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CLINICAL RESEARCH

Risk of myocardial infarction and ischemic stroke in individuals with first-diagnosed paroxysmal vs. non-paroxysmal atrial fibrillation under anticoagulation

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Aims There is conflicting evidence on whether the type of atrial fibrillation (AF) is associated with risk of cardiovascular events, including acute myocardial infarction (MI) and ischemic stroke. The aim of the present study was to investigate whether the risk of MI and ischemic stroke differs between individuals with first-diagnosed paroxysmal vs. non-paroxysmal AF treated with anticoagulants.

Methods and results De-identified electronic medical records from the TriNetX federated research network were used. Individuals with a new diagnosis of paroxysmal AF who had no evidence of other types of AF in their records were 1:1 propensity score-matched with individuals with non-paroxysmal AF, defined as persistent or chronic AF, who had no evidence of other types of AF in their records. All patients were followed for three years for the outcomes of MI and ischemic stroke. Cox proportional hazard models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). In the propensity-matched cohort, among 24 848 well-matched AF individuals [mean age 74.4 ± 10.4; 10 101 (40.6%) female], 410 (1.7%) were diagnosed with acute MI and 875 (3.5%) with ischemic stroke during the three-year follow-up. Individuals with paroxysmal AF had significantly higher risk of acute MI (HR: 1.65, 95%CI: 1.35–2.01) compared to those with non-paroxysmal AF. First diagnosed paroxysmal AF was associated with higher risk of non-ST elevation MI (nSTEMI) (HR: 1.89, 95%CI: 1.44–2.46). No significant association was observed between the type of AF and risk of ischemic stroke (HR: 1.09, 95%CI: 0.95–1.25).

Conclusion Patients with first-diagnosed paroxysmal AF had higher risk of acute MI compared to individuals with non-paroxysmal AF, attributed to the higher risk of nSTEMI among patients with first-diagnosed paroxysmal AF. There was no significant association between type of AF and risk of ischemic stroke.

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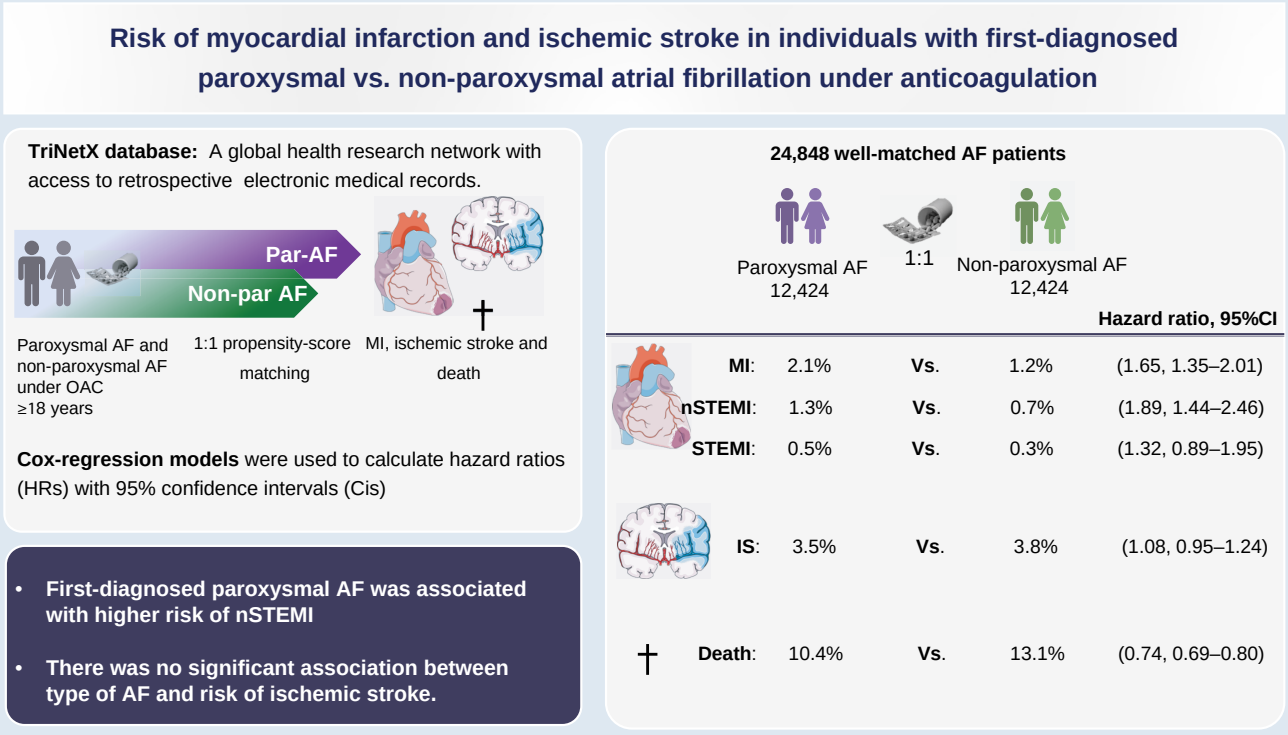
Graphical Abstract



