwide.[1] In particular, cardioembolic stroke commonly caused by atrial fibrillation (AF) is clinically more debilitating and a major public health burden. While anticoagulation including the use of direct oral anticoagulants has markedly improved stroke prevention in patients with AF, residual risks remained significant. In this regard, ischemia-related AF in patients with ischemic heart disease (IHD) may be a common disease entity with manifestations that are potentially amenable to specific risk modification.[2,3]

The role of metabolic reprogramming in IHD and AF has been recognized.[4–6] Trimetazidine is an antianginal agent that inhibits fatty acid oxidation and promotes

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CLINICAL PERSPECTIVE

What Is New?

- This multicenter cohort study investigated a novel hypothesis that treatment with trimetazidine, a metabolic modulator for the relief of symptomatic angina, is associated with a reduced risk of incident and recurrent ischemic stroke in patients with both ischemic heart disease and atrial fibrillation.

What Are the Clinical Implications?

- Trimetazidine may offer a novel therapeutic strategy to reduce stroke risk in patients with ischemic heart disease with atrial fibrillation, suggesting potential benefits beyond its conventional use as an antianginal agent.
- Further studies are needed to confirm our findings and reassess the clinical value of this drug in this patient population.

Nonstandard Abbreviation and Acronym

IHD	ischemic heart disease

cardiomyocyte energy derivation via glucose oxidation. Given that AF burden is directly proportionate to the risk of ischemic stroke in patients with AF,[7] reducing AF burden through ameliorating ischemia in IHD may represent a potential mechanism to reduce stroke risk. Furthermore, randomized controlled trials and meta-analyses have shown that trimetazidine has a protective effect against death and cardiac hospitalizations in patients with heart failure,[6,8–10] and improves cardiac function.[11] Improvements in cardiac pump failure may also favorably impact stroke risk. Owing to these anti-ischemic and anti–heart failure properties of trimetazidine, we hypothesized that this agent may have a protective effect against stroke incidence and recurrence in patients with both IHD and AF.

We therefore carried out this territory-wide, multicenter retrospective cohort study with propensity score matching to test the hypothesis that trimetazidine may impact on risk of stroke in patients with both IHD and AF.

METHODS

Data Availability

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

Study Cohort, Design, and Clinical Definitions

Patient data were collected from the Clinical Data Analysis and Reporting System of the Hospital Authority of Hong Kong, with an underlying catchment population of 7.5 million. The Clinical Data Analysis and Reporting System covered all 42 public hospitals in Hong Kong, which provided clinical services to 90% of the population. Research findings generated from Clinical Data Analysis and Reporting System were described earlier.[12,13]

In this territory-wide, multicenter, retrospective cohort study, we identified 279 894 patients with IHD who were administered anti-anginal therapies during the study period from January 1, 1999, to December 31, 2020. IHD was defined in the presence of ≥1 of the following: previous myocardial infarction; angina pectoris with evidence of inducible ischemia on an exercise treadmill or single photon emission computed tomography; and coronary atherosclerosis confirmed on invasive or computed tomographic coronary angiography. AF was defined as a supraventricular tachyarrhythmia with an uncoordinated atrial activity that was characterized by fibrillatory waves variable in magnitude, morphology, and timing and was associated with irregular ventricular response in the background of intact atrioventricular conduction. An AF episode was defined by a duration of at least 30 seconds. Paroxysmal, persistent, or permanent AF was defined similarly to existing clinical practice.[14]

Subjects were classified as trimetazidine users versus nonusers. Trimetazidine use was defined as its continuous prescription within the study period of at least ≥30 days. Trimetazidine nonusers (controls) were defined as patients with IHD who received long-acting nitrate therapy during the defined study period of at least ≥30 days but without the use of trimetazidine. We adopted long-acting nitrate therapy as the control because it is a first-line antianginal agent commonly prescribed in patients with IHD with a similar clinical indication as trimetazidine (Table S1). For all patients, cohort entry was defined as the time point from first starting trimetazidine or control therapy in the presence of an established AF diagnosis, until events, death, or censored date for nonevents (December 31, 2020) occurred (Figure S1). A blanking period for registration of the primary end point was applied for 30 days immediately after the cohort entry. The intention-to-treat principle was adopted for all analyses within the defined person-time.

Exclusion criteria included any of the following: patients aged <18 years, incomplete sociodemographic or medical records, duplications, and drug exposure of interest <30 days (Figure S2). This study was approved by the Institutional Review Board of the University

of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference Number: UW-23095). The requirement for patient consent was waived due to the retrospective study nature.

