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Relation of the stress hyperglycaemia ratio to residual risk in anticoagulated patients with atrial fibrillation: A report from the prospective Murcia AF Project III cohort

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Abstract

Introduction: Atrial fibrillation (AF) carries residual thromboembolic and cardiovascular risk despite oral anticoagulation (OAC). The stress hyperglycaemia ratio (SHR), derived from admission glucose and glycated haemoglobin (HbA1c), integrates information on both acute glycaemic fluctuations and chronic glycaemic burden. SHR has been associated with adverse outcomes in high-risk populations, but its utility in stratifying residual risk in anticoagulated AF patients remains uncertain. This study evaluated SHR as a marker of thromboembolic and cardiovascular risk in this setting.

Methods: This prospective cohort study included consecutive AF outpatients initiating OAC between January 2016 and November 2021. SHR was calculated, and patients were stratified into low and high SHR groups. Primary outcomes were thromboembolic events (i.e. composite of ischaemic stroke [IS], transient ischaemic attack [TIA] or systemic embolism) and major adverse cardiovascular events (MACEs), comprising myocardial infarction, IS, TIA or cardiovascular death. Secondary outcomes included cardiovascular and all-cause death. Associations were assessed using restricted cubic splines and multivariable Cox models.

Results: A total of 1479 patients (53.1% female; median age 76 years [interquartile range 69–82]; follow-up 1.87 years) were included. During follow-up,

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80 thromboembolic events (5.4%) and 107 MACE (7.2%) occurred. Incidence rates were higher in the low SHR group compared with the high SHR group for both thromboembolic events (4.26 vs 2.50 per 100 person-years) and MACE (5.64 vs 3.34 per 100 person-years). SHR was significantly associated with both thromboembolic risk (p-overall = 0.005; non-linear $p = 0.015$) and MACE (p-overall <0.001; linear $p = 0.053$). In multivariable Cox models, low SHR was independently associated with increased risk of thromboembolic events (adjusted hazard ratio [aHR] 1.73; 95% confidence interval [CI] 1.08–2.76; $p = 0.022$) and MACE (aHR 1.58; 95% CI 1.06–2.37; $p = 0.025$), compared with the high SHR group. No significant associations were observed for secondary outcomes.

Conclusion: In anticoagulated AF patients, low SHR was independently associated with higher residual thromboembolic and cardiovascular risk.

KEYWORDS
atrial fibrillation, MACE, residual risk, stress hyperglycaemia ratio, thromboembolism

1 | INTRODUCTION

Atrial fibrillation (AF) affects approximately 1%–2% of the general population, with a prevalence that continues to rise due to population ageing and the increasing burden of cardiovascular comorbidities.[1] Recent global estimates indicate that AF now affects over 60 million individuals worldwide, with its prevalence more than doubling since 1990 and its incidence continuing to rise. AF is also associated with substantial morbidity and mortality, accounting for more than 8 million disability-adjusted life years and over 300 000 deaths annually.[2,3] It is a well-established risk factor for thromboembolic events, particularly ischaemic stroke (IS), and is also linked to a broader spectrum of adverse cardiovascular outcomes.[4] Although oral anticoagulation (OAC) markedly reduces the risk of thromboembolism, a significant residual burden of cardiovascular events persists even among appropriately anticoagulated AF patients.[5]

This residual risk underscores the complex and multifactorial nature of thromboembolic pathophysiology in AF, extending beyond what is captured by conventional risk scores.[6] Mechanisms such as systemic inflammation, endothelial dysfunction, metabolic dysregulation, and impaired physiological resilience may all contribute to persistent cardiovascular vulnerability in this population.[7,8] As a result, increasing attention has focused on identifying integrative biomarkers that reflect these underlying processes, with the aim of improving risk stratification, particularly in anticoagulated AF patients who remain at elevated cardiovascular risk.[9]

The stress hyperglycaemia ratio (SHR) has emerged as a promising metabolic index that captures the relationship between acute and chronic glycaemic states.[10] Defined as the ratio of admission blood glucose to estimated chronic glycaemia derived from glycated haemoglobin (HbA1c), SHR distinguishes transient glycaemic elevations from long-term hyperglycaemic exposure. Rather than serving as an isolated marker of acute stress, SHR may integrate information on both metabolic flexibility and chronic glycaemic burden, providing a more comprehensive assessment of cardiometabolic status.[11,12]

In various high-risk populations, including individuals with diabetes mellitus,[13] acute coronary syndrome,[14,15] heart failure,[16] and cardiovascular kidney-metabolic syndrome,[17] SHR has been associated with adverse cardiovascular and cerebrovascular outcomes, often following a U- or L-shaped relationship. However, its clinical significance in stable, anticoagulated AF populations remains uncertain. Existing evidence is limited, largely derived from critically ill cohorts, and has mainly focused on all-cause mortality rather than thromboembolic or cardiovascular-specific outcomes.[18–20]

Accordingly, this study aimed to assess the association between SHR levels and residual risk of adverse cardiovascular outcomes in a prospective cohort of AF patients receiving OAC therapy.

2 | METHODS

This prospective, observational cohort study, the Murcia AF Project III (MAFP-III), enrolled ambulatory outpatients newly diagnosed with paroxysmal or persistent AF who were naïve to OAC therapy and initiated treatment with either vitamin K antagonists or direct-acting oral anticoagulants (DOACs) at two anticoagulation clinics located in Murcia, Spain, between January 1, 2016, and November 30, 2021. AF was diagnosed based on a 12-lead electrocardiogram showing irregular R-R intervals and the absence of distinct P waves lasting ≥30 s, in accordance with current European Society of Cardiology guidelines.[21] AF was classified according to its temporal pattern as paroxysmal (self-terminating within 7 days) or persistent (lasting >7 days or requiring cardioversion).

Eligible participants were adults aged ≥18 years. Patients with prosthetic heart valves, rheumatic mitral valve disease or other significant valvular abnormalities were excluded. No additional exclusion criteria were applied. All patients meeting the inclusion criteria were consecutively enrolled, as this was an all-comers study with no prior sample size calculation.

