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Genetic variation in the β_1 -adrenergic receptor is associated with the risk of atrial fibrillation after cardiac surgery

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Abstract

Background: Postoperative atrial fibrillation (PoAF) after cardiac surgery is common and associated with increased morbidity and mortality. Increased sympathetic activation after surgery contributes to PoAF, and beta-blockers are the first-line recommendation for its prevention. We examined the hypothesis that common functional genetic variants in the β_1 -adrenoreceptor, the mediator of cardiac sympathetic activation and drug target of beta-blockers, are associated with the risk for PoAF and with the protective effect of beta-blockers.

Methods: In a prospective cohort study, we studied 947 adult European Americans who underwent cardiac surgery at Vanderbilt University between 1999-2005. We genotyped two variants in the β_1 -adrenoreceptor, rs1801253 (Arg389Gly) and rs1801252 (Ser49Gly), and used logistic regression to examine the association between genotypes and PoAF occurring within 14 days after surgery, before and after adjustment for demographic and clinical covariates.

Results: PoAF occurred in 239 patients (25.2%) and was associated with rs1801253 genotype (adjusted $P=0.008$), with Gly389Gly having an odds ratio of 2.63 (95% confidence interval, 1.42 to 4.89) for PoAF compared to the common Arg389Arg ($P=0.002$). In a predefined subgroup analysis, this association appeared to be stronger among patients without beta-blocker prophylaxis (adjusted OR=7.00; 95% CI, 1.82 to 26.96; $P=0.005$) compared to patients with beta-blocker prophylaxis, among whom the association between rs1801253 genotype and PoAF was not statistically significant (adjusted $P=0.11$).

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Conclusion: The Gly389 variant in the β_1 -adrenoreceptor is associated with PoAF, and this association appears to be modulated by beta-blocker therapy. Future studies of the association of other adrenergic pathway genes with PoAF will be of interest.

Introduction

New-onset atrial fibrillation (AF) is a common complication after cardiac surgery, occurring in 25-40% of patients.^{1,2} Many factors have been implicated in the pathophysiology of postoperative atrial fibrillation (PoAF), including physical trauma to the atria and pericardium, local ischemia, hypoxia, and inflammation, and systemic effects such as neurohumoral activation (including sympathetic activation), volume redistribution, and electrolyte disturbances.^{1,3,4} PoAF is associated with considerable morbidity (e.g., a 3-fold increase in perioperative stroke, infections, renal failure, heart failure, and myocardial infarction) and an estimated 9.7% increase in mortality.¹ Accordingly, patients with PoAF have prolonged postoperative hospital stays and incur substantially higher healthcare costs both during and after hospitalization.³

The important role of the sympathetic nervous system in the pathogenesis of PoAF is illustrated by the effectiveness of β -adrenergic receptor blockers (BB) in its prevention. A recent meta-analysis of 31 randomized controlled trials estimated that the post-operative use of BB is associated with a 30-70% reduction in PoAF (depending on whether pre-operative BB therapy was allowed to be continued in the placebo arm).⁵ Indeed, guidelines published by American and European professional organizations recommend BBs as first choice for the prevention of PoAF after cardiac surgery.^{2,6,7}

The cardiac β_1 -adrenergic receptor (β_1 -AR) is the main mediator of sympathetic activity in the heart and the principal drug target of β -AR blockers. Common genetic variants in the β_1 -AR affect its function and its response to β -blockers *in vitro* and *in vivo*. In particular, the single nucleotide polymorphism (SNPs) rs1801253, resulting in the amino acid substitutions Arg389Gly in the carboxy-terminal intracellular loop, is associated with decreased G-protein coupling and a lesser response to agonist and antagonist in *in vitro* studies of transfected cell models, transgenic mice, and human heart tissue.⁸ A second non-synonymous SNP, rs1801252, resulting in the Ser49Gly variant in the extracellular amino terminal end of β_1 -AR, is associated with increased agonist-promoted receptor down-regulation in transfected cell lines.⁹ Accordingly, a number of translational¹⁰⁻¹² and clinical studies in patients with hypertension, AF, and heart failure with reduced ejection fraction have found genotype-dependent responses to BBs.¹³⁻¹⁹

While *ADRB1* variants were not found in genome-wide association studies to be associated with ambulatory AF, i.e. AF developing outside the context of surgery,²⁰ these variants may play a greater role in AF occurring after cardiac surgery because of the prominent role of the sympathetic nervous system in the pathogenesis of PoAF. There is currently no information about the association of *ADRB1* variants with PoAF.