Definition of Primary End Point

The primary end point was defined as new-onset ischemic stroke (*International Classification of Diseases, Ninth Revision* [*ICD-9*]: 433-436). Secondary end points were defined as any new-onset stroke inclusive of ischemic or hemorrhagic origin (*ICD-9*: 430-438); or recurrence of stroke in those with previous history of stroke (Table S2).

Statistical Analysis

Baseline characteristics were reported as frequencies (percentages) for categorical variables and mean±SD for continuous variables. Balance between groups was assessed using the absolute standardized difference, with an absolute standardized difference <0.1 considered indicative of adequate balance. The difference in event rates between the control and treatment groups was calculated as the absolute risk reduction. The number needed to treat was then computed as the inverse of the absolute risk reduction and rounded to the nearest whole number. Cox proportional hazards regression models were used to derive hazard ratios (HRs) and 95% CIs for the prediction of primary and secondary end points by exposure to trimetazidine in patients with AF. Potential confounders included age, sex, socioeconomic status, cohort recruitment period, and general and cardiovascular comorbidities (Table S3). General comorbidities included chronic obstructive pulmonary disease, chronic liver and kidney diseases, type 2 diabetes, and obesity/overweight. Cardiovascular comorbidities included congestive heart failure, hypertension, hyperlipidemia, myocardial infarction, peripheral artery disease, and medications.

Table 1. Baseline Characteristics of Patients With Ischemia-Related Atrial Fibrillation in Overall and Propensity Score–Matched Cohorts*

	Overall sample (n=12 527)			Propensity score matched (n=1880)		
	Control (n=11 567)	Trimetazidine (n=960)	ASD†	Control (n=920)	Trimetazidine (n=960)	ASD†
Age, mean±SD	77.5±10.3	77.4±10.1	0.01	77.4±9.9	77.4±10.1	0
Sex, male	5042 (43.6)	548 (57.1)	0.27	524 (57.0)	548 (57.1)	0.002
Socioeconomic indicator‡	810 (7.0)	66 (6.9)	0.004	58 (6.3)	66 (6.9)	0.02
Recruitment period						
1999–2000	2283 (19.7)	265 (27.6)	0.19	112 (12.2)	265 (27.6)	0.39
2001–2010	5274 (45.6)	291 (30.3)	0.31	316 (34.3)	291 (30.3)	0.09
2011–2020	4010 (34.7)	404 (42.1)	0.15	492 (53.5)	404 (42.1)	0.23
Chronic obstructive pulmonary disease	1081 (9.3)	95 (9.9)	0.02	43 (4.7)	95 (9.9)	0.20
Obesity/overweight	141 (1.2)	19 (2.0)	0.06	21 (2.3)	19 (2.0)	0.02
Hypertension	5651 (48.9)	593 (61.8)	0.26	498 (54.1)	593 (61.8)	0.16
Diabetes	2943 (25.4)	318 (33.1)	0.17	266 (28.9)	318 (33.1)	0.09
Hyperlipidemia	1185 (10.2)	274 (28.5)	0.48	160 (17.4)	274 (28.5)	0.27
Myocardial infarction	1164 (10.1)	258 (26.9)	0.45	156 (17.0)	258 (26.9)	0.24
Congestive heart failure	5568 (48.1)	439 (45.7)	0.05	419 (45.5)	439 (45.7)	0.004
Peripheral artery disease	202 (1.7)	14 (1.5)	0.02	23 (2.5)	14 (1.5)	0.07
Chronic liver disease	99 (0.9)	33 (3.4)	0.18	7 (0.8)	33 (3.4)	0.18
Chronic kidney disease	1016 (8.8)	106 (11.0)	0.07	79 (8.6)	106 (11.0)	0.08
Aspirin/Antiplatelet therapy§	10 476 (90.6)	914 (95.2)	0.18	881 (95.8)	914 (95.2)	0.03
Anticoagulant therapy‖	4868 (42.1)	602 (62.7)	0.42	466 (50.7)	602 (62.7)	0.24
Lipid-lowering therapy¶	5015 (43.4)	796 (82.9)	0.89	761 (82.7)	796 (82.9)	0.005

ASD indicates absolute standardized difference.
*ASD values <0.1 indicate good balance.
†Values are expressed as frequency (%) unless otherwise specified; statistically significant $P<0.05$.
‡Whether receiving Comprehensive Social Security Assistance, a social security allowance, or not is used for assessing the socioeconomic status.
§Included aspirin/acetylsalicylic acid, clopidogrel, ticagrelor, and prasugrel, from the cohort entry to the censored date.
‖Included dabigatran, rivaroxaban, apixaban, edoxaban, and warfarin, from the cohort entry to the censored date.
¶Included simvastatin, rosuvastatin, pravastatin, fluvastatin, atorvastatin, ezetimibe, fenofibrate, alirocumab, and evolocumab, from the cohort entry to the censored date.