At baseline, comprehensive medical histories were obtained, including socio-demographic data, anthropometric measurements, comorbidities, and concomitant therapies. Stroke risk was assessed using the CHA_2DS_2-VASc and CHA_2DS_2-VA scores,[22,23] while bleeding risk was evaluated using the HAS-BLED score.[24]

The study protocol was approved by the Ethics Committee of the University Hospital Morales Meseguer (reference: EST:20/16) and by that of the University Hospital Virgen de la Arrixaca (reference: 2020-11-12-HCUVA). It was conducted in accordance with the ethical principles of the Declaration of Helsinki (1964) and its subsequent amendments. Written informed consent was obtained from all participants prior to inclusion.

2.1 | Estimation and stratification of the SHR

Admission blood glucose and HbA1c levels were measured at baseline. In this outpatient cohort, "admission glucose" referred to the fasting blood glucose measurement obtained early in the morning during the first anticoagulation clinic visit, prior to the initiation of OAC therapy. Following previous studies,[25–27] SHR was calculated using the established formula: SHR = admission blood glucose (mmol/L)/([1.59 × HbA1c %] − 2.59). Participants were then stratified into low and high SHR groups based on a cut-off value derived from subsequent statistical analyses.

2.2 | Follow-up and clinical outcomes

Follow-up was conducted through in-person interviews during routine outpatient visits to the anticoagulation clinic, in alignment with standard clinical care. For patients who missed scheduled appointments, relevant information and vital status were obtained via review of medical records and follow-up telephone calls. As an observational study, all follow-up procedures were embedded within routine clinical practice, with no additional interventions or study-specific visits implemented.

The primary endpoints were: (i) the occurrence of thromboembolic events, defined as a composite of IS, transient ischaemic attack (TIA) or systemic embolism; and (ii) major adverse cardiovascular events (MACEs), comprising myocardial infarction, IS, TIA or cardiovascular death. Secondary endpoints included cardiovascular and all-cause death. Each adverse event was documented individually, and only the first occurrence of each event type was recorded. The follow-up period continued until the patient's death or a maximum of 2 years, whichever occurred first. No patients were lost to follow-up.

2.3 | Statistical analyses

Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate. Categorical variables were presented as absolute frequencies and percentages. Group comparisons were performed using Student's *t* test or the Mann–Whitney *U* test for continuous variables, and Fisher's exact test or Pearson's chi-square test for categorical variables.

The cut-off value for SHR grouping was determined using the "survminer" package in R, based on maximally selected rank statistics to optimise separation of time-to-event outcomes.[28–30] To assess both overall and non-linear associations between SHR and the primary outcomes, restricted cubic spline (RCS) analyses were conducted with SHR as a continuous variable. The reference point for the splines was set at the identified cut-off. The number of knots was determined based on the Akaike Information Criterion and Bayesian Information Criterion, with the final models employing three knots, placed at the 10th, 50th, and 90th percentiles of the index distribution. The reference value for SHR was defined as the median of the distribution. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were estimated across the full range of SHR. RCS plots were generated to visualise these associations, with dashed vertical lines indicating the knot locations, a red dot marking the reference point (aHR = 1.0), and rug plots along the x-axis displaying the distribution of SHR values in the study population.

Incidence rates with 95% Poisson CIs for the primary outcome were calculated for each SHR group. Rate differences (RDs) were estimated using the high SHR group as the reference.

For thromboembolic events and MACE, cumulative incidence curves were constructed to depict event occurrence over time across SHR categories. Kaplan–Meier curves with log-rank tests were used to compare cardiovascular and all-cause death-free survival between SHR groups.

Multivariable Cox proportional hazards models were used to evaluate the independent association between SHR and both primary and secondary outcomes, considering SHR both as a continuous variable and as a categorical variable (low vs high). Two models were constructed: Model 1 was unadjusted, and Model 2 was adjusted for age, AF type and CHA_2DS_2-VASc score. We reported aHRs with 95% CIs. The proportional hazards assumption was verified using Schoenfeld residuals, and no violations were detected. To assess the robustness of the findings, additional sensitivity analyses were conducted with expanded covariate adjustment: Model 3 adjusted for age, sex, AF type, body mass index (BMI), hypertension, diabetes mellitus, heart failure, prior stroke/TIA/thromboembolism, vascular disease, renal impairment, dyslipidaemia, smoking status and alcohol consumption, and Model 4 further adjusted for lipid-lowering agents, oral hypoglycaemic agents, insulin and antiplatelet therapy.

Cumulative incidence functions (CIFs) for thromboembolic events and MACE were estimated using Fine–Gray competing risk models, considering death as a competing event. Subdistribution hazard ratios (sHRs) with 95% CIs were derived from multivariable Fine–Gray regression analyses adjusted for age, AF type, and CHA_2DS_2-VASc score.

Subgroup analyses were conducted to evaluate the consistency of associations between SHR and both thromboembolic events and MACE across clinically relevant strata (including age, sex, AF type, CHA_2DS_2-VASc score, hypertension, diabetes, history of stroke/TIA

and kidney disease). These analyses were based on formal tests of interaction by including multiplicative interaction terms in the fully adjusted model. Since we did not conduct or interpret multiple within-group effect estimates separately, but rather focused on the statistical significance of interaction terms to assess effect modification, a correction for multiple comparisons was not applied.

All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant. Analyses were performed using STATA v18.0 (StataCorp LLC, College Station, TX, USA), R (R Foundation for Statistical Computing, Vienna, Austria), and SPSS v25.0 (IBM Corp., Armonk, NY, USA).

3 | RESULTS

The overall cohort comprised 3259 AF patients (52.8% female; median age 77 years, IQR 70–83). Of these, 1479 patients (51.3% female; median age 76 years, IQR 69–82) had complete metabolic profiles, including measurements of glucose and HbA1c, and were included in the present analysis (Figure S1, Supporting Information). All were exclusively receiving DOACs. At baseline, 543 (36.7%) were treated with apixaban, 393 (26.6%) with rivaroxaban, 322 (21.8%) with dabigatran and 221 (14.9%) with edoxaban. Dosing and dose-reduction criteria followed the respective summaries of product characteristics. Median CHA_2DS_2-VASc and CHA_2DS_2-VA scores were 4 (IQR 3–5), and the median HAS-BLED score was 3 (IQR 2–4). The median baseline glucose concentration was 6.0 mmol/L (IQR 5.2–7.3), and the median HbA1c was 6.1% (IQR 5.7–6.8).

