

Relationship Among Atrial Fibrillation, CHADS2 Score and Ischaemic Stroke in Patients With Coronary Artery Disease: A Propensity Score Matching Study

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Abstract

Objective: The purpose of this study was to investigate the relationship among atrial fibrillation (AF), CHADS₂ score and ischaemic stroke in patients with coronary artery disease.

Methods: A total of 2335 patients with coronary artery disease were included. They were divided into a nonischaemic stroke group (n=1997) and an ischaemic stroke group (n=388). Propensity score matching (PSM) was used to match ischaemic stroke patients with nonischaemic stroke patients in a 1:4 ratio. The relationship between AF, CHADS₂ score and ischaemic stroke was evaluated using a univariate generalized linear model in different age, body mass index, and coronary artery disease subgroups. Univariate and multivariate generalized linear models were used to evaluate the relationship between AF and ischaemic stroke in different models.

Results: Compared with the nonischaemic stroke group, the rate of AF (8.81% vs. 14.20%, P=0.002) in the ischaemic stroke group was higher. The proportion of patients with ischaemic stroke was significantly different between the AF group and the non-AF group (19.04% vs. 28.74%, P=0.003). With increasing CHADS₂ score, the incidence of AF gradually increased (P for trend <0.001). With increasing AF burden, the rate of ischaemic stroke increased continuously (P for trend <0.001). Subgroup analysis showed that the trend towards increased stroke risk in the AF group was consistent across the various subgroups. Multivariate analysis demonstrated that paroxysmal and nonparoxysmal AF were not associated with ischaemic stroke compared with the absence of AF.

Conclusion: After adjusting for confounding factors, the correlation between AF and ischaemic stroke decreased. Atherosclerotic factors may play an important role in ischaemic stroke in patients with coronary heart disease.

Background

Atrial fibrillation (AF) is a common arrhythmia in clinical practice [1-3]. Although evidence in recent decades has indicated a strong association between AF and ischaemic stroke [4, 5], a gap remains in our understanding of the mechanism underlying this association. The current view is that AF causes blood to clot and emboli to detach, resulting in cerebral embolism [5]. This mechanism has long been considered the leading cause of ischaemic stroke [6]. However, recent studies have shown that the pathogenesis of ischaemic stroke associated with AF is more complex and involves other factors in addition to arrhythmias [7]. Coronary artery disease and ischaemic stroke have similar risk factors [8], such as hypertension and advanced age. The purpose of this study was to explore the relationship among AF, CHADS₂ score and ischaemic stroke in patients with coronary heart disease and to further understand the role of AF in ischaemic stroke in patients with coronary heart disease; the results will have far-reaching significance for future treatment strategies.

Materials And Methods

Study population

This study is a cross-sectional study conducted according to the STROBE guidelines. A total of 2,335 patients with coronary artery disease were admitted to the first department of The Cardiovascular Department of the Second Hospital of Hebei Medical University from September 2016 to May 2019.

Patient demographic information, medical history and laboratory assessments were collected and recorded. As shown in Figure 1, 262 patients were excluded for cerebral haemorrhage, subarachnoid haemorrhage, or unknown stroke history. Finally, 2,335 patients were included in this analysis.

The study population was divided into different subgroups according to sex, age, body mass index, type of coronary artery disease, and CHADS₂ score ≥ 3 .

Coronary artery disease was defined as significant narrowing ($\geq 50\%$) of the coronary lumen detected either invasively or noninvasively and further defined as one or more of the following types: stable coronary artery disease (SCAD), unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), ST-elevation myocardial infarction (STEMI), previous myocardial infarction (previous MI), and ischaemic cardiomyopathy. Specific diagnoses were performed on the basis of standard reference guidelines.

In this study, ischaemic stroke included either a previous history of ischaemic stroke or new onset of ischaemic stroke during hospitalization.

AF was classified into paroxysmal, persistent, long-standing persistent and permanent AF, which were determined according to the 2014 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) task force on practice guidelines and the 2016 European Society of Cardiology (ESC) guidelines[9, 10]. In this study, persistent, long-standing persistent, and permanent AF were grouped and collectively referred to as nonparoxysmal AF.

The CHADS₂ score is a clinically commonly used prediction model to identify the risk of ischaemic stroke in patients with nonvalvular AF, which was calculated by assigning 2 points for ischaemic stroke or transient ischaemic attack and 1 point for each other component, including heart failure, hypertension, age ≥ 75 years and diabetes. The CHADS₂ score was calculated for each patient at discharge.

We defined diabetes mellitus (DM) as a casual plasma glucose concentration ≥ 200 mg/dL, fasting plasma glucose concentration ≥ 126 mg/dL, 2-hour plasma glucose concentration ≥ 200 mg/dL from a 75 g oral glucose tolerance test, or receiving drugs or insulin for DM. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or taking antihypertensive medication. Dyslipidaemia was defined as low-density lipoprotein cholesterol (LDL-C) ≥ 140 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL, or triglycerides ≥ 150 mg/dL. Heart failure included past or current signs and symptoms of heart failure with both low ($< 40\%$) and preserved ejection fraction (EF) ($\geq 40\%$) and/or other clinical evidence of cardiac dysfunction. Chronic kidney disease (CKD) referred to

an estimated glomerular filtration rate <60 mL/min per 1.73 m². Left atrial diameter (LA) and EF were measured by transthoracic echocardiography or transoesophageal echocardiography.