Cox proportional hazards regression analysis was used to assess the risk of incident ischemic stroke and stroke in the overall populations. The analysis included (1) a crude model, (2) potential confounders with a *P* value ≤0.10 in the first model, and (3) all potential confounders. We performed 1:1 propensity score matching without replacement between trimetazidine users and nonusers, matched by age, sex, and socioeconomic status. A caliper width of 0.1 SD of the logit of the propensity score was applied during the matching process to ensure close matches. We also performed the inverse probability of treatment weighting using propensity scores to adjust for confounding in the overall study population as part of a separate sensitivity analysis. The matched cohorts were compared with the overall study population to estimate primary and secondary end points. Balance was assessed using absolute standardized differences. A similar analysis was performed for recurrent ischemic stroke and stroke in patients with preexisting stroke. The proportional hazards assumption for the analysis was tested using Schoenfeld residuals. To evaluate potential effect modification by concomitant medications, we performed subgroup analysis across 3 medication classes: (1) anticoagulant therapy, (2) antiplatelet therapy, and (3) lipid-lowering therapy. We also performed subgroup analysis for subjects in different recruitment periods. Kaplan–Meier curves were generated to visualize cumulative incidence for incident and recurrent ischemic stroke and stroke, respectively. All data were analyzed by using the SPSS/PC statistical package version 29.0 (IBM, Armonk, NY). All *P* values were calculated using a 2-sided approach, and a *P* value <0.05 was considered statistically significant.

RESULTS

The final cohort comprised 34 326 patients with ischemia-related AF, of whom 12 527 had preexisting AF and 21 799 developed de novo AF during the follow-up period. The primary analysis included 12 527 patients with IHD with preexisting AF at baseline (mean age, 77.5±10.3 years; 44.6% men), who were further categorized as trimetazidine users (n=960) versus nonusers (n=11 567). Among this group of patients with IHD, 11.4% had previous myocardial infarction. The prevalence of congestive heart failure was high (48%), 1.7% of patients had coexisting peripheral artery disease. Differences in sex and socioeconomic status were abolished after propensity score matching (Table 1). In terms of trimetazidine use, the median treatment duration was 646.5 (interquartile range, 309.3–945.0) days. A total of 61% of patients on trimetazidine had a treatment duration beyond 500 days.

Trimetazidine and Reduced Ischemic Stroke in Ischemia-Related AF

Over the median follow-up duration of 1133 (interquartile range, 442–2454) days, 2160 patients (17.2%) developed new-onset ischemic stroke (Table S4). Trimetazidine users had significantly lower ischemic stroke incidence compared with nonusers (9.9% versus 17.9%; absolute

