THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Causal Effect of Atrial Fibrillation on Heart Failure Risk in East Asian Ancestry: A Bidirectional Mendelian Randomization Study Using Genome-wide Association Data

ABSTRACT

Background: Atrial fibrillation (AF) and heart failure (HF) are prevalent cardiovascular conditions in East Asia, with a complex interrelationship. The directionality of the causal impact of AF on HF risk remains uncertain. This study employs Mendelian randomization (MR) to investigate the potential causal effect of AF on HF.

Methods: Utilizing summary data from genome-wide association studies (GWAS) within the Medical Research Council Integrative Epidemiology Unit open GWAS database, we analyzed 8180 AF cases and 28 612 controls, alongside 9413 HF cases and 203 040 controls, all of East Asian descent. We conducted MR analysis using the inverse variance weighted (IVW) method, complemented by various sensitivity analyses, including bidirectional MR to assess causality in the reverse direction.

Results: Genetically predicted AF was found to be causally associated with an increased risk of HF in East Asian populations (odds ratio = 1.14, 95% CI: 1.10-1.19, $P < .001$) as per the IVW method. These findings were consistent across multiple MR methods. Sensitivity analyses revealed no significant heterogeneity or pleiotropy. Notably, bidirectional MR analysis showed no causal effect of HF on the risk of developing AF.

Conclusions: The MR analysis supports a unidirectional causal relationship between AF and increased HF risk in East Asian individuals. The absence of a reverse causal effect reinforces the importance of maintaining sinus rhythm to mitigate HF risk. Further research is warranted to corroborate these findings and to explore their clinical implications in depth.

Keywords: Mendelian randomization, atrial fibrillation, heart failure, causal inference

ORIGINAL INVESTIGATION

INTRODUCTION

Heart failure (HF) and atrial fibrillation (AF) are major cardiovascular diseases that pose a global challenge. Heart failure and AF often co-occur in the same patients, with more than a third of AF patients also having HF,[1] and vice versa, up to half of HF patients also having AF. The coexistence of these 2 conditions can worsen each other's prognosis.[2] However, the causal relationship between AF and HF is still unclear in many cases. Although some observational studies have shown an association between AF and HF.[3-5] these findings are prone to confounding and reverse causation.

Recent evidence has highlighted the survival benefits of maintaining sinus rhythm through interventions such as catheter ablation in patients with HF, suggesting a potential therapeutic advantage over medical therapy.[6] This underscores the importance of rhythm control, particularly in the context of HF, where the interplay between AF and HF can be particularly detrimental. Furthermore, the necessity for repeat procedures to maintain sinus rhythm in patients with HF has been recognized, indicating a dynamic approach to the management of these conditions.[6] In addition to pulmonary vein (PV) isolation, the role of extrapulmonary triggers—such as those originating from the left atrial posterior wall, left atrial appendage, ligament of Marshall, coronary sinus, superior vena cava, and

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Received: February 21, 2024
Accepted: April 30, 2024
Available Online Date: June 13, 2024

Cite this article as: Mei Y, Ye F, Yin X, Wu X. Causal effect of atrial fibrillation on heart failure risk in East Asian ancestry: A bidirectional mendelian randomization study using genome-wide association data. *Anatol J Cardiol.* 2024;28(8):399-405.

DOI:10.14744/AnatolJCardiol.2024.4369

Table 1. Description of Contributing Studies

Contribution	Traits	Case	Control	Sample Size	Number of SNPs	Population
Exposure	Atrial fibrillation	8180	28 612	36 792	5 018 048	East Asian
Outcome	Heart failure	9413	203 040	212 453	8 885 805	East Asian

crista terminalis—has become increasingly evident. These non-PV triggers are significant contributors to AF recurrence, especially in patients with persistent AF, and their management is crucial for the long-term maintenance of sinus rhythm.[7]

Mendelian randomization (MR) is a method that can help overcome these limitations.[8,9] In this case, MR uses genetic variants related to the exposure as instrumental variables (IVs), similar to randomized controlled trials, which randomly assign alleles at conception according to Mendel's second law.[10] This way, confounding factors are randomly distributed across the population. After identifying the common variants in the outcome data, the basic principles of MR can be used to evaluate the effect of the suspected exposure factors on disease risk. Thanks to the rapid increase in genome-wide association studies (GWASs) in the past decade, other studies have used MR to establish causal relationships between blood pressure and AF,[11] body mass index (BMI) and AF,[12] and AF and HF in European ancestry.[13] However, evidence for a causal relationship between AF and HF in East Asian ancestry remains scarce.

In this study, we conducted a bidirectional 2-sample MR (TSMR) analysis for the first time to assess causal associations between AF and HF in East Asian ancestry.

METHODS

Data Source

Our analysis relied on GWAS summary data that is curated and centralized by the Medical Research Council Integrative Epidemiology Unit open GWAS database (https://gwas.mrcieu.ac.uk), These data are available through the R package "TwoSampleMR."[14,15] A total of 8180 cases and 28 612 controls for AF from the GWAS for East Asian descents were used in this study (https://gwas.mrcieu.ac.uk/datasets/bbj-a-71/).[16] The outcome variable summary-level association results for the final sets of AF-related SNPs were extracted from the largest meta-analysis of GWASs for HF, which tested associations between 8 885 805 genetic variants and HF in a total of 9413 cases and 203 040 controls of East Asian descents(https://gwas.mrcieu.ac.uk/datasets/bbj-a-109/) (Table 1).

To ensure the robustness of our MR analysis, we verified the independence of the 2 samples. The AF-related SNP data were derived from individuals without HF, and conversely, the HF-related SNP data were sourced from individuals without documented AF. This independence is critical to the validity of our MR findings, as it prevents potential bias that could arise from overlapping samples.

