Background—Postoperative atrial fibrillation (PoAF) is common after coronary artery bypass grafting. We previously showed that atrial fibrillation susceptibility single nucleotide polymorphisms (SNPs) at the chromosome 4q25 locus are associated with PoAF. Here, we tested the hypothesis that a combined clinical and genetic model incorporating atrial fibrillation risk SNPs would be superior to a clinical-only model.

Methods and Results—We developed and externally validated clinical and clinical/genetic risk models for PoAF. The discovery and validation cohorts included 556 and 1164 patients, respectively. Clinical variables previously associated with PoAF and 13 SNPs at loci associated with atrial fibrillation in genome-wide association studies were considered. PoAF occurred in 30% and 29% of patients in the discovery and validation cohorts, respectively. In the discovery cohort, a logistic regression model with clinical factors had good discrimination, with an area under the receiver operator characteristic curve of 0.76. The addition of 10 SNPs to the clinical model did not improve discrimination (area under receiver operator characteristic curve, 0.78; P=0.14 for difference between the 2 models). In the validation cohort, the clinical model had good discrimination (area under the receiver operator characteristic curve, 0.69) and addition of genetic variables resulted in a marginal improvement in discrimination (area under receiver operator characteristic curve, 0.72; P<0.0001).

Conclusions—We developed and validated a model for the prediction of PoAF containing common clinical variables. Addition of atrial fibrillation susceptibility SNPs did not improve model performance. Tools to accurately predict PoAF are needed to risk stratify patients undergoing coronary artery bypass grafting and identify candidates for prophylactic therapies. (Circ Arrhythm Electrophysiol. 2015;8:25-31. DOI: 10.1161/CIRCEP.114.002300.)

Key Words: atrial fibrillation ■ cardiac surgery ■ genetics ■ postoperative complication arrhythmia ■ risk model
WHAT IS KNOWN

- Postoperative atrial fibrillation is a common and clinically important complication of cardiac surgery.
- Multiple common genetic risk variants are associated with ambulatory atrial fibrillation, but whether these also confer risk for postoperative atrial fibrillation is unknown.

WHAT THE STUDY ADDS

- We developed and externally validated a risk prediction model for postoperative atrial fibrillation.
- The model contained commonly available clinical variables and had good discrimination and calibration.
- Genetic variables did not improve the performance of our well-fitted clinical risk model.

Methods

Study Subjects

The discovery cohort included patients in the prospective Vanderbilt Cardiac Surgery Registry who underwent CABG without concurrent valve surgery from November 1999 until November 2004. The validation cohort included patients in the prospective CABG Genomics Program at Brigham and Women’s Hospital and the Texas Heart Institute. Patients who had CAGB without valve surgery after August 2001 were included in the analysis. All analyses were restricted to self-reported white patients to minimize genetic heterogeneity. Only patients who were in sinus rhythm at the time of surgery were included in the analysis. The study complies with the Declaration of Helsinki, the Institutional Review Boards at each participating institution approved the registries, and all patients gave written informed consent.

Patient demographics, biometrics, clinical comorbidities, and other variables were prospectively entered into both registries using standard definitions. PoAF, the primary study end point, was defined as electrocardiographically documented AF, as assessed by inpatient telemetry and 12-lead ECGs during the index hospitalization after surgery. To be considered a case, the episode of AF needed to be of sufficient duration to require specific therapy. Otherwise, there was no specific minimum duration of AF necessary to be considered a case.