Based on the predefined SHR cut-off (Figure 1), 344 patients (23.3%) were categorised into the low SHR group and 1135 (76.7%) into the high SHR group. Baseline characteristics according to SHR group are summarised in Table 1. Notably, patients in the low SHR group were significantly older than those in the high SHR group ($p = 0.002$), with no substantial differences in comorbidity burden between groups.

3.1 | Primary outcomes across SHR groups

During a mean follow-up of 1.87 years (SD 0.4 years), 80 patients (5.4%) experienced a thromboembolic event, and 107 (7.2%) experienced a MACE. Incidence rates of both thromboembolic events (4.26 vs 2.50 per 100 person-years; $p = 0.048$) and MACE (5.64 vs 3.34 per 100 person-years; $p = 0.024$) were significantly higher in the low SHR group compared with the high SHR group (Table 2).

3.2 | Secondary outcomes across SHR groups

During the follow-up period, 43 patients (2.9%) died from cardiovascular causes, and 134 (9.1%) died from any cause. Cardiovascular deaths

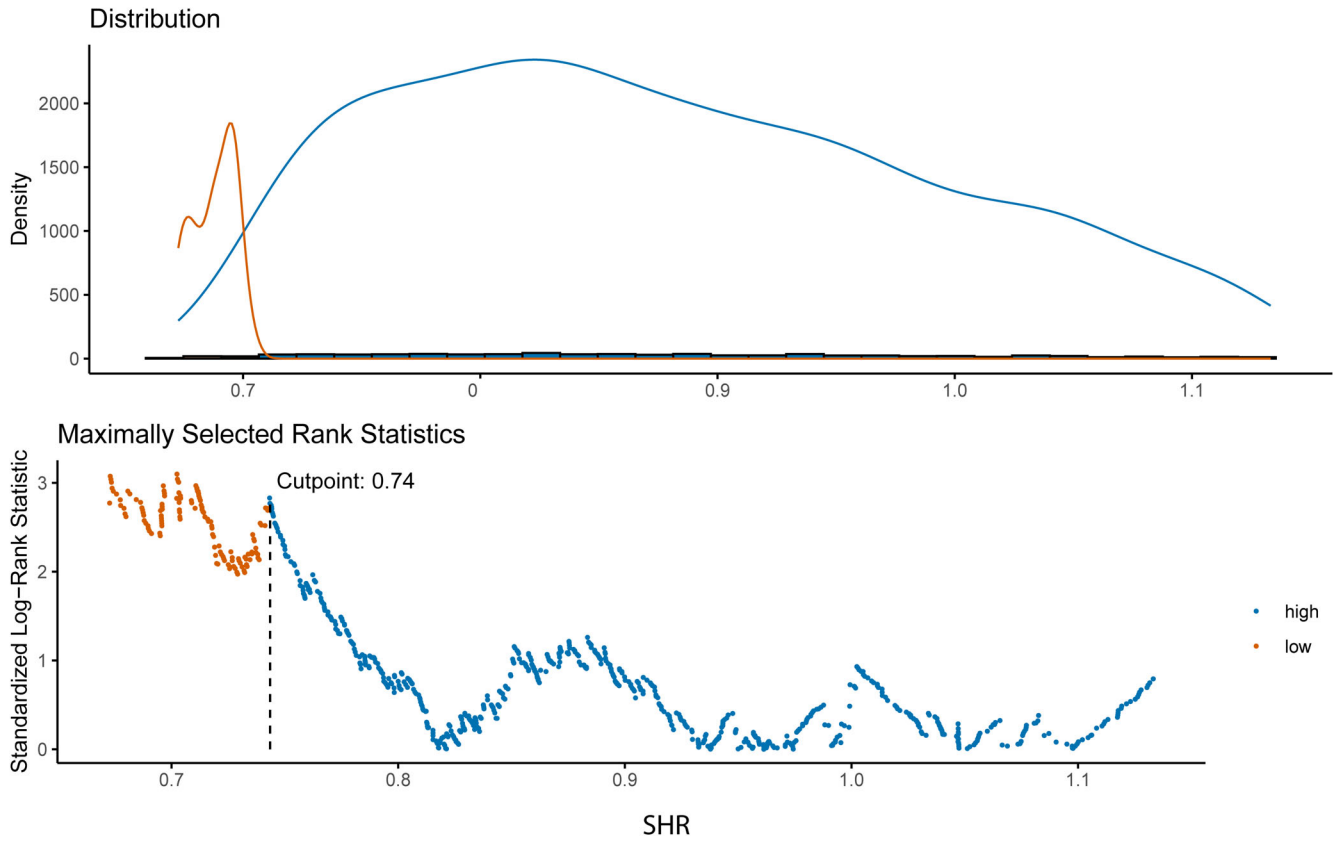

FIGURE 1 Visualisation of the optimal cut-off point for thromboembolic events. SHR, stress hyperglycaemia ratio.

TABLE 1 Baseline clinical characteristics according to SHR group.