Genetic Instrumental Variable Selection

To estimate the causal effect of AF on the risk of HF, we selected genetic variants as IVs in line with the following assumptions: (1) they have a predictive effect for AF, (2) they are independent of confounders, and (3) they do not affect the outcome through any other pathways than through AF.[12] Single nucleotide polymorphisms (SNPs) that reached genome-wide significance ($P < 5 \times 10^{-8}$) were chosen as IVs. To ensure the independence of genetic variants, these SNPs then underwent linkage disequilibrium pruning (distance threshold = 10 000 kb, $r^2 < 0.001$). We subsequently excluded the SNPs associated with potential confounders of the outcome. In our study, coronary artery disease, hypertension, valvular heart disease (VHD), BMI, chronic obstructive pulmonary disease (COPD), alcohol and tobacco consumption were identified as confounders for HF (as identified at http://www.phenoscanner.medschl.cam.ac.uk/) (Supplementary Table 1). The strength of the relationship between the SNP and AF was assessed with an F-statistic calculated as $F = R^2 (n - K - 1)/(1 - R^2) \times K$. This calculation factors in exposure variance (R^2), sample size (n), and the number of SNPs (K). An F-statistic > 10 indicates a significant association between the selected IVs and AF.[17]

Mendelian Randomization Analysis

We used the inverse variance weighting (IVW) method as the main analysis to assess the causal relationship between AF and HF in our TSMR study. The IVW method calculates the exposure effect of each SNP using the Wald ratio method and then performs a weighted linear regression with a forced 0 intercept. When the IV meets 3 basic assumptions, it achieves higher accuracy and power in estimation.[18]

To account for the possible confounding by unknown and unmeasurable factors, we performed the robust adjusted profile score (MR-RAPS), the MR-Egger regression (MR-Egger), the weighted mode, and the weighted median

HIGHLIGHTS

- Novel causal insight: This study provides a novel insight into the causal relationship between atrial fibrillation (AF) and heart failure (HF) risk within the East Asian population, employing Mendelian randomization (MR) analysis.
- Robust methodological approach: Through meticulous selection of genetic instrumental variables and rigorous Mendelian randomization analysis, this study establishes a robust causal association between AF and increased HF risk, offering compelling evidence for the East Asian ancestry.
- Validation of findings: Sensitivity analyses confirm the consistency and reliability of the observed causal relationship, reinforcing the significance of maintaining sinus rhythm in reducing HF risk among individuals predisposed to AF.

estimation to test the robustness of our results. Mendelian randomization-RAPS is an extension of IVW that allows for very weak instruments.[19] The weighted median assumes that at least 50% of the instruments are valid.[20] For the mode-based estimations, simple mode and weighted mode provide a consistent result when there is no pleiotropy among all instruments.[21] Mendelian randomization-Egger method provides estimates that are corrected for pleiotropic effects, but with lower statistical power.[22]

In addition to these analyses, we also conducted a bidirectional MR study. This reverse MR analysis was performed to investigate the potential causal effect of HF on the risk of developing AF.

Sensitivity Analysis

We conducted several sensitivity analyses to further explore the potential heterogeneity and pleiotropy between exposure and outcome. We evaluated the IV using the Cochran's *Q* test, with $P_h < .05$ indicating heterogeneity.[23] As a measure of horizontal pleiotropy, we used the Egger intercept in the MR Egger regression analysis.[22] We performed multi-instrument summary-level MR tests using MR pleiotropy residual sum and outlier test (MR-PRESSO) to detect horizontal pleiotropic outliers.[24] We also performed IVW radial variants and MR-Egger radial variants, which are similar to conventional IVW and MR-Egger regressions, to improve the visualization of the IVW and MR-Egger estimates.[25] Our sensitivity analysis included leave-one-out analysis, accompanied by IVW, to determine the combined effect of the remaining SNPs. The MR analysis is not overly influenced by any single SNP if the combined effect is consistent with the main effect result.

We performed all analyses with R software (version 4.2.1) using R packages ("Two Sample MR," "MR-PRESSO," and "Radial MR"). Statistical significance was defined as a 2-sided *P*-value of less than .05.

Power Calculations

We used the publicly available mRnd web tool, we evaluated the power of our study using a non-centrality parameter approach (http://cnsgenomics.com/shiny/mRnd/).[24] For the binary outcome (HF), we roughly estimated the minimum detectable OR after entering the desired parameters in mRnd (in this study, $\alpha = 0.05$; $R^2 = 0.36$).

RESULTS

Instrumental Variables Validity

We used 17 SNPs as IVs for estimating the causal effect of AF on HF. These SNPs explained 35.6% (R^2) of the variation in AF. In our MR analysis, all the SNPs had high F-statistics ranging from 266.43 to 6110.92, indicating that they were not weak instruments. Table 2 shows the effect estimates of each SNP on both AF and HF. Based on power calculations, our study had 100% power to detect ORs between 1.10 and 1.19 for the association between AF and HF.

Mendelian Randomization Analysis

The results of the 2-sample MR analyses are presented in Table 2. Using the random-effect IVW models, we found that AF was associated with a significant increase in the risk of HF (OR = 1.14, 95% CI: 1.10-1.19, $P < .001$). This association was consistent across the MR-RAPS, MR-Egger, weighted mode, and weighted-median analysis (Table 3, Figure 1).

Additionally, to assess the potential reverse causality, a bidirectional MR analysis was conducted. The results, presented in Supplementary Table 2, did not reveal any significant causal effect of HF on the risk of developing AF, suggesting the observed relationship is unidirectional from AF to HF.

Table 2. Characteristics of Single Nucleotide Polymorphismss Associated with Atrial Fibrillation

