






**Meta-Analysis****FIVE SINGLE-NUCLEOTIDE POLYMORPHISMS IN THE PITX2 GENE AS RISK FACTORS FOR ATRIAL FIBRILLATION**

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**ABSTRACT**

Atrial fibrillation (AF) is a highly prevalent arrhythmia. The involvement of molecular mechanisms in increased AF risk remains uncertain. However, the paired-like homeodomain transcription factor 2 or pituitary homeobox 2 (PITX2) gene has been linked to AF development. A comprehensive search was carried out to identify all eligible case-control studies in order to assess the association between five single-nucleotide polymorphisms (SNPs) in the PITX2 gene and the risk of AF. This meta-analysis employed the Review Manager (RevMan) software version 5.3 (Cochrane). There were 13 clinical studies, with a total of 11,961 subjects, that met the inclusion criteria. These subjects consisted of 4,440 patients with AF and 7,521 controls. The meta-analysis of five SNP types in the PITX2 gene was done using crude odds ratios (ORs). This revealed that rs2200733 increased the risk of AF (OR=1.80; 95% CI=1.53-2.11; p=0.0005; I<sup>2</sup>=80%). On the other hand, the other three SNPs decreased the risk of AF, namely, rs385344 (OR=0.75; 95% CI=0.59-0.95; p=0.002; I<sup>2</sup>=85%), rs6838973 (OR=0.64; 95% CI=0.51-0.81; p=0.0001; I<sup>2</sup>=73%), and rs17570669 (OR=0.80; 95% CI=0.65-0.98; p=0.03; I<sup>2</sup>=70%). However, there was no significant association between rs1003464 and AF (OR=1.21; 95% CI=0.97-1.50; p=0.13; I<sup>2</sup>=83%). In conclusion, depending on the type, SNPs in the PITX2 gene correlate with AF risk factors, either by alleviating or reducing the risk.

**Keywords:** Atrial fibrillation; pituitary homeobox 2 (PITX2) gene; chromosome 4q25; single-nucleotide polymorphisms (SNPs); cardiovascular diseases

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**Highlights:**

1. A genetic variable has been identified as an atrial fibrillation risk factor.
2. Rs2200733 is a type of SNP that increases atrial fibrillation risk, whereas rs3853445, rs6838973, and rs17570669 have the reverse effect.

**INTRODUCTION**

The global atrial fibrillation (AF) prevalence is rising. Data from the United States (US) revealed that approximately two million people suffer from AF, with the number anticipated to rise to six to ten million by 2050 (Morillo et al. 2017). Over 454,000 persons in the US were hospitalized with AF as the primary diagnosis (Benjamin et al. 2019). In Indonesia, the AF prevalence has risen from 7.1%

in 2010 to 9.0% in 2011, 9.3% in 2012, and 9.8% in 2013 (Hutomo & Subagjo 2020).

AF increases the risk of stroke by two to three times, and can also increase the risk of heart failure (Anter et al. 2009, Kamel et al. 2016, Alsagaff et al. 2022). Identifying and screening for AF risk factors may help to prevent future disease and complications. There are numerous risk factors for AF, including hypertension, heart valve disease, and unmodifiable

risk factors (e.g., genetic factors) (Staerk et al. 2017). In the last five years, there has been an increase in genetic study on the prevalence of AF, and various loci have been discovered to have a role in the occurrence of AF (Kornej et al. 2020).

Several studies have found that a gene on the chromosome 4q25 has a significant role in the incidence of AF. One of the largest studies on genetic factors and AF, conducted in Iceland in 2007, indicated that the single-nucleotide polymorphisms (SNPs) rs2200733 and rs10033464 enhanced the incidence of AF. According to studies involving 500 AF and lone AF patients and a control group of 4,476 patients, SNPs rs385344, rs6838973, and rs17570669 affected the onset of AF, notably at loci with minor alleles (Gudbjartsson et al. 2007, Lubitz et al. 2010, Arndt & MacRae 2014). These variants are found around the paired-like homeodomain transcription factor 2 or pituitary homeobox 2 (PITX2) transcription factor gene, which encodes for a homeobox transcription factor (Kirchhof et al. 2011). These are essential for the formation of sinoatrial nodes and left-right asymmetry of the heart (Franco et al. 2017). PITX2 isoform deletion results in congenital malformations, conduction system problems, and myocardial defects (Yuan et al. 2013, Zhao et al. 2015). Its deletion also shortens the duration of the atrial action potential, making AF more susceptible (Bai et al. 2020). In recent five years, there has been no meta-analysis study that discusses the association between the PITX2 gene and the occurrence of AF in diverse populations. This meta-analysis investigated various SNPs in the PITX2 gene of chromosome 4q25 that are correlated with the occurrence of AF.