Keywords Atrial fibrillation • Paroxysmal • Permanent • Myocardial infarction • Ischemic stroke

What's New

- There is no clear association of myocardial infarction (MI) or ischemic stroke with the type of atrial fibrillation (AF).
- Patients with first-diagnosed paroxysmal AF had higher risk of acute MI compared to those with non-paroxysmal AF.
- First-diagnosed AF was associated with higher risk of nSTEMI compared to non-paroxysmal AF, whereas the risk of STEMI was similar among patients with paroxysmal AF and non-paroxysmal AF.
- There was no association between the type of AF and risk of ischemic stroke.

Introduction

Recently, the management of individuals with atrial fibrillation (AF) has evolved to better characterise the arrhythmia[1] and provide integrated care management, including anticoagulation, rhythm control, and management of concomitant cardiovascular comorbidities and risk factors.[2,3] Despite optimal holistic AF treatment,[4] some individuals will experience new cardiovascular events, including myocardial infarction (MI) and ischemic stroke.[5,6] Nonetheless, adherence to an integrated care management approach is associated with improved clinical outcomes.[7]

Several studies have proposed possible differences in the incidence of cardiovascular outcomes in individuals with paroxysmal AF compared to those with persistent or permanent AF. In patients with coronary artery disease undergoing coronary stenting, the presence of paroxysmal AF was associated with higher risk of recurrent MI, compared to non-paroxysmal.[8] In an exploratory analysis of the EdoxabaN vs. wafarin in subjectS UndeRgoing cardiovErsion of Atrial Fibrillation (ENSURE-AF) trial, it was observed that among 2199 patients after electrical cardioversion, MI was more common in patients with paroxysmal AF compared to those with persistent during a follow-up period of 58 days (1% vs. 0.1%).[9] Conversely, a prospective observational study including 3843 AF patients showed that after a median (IQR) follow-up of 3.0 (1.9–4.2) years, both stroke or systemic embolism and MI rates were similar in patients with paroxysmal AF compared to those with persistent and permanent [adjusted hazard ratio (HR):0.91, 95%CI: 0.48–1.72 and adjHR:0.95, 95%CI:0.56–1.59].[10] The early treatment of AF for stroke prevention trial (EAST-AFNET 4) showed that among 1048 patients with first AF episode, after a mean follow-up period of 5.1 years, experienced higher rates of hospitalisation for acute coronary events, compared to those with previous diagnosed paroxysmal or persistent AF.[11]

These contradictory findings underline the need for further evidence to investigate the hypothesis that recently diagnosed paroxysmal AF may be associated with higher risk of MI compared to recently diagnosed non-paroxysmal AF. Therefore, the aim of the current study was to assess whether first-diagnosed paroxysmal AF among patients treated with oral anticoagulants (OACs) is associated with higher risk of acute MI and ischemic stroke compared to non-paroxysmal AF, using real-world data from a global federated health network.