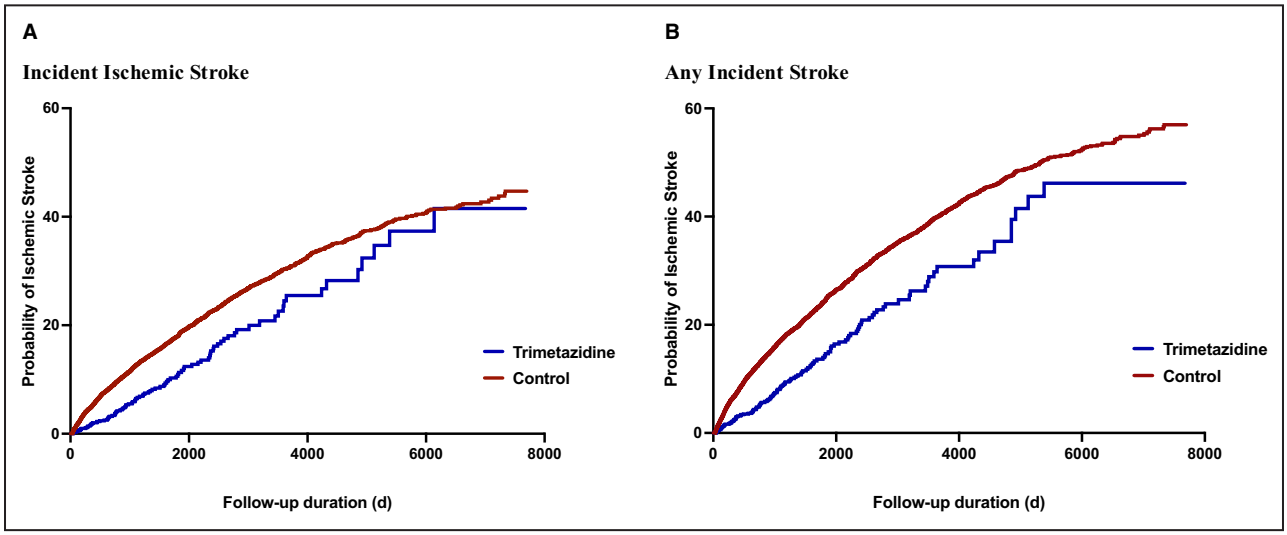

Figure 1. Kaplan–Meier curves for incident stroke according to trimetazidine use.
A, Incident ischemic stroke. Kaplan–Meier curve analysis showed that trimetazidine group had a longer event-free survival from new-onset ischemic stroke compared with control (mean survival, days; control, 5481 [95% CI, 5395–5566]; trimetazidine, 5847 [95% CI, 5466–6229]; log rank [Mantel–Cox], 22.2; *P*<0.001). **B**, Any incident stroke. Event-free survival from any incident stroke was longer in the trimetazidine group than control (mean survival, days; control, 4807 [95% CI, 4720–4894]; trimetazidine, 5473 [95% CI, 5083–5864]; log rank [Mantel–Cox], 38.1; *P*<0.001).

risk reduction, 8.0%, number needed to treat, 13). Using Cox proportional hazards regression, trimetazidine use was associated with a lower risk of new-onset ischemic stroke compared with controls (HR, 0.61 [95% CI, 0.50–0.75]; *P*<0.001; Figure 1A). Such observations remained unchanged after adjustment for potential confounders (HR, 0.55 [95% CI, 0.44–0.68]; *P*<0.001; Table 2, Figure 2). In propensity score–adjusted multivariate analyses, trimetazidine use was independently associated with reduced risk of ischemic stroke (HR, 0.65 [95% CI, 0.52–0.80]; *P*<0.001). In propensity score–matched analyses, a similar risk reduction with trimetazidine was found (HR, 0.54 [95% CI, 0.41–0.71]; *P*<0.001; Table S5).

Secondary End Points

Over the follow-up period, 2933 patients with IHD (23.4%) with AF developed a secondary end point defined as any stroke. Trimetazidine users had significantly lower stroke incidence compared with nonusers (12.7% versus 24.3%; absolute risk reduction, 11.6%, number needed to treat, 9). Trimetazidine use was associated with a lower risk of any stroke compared with control in crude (HR, 0.57 [95% CI, 0.48–0.68]; *P*<0.001; Figure 1B) and multivariable-adjusted analyses (HR, 0.51 [95% CI, 0.42–0.62]; *P*<0.001; Table 3). Propensity score–adjusted multivariate analyses showed a similar risk reduction (HR, 0.60 [95% CI, 0.50–0.73]; *P*<0.001). Furthermore, analyses in the propensity score–matched sample revealed similar findings (HR, 0.47 [95% CI, 0.37–0.60]; *P*<0.001; Table S6).

We further analyzed the risk for recurrence in patients with both IHD and AF who had a history of prior stroke. Trimetazidine use was independently associated with reduced risk of recurrence of both ischemic stroke (HR, 0.51 [95% CI, 0.37–0.69]; *P*<0.001; Table S7) and any stroke (HR, 0.53 [95% CI, 0.45–0.64]; *P*<0.001; Table S8, Figure 3).

Table 2. Predictor for New-Onset Ischemic Stroke in Patients With Ischemia-Related Atrial Fibrillation*