Genotyping

Genotyping was performed for 13 single nucleotide polymorphisms (SNPs) associated with prevalent AF in large genome-wide association studies:12-14: rs13376333 and rs6666258 at 1q21; rs39033239 at 1q24; rs2200733, rs10821415 at 4q25; rs3807989 at 7q31; rs10824026 (G), and rs1152591 (A), rs2106261 (A), and rs7193343 (C), using an additive model (0, 1, or 2 copies of the minor allele) for each SNP. Genotyping for the other 3 SNPs failed quality control measures, and, therefore, these were not included in the analysis. Receiver operator characteristic (ROC) curves were generated for the clinical-only and combined clinical/genetic models in both cohorts. A calibration curve was generated to assess the performance of the combined clinical/genetic model in the validation cohort.16 For this, grouped predicted probabilities for the development of PoAF were plotted against observed probabilities within each group and a curve was fit for the grouped observations. For an ideal prediction model, the curve would be a straight line with a slope equal to 1. The distribution of the grouped observations and the fitted curve provide information about how the model performs for different predicted probabilities.

We derived a simple weighted risk score for PoAF using clinical data from the discovery cohort. Based on the magnitude of odds ratios (ORs) in our logistic regression model, we assigned 1 point each for male sex, hypertension, diabetes mellitus, left ventricular ejection fraction<40%, and PR interval >200 ms, 2 points for age >60 years, and 3 points for a previous history of AF. This resulted in a possible risk score from 0 to 10 points. We then tested the performance of the risk score by applying it to the validation cohort. All statistical analyses were conducted using R version 3.0 with the rms package, STATA v12, or SPSS v22.

Results

Baseline Patient Characteristics and Genotypes

Baseline patient characteristics for the discovery and validation cohorts are presented in Table 1. In the discovery cohort of 556 patients without missing variables, mean age was 62±11 years, 72% were male, and 10% had a previous history of AF. In the validation cohort of 1164 patients, mean age was 64±10, 82% were male, and 4.3% had a previous history of AF.

Minor allele frequencies for the discovery and validation cohorts are presented in Table 2. In the discovery cohort, rs10033464 (at 4q25) was not in Hardy–Weinberg equilibrium and was excluded from further analysis. In the validation cohort, rs6817105 at 4q25 and rs7164883 at 15q24 failed genotyping. Otherwise, all genotyping assays met prespecified quality control measures with >95% call rate and results were in Hardy–Weinberg equilibrium, and genotypes for each of the 10 SNPs were available for every patient included in the main analysis.

Risk Prediction Models for PoAF

PoAF during the index hospitalization after surgery, the primary study end point, occurred in 165 (30%) subjects in the discovery cohort. In the clinical-only model, variables significantly associated with PoAF included age (P<0.0001), longer PR interval (P=0.0006), and a previous history of AF (P<0.0001; Table 3). The largest effect size was seen with previous AF, with an OR of developing PoAF of 6.46 (95% confidence interval, 3.36–12.4). In the combined clinical and genetic model, age, PR interval, and previous AF remained statistically significant. However, none of the SNPs were
Table 1. Baseline Clinical Characteristics for the Discovery and Validation Cohorts

<table>
<thead>
<tr>
<th></th>
<th>Discovery</th>
<th>Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (N=556)</td>
<td>No PoAF (N=391)</td>
</tr>
<tr>
<td>Age, y</td>
<td>62±11</td>
<td>60±11</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>402 (72%)</td>
<td>272 (70%)</td>
</tr>
<tr>
<td>Previous AF</td>
<td>58 (10%)</td>
<td>15 (3.8%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>200 (36%)</td>
<td>136 (35%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>444 (80%)</td>
<td>300 (77%)</td>
</tr>
<tr>
<td>LVEF&lt;40%</td>
<td>107 (19%)</td>
<td>67 (17%)</td>
</tr>
<tr>
<td>Pre-op β-blockers</td>
<td>351 (63%)</td>
<td>254 (65%)</td>
</tr>
<tr>
<td>Post-op β-blockers</td>
<td>487 (88%)</td>
<td>347 (89%)</td>
</tr>
</tbody>
</table>

Age presented as mean±SD. PR interval presented as median [bootstrap 95% confidence interval] in milliseconds. P values were calculated for differences between PoAF and no PoAF with χ² for nominal variables and Mann–Whitney U test for continuous variables. Between-cohort P values reflect differences between the 2 entire cohorts, irrespective of PoAF status. AF indicates atrial fibrillation; LVEF, left ventricular ejection fraction; and PoAF, postoperative atrial fibrillation.