	Low SHR ($N = 344$)	High SHR ($N = 1135$)	p-Value
Demographics			
Age, median [IQR]	78 [71–83]	76 [68–82]	0.002
Sex (female), *n* (%)	179 (52)	580 (51.1)	0.809
AF type, *n* (%)			
Persistent	223 (64.8)	696 (61.3)	0.267
Paroxysmal	121 (35.2)	439 (38.7)	
Comorbidities, *n* (%)			
Hypertension	297 (86.3)	995 (87.7)	0.578
Diabetes mellitus	150 (43.6)	503 (44.3)	0.864
Heart failure	55 (16)	222 (19.6)	0.159
History of stroke/TIA/thromboembolism	97 (28.2)	288 (25.4)	0.329
Vascular disease[a]	83 (24.1)	248 (21.9)	0.416
Renal impairment	76 (22.1)	294 (25.9)	0.174
Dyslipidaemia	211 (61.3)	671 (59.1)	0.502
COPD/OSA	84 (24.4)	276 (24.3)	0.999
History of relevant bleeding	55 (16)	181 (15.9)	0.999
Liver disease	12 (3.5)	48 (4.2)	0.650
History of cancer	42 (12.2)	159 (14)	0.445
Smoking habit	102 (29.7)	359 (31.6)	0.530
Alcoholism	37 (10.8)	134 (11.8)	0.662
Concomitant treatment, *n* (%)			
Antiarrhythmics	76 (22.1)	219 (19.3)	0.289
ACE inhibitors	82 (23.8)	300 (26.4)	0.372
ARBs	169 (49.1)	523 (46.1)	0.352
Calcium channel blockers	104 (30.2)	348 (30.7)	0.933
Beta-blockers	214 (62.2)	739 (65.1)	0.357
Diuretics	223 (64.8)	710 (62.6)	0.484
Antilipemic agents	210 (61)	665 (58.6)	0.293
Oral hypoglycaemic agents	121 (35.2)	423 (37.3)	0.521
Insulin	49 (14.2)	99 (8.7)	0.004
Antiplatelet therapy	38 (11)	117 (10.3)	0.771
Analytical parameters, median [IQR]			
Glucose, mmol/L	5.1 [4.7–5.7]	6.3 [5.5–7.7]	<0.001
HbA1c, %	6.3 [6–7.2]	6 [5.6–6.7]	<0.001
Stroke and bleeding scores, median [IQR]			
CHA_2DS_2-VA	4 [3–5]	4 [3–5]	0.070
CHA_2DS_2-VASc	4 [3–6]	4 [3–5]	0.079
HAS-BLED	3 [2–4]	3 [2–4]	0.069

Abbreviations: ACE inhibitors, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II receptor blockers; COPD/OSA, chronic obstructive pulmonary disease/obstructive sleep apnoea; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; SHR, stress hyperglycaemia ratio; TIA, transient ischaemic attack.

[a]Vascular disease includes coronary artery disease and/or peripheral artery disease.

(2.12 vs 1.33 events per 100 person-years; $p = 0.204$) and all-cause deaths (4.85 vs 4.69 events per 100 person-years; $p = 0.874$) in the low SHR group compared with the high SHR group were numerically higher, but were not statistically significant (Table 2).

3.3 | Association of thromboembolic events with SHR groups

RCS analysis demonstrated a significant overall (p-overall $= 0.005$), and non-linear association (p-non-linear $= 0.015$) between SHR levels

TABLE 2 Incidence rate and rate difference for the different outcomes according to the SHR group.

	Low SHR		High SHR			
	N (%)	Incidence rate[a] (95% CI)	*N* (%)	Incidence rate[a] (95% CI)	RD (95% CI)	*p*-Value
Any thromboembolic event	27 (7.8)	4.26 (2.81–6.20)	53 (4.7)	2.50 (1.88–3.28)	1.76 (0.02–3.50)	0.048
MACE	36 (10.5)	5.64 (3.95–7.81)	71 (6.3)	3.34 (2.60–4.21)	2.30 (0.30–4.30)	0.024
Cardiovascular death	14 (4.1)	2.12 (1.16–3.56)	29 (2.6)	1.33 (0.89–1.92)	0.79 (−0.42–2.00)	0.204
All-cause death	32 (9.3)	4.85 (3.32–6.84)	102 (9)	4.69 (3.83–5.70)	0.15 (−1.76–2.06)	0.874

Abbreviations: CI, confidence interval; MACE, major adverse cardiovascular events; RD, rate difference; SHR, stress hyperglycaemia ratio.
[a]Per 100 person-years.

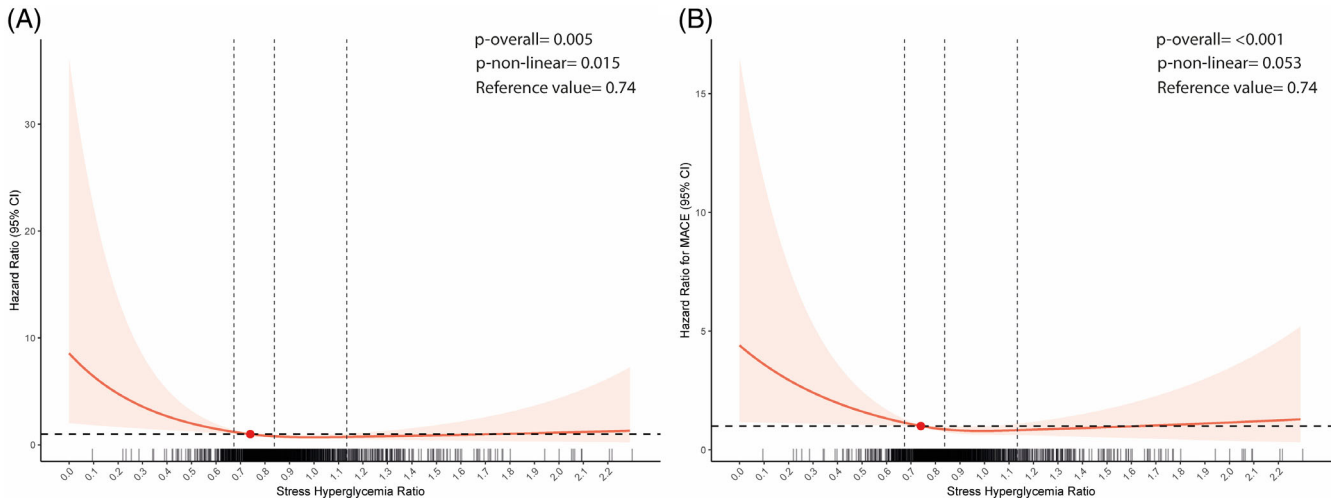

FIGURE 2 Restricted cubic spline analyses illustrating the adjusted associations between the SHR and the risk of thromboembolic events (A) and MACE (B). The solid red line represents the aHR, and the shaded area indicates the 95% CIs. The dashed vertical lines correspond to the spline knots, and the red dot marks the reference value. The rug plots along the x-axes display the distribution of SHR values. aHR, adjusted hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular events; SHR, stress hyperglycaemia ratio.

and thromboembolic risk (Figure 2A). Cumulative incidence curves showed a significantly higher incidence of thromboembolic events in the low SHR group compared with the high SHR group ($p = 0.014$) (Figure 3).