## MATERIALS AND METHODS

A systematic literature search was conducted in this meta-analysis to identify all case-control or prospective cohort studies that investigated the association of five types of SNP (rs2200733, rs10033464, rs385344, rs6838973, rs17570669) in the PITX2 gene against the risk of AF and lone AF. The literature search utilized PubMed, ScienceDirect, ProQuest, EBSCO, Springer, and Cochrane databases, using the following keywords: "gene polymorphism" or "SNP" or "single nucleotide polymorphism" and "atrial fibrillation" or "AF" or "lone AF".

The main criteria in this meta-analysis were all studies that described the association between the five types of SNP and the occurrence of AF. Several additional inclusion criteria were implemented in the literature search: (1) studies investigating patients with AF or lone AF; (2) prospective cohort or case-

control studies; (3) studies using odd ratios (OR) or relative risk parameters (RR), with 95% confidence intervals; (4) studies utilizing independent variables in the form of one or more than five SNPs (rs2200733, rs10033464, rs385344, rs6838973, rs17570669). The collected data were described in a specific format that met the standards for meta-analysis, then the data were classified based on the following criteria: the name of the main author, publication year, country of publication, study design, gender composition, age range, average age, allele frequency, and genotype distribution in each case and control group (Mohanty et al. 2013).

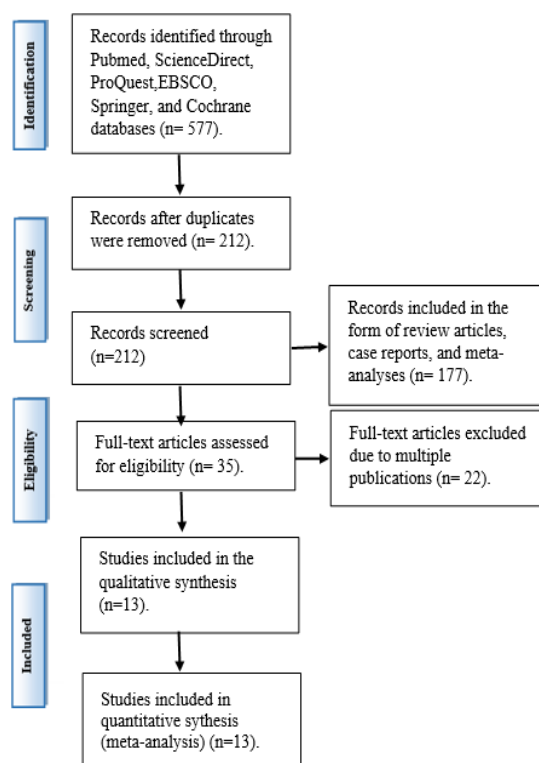


Figure 1. Steps in eliminating studies and extracting data.

A bias risk assessment was performed using the Newcastle–Ottawa Scale (NOS) for cohort and case control studies. The NOS cover four domains, which include selection, comparability, and exposure (Lo et al. 2014). Each question in the comparability domain could be given a "0" star if it is not contemplated, a "1" if the item is contemplated, and a maximum star of "2". The total number of stars represents the quality of the study, which can be interpreted as poor quality (0-2 stars), fair quality (3-5 stars), or good/high quality (6-9 stars).

The Chi-square test was used to assess the Equilibrium Hardy-Weinberg (EHW) in control group. Data recapitulation and analysis were carried out using Software Review Manager (Rev.Man) 5.0

and Comprehensive Meta-Analysis Software 3.3. The data heterogeneity was assessed using the Q statistic and the I<sup>2</sup> statistic, with a significance (p-value) less than 0.05, as suggested by Smith et al. (2012).

### RESULTS

The initial search yielded 577 scientific articles. In the screening process, 212 articles were identified as potentially relevant to this meta-analysis. However, 22 items were duplicates and 177 items were removed because they included 135 review articles, 38 case reports, and 4 meta-analysis articles. As a result, thirteen articles that matched the inclusion criteria for this meta-analysis were obtained.

