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ORIGINAL RESEARCH

Polygenic Risk and Cardiovascular Event Risk in Patients With Atrial Fibrillation With Low to Intermediate Stroke Risk

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BACKGROUND: The clinical utility of the polygenic risk score in predicting cardiovascular events in patients with atrial fibrillation (AF) has not yet been established. This study aimed to determine whether the polygenic risk score for AF might be useful in the risk stratification of AF-related cardiovascular events.

METHODS AND RESULTS: This study included 9597 oral anticoagulation–naive patients with AF with a CHA_2DS_2-VA (congestive heart failure; hypertension; age ≥75 years; diabetes; prior stroke or transient ischemic attack or thromboembolism; vascular disease; and age 65–74 years) score of 0 or 1 from the UK Biobank. Patients were stratified according to polygenic risk score tertiles and observed for the occurrence of ischemic stroke or systemic embolism, myocardial infarction, and heart failure hospitalization. The risks of incident events associated with the polygenic risk score were investigated using inverse probability of treatment weighting. Of 9597 individuals, 3800 (39.6%) were women and the mean±SD age was 65.3±6.4 years. During a median follow-up of 4.6 years (interquartile range, 1.7–7.9 years), the incidence rates of ischemic stroke or systemic embolism, myocardial infarction, and heart failure hospitalization were 0.83, 0.42, and 0.61 per 100 person-years, respectively. Compared with low genetic risk, high genetic risk was associated with a hazard ratio of 1.38 (95% CI, 1.08–1.76; *P*=0.011) for ischemic stroke or systemic embolism, 1.15 (95% CI, 0.82–1.61; *P*=0.422) for myocardial infarction, and 1.02 (95% CI, 0.78–1.34; *P*=0.895) for heart failure hospitalization.

CONCLUSIONS: In patients with AF with low–intermediate stroke risk, genetic risk for AF is associated with increased risk of stroke or systemic embolism.

Key Words: atrial fibrillation ■ polygenic risk score ■ stroke risk

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia and an important risk factor resulting in a 5-fold increased risk of stroke.[1] Preventing stroke and managing anticoagulation are the principal priorities in the management of AF.[2] There are several established risk stratification tools to predict stroke events in patients with AF.[3–5] In current guidelines, the CHA_2DS_2–VA (congestive heart failure; hypertension; age ≥75 years; diabetes; prior stroke or transient ischemic attack or thromboembolism; vascular disease; and age 65–74 years) scoring system is recommended to guide anticoagulation treatment for patients with AF.[6,7] Previous studies have demonstrated that CHA_2DS_2-VASc (congestive heart failure; hypertension; age ≥75 years; prior stroke or transient ischemic attack or thromboembolism;

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CLINICAL PERSPECTIVE

What Is New?

- In this observational study of patients with atrial fibrillation, a polygenic predisposition to atrial fibrillation was associated with an increased risk of ischemic stroke or systemic embolism.

What Are the Clinical Implications?

- The polygenic risk score of atrial fibrillation might enhance subsequent stroke and thromboembolism risk stratification in patients with atrial fibrillation with fewer clinical risk factors.
- Our findings could serve as the basis for future studies aimed at evaluating optimal anticoagulation treatment according to an individual's genetic susceptibility.

Nonstandard Abbreviations and Acronyms

CASTLE-AF	Catheter Ablation versus Standard Conventional Therapy in Patients With Left Ventricular Dysfunction and Atrial Fibrillation
CHA_2DS_2-VA	congestive heart failure; hypertension; age ≥75 years; diabetes; prior stroke, transient ischemic attack, thromboembolism; vascular disease; and age 65 to 74 years
IPTW	inverse probability of treatment weighting
PRS	polygenic risk score

vascular disease; age 65-74 years; and sex category) is useful for identifying "truly low-risk" patients and that oral anticoagulation should be considered in patients with AF at intermediate risk of stroke (CHA_2DS_2-VASc score 1 for men and 2 for women).[7,8] Recent studies have reported that all subgroups of CHA_2DS_2-VASc 1 were associated with a higher incidence of arterial thromboembolism compared with CHA_2DS_2-VASc 0, and oral anticoagulant use in these patients was associated with favorable clinical outcomes.[9,10]

Various clinical risk factors and biomarkers have been associated with AF risk and related complications.[11,12] However, incorporating these clinical risk factors did not improve stroke prediction performance because of their close relationship with the CHA_2DS_2-VASc components. Stroke risk assessment incorporating biomarkers improves stroke risk prediction modestly.[13–16] Current research has revealed that AF genetic factors could identify individuals who are at increased risk for AF, even when the burden of clinical risk factors is low.[17] In addition, the genetic risk of AF is associated with cardioembolic stroke, implying that AF genetic risk could serve as a biomarker for strokes related to AF.[18,19]

Therefore, we hypothesized that the AF polygenic risk score (PRS) could enhance AF-related cardiovascular event risk stratification in patients with fewer clinical risk factors. We aimed to identify patients with AF at low to intermediate clinical stroke risk who were at a higher risk of developing or having subsequent AF-related cardiovascular events based on the genetic risk of AF.