We therefore set out to study the association of common functional genetic β_1 -AR variants with PoAF and with prophylactic BB therapy. For this purpose, we examined the Arg389Gly and Ser49Gly genotypes in the Vanderbilt Cardiac Surgery Registry, a prospective cohort study of patients undergoing cardiac surgery, and examined its association with the incidence of PoAF and with the effectiveness of prophylactic BB therapy.

Methods

Setting

Between November 1999 and May 2005, the Vanderbilt Cardiac Surgery Registry (VCSR) prospectively enrolled consecutive consenting adult patients (age > 18 years) undergoing cardiac surgery at Vanderbilt University Medical Center. The study protocol was approved by the Vanderbilt University Institutional Review Board, and patients gave written informed consent. Information on medical history, preoperative drug treatment, laboratory results, surgical procedures, and postoperative course (medications, onset of cardiac arrhythmias) was extracted by trained data abstractors from the medical records and entered into a computerized database, and DNA samples were stored in the Vanderbilt DNA Resource Core. The VCSR registry has previously contributed data to a number of outcome studies.²¹⁻²⁵

Study population

Among 1,288 patients in the VCSR registry, we limited the population for the present study to self-identified European Americans, because they constitute the great majority of the patients in the VCSR database (90.7%) and thus were the only ethnic group providing sufficient power for analyses. A flow diagram depicting patient exclusions is shown in the Figure 1. We excluded patients who had incomplete follow-up or did not proceed to surgery (n=21), were in AF at the beginning of the operation (n=104), had surgery not requiring cardiopulmonary bypass (n=67), had a heart transplant or Maze procedure as index procedure or in the past (n=17), or had missing genotyping results for both rs1801252 and 1801253 (n=13). The final study cohort included 947 subjects.

Outcome definition

Patients were monitored with continuous telemetry during their hospitalization. We defined cases with postoperative atrial fibrillation as patients diagnosed with new-onset AF within 14 days after surgery, documented by either telemetry tracings or 12-lead ECG, or by the presence of at least two of the five following criteria: Documentation of AF in 1. nurses' notes, 2. in physicians' progress notes, or 3. in the discharge summary, 4. start of medications consistent with a new diagnosis of AF (e.g., beta-blockers, diltiazem, verapamil, amiodarone, warfarin), and 5. a cardiology consultation for AF management.

Clinical covariates

We predefined demographic and clinical parameters that were previously associated with the risk for PoAF^{7,26} and extracted them from the VCSR database. Concomitant diseases (hypertension, heart failure, history of myocardial infarction, history of AF) were defined as present if listed at the preoperative evaluation. A diagnosis of chronic obstructive pulmonary disease was given to patients chronically using inhaled steroids and / or β_2 -adrenergic receptor agonists. We calculated estimated glomerular filtration rate (eGFR) using the CKD-EPI formula.²⁷ The type of heart surgery was classified as either isolated coronary artery bypass grafting (CABG) or complex procedures (e.g., valve surgery, correction of congenital defects) with or without CABG. Vasopressor use was defined as any intra- or postoperative use of vasopressors (dopamine, dobutamine, norepinephrine, vasopressin). Prophylactic use of BBs was defined as beta-blocker use during hospitalization within 14 days after surgery but, in patients with PoAF, before the onset of AF. Discontinuation of BB therapy was considered to have occurred when a patient on chronic preoperative BB therapy did not receive prophylactic beta blocker therapy after the surgery. Antiarrhythmic therapy included therapy with amiodarone, flecainide, propafenone, digoxin, or procainamide.

SNP selection and genotyping

Based on previous studies,^{10,16,19} we selected the two common, functional SNPs in the *ADRB1* candidate gene, rs1801252 and rs1801253, for genotyping. Both SNPs were genotyped by the Vanderbilt DNA Resources Core using TaqMan® SNP genotyping assays (Applied Biosystems, Foster City, California, USA). Genotypes were not available in 15 (1.5%) and 10 patients (1.0%) for rs1801252 and rs1801253, respectively. The overall genotyping call rates for these SNPs were >97%. Neither SNP deviated from Hardy-Weinberg equilibrium expectations in cases or controls ($P > 0.05$), and minor allele frequencies were in the expected range.¹⁰

