

Polygenic Risk Scores for Predicting Adverse Outcomes After Coronary Revascularization



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Coronary procedures predispose patients to adverse events. To improve our understanding of the genetic factors underlying postoperative prognosis, we studied the association of polygenic risk scores (PRSs) with postprocedural complications in coronary patients who underwent revascularization. The study sample comprised 8,296, 6,132, and 13,082 patients who underwent percutaneous coronary intervention, coronary artery bypass grafting, or any revascularization, respectively. We genotyped all subjects and identified adverse events during follow-up of up to 30 years by record linkage with nationwide healthcare registers. We computed PRSs for each postoperative adverse outcome (atrial fibrillation [AF], myocardial infarction, stroke, and bleeding complications) for all participants. Cox proportional hazards models were used to examine the association between PRSs and outcomes. A 1-SD increase in AF-PRS was associated with greater risk of postoperative AF with hazard ratios of 1.22 (95% confidence interval [CI] 1.16 to 1.28), 1.15 (95% CI 1.10 to 1.20) and 1.18 (95% CI 1.14 to 1.22) after percutaneous coronary intervention, coronary artery bypass grafting, and any revascularization, respectively. In contrast, the association of each PRSs with other postoperative complications was nonexistent to marginal. Inclusion of the AF-PRS in a model with a clinical risk score resulted in significant model improvement (increase in model c-statistic 0.0059 to 0.0098 depending on procedure; $p < 0.0002$ for all). In conclusion, our results demonstrate that PRS can be used for AF risk-prediction in patients who underwent revascularization. The AF-PRS could potentially be used to improve AF prevention and outcomes in patients who underwent revascularization. © 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) (Am J Cardiol 2022;167:9–14)

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**A list of FinnGen investigators is available in the Supplement.

See page 14 for disclosure information.

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Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are standard revascularization methods in patients with significant coronary heart disease.¹ Although prognosis after revascularization has improved in recent years,² the long-term mortality and morbidity in patients with PCI and patients with CABG are markedly higher than in the general population.³ Patients who undergo revascularization procedures are prone to several adverse cardiovascular events, including atrial fibrillation (AF), myocardial infarction (MI), stroke and bleeding complications. In particular, new-onset AF is remarkably common among cardiac surgery patients and associates with worse postoperative prognosis in both CABG and PCI patients.^{4–6} Heritability of common diseases is often mediated by numerous genetic variants that individually contribute only small effects.^{7,8} Genome-wide polygenic risk scores (PRSs), consisting of data from up to 5 million single nucleotide polymorphisms (SNPs) can be used in disease risk prediction and reclassification together with conventional clinical risk factors and risk scores. PRSs have been shown to be able to predict several cardiovascular diseases in the general population.^{7,8} However, their ability to predict risk of AF and other major postrevascularization complications has not been studied to date. To improve our understanding of the genetic factors underlying postoperative prognosis and complications, we combined genetic and healthcare register data from nearly 15,000 FinnGen study⁹ participants to assess the association of PRSs with AF, MI,

stroke, and bleeding complications in coronary patients who underwent revascularization

The data Freeze 6 of the Finnish FinnGen study (autumn 2020) include 260,405 genotyped participants (57% women, mean age 59 years) with samples collected from biobanks and prospective epidemiological surveys.⁷ We used a convenience sample of 8,296, 6,132, and 13,082 patients who underwent at least 1 PCI, CABG, or any revascularization (both PCI and/or CABG), and had no prevalent AF. If a patient had undergone both PCI and CABG, the first event was selected as a revascularization event. The study complies with the Declaration of Helsinki, and the Coordinating Ethical Committee of the Hospital District of Helsinki and Uusimaa approved FinnGen study protocol. All participants gave informed written consent.

The participants were linked by a unique personal identification number to nationwide hospital discharge, causes-of-death, and drug reimbursement registries. The follow-up time in our study extends from 1985 to 2018. Time at CABG, PCI, and CABG or PCI was used as the baseline in all analyses. The outcome variables were AF, MI, stroke, intracranial bleeding (IC bleeding), and gastrointestinal bleeding (GI bleeding). These outcome variables were pre-specified based on previous knowledge about common adverse events after cardiac procedures. We created 15 separate datasets for each combination of a preceding operation and the next disease event and excluded the patients with prevalent disease events (events before baseline). In addition, we calculated the CHA₂DS₂-VAsC clinical risk score for each participant based on age, gender, heart failure, hypertension, diabetes, stroke, and vascular disease status at the time of operation.¹⁰ Although originally designed for prediction of stroke in patients with AF, CHA₂DS₂-VAsC has also been successfully used to predict AF.^{11–13} Diagnoses were mainly based on the International Classification of Diseases (ICD)-8, ICD-9, and ICD-10 (Supplementary Table S1).