As shown in Table 1, eleven studies, including a

total of 8,388 cases and 13,526 controls, examined the association of SNP rs2200733 with the risk of AF. A study by Mohanty et al. (2013) revealed a strong correlation between rs2200733 and AF occurrences, with a p-value of 0.006. The prevalence of the recessive allele (T allele) in patients with AF was 26.9%, whereas it was 14.5% in controls. Furthermore, Kalinderi et al. (2015) discovered that the T allele was more common in AF patients. A significant association between rs2200733 and AF events was also reported in studies by Lee et al. (2010), Lubitz et al. (2010), Olesen et al. (2012), Kolek et al. (2014), Kiliszek et al. (2016), and Zhao et al. (2017).

However, according to Bhanushali et al. (2017), rs2200733 was not related with AF. A similar finding was found in a study by Henningsen (2010). When these eleven studies were statistically

Table 1. Association between SNP rs2200733 and AF.

| Study or Subgroup   | Experimental |             | Control |              | Weight        | Odds Ratio          |                     | Odds Ratio<br>M-H, Random, 95% CI |
|---|--------------|-------------|---------|--------------|---------------|---------------------|---------------------|-----------------------------------|
|   | Events       | Total       | Events  | Total        |               | M-H, Random, 95% CI | M-H, Random, 95% CI |                                   |
| Anselmi 2012  | 19           | 66          | 104     | 696          | 5.4%          | 2.30                | [1.30, 4.08]        |                                   |
| Bhanushali 2016   | 10           | 82          | 15      | 114          | 3.1%          | 0.92                | [0.39, 2.16]        |                                   |
| Henningen 2011  | 56           | 392         | 36      | 352          | 7.0%          | 1.46                | [0.94, 2.29]        |                                   |
| Kalinderi 2015  | 94           | 334         | 46      | 256          | 7.8%          | 1.79                | [1.20, 2.66]        |                                   |
| Kiliszek 2011   | 251          | 778         | 133     | 1092         | 10.7%         | 3.43                | [2.71, 4.35]        |                                   |
| Kolek 2014  | 146          | 876         | 310     | 2806         | 11.1%         | 1.61                | [1.30, 1.99]        |                                   |
| Lee 2010  | 267          | 400         | 192     | 316          | 9.4%          | 1.30                | [0.95, 1.76]        |                                   |
| Lubitz 2010   | 340          | 1580        | 282     | 2354         | 11.9%         | 2.01                | [1.69, 2.39]        |                                   |
| Olesen 2012   | 67           | 418         | 111     | 1068         | 9.0%          | 1.65                | [1.19, 2.28]        |                                   |
| Shi 2009  | 495          | 766         | 856     | 1702         | 11.8%         | 1.81                | [1.51, 2.15]        |                                   |
| Zhao 2016   | 1680         | 2696        | 1445    | 2770         | 12.8%         | 1.52                | [1.36, 1.69]        |                                   |
| <b>Total (95% CI)</b>   |              | <b>8388</b> |         | <b>13526</b> | <b>100.0%</b> | <b>1.78</b>         | <b>[1.50, 2.11]</b> |                                   |
| Total events  |              | 3425        | 3530    |              |               |                     |                     |                                   |
| Heterogeneity: Tau <sup>2</sup> = 0.06; Chi <sup>2</sup> = 49.01, df = 10 (P < 0.00001); I <sup>2</sup> = 80% |              |             |         |              |               |                     |                     |                                   |
| Test for overall effect: Z = 6.60 (P < 0.00001)   |              |             |         |              |               |                     |                     |                                   |

Table 2. Association between SNP rs10033464 and AF.