Statistical analysis

The investigators performed the data analysis using Empower (R) (www.empowerstats.com, X&Y solutions, Inc. Boston MA) and R 3.6.3 (<http://www.R-project.org>). Continuous variables in this study did not conform to a normal distribution, which were described as the median and interquartile range (IQR) and compared using the Mann-Whitney test. Categorical variables were expressed as counts and composition ratios and were compared using the chi-square test or Fisher exact test as appropriate.

Given the inherent differences between patients with or without ischaemic stroke, we calculated a propensity score for the following variables: sex, age, and body mass index. The propensity score was estimated by using a logistic regression model. The matching process was based on the nearest neighbour matching method without replacement, under a 0.01 calliper to perform 1:4 matching, which yielded subjects with stroke and matched subjects without stroke. A standardized difference of less than 0.1 indicated an excellent balance after PSM.

To control for potential covariates, we used multivariate generalized linear regression models. We constructed two models for the association of AF with ischaemic stroke. This multivariate analysis, adjusting for any possible confounding variables of statistical significance in the univariate analysis ($P < 0.1$), was performed to identify independent risk predictors. We also adjusted for features that, when added to this model, changed the matched odds ratio by at least 10%. The Cochran–Mantel–Haenszel test was used in the analysis to calculate P for trend. The likelihood ratio test followed the tests for impact adjustment for subgroup markers. A two-tailed P value < 0.05 was considered statistically significant in this study. The missing values were not deleted or filled, and the empty values were directly retained for data analysis.

Results

Patient characteristics

A total of 2335 patients with coronary artery disease were enrolled in this study, including 1,997 patients without ischaemic stroke (85.52%) and 338 patients with ischaemic stroke (14.48%). The matched cross-sectional analysis included 1,685 patients (1,348 patients without ischaemic stroke and 337 patients with it). The patients' baseline characteristics before and after matching are shown in Table 1.

Before PSM, compared with the nonischaemic stroke group, the ischaemic stroke group was older (63.00 vs 65.00, $P < 0.001$), and its proportions of SCAD (6.41% vs 10.65%, $P = 0.005$), STEMI (3.96% vs 6.80%, $P = 0.018$), and previous MI (10.27% vs 14.50%, $P = 0.021$) were higher. The proportion of UA (73.66% vs 67.75%, $P = 0.024$) was lower, and the proportions of heart failure (15.62% vs 21.30%, $P = 0.009$), hypertension (65.45% vs 77.51%, $P < 0.001$), AF (8.81% vs 14.20%, $P = 0.002$), CKD (1.95% vs 3.85%,

P=0.043), and aortic atherosclerosis (26.81% vs 84%, P<0.001) were higher. The creatinine levels (69.00 vs 72.00, P=0.001), pulse wave velocity (PWV) (1556.50 vs 1623.00, P<0.001) and CHADS₂ scores (1.00 vs 3.00, P<0.001) were also higher. These differences were statistically significant.

After PSM, compared with the nonischaemic stroke group, the proportions of STEMI (3.78% vs 6.53%, P=0.027), UA (73.37% vs 67.95%, P=0.047), hypertension (66.69% vs 77.74%, P<0.001), AF (8.83% vs 14.24%, P=0.003), and aortic atherosclerosis (28.94% vs 43.98%, P < 0.001) were higher in the ischaemic stroke group. The serum creatinine level (70.00 vs 72.00, P=0.018) and CHADS₂ score (1.00 vs 3.00, P<0.001) were also higher. These differences were statistically significant.

A comparison of the baseline data of patients with and without AF after PSM is shown in Table 2. Compared with the non-AF group, the AF group was older (63.50 vs 69.00, P<0.001); had higher rates of SCAD (4.61% vs 31.14%, P<0.001), previous MI (10.94% vs 17.37%, P=0.014), ischaemic cardiomyopathy (1.58% vs 5.99%, P<0.001), and UA (74.57% vs 51.50%; had lower rates of STEMI (4.68% vs 1.20%, P=0.036), heart failure (13.90% vs 53.29%, P<0.001), valvular heart disease (1.91% vs 6.59%, P<0.001), CKD (1.84% vs 4.79%, P=0.012), smoking (19.50% vs 12.57%, P=0.03), and aortic atherosclerosis (30.53% vs 44.58%); and had higher serum creatinine level (69.00 vs 79, P<0.001), LA (34.00 vs 38.00, P<0.001), PWV (1565.00 vs 1734.75, P<0.001), and CHADS₂ score (1.00 vs 2.00, P<0.001). Furthermore, ABI (1.08 vs 1.06, P=0.004) and EF (61.74% vs 60.78%, P<0.001) were lower. These differences were statistically significant. The proportion of patients with ischaemic stroke was significantly different between the two groups (19.04% vs 28.74%, P=0.003).

Subgroup analysis

A subgroup analysis defined by baseline characteristics between the AF group and the non-AF group was performed (Figure 3). A trend towards increased risk of stroke in the AF group was observed among the following subgroups: male, age ≥ 65 years, BMI $\geq 24\text{kg/m}^2$, non-UA, non-NSTEMI, non-STEMI, non-previous MI and nonischaemic cardiomyopathy. Interestingly, AF seemed to be a protective factor in the CHADS₂ ≥ 3 subgroup. Meanwhile, the subgroup analysis did not indicate any significant interactions between ischaemic stroke and these stratification variables.

