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ARTICLE

# Association of Angina, Myocardial Infarction and Atrial Fibrillation-A Bidirectional Mendelian Randomization Study

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## Abstract

**Aims/Background** Coronary heart disease (CHD) and atrial fibrillation (AF) exhibit a close relationship, yet the existing body of research predominantly relies on observational study methodologies, posing challenges in establishing causal relationships. The objective of our study is to investigate the causal linkages between coronary atherosclerosis (CAAs), angina pectoris, myocardial infarction (MI), and AF.

**Methods** This study utilizes a two-sample Mendelian randomization (TSMR) methodology, leveraging genetic variation as a means of evaluating causality. Mendelian randomization is grounded in three primary assumptions: (1) the genetic variant is linked to the exposure, (2) the genetic variant is independent of confounding factors, and (3) the genetic variant influences the outcome solely through the exposure.

**Results** The results of our study suggest a genetic predisposition in which CAAs, angina, and MI may enhance susceptibility to AF, while AF may reciprocally elevate the risk of CAAs.

**Conclusion** In light of these findings, it is recommended that patients with CHD undergo regular cardiac rhythm monitoring, and that patients with AF receive anticoagulant and antiplatelet therapy whenever feasible. This study posits a practical implication for clinical practice.

**Key words: coronary arterial atherosclerosis; angina; myocardial infarction; atrial fibrillation; Mendelian randomization; genetics**

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## Introduction

Coronary heart disease (CHD) is a significant cardiovascular ailment with a worldwide prevalence ranging from approximately 4.6% to 9.2% (Mensah et al, 2019). It is responsible for the deaths of approximately 7 million individuals annually (Ralapanawa and Sivakanesan, 2021), making it one of the primary causes of mortality on a global scale. CHD is distinguished by the formation of atherosclerosis in the coronary arteries, resulting in the narrowing or blockage of the coronary artery lumen or microvessels (Faroux et al, 2019; Maisano, 2020). This progression ultimately leads to myocardial cell infarction and hypoxia, which are hallmark features of the disease, manifesting as symptoms such as angina pectoris and myocardial infarction (MI) (Fisher et al, 2019). Atrial fibrillation (AF) is the predominant clinical arrhythmia and the leading cause of arrhythmia-related hospital admissions

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(Tatangelo et al, 2023), affecting 1–2% of the global population (Go et al, 2001). AF is linked to heightened cardiovascular morbidity and mortality, contributing to a substantial and escalating financial strain on healthcare systems (Sheth et al, 2023). It is estimated that 6–21% of individuals with CHD also have concurrent AF (Schmitt et al, 2009), while CHD is present in 20–30% of patients with AF (Kralev et al, 2011; Nabauer et al, 2009; Nieuwlaat et al, 2005).

Several studies have demonstrated that CHD is an independent risk factor for AF (Benjamin et al, 1994; Kannel et al, 1983). For instance, the Framingham study observed a twofold increase in the incidence of AF in men with CHD and a threefold increase in women with CHD (Alonso et al, 2013) who experienced transient AF. Additionally, a study involving 13,153 patients with CHD receiving optimal treatment revealed that 4.1% developed AF over an average follow-up period of 3.5 years (Tomasdottir et al, 2021). In the Finnish ARTEMIS study, which included 1710 CHD patients with sinus rhythm, AF occurred in 8.4% of participants during a mean follow-up of 5.7 years. However, it should be noted that the study did not exclude individuals with a history of previous AF (Nortamo et al, 2017). In a separate trial involving 7665 patients diagnosed with CHD, it was observed that the incidence of AF in patients without a prior history of AF was 1.64 per 100 patient-years over an average follow-up period of 4.9 years (Otterstad et al, 2006). Additionally, AF has been identified as a potential factor in the development of CHD (Goette et al, 2016), with AF serving as an independent predictor associated with a 2.2-fold increased likelihood of experiencing new coronary events (Aronow et al, 1995). The REGARDS study further demonstrated that the incidence of MI in patients with AF was approximately twice as high (Soliman et al, 2014). Furthermore, findings from the ALLHAT study indicated that the presence of baseline AF or atrial flutter significantly raised the risk of fatal CHD or nonfatal MI (hazard ratio [HR] = 1.64, $p < 0.01$) (Haywood et al, 2009).