	Crude model		Multivariable model 1		Multivariable model 2	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.03 (1.02–1.03)	<0.001†	1.02 (1.02–1.03)	<0.001†	1.03 (1.02–1.03)	<0.001†
Sex, male	0.68 (0.63–0.74)	<0.001†	0.79 (0.72–0.87)	<0.001†	0.80 (0.73–0.88)	<0.001†
Socioeconomic indicator	0.93 (0.79–1.09)	0.35	…	…	0.94 (0.80–1.11)	0.47
Recruitment period						
1999–2000	Reference	<0.001†	Reference	<0.001†	Reference	<0.001†
2001–2010	0.84 (0.76–0.93)	<0.001†	0.78 (0.70–0.86)	<0.001†	0.76 (0.68–0.84)	<0.001†
2011–2020	0.64 (0.56–0.72)	<0.001†	0.58 (0.51–0.66)	<0.001†	0.54 (0.47–0.62)	<0.001†
Chronic obstructive pulmonary disease	0.93 (0.79–1.09)	0.35	…	…	0.89 (0.75–1.06)	0.20
Obesity/overweight	0.87 (0.56–1.35)	0.52	…	…	1.15 (0.71–1.87)	0.57
Hypertension	1.18 (1.08–1.28)	<0.001†	1.20 (1.10–1.32)	<0.001†	1.18 (1.07–1.29)	<0.001†
Diabetes	1.06 (0.96–1.17)	0.28	…	…	1.08 (0.96–1.20)	0.20
Hyperlipidemia	0.79 (0.68–0.91)	0.001†	0.84 (0.72–0.99)	0.03†	0.82 (0.70–0.97)	0.02†
Congestive heart failure	1.08 (0.99–1.18)	0.07	1.00 (0.91–1.10)	0.98	0.99 (0.90–1.09)	0.88
Myocardial infarction	0.85 (0.73–0.99)	0.04†	0.90 (0.76–1.05)	0.18	0.89 (0.76–1.05)	0.17
Peripheral artery disease	1.28 (0.86–1.90)	0.22	…	…	1.21 (0.81–1.80)	0.35
Chronic kidney disease	1.03 (0.86–1.25)	0.74	…	…	1.18 (0.97–1.44)	0.11
Chronic liver disease	0.59 (0.32–1.06)	0.08	0.73 (0.39–1.37)	0.33	0.71 (0.38–1.33)	0.29
Aspirin/Antiplatelet therapy‡	1.91 (1.53–2.39)	<0.001†	2.11 (1.66–2.67)	<0.001†	2.11 (1.67–2.67)	<0.001†
Anticoagulant therapy§	0.92 (0.85–1.00)	0.05	1.26 (1.14–1.39)	<0.001†	1.27 (1.15–1.40)	<0.001†
Lipid-lowering therapy‖	0.84 (0.77–0.91)	<0.001†	1.04 (0.94–1.15)	0.45	1.04 (0.94–1.15)	0.50
Trimetazidine use	0.61 (0.50–0.75)	<0.001†	0.55 (0.44–0.69)	<0.001†	0.55 (0.44–0.68)	<0.001†
Trimetazidine use (propensity score adjusted)¶	…	…	…	…	0.65 (0.52–0.80)	<0.001†

HR indicates hazard ratio.

*HR prediction estimates and 95% CI explained by variable of interest as shown by univariable and multivariable Cox proportional hazards regression; crude model: unadjusted; multivariable model 1: adjusted for potential confounders with *P* value ≤0.10 in crude model; multivariable model 2: adjusted for all potential confounders as defined a priori.

†Statistically significant (*P*<0.05).

‡Included aspirin/acetylsalicylic acid, clopidogrel, ticagrelor, and prasugrel, from the cohort entry to the censored date.

§Included dabigatran, rivaroxaban, apixaban, edoxaban, and warfarin, from the cohort entry to the censored date.

‖Included simvastatin, rosuvastatin, pravastatin, fluvastatin, atorvastatin, ezetimibe, fenofibrate, alirocumab, and evolocumab, from the cohort entry to the censored date.

¶Trimetazidine use adjusted by propensity scores only (matched by sex, age, socioeconomic status, aspirin/antiplatelet therapy, and lipid-lowering therapy).

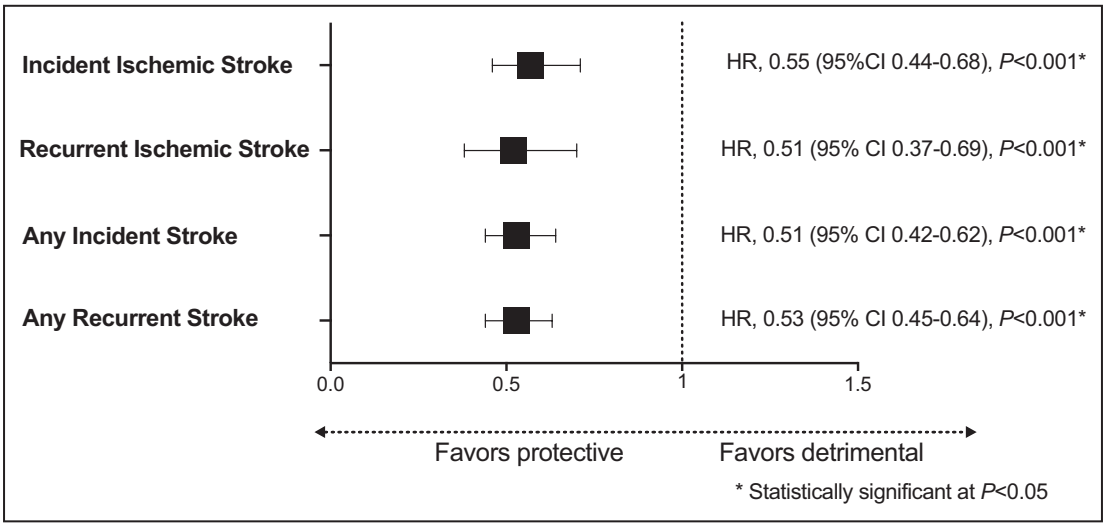

Figure 2. HR estimates for primary and secondary end points.
Trimetazidine use was also associated with reduced hazard ratios for incident ischemic stroke, any incident stroke, and recurrence of ischemic or any stroke (each estimate presented in figure). HR indicates hazard ratio.