METHODS

Study Population

The UK Biobank is a nationwide cohort comprising >500 000 participants aged 40 to 70 years throughout the United Kingdom between 2006 and 2010. During recruitment, participants completed an extensive range of physical measures, provided information on their lifestyle and medical history using self-reported touchscreen questionnaires and interviews, and consented to have their health information followed up through linkages to electronic health records. The details of the study design and data collection have been previously described.[20] The study population consisted of participants of European descent with incident AF and a CHA_2DS_2-VA score of 0 or 1 after enrollment in the UK Biobank. Patients with AF with unavailable PRS data; not of European descent; a CHA_2DS_2-VA score ≥2, including the presence of a prior stroke, transient ischemic attack, systemic embolism, age ≥75 years or >2 other relevant conditions; valvular heart disease, such as prosthetic heart valve and mitral valve stenosis; history of oral anticoagulant use; or missing data of covariates were excluded. After these exclusions, 9597 participants were included in the analysis (Figure 1). The index date was the date of AF diagnosis. UK Biobank received ethical approval from the Northwest Multicenter's research ethics committee. The UK Biobank data were available to researchers after the acceptance of the research proposal by the UK Biobank. Written informed consent was obtained from all participants during recruitment. This study has been conducted using the UK Biobank Resource (application number 77793). This study was approved by the institutional review board of Yonsei University Health System (4-2024-0172).

Polygenic Risk Score

The AF PRS for the study population was obtained from the -results of UK Biobank. It was calculated by aggregating the effect sizes of each genetic variant multiplied