As shown in Table 3, the unadjusted Cox proportional hazards models indicated that continuous SHR was significantly associated with thromboembolic events (HR 1.45; 95% CI 1.07–1.95; $p = 0.017$), and patients in the low SHR group had a higher risk of thromboembolic events compared with those in the high SHR group (HR 1.78; 95% CI 1.12–2.84; $p = 0.015$). These associations remained statistically significant after adjustment for age, AF type and CHA_2DS_2-VASc score, both when SHR was analysed as a continuous variable (aHR 1.39; 95% CI 1.02–1.90; $p = 0.035$) and when comparing SHR categories, with patients in the low SHR group exhibiting a significantly higher risk than those in the high SHR group (aHR 1.73; 95% CI 1.08–2.76; $p = 0.022$).

These associations remained consistent in sensitivity analyses with progressively expanded adjustment for clinical variables and concomitant cardiovascular and metabolic therapies, confirming the robustness of the findings (Table S1).

To account for the competing risk of death, adjusted CIF curves for thromboembolic events were constructed using the Fine–Gray method (Figure S2). The results were consistent with the main analyses, showing a higher cumulative incidence of thromboembolic events in the low SHR group compared with the high SHR group. In the Fine–Gray subdistribution hazard model, low SHR was independently associated with an increased risk of thromboembolic events (sHR 1.67; 95% CI 1.04–2.68; $p = 0.033$).

3.4 | Association of MACE with SHR groups

RCS analysis revealed a significant overall association between SHR levels and MACE (*p*-overall <0.001), with no evidence of non-linearity (*p*-non-linear = 0.053) (Figure 2B). Cumulative incidence curves demonstrated a significantly higher incidence of MACE in the low SHR group (Figure 3).

As presented in Table 3, the unadjusted Cox proportional hazards models demonstrated that continuous SHR was significantly associated with MACE (HR 1.33; 95% CI 1.03–1.73; $p = 0.030$). Similarly, individuals in the low SHR group showed a greater risk of MACE compared with those in the high SHR group (HR 1.70; 95% CI 1.14–2.55; $p = 0.009$). These relationships persisted after adjustment for age, AF

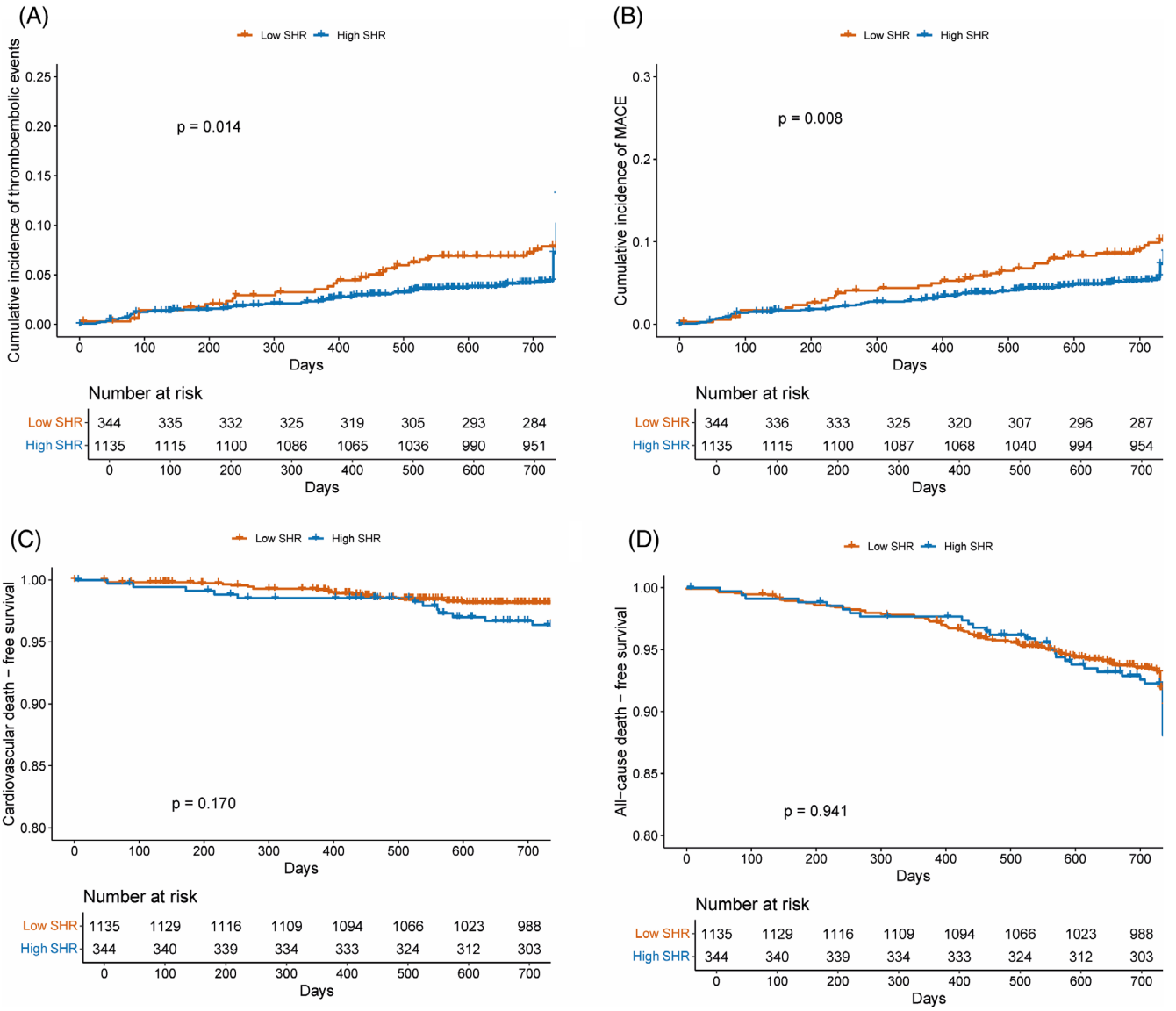

FIGURE 3 Cumulative incidence and Kaplan–Meier survival curves in SHR groups for thromboembolic events (A), MACE (B), cardiovascular death (C), and all-cause death (D). MACE, major adverse cardiovascular events; SHR, stress hyperglycaemia ratio.

type, and CHA_2DS_2-VASc score, both when SHR was considered a continuous variable (aHR 1.35; 95% CI 1.04–1.76; $p = 0.026$) and in the categorical analysis, where the low SHR group remained at significantly higher risk than the high SHR group (aHR 1.58; 95% CI 1.06–2.37; $p = 0.025$).

