Published in final edited form as:

Crit Care Med. 2020 January ; 48(1): 22–30. doi:10.1097/CCM.0000000000004034.

Clinical and Genetic Contributors to New-Onset Atrial Fibrillation in Critically Ill Adults

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Abstract

Objective—New-onset atrial fibrillation (New AF) during critical illness is an independent risk factor for mortality. The ability to identify patients at high risk for new AF is limited. We hypothesized that genetic susceptibility contributes to risk of new AF in the ICU.

Design—Retrospective sub-study of a prospective observational cohort study.

Setting—Medical and general surgical ICUs in a tertiary academic medical center.

Patients—1,369 critically ill patients admitted to the ICU for at least 2 days with no known history of AF who had DNA available for genotyping.

Interventions—None.

Measurements—We genotyped 21 single nucleotide polymorphisms (SNPs) associated with AF in ambulatory studies using a Sequenom platform. We collected demographics, medical history, and development of new AF during the first four days of ICU admission.

Main Results—New AF occurred in 98 (7.2%) patients and was associated with age, male sex, coronary artery disease, and vasopressor use. SNPs associated with new AF were rs3853445 (near

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Conflict of Interest Statement: The authors have no relevant conflicts of interest to report.

PITX2, $p = 0.0002$), rs6838973 (near *PITX2*, $p = 0.01$), and rs12415501 (in *NEURL*, $p = 0.03$) on univariate testing. When controlling for clinical factors, rs3853445 (odds ratio [OR]: 0.47, 95% confidence interval [CI]: 0.30–0.73, $p = 0.001$) and rs12415501 (OR: 1.72, 95% CI: 1.27–2.59 $p = 0.01$) remained significantly associated with new AF. The addition of genetic variables to clinical factors improved new AF discrimination in a multivariable logistic regression model (C-statistic 0.78 vs 0.82, $p = 0.0009$).

Conclusions—We identified several SNPs associated with new AF in a large cohort of critically ill ICU patients, suggesting there is genetic susceptibility underlying this common clinical condition. This finding may provide new targets for future mechanistic studies and additional insight into the application of genomic information to identify patients at elevated risk for a common and important condition in the ICU.

MeSH Terms:

Atrial Fibrillation/genetics; Critical Illness; Genetic Predisposition to Disease; Polymorphism; Single Nucleotide; Retrospective Studies; Risk Factors

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults both in the ambulatory setting and during critical illness (1–7). In the intensive care unit (ICU), AF is independently associated with increased ICU and hospital length-of-stay as well as increased in-hospital mortality, particularly in the setting of sepsis (4, 6, 8). In a prospective observational cohort study of AF in critical illness, patients with new AF – defined as AF during critical illness with no known history of AF – had increased vasopressor requirements, greater cumulative positive fluid balance, increased diastolic dysfunction, and larger left atrial size relative to patients with AF during critical illness who had a prior history of AF as an outpatient (6).

The pathophysiology of new AF during critical illness is poorly understood, although myocardial ischemia, myocardial stretching, electrolyte disturbances, systemic and local inflammation, and adrenergic overload are all thought to contribute (7, 9–14). Genetic risk for new AF in the ICU has not been described.

In the ambulatory setting, a family history of AF is associated with an approximately 1.8-fold increase in risk for AF (15). Both targeted studies (16–19) and genome-wide association studies (GWAS) (17, 20–23) have identified genetic loci associated with ambulatory AF. Candidate genes associated with ambulatory AF include cardiac ion channels (16, 18, 22, 23), gap junction proteins (19), and transcription factors involved in cardiac embryogenesis (17–20, 22, 23) or cardiomyocyte differentiation (22, 23). Despite the extensive data in ambulatory AF, the role of genetic loci in new AF during critical illness remains unclear.

To investigate this question, we designed a retrospective study to characterize AF-associated genetic polymorphisms in an ICU population during critical illness. We hypothesized that these common genetic polymorphisms would influence risk of new AF in critically ill adults.