Methods

Data availability statement and ethical approval

TriNetx is a research network utilized for several scientific purposes, compliant with the Health Insurance Portability and Accountability Act and the

US federal law which protects the privacy and security of healthcare data, including de-identified data as per the de-identification standard of the HIPAA Privacy Rule (https://trinetx.com/real-world-resources/publications/). To comply with legal frameworks and ethical guidelines guarding against data re-identification, the identity of participating Healthcare Organizations (HCOs) and their individual contribution to each dataset are not disclosed. A typical HCO is a large academic health center with data coming from majority of its affiliates. A single HCO frequently has more than one facility, including main and satellite hospitals. The data are stored on the TriNetX database via a physical server at the institution's data centre or a virtual hosted appliance. The TriNetX platform comprises of a series of these appliances connected into a federated network. This network can broadcast queries to each appliance. The network members are mainly in the United States, with an additional six HCOs in other countries that include the United Kingdom, Germany, Italy, Israel, and Singapore.[12]

The TriNetX platform only uses aggregated counts and statistical summaries of de-identified information. No protected health information or personal data is made available to the users of the platform. Studies using the TriNetX health research network do not need ethical approval as no patient identifiable information is received.

To gain access to the data in the TriNetX research network, requests are directed to TriNetX and a data sharing agreement is required.

Study design

This was a retrospective observational study conducted within TriNetX, which is a global federated health research network with access to electronic medical records (EMRs) from participating HCOs including academic medical centres, specialty physician practices, and community hospitals covering approximately 69.8 million individuals, from the United States, United Kingdom, Germany, Italy, Israel, and Singapore. Within this network, available data include demographics, diagnoses using International Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification (ICD-10-CM) codes, and medications. Further information can be found online (https://trinetx.com/company-overview/). Details related to TriNetX database can be found in Supplemental material.

Cohort

The searches on the TriNetX online research platform were performed on 30 March 2023 for individuals with new diagnosis of paroxysmal, persistent or chronic AF (ICD-10-CM code I48.0, I48.1, or I48.2, respectively) who were treated with any OAC within one month after the diagnosis of AF and were followed-up for 3 years or until death. At the time of the search, there were 66 participating HCOs that returned data on the platform based on the search parameters described above (59% US, 2% ex-US, and 39% from other countries). The baseline index event date was the date that a patient was diagnosed for the first time with either paroxysmal or non-paroxysmal AF.

The cohort was divided into two groups using electronic health records according to the type of AF: individuals with new diagnosis of paroxysmal AF (ICD-10-CM code I48.0) who had no evidence of other types of AF in their records and individuals with non-paroxysmal AF, [corresponding to persistent (defined as AF that does not terminate within seven days, or that requires repeat pharmacological or electrical cardioversion: ICD-10-CM code I48.1) or chronic AF (defined as either permanent or unspecified, chronic AF which refers to any persistent, longstanding persistent or permanent AF: ICD-10-CM code I48.2)], who had no evidence of other types of AF in their records. Individuals with diagnoses of typical AF, atypical AF, and unspecified AF or atrial flutter were excluded from the analysis (ICD-10-CM code I48.3, I48.4, and I48.9, respectively).

Outcome

The outcomes of interest were the diagnosis of acute MI [captured with the ICD-10-CM code I21 in the database, including ST-elevation MI (STEMI), non ST-elevation MI (nSTEMI), and unspecified MI] and ischemic stroke (ICD-10-CM code I63) during a follow-up period of 3 years. Two exploratory analyses were performed: (i) to investigate the association of AF type with the outcomes of STEMI and nSTEMI and (ii) excluding individuals with history of acute MI and ischemic stroke before the diagnosis of AF were performed to investigate the association of AF type with the occurrence of incident acute MI and ischemic stroke.