Association between atrial fibrillation and ischaemic stroke in multivariate analysis

The univariate analysis of the relationship between AF and ischaemic stroke after PSM showed that paroxysmal AF was not associated with ischaemic stroke, while nonparoxysmal AF was associated with ischaemic stroke (OR=1.90, 95% CI: 1.16-3.10, P=0.0104). Multivariate analysis showed that in model I and model II, neither paroxysmal nor nonparoxysmal AF was associated with ischaemic stroke compared with no AF (Table 3). Model I was adjusted for stable angina, aortic atherosclerosis, LA, PWV, and CHADS₂ score. Model II was adjusted for STEMI, previous MI, ischaemic cardiomyopathy, CKD, and factors in model I.

Relationship among atrial fibrillation, CHADS₂ score and ischaemic stroke

With increasing CHADS₂ score, the incidence of AF gradually increased (P for trend <0.001, Figure 3(a)). A similar association was observed with increasing AF burden: the rate of ischaemic stroke increased continuously (P for trend <0.001, Figure 3(b)).

Discussion

Atrial fibrillation and ischaemic stroke have common risk factors

The results of this study suggest that age, heart failure, hypertension, CKD, creatinine level, aortic atherosclerosis, PWV, and CHADS₂ scores are associated with ischaemic stroke and AF.

Previous studies have shown that age, male sex, hypertension, DM, valvular heart disease, heart failure, coronary artery disease, CKD, inflammatory disease, obstructive sleep apnoea syndrome and smoking are common risk factors for AF and ischaemic stroke[9, 11, 12]. Potential risk factors, such as obesity and metabolic syndrome, contribute to the development of AF and atrial cardiomyopathy through a variety of mechanisms [13]. The Framingham Heart Study [14] pointed out that the lifetime risk of AF was approximately 20% with an optimal risk profile, lower than that with a high-risk profile (38.4%). The UK Biobank study [13] confirmed that there were significant differences in AF risk between the ideal lifestyle group, the general lifestyle group, and the weak lifestyle group, regardless of genetic risk. As more common risk factors were considered, the association between AF and ischaemic stroke was reduced, suggesting a confounding pattern.

Possible mechanism of ischaemic stroke in patients with coronary artery disease complicated with AF

In patients with coronary heart disease, the univariate analysis showed that AF was associated with ischaemic stroke, while the association between AF and ischaemic stroke decreased or even disappeared after the multivariate analysis, which adjusted for other risk factors. In the subgroup analysis, AF appeared to be a protective factor in the CHADS₂ ≥3 subgroup. It is speculated that the risk of ischaemic stroke does not increase after the CHADS₂ score reaches a certain threshold in patients with coronary artery disease. These findings suggest that atherosclerotic factors may play an important role in ischaemic stroke in patients with coronary heart disease.

Relationship between atrial fibrillation burden and ischaemic stroke

In this study, the univariate analysis showed that paroxysmal AF was not associated with ischaemic stroke, while nonparoxysmal AF was associated with ischaemic stroke. The trend test showed that with increasing AF burden, the rate of ischaemic stroke increases continuously. These findings suggest that compared with patients with paroxysmal AF, patients with nonparoxysmal AF have a higher risk of ischaemic stroke; that is, AF burden is positively correlated with ischaemic stroke.

Although many studies have found a dose-response relationship between AF load and ischaemic stroke [15-17], not all the results are consistent. The recent KP-Rhythm study identified a higher risk of stroke in

the high-load group (>11%, approximately 2.5 h/24 h) [17]. There is no uniform standard for AF burden thresholds that significantly increase the risk of thrombosis^[52, 53]. The current guidelines [9, 10] generally consider that if the duration of AF is less than 48 hours, there is no need to perform transoesophageal echocardiography. Regardless of the CHA₂DS₂-VASc score and the method used to restore the sinus rhythm, cardioversion can be performed without anticoagulation. However, whether the 48-hour threshold applies to all patients with AF is debatable[18]. In addition, a brief episode of subclinical AF doubles the risk of ischaemic stroke in elderly patients [19]. However, there was no significant increase in the risk of ischaemic stroke in young, healthy patients with AF [20]. Additionally, the atrial remodelling seen in animal models of AF occurred at least a week after continuous rapid pacing [21]. Therefore, any atrial changes caused by AF are unlikely to explain the association between a short (6-minute) AF episode and an increased risk of ischaemic stroke [19]. Overall, these conflicting data are insufficient to establish a clear dose-response relationship between AF burden and the risk of ischaemic stroke.

In addition, if AF, an arrhythmia, is the primary cause of thromboembolism, then rhythm control to reduce the AF load should significantly reduce or eliminate the risk of ischaemic stroke. However, in a meta-analysis of eight randomized clinical trials, rhythm control did not affect the risk of ischaemic stroke [22]. The CABANA study, involving 2,204 patients in 126 centres in 10 countries, suggested that catheter ablation of AF, although more effective for rhythm control than drug therapy, also did not reduce the incidence of ischaemic stroke [23]. At present, no large-scale clinical study has demonstrated that maintaining sinus rhythm in patients with AF can prevent ischaemic stroke, and there is no substantial evidence to support the safety of discontinuation of anticoagulant drugs after AF ablation. There is no reliable evidence that AF is a necessary condition for atrial thrombus formation.