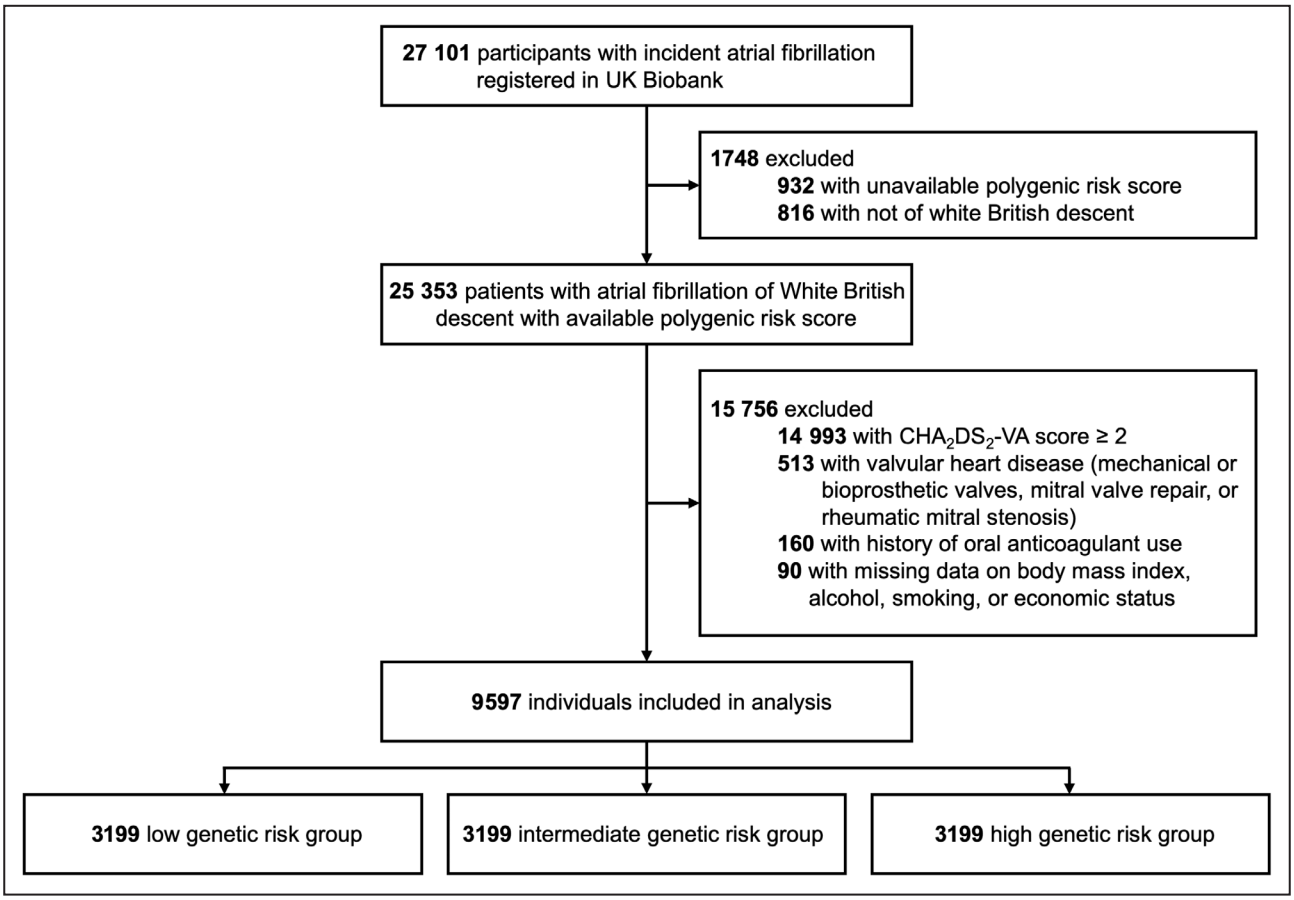

Figure 1. Study population.
CHA_2DS_2-VA indicates congestive heart failure; hypertension; age ≥75 years; diabetes; prior stroke or transient ischemic attack or thromboembolism; vascular disease; and age 65 to 74 years.

by the allele dosage. The effect sizes of the association between single-nucleotide polymorphism and disease were estimated based on external genome-wide association studies data using a fixed-effect inverse variance meta-analysis. Detailed methods for generating the PRS have been previously described.[21] The PRS was classified into tertiles to categorize patients with AF into low, intermediate, and high groups.

Outcomes

The outcome of this study was the occurrence of AF-related cardiovascular events, including ischemic stroke or systemic embolism, myocardial infarction (MI), and heart failure (HF) hospitalizations. The outcomes were defined as self-reported medical conditions or the first event occurring during at least 2 different days of hospital visits (primary care data) or the first admission (hospital inpatient data) with the *International Classification of Diseases, Tenth Revision* (*ICD-10*), code. Detailed definitions of the outcomes and comorbidities are presented in Tables S1 and S2, respectively. Data were collected from the date of AF diagnosis. Hospital registry-based follow-up records were available up to March 31, 2021, in England and Scotland, and February 28, 2018, in Wales. The cohorts were followed up until the occurrence of the outcome, death, loss to follow-up, or the end of the study, whichever occurred first.

Covariates

Ethnicity was assessed using self-reported questionnaires and categorized as Asian, Black, White, or mixed. Participants provided their history of smoking status (nonsmoker, ex-smoker, and current smoker). Participants were asked separately about their weekly and monthly consumption of pints of beer, glasses of red wine, glasses of white wine/champagne, glasses of fortified wine, measures of spirits/liqueurs, and glasses of other alcohol during the baseline visit. All alcoholic drinks were assumed to contain 10 grams of alcohol per portion except a pint of beer, which was supposed to contain 20 grams of alcohol. Total weekly and monthly consumption of alcohol was summed up for each participant. For an estimation of alcohol intake in grams per day, weekly and monthly consumption was divided by 7 and 30.4375, respectively.[22,23] History of

oral anticoagulant use was defined as any prescription of direct oral anticoagulants or warfarin before the date of AF diagnosis, based on records of prescribed medications, documented in the primary care data, which included drug codes, prescription dates, and quantities. Economic status was estimated using the Townsend Deprivation Index and sorted into 5 categories based on the UK census data. Demographic characteristics, including body mass index, drinking and smoking habits, and economic status were established at the time of enrollment. Components of the CHA_2DS_2-VA, such as congestive HF (CHF), hypertension, age, diabetes, and vascular disease, were defined at the date of AF diagnosis.

Inverse Probability of Treatment Weighting

To account for potential systematic differences between exposure groups, inverse probability of treatment weighting (IPTW) based on multinomial propensity scores was applied.[24–26] This method created a weighted cohort in which participants differed by PRS but were balanced across other measured covariates. Propensity scores were calculated using generalized boosted models with 10 000 regression trees incorporating covariates such as age, sex, body mass index, alcohol consumption, smoking habits, economic status, and clinical variables including CHF, hypertension, diabetes, vascular disease, dyslipidemia, chronic kidney disease, and end-stage renal disease. The balance measures across iterations of the gradient boosting algorithm were estimated to ensure that the model adequately balanced covariates. Standardized differences were used to estimate the differences in baseline characteristics between the PRS groups.