Table 2. Minor Allele Frequencies for Atrial Fibrillation Susceptibility Loci

<table>
<thead>
<tr>
<th>Chr.</th>
<th>Locus</th>
<th>Discovery Total (N=556), %</th>
<th>No PoAF (N=391), %</th>
<th>PoAF (N=165), %</th>
<th>P Value</th>
<th>Validation Total (N=1164), %</th>
<th>No PoAF (N=828), %</th>
<th>PoAF (N=336), %</th>
<th>P Value</th>
<th>Between-Cohort P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q21</td>
<td>rs13376333 (C/T)</td>
<td>30.3</td>
<td>28</td>
<td>35.8</td>
<td>0.04</td>
<td>29.6</td>
<td>28.7</td>
<td>31.8</td>
<td>0.24</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>rs66668258 (G/C)</td>
<td>30.8</td>
<td>28</td>
<td>37.3</td>
<td>0.01</td>
<td>25</td>
<td>24.2</td>
<td>27.2</td>
<td>0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1q24</td>
<td>rs39003239 (G/A)</td>
<td>39.1</td>
<td>38.7</td>
<td>40</td>
<td>0.80</td>
<td>56.8</td>
<td>57.9</td>
<td>54.3</td>
<td>0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4q25</td>
<td>rs2200733 (T/C)</td>
<td>11.1</td>
<td>10.5</td>
<td>12.4</td>
<td>0.62</td>
<td>12.8</td>
<td>10.7</td>
<td>17.9</td>
<td>&lt;0.001</td>
<td>0.25</td>
</tr>
<tr>
<td>7q31</td>
<td>rs3807899 (G/A)</td>
<td>45.1</td>
<td>44.2</td>
<td>47.3</td>
<td>0.55</td>
<td>41</td>
<td>41</td>
<td>41.1</td>
<td>0.90</td>
<td>0.009</td>
</tr>
<tr>
<td>9q22</td>
<td>rs10821415 (C/A)</td>
<td>37.2</td>
<td>36.6</td>
<td>38.8</td>
<td>0.80</td>
<td>44.3</td>
<td>44.3</td>
<td>44.2</td>
<td>0.53</td>
<td>0.001</td>
</tr>
<tr>
<td>10q22</td>
<td>rs10824026 (A/G)</td>
<td>18.8</td>
<td>19.6</td>
<td>17</td>
<td>0.17</td>
<td>15.5</td>
<td>16.7</td>
<td>12.6</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>14q23</td>
<td>rs1152591 (G/A)</td>
<td>42.5</td>
<td>42.7</td>
<td>42.1</td>
<td>0.70</td>
<td>47.7</td>
<td>48.3</td>
<td>46.3</td>
<td>0.52</td>
<td>0.02</td>
</tr>
<tr>
<td>16q22</td>
<td>rs2106261 (G/A)</td>
<td>17.9</td>
<td>17.8</td>
<td>18.2</td>
<td>0.44</td>
<td>14.4</td>
<td>13.4</td>
<td>17</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>rs7193343 (C/T)</td>
<td>16.5</td>
<td>16.2</td>
<td>17</td>
<td>0.94</td>
<td>15.3</td>
<td>14.4</td>
<td>17.6</td>
<td>0.16</td>
<td>0.57</td>
</tr>
</tbody>
</table>

PoAF indicates postoperative atrial fibrillation.
our results suggest a limited role of these SNPs in predicting PoAF. One reason for this finding might be that the triggers for PoAF are primarily driven by clinical risk factors and common AF risk alleles do not have a significant impact on the incidence of PoAF, especially if only a limited number of genetic variables are considered. Alternatively, one or more of the SNPs we studied might be strongly associated with clinical predictors (especially prior history of AF), and, therefore, the predictive information of these SNPs might already be accounted for by the clinical factors in our model.