Sensitivity Analysis

In the subgroup analysis, the interaction between trimetazidine and anticoagulant use was nonsignificant (P=0.53). Trimetazidine was associated with a reduced incident ischemic stroke risk in both anticoagulant users (HR, 0.72 [95% CI, 0.56–0.92]; P=0.01) and nonusers (HR, 0.49 [95% CI, 0.34–0.70]; P<0.001; Table S9). Trimetazidine use was associated with a reduced incident ischemic stroke risk over a different recruitment period: 1999–2000 (HR, 0.63 [95% CI, 0.46–0.85]; P=0.003), 2001–2010 (HR, 0.66 [95% CI, 0.53–0.83]; P<0.001), and 2011–2020 (HR, 0.48 [95% CI, 0.30–0.78]; P=0.003). Furthermore, trimetazidine use is associated with reduced incident AF in patients with IHD (Table S10).

DISCUSSION

To our knowledge, this is the first clinical study that investigated the potential role of trimetazidine in ameliorating the risk of stroke in patients with both IHD and AF. Our study revealed an overall 40% HR reduction in ischemic stroke associated with trimetazidine use. Such observations remained statistically robust after meticulous adjustments for potential confounders and propensity score matching. Furthermore, a similar risk reduction in stroke recurrence is also found with trimetazidine. Altogether, these findings may potentially provide a new therapeutic avenue for stroke prevention in ischemia-related AF.

Albeit novel, our observations are well substantiated with biological plausibility and preclinical experimental evidence.[15,16] The fundamental explanatory mechanism is via the modulation of cardiac energetics by trimetazidine. Trimetazidine dihydrochloride, an antianginal drug clinically used in various jurisdictions, specifically blocks long-chain 3–ketoacyl coenzyme A thiolase in the mitochondria.[17] In doing so, trimetazidine inhibits β oxidation of fatty acids in cardiomyocytes and redirects substrate use to rely preferentially on glucose oxidation. Compared with oxidative phosphorylation, the glycolytic biochemical pathways consume relatively fewer oxygen molecules per unit of energy derived, thus reducing oxygen consumption.

Atrial ischemia creates a direct substrate for the maintenance of AF, through slowing of conduction and promotion of reentry.[2,18] By relieving atrial myocardial ischemia, trimetazidine may reduce AF burden and thereby risk of stroke, given that AF burden is positively related to stroke.[7] In addition to its anti-ischemic effect, trimetazidine may also exert direct electrophysiological effects on the myocardium. Research showed that trimetazidine reduced QT dispersion in acute myocardial infarction, which indicates electrical inhomogeneity[19] and provides a substrate for reentrant arrhythmias. In a nonrandomized study of patients with heart failure on standard therapy, trimetazidine reduced electrocardiographic P-wave duration and dispersion, which are important precursors for AF.[20] Also, there are other potential mechanisms through which trimetazidine may indirectly modulate the risk of AF and its burden, including antioxidant effect and improvement of endothelial dysfunction,[6] inhibition of myocardial fibrosis,[21] and reduction of whole-body metabolism.[9]

Disease manifestation of AF and its response to treatment could be substrate specific.[22] Given the inextricable pathophysiological links between IHD and AF[3] and ischemia-related AF as a unique clinical entity may

Table 3. Predictor for Any New-Onset Stroke in Patients With Ischemia-Related Atrial Fibrillation*