The established relationship between CHD and AF is frequently examined through observational studies, which present challenges in establishing causality. Mendelian randomization, a method that utilizes genetic variation, is employed to investigate causal relationships. Observational studies are susceptible to potential confounding variables, which may result in associations that are not necessarily causal. Mendelian randomization leverages naturally occurring genetic variation within the population as an instrument for simulating the conditions of a randomized controlled trial, thereby mitigating the influence of confounding variables. Through the examination of the association between genetic variation and the exposure variable of interest in relation to disease outcomes, causal inferences regarding the impact of the exposure variable on the disease can be drawn (König and Greco, 2018).

In order to gain a more comprehensive understanding of the complex interplay between CHD and AF, our study seeks to investigate the reciprocal causal relationship between coronary atherosclerosis (CAAs), angina pectoris, MI, and AF using bidirectional Mendelian randomization techniques.

# Methods

## Data Source

A bidirectional two-sample Mendelian randomization (TSMR) study was conducted to examine the causal relationships between CAAs, angina, MI, and AF utilizing data from the publicly accessible genome-wide association study (GWAS) database (Lawlor, 2016). Ethical approval was deemed unnecessary as the study involved a reanalysis of previously published data. General GWAS data for CAAs, angina, MI, and AF were sourced from the Integrative Epidemiology Unit (IEU) for this bidirectional TSMR study (Elsworth et al, 2020). OpenGWAS dataset of CAAs (GWAS ID: ukb-d-I9_CORATHER) is European ancestry with 14,334 cases and 361,194 controls. OpenGWAS dataset of angina (GWAS ID: ebi-a-GCST90038609) includes 15,527 cases and 484,598 controls of European ancestry. OpenGWAS dataset of MI (GWAS ID: ebi-a-GCST90038610) built by Hartiala et al (2021), includes 11,081 cases and 484,598 controls of European ancestry. The summary statistics for AF were required from Nielsen's study which includes 60,620 cases and 1,030,836 controls of European ancestry (Nielsen et al, 2018) (**Supplementary Table 1**).

## Statistical Analysis

Mendelian randomization is based on three main assumptions: (1) the genetic variant is associated with the exposure; (2) the genetic variant is not related to confounders; (3) the genetic variant affects the outcome only through exposure (Emdin et al, 2017). We used the TwoSampleMR package in R version 4.3.0 (Developed by Ross Ihaka and Robert Gentleman at the University of Auckland in New Zealand) for TSMR analysis. Inverse Variance Weighting (IVW), MR-Egger and weighted median methods were used to ensure robustness (Burgess et al, 2013, 2017a; Burgess and Thompson, 2017b). Outliers were assessed using the leave-one-out method (Mokry et al, 2016). To fulfill these three hypotheses (Fig. 1), we obtained single nucleotide polymorphisms (SNPs) associated with exposure at the GWAS significance ($p < 5 \times 10^{-8}$). Linkage disequilibrium in IVs for exposure were eliminated by a clustering algorithm with $R^2 = 0.001$, >10,000 kb. SNPs which are presented in the outcome or having palindromic structures were removed. In addition, confounders were removed using https://ldlink.nih.gov/?tab=ldtrait. Heterogeneity assessed using Cochran Q (Mendelian randomization based on two samples, so heterogeneity is allowed). MR-Egger regression analysis was used to assess directional horizontal pleiotropy. The horizontal multidirectional pathways were indicated if the intercept of the MR-Egger regression analysis was $p < 0.05$, then SNPs with horizontal multidirectional were eliminated using the MRPRESSO method (**Supplementary Table 2**).