PoAF is a common adverse event after cardiac surgery. In a large cohort of >18,000 patients undergoing cardiac surgery, the prevalence of PoAF was 19% and did not differ between on-pump and off-pump cases.11 In another large multicenter

Table 3. Multivariable Logistic Regression Models for the Development of Postoperative Atrial Fibrillation in the Discovery Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Combined Clinical/Genetic Model</th>
<th>Clinical-Only Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5 y)</td>
<td>0.2435 (0.0105) 1.28 (1.25–1.3)</td>
<td>&lt;0.0001 0.2355 (0.0103) 1.27 (1.24–1.29)</td>
</tr>
<tr>
<td>PR interval (per 20 ms)</td>
<td>0.154 (0.0044) 1.36 (1.35–1.37)</td>
<td>0.0005 0.292 (0.0042) 1.34 (1.33–1.35)</td>
</tr>
<tr>
<td>Previous AF</td>
<td>1.9475 (0.3449) 7.01 (3.57–13.8)</td>
<td>&lt;0.0001 1.8653 (0.3335) 6.46 (3.36–12.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.6006 (0.3013) 1.82 (1.01–3.29)</td>
<td>0.05 0.5527 (0.2983) 1.74 (0.97–3.12)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.1283 (0.2243) 1.14 (0.73–1.76)</td>
<td>0.57 0.1552 (0.2162) 1.17 (0.76–1.78)</td>
</tr>
<tr>
<td>LVEF&lt;40%</td>
<td>0.356 (0.2648) 1.43 (0.85–2.4)</td>
<td>0.18 0.3806 (0.2605) 1.46 (0.88–2.44)</td>
</tr>
<tr>
<td>Pre-op β-blocker</td>
<td>−0.0148 (0.2258) 0.99 (0.63–1.53)</td>
<td>0.95 −0.0749 (0.2196) 0.93 (0.6–1.43)</td>
</tr>
<tr>
<td>Post-op β-blocker</td>
<td>−0.2621 (0.3163) 0.77 (0.41–1.43)</td>
<td>0.41 −0.1911 (0.3084) 0.83 (0.45–1.51)</td>
</tr>
<tr>
<td>rs13376333 (T)</td>
<td>−0.9951 (0.8129) 0.37 (0.08–1.82)</td>
<td>0.22 ... ...</td>
</tr>
<tr>
<td>rs6666258 (G)</td>
<td>1.3839 (0.797) 3.99 (0.84–19)</td>
<td>0.08 ... ...</td>
</tr>
<tr>
<td>rs3903239 (A)</td>
<td>−0.158 (0.1631) 0.85 (0.62–1.18)</td>
<td>0.33 ... ...</td>
</tr>
<tr>
<td>rs2200733 (T)</td>
<td>0.2145 (0.2398) 1.24 (0.77–1.98)</td>
<td>0.37 ... ...</td>
</tr>
<tr>
<td>rs3807989 (A)</td>
<td>0.0531 (0.1589) 1.05 (0.77–1.44)</td>
<td>0.74 ... ...</td>
</tr>
<tr>
<td>rs10821415 (A)</td>
<td>0.1051 (0.1482) 1.11 (0.83–1.49)</td>
<td>0.48 ... ...</td>
</tr>
<tr>
<td>rs10824026 (G)</td>
<td>−0.2249 (0.1959) 0.8 (0.54–1.17)</td>
<td>0.25 ... ...</td>
</tr>
<tr>
<td>rs1152591 (A)</td>
<td>0.212 (0.1506) 1.24 (0.92–1.66)</td>
<td>0.16 ... ...</td>
</tr>
<tr>
<td>rs2106261 (A)</td>
<td>−0.2831 (0.333) 0.75 (0.39–1.45)</td>
<td>0.4 ... ...</td>
</tr>
<tr>
<td>rs7193343 (C)</td>
<td>−0.1107 (0.3475) 0.9 (0.45–1.77)</td>
<td>0.75 ... ...</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio; and SE, standard error.