Statistical analysis

We summarized patient characteristics using descriptive statistics (means $\pm$ standard deviation (SD) for continuous variables, and proportions for ordinal and categorical variables). We compared demographic and clinical variables between subjects with and without PoAF using independent t-test or χ^2 test, as appropriate. Genotype distributions were tested for Hardy-Weinberg equilibrium using χ^2 test with one degree of freedom. To examine the association of genotypes with PoAF, we performed logistic regression analyses using PoAF as outcome and rs1801252 and rs1801253 genotypes as independent variables. Various genetic models have been used in previous *ADRB1* studies, and we therefore coded genotypes as categorical variables (assuming genotype categories as genetic model) without presuming a specific mode of inheritance. This approach yields an overall P-value for genotype effect (Wald statistics) as well as odds ratios (ORs) and 95% confidence intervals (CIs) for each genotype compared to the reference genotype (wildtype homozygotes). Logistic regression analyses were performed with and without adjustment for the following covariates (entered as single block): Age, sex, body mass index (BMI), eGFR, history of AF, myocardial infarction, heart failure, hypertension, diabetes mellitus, COPD, type of surgery (isolated CABG or complex surgery), use of vasopressors, prophylactic treatment with BB, discontinuation of BB, and treatment with antiarrhythmic drugs, angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), and statins. In a reduced model, we adjusted for only 4 major clinical confounders (age, sex, history of atrial fibrillation, and complex surgical procedure)²⁶ to account for potential model overfitting. We also predefined a subgroup analysis in patients with and without prophylactic BB use because of the known association of *ADRB1* genotypes with response to BBs, and tested for the interaction between prophylactic BB use and genotype by adding an interaction term (prophylactic BB use $\times$ genotype) in the logistic regression analyses. As sensitivity analyses, we also performed these analyses after excluding 89 patients with a previous history of AFib and 73 cases in whom PoAF had not been documented by ECG or telemetry tracing. Data are presented as mean $\pm$ standard deviation (SD), and odds ratios (OR), derived from the logistic regression analysis, with 95% confidence intervals (95% CI). All tests were two-sided, and p-values < 0.05 were considered significant. All analyses were performed using the statistical softwares packages SPSS v.21 (IBM® SPSS® Inc., Chicago, IL) and STATA v.11 (StataCorp, College Station, TX).

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Results

Patients

A total of 947 European Americans in the VCSR registry met our inclusion/exclusion criteria and composed the final study population (Figure 1). Descriptive statistics for demographic and clinical variables and genetic data are presented in Tables 1 and 2. Most patients (n=677, 71.5%) received prophylactic postoperative BB therapy.

Clinical risk factors of PoAF

PoAF occurred in 239 of 947 patients (25.2%) and was diagnosed based on ECG/telemetry recording (n=160, 67%), discharge summary (n=72, 30%), or a consult for atrial fibrillation (n=7, 3%), the latter 2 categories requiring at least one additional diagnostic criterion. Patients with PoAF were significantly older and more likely to have a history of AF, hypertension, and heart failure (Table 1, all $P<0.013$). Other clinical covariates associated with PoAF outcome included complex surgery type (valve surgery $\pm$ CABG) vs. isolated CABG, treatment with vasopressors and ACE-I or ARBs, and the discontinuation of BB treatment, while postoperative use of BB was associated with a lower risk for PoAF (all $P<0.014$; Table 1). After adjustment for all clinical covariates and the two genetic markers (rs1801252 and rs1801253), increased age, history of AF, higher eGFR, complex surgery type, and BB discontinuation were associated with a higher incidence of PoAF, while prophylactic BB treatment was associated with a lower risk (Supplementary Table 1).

Incidence of PoAF and *ADRB1* genotypes

The crude incidence of PoAF differed by rs1801253 genotype, but this trend did not reach statistical significance (overall $P=0.085$; Table 2). The incidence of PoAF in patients homozygous for the minor allele (Gly389Gly) was 36.1%, compared to 23.9% in patients with the common CC genotype (Arg389Arg; unadjusted OR=1.80, $P=0.026$). After adjustment for all covariates, rs1801253 genotype was significantly associated with PoAF (overall $P=0.008$), and homozygotes for the minor allele (Gly389Gly) had an OR of 2.63 for PoAF compared to the common Arg389Arg genotype ($P=0.002$; Table 2; Figure). The association of Gly389Gly with PoAF was largely unaffected after excluding 89 subjects with a previous history of AF (adjusted OR, 2.95; 95% CI, 1.53 to 5.69; $P=0.001$) and 73 cases without ECG- or telemetry documentation of PoAF (adjusted OR, 3.71; 95% CI, 1.91 to 7.20; $P<0.001$). Additionally, a reduced model adjusting for only 4 major clinical covariates (age, sex, history of atrial fibrillation, and complex surgical procedure) yielded a similar association of Gly389Gly with PoAF (adjusted OR, 2.41; 95% CI, 1.35 to 4.30; $P=0.003$). In contrast, heterozygous patients (Arg389Gly genotype) did not have an increased risk of PoAF compared with the reference group in the unadjusted (OR=1.09, $P=0.60$) or adjusted models (OR=1.07, $P=0.74$; Table 2; Figure).