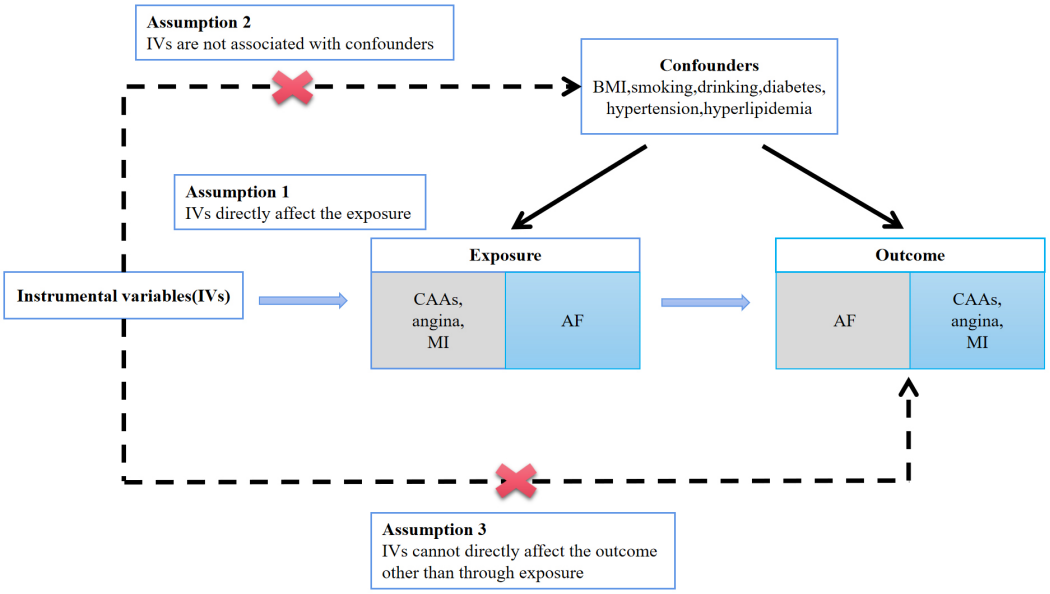


**Fig. 1. The summary diagram of Mendelian randomization assumptions.** Abbreviations: CAAs, coronary arterial atherosclerosis; MI, myocardial infarction; AF, atrial fibrillation; BMI, body mass index; IVs, instrumental variables.

# Results

## Factual Results

A bidirectional Mendelian randomization analysis was undertaken to examine the potential causal associations between coronary artery diseases (CAAs, angina, MI) and AF utilizing GWAS data.

Initially, coronary artery diseases were utilized as the exposure variable, with AF as the resultant disease outcome. Subsequently, single nucleotide polymorphisms associated with the exposure were identified as instrumental variables (IVs) to evaluate the potential causal impacts of genetic variations on AF. A total of twenty-eight SNPs linked to CAAs were employed as genetic IVs (**Supplementary Table 3**). The odds ratios (ORs) and 95% confidence intervals (CIs) from MR-Egger, weighted median, and IVW analyses were: 1.438 (1.433, 1.444; $p < 0.001$), 1.753 (1.731, 1.774; $p < 0.001$), 1.207 (1.023, 1.425; $p = 0.026$). Twenty-two SNPs linked to angina were employed as genetic IVs (**Supplementary Table 4**). The ORs and 95% CIs from MR-Egger, weighted median, and IVW analyses were: 1.101 (1.061, 1.143; $p < 0.001$), 1.091 (1.034, 1.150; $p = 0.001$), 1.218 (1.100, 1.349; $p < 0.001$). Thirteen SNPs associated with MI were utilized as genetic IVs (**Supplementary Table 5**). The ORs and 95% CIs from MR-Egger, weighted median, and IVW analyses were: 1.204 (1.020, 1.421; $p = 0.028$), 1.627 (1.407, 1.882; $p < 0.001$), 1.517 (1.346, 1.709; $p < 0.001$) (Table 1).