		Atria Fibrillation						Heart Failure			
SNP	**EA/OA**	**Beta**	**EAF**	**SE**	***P***	***R*-Squared**	***F*-Statistic**	**Beta**	**EAF**	**SE**	***P***
rs10024737	C/T	0.27	0.07	0.04	2.18E-11	0.01	377.81	0	0.08	0.03	.84
rs1049334	A/G	−0.19	0.29	0.02	1.83E-14	0.01	521.97	−0.03	0.29	0.02	.08
rs10920555	A/G	−0.2	0.2	0.03	2.29E-13	0.01	482.25	−0.01	0.2	0.02	.76
rs12044963	T/G	0.15	0.5	0.02	1.13E-11	0.01	396.33	0.03	0.5	0.02	.04
rs12415501	T/C	0.36	0.09	0.04	2.92E-24	0.02	774.36	0.01	0.08	0.03	.68
rs12597202	C/T	−0.18	0.21	0.03	6.96E-11	0.01	417.56	−0.01	0.22	0.02	.54
rs12777530	T/C	0.16	0.21	0.03	5.03E-10	0	318.48	0.02	0.2	0.02	.22
rs1675334	C/G	−0.13	0.71	0.03	2.27E-08	0	266.43	0.01	0.71	0.02	.49
rs2359171	A/T	0.29	0.31	0.02	1.26E-36	0.03	1347.95	0.06	0.3	0.02	0
rs2384407	A/G	0.17	0.42	0.02	4.90E-15	0.01	524.95	0.02	0.42	0.02	.16
rs2540953	A/G	-0.16	0.35	0.02	7.45E-12	0.01	428	−0.02	0.35	0.02	.33
rs4115272	A/G	−0.23	0.36	0.02	4.47E-25	0.03	957.44	−0.04	0.36	0.02	.03
rs639652	A/G	−0.13	0.46	0.02	4.43E-09	0	292.47	−0.02	0.46	0.02	.14
rs6928224	T/C	−0.14	0.31	0.02	2.84E-08	0	288.89	0.02	0.32	0.02	.17
rs72798854	A/G	0.13	0.34	0.02	6.70E-09	0	286.93	0.04	0.35	0.02	.01
rs7434417	G/A	0.54	0.45	0.02	9.66E-135	0.14	6110.92	0.08	0.45	0.02	0
rs7698692	A/G	0.13	0.51	0.02	4.24E-10	0	333.25	0	0.51	0.02	.69

EA, effect allele; EAF, effect allele frequency; OA, other allele; SE, standard error; SNP indicates single nucleotide polymorphism.

Table 3. Mendelian Randomization Estimates from Each Method of Assessing the Causal Effect of Atrial Fibrillation on the Risk of Heart Failure

MR Method	No. of SNPs	Beta	SE	*P*	OR (95% CI)	Cochran's *Q P* (I^2)	MR-Egger Intercept (*P*)	Outliers from MRPRESSO
Inverse variance weighted	17	0.13	0.02	3.40E-11	1.14 (1.10-1.19)	0.27 (17.7%)	−0.01 (0.28)	NA
Robust adjusted profile score	17	0.14	0.02	4.42E-12	1.15 (1.10-1.20)			
MR Egger	17	0.17	0.04	0.000847	1.19 (1.11-1.23)	0.27 (95.2%)		
Weighted mode	17	0.16	0.03	3.01E-05	1.17 (1.11-1.23)			
Weighted median	17	0.15	0.03	2.48E-09	1.17 (1.11-1.23)			

CI, confidence interval; MR, Mendelian randomization; OR, odds ratio; SE, standard error; SNP, single-nucleotide polymorphism.

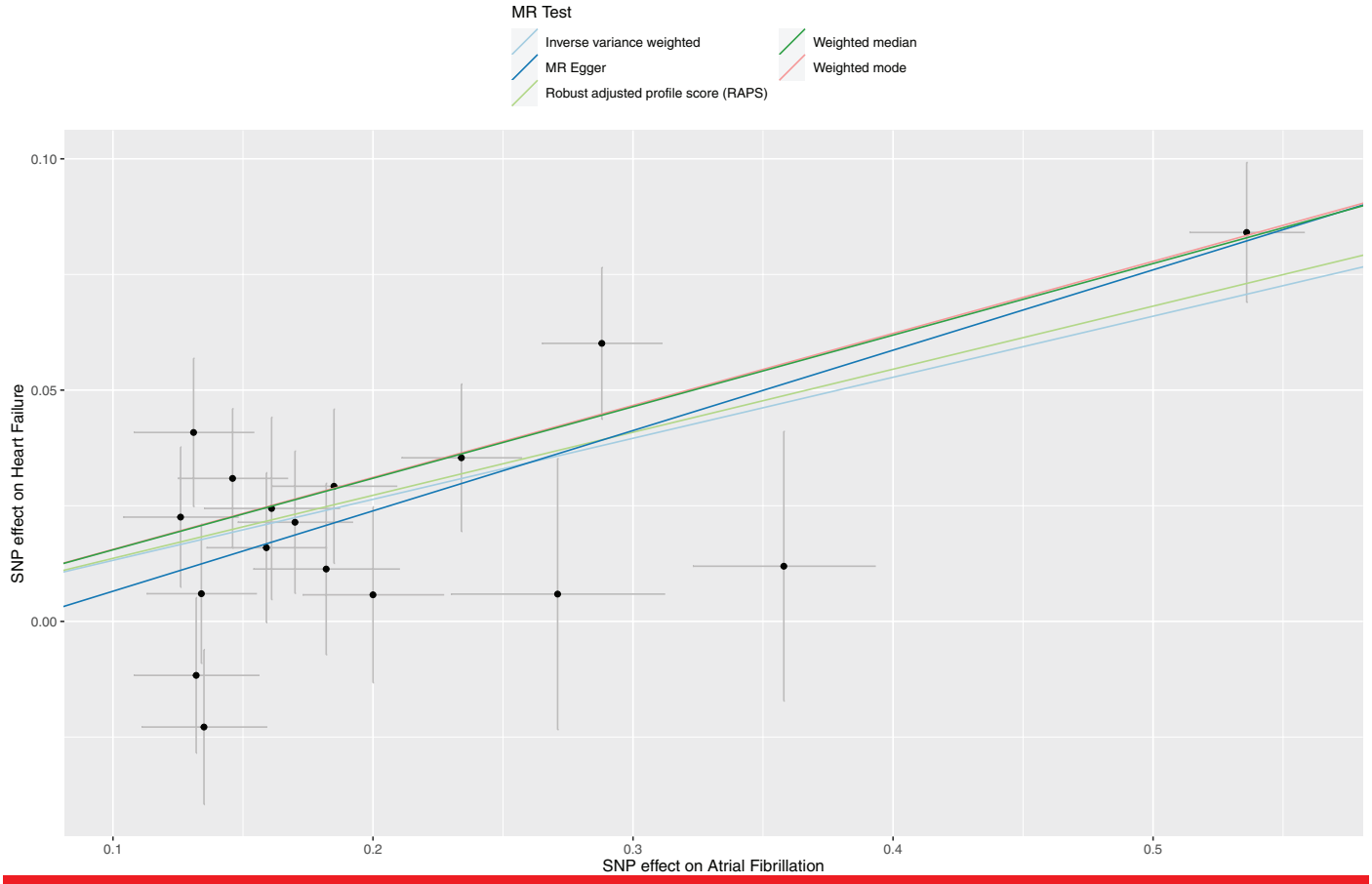

Figure 1. Scatter plot of SNPs associated with AF and the risk of HF. The plot related the effect sizes of the SNP-AF association (*x*-axis,) and the SNP–HF associations (*y*-axis) with 95% confidence intervals. The regression slopes of the lines correspond to causal estimates using 5 Mendelian randomization methods [the inverse variance weighted method, robust adjusted profile score (MR-RAPS), the MR-Egger regression (MR-Egger), the weighted mode and the weighted median estimation (WME)]. AF, atrial fibrillation; HF, heart failure; MR, Mendelian randomization; SNP, single-nucleotide polymorphism.