Figure. A, Receiver operator characteristic (ROC) curves for the discovery cohort combined clinical/genetic model (blue line; area under the ROC curve, 0.78), discovery cohort clinical-only model (red line; area under the ROC curve, 0.763), validation cohort combined clinical/genetic model (green line; area under the ROC curve, 0.72), and validation cohort clinical-only model (brown line; area under the ROC curve, 0.688). B, Calibration curve for the validation cohort combined clinical/genetic model. Patients were grouped based on predicted probability of developing postoperative atrial fibrillation, predicted probabilities were plotted against actual probabilities, and a curve was fit to the data. For an ideal prediction model, this curve would represent a straight line with a slope equal to 1.
Veterans Administration study, including >3800 patients, the overall incidence of PoAF was 30% and was the highest among patients undergoing CABG with mitral valve replacement (60%) and the lowest among patients having CABG without valve surgery (28%).

PoAF is an important predictor of morbidity and mortality. In a case-control study of >6400 patients who underwent CABG at a single center, PoAF was independently associated with stroke (OR, 2.0), in-hospital mortality (OR, 1.7), and long-term mortality (OR, 1.5). The aforementioned Veterans Administration study found that PoAF was independently associated with stroke (OR, 2.2), heart failure (OR, 3.3), intensive care unit readmission (OR, 3.3), reintubation (OR, 4.3), in-hospital mortality (OR, 2.0), and 6-month mortality (OR, 2.2). In a separate study of >6700 patients who underwent CABG, PoAF was associated with increased mortality at 1, 5, and 10 years after surgery. Importantly, in the modern era of healthcare cost containment, the average length of stay for patients who developed PoAF in another study was increased by 4.9 days after full adjustment for covariates, corresponding to an increase in hospital cost of $10,055 per patient. PoAF also predicted intensive care unit and hospital length of stay in a separate multicenter study (3.6 versus 2 days and 10 versus 7 days, respectively).

Multiple strategies for preventing PoAF have been studied, including therapy with β-blockers, antiarrhythmic drugs (AADs), magnesium, colchicine, atrial pacing, and posterior pericardiotomy. Oral β-blockers have been consistently shown to reduce the development of PoAF and are recommended for virtually all patients undergoing cardiac surgery. However, even with β-blockade, the incidence of PoAF remains high. Several studies have shown that prophylactic use of amiodarone or sotalol in the perioperative period reduces the incidence of the arrhythmia. In a meta-analysis of randomized trials, the OR (95% confidence interval) for development of PoAF for sotalol versus β-blocker was 0.42 (0.26–0.65) and for amiodarone versus placebo, it was 0.48 (0.4–0.57). In fact, the use of amiodarone or sotalol for PoAF prophylaxis in selected patients has been recommended by the American College of Cardiology, the American College of Chest Physicians, and the Canadian Cardiovascular Society. However, these recommendations have not been widely incorporated into clinical practice.

It is unclear why clinicians do not routinely use prediction tools and prophylactic strategies (other than use of β-blockers) to prevent PoAF after cardiac surgery. We and others have postulated that there is a reluctance to expose patients to the potential adverse effects of prophylactic AADs. An individualized approach, whereby only high-risk patients are selected for perioperative use of AADs, might maximize benefits for these patients while minimizing the exposure of low-risk patients to the potential adverse drug effects. Thus, highly accurate methods of predicting which patients will develop PoAF are needed. However, to be widely accepted into clinical practice, prediction tools must also be simple to use. We therefore developed a simple risk score for the prediction of PoAF. The score performed well in our discovery cohort and also in our independent validation cohort. In both cohorts, a score ≥5 predicted a >40% risk of PoAF. Our score should assist clinicians in risk stratifying patients and identifying those who would benefit from additional preventative therapies such as prophylactic AADs.

