Prediction of Atrial and Ventricular Arrhythmias using Multiple Cardiovascular Risk Factor Polygenic Risk Scores

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Abstract

Background: Atrial fibrillation (AF) prediction improves by combining clinical scores with a polygenic risk score (PRS) for AF (AF-PRS), but there are limited studies of PRS for ventricular arrhythmia (VA) prediction.

Objective: We assessed the value of including multiple PRS for cardiovascular risk factors (CV-PRS) for incident AF and VA prediction.

Methods: We used 158,733 individuals of European ancestry from UK Biobank to build three models for AF: CHARGE-AF (AF1), AF1 + AF-PRS (AF2), AF2 + CV-PRS (AF3). Models for VA included sex and age (VA1), VA1 + coronary artery disease (CAD) PRS (CAD-PRS, VA2), and VA2 + CV-PRS (VA3), conducting separate analyses in subjects with and without ischemic heart disease (IHD). Performance was evaluated in individuals of European (N=158,733), African (N=7,200), South Asian (N=9,241) and East Asian (N=2,076) ancestry from UK Biobank.

Results: AF2 had a higher C-index than AF1 (0.762 versus 0.746, $P<0.001$), marginally improving to 0.765 for AF3 ($P<0.001$, including PRS for heart failure, electrocardiogram and cardiac magnetic resonance measures). In South Asians, AF2 C-index was higher than AF1 ($P<0.001$). For VA, the C-index for VA2 was greater than VA1 (0.692 versus 0.681, $P<0.001$) in Europeans, which was also observed in South Asians ($P<0.001$). VA3 improved prediction of VA in individuals with IHD.

Conclusion: CV-PRS improved AF prediction compared to CHARGE-AF and AF-PRS. A CAD-PRS improved VA prediction, while CV-PRS contributed in IHD. AF- and CAD-PRS were transferable to individuals of South Asian ancestry. Our results inform of the use of CV-PRS for personalised screening.

Keywords: atrial fibrillation, ventricular arrhythmia, polygenic risk scores, risk prediction, UK Biobank

Abbreviations

AF: atrial fibrillation

CAD: coronary artery disease

CHARGE: Cohorts for Heart and Aging Research in Genetic Epidemiology

ECG: electrocardiogram

ICD-10: international classification of diseases, tenth revision

IHD: ischaemic heart disease

MRI: magnetic resonance image

PRS: polygenic risk score

VA: ventricular arrhythmia

Introduction

Atrial and ventricular arrhythmia are a cause of substantial morbidity and mortality in the general population. Atrial fibrillation (AF) is the most common cardiac arrhythmia and associated with increased risk for cardioembolic stroke and heart failure[1]. Ventricular arrhythmia (VA) are the primary cause of sudden cardiac death, with ~50% of these deaths occurring in individuals considered low risk using current clinical criteria[2]. Therefore, AF and VA risk stratification tools need to improve the identification of high-risk individuals in low-risk populations who may benefit from early implementation of primary prevention strategies.

The Cohorts for Heart and Aging Research in Genetic Epidemiology (CHARGE)-AF score was developed for primary screening of incident AF risk in the general population[3]. A polygenic risk score (PRS) combining an individual's genetic predisposition for AF showed a strong association with AF risk independently from traditional risk factors[4]. When combined with the CHARGE-AF score, three-times more AF cases were identified compared to CHARGE-AF alone[5]. For VA, there is no established clinical score, but male sex and age are the main risk factors in the general population[6]. A recent study has reported a coronary artery disease (CAD) PRS is associated with sudden cardiac death in patients with CAD and cardiovascular comorbidities independently from sex and age, with a 70% improvement in discrimination when combined with clinical risk factors[7].

Most AF or VA risk factors, including electrocardiogram (ECG) or cardiac magnetic resonance images (MRI) markers, are heritable, with over 1,000 significant loci combined[4, 8-25]. Our recent work showed that the combination of a CAD PRS with PRS for several cardiovascular risk factors has a better performance in predicting incident CAD risk in the general population than a CAD PRS alone[26]. Nevertheless,

the AF and VA predictive value of PRS for these risk factors is still unknown, although this investigation would inform on their utility in risk stratifying individuals who are otherwise healthy, where there are potentially few confounding factors.