Statistical analysis

All statistical analyses were performed on the TriNetX online research platform. Baseline characteristics were compared using chi-squared tests for categorical variables and independent-sample *t*-tests for continuous variables. We performed 1:1 propensity score matching to create balanced cohorts. The following variables were included in the propensity score matching: age, sex, ethnicity, co-morbidities (heart failure, arterial hypertension, ischemic stroke, dyslipidemia, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, sleep apnoea, and overweight), concomitant medication (lipid-lowering treatments, beta blockers, ACE inhibitors, angiotensin II inhibitors, prior use of antiplatelet, insulin, metformin), and cholesterol levels (low-density lipoprotein cholesterol and total cholesterol) (see Supplementary material online, *Table S1*). After propensity score matching, Cox-proportional hazard models were used to calculate HRs and 95% confidence intervals (CIs) to assess the associations between the type of AF (i.e. first-diagnosed paroxysmal vs. non-paroxysmal) and the outcome of interest. Participants were censored when they experienced the outcome of interest or when they died. All analyses were performed in the TriNetX platform which uses R's survival package v3.2–3.

Results

Cohort characteristics before and after propensity score matching

The initial cohort consisted of 39 290 individuals with AF who were treated with OACs (91% from the United States, 2% from Ex-US regions and 7% from unknown regions). Of these, 26 558 (67.5%) had paroxysmal AF and 12 732 (32.5%) had non-paroxysmal AF (from 53 and 54 health care organisations, respectively). Baseline characteristics of the included patients before propensity score matching are presented in Supplementary material online, *Table*. After propensity score matching on a 1:1 ratio, the final cohort consisted of 24 848 well-matched AF individuals (mean age 74.4 ± 10.4; 10 101 (40.6%) female) divided in two groups of 12 424, followed for 3 years. The baseline characteristics of the propensity-score matched cohort are summarized in *Table 1*.

Type of AF and risk of mi

After propensity-score matching, among 24 848 individuals, 410 (1.7%) were diagnosed with an acute MI within 3 years of AF diagnosis, of which 260 (2.1%) occurred in individuals with paroxysmal AF and 150 (1.2%) in individuals with non-paroxysmal AF (HR: 1.65, 95%CI: 1.35–2.01, Supplementary material online, *Figure SA*) (*Table 2*). In the exploratory propensity-score matched analysis regarding the type of MI, first diagnosed paroxysmal AF was associated with significantly higher risk of nSTEMI (1.3% vs. 0.7%; HR: 1.89, 95%CI: 1.44–2.46) compared to patients with permanent AF, whereas first diagnosed paroxysmal AF was not associated with higher risk of STEMI (0.5% vs. 0.3%; HR: 1.32, 95%CI: 0.89–1.95).

In the exploratory propensity-score matched analysis excluding patients with prior MI, 1027 individuals with an MI prior to the diagnosis of AF were excluded. A diagnosis of first-ever acute MI during follow-up was reported in 135 (1.1%) among 11 831 individuals with paroxysmal AF and 75 (0.6%) among 11 990 individuals with non-paroxysmal AF (HR: 1.72, 95%CI: 1.29–2.27) (*Table 2*).

Type of AF and risk of ischemic stroke and death

After propensity-score matching, 875 (3.5%) were diagnosed with ischemic stroke within 3 years of AF diagnosis, of which 466 (3.8%) occurred in individuals with paroxysmal AF and 409 (3.3%) in individuals with non-paroxysmal AF (HR: 1.08, 95%CI: 0.95–1.24; Supplementary material online, *Figure SB*) (*Table 2*).

Table 1 Baseline characteristics of individuals with paroxysmal and non-paroxysmal atrial fibrillation (AF) in the propensity-score matched analysis