We subsequently investigated AF as the exposure variable and coronary artery disease as the disease outcome, utilizing IVs associated with the exposure to assess the potential causal impacts of genetic variations on coronary artery disease. In the case of CAAs as the focus of the study, we identified a total of 111 IVs (**Supplementary Table 6**). The outcomes of the MR-Egger, weighted median, and

**Table 1. The bidirectional MR analysis of CAAs, angina, MI and AF.**

| Exposure | Outcome | Method | nsnp | *p* | OR | Lower CI | Upper CI |
|---|---|---|---|---|---|---|---|
| CAAs | AF | MR-Egger | 28 | <0.001 | 1.438 | 1.433 | 1.444 |
| | | Weighted median | 28 | <0.001 | 1.753 | 1.731 | 1.774 |
| | | Inverse variance weighted | 28 | 0.026 | 1.207 | 1.023 | 1.425 |
| AF | CAAs | MR-Egger | 111 | 0.045 | 1.002 | 1.000 | 1.004 |
| | | Weighted median | 111 | 0.022 | 1.003 | 1.000 | 1.006 |
| | | Inverse variance weighted | 111 | <0.001 | 1.004 | 1.002 | 1.006 |
| Angina | AF | MR-Egger | 22 | <0.001 | 1.101 | 1.061 | 1.143 |
| | | Weighted median | 22 | 0.001 | 1.091 | 1.034 | 1.150 |
| | | Inverse variance weighted | 22 | <0.001 | 1.218 | 1.100 | 1.349 |
| AF | Angina | MR-Egger | 104 | 0.690 | 0.999 | 0.996 | 1.003 |
| | | Weighted median | 104 | 0.334 | 1.001 | 0.999 | 1.003 |
| | | Inverse variance weighted | 104 | 0.181 | 1.001 | 1.000 | 1.003 |
| MI | AF | MR-Egger | 13 | 0.028 | 1.204 | 1.020 | 1.421 |
| | | Weighted median | 13 | <0.001 | 1.627 | 1.407 | 1.882 |
| | | Inverse variance weighted | 13 | <0.001 | 1.517 | 1.346 | 1.709 |
| AF | MI | MR-Egger | 103 | 0.504 | 0.999 | 0.995 | 1.002 |
| | | Weighted median | 103 | 0.728 | 1.000 | 0.998 | 1.001 |
| | | Inverse variance weighted | 103 | 0.091 | 1.002 | 1.000 | 1.003 |

Abbreviations: CAAs, coronary arterial atherosclerosis; MI, myocardial infarction; AF, atrial fibrillation; nsnp, the number of single nucleotide polymorphisms.

IVW analyses are presented below 1.002 (1.000, 1.004; $p = 0.045$), 1.003 (1.000, 1.006; $p = 0.022$), and 1.004 (1.002, 1.006; $p < 0.001$). We employed 104 IVs to assess angina as the outcome (**Supplementary Table 7**). The results from MR-Egger, weighted median, and IVW analyses were: 0.999 (0.996, 1.003; $p = 0.690$), 1.001 (0.999, 1.003; $p = 0.334$), and 1.001 (1.000, 1.003; $p = 0.181$). We examined 103 IVs in relation to MI as the dependent variable (**Supplementary Table 8**). The findings obtained from the MR-Egger, weighted median, and IVW analyses were as follows: 0.999 (0.995, 1.002; $p = 0.504$), 1.000 (0.998, 1.001; $p = 0.728$), and 1.002 (1.000, 1.003; $p = 0.091$) (Table 1).

## Resultant Findings

The results of our study indicate a potential causal relationship between genetic variations linked to CAAs (Fig. 2A), angina (Fig. 2C), and MI (Fig. 2E), and the onset of AF. Furthermore, our findings suggest a potential causal relationship between genetic variations associated with AF and the formation of CAAs (Fig. 2B). Our study did not establish a causal link between genetic variations associated with AF and the incidence of angina (Fig. 2D) and MI (Fig. 2F). In the Mendelian randomization analysis, we employed three calculation methods to ensure the reliability of our findings, all of which produced consistent results.