METHODS

Study Design

This is a retrospective sub-study of a previously-published prospective observational cohort of 1,770 critically ill adults aged ≥ 18 years admitted to the Medical or Surgical ICUs at Vanderbilt University Medical Center (6). All subjects were enrolled in the Validating Acute Lung Injury Markers for Diagnosis (VALID) Study within 24 hours of ICU admission (24). As previously reported, patients were excluded if they were < 18 years of age, died or were discharged from the ICU within 48 hours, were expected to transfer out of the ICU within 4 hours of enrollment, admitted in another hospital ICU for > 3 days prior to enrollment, or experienced a cardiac arrest prior to enrollment. Patients were also excluded if they were admitted for uncomplicated overdose, routine post-operative care after cardiothoracic surgery, or had a history of severe chronic lung disease. We included patients who had a DNA sample available for genotyping and did not have a history of AF prior to admission by review of the medical record. The Vanderbilt University Institutional Review Board approved the study protocol (IRB #051065). Informed consent was obtained from the patient or the designated surrogate medical decision maker whenever possible. A waiver of consent was approved when the patient was unable to give consent and no surrogate decision maker could be identified. The presence of AF, as well as other patient characteristics including demographics and cardiovascular history were gathered from the medical record by study personnel daily through the morning of ICU day 5.

We defined new AF as AF occurring in an ICU patient with no prior history of AF as determined by patient history and review of the medical record (6). Study personnel specifically reviewed physician progress notes, nursing notes, vitals flowsheets (where cardiac rhythm was documented hourly), and EKG interpretations by a cardiologist. We included both sustained AF and paroxysmal AF. We defined no AF as the absence of AF in the ICU and the absence of any history of AF by review of the medical record. Patients with a history of AF prior to ICU admission were excluded.

Genotyping

We extracted genomic DNA from blood samples obtained at enrollment into the VALID study. We assayed 25 single-nucleotide polymorphism (SNP) loci based on results of several ambulatory AF GWAS available at the time of this study (17, 19, 20, 23, 25–27). Primer sequences were designed based on publicly available reference sequences (28). Genotyping was performed by the Vanderbilt Technologies for Advanced Genomics (VANTAGE) core using a Sequenom platform (San Diego, CA). Pre-specified quality control measures included genotyping efficiency of $>95\%$ for each SNP locus as well as $>95\%$ for each individual. We used the R package Hardy-Weinberg (29) to assess departure from Hardy-Weinberg Equilibrium by Pearson's Chi-Square test or Fisher's exact test at each SNP locus in the no AF population, stratified by race (Caucasian vs Non-Caucasian).

Statistical Analysis

The primary outcome was presence of new AF during the study period. We performed univariate testing for new AF versus no AF for each SNP under multiplicative and additive

models. We used Fisher's exact test on allele frequencies for the multiplicative model and the Cochran-Armitage Test on genotype frequencies for the additive model. Based on a cohort of 98 new AF cases and 1271 controls, we calculated that the study had 80% power to detect an allelic odds ratio (OR) of 1.8 to 2.2 for SNPs with minor allele frequencies of 0.1 to 0.4, assuming a Type I error rate of 0.05 (30).

Due to the high number of potential predictor variables relative to the number of outcome events, we initially included only the clinical risk factors for AF in critical illness that were previously identified in this cohort (6). We then applied a least absolute shrinkage and selection operator (LASSO) regression model (31) to select predictor variables to retain while avoiding selection of co-linear variables. We selected a shrinkage parameter (λ) of 0.0057 which minimized the model deviance.

We tested a multivariable logistic regression model consisting of all clinical variables retained by the LASSO regression (the clinical model) to determine the OR and 95% confidence intervals (CI) of each predictor variable's effect on the primary outcome. The clinical model included age, sex, history of coronary artery disease (CAD), and receipt of vasopressors at any time during the study period. We defined CAD as the presence of a prior diagnosis of myocardial infarction, unstable angina, stable angina, or prior coronary revascularization from review of the medical record.