FinnGen DNA samples were genotyped, filtered, and imputed as previously described.⁷ To avoid overfitting, we obtained GWAS summary statistics for AF, MI, stroke, IC bleeding, and GI bleeding from the United Kingdom Biobank.¹⁴ PRSs were calculated for all patients in our dataset using 1,086,476 SNPs, and PRS continuous shrinkage (CS) pipeline. PRS-CS uses GWAS summary statistics, a linkage disequilibrium reference panel, and high-dimensional Bayesian regression with CS priors to calculate SNP effect sizes.¹⁵

We used Cox proportional hazards models (R package survival and survminer) to examine the association between PRSs and corresponding disease end points after the procedure. All Cox models were adjusted by age at operation, operation year, genotyping batch, and the first 10 genetic principal components. Time between the procedure and disease event was used as the time scale. Patients were censored at death or at the end of follow-up (December 31, 2018). First, we calculated hazard ratios (HRs) per 1-SD increase for all 5 diseases (AF, MI, stroke, IC bleeding, and GI bleeding) and based on these results, selected AF for more detailed analysis. We then categorized AF PRS into 5 bins based on percentiles (<2.5, 2.5 to 20, 20 to 80, 80 to 97.5, and >97.5) and calculated HRs using the largest 20%

to 80% bin as the reference. In these analyses, CHA₂DS₂-VAsC score was also included as a covariate.

In addition, we quantified the added predictive value of AF PRS to clinical CHA₂DS₂-VAsC risk score and in predicting postoperative AF by calculating the increase in Harrell's C-statistics when the AF PRS was added to a model with CHA₂DS₂-VAsC alone¹⁶ (R package compareC). Obesity and valvular heart disease (VHD) were included as additional covariates in these analyses. To illustrate the added impact of clinical and genetic risk on AF risk prediction, we plotted the survival curves for patients in the lowest and highest deciles of AF PRS and CHA₂DS₂-VAsC score. We assessed the proportional hazards assumptions by inspecting Schoenfeld residuals and log-minus-log plots. We considered a 2-sided Bonferroni-corrected p value of 0.05 / 15 = 0.003 significant. We used R 4.0.3 (R Core Team 2020) for all computations.

The study sample characteristics are shown in Supplementary Table S2 and Table 1.

We studied associations between 5 PRSs (AF, MI, stroke, IC bleeding, and GI bleeding) and corresponding disease events after revascularization. An increasing AF PRS was associated with higher incidence of postoperative AF (Table 2). The HRs for AF per 1 SD increase in the PRS were 1.22 (95% confidence interval [CI] 1.16 to 1.28) after PCI, 1.15 (95% CI 1.10 to 1.20) after CABG and 1.18 (95% CI 1.14 to 1.22) after any revascularization (all p values < 1 × 10⁻¹⁰). However, the PRSs were not significantly associated with the other outcomes after Bonferroni correction, with exception of modest association for stroke (HR 1.13; 95% CI 1.05 to 1.21) and MI (HR 1.11; 95% CI 1.04 to 1.19) after CABG.

Based on the previous results, we focused on AF in more detailed analyses. The rate of new-onset postoperative AF in PRS bins is presented in Table 3. Incidence rate increased from 1.89 to 3.19 per 100 patient-years in bottom 2.5% versus top 2.5%, respectively, after any revascularization indicating diverging trajectories in high versus low genetically susceptible patients in the long-term (Figure 1). For patients in the top 2.5% AF PRS after any revascularization, the HR for AF was 1.54 (95% CI 1.28 to 1.86) and 0.68 (95% CI 0.53 to 0.86) for the lowest 2.5% (Figure 1, Table 3), compared with the reference group. After PCI, the highest genetic risk group had a HR 1.89 (95% CI 1.48 to 2.41) for AF; whereas in the lowest genetic risk group, the HR was 0.76 (95% CI 0.55 to 1.04). After CABG, the HRs were 1.19 (95% CI 0.91 to 1.56) in the top 2.5 PRS percentile and 0.59 (95% CI 0.43 to 0.82) in the bottom 2.5% percentile.