| Study or Subgroup   | Experimental |             | Control |              | Weight        | Odds Ratio          |                     | Odds Ratio<br>M-H, Random, 95% CI |
|---|--------------|-------------|---------|--------------|---------------|---------------------|---------------------|-----------------------------------|
|   | Events       | Total       | Events  | Total        |               | M-H, Random, 95% CI | M-H, Random, 95% CI |                                   |
| Bhanushali 2016   | 19           | 82          | 13      | 114          | 7.0%          | 2.34                | [1.08, 5.07]        |                                   |
| Kiliszek 2011   | 93           | 770         | 83      | 1087         | 16.7%         | 1.66                | [1.22, 2.27]        |                                   |
| Lee 2010  | 88           | 400         | 58      | 328          | 15.1%         | 1.31                | [0.91, 1.90]        |                                   |
| Lemmens 2010  | 189          | 1888        | 540     | 6234         | 20.6%         | 1.17                | [0.99, 1.40]        |                                   |
| Lubitz 2010   | 142          | 1580        | 200     | 2354         | 19.2%         | 1.06                | [0.85, 1.33]        |                                   |
| Zhao 2016   | 500          | 2706        | 597     | 2756         | 21.5%         | 0.82                | [0.72, 0.94]        |                                   |
| <b>Total (95% CI)</b>   |              | <b>7426</b> |         | <b>12873</b> | <b>100.0%</b> | <b>1.21</b>         | <b>[0.94, 1.54]</b> |                                   |
| Total events  |              | 1031        | 1491    |              |               |                     |                     |                                   |
| Heterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 28.64, df = 5 (P < 0.0001); I <sup>2</sup> = 83% |              |             |         |              |               |                     |                     |                                   |
| Test for overall effect: Z = 1.50 (P = 0.13)  |              |             |         |              |               |                     |                     |                                   |

Table 3. Association between SNP rs3853445 and AF.

| Study or Subgroup  | Experimental |             | Control |             | Weight        | Odds Ratio          |                     | Odds Ratio<br>M-H, Random, 95% CI |
|--|--------------|-------------|---------|-------------|---------------|---------------------|---------------------|-----------------------------------|
|  | Events       | Total       | Events  | Total       |               | M-H, Random, 95% CI | M-H, Random, 95% CI |                                   |
| Kiliszek 2011  | 154          | 820         | 303     | 1110        | 29.7%         | 0.62                | [0.49, 0.77]        |                                   |
| Lubitz 2010  | 316          | 1580        | 612     | 2354        | 34.0%         | 0.71                | [0.61, 0.83]        |                                   |
| Zhao 2016  | 832          | 2676        | 895     | 2728        | 36.3%         | 0.92                | [0.82, 1.04]        |                                   |
| <b>Total (95% CI)</b>  |              | <b>5076</b> |         | <b>6192</b> | <b>100.0%</b> | <b>0.75</b>         | <b>[0.59, 0.95]</b> |                                   |
| Total events   |              | 1302        | 1810    |             |               |                     |                     |                                   |
| Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 13.78, df = 2 (P = 0.001); I <sup>2</sup> = 85% |              |             |         |             |               |                     |                     |                                   |
| Test for overall effect: Z = 2.36 (P = 0.02)   |              |             |         |             |               |                     |                     |                                   |

analyzed, there was a positive correlation between SNP rs2200733 and the prevalence of AF (OR=1.78, 95% CI=1.5-2.11, p<0.00001). It implies that subjects with recessive alleles (T) were more likely to experience AF episodes than subjects with dominant alleles (C).

Six studies with 7,426 cases and 12,873 controls were analyzed, as seen in Table 2. According to Bhanushali et al. (2017), there was a substantial connection between rs10033464 (T allele) with AF occurrences when compared to a control group. Kiliszek et al. (2016) also found that rs10033464 was related to an increased risk of AF. Zhao et al. (2017) obtained comparable results to the previous research. However, Lee et al. (2010) found that rs10033464 was not significantly associated to the occurrence of AF in their study. A similar notion was also stated by Lubitz et al. (2010). The analysis of these six studies revealed no significant correlation between SNP rs 10033464 and the risk of AF (OR=1.21, 95% CI=0.94-1.54, p=0.13, I<sup>2</sup>=83%).

There were only three studies investigating rs3853445 and AF, with a total of 5,076 cases and 6,192 controls (Table 3). A study by Kiliszek et al. (2016) did not show any significant correlation between rs3853445 and AF. Conversely, Lubitz et al. (2010) discovered that a minor allele of SNP rs3853445 was associated with a decreased risk of AF. The analysis discovered a significant negative correlation between SNPrs3853445 and the risk of AF (OR=0.75, 95% CI=0.59-0.95, p=0.2).