We then tested a combined clinical and genetic risk model consisting of the aforementioned clinical risk factors in addition to all SNPs retained by the LASSO regression (the combined model). Receiver operating characteristic (ROC) curves were constructed for both the clinical and combined risk models. As a sensitivity analysis, we repeated the multivariable logistic regression using the clinical risk factors and all genotyped SNPs to assess the ROC characteristics. We also assessed the robustness of our findings by repeating univariate testing in the subset of patients with sepsis ($n = 767$), and by testing the effect of timing of vasopressor initiation versus the onset of new AF in the combined model. Differences between models were assessed using the likelihood ratio test. We used Plink version 1.9 (32) and R version 3.3 (R Core Team. Vienna, Austria) for genetic association testing and RStudio version 1.0.147 (RStudio, Inc. Boston, MA) for data visualization.

RESULTS

Study Population

The study population included 1369 patients who had DNA available for genotyping. Among these patients, 98 (7.2%) experienced new AF and 1271 (92.8%) had no AF during the study period. Demographic and clinical characteristics are shown in Table 1. Consistent with our previous report (6), patients with new AF were older, more likely to be male, had higher severity of illness as measured by APACHE II (33) scores and number of organ failures, and were more likely to have known AF clinical risk factors. New AF was associated with an increased vasopressor requirement, longer ICU and hospital length-of-stay, and higher in-hospital mortality compared with no AF.

Genotyping

Genotype distributions and study population minor allele frequencies for the genotyped SNPs are shown in Supplemental Digital Content - Table 1. rs17570669, rs12370365, rs2723065, and rs7164883 failed genotyping due to low genotyping efficiency and were excluded from the analysis. The remaining twenty-one successfully genotyped SNPs were in Hardy-Weinberg equilibrium in the control (no AF) population (Supplemental Digital Content - Figure 1).

Several SNPs associated with ambulatory AF also associate with new AF

To test the association of each individual SNP with new AF, we tested the allele frequencies of each SNP under a multiplicative model using the Fisher's exact test, the results of which are shown in Figure 1 and Table 2. Three SNPs rs3853445 (near *PITX2*, $p = 0.0002$), rs6838973 (near *PITX2*, $p = 0.01$), and rs12415501 (in *NEURL*, $p = 0.03$) were significantly associated with differential risk for new AF. Results of testing genotype frequencies under an additive model did not substantially differ from the multiplicative model (Supplemental Digital Content - Table 2). There was no detected association between these SNPs and mortality (data not shown). To further explore the relationship between these SNPs and new AF in the ICU, we performed a sensitivity analysis in the subgroup of patients with severe sepsis ($n = 767$). This analysis demonstrated similar associations between AF SNPs and new AF risk in the presence of sepsis (Supplemental Digital Content - Figure 2).

Patients with new AF are older, have more coronary artery disease, and require more vasopressor support than patients with no AF in multivariable analysis

After selection of variables to retain using the LASSO model (Supplemental Digital Content - Table 3), we used a multivariable logistic regression model to assess the relative contributions of the retained clinical variables to new AF in the study population (Table 3). The clinical variables significantly associated with new AF included age ($p < 0.0001$), male sex ($p = 0.002$), CAD ($p = 0.025$), and receipt of vasopressors ($p < 0.0001$). Receipt of vasopressors had the largest effect size with an OR of 2.59 (95% CI 1.67–4.09).

SNPs associated with *PITX2* and *NEURL* remain associated with New AF when controlling for clinical variables

The SNPs retained by the LASSO regression were combined with the retained clinical variables to assess the independent association of these genes with new AF (Supplemental Digital Content - Table 3). In the combined model, age, male sex, CAD, and receipt of vasopressors remained significantly associated with new AF (Table 3). SNPs that remained significantly associated with risk of new AF when controlling for clinical variables were rs3853445 (C allele, OR 0.47, 95% CI [0.30, 0.73], $p = 0.001$) and rs12415501 (T allele, OR 1.72, 95% CI [1.27, 2.59], $p = 0.01$). OR and 95% CIs of all variables included in the combined model are illustrated in Figure 2.

Comparison of clinical and combined models

ROC curves for both the clinical and combined models demonstrated good discrimination with C-statistic of 0.78 and 0.82, respectively (Supplemental Digital Content - Figure 3).