Statistical Analysis

Baseline characteristics were compared among study groups, with categorical variables expressed as frequencies and percentages and continuous variables expressed as mean±SD. Balance between each group was estimated by standardized differences of all covariates, using a threshold of 0.1 to indicate imbalance.[27] Weighted incidence rates were calculated as the number of events per 100 person-years by applying each individual's corresponding weight to their incidence. Cox proportional hazard regression using IPTW was used to estimate the hazard ratio (HR) of the risk of AF-related cardiovascular events between the different PRS groups during the entire follow-up period. Multivariable Cox regression analyses were adjusted for age, sex, body mass index, smoking habit, alcohol consumption, economic status, CHF, hypertension, diabetes, dyslipidemia, vascular disease, chronic kidney disease, and end-stage renal disease. The proportional hazards assumption was assessed by examining the Schoenfeld residuals. Restricted cubic splines were used to estimate the potential nonlinearity of the associations between the PRS levels and outcomes. The reference value for the spline curve was the median value of the low PRS tertile. Three knots were placed at the reference value and the thresholds of the PRS tertile distribution. We used Bonferroni correction to adjust for multiple testing and considered 2-sided P values <0.0166 (P<0.05, divided by the number of tests, ie, 0.05/3) statistically significant. Statistical analyses were conducted using R software version 4.3.3 (R Foundation for Statistical Computing, www.R-project.org).

Sensitivity Analysis

We conducted sensitivity analyses in a subset of unrelated individuals using genetic kinship to account for potential biases from shared genetic backgrounds. In addition, we repeated the analyses after excluding individuals with a history of MI or CHF to further evaluate the impact of PRS on these outcomes. To evaluate the utility of PRS across various risk scores, we calculated the C2HEST,[28] HATCH,[29] and CHARGE-AF[30] scores at the time of AF diagnosis. We estimated the incidence rates of outcomes stratified by PRS tertiles and by C2HEST (0–1), HATCH (0–1), and CHARGE-AF (tertiles 1–2) within the study population.

RESULTS

Population Characteristics

Of the 27 101 patients newly diagnosed with AF during the follow-up period, 2832 (29.5%) with CHA_2DS_2-VA 0 and 6765 (70.5%) with CHA_2DS_2-VA 1 met the inclusion criteria (Figure 1). For the CHADS-VA 1 group, the subsets were as follows: 92 with CHF (1.4%), 889 with hypertension (13.1%), 107 with diabetes (1.6%), 99 with vascular disease (1.5%), and 5578 aged 65 to 74 years (82.5%). The mean±SD age of the cohort was 65.3±6.4 years. The baseline characteristics of the PRS groups are described in Table 1. Patients with AF who had a higher PRS were more likely to be younger and have a lower CHA_2DS_2-VA score but more hypertension as compared with those who had a lower PRS. After IPTW, all baseline characteristics showed standardized differences of <0.1.

Association of PRS With AF-Related Cardiovascular Events

During a median follow-up of 4.6 years (interquartile range, 1.7–7.9 years), 875 (9.1%) patients experienced AF-related cardiovascular events (406 ischemic stroke or systemic embolism, 208 MI, and 304 HF hospitalization). The weighted incidence rates of ischemic

