SUPPLEMENTAL MATERIAL

METHODS

Study Design and Description of Study Population

Our cohort consisted of 1047 adults of European ancestry identified through the BioVU resource who were exposed to cardiac surgery at Vanderbilt University Medical Center (VUMC) between 1997 and 2019, and had no history of atrial fibrillation prior to surgery. BioVU is VUMC's DNA biobank linked to a de-identified electronic health record at VUMC, and had extant genotyping data on Infinium® Expanded Multi-Ethnic Genotyping Array (MEGA^{EX}, Illumina Inc., San Diego, CA, USA) as part of an institutional initiative to genotype a large, diverse patient population (**Figure I**). This study was approved by the Institutional Review Board (IRB) at VUMC.

We used Current Procedural Terminology (CPT) codes to identify individuals who underwent coronary artery bypass grafting or heart valve surgery. Among this cohort, potential cases were patients with ICD-9 codes 427.31-2 or ICD-10 codes I48*. All potential cases were manually reviewed by AR, MA, YH and MDK to confirm the presence of AF and ascertain the timing of the AF with respect to the cardiac surgery. The manual review included examination of ECG reports, progress notes, nursing notes, discharge summaries, and changes in medication in order to confirm new-onset postoperative AF.[12] Subjects with a history of preoperative AF, including persistent AF, were excluded. Cases were subjects with a new-onset PoAF that occurred within 10 days after cardiac surgery. Subjects without a new-onset postoperative AF were considered controls in the present study (**Figure II**).

Patient demographics (age, sex), preoperative (history of chronic obstructive pulmonary disease, preoperative angiotensin-converting enzyme inhibitor use, beta-blocker use, nonsteroidal anti-inflammatory drug use, and statin) and procedural factors (type and year of cardiac surgery), which have previously been identified as risk factor for postoperative AF,[11] were also extracted for each subject.

Genetic Data

Subjects were genotyped using DNA extracted from discarded plasma samples and by using the Illumina MEGA^{EX} array, Illumina, Inc. (San Diego, CA, USA), as previously described.[22] Sample and genotype quality control of data flow included assessment of call rates, gender check, cryptic relatedness, SNP missingness and the Hardy-Weinberg equilibrium, as previously described.[23] We used the EIGENSTRAT method in EigenSoft version 7.2.1. program to generate principal components (PCs) to control for population stratification.[24] Adjustment for PCs is essential in genetic studies in order to control population stratification. The issue of population stratification is typically exacerbated with PRS, which can function as stratifying variables. To ensure that our results are not due to population stratification, we have included genetic PCs in all analyses.

We imputed genotypes of the Haplotype Reference Consortium with the Michigan Imputation Server using Minimac4 in conjunction with the 1000 genome phase three reference panel (version r.1.4.1).[25] We selected variants with $R^2 \geq 0.7$ and minor allele frequency (MAF) $\geq$ 0.1% resulting in more than 21.1 million imputed variants available after quality control and filtering.

Genome-wide Polygenic Risk Scoring for Postoperative Atrial Fibrillation

The PoAF PRS was generated using a clumping algorithm to select a linkage-disequilibrium reduced set of SNPs ($r^2 < 0.05$) with a minor allele frequency>5% associated with AF ($p < 5 \times 10^{-3}$) using a reference population of 72,624 white European ancestry individuals.[26] The final score comprised 2746 SNPs. For each individual, the PRS was computed by multiplying the SNP weighting by the allele dose for each SNP and summing up the products. This PRS represents the burden of additive genetic risk an individual carries based on their genotypes for the 2746 SNPs.

Statistical Analysis

Descriptive statistics of clinical variables are presented as frequency and percentage for categorical variables and median [interquartile range] for continuous variables.

Logistic regression models were used to test the association between the PoAF PRS and the risk of PoAF. The PoAF PRS was standardized to a mean of 0 and standard deviation of 1, so odd-ratios represent the change in AF risk per standard deviation change in the PRS. All regression models were adjusted for age, sex, clinical (chronic obstructive pulmonary disease, preoperative medications: angiotensin-converting enzyme inhibitor use, beta-blocker use, nonsteroidal anti-inflammatory drug use, statin use) and surgical (year of surgery, coronary artery bypass graft surgery, heart valve surgery) variables and 4 principal components to correct for population stratification.