The improved discrimination with the combined model compared to the clinical model was statistically significant by the likelihood ratio test ($p = 0.0009$). Including all 21 SNPs in a combined model did not significantly improve discrimination compared with the combined model containing the LASSO-retained SNPs ($p = 0.98$). We also tested whether timing of vasopressor utilization altered the relationship between AF SNPs and new AF. The majority of patients with new AF received vasopressors on the same day or a day preceding onset of AF ($n = 55$, 56%, Supplemental Digital Content - Table 4), and this sensitivity analysis did not substantially change the associations between AF SNPs and risk of new AF (Supplemental Digital Content - Figure 4).

DISCUSSION

In a cohort of critically ill medical and surgical ICU patients, we identified several genetic loci associated with new AF risk during critical illness. The two SNPs most strongly associated with new AF in this cohort were rs3853445 (near *PITX2*) and rs12415501 (in *NEURL*). However, many other SNPs frequently associated with ambulatory AF risk, such as rs2200733 (near *PITX2*) (17, 18, 20, 21), did not associate with new AF. Collectively, these data suggest a role of SNPs near *PITX2* and in *NEURL* in new AF risk during critical illness, although the index SNPs differ from those associated with ambulatory AF.

The SNP rs3853445 is located in chromosome 4q25, a region frequently associated with ambulatory AF (17–21, 23, 34). This locus is a non-coding intergenic region that is closest to the gene *PITX2* (28, 35). *PITX2* is a member of a homeobox transcription factor family that influences the establishment of left-right asymmetry in several organs including heart, lungs, and abdominal organs (35). In murine models, *PITX2* suppresses expression of sinoatrial node-specific genes in the left atrium, and *PITX2* mutants have increased frequency of atrial arrhythmias (36). *PITX2* also promotes myocardial regeneration by influencing expression of antioxidant genes such as superoxide dismutases, glutathione peroxidase, and components of the electron transport chain (37). Critical illness states including sepsis (38–40), the acute respiratory distress syndrome (ARDS) (41), and polytrauma (42, 43) are all associated with marked increases in oxidative stress and alterations in the antioxidant response. Further studies are needed to test whether this SNP alters *PITX2* function to explain its association with new AF. Future potential mechanistic studies to test the hypothesis that *PITX2* affects new AF risk during critical illness could include measuring the electrophysiologic effects of experimental sepsis in *PITX2* haploinsufficient mice (36) or measuring expression of micro-RNAs (*miR*) regulated by *PITX2* (including *miR-17-92* and *miR-106b-25*) (44). Measurements of biochemical markers of oxidative stress could be used to test the hypothesis that *PITX2* variation affects myocardial capacity to maintain oxidative homeostasis during critical illness.

The SNP rs12415501 is located in chromosome 10q24.33 and is intronic within the gene *NEURL* (19, 28). *NEURL* is a E3 ubiquitin ligase expressed during embryonic development in many organ systems including the heart (45). The SNP does not have direct coding significance, and it is unknown if rs12415501 impacts *NEURL* transcription or mRNA splicing. A knockdown model of the *NEURL* ortholog in zebrafish demonstrated a prolonged atrial action potential duration (19). Furthermore, the protein products of *NEURL*

and *PITX2* can directly interact in vitro in a kidney fibroblast cell line (19). Although little has been reported regarding the functional effects of this gene during AF, future mechanistic studies in *NEURL* knockdown models may be feasible as zebrafish knockdowns exhibited only mild developmental delay (19).

The addition of genetic risk markers to clinical variables improved discrimination for new AF. Our combined clinical and genetic model had a C-statistic of 0.82, which was significantly improved compared to a model using only clinical risk variables (C-statistic of 0.78, $p = 0.0009$). The practical application of genomics to predict risk of outcomes in critical care remains a subject of intense inquiry (46). Current GWAS technology in research applications allows a turnaround time of 2 days (47). Forty-seven percent of new AF patients in our cohort first developed AF >36 hours after ICU admission. Therefore, if GWAS testing to inform AF risk was initiated at the time of ICU admission, the results would be available to alter clinical care for a substantial proportion of patients who would ultimately develop new AF. Genetic risk for complications of critical illness could be used in the future to guide clinical decision making or to enrich clinical trials for patients at greater risk for the condition of interest. Somewhat unexpectedly, only a minority of SNPs previously associated with ambulatory AF were associated with risk of new AF in our cohort. This may reflect a greater importance of environmental factors in new AF during critical illness compared with ambulatory AF, particularly acute physiologic stressors such as adrenergic medications, myocardial ischemia, and systemic inflammation (7). Kolek et al. found that the addition of genetic information at many of the same loci did not significantly improve the prediction of post-operative AF risk following cardiac surgery (48), suggesting that the impact of genetic AF risk factors may depend on the clinical context. Furthermore, there may exist other genetic risk factors for new AF that were not tested in the current study. Further work will be needed to determine whether genetics influences other clinical outcomes in this population.