Table 1. Baseline Characteristics at the Time of AF Diagnosis

AF PRS tertiles	Low (n=3199)	Intermediate (n=3199)	High (n=3199)	*P* value	Maximum pairwise standardized mean difference*	
					Before IPTW	After IPTW
Age at index date, y	65.6±6.5	65.6±6.4	64.8±6.4	<0.001	0.086	0.006
Women	1266 (39.6)	1250 (39.1)	1284 (40.1)	0.685	0.014	0.012
BMI				0.177	0.042	0.010
<25	966 (30.2%)	897 (28.0%)	932 (29.1%)			
25–29	1388 (43.4%)	1376 (43.0%)	1379 (43.1%)			
>30	845 (26.4%)	926 (28.9%)	888 (27.8%)			
Alcohol				0.556	0.027	0.024
None	223 (7.0%)	221 (6.9%)	193 (6.0%)			
1 or 2 times per wk	1390 (43.5%)	1399 (43.7%)	1396 (43.6%)			
≥3 times per wk	1586 (49.6%)	1579 (49.4%)	1610 (50.3%)			
Alcohol intake, g/d	19.01±24.2	18.63±22.5	18.91±22.9	0.790	0.011	0.009
Smoking				0.086	0.050	0.018
Nonsmoker	1540 (48.1%)	1527 (47.7%)	1590 (49.7%)			
Ex-smoker	1257 (39.3%)	1322 (41.3%)	1237 (38.7%)			
Current smoker	402 (12.6%)	350 (10.9%)	372 (11.6%)			
CHA_2DS_2-VA				<0.001	0.075	0.010
0	874 (27.3%)	919 (28.7%)	1039 (32.5%)			
1	2325 (72.7%)	2280 (71.3%)	2160 (67.5%)			
Heart failure	40 (1.3%)	29 (0.9%)	23 (0.7%)	0.087	0.036	0.014
Hypertension	277 (8.7%)	272 (8.5%)	340 (10.6%)	0.005	0.048	0.011
Age 65–74 y	1931 (60.4%)	1916 (59.9%)	1731 (54.1%)	<0.001	0.084	0.006
Diabetes	46 (1.4%)	27 (0.8%)	34 (1.1%)	0.073	0.037	0.013
Vascular disease	31 (1.0%)	36 (1.1%)	32 (1.0%)	0.807	0.010	0.012
Dyslipidemia	506 (15.8%)	505 (15.8%)	498 (15.6%)	0.956	0.005	0.007
ESRD or CKD	77 (2.4%)	51 (1.6%)	55 (1.7%)	0.038	0.039	0.015
Economic status				0.784	0.038	0.014
Quartile 1 (lowest)	399 (12.5%)	418 (13.1%)	399 (12.5%)			
Quartile 2	405 (12.7%)	406 (12.7%)	438 (13.7%)			
Quartile 3	456 (14.3%)	462 (14.4%)	472 (14.8%)			
Quartile 4	659 (20.6%)	616 (19.3%)	616 (19.3%)			
Quartile 5 (highest)	1280 (40.0%)	1297 (40.5%)	1274 (39.8%)			

Values are mean±SD or number (percentage). AF indicates atrial fibrillation; BMI, body mass index; CHA_2DS_2-VA, congestive heart failure; hypertension; age ≥75 years; diabetes; stroke, transient ischemic attack, thromboembolism; vascular disease; and age 65 to 74 years; CKD, chronic kidney disease; ESRD, end-stage renal disease; IPTW, inverse probability of treatment weighting; and PRS, polygenic risk score.

*Proposed cutoffs for acceptable standardized differences ranged from 0.1 to 0.25.

stroke or systemic embolism, MI, and HF hospitalization tended to increase as the PRS for AF increased (Figure 2). Compared with patients with a low PRS, patients with a high PRS had a 38% increase in risk of ischemic stroke or systemic embolism (hazard ratio [HR], 1.38 [95% CI, 1.08–1.76]; *P*=0.011) in the IPTW analysis (Table 2). The results remained essentially unchanged regardless of whether an IPTW or multivariable adjustment modeling approach was used for all outcomes. The cumulative incidence of AF-related cardiovascular events revealed increased rates of ischemic stroke or systemic embolism in the high PRS group compared with that in the low PRS group (Figure 3).

The adjusted HR per SD of the AF PRS was 1.11 (95% CI, 1.01–1.22; *P*=0.036) for ischemic stroke or systemic embolism, 0.99 (95% CI, 0.86–1.14; *P*=0.904) for MI, and 1.03 (95% CI, 0.92–1.15; *P*=0.617) for HF hospitalization (Table S3). In restricted cubic spline models, the risks of ischemic stroke or systemic embolism increased steadily with increasing AF PRS. However, the PRS score did not significantly increase the risk of MI and HF hospitalization (Figure 4).