We, thus, hypothesised that additional PRS for AF and VA cardiovascular risk factors, including ECG and MRI risk markers in combination with clinical scores, may capture additional electrophysiological mechanisms relevant for risk stratification. We have tested this in a middle-aged population of European ancestry without prevalent cardiovascular disease at recruitment (Figure 1), as well as in individuals with African, South and East Asian ancestry. We additionally performed sex-stratified analyses and repeated incident VA association analyses in individuals with and without prevalent ischaemic heart disease (IHD).

Methods

Study population

UK Biobank is a prospective study of 502,505 individuals, aged 40 to 69 years old at recruitment (2006 - 2008). UK Biobank has approval from the North West Multi-Centre Research Ethics Committee, and all participants provided informed consent. The research reported in this paper adhered to the Helsinki Declaration as revised in 2013. For AF and VA, individuals with a diagnosis of CAD, VA, AF or heart failure at recruitment were excluded using international Classification of Diseases, Tenth Revision (ICD-10) codes (Supplementary Table 1). The main analysis included 398,716 unrelated individuals of European-ancestry (Figure 2). A subset of 81,251 individuals who participated in the UK Biobank exercise stress test or in the imaging study was used to obtain the list of variants and weights to build the optimal PRS for each cardiovascular risk factor trait. The remaining 317,465 independent individuals

were further split into training (50%) and test (50%) subsets. The training subset was used to derive specific models associated with incident AF and VA, and their performance was evaluated in the test subset (Figure 2). Models were additionally tested in unrelated individuals without prevalent CAD, VA, AF or HF of African (N = 7,200), South Asian (N = 9,241) and East Asian (N = 2,076) ancestry from UK Biobank, given their different genetic background.

AF and VA risk definition

The primary endpoints of the study were incident AF and VA as recorded in hospital episode statistics using ICD10 codes I48, I480, I481, I482 and I489 for AF and I460, I461, I472 and I490 for VA. Follow-up was from the study inclusion date until November, 2022 (median of 13.6 years, interquartile range of 1.2 years).

Calculation of polygenic risk scores

Selection of each PRS was based on a prior electrophysiological hypothesis for their association with risk of AF or VA. In total, 36 PRS for clinical risk factors and ECG and MRI measures were derived (Supplementary Methods, Table 1). All PRS were standardised by subtracting the mean and dividing by their standard deviation so that their effect sizes in the models were comparable.

Training of statistical models

In the training set, we fitted three models: CHARGE-AF (AF1), CHARGE-AF and the AF PRS (AF2)[4], and AF2 and the other 35 PRS (AF3). The CHARGE-AF score was calculated using the original model originally described[3]. Models 2 and 3 were

also adjusted for the genetic array and the first 10 principal components[26]. PRS were included as continuous variables in the models.

For each model, we performed univariable logistic regression analyses to determine the relationship between each risk factor and incident AF risk[27]. Then, we took forward into multivariable logistic regression models, clinical risk factors or PRS that were significantly associated with AF ($P < 0.05$) using backward stepwise elimination to remove markers with a non-significant association with the Akaike information criterion ("stepAIC" function from the "MASS" package in R).

We followed a similar approach for the prediction of VA risk, also fitting three models: sex and age (VA1), sex, age and a CAD PRS[4] (VA2), and sex, age, a CAD PRS and the other 35 PRS (VA3).

Test of statistical models

In the independent test subset (Figure 2), we calculated risk scores as the weighted sum of significant clinical risk factors and PRS in the respective multivariable models from the training set, weighted by the corresponding beta coefficients[26, 27].

Performance of the risk scores was evaluated by measuring the concordance index (C-index). We used bootstrapping to calculate a population of C-indices and to extract confidence intervals. Then, the likelihood ratio test (LRT, package "lmtest" in R) was used to compare nested models. Calibration of the models was evaluated using the integrated calibration index and the scaled Brier score ('psfmi' library in R); calibration plots were made using the 'predtools' library in R The net reclassification improvement (NRI) was computed using the package "PredictABEL" in R to quantify the added predictive value of each score beyond that from the corresponding

preceding one for both AF and VA risk. The risk categories used for the NRI analysis were equivalent to the event rate for each endpoint.