With regards to clinical risk factors for new AF, we found that age, sex, history of CAD, and vasopressors use moderately discriminated the risk of new AF (C-statistic 0.78). These findings are consistent other studies of new AF in ICU populations, as well as our previous report (6, 14, 49). Klouwenberg et al. reported that age, vasopressor use, inflammation as measured by C-reactive protein, renal failure, and highest fraction of inspired oxygen most strongly predicted new AF risk in 1,782 critically ill adults with sepsis (14). Moss et al. reported that acute respiratory failure, age over 60 years, and sepsis most strongly correlated with new AF over 8,356 ICU admissions (49). They also reported correlations with vasopressor use, post-operative state, severity of illness, active hemorrhage, valvular heart disease, sex, and chronic pulmonary disease (49).

This study has several strengths. It is the first study of genetic risk for new AF in a mixed medical and surgical ICU population. Subjects were well-phenotyped for clinical factors that affect new AF. Additionally, we specifically tested SNPs known to associate with ambulatory AF risk. Although mechanistic experiments were beyond the scope of this initial study, the tested SNPs are linked to genes with rational pathophysiologic mechanisms that provide testable hypotheses for future studies on the mechanisms of new AF during critical illness. This study also has some limitations. The sample size in the study cohort limited our

statistical power to detect associations of SNPs with new AF. This study had 80% power to detect an allelic OR of 1.8 to 2.2 on univariate testing, therefore the study may be underpowered to detect smaller effect sizes. Additionally, the SNPs included in this study only capture a portion of the heritable risk for AF. More recent ambulatory AF GWAS have identified additional novel SNPs and genetic loci associated with ambulatory AF that were unknown at the time of this study (50, 51). A positive family history of AF could potentially impact AF risk during critical illness (15), however we were unable to test this hypothesis because this element of family history was not consistently documented in the medical record. Although our chart review process included hourly telemetry reports and electronic searches for AF in the medical record, we cannot exclude the possibility of misclassification of subjects who may have experienced AF that was not clinically documented. Undetected “subclinical” paroxysmal AF may occur in up to 8% of ICU patients (49). Addition of automated analysis algorithms to ICU heart rhythm monitors may increase detection of new AF, reduce misclassification, and increase statistical power of future studies (49). Finally, we did not have sufficient sample size to divide our cohort into derivation and validation cohorts. As this is the first cohort study of the genetic basis of new AF during critical illness, validation of these findings in an independent ICU population should be performed.

CONCLUSIONS

In this study, we identified several SNPs associated with increased risk of new AF in a large cohort of critically ill adults. When controlling for clinical factors including age, sex, CAD, and vasopressor requirement, SNPs near *PITX2* and in *NEURL* remained significantly associated with new AF. These data identify targets for future mechanistic studies into the pathophysiology of new AF during critical illness, and provide insight into the potential application of genomic information to identify patients at elevated risk for a common and clinically important condition in the ICU.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Sources of Funding:

This work is supported by NIH T32 GM108554 (VEK), NIH HL 138737 (DD), NIH HL 135849 (LBW and JAB), NIH HL 103836 (LBW), NIH HL 136888 (CMS), Parker B. Francis Foundation (CMS), and Vanderbilt Faculty Research Scholars (CMS). The project publication described was supported by CTSA award No. UL1 TR002243 from the National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

Copyright form disclosure: Drs. Kerchberger, Koyama, Shoemaker, Darbar, Ware, and Shaver received support for article research from the National Institutes of Health (NIH). Dr. Darbar’s institution received funding from NIH R01 HL138737. Dr. Ware’s institution received funding from Boehringer Ingelheim and Global Blood Therapeutics (research grants). Dr. Shaver’s institution received funding from NIH (K08), Parker B Francis Foundation, and Vanderbilt Faculty Research Scholars. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Figure 1. Allelic association between single nucleotide polymorphism variants and new atrial fibrillation