Clinical risk factors for the development of PoAF, including age, hypertension, prior AF, heart failure, obesity, prolonged PR interval, tobacco use, and history of myocardial infarction, have been thoroughly studied. As a result, several risk assessment tools to predict PoAF have been developed. We previously conducted a multi-center study of the association of 4q25 SNPs with PoAF. Seven 4q25 SNPs were independently associated with PoAF, and addition of 4q25 genotypes to a clinical risk prediction model improved discrimination (area under the ROC curve, 0.720 versus 0.702; P<0.0001). These data suggested that the addition of genetic information could improve the ability to identify patients at high risk for PoAF. However, we were not able to reproduce this finding in this study.

Our study has several important limitations that should be considered when interpreting the results. As with all retrospective studies, ours is prone to the effects of bias and unmeasured confounders. The final patient cohorts analyzed were selected from larger cardiac surgery registries based on the presence of complete data, and it is possible that our findings were affected by nonrandom missing variables. There were significant differences in clinical and genetic factors between the discovery and validation cohorts (Tables 1 and 2) that might

Table 4. Simple Risk Score for the Prediction of Postoperative Atrial Fibrillation

<table>
<thead>
<tr>
<th>Score</th>
<th>Discovery Cohort (N=556)</th>
<th>Validation Cohort (N=1164)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients With Score</td>
<td>Incidence of PoAF (%)</td>
</tr>
<tr>
<td>0–1</td>
<td>66</td>
<td>7.6</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>113</td>
<td>19.5</td>
</tr>
<tr>
<td>4</td>
<td>125</td>
<td>34.4</td>
</tr>
<tr>
<td>5</td>
<td>83</td>
<td>44.6</td>
</tr>
<tr>
<td>≥6</td>
<td>69</td>
<td>66.7</td>
</tr>
</tbody>
</table>

Calculation of score: 1 point each for male sex, hypertension, diabetes mellitus, left ventricular ejection fraction <40%, and PR interval >200 ms; 2 points for age >60 years; and 3 points for a previous history of atrial fibrillation.

PoAF indicates postoperative atrial fibrillation.
account for the divergent results between the cohorts with regard to improved model performance with the addition of genetic factors. The definition of our primary end point, PoAF documented by 12 lead ECG or telemetry of sufficient duration to warrant specific therapy, was chosen to be consistent with previous studies. However, use of a more precise definition (eg, PoAF of ≥25 minutes duration) might have led to different study results. To reduce variability, we chose a priori to limit our study to patients undergoing CABG without any concurrent procedures. However, excluding patients undergoing concurrent valve and structural procedures might limit the generalizability of our findings to broader patient populations.

In conclusion, we developed an accurate risk prediction model for PoAF in patients undergoing CABG based on readily available clinical variables. Importantly, we validated our model in a geographically independent cohort, a crucial step before any risk prediction model can be implemented in routine clinical practice. However, we were unable to prove our primary hypothesis that addition of AF susceptibility alleles would result in a clinically meaningful improvement in risk prediction model performance. Even in the current era of near ubiquitous use of postoperative β-blockers, the risk for the development of AF after cardiac surgery remains high. Other preventative strategies, including the use of AADs for selected high-risk patients, have been recommended but are seldom utilized.

The ability to accurately identify patients at high risk for PoAF through the use of a prediction model should allow for an individualized approach wherein AADs, with their inherent potential toxicities, are used in patients who stand to benefit the most and avoided in others, potentially maximizing clinical benefits while reducing adverse drug reactions.

Sources of Funding
This work was supported by grants from the National Heart, Lung, and Blood Institute at the National Institutes of Health (grant numbers HL65962, HL068774, HL056693, and HL092217).

Disclosures
None.

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Genetic and Clinical Risk Prediction Model for Postoperative Atrial Fibrillation

_Circ Arrhythm Electrophysiol._ 2015;8:25-31; originally published online January 7, 2015; doi: 10.1161/CIRCEP.114.002300

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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