Next, for each score and endpoint, we identified two risk groups based on their training-specific optimal cutoff, calculated as the value of the score that jointly maximized both sensitivity and specificity values using the "cutpointr" package in R. Thus, risk groups were defined as: low-risk (test score values < optimal cutoff) and high-risk (test score values > optimal cutoff). Odds ratios (ORs) were calculated using the low-risk group as a reference. To evaluate the dependency of the results on the choice of threshold, we repeated the low- and high-risk split using the cut-off value that marks the 90^{th} percentile of the scores in the training set.

Finally, we performed survival analyses; Kaplan-Meier curves were derived using the optimal cutoff values, with a comparison of cumulative events performed by using log-rank tests, and plotted using the "survminer" package in R. Hazard ratios (HRs) were derived taking the low-risk group as a reference using univariable Cox regression analyses.

Sex-stratified analyses

To investigate sex-specific contributions of the multiple PRS for incident AF and VA risk stratification, we performed sex-stratified analyses by repeating the training and testing of statistical models in men and women separately.

Incident VA prediction in individuals with and without IHD

Finally, we performed separate incident VA association analyses by repeating the training and testing of statistical models in individuals with and without prevalent

IHD to determine whether the underlying aetiology of VA affects PRS performance (Supplementary Methods, Supplementary Figures 1 and 2).

Performance assessment in Non-European ancestries

To assess the generalisability and performance of the statistical models trained in the European individuals for non-European ancestry individuals, we tested in individuals with African, South Asian and East Asian ancestry. To reduce the variation in the PRS distribution due to genetic ancestry, we used the residuals from a linear model after regressing each PRS on the first 4 genetic PCs, as previously described[28].

Results

The study population consisted of 138,929 men, with a median (interquartile range) age of 58 (13) years old. The demographic characteristics of this population are shown in Table 2.

Prediction of incident AF

During the follow-up period, there were 10,411 AF cases (6.6%) in each of the training and test sets (Figure 2). The C-index for AF1 (CHARGE-AF) was 0.746 (0.742 – 0.751) in the test set, which significantly increased to 0.762 (0.757 – 0.766, $P < 2.2 \times 10^{-16}$) when using AF2 (CHARGE-AF + AF PRS, Figure 3). The C-index for AF3 was statistically significantly higher than that for AF2 (0.765 [0.760 - 0.769], $P < 2.2 \times 10^{-16}$. The PRS for HF, TMR after exercise, BMI, QT dynamics during exercise, left ventricular ejection fraction (LVEF), Tpe interval, resting HR, left ventricular ejection systolic volume (LVESV), left atrial active minimum volume (LAmin), Brugada syndrome, QRS duration and QT interval (in decreasing order of magnitude and direction of effect) remained significantly associated with incident AF in AF3 (Figure

3). The overall mean NRI was 0.288 (0.268 – 0.308, $P < 0.001$) for AF2 versus AF1, and 0.110 (0.090 – 0.130, $P < 0.001$) for AF3 versus AF2 (Supplementary Tables 2 and 3). Calibration metrics and overall performance of each model using the 'optimal' and the 90th percentile thresholds are shown in Supplementary Table 4 and Supplementary Figure 3). Finally, OR values and 95% CI for individuals in the high-risk group versus those in the low-risk group progressively increased from 4.85 (4.63 - 5.08) for AF1, to 5.24 (5.01 – 5.48) for AF2, and 5.56 (5.31 – 5.83) for AF3 (Figure 3). Hazard ratio (HR) values increased from 4.83 for AF1, to 5.17 for AF2 and to 5.49 for AF3 (Figure 4).