Antithrombotic therapy in coronary artery disease patients with atrial fibrillation

Beyond one year after coronary stenting, current guidelines[9, 24-26] have consistently recommended lifelong oral anticoagulant medication without antiplatelet therapy in patients with AF. However, the evidence for discontinuation of antiplatelet therapy in the above guidelines is insufficient, and the above decision was made based on a small number of observational studies [27]. The 2018 ESC guidelines for myocardial revascularization [28] suggested that aspirin should be taken lifelong for secondary prevention of SCAD after PCI, and even the duration of dual antiplatelet therapy should be extended for acute coronary syndrome (ACS). In patients with AF and SCAD beyond one year after PCI or ACS, the optimal antithrombotic regimen remains uncertain. According to this study of patients with coronary artery disease, there are many risk factors for systemic atherosclerosis, which can cause ischaemic stroke through atrial and nonatrial mechanisms. These patients may require a dual antithrombotic combination of oral anticoagulation and single antiplatelet therapy to avoid systemic embolism and stroke. The OAC-ALONE trial failed to establish the noninferiority of oral anticoagulation alone compared with a regimen of oral anticoagulation and single antiplatelet therapy because patient enrolment was prematurely terminated, leading to an underpowered sample size [29]. The AFIRE study demonstrated that rivaroxaban monotherapy was noninferior to combination anticoagulant therapy for efficacy and superior for major bleeding events in patients with AF and stable coronary artery disease [30]. However,

the available evidence falls short of level 1 and class A status, and whether the current recommendation of anticoagulation alone beyond one year after coronary stenting is an optimal strategy remains to be further studied [31, 32].

Study strength and limitations

The innovation of this study is that the object of this study is specifically patients with coronary artery disease, who tend to have a higher degree of atherosclerosis than patients with AF alone, and atherosclerotic factors may play a more significant role in the mechanism of ischaemic stroke.

The limitations of this study are that it was a retrospective cross-sectional study, and ischaemic stroke, CHADS₂ score, and AF were measured at the same time. Complex aortic plaques and peripheral artery disease were not examined in these patients, so we cannot calculate the CHA₂DS₂-VASc score and explore its relationship with ischaemic stroke, which still needs further research.

Conclusion

After adjusting for confounding factors, the correlation between AF and ischaemic stroke abated. Thus, the idea that prompted the current thinking that AF leads to cerebral embolism is incomplete. A direct link between ischaemic stroke and AF is not consistent with Hill's principle of timeliness, specificity, and concentration-response relationship. In contrast, induction of AF by abnormal and systemic atherosclerosis risk factors and an abnormal atrial substrate model conforms to the existing evidence of ischaemic stroke. Thus, emphasizing systemic treatment for vascular risk factors can reduce the incidence of AF along with that of ischaemic stroke and reduce the burden of this disabling disease.

Abbreviations

BMI: body mass index; CAD: coronary artery disease; SCAD: stable coronary artery disease; UA: unstable angina; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; previous MI: previous myocardial infarction; AF: atrial fibrillation; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; LDL-C: low-density lipoprotein cholesterol; LA: left atrial diameter; EF: ejection fraction; PWV: pulse wave velocity; ABI: ankle-brachial index

Declarations

Acknowledgements

Not applicable.

Authors' contributions

Study conception and design was performed by BQS, DML, and WC. Data collection was performed by BQS, DML, QW, XG, QH, GQG and XRQ. Statistical analysis and the interpretation of the data were

performed by BQS. BQS wrote the first draft of the paper; DML and WC revised the article. This manuscript was read and approved by all credited authors.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was conducted in line with the principles of the Helsinki Declaration. Ethical approval was given by the Research Ethics Committee of the Second Hospital of Hebei University. The present study retrospectively analysed anonymized data, thus no informed consent was required.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Comparison of baseline characteristics