Plot of odds ratios (OR, black dots) and 95% confidence intervals (CI, black lines) for the minor allele of each single-nucleotide polymorphism (SNP). Red dashed line is OR = 1.0 (no difference in new AF between minor and major alleles). An OR greater than 1.0 indicates the minor allele is associated with a higher risk of new AF. An OR less than 1.0 indicates the major allele is associated with a higher risk of new AF.

Figure 2. Risk factors for new atrial fibrillation in combined multivariable model

Plot of odds ratios (OR, dots) and 95% confidence intervals (CI, black lines) for clinical variables and the minor allele for each SNP. OR for each SNP is expressed as per copy of the minor allele. CAD: Coronary artery disease.

Table 1.**Demographic and Clinical Characteristics of Study Population**

	New Atrial Fibrillation (n = 98)	No Atrial Fibrillation (n = 1271)	p^a
Demographics			
Age (years)	66.4 (12.7)	54.6 (14.7)	< 0.001
Male Sex	67 (68%)	656 (52%)	0.002
Weight (kg)	86.0 (24.1)	82.0 (27.0)	0.157
Caucasian Race	89 (91%)	1056 (83%)	0.064
Medical ICU (vs Surgical ICU)	62 (63%)	897 (71%)	0.159
Comorbid Medical Conditions			
Chronic Kidney Disease	28 (29%)	249 (20%)	0.045
Diabetes	33 (34%)	381 (30%)	0.513
Chronic Liver Disease	13 (13%)	182 (14%)	0.89
Congestive Heart Failure	17 (17%)	118 (9%)	0.016
Coronary Artery Disease	25 (26%)	133 (11%)	< 0.001
Prior Stroke	13 (13%)	98 (8%)	0.08
Hypertension	61 (62%)	614 (48%)	0.011
Dyslipidemia	33 (34%)	292 (23%)	0.023
ICU / Hospitalization Characteristics			
ICU Length of Stay (days)	8.0 [4.0, 15.75]	5.0 [3.0, 9.0]	< 0.001
Severe Sepsis on Admission	60 (61%)	707 (56%)	0.332
Receipt of any Vasoactive Medication during Study Period	64 (65%)	533 (42%)	0.009
Duration of Vasoactive Medications (days)	1.0 [0.0, 3.0]	0.0 [0.0, 2.0]	< 0.001
APACHE II	27 (8.1)	25 (8.4)	0.021
Total Organ Failures during Study Period	2.0 (0.9)	1.6 (1.1)	0.001
In-Hospital Mortality	29 (30%)	204 (16%)	0.001

Data are presented n (%) for categorical variables, mean (standard deviation) for continuous variables with normal distributions, and median [interquartile range] for continuous variables with non-normal distributions. bpm – beats per minute.

^a Group-wise comparison testing performed using Chi-squared test for categorical variables, one-way ANOVA for continuous variables with normal distributions, and Kruskal-Wallis Test for continuous variables with non-normal distributions.

Table 2.