Only two of the selected studies investigated the association between rs6838973 and AF, with a total of 807 cases and 1,492 controls (Table 4). Kiliszek

et al. (2016) reported that rs6838973 had a substantial protective effect against AF. Lubitz et al (2010) reached a similar conclusion in their study. A statistical analysis was performed, and it was discovered that there was a considerably negative correlation between SNP rs6838973 and the probability of AF (OR=0.64, 95% CI=0.59-0.81, p=0.0001).

Table 5 shows that only two of the selected studies reported on rs17570669 and AF, with a total of 157 cases and 279 controls. According to the findings of a study by Kiliszek et al. (2016), rs17570669 had a protective effect against AF. In a study by Lubitz et al. (2010), rs17570669 was associated with a lower risk of AF after an additional adjustment of the rs2200733 genotype. A significant negative correlation was found between SNP rs17570669 and the likelihood of AF incidence (OR=0.80, 95% CI=0.65-0.98, p=0.03).

**DISCUSSION**

A meta-analysis of five types of SNP (rs2200733, rs10033464, rs385344, rs6838973, rs17570669) found in the PITX2 gene of chromosome 4q25 was conducted in this study. The PITX2 gene, also known as the paired-like homeodomain transcription factor 2 or pituitary homeobox 2 (PITX2), is located on chromosome 4q25. This gene is involved in the formation of cardiac asymmetry. Damage to this gene was found to play a role in the development of congenital defects, such as atrial isomerism, double outlet right ventricle (DORV), aortic arch anomalies, and malignant right coronary artery (Henningesen et al. 2010, Purwowyoto & Surya 2021). The PITX2 gene also served a role in AF, according to a genome-

Table 4. Association between SNP rs6838973 and AF.

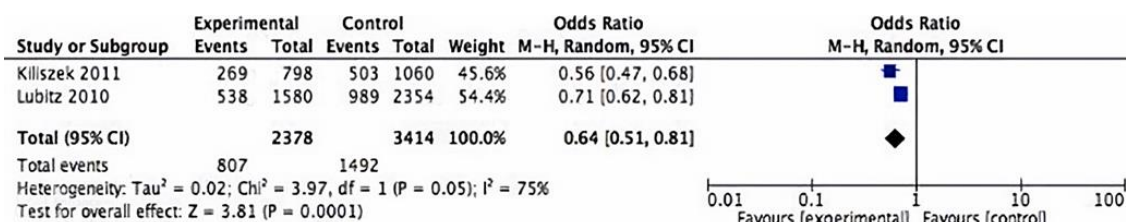
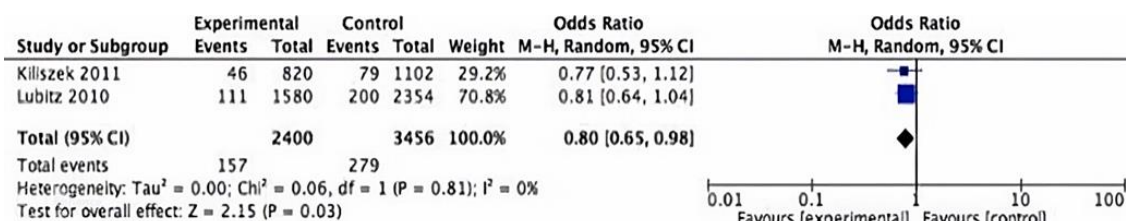


Table 5. Association between SNP rs17570669 and AF.





wide association study (GWAS) conducted in 2007. A study conducted on 550 patients and 4,476 controls discovered that SNP rs22000733 in the PITX-2 gene was involved in the incidence of AF. Following this study, another investigation focusing on the association between SNP and the occurrence of AF discovered some other SNPs, including rs10033464, rs385344, rs6838973, and rs17570669, which were predicted to have a link with the occurrence of AF (Lubitz et al. 2010, Schnabel et al. 2011, Bhanushali et al. 2017).