| | Before PSM | | | After PSM | | |
|----------------------------|----------------------------|------------------------|---------|----------------------------|------------------------|---------|
| | Without stroke (n=1997) | With stroke (n=338) | P value | Without stroke (n=1348) | With stroke (n=337) | P value |
| Sex | | | 0.771 | | | 0.980 |
| Female | 828 (41.46%) | 143 (42.31%) | | 573 (42.51%) | 143 (42.43%) | |
| Male | 1169 (58.54%) | 195 (57.69%) | | 775 (57.49%) | 194 (57.57%) | |
| Age (years) | 63.00 (55.00-69.00) | 65.00 (60.00-72.00) | <0.001 | 64.00 (58.00-70.00) | 65.00 (60.00-72.00) | <0.001 |
| BMI (kg/m ²) | 25.39 (23.44-27.68) | 25.50 (23.23-27.68) | 0.929 | 25.39 (23.29-27.68) | 25.50 (23.23-27.68) | 0.941 |
| CAD type | | | | | | |
| SCAD | 128 (6.41%) | 36 (10.65%) | 0.005 | 86 (6.38%) | 36 (10.68%) | 0.006 |
| UA | 1471 (73.66%) | 229 (67.75%) | 0.024 | 989 (73.37%) | 229 (67.95%) | 0.047 |
| NSTEMI | 286 (14.32%) | 41 (12.13%) | 0.283 | 201 (14.91%) | 41 (12.17%) | 0.199 |
| STEMI | 79 (3.96%) | 23 (6.80%) | 0.018 | 51 (3.78%) | 22 (6.53%) | 0.027 |
| Previous MI | 205 (10.27%) | 49 (14.50%) | 0.021 | 146 (10.83%) | 49 (14.54%) | 0.057 |
| Ischaemic cardiomyopathy | 34 (1.70%) | 11 (3.25%) | 0.082 | 23 (1.71%) | 11 (3.26%) | 0.069 |
| Heart failure | 312 (15.62%) | 72 (21.30%) | 0.009 | 228 (16.91%) | 72 (21.36%) | 0.056 |
| Hypertension | 1307 (65.45%) | 262 (77.51%) | <0.001 | 899 (66.69%) | 262 (77.74%) | <0.001 |
| Dyslipidaemia | 605 (30.30%) | 95 (28.11%) | 0.417 | 414 (30.71%) | 94 (27.89%) | 0.313 |
| Total cholesterol (mmol/L) | 3.99 (3.40-4.67) | 3.94 (3.32-4.76) | 0.544 | 4.00 (3.37-4.68) | 3.94 (3.32-4.76) | 0.478 |
| LDL-C (mmol/L) | 2.51 (1.92-3.11) | 2.45 (1.91-3.15) | 0.615 | 2.51 (1.90-3.11) | 2.45 (1.91-3.15) | 0.567 |

| | | | | | | |
|--------------------------|---------------------------|---------------------------|--------|---------------------------|---------------------------|--------|
| Valvular heart disease | 43 (2.15%) | 8 (2.37%) | 0.840 | 32 (2.37%) | 8 (2.37%) | 1 |
| AF | 176 (8.81%) | 48 (14.20%) | 0.002 | 119 (8.83%) | 48 (14.24%) | 0.003 |
| AF type | | | <0.001 | | | 0.003 |
| No | 1821 (91.19%) | 290 (85.80%) | | 1229 (91.17%) | 289 (85.76%) | |
| Paroxysmal AF | 106 (5.31%) | 22 (6.51%) | | 69 (5.12%) | 22 (6.53%) | |
| Nonparoxysmal AF | 70 (3.51%) | 26 (7.69%) | | 50 (3.71%) | 26 (7.72%) | |
| DM | 551 (27.59%) | 102 (30.18%) | 0.327 | 378 (28.04%) | 102 (30.27%) | 0.418 |
| COPD | 40 (2.00%) | 7 (2.07%) | 0.836 | 30 (2.23%) | 7 (2.08%) | 0.868 |
| CKD | 39 (1.95%) | 13 (3.85%) | 0.043 | 23 (1.71%) | 13 (3.86%) | 0.015 |
| Creatine (μmol/L) | 69.00 (59.00-80.95) | 72.00 (61.30-86.00) | 0.001 | 70.00 (59.00-82.00) | 72.00 (61.30-86.00) | 0.011 |
| Fatty liver | 39 (1.95%) | 5 (1.48%) | 0.670 | 30 (2.23%) | 5 (1.48%) | 0.393 |
| Smoker | 409 (20.48%) | 57 (16.86%) | 0.124 | 261 (19.36%) | 56 (16.62%) | 0.249 |
| Drinker | 347 (17.38%) | 47 (13.91%) | 0.115 | 224 (16.62%) | 46 (13.65%) | 0.184 |
| Aortic atherosclerosis | 529 (26.81%) | 146 (43.84%) | <0.001 | 386 (28.94%) | 146 (43.98%) | <0.001 |
| LA (mm) | 34.00 (32.00-37.00) | 35.00 (32.00-37.00) | 0.073 | 34.00 (32.00-37.00) | 35.00 (32.00-37.00) | 0.024 |
| EF (%) | 61.74 (60.61-62.89) | 61.70 (60.64-62.77) | 0.574 | 61.74 (60.61-62.86) | 61.70 (60.64-62.77) | 0.73 |
| PWV (cm/s) | 1556.50 (1367.50-1798.50) | 1623.00 (1418.00-1906.50) | <0.001 | 1575.25 (1388.00-1814.38) | 1625.00 (1418.00-1908.62) | 0.022 |
| ABI | 1.09 (1.02-1.156) | 1.08 (0.97-1.16) | 0.057 | 1.08 (1.01-1.16) | 1.08 (0.97-1.16) | 0.005 |
| CHADS ₂ score | 1.00 (1.00-2.00) | 3.00 (3.00-4.00) | <0.001 | 1.00 (1.00-2.00) | 3.00 (3.00-4.00) | ∞0.001 |

Abbreviations: *BMI* body mass index, *CAD* coronary artery disease, *SCAD* stable coronary artery disease, *UA* unstable angina, *NSTEMI* non-ST-elevation myocardial infarction, *STEMI* ST-elevation myocardial

infarction, previous *MI* previous myocardial infarction, *AF* atrial fibrillation, *DM* diabetes mellitus, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *LDL-C* low-density lipoprotein cholesterol, *LA* left atrial diameter, *EF* ejection fraction, *PWV* pulse wave velocity, *ABI* ankle-brachial index