In sex-specific analyses, AF2 had a significantly higher C-index than AF1 in both men (N = 69,432 in the test set, 6,151 AF cases) and women (N = 89,300 in the test set, N = 4,260 AF events). In men, AF2 showed an NRI of 0.287, and OR and HR values for AF1 and AF2 of 4.05 and 4.55, and 4.04 and 4.48, respectively. In women, NRI was 0.284, and OR and HR values were 5.36 for AF2 versus 4.86 for AF1, and 5.30 for AF2 versus 4.85 for AF1 (Supplementary Figures 3, 4 and 5, Supplementary Tables 5, 6 and 7). However, CV-PRS (the same PRS from the main analysis, except for the PRS for TMR after exercise, QT dynamics during exercise, LVEF, Tpe interval and LAmin and the addition of CAD and the PR interval) only showed a significant contribution in men. These jointly increased the C-index to 0.772 ($P = 4.6 \times 10^{-4}$) and the OR to 4.51, with an NRI of 0.121 (0.094 – 0.147, $P < 0.001$, Supplementary Figure 4, Supplementary Table 7).

We tested the performance of each model trained in the main analysis in individuals with African (166 AF cases), South Asian (275 AF cases) and East Asian (42 AF cases) ancestry. In individuals of South Asian ancestry, AF2 had a significantly higher C-index than AF1 (0.787 [0.760 – 0.813] versus 0.774 [0.746 – 0.802], $P = 2.9$

x 10^{-5}), which significantly increased to 0.791 (0.764 – 0.817), P =1.8 x 10^{-4}, for model AF3 (Supplementary Table 4, Supplementary Figure 6). The ORs were 6.52 (4.87 – 8.72) for AF1, 7.08 (5.31 – 9.45) for AF2, and 7.59 (5.64 - 10.22) for AF3, and the HR values were 6.61, 7.16 and 7.64, respectively. In individuals with African or East Asian ancestry, AF2 or AF3 did not significantly improve the predictive value already provided by CHARGE-AF in AF1 alone however there were a smaller number of cases in these ancestry groups.

Prediction of incident VA risk

For prediction of incident VA, there were 621 and 622 VA cases (0.4%) in the training and test sets, respectively (Figure 2). VA1 (sex and age) showed a C-index of 0.681 (0.660 – 0.701), which significantly increased for VA2 (sex, age and a CAD PRS, 0.692 [0.671 – 0.712], P = 4.1 x 10^{-11}, Figure 4). NRI was 0.314 (0.236 – 0.392, P < 0.001, Supplementary Table 8), calibration and performance metrics are shown in Supplementary Table 9 and Supplementary Figure 7). OR and HR values were 3.11 (2.64 - 3.67) and 3.27 (2.76 - 3.88), and 3.20 and 3.36, respectively (Figures 5 and 6). After fitting model VA3, the PRS for HF, QT dynamics during exercise, HDL and QT interval remained significantly associated with incident VA, independently from sex, age and the CAD PRS. However in combination, they did not improve discrimination compared to VA2 (Figure 5). HR values were 3.20 for VA1, 3.36 for VA2 and 3.26 for VA3 (Figure 6).

Sex-specific analyses (69,465 men in the training set, 441 VA cases, and 69,464 men in the test set, 441 VA cases) showed similar findings, with VA2 having a significantly higher performance than VA1, but the contribution of CV-PRS not being

286 statistically significant (Supplementary Figures 8 and 9, Supplementary Tables 10 and
287 11).

288 There were 561 VA cases (5%) in both the training and test sets in individuals
289 with prevalent IHD. Age was not significantly associated with incident VA, and sex
290 alone had a C-index of 0.545 (0.528 – 0.563). The CAD PRS was not significantly
291 associated with incident VA. Thus, VA3 included sex and the PRS for DBP and DCM
292 (the two PRS that remained significantly associated in model VA3). There was a
293 significant increase in the C-index to 0.592 (0.560 – 0.624, $P = 8.5 \times 10^{-3}$) with a mean
294 NRI of 0.216 (0.0972 – 0.3352, $P = 0.004$, Supplementary Tables 9 and 12,
295 Supplementary Figure 10). OR and HR values were 1.86 (1.44 - 2.42) and 1.84
296 (Supplementary Figure 11). In individuals without IHD, there were 653 VA cases
297 (0.2%) in both training and test subsets. The C-index was 0.654 (0.625 – 0.684) for
298 VA1, and the OR was 3.01 (2.41 - 3.75). However, the addition of the CAD PRS (VA2),
299 or VA3 (here the PRS for HF and the spatial QRST angle were the only two PRS that
300 remained significantly associated with incident VA), did not significantly improve model
301 performance (Supplementary Table 12).