The rs1801252 genotype (Ser49Gly variant) was not significantly associated with PoAF before and after adjustment for all covariates (Table 2).

In a predefined subgroup analysis, we compared patients with and without prophylactic treatment with BB (Table 3). In patients receiving BB prophylaxis (n=672), the association between rs1801253 genotype and PoAF was not statistically significant (overall adjusted $P=0.11$). In contrast, among patients without BB prophylaxis (n=256), the association between rs1801253 genotype and PoAF was statistically significant (overall adjusted $P=0.018$): Patients with the Gly389Gly genotype had a PoAF incidence of 64.7% compared to 35.6% in patients with the Arg389Arg reference genotype (adjusted OR= 7.00; $P=0.005$; Table 3; Figure). However, when adding an interaction term to the logistic regression model,

there was no statistically significant interaction between rs1801253 genotype and prophylactic BB use (overall $P=0.23$ for interaction term).

For the rs1801252 genotype (Ser49Gly variant), there was no significant overall association with PoAF regardless of prophylactic BB therapy (adjusted $P>0.13$; Table S2). Among the subgroup of heterozygous patients using BB prophylaxis, there was a weak association with increased PoAF risk that was no longer statistically significant after adjustment (Table S2).

Discussion

In this hypothesis-driven study, we found an association of a functional genetic marker in the β_1 -AR (rs1801253 GG genotype, denoting the Gly389Gly variant) with the risk for PoAF. This association was more pronounced after adjustment for covariates known to affect the risk of PoAF, and was especially prominent in patients who did not receive prophylactic beta-blocker treatment.

In view of its important prognostic significance, a large number of studies have identified clinical risk factors predicting the risk for PoAF.^{26,28-30} Recently, genetic variants have been found to be associated with increased risk of PoAF after adjustment for clinical covariates.^{21,31,32} These markers were studied because they were associated with AF in ambulatory populations, i.e. AF developing outside the context of surgery. Thus, genetic markers related to adrenergic receptor signaling pathways were not considered, likely because in genome-wide association studies they were not identified as risk markers for AF.^{20,33} Considering the prominent role of sympathetic activity in the pathogenesis of PoAF⁴ we examined the hypothesis that two common functional genetic markers in the β_1 -AR gene would affect the risk of PoAF. Our findings suggest that some genetic variants may be associated in particular with AF occurring after cardiac surgery although they were not implicated in ambulatory AF even in large, systematic genome-wide association studies, reflecting the potential role of these markers in pathways characterizing post-operative perturbations such as sympathetic activation, inflammation, and oxidative stress.⁴ In fact, two genetic markers in inflammatory pathways have been associated with PoAF in preliminary studies.^{34,35}

A number of previous studies have shown that the *ADRB1* rs1801253 variant affects β_1 -AR function and response to BB therapy. In *in vitro* and animal studies, the rs1801253 CC genotype, encoding the Arg389Arg β_1 -AR, has been associated with enhanced signal transduction and greater responses to agonist and antagonists,³⁶ and in subjects with hypertension and heart failure, Arg389 carriers showed a greater response to beta blocker treatment.^{16,17} However, chronic hyperactive adrenergic signaling through the Arg389 β_1 -AR appears to result in enhanced receptor desensitization by depressed coupling compared to the Gly389 variant.^{36,37} This enhanced agonist-promoted desensitization in Arg389 carriers^{36,38} may have a protective effect against the sudden postoperative sympathetic surge. Compatible with these observations, we found in the present study a lower risk for PoAF associated with Arg389, and an increased risk with Gly389. Interestingly, in a recent study in high-risk patients undergoing surgery with spinal block, carriers of the Gly389 variant were at higher risk for a postoperative composite cardiovascular outcome (cardiovascular mortality, nonfatal myocardial infarction, unstable angina, congestive heart failure, and stroke) compared to the Arg389Arg variant (OR=1.87; $P=0.04$).³⁹