This finding further strengthens the evidence for a causal role of AF in the development of HF within the East Asian population studied.

Validation of Sensitivity Analysis

We performed several sensitivity analyses to assess the potential heterogeneity and pleiotropy between exposure and outcome. Neither the Cochran's Q-test nor the MR-Egger regression analysis detected any heterogeneity or horizontal pleiotropy ($P_h = .27$, $P_{intercept} = .28$) (Table 3). Moreover, the MR-PRESSO results and the radial plot did not identify any outlier SNPs (Figure 2). The leave-one-out analysis showed that the overall effect of AF on HF was not influenced by any single SNP (Figure 3).

DISCUSSION

Epidemiological studies have identified several cardiovascular risk factors that are strongly associated with the development of HF. One of the most common and potent risk factors for HF is AF. However, the association between AF and HF may be confounded by several factors, such as aging, CVD, hypertension, VHD, BMI, and COPD, which are prevalent in

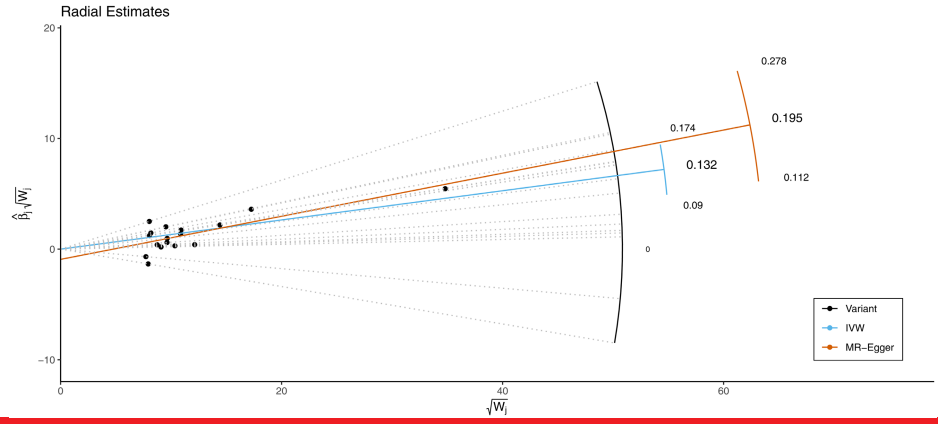

Figure 2. Radial plots to visualize individual outlier single nucleotide polymorphisms (SNPs) in the Mendelian randomization estimates for association between atrial fibrillation with heart failure. Black dots show valid SNPs and purple dots display invalid outlier SNPs. There is no significant outlier SNP in present plots. IVW, inverse variance weighted.