	Paroxysmal AF $n = 12\,428$	Non-paroxysmal AF $n = 12\,428$	*P*-value
Demographics			
Age, years (±SD)	74.3 (±10.2)	74.5 (±10.5)	0.070
Female, *n* (%)	5037 (40.5)	5064 (40.8)	0.727
Comorbidities			
Heart failure, *n* (%)	1257 (10.1)	1348 (10.8)	0.060
Arterial hypertension, *n* (%)	2876 (23.1)	2986 (24)	0.100
Ischemic heart disease, *n* (%)	1539 (12.4)	1639 (13.2)	0.057
Ischemic Stroke, *n* (%)	358 (2.9)	393 (3.2)	0.195
Dyslipidaemia, *n* (%)	1960 (15.8)	2018 (16.2)	0.316
Diabetes mellitus, *n* (%)	1135 (9.1)	1203 (9.7)	0.140
Chronic kidney disease, *n* (%)	642 (5.2)	680 (5.5)	0.195
Overweight/obese, *n* (%)	532 (4.3)	540 (4.3)	0.182
Chronic obstructive pulmonary disease, *n* (%)	495 (4.0)	537 (4.3)	0.182
Sleep apnoea, *n* (%)	389 (3.1)	399 (3.2)	0.717
Concomitant medications and lipid levels			
Lipid-lowering treatment, *n* (%)	2067 (16.6)	2123 (1.1)	0.343
Beta blockers, *n* (%)	2393 (19.3)	2485 (20)	0.142
ACE inhibitors, *n* (%)	1145 (9.2)	1176 (9.5)	0.499
Angiotensin II inhibitors, *n* (%)	820 (6.6)	826 (6.6)	0.878
Insulin, *n* (%)	823 (6.6)	849 (6.8)	0.510
Metformin, *n* (%)	483 (3.9)	454 (3.7)	0.334
Antiplatelet, *n* (%)	2031 (16.3)	2088 (16.8)	0.331
LDL cholesterol, mg/dL (±SD)	86.4 (±33.8)	81.5 (±33.3)	<0.001

AF, atrial fibrillation; SD, standard deviation; ACE, angiotensin converting enzyme; LDL, low-density lipoprotein

In the exploratory propensity-score matched analysis excluding patients with prior ischemic stroke, 1491 individuals with an ischemic stroke that occurred before the diagnosis of AF were excluded. A diagnosis of first-ever ischemic stroke during follow-up was reported in 185 (1.6%) among 11 687 individuals with paroxysmal AF and 200 (1.7%) among 11 670 individuals with non-paroxysmal AF (HR: 0.87, 95%CI: 0.71–1.07) (*Table 2*).

After propensity-score matching 2912 (11.7%) of the patients died during follow-up, of which 1287 (10.4%) among those with paroxysmal AF and 1625 (13.1%) among those with non-paroxysmal AF (HR: 0.74, 95%CI: 0.69–0.80; Supplementary material online, *Figure SC*) (*Table 2*).

Discussion

In this propensity-score matched analysis of >24 000 individuals with AF under OAC treatments, who were followed for 3 years, those with first-diagnosed paroxysmal AF had significantly higher risk of acute MI compared to individuals with non-paroxysmal AF. This reduction was associated with a significant reduction of the risk of nSTEMI among patients with first-diagnosed paroxysmal AF compared to those with non-paroxysmal. The risk of ischemic stroke was similar in patients with both paroxysmal and non-paroxysmal-AF.

The association of recently diagnosed paroxysmal AF with higher risk of MI, could potentially be explained through the effect that brief AF episodes exert on the ventricles at a cellular and microcirculatory level. Previous studies in humans have shown that during induced acute AF, there is a beat-to-beat flow variability affecting the diastolic coronary flow and in turn, coronary flow is being reduced compared to patients on sinus rhythm at the same heartrate.[13] Recently, a computational analysis based on the simulation of fluid dynamics confirmed that AF and beat-to-beat flow variability significantly reduces coronary flow, particularly in left ventricle's subendocardial layers.[14] Furthermore, during the acute atrial tachyarrhythmia, angiotensin 1-receptor-mediates oxidative stress in the myocardium of the left ventricle and consequent lack of nitric oxide.[15,16] In turn, this may lead to impaired microvascular blood flow and ventricular ischaemia.[15,16] On the contrary, in patients with chronic AF, effective rate control together with chronic remodelling changes in left atrium may counterbalance the flow variation and oxidative stress, rendering ventricular ischemia less likely.[8,15,17] These data may support our results, proposing a potential mechanistical association between first-diagnosed paroxysmal AF and MI, given that patients with paroxysmal AF had higher risk of nSTEMI, rather STEMI. Despite the potential causative and mechanistic associations of first-diagnosed paroxysmal AF on MI, the nature of this association is rather speculative.