A pre-specified subgroup analysis provided some evidence for the modification of the PoAF-genotype association by beta blocker prophylaxis. The association of rs1801253 genotype with PoAF was not statistically significant among patients receiving beta blocker prophylaxis (overall $P=0.11$). In contrast, in the much smaller subgroup of patients *without*

BB prophylaxis, the association between genotype and PoAF was stronger (adjusted overall $P=0.018$), with an estimated OR for PoAF of 7.00 (95% CI, 1.82 to 26.96) for the Gly389Gly genotype compared to the reference Arg389Arg genotype ($P=0.005$). This wide CI presumably reflected the comparatively few cases in this genotype group among non-users of BB prophylaxis and in fact overlapped with that of the Gly389Gly genotype effect in patients *with* BB prophylaxis (OR=2.18; 95% CI, 1.03 to 4.63). Also, on formal testing the interaction term between rs1801253 genotype and prophylactic BB use was not statistically significant (overall $P=0.23$). In summary, the Gly389Gly genotype appears to convey a significantly increased risk for PoAF, and this risk may be attenuated by treatment with β_1 -AR antagonists. This appears to be a biologically plausible constellation within the triad of genetic variant, disease risk, and pharmacogenetic treatment effect. Consistent with these observations, in a recent study of patients with AF, carriers of the Gly389 variant responded better to rate-control therapy (most commonly based on BBs) than patients homozygous for the Arg389 variant.¹⁸

Our study has a number of strengths and limitations. We adjusted our analyses for a large number of covariates, including for those most relevant to adrenergic pathways, e.g. prophylactic beta blocker use and beta blocker discontinuation. Indeed, our analyses validated the association of many of the previously described covariates with PoAF. However, we did not include other genetic markers known to predict PoAF, e.g. markers in the 4q25 locus.^{21,32} Yet, these markers are not located on the same chromosome as the *ADRB1* gene, and it is therefore likely that the effect of rs1801253 is independent of theirs. Although our total sample size was rather large, some genotype subgroups, in particular among non-users of BB prophylaxis, were rather small, resulting in wide confidence intervals for the estimated odds ratios. Larger populations will be necessary for more precise estimates. In addition, we studied only European Americans, and cannot extrapolate our findings to populations of non-European descent. Finally, although our findings, using a single candidate gene approach to test a specific hypothesis, are biologically plausible, they should be validated in larger independent cohorts from diverse populations.

In conclusion, we report the association of a functional genetic variant in β_1 -AR (Gly389) with PoAF. Thus, genetic variants in sympathetic pathways appear to be reasonable candidate markers for the risk for PoAF, reflecting the role of sympathetic activation in the pathophysiology of PoAF. Future studies identifying additional genetic markers in pathways associated with postoperative perturbations and incorporating them into clinical and genetic risk scores will be of interest, since robust PoAF risk prediction tools would be helpful to individualize prophylactic drug treatment.

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Figure 1. Study cohort flow diagram depicting patient exclusions

Starting with a total of 1,288 patients in the VCSR registry, 341 patients (26%) were excluded, resulting in a study cohort of 947 patients.

Figure 2. Adjusted odds ratios for PoAF in *ADRB1* rs1801253 genotypes, stratified by use of prophylactic beta blockers

The Gly389Gly genotype was associated with significantly increased risk for PoAF, and this effect appeared to be more prominent in patients not using beta blocker prophylaxis. Points represent the point estimate of the OR, horizontal bars the 95% CI. ORs represent risks compared to the reference genotype (Arg389Arg).

Table 1

Demographic and clinical variables in 947 European Americans with and without PoAF. Data presented as mean±SD or n (%). P-values for unadjusted comparisons between patients with and without PoAF using χ^2 -test or independent t-test. BMI = body mass index; H/o = Past history of; eGFR = estimated glomerular filtration rate; COPD = chronic obstructive pulmonary disease; CABG = coronary artery bypass grafting; BB = beta blockers; ACE-I = angiotensin converting enzyme inhibitors; ARBs = angiotensin receptor blockers;