We used the CHA₂DS₂-VAsC score to predict postoperative new-onset AF. The Pearson correlation coefficients between CHA₂DS₂-VAsC scores and AF PRSs ranged between -0.02 and 0.006, depending on the dataset, implying a low correlation between clinical and genetic risk scores. If included in the same model, both scores were associated with incident AF (Figure 2). After any revascularization, and while also adjusting for obesity and VHD, the HR for AF per 1-SD increase in CHA₂DS₂-VAsC was 1.24 (95% CI 1.19 to 1.30) and 1.19 (95% CI 1.15 to 1.23) per 1-SD increase in AF PRS. Accordingly, the C-statistics increased significantly by 0.0074 (95% CI 0.0047 to

Table 1
Study sample characteristics at the time of the procedure

Variable	Revascularization (n = 13,082)			CABG (n = 6,132)			PCI (n = 8,296)		
	All	AF	No AF	All	AF	No AF	All	AF	No AF
Number of patients	13,082	3,556	9,526	6,132	2,127	4,005	8,296	1,854	6,442
Follow up, years±SD	9.9 ± 6.7	8.1 ± 6.8	10.6 ± 6.5	10.9 ± 7.8	8.9 ± 7.6	12.0 ± 7.7	8.9 ± 5.5	6.7 ± 5.3	9.6 ± 5.4
Age, years±SD	73.3 ± 9.57	72.51 ± 9.29	73.6 ± 9.66	74.07 ± 8.88	72.51 ± 8.98	74.90 ± 8.71	72.79 ± 9.89	72.48 ± 9.44	72.8 ± 10.01
Women	3,169 (24.2%)	777 (21.9%)	2,392 (25.1%)	1,118 (18.2%)	377 (17.7%)	741 (18.5%)	2,312 (27.9%)	477 (25.7%)	1,835 (28.5%)
CHA₂DS₂-VAsC score±SD	1.95 ± 1.57	2.12 ± 1.58	1.89 ± 1.57	2.10 ± 1.57	2.15 ± 1.60	2.07 ± 1.56	1.96 ± 1.61	2.24 ± 1.59	1.89 ± 1.60
Heart failure	1,130 (8.6%)	448 (12.6%)	682 (7.2%)	713 (11.6%)	310 (14.6%)	403 (10.1%)	626 (7.5%)	240 (12.9%)	386 (6.0%)
Hypertension	5,251 (40.1%)	1,573 (44.2%)	3,678 (38.6%)	2,752 (44.9%)	974 (45.8%)	1,778 (44.4%)	3,212 (38.7%)	823 (44.4%)	2,389 (37.1%)
Age ≥75 y	1,777 (13.6%)	518 (14.6%)	1,259 (13.2%)	699 (11.4%)	234 (11.0%)	465 (11.6%)	1,296 (15.6%)	355 (19.1%)	941 (14.6%)
Diabetes	2,796 (21.4%)	705 (19.8%)	2,091 (22.0%)	1,475 (24.1%)	437 (20.5%)	1,038 (25.9%)	1,778 (21.4%)	394 (21.3%)	1,384 (21.5%)
Prior stroke or TIA	1,039 (7.9%)	320 (9.0%)	719 (7.5%)	496 (8.1%)	206 (9.7%)	290 (7.2%)	699 (8.4%)	166 (9.0%)	533 (8.3%)
Vascular disease	3,495 (26.7%)	1,117 (31.4%)	2,378 (25.0%)	2,435 (39.7%)	866 (40.7%)	1,569 (39.2%)	1,793 (21.6%)	509 (27.5%)	1,284 (19.9%)
Age 65–74 y	4,060 (31.0%)	1,228 (34.5%)	2,832 (29.7%)	1,983 (32.3%)	731 (34.4%)	1,252 (31.3%)	2,587 (31.2%)	665 (35.9%)	1,922 (29.8%)
Valvular heart disease, n (%)	2,042 (15.6%)	583 (16.4%)	1,459 (15.3%)	1,445 (23.6%)	452 (21.3%)	993 (24.8%)	1,016 (12.2%)	266 (14.3%)	750 (11.6%)
Obesity, n (%)	328 (2.5%)	93 (2.6%)	235 (2.5%)	158 (2.6%)	54 (2.5%)	104 (2.6%)	226 (2.7%)	63 (3.4%)	163 (2.5%)

Prevalent cases of atrial fibrillation have been removed.