Table 2 Comparison of baseline characteristics after PSM with or without AF

| | Non-AF group (n=1518) | AF group (n=167) | P value |
|----------------------------|-----------------------|---------------------|---------|
| Sex | | | 0.505 |
| Female | 641 (42.23%) | 75 (44.91%) | |
| Male | 877 (57.77%) | 92 (55.09%) | |
| Age (years) | 63.50 (58.00-70.00) | 69.00 (63.00-77.00) | <0.001 |
| BMI (kg/m ²) | 25.39 (23.23-27.68) | 25.69 (23.44-27.68) | 0.872 |
| CAD type | | | |
| SCAD | 70 (4.61%) | 52 (31.14%) | <0.001 |
| UA | 1132 (74.57%) | 86 (51.50%) | <0.001 |
| NSTEMI | 225 (14.82%) | 17 (10.18%) | 0.104 |
| STEMI | 71 (4.68%) | 2 (1.20%) | 0.036 |
| Previous MI | 166 (10.94%) | 29 (17.37%) | 0.014 |
| Ischaemic cardiomyopathy | 24 (1.58%) | 10 (5.99%) | <0.001 |
| Heart failure | 211 (13.90%) | 89 (53.29%) | <0.001 |
| Hypertension | 1041 (68.58%) | 120 (71.86%) | 0.385 |
| Dyslipidaemia | 456 (30.04%) | 52 (31.14%) | 0.769 |
| Total cholesterol (mmol/L) | 4.00 (3.39-4.70) | 3.83 (3.28-4.70) | 0.229 |
| LDL-C (mmol/L) | 2.52 (1.91-3.12) | 2.32 (1.88-3.09) | 0.301 |
| Valvular heart disease | 29 (1.91%) | 11 (6.59%) | <0.001 |
| DM | 430 (28.33%) | 50 (29.94%) | 0.661 |
| COPD | 35 (2.31%) | 2 (1.20%) | 0.354 |
| CKD | 28 (1.84%) | 8 (4.79%) | 0.012 |
| Creatine (µmol/L) | 69.00 (59.00-81.00) | 79.85 (68.00-94.75) | <0.001 |
| Fatty liver | 33 (2.17%) | 2 (1.20%) | 0.401 |
| Smoker | 296 (19.50%) | 21 (12.57%) | 0.03 |
| Drinker | 249 (16.40%) | 21 (12.57%) | 0.201 |
| Aortic atherosclerosis | 458 (30.53%) | 74 (44.58%) | <0.001 |

| | | | |
|--------------------------|---------------------------|---------------------------|--------|
| LA (mm) | 34.00 (32.00-36.00) | 38.00 (35.00-42.50) | <0.001 |
| EF (%) | 61.74 (60.64-62.89) | 60.78 (55.48-62.05) | 0.001 |
| PWV (cm/s) | 1565.00 (1387.75-1810.75) | 1734.75 (1505.88-2149.62) | <0.001 |
| ABI | 1.08 (1.00-1.16) | 1.06 (0.94-1.14) | 0.004 |
| CHADS ₂ score | 1.00 (1.00-2.00) | 2.00 (1.00-3.00) | <0.001 |
| Stroke | 289 (19.04%) | 48 (28.74%) | 0.003 |

Abbreviations: *BMI* body mass index, *CAD* coronary artery disease, *SCAD* stable coronary artery disease, *UA* unstable angina, *NSTEMI* non-ST-elevation myocardial infarction, *STEMI* ST-elevation myocardial infarction, previous *MI* previous myocardial infarction, *AF* atrial fibrillation, *DM* diabetes mellitus, *COPD* chronic obstructive pulmonary diseases, *CKD* chronic kidney disease, *LDL-C* low-density lipoprotein cholesterol, *LA* left atrial diameter, *EF* ejection fraction, *PWV* pulse wave velocity, *ABI* ankle-brachial index

Table 3 Univariate and multivariate analysis of the association between AF and ischaemic stroke after PSM

| | Univariate | Model I | Model II |
|---------------|-------------------------|-------------------------|-------------------------|
| AF | OR (95% CI) P value | OR (95% CI) P value | OR (95% CI) P value |
| No | 1.0 | 1.0 | 1.0 |
| Paroxysmal | 1.36 (0.83-2.23) 0.2296 | 0.97 (0.49-1.94) 0.9309 | 0.97 (0.48-1.94) 0.9271 |
| Nonparoxysmal | 2.21 (1.35-3.61) 0.0015 | 1.06 (0.47-2.40) 0.8876 | 1.01 (0.44-2.32) 0.9776 |

Model I was adjusted for stable angina, aortic atherosclerosis, left atrial diameter, pulse wave velocity, and CHADS₂ score.

Model II was adjusted for STEMI, previous myocardial infarction, ischaemic cardiomyopathy, CKD, and factors in model I.