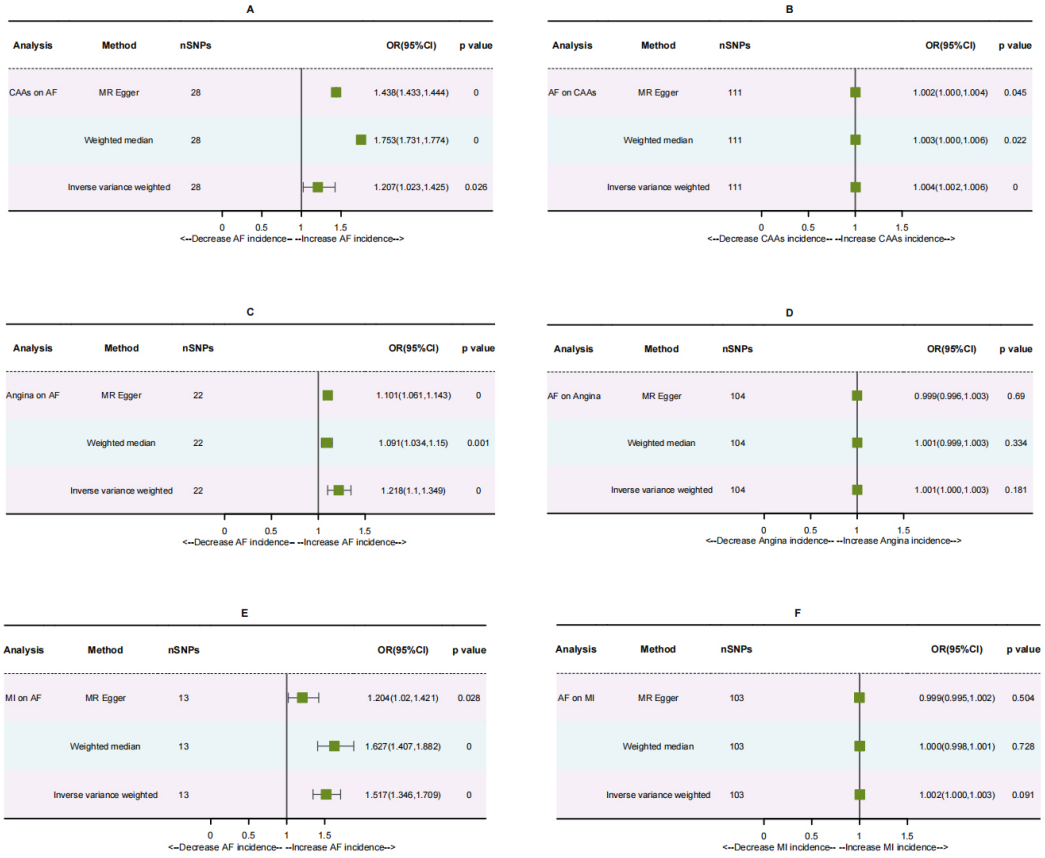


**Fig. 2. The forest plot of bidirectional MR analysis.** (A) CAAs as the exposure, AF as the outcome, 28 IVs. (B) AF as the exposure, CAAs as the outcome, 111 IVs. (C) Angina as the exposure, AF as the outcome, 22 IVs. (D) AF as the exposure, angina as the outcome, 104 IVs. (E) MI as the exposure, AF as the outcome, 13 IVs. (F) AF as the exposure, MI as the outcome, 103 IVs. Abbreviations: CAAs, coronary arterial atherosclerosis; MI, myocardial infarction; AF, atrial fibrillation; IVs, instrumental variables.

## Discussion

Our research findings suggest a potential genetic predisposition to AF in individuals with CHD, including CAAs, angina, and MI. Additionally, our study indicates a potential genetic association between AF and CAAs.