Univariate Testing of Allele Frequencies in Study Population

SNP	Gene	Minor / Major Alleles	MAF New AF	MAF No AF	Minor Allele Odds Ratio	95% Confidence Intervals	<i>p</i> ^a
rs3853445	PITX2	C / T	0.14	0.25	0.47	0.30; 0.72	0.0002
rs10033464	PITX2	T / G	0.07	0.12	0.59	0.31; 1.03	0.06
rs4400058	PITX2	A / G	0.07	0.11	0.62	0.33; 1.09	0.09
rs6838973	PITX2	T / C	0.31	0.4	0.67	0.48; 0.92	0.01
rs10507248	TBX5	G / T	0.23	0.29	0.73	0.51; 1.04	0.08
rs7193343	ZFHX3	T / C	0.13	0.17	0.76	0.47; 1.17	0.23
rs10824026	SYNPO2L	G / A	0.19	0.23	0.81	0.54; 1.17	0.29
rs2106261	ZFHX3	A / G	0.15	0.17	0.84	0.54; 1.27	0.43
rs13216675	GJA1	C / T	0.26	0.28	0.91	0.64; 1.28	0.62
rs3807989	CAV1	A / G	0.42	0.44	0.93	0.68; 1.26	0.65
rs4642101	CAND2	T / G	0.35	0.36	0.95	0.69; 1.30	0.76
rs6666258	KCNN3	C / G	0.30	0.31	0.97	0.69; 1.34	0.87
rs13376333	KCNN3	T / C	0.30	0.30	1.00	0.71; 1.38	1.00
rs1152591	SYNE2	T / C	0.44	0.43	1.03	0.76; 1.39	0.88
rs3903239	PRRX1	C / T	0.42	0.41	1.05	0.77; 1.42	0.76
rs1448818	PITX2	G / T	0.29	0.26	1.16	0.83; 1.62	0.36
rs10821415	C9orf3	A / C	0.41	0.37	1.18	0.87; 1.61	0.28
rs6817105	PITX2	C / T	0.14	0.12	1.22	0.77; 1.87	0.36
rs2200733	PITX2	T / C	0.14	0.11	1.27	0.80; 1.95	0.29
rs2040862	WNT8A	T / C	0.19	0.15	1.32	0.89; 1.93	0.15
rs12415501	NEURL	T / C	0.19	0.13	1.56	1.04; 2.29	0.03

SNP = Single-nucleotide polymorphism, MAF = Minor allele frequency.

^aBy Fisher's Exact Test for allele frequencies.

SNPs in boldface were included in the multivariable logistic regression.

Table 3.

Comparison of Multivariable Logistic Regression Models for New Atrial Fibrillation

Variable	Clinical Model				Combined Model			
	Beta (SE)	OR	[95% CI]	<i>p</i>	Beta (SE)	OR	[95% CI]	<i>p</i>
Age (per 10 years)	0.62 (0.09)	1.85	[1.55; 2.22]	< 0.0001	0.61 (0.09)	1.85	[1.54; 2.23]	< 0.0001
Male Sex	0.71 (0.24)	2.04	[1.30; 3.27]	0.002	0.73 (0.24)	2.07	[1.30; 3.35]	0.003
CAD	0.60 (0.27)	1.81	[1.06; 3.02]	0.025	0.68 (0.28)	1.97	[1.13; 3.36]	0.014
Required Vasopressor	0.95 (0.23)	2.59	[1.67; 4.09]	< 0.0001	0.96 (0.24)	2.62	[1.66; 4.19]	< 0.0001
rs3853445 (C) <i>PITX2</i>					-0.75 (0.23)	0.47	[0.30; 0.73]	0.001
rs10033464 (T) <i>PITX2</i>					-0.32 (0.31)	0.73	[0.40; 1.32]	0.30
rs10507248 (G) <i>TBX5</i>					-0.26 (0.19)	0.77	[0.53; 1.11]	0.17
rs7193343 (T) <i>ZFHX3</i>					-0.27 (0.23)	0.76	[0.47; 1.18]	0.24
rs10824026 (G) <i>SYNPO2L</i>					-0.21 (0.19)	0.81	[0.55; 1.17]	0.28
rs4642101 (T) <i>CAND2</i>					-0.18 (0.17)	0.84	[0.60; 1.16]	0.30
rs1448818 (G) <i>PITX2</i>					0.21 (0.18)	1.23	[0.86; 1.75]	0.25
rs10821415 (A) <i>C9orf3</i>					0.19 (0.16)	1.21	[0.88; 1.64]	0.24
rs2200733 (T) <i>PITX2</i>					0.31 (0.24)	1.36	[0.83; 2.17]	0.21
rs2040862 (T) <i>WNT8A</i>					0.19 (0.21)	1.22	[0.80; 1.81]	0.35
rs12415501 (T) <i>NEURL</i>					0.54 (0.21)	1.72	[1.27; 2.59]	0.010

Variables in boldface are significantly associated with new AF ($p < 0.05$) in the combined clinical and genetics model.

Single nucleotide polymorphism markers are presented as reference SNP cluster ID (minor allele). CAD: Coronary artery disease