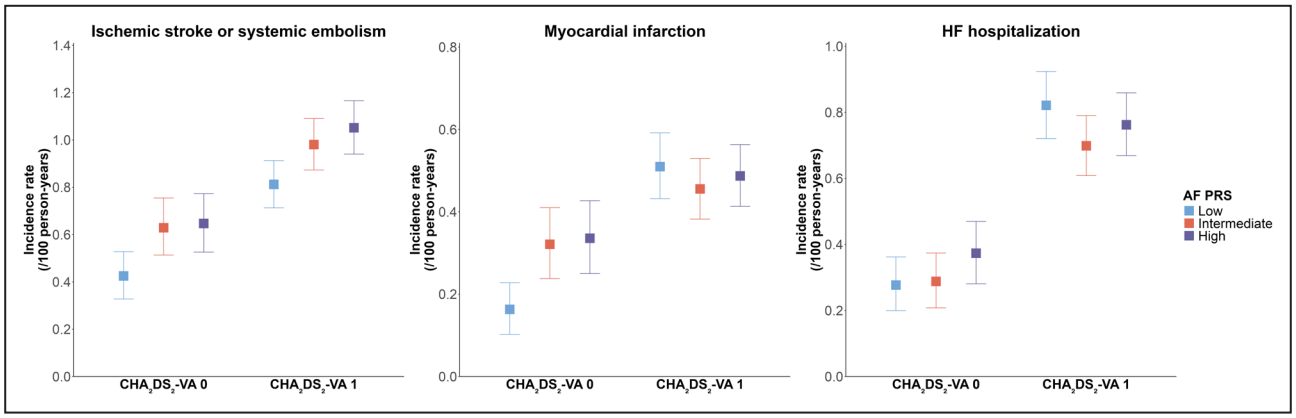

Figure 2. Weighted incidence rate of ischemic stroke or systemic embolism, myocardial infarction, and HF hospitalization, stratified by clinical risk factors and AF PRS.
AF indicates atrial fibrillation; CHA_2DS_2-VA, congestive heart failure; hypertension; age ≥75 years; diabetes; stroke, transient ischemic attack, thromboembolism; vascular disease; and age 65 to 74 years; HF, heart failure; and PRS, polygenic risk score.

Sensitivity Analysis

Sensitivity analyses in a subset of unrelated individuals showed largely consistent results (Table S4). The results remained qualitatively unchanged in the subgroups excluding 171 patients with a history of MI or CHF (Table S5). The incidence rates of ischemic stroke or systemic embolism, MI, and HF hospitalization, stratified by AF PRS and the C2HEST, HATCH, and CHARGE-AF scores, are illustrated in Figure S1. Notably, the incidence of ischemic stroke or systemic embolism tended to rise with higher PRS across various risk scores.

DISCUSSION

In this observational analysis of patients with AF, there was an incremental association between the PRS and ischemic stroke or systemic embolism, while the risks of MI and HF hospitalizations were not statistically significant. These findings suggest that genetic susceptibility to AF, as quantified by the PRS, may be an important prognostic factor for stroke and thromboembolism in patients with incident AF.

Genetic Risk of AF

AF and its burden are strongly associated with an increased risk of ischemic stroke and thromboembolic events.[31,32] Genetic factors could play a significant role in predicting prognosis in patients with AF. A previous study reported that rare variants in cardiomyopathy and arrhythmia genes may be associated with increased risk of mortality among patients with AF.[33] A PRS for predicting ischemic stroke in patients with

Table 2. Incidence Rates and HRs for Ischemic Stroke or Systemic Embolism, MI, and HF Hospitalization, Stratified by AF PRS

	Case	Incidence rate (per 100 PY)	HR (95% CI)			
			Adjusted	*P* value	Weighted	*P* value
Ischemic stroke or systemic embolism						
Low PRS	112	0.70	1		1	
Intermediate PRS	140	0.86	1.25 (0.98–1.60)	0.077	1.27 (0.99–1.63)	0.060
High PRS	154	0.91	1.39 (1.09–1.77)	0.009*	1.38 (1.08–1.76)	0.011*
Myocardial infarction						
Low PRS	64	0.40	1		1	
Intermediate PRS	68	0.41	1.04 (0.74–1.47)	0.824	1.05 (0.75–1.49)	0.774
High PRS	76	0.44	1.18 (0.85–1.65)	0.329	1.15 (0.82–1.61)	0.422
Heart failure hospitalization						
Low PRS	103	0.65	1		1	
Intermediate PRS	94	0.57	0.89 (0.67–1.18)	0.413	0.88 (0.67–1.17)	0.372
High PRS	107	0.62	1.03 (0.78–1.35)	0.832	1.02 (0.78–1.34)	0.895

AF indicates atrial fibrillation; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; PRS, polygenic risk score; and PY, person-years.
*Statistically significant after applying Bonferroni correction.