The study demonstrates several key strengths. Firstly, the use of Mendelian randomization allowed for the establishment of causal relationships. Secondly, the incorporation of three different methodologies (IVW, MR-Egger, and weighted median) enhanced the robustness and dependability of the study findings. Thirdly, the bidirectional Mendelian randomization analysis conducted to explore the relationship between the three subtypes of CHD and AF contributed to a more comprehensive understanding of this association. Nevertheless, it is important to acknowledge the limitations of this study, as the data primarily reflect a European population, limiting the applicability of the findings to more diverse populations. Additional research involving other populations or larger sample sizes is necessary to confirm the conclusions drawn from this study. Further exploration is imperative to gain

a comprehensive understanding of the mechanisms driving the causal relationship between CHD and AF.

CHD is widely acknowledged as a risk factor for AF (Liang and Wang, 2021). Following adjustment for a history of CHD, elevated coronary artery calcification scores ($\geq$1000) were found to be independently linked to AF, indicating a possible association between CAAs and AF even in the absence of significant luminal narrowing (Lee et al, 2022). The 5-year cumulative occurrence of AF in individuals with a history of acute MI ranges from 6–21%, surpassing the incidence observed in the general population (3%) (Bang et al, 2014; Sarkisian et al, 2016; Seet et al, 2011). A case-control study conducted by Lau et al (2009) revealed a heightened incidence of obstructive CHD among individuals with paroxysmal or persistent AF, as determined through multilayer helical computed tomography coronary angiography (Nucifora et al, 2009). Lau's investigation (2009) further demonstrated that among a cohort of 3393 patients diagnosed with MI, 149 patients (4.4%) experienced their initial episode of AF during the acute phase of MI. Subsequent continuous electrocardiogram monitoring of MI patients within 48 hours of hospital admission confirmed symptomatic AF in 5% of cases and asymptomatic AF in 16% of cases (Lau et al, 2009). In randomized controlled trials involving patients with nonvalvular AF, a history of MI was found in 14–18% of patients, with subsequent follow-up revealing an annual incidence of MI ranging from 0.51–1.1% (Ruff et al, 2014). Meta-analyses consistently demonstrate that 2–25% of patients without prior AF develop AF during or following an acute MI (He et al, 2019; Jabre et al, 2011; Luo et al, 2018). The pathophysiological mechanisms underlying AF encompass reentry, focal ectopic activity, and neural remodeling, all of which may be attributed to coronary artery disease (Liang and Wang, 2021). The presence of AF in patients with CHD is influenced by various factors, including cardiomyocyte properties (Zukela et al, 2015), connexin proteins (Guo and Yang, 2022), fibrosis (van Diepen et al, 2010), inflammatory factors (Aronson et al, 2007; Marcus et al, 2008), and the innate immune system (Aronson et al, 2011; Asanin et al, 2005; Bahouth et al, 2010; Zhang et al, 2018).

Drawing from both clinical observations and mechanistic studies, the findings of this research serve to reinforce the established causal link between CHD and AF. Regular monitoring of cardiac rhythm in individuals with CHD holds substantial clinical significance in the timely identification of AF, prevention of stroke and other thromboembolic complications, optimization of treatment efficacy, and enhancement of patient prognosis. For instance, the integration of contemporary technologies like smartphones enables more convenient cardiac rhythm monitoring, thereby facilitating improved healthcare management for CHD patients.

Research findings indicate that a significant proportion of patients with AF may develop CHD, with studies reporting rates ranging from 20–30% (Kralev et al, 2011; Nabauer et al, 2009; Nieuwlaat et al, 2005). Additionally, a study involving 51 patients with sinus node atherosclerosis found that 41.2% had a history of supraventricular arrhythmia, primarily attributed to AF (Staerk et al, 2017). The etiology of AF remains incompletely understood, but emerging evidence suggests that both AF and CAAs are linked to an inflammatory response and a prothrombotic

state. Furthermore, our study provides further support for the association between AF-related genetic variants and the development of CAAs. Active intervention with risk factors such as obesity, dyslipidemia, hypertension, diabetes mellitus, and poor lifestyle may potentially delay or reduce the development of CAAs in patients with AF.