Figures

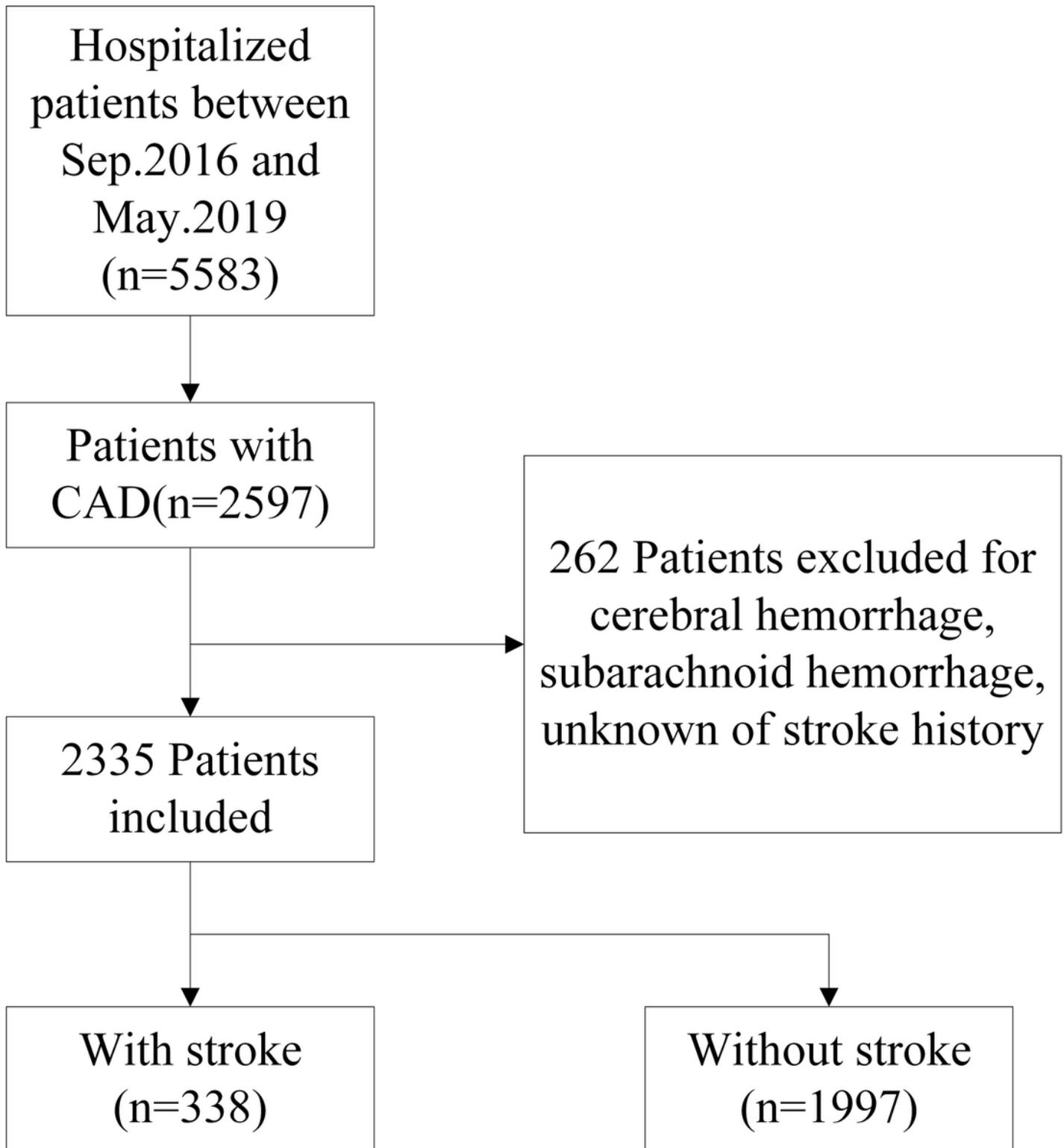
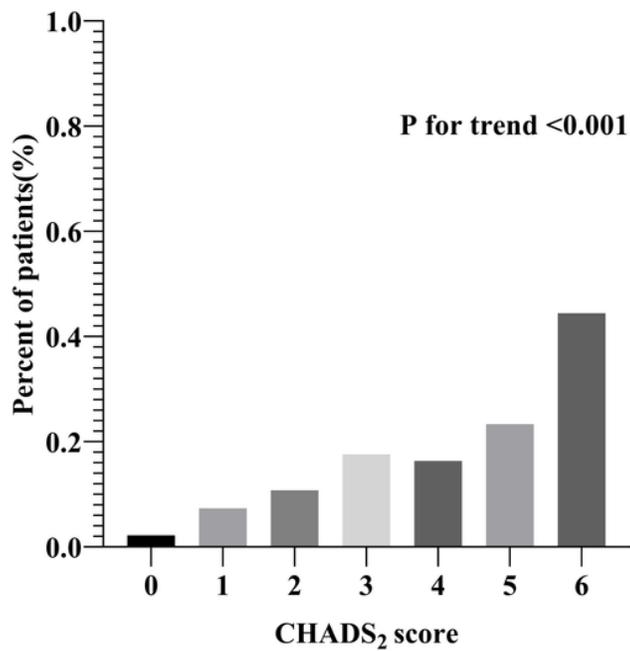
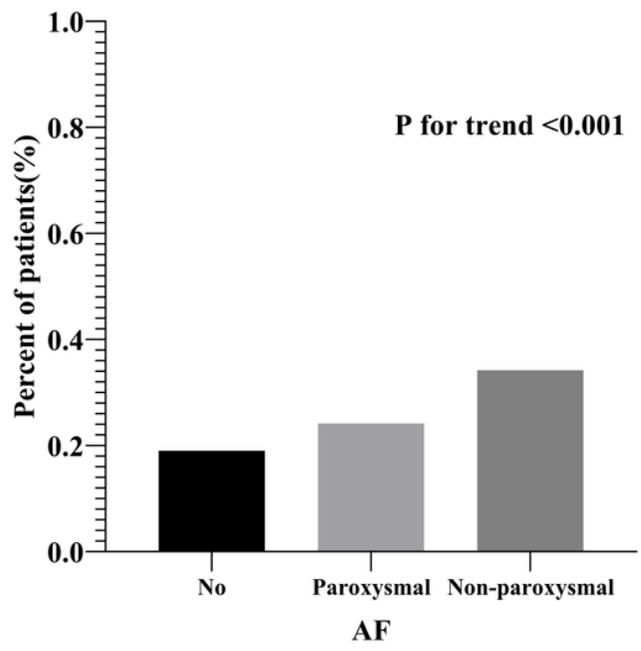