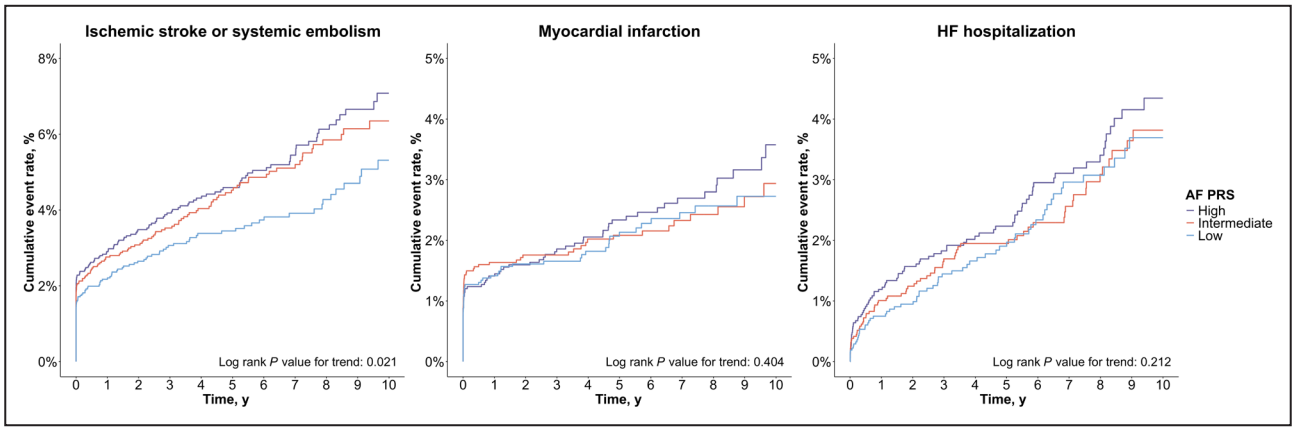

Figure 3. Weighted cumulative incidence of ischemic stroke or systemic embolism, myocardial infarction, and HF hospitalization, stratified by AF PRS. AF indicates atrial fibrillation; HF, heart failure; and PRS, polygenic risk score.

AF significantly improved risk prediction over the clinical risk scores.[34] The genetic risk of AF was higher specifically in individuals with cardioembolic stroke but not in those with other types of stroke.[18,35] Recent genome-wide association studies have demonstrated that several loci are associated with both AF and ischemic stroke.[36,37] Experimental studies using a mouse knockout model have revealed the impact of zinc finger homeobox 3 (Zfhx3) loss as the causative gene at the 16q22 locus for AF and ischemic stroke.[38] Consistently, this study demonstrated that a high PRS was associated with ischemic stroke or systemic embolism among patients with AF who have low to intermediate clinical stroke risk.

Meta-analyses have demonstrated that AF is associated with an increased risk of MI and HF.[39–41] The development of MI and HF in patients with AF is attributed not only to the effects of the AF rhythm itself but also to shared risk factors for cardiovascular events. Atrial structural remodeling after AF is a risk factor for adverse outcomes. Left atrial fibrosis, quantified by late gadolinium enhancement in cardiac magnetic resonance imaging, was associated with an increased risk of cardiovascular events among patients with AF, although its association with each specific component, such as MI, HF, and cardiovascular death, was not pronounced.[42] The subanalysis of the CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients With Left Ventricular Dysfunction and Atrial Fibrillation) trial suggested that the AF burden at baseline was not predictive of HF hospitalization, but lowering AF burden after catheter ablation was associated with a significant decrease in HF hospitalization.[43] A recent study reported that younger age at AF diagnosis is associated with a higher risk of subsequent cardiovascular diseases, potentially influenced by genetic predisposition or shared cardiovascular risk factors.[44] In our study, patients with AF who had a high PRS were generally younger and had fewer comorbidities. Genetic susceptibility to AF

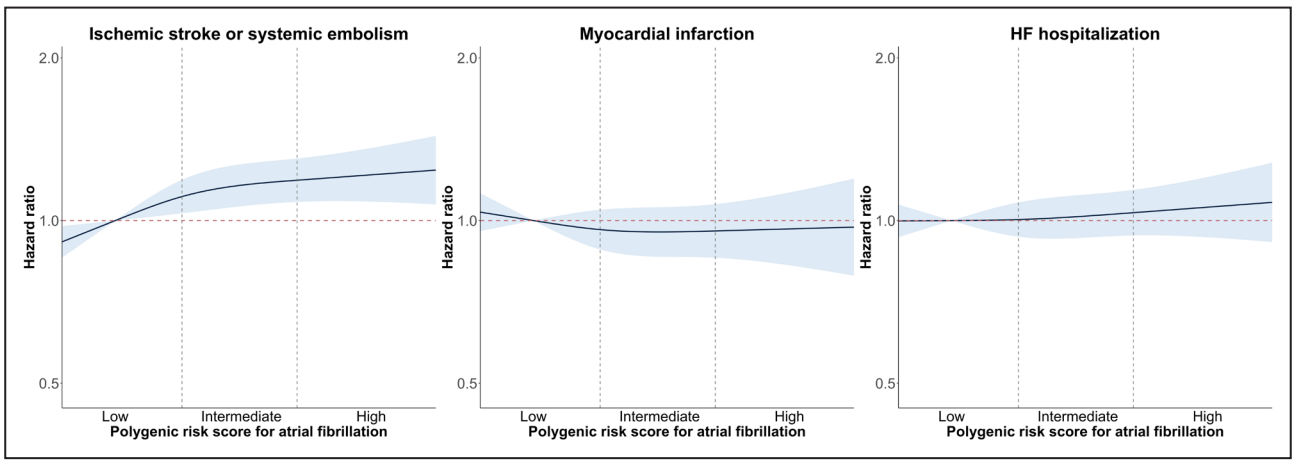

Figure 4. Nonlinear dose–response analysis of atrial fibrillation polygenic risk score and the risk of ischemic stroke or systemic embolism, myocardial infarction, and HF hospitalization. HF indicates heart failure.