The association remained robust after further adjustment for additional clinical factors and concomitant cardiometabolic treatments, with consistent effect estimates (Table S1).

To account for the competing risk of death, adjusted CIF curves for MACE were constructed using the Fine–Gray method (Figure S2). The results were consistent with the main analyses, showing a higher cumulative incidence of MACE in the low SHR group compared with the high SHR group. In the Fine–Gray subdistribution hazard model, low SHR was independently associated with an increased risk of MACE (sHR 1.60; 95% CI 1.06–2.41; $p = 0.026$).

3.5 | SHR groups and secondary outcomes

Kaplan–Meier curves revealed no significant differences between SHR groups for cardiovascular death (log-rank $p = 0.170$) or all-cause death (log-rank $p = 0.941$) (Figure 3).

After adjustment for age, AF type and CHA_2DS_2-VASc score, the Cox proportional hazards models showed no significant association between continuous SHR and cardiovascular death (aHR 1.22; 95% CI 0.82–1.82; $p = 0.326$), nor was cardiovascular death increased in the low SHR group compared with the high SHR group (aHR 1.45; 95% CI 0.77–2.75; $p = 0.253$). Similarly, no significant differences were observed for all-cause death, either when SHR was analysed as a continuous variable (aHR 1.35; 95% CI 0.73–2.48; $p = 0.339$) or by categories (aHR 0.92; 95% CI 0.62–1.38; $p = 0.690$) (Table 3).

TABLE 3 Association between SHR and risk of clinical outcomes expressed as hazard ratios.

	Model I			Model II	
	N (%)	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Any thromboembolic event					
Continuous SHR		1.44 (1.07–1.95)	0.017	1.39 (1.02–1.90)	0.035
Low SHR	27 (7.8)	1.78 (1.12–2.84)	0.015	1.73 (1.08–2.76)	0.022
High SHR	53 (4.7)	Reference		Reference	
MACE					
Continuous SHR		1.33 (1.03–1.73)	0.030	1.35 (1.04–1.76)	0.026
Low SHR	36 (10.5)	1.70 (1.14–2.55)	0.009	1.58 (1.06–2.37)	0.025
High SHR	71 (6.3)	Reference		Reference	
Cardiovascular death					
Continuous SHR		1.32 (0.88–1.99)	0.183	1.22 (0.82–1.82)	0.326
Low SHR	14 (4.1)	1.56 (0.82–2.95)	0.173	1.45 (0.77–2.75)	0.253
High SHR	29 (2.6)	Reference		Reference	
All-cause death					
Continuous SHR		1.54 (0.81–2.95)	0.191	1.35 (0.73–2.48)	0.339
Low SHR	32 (9.3)	1.02 (0.68–1.51)	0.943	0.92 (0.62–1.38)	0.690
High SHR	102 (9)	Reference		Reference	

Note: Model I: unadjusted. Model II: adjusted for age, AF type and CHA_2DS_2-VASc score.
Abbreviations: CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; SHR, stress hyperglycaemia ratio.

The sensitivity analysis, incorporating additional adjustments, further corroborated these findings (Table S1).

3.6 | Subgroup analysis

The association between low SHR levels and the risk of thromboembolic events and MACE remained directionally consistent across all clinical subgroups, with no significant interactions detected (all *p* for interaction >0.05).

Statistically significant associations with thromboembolic risk were observed in specific subgroups, including patients aged ≥65 years ($p = 0.022$), males ($p = 0.016$), and those with hypertension ($p = 0.007$), diabetes ($p = 0.004$), no prior stroke/TIA/thromboembolism ($p = 0.005$) and those without vascular disease ($p = 0.037$) (Figure 4A).

Similarly, significant associations with MACE risk were identified in selected subgroups: patients aged ≥65 years ($p = 0.018$), males ($p = 0.029$), those with AF paroxysmal ($p = 0.005$), low CHA_2DS_2-VASc score ($p = 0.010$), hypertension ($p = 0.005$), diabetes ($p = 0.023$), no prior stroke/TIA/thromboembolism ($p = 0.014$) and those without vascular disease ($p = 0.043$) (Figure 4B).

4 | DISCUSSION

In this large, prospective cohort of anticoagulated AF patients, our principal findings are as follows: (i) lower SHR levels were independently associated with an increased risk of thromboembolic events and MACE, even after adjustment for conventional clinical risk factors. Patients in the low SHR group showed significantly reduced event-free survival and higher incidence rates of both primary endpoints compared with those in the high SHR group; (ii) rates of cardiovascular and all-cause death were numerically higher in the low SHR group, although these differences did not reach statistical significance; and (iii) the association between low SHR and the risk of thromboembolic events and MACE was consistent across all clinical subgroups, with particularly pronounced associations observed in patients aged ≥65 years, males, those with diabetes, and individuals without a history of stroke/TIA/thromboembolism, or established vascular disease.