A longitudinal cohort study conducted on adult residents of Olmsted County, MN, USA found that AF was associated with a significantly increased risk of new coronary ischemic events (Miyasaka et al, 2007). Subsequent research confirmed a risk ratio of 8.16 (95% confidence interval 2.89–23.09, $p < 0.001$) for coronary death and 3.80 (95% confidence interval 1.45–9.94, $p = 0.007$) for major coronary events in patients with AF (Marte et al, 2009). Among the 3393 patients diagnosed with MI, 387 individuals (11.4%) had a confirmed history of AF (Lau et al, 2009). Additionally, a separate cohort study involving 155,071 patients revealed that 4.9% had a history of paroxysmal AF and 3% had a history of chronic AF (Pokorney and Navar, 2016). Randomized controlled trials focusing on patients with nonvalvular AF indicated that 14–18% of patients had a history of MI, with subsequent follow-up demonstrating an annual MI incidence rate of 0.51–1.1% (Ruff et al, 2014). Furthermore, a study tracking 648 MI events over a median follow-up period of 6.9 years (median 4.5 years) found that AF was independently linked to an elevated risk of MI (Soliman et al, 2014). Our study did not identify a genetic association between AF and angina and MI. This lack of correlation may be due to the complex interplay of diverse environmental and lifestyle factors influencing angina and MI. Therefore, it is unlikely that a single genetic variant alone can explain the risk of developing angina and MI, in contrast to CAAs. The left atrium in individuals with AF, the diminished responsiveness of myofibrils to calcium ions, and the temporary decline in intracellular calcium levels resulting in atrial contractile impairment (Yeh et al, 2008), as well as the heightened platelet activity and activation of the coagulation system contributing to the vulnerability of AF patients to thromboembolism (O'Neal et al, 2015; Yip et al, 2006), are potential significant factors in the pathogenesis of angina pectoris and MI in this patient population. Based on the findings of our study, the implementation of early anticoagulation and antiplatelet therapy for individuals with AF, in conjunction with lifestyle modifications, vigilant monitoring of blood pressure and blood glucose levels, routine cardiovascular risk evaluations, appropriate pharmacological interventions, and encouragement of patient self-care, represents a holistic preventive approach that has the potential to mitigate acute coronary events and enhance patient prognoses.

## Conclusion

This bidirectional Mendelian randomization study offers persuasive evidence of the increased risk of AF associated with CHD. Furthermore, it suggests a causal relationship between AF and CAAs at the genetic level, while indicating that the association of AF with angina pectoris and MI may be impacted by non-genetic factors. Consequently, the study recommends routine cardiac rhythm monitoring

for CHD patients in clinical practice, as well as anticoagulation and antiplatelet therapy for individuals with AF whenever feasible.

## Key Points

- Coronary heart disease and atrial fibrillation are common, serious heart conditions that greatly affect patients' lives and survival.
- Many studies have found a link between coronary heart disease and atrial fibrillation, but it's unclear if one causes the other.
- This study uses genetic data and Mendelian randomization to determine if coronary heart disease causes atrial fibrillation.
- Our study suggests a possible genetic link between atrial fibrillation and conditions like coronary artery atherosclerosis, angina, and myocardial infarction.
- We recommend routine heart rhythm checks for coronary heart disease patients and suggest anticoagulation and antiplatelet treatments for those with atrial fibrillation to improve their prognosis.

## Availability of Data and Materials

Single nucleotide polymorphism (SNP)-phenotype association data were obtained from the Integrated Epidemiology Unit (IEU) OpenGWAS database (https://gwas.mrcieu.ac.uk/datasets/).

## Author Contributions

(I) Conception and design: HZ, WL; (II) Administrative support: WL, YH; (III) Provision of study materials or patients: LC, YW, JC, QL, YZ, YX; (IV) Collection and assembly of data: LC, SL, ZP, QZ, CZ, NL, YH; (V) Data analysis and interpretation: LC; (VI) Manuscript writing: All authors. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

## Acknowledgement

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## Conflict of Interest

Not applicable.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0137.

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