The findings of this analysis shed further light on recent contradictory reports about associations between type of AF and the risk of MI, and provide evidence to support findings of recent exploratory analyses of randomized controlled trials suggesting the risk of MI in individuals with AF is associated with the type of AF.[8,9,11] In an ENTRUST-AF-PCI subgroup analysis, following successful percutaneous coronary

Table 2 Risk of myocardial infarction and ischemic stroke in patients with paroxysmal and non-paroxysmal atrial fibrillation

	Paroxysmal AF Events/included patients	Non-paroxysmal AF Events/included patients	Hazard ratio (95%CI)
Acute myocardial infarction			
All included patients	260/12 424	150/12 424	1.65 (1.35–2.01)
nSTEMI	161/12 424	81/12 424	1.89 (1.44–2.46)
STEMI	60/12 424	43/12 424	1.32 (0.89–1.95)
Excluding those with previous myocardial infarction	135/11 831	75/11 990	1.72 (1.29–2.27)
Ischemic stroke			
All included patients	466/12 424	409/12 424	1.08 (0.95–1.24)
Excluding those with previous ischemic stroke	185/11 687	200/11 670	0.87 (0.71–1.07)
Death	1287/12 424	1625/12 424	0.74 (0.69–0.80)

CI, confidence intervals; nSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction

intervention, individuals with paroxysmal AF had high risk of acute MI compared to non-paroxysmal AF (4.87% vs. 2.01%, respectively).[8] In an ENSURE-AF subgroup analysis, following electrical cardioversion, MI was more frequent in individuals with paroxysmal vs. persistent AF (1.0% vs. 0.1%, respectively).[9] In an EAST-AFNET 4 analysis, the incidence rates of hospitalization for an acute coronary syndrome were highest among individuals with the first AF episode compared to those with paroxysmal and persistent AF (1.50 compared to 0.64 and 0.50, respectively, P for interaction = 0.032).[11] Collectively, the results of the present large-scale real-world analysis confirm the hypothesis generated by previous post-hoc exploratory analyses of trials in individuals with AF that paroxysmal AF, and more specifically recently diagnosed paroxysmal AF, may exert an additional risk factor for MI, even in the absence of previous MI.

The association between paroxysmal AF and the risk of MI could have implications for cardiovascular prevention strategies in individuals with paroxysmal AF, especially given that a significant proportion of this population has underlying coronary artery disease. A recent retrospective study showed that coronary CT angiography identified underlying coronary artery disease in 39% of individuals with paroxysmal of first-diagnosed AF.[18] In this context, coronary CT angiography is integrated in the diagnostic work-up of individuals with paroxysmal or first-diagnosed AF.[18] In addition, intensive strategies aiming to more efficient control of the atherosclerotic risk factors beyond OAC treatment, which could include lifestyle changes like smoking cessation, exercise and physical activity interventions, adoption of Mediterranean diet, and better weight control, as well as pharmaceutical interventions to control related comorbidities such as diabetes mellitus and dyslipidemia more efficiently. Accordingly, several retrospective studies showed that statin treatment in individuals with AF is associated with reduced risk for cardiovascular events.[19–21]