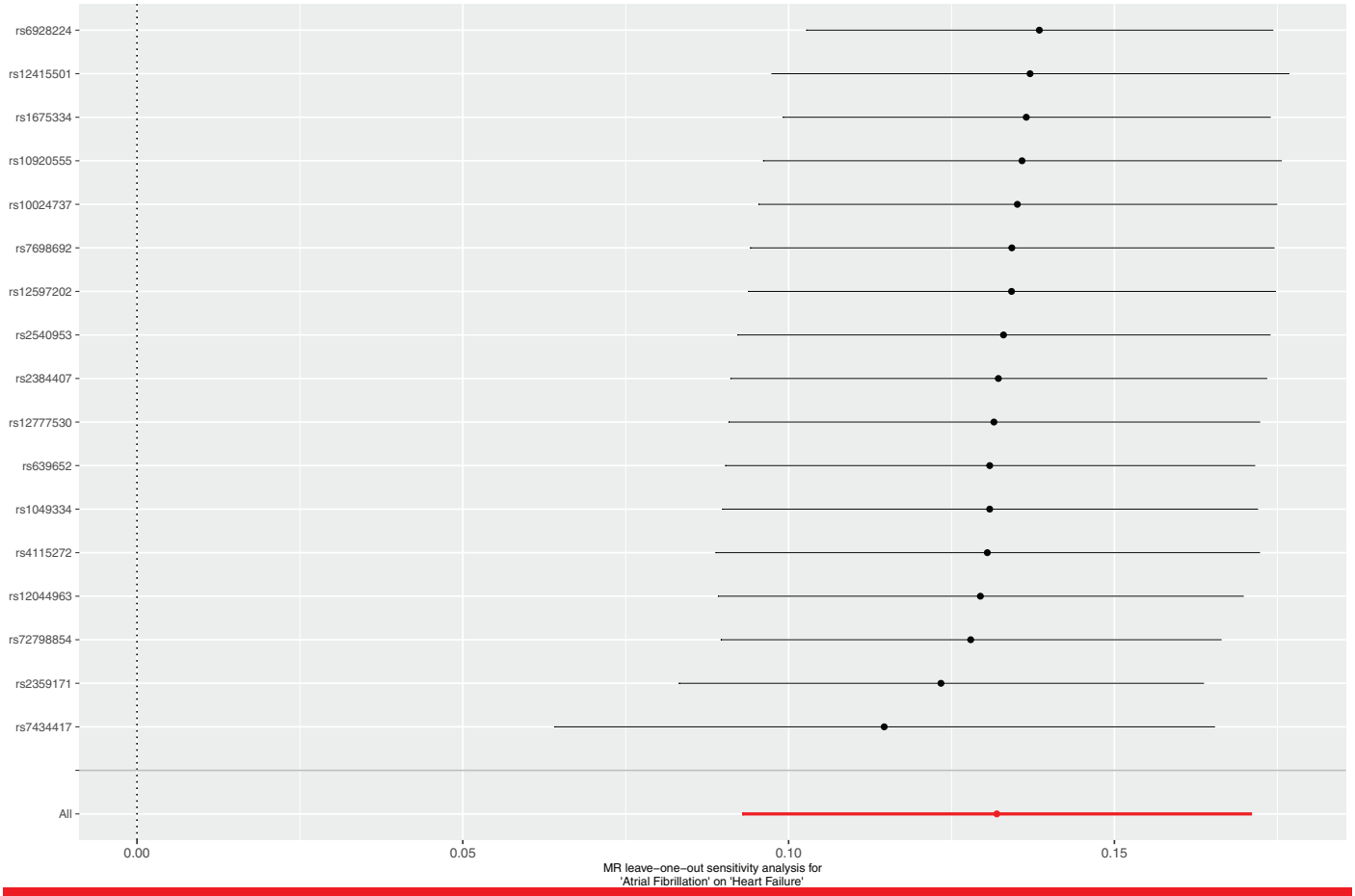

Figure 3. Leave-one-out analysis of Mendelian randomization (MR) estimates of genetic risk of atrial fibrillation on heart failure. Black boxes corresponding to each of the single nucleotide polymorphisms (SNPs) denote odds ratios derived from inverse variance weighted (IVW) after leaving the corresponding SNP in turns. The red box corresponding to "ALL" indicates the pooled IVW MR estimate. Horizontal lines denote a 95% confidence interval.

both conditions. Using MR, we demonstrated for the first time a causal relationship between AF and HF in East Asian populations. Our sensitivity analysis showed that the causal effect was not significantly affected by other established risk factors for both conditions, such as CVD, hypertension, and VHD. According to the last randomized trial EAST-AFNET4 and CABANA sub-analysis early rhythm control performed with catheter ablation of AF improves survival and prevents HF.[26] Our results are in line with other MR studies and support the hypothesis that HF can be prevented by controlling AF.

Previous studies have shown that AF can lead to left-ventricular systolic dysfunction and increase the mortality and morbidity of HF.[5] Therefore, our findings imply that public health interventions are needed to emphasize the importance of adequate AF management in reducing the global burden of HF and its severe complications.

The mechanisms underlying the pathogenesis of HF in AF patients may involve several pathways. Atrial fibrillation is associated with adverse hemodynamic changes, such as loss of atrial systole, ventricular rate irregularity, and chronotropic incompetence. Under normal sinus rhythm, atrial contraction contributes 20%-25% of the total left ventricular stroke volume.[27] The loss of atrial contractility can precipitate HF, especially in cases where the ventricular filling is compromised, such as in CVD or hypertension. Atrial fibrillation also causes a decrease in cardiac output, which is accompanied by an increase in neurohumoral vasoconstrictors. The activation of neurohumoral systems is a hallmark of HF and is associated with left ventricular dysfunction.[28] Tachycardia-mediated cardiomyopathy is a common consequence of AF.[29,30] Increased heart rates are associated with abnormal calcium signaling between the surface membranes of cardiomyocytes and the sarcoplasmic reticulum, as well as reduced sarcoplasmic calcium levels. This results in decreased myocardial contractility and dilatation. The effect of AF on atrial function has also been extensively studied. Chronic AF causes intracellular oxidative stress, which leads to calcium overload and the initiation of the inflammatory cascade. This causes both the persistence of the arrhythmia and the remodeling of the atrium, resulting in fibrosis. This chronic condition is known as "atrial cardiomyopathy" in the medical literature.[31] Patients with highly symptomatic AF have been shown to have diffuse left ventricular (LV) fibrosis.[32] There was a positive correlation between the degree of ventricular fibrosis and AF burden, independent of age or systolic dysfunction. Even patients with lone AF had diffuse LV fibrosis compared to healthy controls. Based on our findings, we suggest that physicians can take several measures in clinical practice to improve patient outcomes. Specifically, physicians should be aware that patients with AF have an increased risk of developing HF and should monitor them closely for signs and symptoms of HF. Moreover, physicians can work to identify and treat the underlying causes of AF, such as hypertension, diabetes, and obesity. Treating these underlying conditions may help to prevent or delay the onset or progression of HF in patients with AF. Furthermore, physicians can consider early intervention strategies for patients with AF, such as anticoagulation therapy and rhythm control, which may help to reduce the risk of HF and other adverse outcomes. Overall, our findings suggest that physicians should take a proactive approach to managing patients with AF in order to reduce the risk of HF and improve patient outcomes. Further studies are needed to confirm these findings and explore the clinical implications in more detail.

Our study has several notable strengths. First, we conducted a comprehensive analysis of incident HF and robust GWAS using a very large sample size to obtain genetic instruments for MR analysis. Moreover, our MR method yielded more reliable effect estimates than conventional observational studies by minimizing the confounding and reverse causation. Last, a rigorous process was applied to select and validate the IVs, reducing the bias caused by inappropriate IVs.

However, our study also has some limitations. First, due to the scarcity of data resources, we could not perform stratified analyses or adjust for covariates. Second, since MR assumes a linear relationship between exposure and outcome, the nonlinear association between AF and HF risk could not be evaluated. Third, the dissemination of our findings to other populations was hampered by the East Asian ancestry of the samples.

CONCLUSION

Our TSMR analysis substantiates a genetic causal relationship between AF and HF risk among East Asian populations. The findings reinforce the clinical relevance of sinus rhythm preservation in individuals predisposed to HF. Additionally, our bidirectional MR analysis did not demonstrate a causal effect of HF on AF, suggesting a unidirectional causality from AF to HF. These insights necessitate further research to validate and elucidate the clinical ramifications of our study comprehensively.

Data Availability: This study used publicly available GWAS summary data that can be accessed from https://gwas.mrcieu.ac.uk/.

Ethics Committee Approval: No ethics approval was required as this study used public summary data.

Informed Consent: The data for this study is sourced from public datasets, and the patients' written informed consent forms have already been signed in the original research.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception – X.W.; Data Curation – X.W., Y.M.; Analysis – X.W., Y.M.; Investigation – F.Y., X.Y.; Methodology – X.W., F. Y.; Supervision – X.W.; Original Draft – X.W., Y.M.; Review and Editing – X.W.

Acknowledgments: The authors are grateful to all the researchers who shared their GWAS data publicly.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: This work was funded by the Project of Zhejiang Provincial Scientific Research Foundation of Traditional Chinese Medicine (2021ZA147).