302 We finally tested the performance of each model trained in the main analysis in
303 individuals of African, South and East-Asian ancestries. We observed that, in
304 individuals with South Asian ancestry (46 VA cases), VA2 had a significantly higher C-
305 index than VA1 (0.722 [0.648 – 0.796] versus 0.640 [0.579 – 0.700], $P = 3.2 \times 10^{-4}$).
306 However, the C-index of VA3 was not significantly higher than that of score 2 ($P = 1.7$
307 $\times 10^{-1}$, Supplementary Table 9, Supplementary Figure 12). The OR and HR values
308 were 3.56 (1.76 – 7.17) and 4.10 for VA1, 2.41 (1.30 - 4.47) and 4.3 for VA2, and 2.26
309 (1.26 - 4.08) and 5.60 for VA3. In individuals with African (22 VA events) or East Asian

ancestry (3 VA events), VA2 or VA3 did not significantly improve the performance compared with VA1 alone.

Discussion

In this work, we assessed the contribution of PRS for cardiovascular risk factors in the prediction of incident AF and VA in a large middle-aged population. We have validated the improvement in incident AF risk stratification provided by the combination of an AF PRS with the CHARGE-AF score, and observed that the inclusion of multiple CV-PRS further improved discrimination. For incident VA, we observed that a CAD PRS significantly improved risk stratification compared to sex and age alone, but the addition of the multiple CV-PRS only improved discrimination in individuals with prevalent IHD. We also demonstrated that our models using AF and CAD PRS for incident AF and VA risk prediction are potentially transferable in individuals of South Asian ancestry.

It has been reported previously that the combination of polygenic risk for AF with the CHARGE-AF clinical score improves incident AF risk prediction over CHARGE-AF alone in patients with and without cardiovascular diseases and risk factors[5]. Our work builds on these findings demonstrating that inclusion of genetic predisposition for cardiovascular risk factors provides an incremental improvement in AF risk prediction in healthy middle-aged individuals of European ancestry. Results showed that genetically-predicted shorter ventricular depolarisation and repolarisation times were associated with increased AF risk, confirming previous observations having also now performed adjustment for additional CV risk factors[14]. Finally, the contribution of MRI markers like LVEF or left ventricular ejection systolic volume

highlights the role for genetically-determined differences in ventricular structure in AF risk, potentially through atrial mechanical and cardiac ion channel remodelling.

Our sex-stratified analyses enabled the investigation of the potential contribution to risk prediction of CV-PRS in each sex separately, as well as the specific genetic architecture of AF and VA. The PRS for cardiovascular risk factors that significantly contributed to AF risk in men predominantly overlapped with those from the main analysis. However, the PRS for LVEF, Tpe interval and resting HR were no longer significant in model AF3, and were replaced by the PRS for CAD and the PR interval. In women, inclusion of PRS for cardiovascular risk factors did not significantly contribute to AF risk prediction. The addition of the CAD PRS in the model for men suggests genetic-predisposition to development of an ischemic substrate is an important contributor to AF risk compared to women, as previously reported[29], as well as abnormalities in cardiac conduction, which have extensively been linked with AF[13].

Sandhu and colleagues recently demonstrated the added value of a CAD PRS to sex and age in stratifying patients with documented IHD on coronary angiography and cardiovascular comorbidities, according to SCD risk[7]. Our study is the first to report the added value of a CAD PRS to sex and age for prediction of incident VA in the general population, and this improvement held when analysing women and men separately. IHD is the most common risk factor for VA and SCD in middle-aged individuals[6], and identification of individuals early in life with a higher genetic predisposition could improve SCD prevention strategies. Interestingly, our results did not show an added value for the CAD PRS to sex and age alone when performing the analysis separately in individuals with and without prevalent IHD. These findings suggest that while a CAD PRS associates with risk for developing IHD, it does not

358 offer improvements in VA risk stratification when considering the underlying aetiology
359 for arrhythmia.