To our knowledge, this is the first prospective study to evaluate the role of SHR in characterising residual thromboembolic and cardiovascular risk among anticoagulated AF patients, a population in which conventional risk scores may not fully capture the complex and multifactorial nature of ongoing cardiovascular vulnerability.[6,31] Rather than representing a single pathophysiological process, SHR may integrate multiple aspects of metabolic dysregulation, including acute glycaemic fluctuations, chronic hyperglycaemic exposure and impaired physiological resilience. In this context, SHR may serve as a composite biomarker of metabolic stress and cardiovascular vulnerability, reflecting transient but clinically relevant perturbations in neurohormonal and inflammatory pathways not accounted for by baseline comorbidities or chronic glycaemic status.[10,32]

Previous studies have explored the association between SHR and cardiovascular outcomes in diabetes,[13] acute coronary syndrome,[14,15] heart failure[16] and cardiovascular-kidney-metabolic syndrome.[17] In

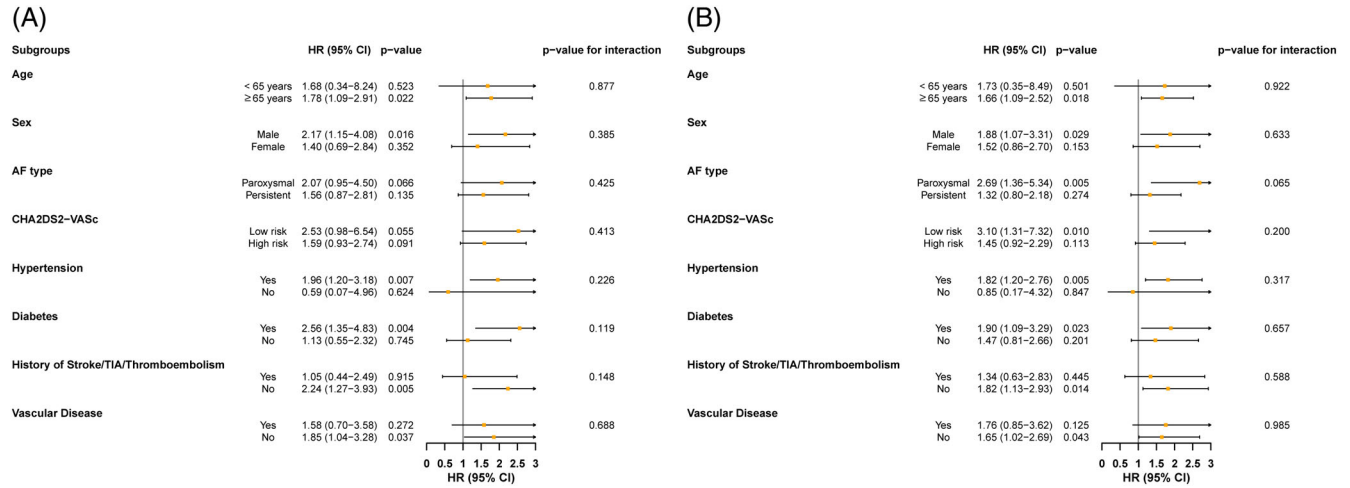

FIGURE 4 Hazard ratios for SHR across clinical subgroups for thromboembolic events (A) and MACE (B), derived from Cox regression analysis. AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; TIA, transient ischaemic attack.

the setting of AF, the prognostic value of SHR has only been examined in relation to all-cause death, and primarily in critically ill patients.[18–20] To date, no studies have assessed its association with the residual risk of thromboembolic events in stable, anticoagulated AF cohorts. Therefore, our findings address a critical gap in the understanding of residual risk in this population and suggest that SHR may represent a valuable tool for enhancing risk stratification beyond conventional clinical scoring systems.

The association between low SHR and increased cardiovascular risk may initially seem counterintuitive, as stress hyperglycaemia is commonly linked to adverse outcomes in acute settings.[33] Although prior studies have frequently described a U-shaped relationship between SHR and prognosis, with excess risk at both low and high SHR values,[13,14,34,35] the association observed in our study followed a distinctly L-shaped pattern. Risk increased at low SHR levels but did not rise at higher SHR values. This difference may reflect the ambulatory nature of our cohort, where admission glucose is less influenced by acute stress responses than in hospitalised or critically ill populations, making high SHR values less prevalent.

Low SHR in this context may not necessarily indicate an inadequate stress response, but rather reflect chronic hyperglycaemia, reduced metabolic flexibility, or physiological frailty. These factors are common in older AF patients and have been independently linked to adverse cardiovascular outcomes.[36] Alternatively, low SHR might denote diminished physiological reserve or subclinical metabolic exhaustion, where glucose homeostasis fails to respond appropriately to physiological demands. In contrast, elevated SHR values typically reflect disproportionately high acute glucose levels relative to baseline HbA1c and have been associated with increased sympathetic activation, endothelial dysfunction, and systemic inflammation in high-risk populations such as those with acute coronary syndromes or sepsis.[14,15,34] While this phenotype is less prevalent in stable, anticoagulated AF populations, it may still signify unrecognised comorbidity or excessive physiological stress.

Importantly, SHR incorporates both acute (admission blood glucose) and chronic (HbA1c) glycaemic parameters, thereby serving as an integrated marker of metabolic stress.[10–12] A low SHR may occur despite chronically elevated HbA1c, suggesting that chronic metabolic exposure, rather than an isolated acute dysregulation, could underlie part of the observed risk. Chronic hyperglycaemia contributes to vascular inflammation, endothelial dysfunction, platelet activation, and prothrombotic states,[37,38] all of which play a central role in the pathogenesis of thromboembolic events and adverse cardiovascular outcomes in AF.

In this stable outpatient population, low SHR may thus represent a composite signal of both long-standing metabolic burden and impaired physiological reserve, rather than a single mechanistic process.[39] Because patients were not experiencing acute illness at baseline, fasting glucose levels were less likely to capture an acute stress response, and normal glucose values may have masked underlying metabolic dysfunction. Although HbA1c levels were modest and similar across SHR groups, subtle chronic hyperglycaemia or cumulative vascular injury could still contribute to the association observed. Future studies combining SHR with HbA1c stratification, measures of frailty, and longitudinal glycaemic trajectories are warranted to disentangle these overlapping mechanisms.

Beyond dysglycaemia, SHR may also capture broader metabolic stress pathways that promote cardiovascular injury. Acute glucose fluctuations can trigger oxidative stress, increase mitochondrial dysfunction, and amplify the production of advanced glycation end products, which in turn activate pro-inflammatory cascades such as NF-κB signalling.[40,41] These processes impair nitric oxide bioavailability, exacerbate endothelial dysfunction, and promote vascular inflammation, while simultaneously enhancing platelet activation and coagulation, favouring a prothrombotic milieu even under anticoagulation.[42] These pathophysiological links may partly explain the observed association between low SHR and residual thromboembolic risk in AF.