The present study shows that the risk of ischemic stroke was similar among OAC-treated patients with paroxysmal and non-paroxysmal AF, while patients with non-paroxysmal AF had higher risk of mortality during follow-up. Consistent with our results, a recent prospective Swiss study including 3843 AF patients showed that persistent and permanent AF were not associated with higher risk of ischemic stroke or systemic embolism.[10] On the contrary, several observational studies as well as subgroup analyses of randomized controlled trials showed that individuals with non-paroxysmal AF have higher risk of ischemic stroke compared to paroxysmal.[22,23] Whether non-paroxysmal and chronic AF is associated with higher risk of future thromboembolic events compared to paroxysmal AF, is still unclear although the inherent risk may be driven by the presence of associated stroke risk factors.[24] Of note, the risk of mortality was lower among patients with paroxysmal AF compared to those with non-paroxysmal. This may be potentially attributed to other confounding factors and concomitant diseases which may have risen during follow-up, such as heart failure or renal disease. In the EURObservational Research Programme–Atrial Fibrillation, which included patients with first-ever diagnosed AF, paroxysmal AF was associated with lower risk of mortality compared to non-paroxysmal, while independent predictors of death were heart failure and renal disease.[25] In a Danish national cohort, HF diagnosis prior to AF was associated higher absolute risk of death compared to both AF before HF and AF diagnosed concurrently with HF.[26]

Strengths and limitations

The main strengths of this study are the large number of individuals included in the analysis, the follow-up period of three years, and the use of propensity score matching to control for clinically and prognostically relevant factors and minimize the risk of bias from confounding. Nonetheless, several limitations of this analysis are noteworthy. HCO EMR data are subject to entry errors and data gaps, and some health conditions may be underreported and represent missing data which may affect the results. However, the large number of included patients and data may lessen the effect of entry or capture errors in the outcomes of interest. Also, outcomes which occurred outside the TriNetX network may have not been well captured. Specifically in this study, there were no available data on how paroxysmal AF was diagnosed and whether this was through 24 h Holter or implantable loop recorders, while we couldn't export specific data regarding the timing of the MI in relation to AF paroxysm. Additionally, there were no available data on AF paroxysms after the diagnosis of paroxysmal AF and we were not able to correlate potential future AF paroxysms with the occurrence of MI or stroke. Regarding the MI subtypes, in the present study only nSTEMI and STEMI were investigated, while the subtype diagnosis of unknown MI, was not investigated and may have affected the results in the exploratory analysis. Moreover, residual confounding may have influenced the results, including socioeconomic status, risk factor control, anticoagulation after control, use of AF interventions, and lifestyle factors[27–29] or the CHA_2DS_2-VASc which are not available in EMR data. Also, as the data included in this cohort originated predominantly from US HCOs, which may not be representative of the wider global population, therefore the generalizability of these results needs to be explored and confirmed beyond this cohort. Finally, we were unable to take in account the effect of ablation or pharmacological rhythm control after the diagnosis since patients could only be matched based on the characteristics before the diagnosis of AF.

In conclusion, this large real-world propensity-score matched analysis shows that among individuals treated with OACs, those with first-

diagnosed paroxysmal AF have higher risk of acute MI, a finding which was driven by a significant increase in nSTEMI, compared to individuals with non-paroxysmal AF, while the risk of ischemic stroke was similar in patients with paroxysmal and non-paroxysmal AF. Paroxysmal AF was associated with lower risk of death compared to non-paroxysmal AF. The presence of first-diagnosed paroxysmal AF may serve as cardiovascular risk factor to further investigate and stratify patients potentially at higher risk of acute coronary disease. Whether the type of AF has a causative association with either acute MI or ischemic stroke, needs to be investigated in dedicated prospective randomized trials.

Supplementary material

Supplementary material is available at *Europace* online.

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G.N. contributed to study concept, study design, data acquisition, statistical analysis and interpretation, preparation of article, and study supervision. D.S. contributed to study design, data acquisition, statistical analysis and interpretation, preparation of article, and critical revision of the final draft. B.J.R.B. contributed critical revision of article. S.L.H. contributed to critical revision of article. A.A.R. contributed to critical revision of article. P.A. contributed to critical revision of article. G.Y.H.L. contributed to study concept and critical revision of article.

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Data availability

The data underlying this article were accessed from TriNetX (https://live.trinetx.com). To gain access to the data in the TriNetX research network, a request can be made to TriNetX (https://live.trinetx.com), but costs may be incurred, a data sharing agreement would be necessary, and no patient identifiable information can be obtained.

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