Abbreviations: AF = atrial fibrillation; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

Table 2
Association between polygenic risk scores and adverse outcomes

PRS	Revascularization			CABG			PCI		
	HR (95% CI)	p Value	Cases / Controls	HR (95% CI)	p Value	Cases / Controls	HR (95% CI)	p Value	Cases / Controls
AF	1.18 (1.14–1.22)	5.1×10^{-23}	3,556/9,526	1.15 (1.10–1.20)	1.0×10^{-10}	2,127/4,005	1.22 (1.16–1.28)	5.7×10^{-17}	1,854/6,442
MI	1.06 (1.00–1.12)	0.035	1,322/7,823	1.13 (1.05–1.21)	0.0017	746/4,141	1.02 (0.95–1.10)	0.59	715/4,373
Stroke	1.05 (1.00–1.11)	0.048	1,479/13,902	1.11 (1.04–1.19)	0.002	881/6,513	0.98 (0.91–1.06)	0.62	757/8,931
IC bleeding	1.02 (0.89–1.16)	0.79	273/14,568	1.02 (0.86–1.21)	0.83	144/6,829	0.94 (0.79–1.13)	0.51	123/9,402
GI bleeding	1.08 (1.00–1.17)	0.061	607/14,468	1.05 (0.94–1.17)	0.43	326/6,793	1.08 (0.97–1.20)	0.17	349/9,314

The Cox proportional hazard models were calculated per 1 SD increase in PRS. Models were adjusted by age, gender, sample collection year, genotyping batch, and the first 10 genetic principal components. The significance level after Bonferroni correction is $0.05/15 = 0.003$.

Abbreviations: AF = atrial fibrillation; CABG = coronary artery bypass grafting; CI = confidence interval; GI bleeding = gastrointestinal bleeding; HR = hazard ratio; IC bleeding = intracranial bleeding; MI = myocardial infarction; PCI = percutaneous coronary intervention; PRS = polygenic risk score.

Table 3
Hazard ratios of AF onset after revascularization in AF-PRS categories

PRS	Revascularization				CABG				PCI			
	Cases / Controls	Per 100 Person-y	HR (95% CI)	p Value	Cases / Controls	Per 100 Person-y	HR (95% CI)	p Value	Cases / Controls	Per 100 Person-y	HR (95% CI)	p Value
<2.5%	3,556/9,526	1.86	0.68 (0.53–0.86)	0.0013	2,127/4,005	1.91	0.59 (0.43–0.82)	0.0013	1,854/6,442	1.92	0.76 (0.55–1.04)	0.09
2.5%–20%	71/283	2.10	0.85 (0.78–0.93)	7.0×10^{-4}	40/130	2.31	0.82 (0.72–0.92)	0.0011	40/180	2.00	0.88 (0.78–1)	0.059
20%–80%	569/1,830	2.33	ref	ref	338/780	2.69	ref	ref	299/1,230	2.13	ref	ref
80%–97.5%	2,103/5,749	2.76	1.28 (1.17–1.39)	3.2×10^{-8}	1,300/2,423	2.98	1.21 (1.08–1.36)	0.00091	1,067/3,890	2.66	1.35 (1.2–1.52)	8.9×10^{-7}
>97.5%	695/1,484	3.19	1.54 (1.28–1.86)	5.9×10^{-6}	391/594	2.92	1.19 (0.91–1.56)	0.20	377/1,021	3.51	1.89 (1.48–2.41)	3.1×10^{-7}

The Cox proportional hazard models were adjusted by CHA₂DS₂-VAsC score, age, gender, sample collection year, genotyping batch, and the first 10 genetic principal components. The significance level after Bonferroni correction is 0.05/15 = 0.003.

Abbreviations: AF = atrial fibrillation; CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; PCI = percutaneous coronary intervention; PRS = polygenic risk score.

0.0102), 0.0058 (95% CI 0.0027 to 0.0088), and 0.0094 (95% CI 0.0052 to 0.0137) for any revascularization, CABG, and PCI, respectively, when AF PRS was included into a model with CHA₂DS₂-VAsC score, obesity, and VHD (Table 4).

Our results demonstrate that an AF-PRS can be used to improve AF risk prediction after revascularization over and above standard clinical risk factors. AF-PRS could potentially be used to enhance AF prevention and prognosis in patients undergoing revascularization. The association between PRSs and other postrevascularization adverse events, such as MI, stroke, and bleeding complications, was limited.