	Crude model		Multivariable model 1		Multivariable model 2	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.03 (1.02–1.03)	<0.001†	1.03 (1.02–1.03)	<0.001†	1.03 (1.03–1.03)	<0.001†
Sex, male	0.71 (0.65–0.76)	<0.001†	0.83 (0.77–0.90)	<0.001†	0.84 (0.78–0.91)	<0.001†
Socioeconomic indicator	1.05 (0.92–1.20)	0.46	…	…	1.06 (0.93–1.22)	0.39
Recruitment period						
1999–2000	Reference	<0.001†	Reference	<0.001†	Reference	<0.001†
2001–2010	0.87 (0.80–0.94)	0.001†	0.81 (0.74–0.89)	<0.001†	0.80 (0.73–0.88)	<0.001†
2011–2020	0.69 (0.62–0.77)	<0.001†	0.61 (0.54–0.68)	<0.001†	0.59 (0.53–0.67)	<0.001†
Chronic obstructive pulmonary disease	0.89 (0.78–1.03)	0.12	…	…	0.85 (0.73–0.99)	0.03†
Obesity/overweight	0.82 (0.56–1.20)	0.30	…	…	1.05 (0.69–1.59)	0.83
Hypertension	1.18 (1.10–1.27)	<0.001†	1.14 (1.05–1.23)	0.002†	1.13 (1.04–1.23)	0.003†
Diabetes	1.18 (1.08–1.28)	<0.001†	1.21 (1.10–1.32)	<0.001†	1.21 (1.10–1.32)	<0.001†
Hyperlipidemia	0.81 (0.72–0.92)	<0.001†	0.84 (0.73–0.96)	0.01†	0.84 (0.73–0.96)	0.01†
Congestive heart failure	1.16 (1.08–1.25)	<0.001†	1.02 (0.94–1.11)	0.59	1.03 (0.95–1.11)	0.55
Myocardial infarction	0.91 (0.80–1.03)	0.15	…	…	0.96 (0.84–1.10)	0.53
Peripheral artery disease	1.27 (0.91–1.78)	0.17	…	…	1.11 (0.79–1.57)	0.56
Chronic kidney disease	1.18 (1.01–1.38)	0.03†	1.26 (1.08–1.49)	0.004†	1.27 (1.08–1.49)	0.004†
Chronic liver disease	0.97 (0.65–1.45)	0.88	…	…	1.04 (0.66–1.61)	0.88
Aspirin/Antiplatelet therapy‡	1.53 (1.29–1.82)	<0.001†	1.69 (1.40–2.03)	<0.001†	1.69 (1.41–2.03)	<0.001†
Anticoagulant therapy§	0.88 (0.82–0.95)	<0.001†	1.21 (1.11–1.31)	<0.001†	1.20 (1.10–1.30)	<0.001†
Lipid-lowering therapy‖	0.80 (0.75–0.86)	<0.001†	0.99 (0.91–1.08)	0.82	0.99 (0.90–1.08)	0.75
Trimetazidine use	0.57 (0.48–0.68)	<0.001†	0.51 (0.42–0.61)	<0.001†	0.51 (0.42–0.62)	<0.001†
Trimetazidine use (propensity score adjusted)¶	…	…	…	…	0.60 (0.50–0.73)	<0.001†

HR indicates hazard ratio.

*HR prediction estimates and 95% CI explained by variable of interest as shown by univariable and multivariable Cox proportional hazards regression; crude model: unadjusted; multivariable model 1: adjusted for potential confounders with *P* value ≤0.10 in crude model; multivariable model 2: adjusted for all potential confounders as defined a priori.

†Statistically significant ($P<0.05$).

‡Included aspirin/acetylsalicylic acid, clopidogrel, ticagrelor, and prasugrel, from the cohort entry to the censored date.

§Included dabigatran, rivaroxaban, apixaban, edoxaban, and warfarin, from the cohort entry to the censored date.

‖Included simvastatin, rosuvastatin, pravastatin, fluvastatin, atorvastatin, ezetimibe, fenofibrate, alirocumab, and evolocumab, from the cohort entry to the censored date.

¶Trimetazidine use adjusted by propensity scores only (matched by sex, age, socioeconomic status, aspirin/antiplatelet therapy, and lipid-lowering therapy).

deserve further specific attention. Significant coronary disease is an independent predictor for the risk of stroke in nonvalvular AF and is incorporated into stroke risk scores.[23] Nevertheless, how modulation of ischemia in patients with both IHD and AF might reversibly impact stroke risk remained unclear. Moreover, nearly half of our patient sample had congestive heart failure. Previous trials showed that trimetazidine improves symptoms and cardiac function in patients with heart failure and reduces death and cardiovascular hospitalizations.[10,11] It is possible that the observed beneficial effects in our sample of patients with both IHD and AF are at least partially mediated via heart failure protection.

At present, trimetazidine is indicated under class IIb recommendation of the European Society of Cardiology 2019 guidelines for relief of symptomatic angina as a second-line therapy.[24] In contrast with other antianginal agents, trimetazidine exerts no hemodynamic effect.[25] This makes it favorable as a therapeutic option for those who cannot tolerate medications with negative inotropic or bradycardic effects. However, this drug is currently not licensed in the United States and the United Kingdom. In fact, the European Medicines Agency recommended a restriction on its use in 2012, owing to its potential concerns in relation to Parkinsonian symptoms. However, postmarketing surveillance data showed that the risk of drug-induced Parkinsonism is low, approximating 0.36 per 100 000 person-years, and typically resolves within 4 months of cessation. With culminating evidence on the potential benefits of trimetazidine for cardiovascular diseases beyond the conventional arena of antianginal therapy, the clinical value of this drug may be reassessed in due course.