360 Beyond the presence of ischemia, the causes of malignant VA are multifactorial
361 including cardiomyopathies and inherited channelopathies, which might be reflected
362 on ECG and MRI risk factors through the effects of structural changes, including
363 fibrosis and post myocardial infarction remodeling[6]. In our work, we observed that the
364 PRS for HF, QT dynamics during exercise, HDL and QT interval remained significantly
365 associated with incident VA risk after adjusting for sex, age and the CAD PRS, but
366 they did not provide an improvement in risk stratification value. This may be due to
367 small individual effect sizes. In sex-stratified analyses there were similar observations.
368 However, when analysing individuals with prevalent IHD, we observed that inclusion
369 of the PRS for DBP and DCM significantly improved VA risk prediction. The
370 incremental gain by including a DCM PRS could suggest an interaction of ischaemic
371 and non-ischaemic aetiologies in genetically predisposed individuals that contributes
372 to VA risk[7]. Thus, our results extend the observations of Sandhu et al.[7], and warrant
373 testing of these models in other cohorts including those considered clinically high risk.

374 We also tested the performance of the models trained using individuals with
375 European ancestry in non-European ancestry groups. We observed that the AF and
376 CAD PRS significantly contribute to incident AF and VA prediction, respectively, in
377 South Asian ancestry individuals, but not in individuals with African or East Asian
378 ancestry. These findings suggest a good transferability of the AF PRS to a South Asian
379 population, and confirms previous observations for the generalisability of the CAD
380 PRS[28]. The absence of a significant improvement in African and East Asian individuals
381 could be due to a smaller number of cases, however they may also reflect a need for
382 ancestry-specific PRS for these two populations[30]. Including multiple CV-PRS in AF3

did not improve the performance of AF2 in South Asian ancestry individuals, however it is of interest that the predictive value of CHARGE-AF alone in these individuals was better than AF3 (CHARGE-AF, AF PRS and PRS for multiple cardiovascular risk factors) in European ancestry individuals. This may reflect a greater prevalence of advanced cardiovascular disease in these individuals, that could lessen the additive effect of PRS (Supplementary Table 13).

Regarding the clinical implications of our findings, although the combined models are statistically significantly stronger than the clinical risk scores, the improvement is marginal. However, even a small improvement in predictive accuracy can be clinically relevant, particularly if it shifts an individual's risk classification from a lower to a higher risk category, as shown in our NRI results. Our results could inform the design of clinical studies to investigate the utility of these PRSs in patient cohorts and higher risk populations, to identify individuals that would benefit most from more intensive screening for earlier AF detection that would facilitate prompt initiation of anticoagulation.

A strength of this work is that we developed specific models for prediction of incident AF and VA, both in the overall population, and in men and women separately. Thus, the results are not biased by an 'a priori' specific selection of PRS for each outcome. Moreover, we used one of the largest cohorts available with detailed phenotypic and genetic data and relatively long follow-up. In addition, the inclusion of PRS for robust ECG and MRI risk markers allows an extended characterisation of the genetic architecture of AF and VA risk. There are also some limitations in our study. Firstly, the study is limited to the UK Biobank cohort, which is known to have a healthy volunteer selection bias. Calculation of optimal PRS was performed independently from the samples used to train and test the models, thus minimizing the risk of

overfitting. However, validation of these findings in other cohorts at different levels of risk and in other ethnicities will provide support for further generalizability. We used variants and effect sizes from multi-ancestry GWAS whenever possible to optimise transferability across ancestries, following findings from previous studies[8]. However, multi-ancestry GWAS on ECG and MRI traits are not currently available.

In conclusion, in this large middle-aged population-based cohort, the inclusion of PRS for cardiovascular risk factors provides an incremental improvement in prediction of incident AF risk when combined with the CHARGE-AF clinical score and an AF PRS. Regarding VA risk, although they did not improve the risk stratification value of sex, age and a CAD PRS for incident VA prediction in the main analysis, they showed a significant contribution in individuals with IHD. Our results also indicate a good transferability of the European AF and CAD PRS for AF and VA risk prediction, respectively, in South Asian ancestry individuals.