Postrevascularization complications are common and are related to increased morbidity and mortality.^{17,18} Thus, reducing these adverse events is in the clinicians' and patients' interest. Certain complications, such as immediate postprocedural mortality and bleeding complications, are often related to the technical performance of the procedure.¹⁹ However, some patients may have underlying risk factors for later complications, and identification of these patients through the use of novel biomarkers could improve treatment outcomes. PRSs have been previously widely used for predicting first-onset cardiovascular disease in the general population.^{7,20} Our results add to this body of work by establishing that PRSs can also be used to predict adverse outcomes in patients with established coronary heart disease who are undergoing coronary revascularization.

We show that the cumulative incidence of postrevascularization new-onset AF is high, irrespective of AF-PRS status. Nevertheless, the trajectories between different AF-PRS groups diverge considerably. After either type of revascularization, 1 of 4 patients in the bottom 2.5% PRS group had AF at 20 years, whereas every second patient with high AF-PRS had AF. PRS was a strong predictor of postoperative AF particularly in patients with PCI. As AF is more common after CABG than PCI,^{21,22} it appears that the impact of the surgical procedure itself on AF risk is so high that the significance of genetic factors is somewhat diminished. In contrast, after PCI (a less invasive procedure than CABG), patients with a high genetic susceptibility for postprocedural AF are at a clearly increased risk. However, our results also demonstrate that AF prediction using a PRS is possible and adds incremental predictive value in both patients with PCI and patients with CABG.

Several known clinical risk factors, such as increasing age, high blood pressure, and previous MI predispose to post-PCI AF.²² Despite adjusting for the obesity, VHD, and CHA₂DS₂-VAsC score that includes age, gender, heart failure, hypertension, diabetes, stroke, and vascular disease at the time of the operation as its components, we observed that an AF-specific PRS was associated with incident AF and that model discrimination was notably improved. In contrast, the association of PRSs with postoperative MI, stroke, and bleeding complications was modest. According to results from previous studies, the risk profiles for both stroke and MI are multifactorial, consisting of multiple genetic, lifestyle, therapeutic, and procedural risk factors with small effect sizes.^{23–25} In the case of bleeding complications, our results suggest that clinical risk factors and

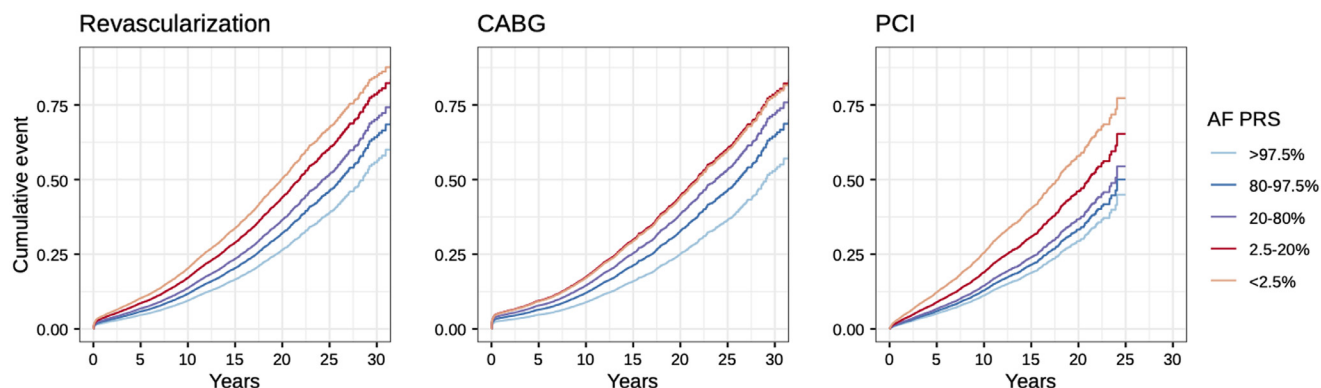


Figure 1. Cumulative risk of atrial fibrillation by PRS categories after revascularization. Number of patients: revascularization $n = 13,082$, CABG $n = 6,132$ and PCI $n = 8,296$. We adjusted the models for $\text{CHA}_2\text{DS}_2\text{-VASc}$ score, age, gender, sample collection year, genotyping batch, and the first 10 genetic principal components.