REFERENCES

1. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation*. 2016;133(5):484-492. [CrossRef]
2. Sossalla S, Vollmann D. Arrhythmia-induced cardiomyopathy. *Dtsch Ärztebl Int*. 2018;115(19):335-341. [CrossRef]
3. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation*. 2003;107(23):2920-2925. [CrossRef]

4. Pabel S, Sossalla S. Atrial fibrillation and heart failure: novel insights into the chicken and egg dilemma. *Eur Heart J*. 2022;43(36):3376-3378. [CrossRef]
5. Willems S, Meyer C, de Bono J, et al. Cabins, castles, and constant hearts: rhythm control therapy in patients with atrial fibrillation. *Eur Heart J*. 2019;40(46):3793-3799c. [CrossRef]
6. Şaylık F, Çınar T, Akbulut T, Hayıroğlu Mİ. Comparison of catheter ablation and medical therapy for atrial fibrillation in heart failure patients: a meta-analysis of randomized controlled trials. *Heart Lung*. 2023;57:69-74. [CrossRef]
7. Nesapiragasan V, Hayıroğlu Mİ, Sciacca V, Sommer P, Sohns C, Fink T. Catheter ablation approaches for the treatment of arrhythmia recurrence in patients with a durable pulmonary vein isolation. *Balk Med J*. 2023;40(6):386-394. [CrossRef]
8. Smith GD, Ebrahim S. Mendelian randomization: prospects, potentials, and limitations. *Int J Epidemiol*. 2004;33(1):30-42. [CrossRef]
9. Smith GD, Timpson N, Ebrahim S. Strengthening causal inference in cardiovascular epidemiology through Mendelian randomization. *Ann Med*. 2008;40(7):524-541. [CrossRef]
10. Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32(1):1-22. [CrossRef]
11. Yang S, Pudasaini R, Zhi H, Wang L. The relationship between blood lipids and risk of atrial fibrillation: univariable and multivariable Mendelian randomization analysis. *Nutrients*. 2021; 14(1). [CrossRef]
12. Ma M, Zhi H, Yang S, Yu EYW, Wang L. Body mass index and the risk of atrial fibrillation: a Mendelian randomization study. *Nutrients*. 2022;14(9). [CrossRef]
13. Kwok MK, Schooling CM. Mendelian randomization study on atrial fibrillation and cardiovascular disease subtypes. *Sci Rep*. 2021;11(1):18682. [CrossRef]
14. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. *eLife*. 2018;7. [CrossRef]
15. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS Genet*. 2017;13(11):e1007081. [CrossRef]
16. Low SK, Takahashi A, Ebana Y, et al. Identification of six new genetic loci associated with atrial fibrillation in the Japanese population. *Nat Genet*. 2017;49(6):953-958. [CrossRef]
17. Pierce BL, Burgess S. Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators. *Am J Epidemiol*. 2013;178(7):1177-1184. [CrossRef]
18. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol*. 2013;37(7):658-665. [CrossRef]
19. Zhao Q, Wang J, Hemani G, Bowden J, Small DS. Statistical inference in two-sample summary-data Mendelian randomization using robust adjusted profile score. *Ann Statist*. 2020; 48(3):1742-1769. [CrossRef]
20. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40(4):304-314. [CrossRef]
21. Zheng J, Baird D, Borges M-C, et al. Recent developments in Mendelian randomization studies. *Curr Epidemiol Rep*. 2017; 4(4):330-345. [CrossRef]
22. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2):512-525. [CrossRef]
23. Greco MF, Minelli C, Sheehan NA, Thompson JR. Detecting pleiotropy in Mendelian randomisation studies with summary data and a continuous outcome. *Stat Med*. 2015;34(21):2926-2940. [CrossRef]
24. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50(5):693-698. [CrossRef]
25. Sanderson E, Davey Smith G, Windmeijer F, Bowden J. An examination of multivariable Mendelian randomization in the single-sample and two-sample summary data settings. *Int J Epidemiol*. 2019;48(3):713-727. [CrossRef]
26. Palamà Z, Nesti M, Robles AG, et al. Tailoring the ablative strategy for atrial fibrillation: a state-of-the-art review. *Cardiol Res Pract*. 2022;2022:9295326. [CrossRef]
27. Meisner JS, Keren G, Pajaro OE, et al. Atrial contribution to ventricular filling in mitral stenosis. *Circulation*. 1991;84(4):1469-1480. [CrossRef]
28. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. *Nat Rev Cardiol*. 2017;14(1):30-38. [CrossRef]
29. Dandamudi G, Rampurwala AY, Mahenthiran J, Miller JM, Das MK. Persistent left ventricular dilatation in tachycardia-induced cardiomyopathy patients after appropriate treatment and normalization of ejection fraction. *Heart Rhythm*. 2008; 5(8):1111-1114. [CrossRef]
30. Jais P, Sanders P, Hsu LF, Hocini M, Haissaguerre M. Catheter ablation for atrial fibrillation. *Heart (Br Card Soc)*. 2005;91(1):7-9. [CrossRef]
31. Bergau L, Bengel P, Sciacca V, Fink T, Sohns C, Sommer P. Atrial fibrillation and heart failure. *J Clin Med*. 2022;11(9). [CrossRef]
32. Ling LH, Kistler PM, Ellims AH, et al. Diffuse ventricular fibrosis in atrial fibrillation: noninvasive evaluation and relationships with aging and systolic dysfunction. *J Am Coll Cardiol*. 2012;60(23):2402-2408. [CrossRef]