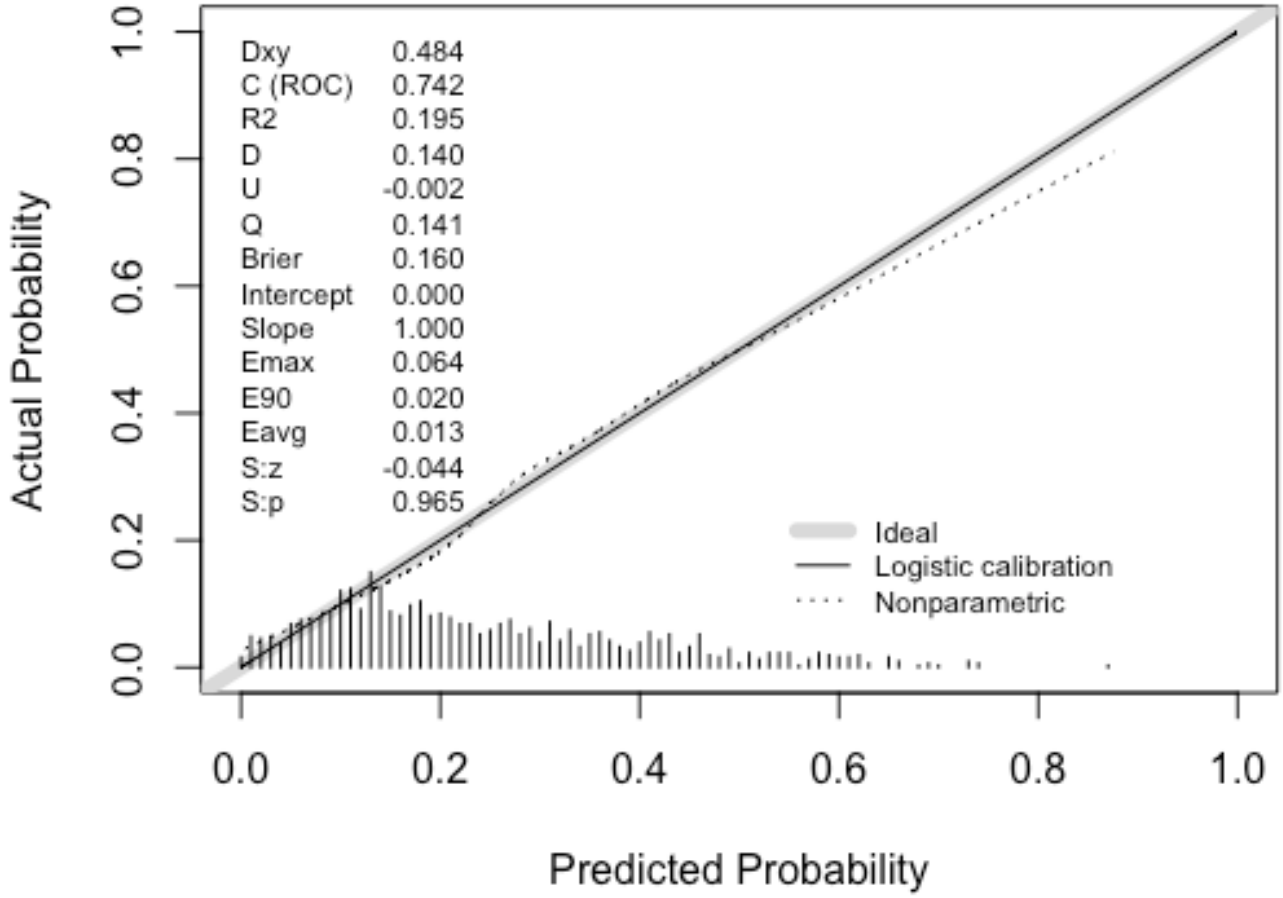
The C-statistic was used to assess model discrimination, as previously described.[27] Bootstrapping was used to calculate 95% confidence intervals (CI) for C statistics and for the difference in C-statistic when the PRS was added to the clinical model. A 95% CI that did not include 0 was considered significant. A likelihood ratio test was used to ascertain improvement in a model performance when the PRS was added to a standard model comprising clinical predictors for postoperative AF.

The Integrated Discrimination Improvement Index (IDI) and Net Reclassification Improvement (NRI) were used to assess risk reclassification when the PRS was added to a logistic regression model that adjusted for standard clinical predictors.[28,29] The IDI quantifies the extent that addition of a covariate to a predictive model increased risk estimates among those with incident AF and decreased risk in those without AF. The NRI was used to assess reclassification of individuals among the following risk categories that were defined using the risk categories defined by the multicenter risk index for postoperative atrial after cardiac surgery: low-risk (< 17%), medium-risk (17% to 52%), and high-risk ($\geq$ 52%).[7] The risk thresholds were defined using the predicted probabilities from the standard model, with the low-risk threshold defined as the first quartile (Q1) and high risk as the third quartile (Q3). Bootstrapping was used to determine 95% CI.

All statistics tests were two-sided. A p-value<0.05 was considered statistically significant, unless otherwise noted. Analyses were performed using R version 4.0.0. The calibration plot was produced using the val.prob (https://cran.r-project.org/web/packages/rms/index.html) function from the rms package. The likelihood

ratio test was performed using the lrtest function from the lmtest package.[30] The NRI and IDI analyses were conducted using the package PredictABLE version 1.2-4.[31]

Supplemental Figure I: Calibration plot of the standard clinical model that included age, sex, clinical (chronic obstructive pulmonary disease, preoperative medications: angiotensin-converting enzyme inhibitor use, beta-blocker use, nonsteroidal anti-inflammatory drug use, statin use) and surgical (year of surgery, coronary artery bypass graft surgery, heart valve surgery) variables.



Supplemental Figure II: Calibration plot of the standard clinical model after the addition of the atrial fibrillation polygenic risk score.