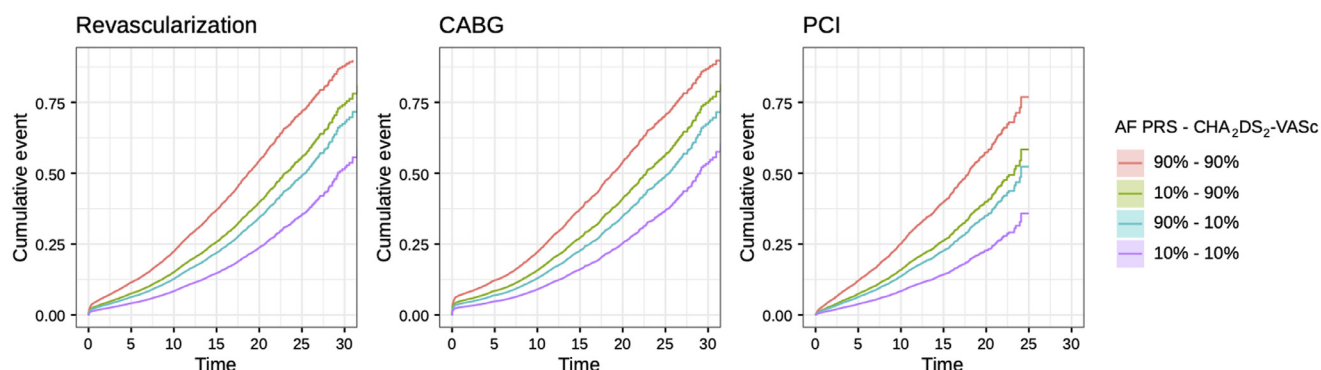


Figure 2. Cumulative risk of atrial fibrillation by clinical and genetic risk scores after revascularization. Number of patients: revascularization $n = 13,082$, CABG $n = 6,132$ and PCI $n = 8,296$. Highest and lowest deciles for AF PRS and $\text{CHA}_2\text{DS}_2\text{-VASc}$ score are shown. We adjusted the Cox models for age, gender, sample collection year, genotyping batch, and the first 10 genetic principal components.

postoperative medication may affect these complications more than genetic susceptibility.

The strength of our study includes a large, representative nationwide sample of nearly 15,000 patients who underwent revascularization, genotyping, and follow-up for postoperative complications. However, our methods have some limitations that warrant discussion. For instance, the clinical risk score used for AF prediction was $\text{CHA}_2\text{DS}_2\text{-VASc}$, which was originally designed for assessing stroke risk. However, this score includes risk factors (e.g., age, gender, heart failure, hypertension, diabetes, stroke, and vascular disease), which are also relevant AF risk factors. In addition, $\text{CHA}_2\text{DS}_2\text{-VASc}$ has been widely and successfully used also for AF prediction.^{3–5} Another potentially important limitation is that the preoperative risk factors and postoperative diagnoses of MI, stroke, bleeding complications,

and AF were based on registry data, which may not capture all relevant outcome events. This is especially true for AF, which is in some cases, is treated solely in primary care units. Furthermore, we did not have access to all known AF risk factors, such as smoking, surgical procedure, or echo findings. Fourth, because our PRSs consisted mainly of patients of European ancestry, our results may not be generalizable to patients from other genetic backgrounds.

In the present study, we demonstrate that an AF-specific PRS is associated with new-onset AF after revascularizations, and that this PRS improves risk prediction over clinical risk factors. PRSs demonstrate only weak associations with other postoperative adverse events (MI, stroke, and bleeding complications). Our results suggest that PRS can be used for clinical AF risk prediction in patients undergoing revascularization in addition to the general population.

Table 4

Improvement in model discrimination (C-index) after including AF PRS in the model with $\text{CHA}_2\text{DS}_2\text{-VASc}$ score

Procedure	Model 1 C-Index: $\text{CHA}_2\text{DS}_2\text{-VASc}$	Model 2 C-Index: Model 1 + VHD+Obesity	Model 3 C-Index: Model 2 + PRS	Difference Model 2 versus Model 3 (95% CI)	p Value
Revascularization	0.6679	0.6746	0.6820	0.0074 (0.0047–0.0102)	2×10^{-7}
CABG	0.6677	0.6737	0.6795	0.0058 (0.0027–0.0088)	2×10^{-4}
PCI	0.6769	0.6814	0.6908	0.0094 (0.0052–0.0137)	1×10^{-5}

AF = atrial fibrillation; CABG = coronary artery bypass grafting; CI = confidence interval; C-index = Harrell's concordance index; HR = hazard ratio; PCI = percutaneous coronary intervention; PRS = polygenic risk score; VHD = valvular heart disease.

The AF-PRS could be potentially used in the future to identify patients undergoing revascularization who are at highest risk for postoperative AF and to improve AF prevention and clinical outcomes in these patients.

Disclosures

The authors have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2021.11.046>.

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