Limitations

Despite the encouraging findings, we need to interpret the findings with caution and acknowledge several key

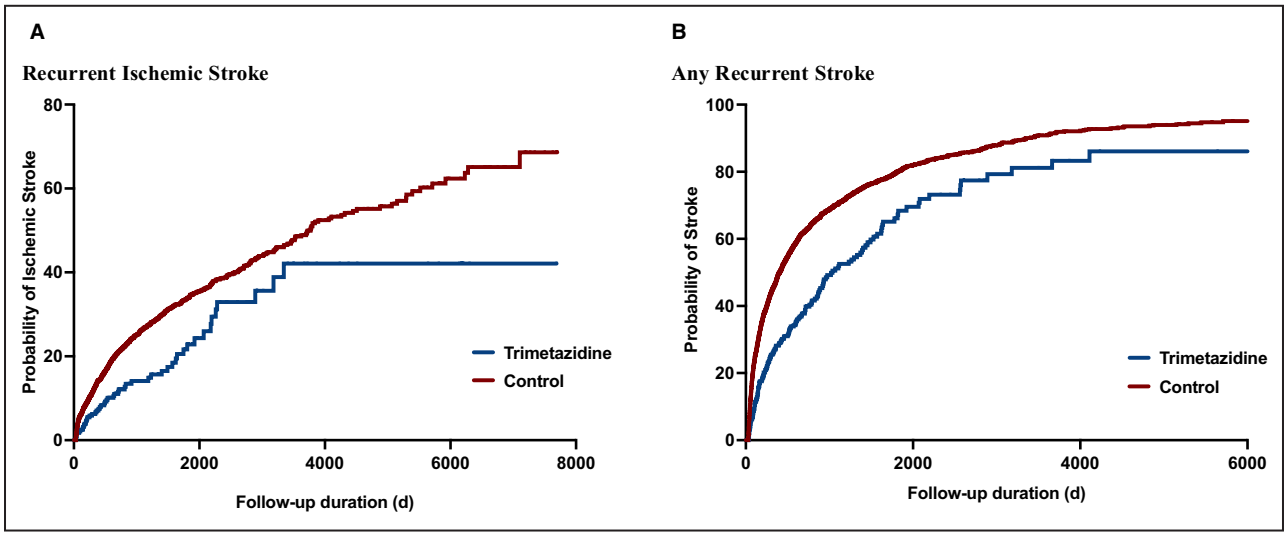

Figure 3. Kaplan–Meier curves for recurrent stroke according to trimetazidine use.
A, Recurrent ischemic stroke. Kaplan–Meier curve analysis showed that trimetazidine group had a longer event-free survival from recurrent ischemic stroke compared with control (mean survival, days; control, 4104 [95% CI, 3889–4319]; trimetazidine, 5153 [95% CI, 4472–5834]; log rank [Mantel–Cox], 13.7; $P<0.001$). **B**, Any recurrent stroke. Event-free survival from any recurrent stroke was longer in the trimetazidine group than control (mean survival, days; control, 1183 [95% CI, 1094–1272]; trimetazidine, 1851 [95% CI, 1493–2208]; log rank [Mantel–Cox], 45.2; $P<0.001$).

limitations. First, the inherent observational nature of the study renders us unable to definitively make a conclusion on causality. Nevertheless, we adopted meticulous sensitivity analyses and propensity score matching, and coherent findings were obtained. Furthermore, this is probably one of the largest available clinical databases of trimetazidine in patients with both IHD and AF worldwide. Second, we did not collect data on the paroxysmal versus persistent nature of AF in our patients, nor their AF burden. The nature of ischemia-related AF in these patients with IHD were presumed and could not be verified. Moreover, due to limitations in data availability, we were unable to adjust for all potential confounding variables in our multivariate regression models. Third, we assumed a strictly linear relationship for the continuous variables, which may fail to capture complex associations and introduce bias. Nevertheless, we adjusted for important covariates in the Cox regression models to mitigate residual confounding. Fourth, there are no available data on mechanisms and biochemical measurements on metabolic reprogramming of the atrial myocardium. The postulated chain of causation was hypothetical; therefore, further randomized controlled trials and mechanistic studies on trimetazidine in patients with ischemia-related AF are needed to confirm our observation and elucidate the underlying mechanisms.

CONCLUSIONS

Treatment with trimetazidine is associated with a lower risk of both incident and recurrent stroke in patients with both IHD and AF. Mechanisms underlying such observations remained unclear. These findings warrant further investigation in future mechanistic studies and randomized controlled trials.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S10
Figures S1–S2

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