	All subjects (n=947)	PoAF (n=239)	No PoAF (n=708)	P-value
Age, years	58.8±14.3	65.1±12.6	56.7±14.2	<0.001
Female sex	319 (33.7%)	71 (29.7%)	248 (35.0%)	0.13
BMI, kg/m ²	28.7±15.4	28.5±6.5	28.8±5.8	0.55
H/o atrial fibrillation	89 (9.4%)	47 (19.7%)	42 (5.9%)	<0.001
H/o myocardial infarction	390 (41.2%)	98 (41.0%)	292 (41.2%)	0.95
Heart failure	201 (21.2%)	64 (26.8%)	137 (19.4%)	0.013
Hypertension	649 (68.5%)	181 (75.7%)	468 (66.1%)	0.005
Diabetes mellitus	260 (27.5%)	76 (31.8%)	184 (26.0%)	0.08
eGFR, ml/min*1.73 m ²	76.8±24.8	72.9±24.6	78.0±24.7	0.57
COPD	109 (11.5%)	36 (15.1%)	73 (10.3%)	0.047
Surgery type: Isolated CABG Complex surgery	590 (62.3%) 357 (37.7%)	133 (55.6%) 106 (44.4%)	457 (64.5%) 251 (35.5%)	0.014
Use of vasopressors	784 (82.8%)	215 (90.0%)	569 (80.4%)	0.001
Prophylactic BB	677 (71.5%)	135 (56.5%)	542 (76.6%)	<0.001
BB discontinuation	105 (11.1%)	52 (21.8%)	53 (7.5%)	<0.001
Antiarrhythmic drugs	52 (5.5%)	25 (10.5%)	27 (3.8%)	<0.001
ACE-I or ARBs	475 (50.2%)	141 (59.0%)	334 (47.2%)	0.002
Statins	400 (42.2%)	101 (42.3%)	299(42.2%)	0.99

Table 2

PoAF risk stratified by rs1801253 and rs1801252 genotypes. 10 and 14 patients had undetermined genotypes for rs1801253 and rs1801252, respectively. *Overall P-values for rs1801253 genotype (Wald statistics) were P=0.085 and P=0.008 for unadjusted and adjusted analyses, respectively. ** Overall P-values (Wald statistics) for rs1801252 genotype were P=0.38 and P=0.18 for unadjusted and adjusted analyses, respectively. The adjusted model included the following covariates: Age, sex, BMI, complex surgery, hypertension, diabetes, heart failure, history of myocardial infarction, COPD, previous history of atrial fibrillation, eGFR (quintiles), use of beta-blockers, ACE-I or ARBs, antiarrhythmic therapy, statin use, use of vasopressors, beta-blocker discontinuation, and rs1801253 and rs1801252 genotypes.

		Unadjusted analysis		Adjusted analysis	
No. of minor alleles	Incident PoAF	Odds Ratios (95% CI)	P-value	Adjusted ORs (95% CI)	P-value
rs1801253					
0	125/523 (23.9%)	Reference*		Reference*	
1	87/342 (25.4%)	1.09 (0.79 to 1.49)	0.60	1.07 (0.73 to 1.55)	0.74
2	26/72 (36.1%)	1.80 (1.07 to 3.04)	0.026	2.63 (1.42 to 4.89)	0.002
rs1801252					
0	170/705 (24.1%)	Reference**		Reference**	
1	60/211 (28.4%)	1.25 (0.89 to 1.77)	0.21	1.31 (0.87 to 1.98)	0.19
2	3/16 (18.8%)	0.73 (0.21 to 2.58)	0.62	0.33 (0.06 to 1.91)	0.22

Table 3

Risk for PoAF in rs1801253 genotype groups stratified by prophylactic use of BB. rs1801253 was associated with PoAF in patients without prophylactic BB therapy (*overall P=0.077 and P=0.018 for unadjusted and adjusted analyses, respectively), but the association was weaker in patients with prophylactic treatment (*Overall P=0.37 and P=0.11 for unadjusted and adjusted analyses, respectively).

		Unadjusted analysis		Adjusted analysis	
rs1801253 minor alleles	Incident PoAF	ORs (95% CI)	P- value	Adjusted ORs (95% CI)	P- value
No prophylactic BB treatment (n=256)					
0	53/149 (35.6%)	Reference*		Reference*	
1	40/99 (40.4%)	1.23 (0.73 to 2.07)	0.44	1.25 (0.66 to 2.35)	0.50
2	11/17 (64.7%)	3.32 (1.16 to 9.49)	0.025	7.00 (1.82 to 26.96)	0.005
Prophylactic BB treatment (n=672)					
0	72/374 (19.3%)	Reference**		Reference**	
1	47/243 (19.3%)	1.01 (0.67 to 1.51)	0.98	1.03 (0.64 to 1.66)	0.90
2	15/55 (27.3%)	1.57 (0.82 to 3.00)	0.17	2.18 (1.03 to 4.63)	0.042