The conclusion of this meta-analysis showed that the roles of SNPs in the incidence of AF differed from each other. A meta-analysis conducted in 2012 indicated that the existence of minor alleles in SNP rs22000733 had a positive correlation with AF among the majority of AF patients in Europe (OR=1.89). This is remarkably comparable to the results obtained from this study, with the OR for the incidence of AF being 1.78. However, the population in this meta-analysis was more diverse than the sample in the 2012 meta-analysis. From the eleven selected studies, three were conducted in East Asia, one in Central Asia (India), four in Europe, and three in America. Diverse populations might lead to consistent results, which found that SNPs had significant roles in the incidence of AF (Smith et al. 2012). On the other hand, Bhanushali et al. (2017) determined that SNP rs22000733 had no significant correlation to the incidence of AF (OR=0.92). This could happen, however, because the number of samples used was only 25, consisting of 10 AF patients and 15 controls. In studies with hundreds or thousands of samples, such as those conducted by Zhao et al. (2017), Kolek et al. (2014), Kalinderi et al. (2015), SNP rs22000733 consistently demonstrated a positive correlation with the incidence of AF.

A meta-analysis of SNPs rs3853445, rs6838973, and rs17570669 found that minor alleles in the three SNPs had a protective effect against the occurrence of AF. Kiliszek et al. (2016) and Lubitz et al. (2010) conducted two major investigations that had a significant impact in this result. Kiliszek et al. (2016) conducted a study in Poland with 400 AF cases and 550 controls. Several novel SNPs (i.e., rs3853445, rs6838973, and rs17570669) in the PITX2 gene were investigated for their association with the occurrence of AF. Lubitz et al. (2010) observed in a prior study that the three SNPs listed above showed a negative correlation with the occurrence of AF. The study had discovered no significant relation between SNP and the occurrence of AF due to the smaller sample size. To draw conclusions on the protective effects of SNP on AF, studies with bigger sample sizes are required.

Finally, SNP rs10033464 was discovered to have no statistically significant relationship with the prevalence of AF. However, the findings of some of the studies included in this meta-analysis were not consistent. Among these studies were those by Bhanushali et al. (2017), who reported a positive correlation of the SNP to the occurrence of AF (OR=2.34), and Lemmens et al. (2010) who only identified a minor correlation. Other studies, on the other hand, discovered a negative association between the SNP and the occurrence of AF (OR=0.80), as well as an insignificant impact of the SNP on the risk of AF (Lee et al. 2010, Zhao et al. 2017). The discrepancies in the results among the selected studies might be attributed to the ethnicity of the subjects involved. Genetic information contains historical, anthropological, and statistical characteristics that vary across ethnicities (Sulistyorini et al. 2017, Yudianto et al. 2017). According to research conducted by Bhanushali et al. (2017), minor allele frequency was more common in Utah (US) residents of Northern and Western European ancestry, as well as Gujarati Indians in Houston (US), whereas allelic frequency differences were more common in Han Chinese in Beijing (China), Yoruba in Ibadan (Nigeria), and Japanese in Tokyo (Japan).

Several investigations on the relevance of genetic polymorphism in the occurrence of AF have indicated a significant association. However, the mechanism of how these genes affect the pathophysiology of AF is unknown (Olesen et al. 2012). An animal study demonstrated that animals with a PITX2 deficiency did not develop pulmonary myocardial sleeves (Chinchilla et al. 2011). Clinical research revealed that the sleeves induced ectopic beats, which play a crucial role in the atrial fibrillation process (Stavrakis et al. 2015). This mechanism is connected to AF ablation, which entails the electrical isolation of those sleeves in the pulmonary veins (Maesen et al. 2016). A better understanding of AF in general could improve the quality of cardiovascular disease healthcare services, such as the classification of AF using new methods (Yazid & Rahman 2020).

### Strength and limitations

Understanding the genetic polymorphisms that contribute to the risk factor of AF could accelerate healthcare-seeking behavior and a reduction in AF mortality. The purpose of this meta-analysis was also to identify five SNPs as factors that could affect the risk of AF. This meta-analysis covered numerous studies with subjects from a wide range of ethnicities. However, the heterogeneous study sample might have caused variability in the obtained data.

## CONCLUSION

This present meta-analysis identified five types of SNP as risk factors for atrial fibrillation (AF) across several studies and demographics. Individuals carrying rs2200733 are at a higher risk of developing AF. Conversely, rs3853445, rs6838973, and rs17570669 demonstrated a protective effect against AF.

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## Conflict of interest

None.

## Funding disclosure

None.

## Author contribution

RP, IM, and II designed the study, gathered the data, and conducted the data analysis. RP and JA interpreted the data for the study and drafted the manuscript. BD and BP revised the manuscript for important intellectual content and approved the final version for publication.

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