Figure 1

Patient selection flowchart.



(a)



(b)

Figure 2

(a) Association between CHADS2 score and AF. (b) Association between AF type and ischaemic stroke.

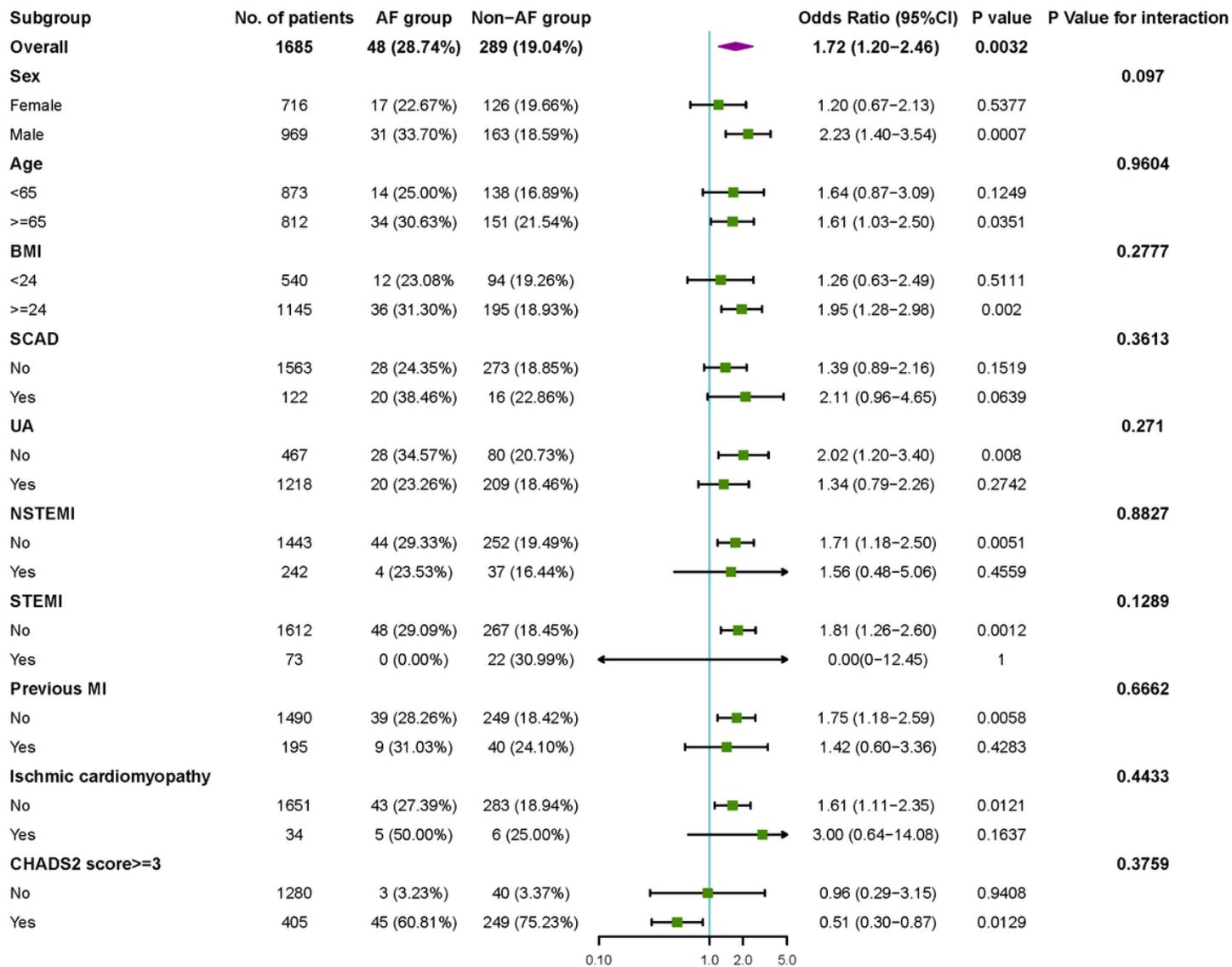


Figure 3

Association between AF and ischaemic stroke in prespecified and exploratory subgroups after PSM. P for interaction is based on the likelihood ratio test. Abbreviations: BMI body mass index, SCAD stable coronary artery disease, UA unstable angina, NSTEMI non-ST-elevation myocardial infarction, STEMI ST-elevation myocardial infarction, previous MI previous myocardial infarction