These observations highlight the potential value of SHR as a biomarker that captures both transient metabolic derangements and cumulative glycaemic burden. In anticoagulated AF patients, where residual thromboembolic risk persists despite optimal therapy, SHR may offer additional prognostic information beyond conventional risk scores, helping to identify individuals with unrecognised metabolic vulnerability.

Despite the lack of direct comparisons, our findings are consistent with previous studies. For example, Yang et al.[14] explored the association between SHR and cardiovascular outcomes in 5562 patients with acute coronary syndrome over a 2-year follow-up. When compared with those in the third quintile (Q3), individuals in both the lowest (Q1) and highest (Q5) quintiles showed significantly lower major adverse cardiovascular and cerebrovascular events (MACCE)-free survival ($p < 0.001$). Similarly, Liu et al.[35] investigated 12 899 patients undergoing non-cardiac surgery, stratifying them into tertiles according to SHR levels. After adjusting for confounders, the risk of MACCE within 30 days postoperatively was 1.34-fold higher in the highest tertile (T3) (95% CI 1.08–1.66, $p = 0.007$) and 1.35-fold higher in the lowest tertile (T1) (95% CI 1.08–1.68, $p = 0.008$), compared to the middle tertile (T2). Additionally, Ding et al.[13] analysed 11 160 individuals with diabetes or prediabetes and reported a non-linear, L-shaped association between SHR and cardiovascular mortality. Over a mean follow-up of 84.9 months, patients in the third quartile (Q3) had significantly lower cardiovascular mortality compared with those in the lowest quartile (Q1), both after adjustment for age, sex and race (aHR 0.66, 95% CI 0.45–0.96; $p = 0.032$) and after additional adjustment for conventional cardiovascular risk factors (aHR 0.68, 95% CI 0.46–0.99; $p = 0.049$). These findings align with our results and support the biological plausibility of an increased risk associated with low SHR levels.

Taken together, our findings suggest that lower SHR values identify a subset of anticoagulated AF patients who remain at higher residual risk for adverse cardiovascular outcomes. While causality cannot be inferred, the consistency of the association across multiple adjusted and sensitivity analyses supports the hypothesis that SHR reflects clinically relevant metabolic and physiological vulnerability. Derived from standard laboratory parameters, SHR offers a simple and cost-effective biomarker that integrates both acute and chronic glycaemic information. Its prognostic value likely reflects the interplay between chronic metabolic burden, physiological frailty, and diminished stress adaptability, factors not captured by traditional clinical scores such as CHA_2DS_2-VASc or CHA_2DS_2-VA.

In this context, incorporating SHR into existing risk models could enhance risk stratification in anticoagulated AF patients and support more personalised management strategies. Given the persistent residual risk in this population despite optimal anticoagulation, SHR may help uncover subclinical metabolic vulnerability and inform targeted preventive interventions beyond standard care.

4.1 | Limitations

This study has several limitations that should be acknowledged. First, its observational design precludes definitive causal inference. Although extensive adjustment for known confounders was performed, residual confounding from unmeasured or unknown variables cannot be entirely excluded. Second, all participants were receiving OAC therapy at baseline, which may limit the generalisability of our findings to OAC-naïve individuals or those managed with alternative therapeutic strategies. Third, the cohort was predominantly White European and recruited from two academic centres in Spain, which may restrict the external validity of the findings in more ethnically diverse or geographically distinct populations.[43] This is particularly relevant given reported ethnic differences in AF epidemiology and AF-related complications, including stroke and bleeding.[44,45] Fourth, SHR was calculated from glucose and HbA1c values obtained at a single time point, which does not capture intra-individual variability or temporal fluctuations related to acute illness, dietary changes, or pharmacological interventions. While this pragmatic approach is consistent with previous SHR studies, it may underestimate dynamic metabolic stress responses over time. Future research incorporating longitudinal glycaemic profiling or repeated SHR assessments could provide additional prognostic value and help refine metabolic risk stratification in anticoagulated AF patients.[46] Fifth, SHR is a calculated index that reflects the mismatch between acute and chronic glycaemia rather than a directly measured biomarker. Although this measure has been validated and widely used, it may be susceptible to variability in individuals with borderline glucose or HbA1c values or transient physiological disturbances such as dehydration or infection. Sixth, the incidence of certain secondary outcomes, particularly cardiovascular death, was relatively low in this stable outpatient cohort. This may have reduced statistical power for these analyses and contributed to wider confidence intervals, limiting the precision of the corresponding effect estimates. Nonetheless, directional consistency was observed across outcomes, supporting the robustness of the associations and warranting confirmation in larger studies with longer follow-up. Seventh, we did not evaluate other metabolic or inflammatory biomarkers that may interact with SHR or provide complementary prognostic information on residual thromboembolic and cardiovascular risk. Finally, a small proportion of patients switched between DOACs (approximately 10%) during follow-up. Although these treatment changes were infrequent and unlikely to have influenced the metabolic parameters or outcomes evaluated, this possibility cannot be entirely excluded.

5 | CONCLUSION

In this cohort of anticoagulated AF patients, lower SHR levels were independently associated with an increased risk of thromboembolic events and MACE, even after adjustment for conventional clinical risk factors. These findings suggest that SHR may serve as a valuable biomarker for identifying residual thromboembolic and cardiovascular risk in this patient population and may support enhanced risk stratification approaches.

AUTHOR CONTRIBUTIONS

Eva Soler-Espejo, Yang Chen, and José Miguel Rivera-Caravaca, and José Antonio Sánchez-Salas performed statistical analyses and drafted

the manuscript. Eva Soler-Espejo, José Miguel Rivera-Caravaca, María Asunción Esteve-Pastor and Vanessa Roldán contributed to data collection. Francisco Marín, Vanessa Roldán and Gregory Y.H. Lip conceived and supervised the study, and critically revised the manuscript. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

José Miguel Rivera-Caravaca: Consultant for Idorsia Pharmaceuticals Ltd. Francisco Marín is consultant and speaker for Boehringer-Ingelheim and BMS/Pfizer. Gregory Y.H. Lip: consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos. No fees are received personally. He is a National Institute for Health and Care Research (NIHR) Senior Investigator and co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 899871. There is nothing to disclose for other authors.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Derived data supporting the findings of this study are available from the corresponding author, Vanessa Roldán, on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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