Supplementary Table 1. The Results of Phenoscanner Analysis for Each SNP

SNP	RSID	hg19_ coordinates	hg38_ coordinates	a1	a2	Trait	EFO	Study	Pmid	Ancestry	Year	Beta	SE	*P*	Direction	n	n_ cases	n_ controls	n_ studies	unit	dataset
rs639652	rs639652	chr1:170612873	chr1:170643732	G	A	Atrial fibrillation	EFO_0000275	Low SK	28416822	Mixed	2017	0.1266	0.02152	4.00E-09	+	-	-	-	-	log OR	NHGRI-EBI_ GWAS_Catalog
rs639652	rs639652	chr1:170612873	chr1:170643732	G	A	Atrial fibrillation and flutter	EFO_0000275	Neale B	UKBB	European	2017	0.001317	0.000259	3.52E-07	+	337199	3818	333381	1	risk diff	Neale-B_UKBB_ EUR_2017
rs639652	rs639652	chr1:170612873	chr1:170643732	G	A	Self-reported atrial fibrillation	EFO_0000275	Neale B	UKBB	European	2017	0.000988	0.000216	4.78E-06	+	337159	2650	334509	1	risk diff	Neale-B_UKBB_ EUR_2017
rs639652	rs639652	chr1:170612873	chr1:170643732	G	A	Self-reported lymphoma	EFO_0000574	Neale B	UKBB	European	2017	0.000204	4.04E-05	4.74E-07	+	337159	92	337067	1	risk diff	Neale-B_UKBB_ EUR_2017
rs12044963	rs12044963	chr1:112392360	chr1:111849738	G	T	Smallpox vaccine cytokine responses	-	Kennedy RB	22610502	Mixed	2012	NA	NA	9.43E-10	NA	711	-	-	-	-	GRASP
rs12044963	rs12044963	chr1:112392360	chr1:111849738	G	T	Atrial fibrillation	EFO_0000275	Low SK	28416822	Mixed	2017	-0.1044	0.01329	4.00E-15	-	-	-	-	-	log OR	NHGRI-EBI_ GWAS_Catalog
rs12044963	rs12044963	chr1:112392360	chr1:111849738	G	T	Immune reponse to smallpox secreted IFN alpha	EFO_0004645;EFO_0004873	Kennedy RB	22610502	Mixed	2012	NA	NA	9.00E-10	NA	-	-	-	-	-	NHGRI-EBI_ GWAS_Catalog
rs2540953	rs2540953	chr2:65272362	chr2:65045228	G	A	Atrial fibrillation	EFO_0000275	Low SK	28416822	Mixed	2017	0.08984	0.01064	3.00E-17	+	-	-	-	-	log OR	NHGRI-EBI_ GWAS_Catalog
rs2540953	rs2540953	chr2:65272362	chr2:65045228	G	A	Systolic blood pressure	EFO_0006335	Neale B	UKBB	European	2017	0.01194	0.002467	1.32E-06	+	317754	0	317754	1	IVNT	Neale-B_UKBB_ EUR_2017
rs7434417	rs7434417	chr4:111708438	chr4:110787282	A	G	Acute appendicitis	EFO_0007149	Neale B	UKBB	European	2017	-0.00127	0.000283	7.72E-06	-	337199	1676	335523	1	risk diff	Neale-B_UKBB_ EUR_2017
rs7434417	rs7434417	chr4:111708438	chr4:110787282	A	G	Atrial fibrillation and flutter	EFO_0000275	Neale B	UKBB	European	2017	-0.00762	0.000425	8.14E-72	-	337199	3818	333381	1	risk diff	Neale-B_UKBB_ EUR_2017
rs7434417	rs7434417	chr4:111708438	chr4:110787282	A	G	Illnesses of father: stroke	EFO_0000712	Neale B	UKBB	European	2017	-0.00685	0.001537	8.32E-06	-	294757	46007	248750	1	risk diff	Neale-B_UKBB_ EUR_2017
rs7434417	rs7434417	chr4:111708438	chr4:110787282	A	G	Self-reported atrial fibrillation	EFO_0000275	Neale B	UKBB	European	2017	-0.00673	0.000355	4.12E-80	-	337159	2650	334509	1	risk diff	Neale-B_UKBB_ EUR_2017
rs7434417	rs7434417	chr4:111708438	chr4:110787282	A	G	Treatment with bisoprolol	EFO_0007056	Neale B	UKBB	European	2017	-0.0027	0.000485	2.76E-08	-	337159	4985	332174	1	risk diff	Neale-B_UKBB_ EUR_2017
rs7434417	rs7434417	chr4:111708438	chr4:110787282	A	G	Treatment with digoxin	EFO_0007056	Neale B	UKBB	European	2017	-0.00224	0.000201	9.67E-29	-	337159	846	336313	1	risk diff	Neale-B_UKBB_ EUR_2017
rs7434417	rs7434417	chr4:111708438	chr4:110787282	A	G	Treatment with flecainide	EFO_0007056	Neale B	UKBB	European	2017	-0.00127	0.000164	1.17E-14	-	337159	560	336599	1	risk diff	Neale-B_UKBB_ EUR_2017
rs7434417	rs7434417	chr4:111708438	chr4:110787282	A	G	Treatment with sodium warfarin	EFO_0007056	Neale B	UKBB	European	2017	-0.00062	0.000117	8.99E-08	-	337159	284	336875	1	risk diff	Neale-B_UKBB_ EUR_2017
rs7434417	rs7434417	chr4:111708438	chr4:110787282	A	G	Treatment with sotalol	EFO_0007056	Neale B	UKBB	European	2017	-0.00095	0.000161	4.19E-09	-	337159	540	336619	1	risk diff	Neale-B_UKBB_ EUR_2017
rs7434417	rs7434417	chr4:111708438	chr4:110787282	A	G	Treatment with warfarin	EFO_0007056	Neale B	UKBB	European	2017	-0.00438	0.000402	1.14E-27	-	337159	3404	333755	1	risk diff	Neale-B_UKBB_ EUR_2017
rs4115272	rs4115272	chr4:111783760	chr4:110862604	G	A	Atrial fibrillation and flutter	EFO_0000275	Neale B	UKBB	European	2017	0.002004	0.000319	3.51E-10	+	337199	3818	333381	1	risk diff	Neale-B_UKBB_ EUR_2017
rs4115272	rs4115272	chr4:111783760	chr4:110862604	G	A	Self-reported atrial fibrillation	EFO_0000275	Neale B	UKBB	European	2017	0.001759	0.000267	4.26E-11	+	337159	2650	334509	1	risk diff	Neale-B_UKBB_ EUR_2017
rs10024737	rs10024737	chr4:174448143	chr4:173526992	C	T	Cause of death: asthma															
rs10024737	rs10024737	chr4:174448143	chr4:173526992	C	T	Cause of death: epilepsy															
rs10024737	rs10024737	chr4:174448143	chr4:173526992	C	T	Cause of death: stroke															
rs7698692	rs7698692	chr4:174604104	chr4:173682953	A	G	Atrial fibrillation	EFO_0000275	Low SK	28416822	Mixed	2017	0.1213	0.01506	8.00E-16	+	-	-	-	-	log OR	NHGRI-EBI_ GWAS_Catalog
rs72798854	rs72798854	chr5:139698365	chr5:140318780	A	G	Fluid intelligence score	-	Neale B	UKBB	European	2017	-0.05143	0.01118	4.23E-06	-	108818	0	108818	1	-	Neale-B_UKBB_ EUR_2017