was significantly associated with an increased risk of ischemic stroke or systemic embolism but not with the risk of MI or HF hospitalization.

Clinical Implication

Previous studies have demonstrated a causal relationship between certain genes and the development of AF.[45–47] The integration of AF PRS into clinical risk tools substantially improves the predictive accuracy.[48] Several studies have found an association between AF PRS and cardiovascular disease. A Mendelian randomization study demonstrated the causal effect of genetically predicted AF on dementia mediated by ischemic stroke.[49] AF PRS was associated with incident HF and demonstrated improved 10-year risk prediction for HF compared with an established HF risk equation.[50] In addition, the PRS may have potential clinical utility in estimating therapeutic value. Prior research has shown that individuals with a high coronary artery disease PRS derive greater benefit from statin therapy.[51,52] Similarly, several studies have suggested that stratifying risk by diabetes PRS may help identify subgroups that benefit more from lifestyle modifications or sulfonylurea therapy.[53,54] Future research is warranted to determine whether integrating genetic information with clinical risk could guide anticoagulation decision-making in patients with AF who have low to intermediate stroke risk.

Strengths

To the best of our knowledge, this is the first cohort study to compare the incidence of AF-related cardiovascular events in patients with AF, stratified by PRS. Our study established an association between the PRS and cardiovascular events in patients with AF. Our findings imply that the AF PRS is useful not only for predicting the occurrence of AF but also for determining prognosis. Because AF and cardiovascular events share common risk factors that might confound or mediate the relationship between AF PRS and AF-related cardiovascular events, we excluded patients with a CHA_2DS_2-VA score ≥2. Although individuals with a high PRS tended to be younger and have a low CHA_2DS_2-VA score, the association between AF PRS and ischemic stroke or systemic embolism was statistically significant. These results remained significant even after balancing with IPTW.

Limitations

Participants in the UK Biobank do not fully reflect the demographics of the general British population. Attributable to healthy volunteer selection bias, individuals exhibited different sociodemographic, lifestyle, and health-related characteristics.[20] Genetic associations with prognosis or subsequent events are susceptible to index event bias, arising from selecting participants based on their disease status.[55] These biases could lead to an underestimation of the association between exposure and outcomes or even generate paradoxical results. To address this bias, IPTW was utilized for adjustment.[56] The PRS was primarily derived from genome-wide association studies data for individuals of European ancestry, which may limit its applicability to other racial and ethnic populations. Integrating PRS derived from additional genome-wide association study data sets of individuals with diverse ancestries is needed to enhance the generalizability of PRS in future research. In addition, as the outcome definition was based on *ICD-10* codes, it was limited to assessing the associations between PRS and AF patterns or burden, which could be a significant confounding factor. Finally, because the study outcomes were components of the CHA_2DS_2-VA score, the trajectory of the CHA_2DS_2-VA score during the follow-up period was not considered.

CONCLUSIONS

In this observational analysis of patients with AF, a polygenic predisposition to AF was associated with an increased risk of ischemic stroke or systemic embolism. Notably, the AF PRS was not independently associated with MI and HF hospitalization. This study contributes to the growing body of evidence highlighting the prognostic value of genetic risk as an important risk factor for stroke and thromboembolism in patients with incident AF. Further prospective studies are needed to determine the nature of cardiac remodeling based on the AF PRS and to assess whether anticoagulation could lower the risk in these patients.

ARTICLE INFORMATION

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Disclosures

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Data Sharing Statement

All researchers in academic, commercial, and charitable settings can apply to use the UK Biobank resource for health-related research in the public interest (www.ukbiobank.ac.uk/registerapply/).

Ethics Approval and Consent to Participate

UK Biobank received ethical approval from the Northwest Multicenter's research ethics committee. UK Biobank data are available to researchers after acceptance of the research proposal to the UK Biobank. Written informed consent was obtained from all participants during recruitment. This study was approved by the institutional review board of Yonsei University Health System (4-2024-0172).

Supplemental Material

Data S1

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