(*Continued*)

Supplementary Table 1. The Results of Phenoscanner Analysis for Each SNP (Continued)

SNP	RSID	hg19_ coordinates	hg38_ coordinates	a1	a2	Trait	EFO	Study	Pmid	Ancestry	Year	Beta	SE	*P*	Direction	n	n_ cases	n_ controls	n_ studies	unit	dataset
rs72798854	rs72798854	chr5:139698365	chr5:140318780	A	G	Qualifications: college or university degree	EFO_0004784	Neale B	UKBB	European	2017	-0.00649	0.001414	4.47E-06	-	334070	106305	227765	1	risk diff	Neale-B_UKBB_ EUR_2017
rs6928224	rs6928224	chr6:122407982	chr6:122086836	C	T	Pulse rate	EFO_0004326	Neale B	UKBB	European	2017	-0.01397	0.002613	8.91E-08	-	317756	0	317756	1	IVNT	Neale-B_UKBB_ EUR_2017
rs1049334	rs1049334	chr7:116200380	chr7:116560326	A	G	Atrial fibrillation	EFO_0000275	Low SK	28416822	Mixed	2017	-0.1848	0.02416	2.00E-14	-	-	-	-	-	log OR	NHGRI-EBI_ GWAS_Catalog
rs1675334	rs1675334	chr9:93653260	chr9:90890978	G	C	Atrial fibrillation	EFO_0000275	Low SK	28416822	Mixed	2017	0.08342	0.01843	6.00E-06	+	-	-	-	-	log OR	NHGRI-EBI_ GWAS_Catalog
rs1675334	rs1675334	chr9:93653260	chr9:90890978	G	C	Self-reported oesophageal disorder	EFO_0009544	Neale B	UKBB	European	2017	0.000302	6.15E-05	9.64E-07	+	337159	205	336954	1	risk diff	Neale-B_UKBB_ EUR_2017
rs12415501	rs12415501	chr10:105324774	chr10:103565017	C	T	Atrial fibrillation	EFO_0000275	Low SK	28416822	Mixed	2017	-0.3577	0.03521	3.00E-24	-	-	-	-	-	log OR	NHGRI-EBI_ GWAS_Catalog
rs12415501	rs12415501	chr10:105324774	chr10:103565017	C	T	Atrial fibrillation	EFO_0000275	Nielsen JB	29290336	European	2018	-0.2231	0.02917	2.00E-14	-	-	-	-	-	log OR	NHGRI-EBI_ GWAS_Catalog
rs12415501	rs12415501	chr10:105324774	chr10:103565017	C	T	Atrial fibrillation and flutter	EFO_0000275	Neale B	UKBB	European	2017	-0.0022	0.000374	4.20E-09	-	337199	3818	333381	1	risk diff	Neale-B_UKBB_ EUR_2017
rs12415501	rs12415501	chr10:105324774	chr10:103565017	C	T	Self-reported atrial fibrillation	EFO_0000275	Neale B	UKBB	European	2017	-0.00144	0.000312	4.02E-06	-	337159	2650	334509	1	risk diff	Neale-B_UKBB_ EUR_2017
rs2384407	rs2384407	chr12:114789226	chr12:114351421	A	G	Atrial fibrillation and flutter	EFO_0000275	Neale B	UKBB	European	2017	0.001795	0.000294	1.08E-09	+	337199	3818	333381	1	risk diff	Neale-B_UKBB_ EUR_2017
rs2384407	rs2384407	chr12:114789226	chr12:114351421	A	G	Self-reported atrial fibrillation	EFO_0000275	Neale B	UKBB	European	2017	0.001157	0.000246	2.52E-06	+	337159	2650	334509	1	risk diff	Neale-B_UKBB_ EUR_2017
rs2359171	rs2359171	chr16:73053022	chr16:73019123	A	T	Atrial fibrillation and flutter	EFO_0000275	Neale B	UKBB	European	2017	0.003629	0.000344	5.46E-26	+	337199	3818	333381	1	risk diff	Neale-B_UKBB_ EUR_2017
rs2359171	rs2359171	chr16:73053022	chr16:73019123	A	T	Self-reported atrial fibrillation	EFO_0000275	Neale B	UKBB	European	2017	0.00251	0.000287	2.48E-18	+	337159	2650	334509	1	risk diff	Neale-B_UKBB_ EUR_2017
rs2359171	rs2359171	chr16:73053022	chr16:73019123	A	T	Treatment with digoxin	EFO_0007056	Neale B	UKBB	European	2017	0.000762	0.000163	2.94E-06	+	337159	846	336313	1	risk diff	Neale-B_UKBB_ EUR_2017
rs2359171	rs2359171	chr16:73053022	chr16:73019123	A	T	Treatment with warfarin	EFO_0007056	Neale B	UKBB	European	2017	0.001633	0.000325	5.16E-07	+	337159	3404	333755	1	risk diff	Neale-B_UKBB_ EUR_2017

Supplementary Table 2. MR estimates from Each Method of Assessing the Causal Effect of Heart Failure on the Risk of Atrial Fibrillation

MR Method	No. of SNPs	Beta	SE	*P*	OR (95% CI)
Inverse variance weighted	9	1.19	0.75	0.11	3.29 (0.76-14.31)
Robust adjusted profile score (RAPS)	9	0.44	0.33	0.18	1.56 (0.81-2.98)
MR Egger	9	0.64	3.82	0.87	1.90 (0.001-3386.21)
Weighted mode	9	0.08	0.16	0.64	1.08 (0.78-1.49)
Weighted median	9	0.14	0.16	0.38	1.15 (0.84-1.57)

MR, Mendelian randomization; SNP, single-nucleotide polymorphism; SE, standard error; OR, odds ratio; CI, confidence interval.