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Main Tables

Table 1: List of polygenic risk scores included in the analysis.

Trait	N variants	GWAS Paper	Includes UK Biobank	Derivation method
AF	6,730,541	-	No	PGS Catalog (PGS000016)
CAD	6,630,150	-	No	PGS Catalog (PGS000013)
HF	909,256	Wang 2023	No	PRScs
Diabetes	6,917,436	-	No	PGS Catalog (PGS000014)
BMI	2,100,302	-	No	PGS Catalog (PGS000027)
SBP	1,108,568	Evangelou 2018	No	PRScs
DBP	1,110,407	Evangelou 2018	No	PRScs
PP	1,108,602	Evangelou 2018	No	PRScs
HDL	1,107,495	Hoffmann 2018	No	PRScs
LDL	1,107,494	Hoffmann 2018	No	PRScs
triglycerides	1,107,494	Hoffmann 2018	No	PRScs
Resting HR	1,108,747	van de Vegte 2023	No	PRScs
HR Response to exercise	14	Ramírez 2018	Yes	Lead SNVs
HR Response to recovery	16	Ramírez 2018	Yes	Lead SNVs
PR	583	Ntalla 2020	No	Lead SNVs
QRS	135	Young 2022	No	Lead SNVs
QT	227	Young 2022	No	Lead SNVs
JT	205	Young 2022	No	Lead SNVs
spQRSTa	53	Young 2022	No	Lead SNVs
QT dynamics during exercise	19	van Duijvenboden 2020	Yes	Lead SNVs
QT dynamics during recovery	3	van Duijvenboden 2022	Yes	Lead SNVs
Tpe interval	28	Ramírez 2020	Yes	Lead SNVs
TMRex	8	Ramírez 2019	Yes	Lead SNVs
TMRrec	8	Ramírez 2019	Yes	Lead SNVs
Brugada syndrome	21	Barc 2022	No	Lead SNVs
DCM	13	Tadros 2021	Yes (controls)	Lead SNVs
HCM	16	-	Yes (controls)	PGS Catalog (PGS000778)
LAAEF	6	Ahlberg 2021	Yes	Lead SNVs
LAmin	3	Ahlberg 2021	Yes	Lead SNVs
LVEDV	22	Pirrucello 2020	Yes	Lead SNVs
LVESV	32	Pirrucello 2020	Yes	Lead SNVs

LVEF	19	Pirrucello 2022	Yes	Lead SNVs
LVM	465	-	Yes	PGS Catalog (PGS003427)
RVESV	21	Pirrucello 2022	Yes	Lead SNVs
RVEDV	14	Pirrucello 2022	Yes	Lead SNVs
RVEF	12	Pirrucello 2022	Yes	Lead SNVs

Table 2: Characteristics of the cohort.

Risk factor or endpoint	All N = 317,465	Training N = 158,733	Test N = 158,732	*P*
Male sex, n (%)	138,929 (43.76)	69,362 (43.70)	69,567 (43.83)	0.462
Age	58 (13)	58 (13)	58 (13)	0.350
Diabetes mellitus, n (%)	13,847 (4.36)	6,836 (4.31)	7,011 (4.42)	0.128
Hypertension, n (%)	207,715 (65.43)	103,995 (65.52)	103,720 (65.34)	0.303
Median CHA2DS2-VA score[31] (IQR)	1 (1)	1 (1)	1 (1)	0.394
Median Height (IQR), cm	168 (14)	168 (14)	168 (14)	0.213
Median Weight (IQR), kg	76.2 (21.1)	76.2 (21.0)	76.2 (21.1)	0.724
Previous or current smoker, n (%)	34,915 (11.00)	17,471 (11.01)	17,444 (10.99)	0.879
Use of antihypertensive medications, n (%)	58,237 (18.34)	29,099 (18.33)	29,138 (18.36)	0.857
Median CHARGE-AF score (IQR)	11.70 (1.45)	11.70 (1.45)	11.70 (1.45)	0.542
Incident AF events, n (%)	20,822 (6.56)	10,411 (6.56)	10,411 (6.56)	1.000
Incident VA events, n (%)	1,243 (0.39)	622 (0.39)	621 (0.39)	0.977

IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; AF, atrial fibrillation; VA, ventricular arrhythmias

Main figures

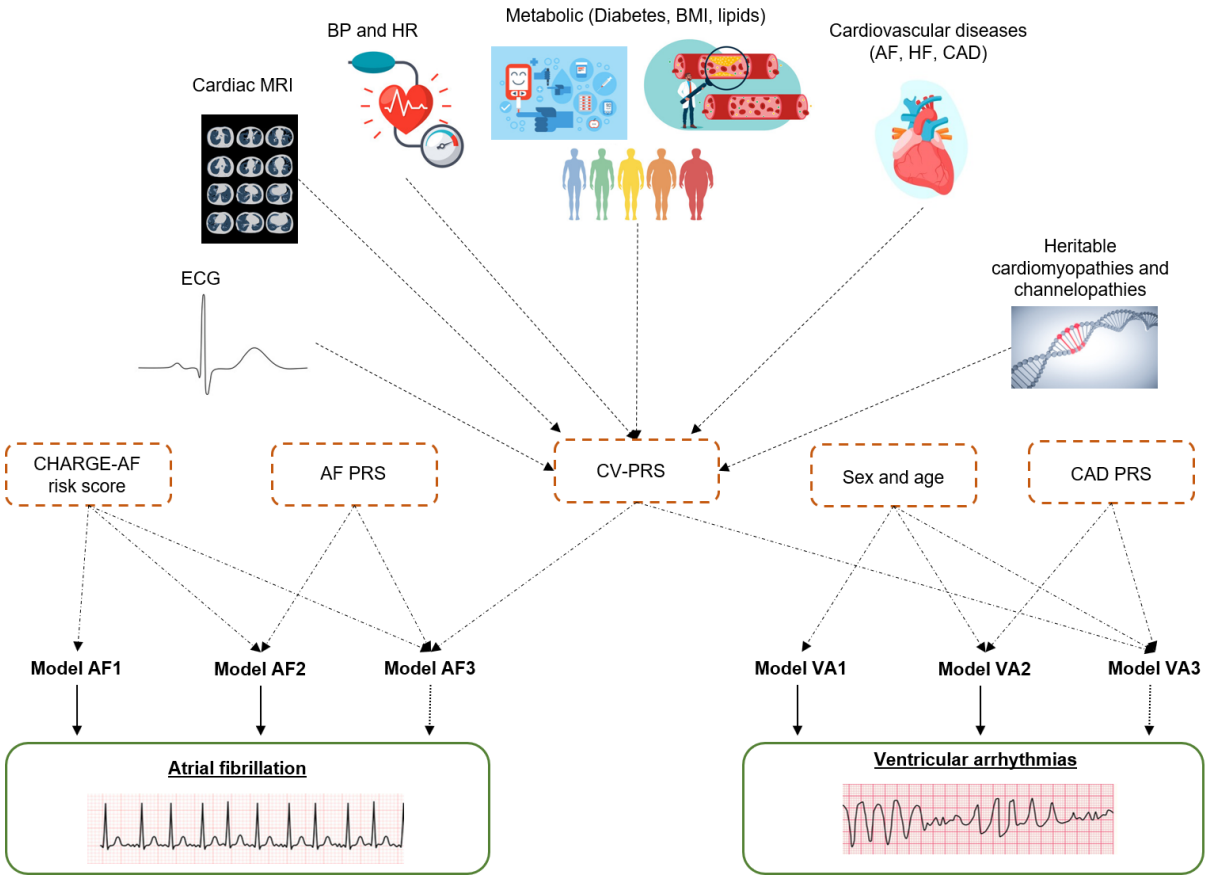


Figure 1: Overview of the models and PRS evaluated in this study to predict incident atrial fibrillation and ventricular arrhythmic risk.

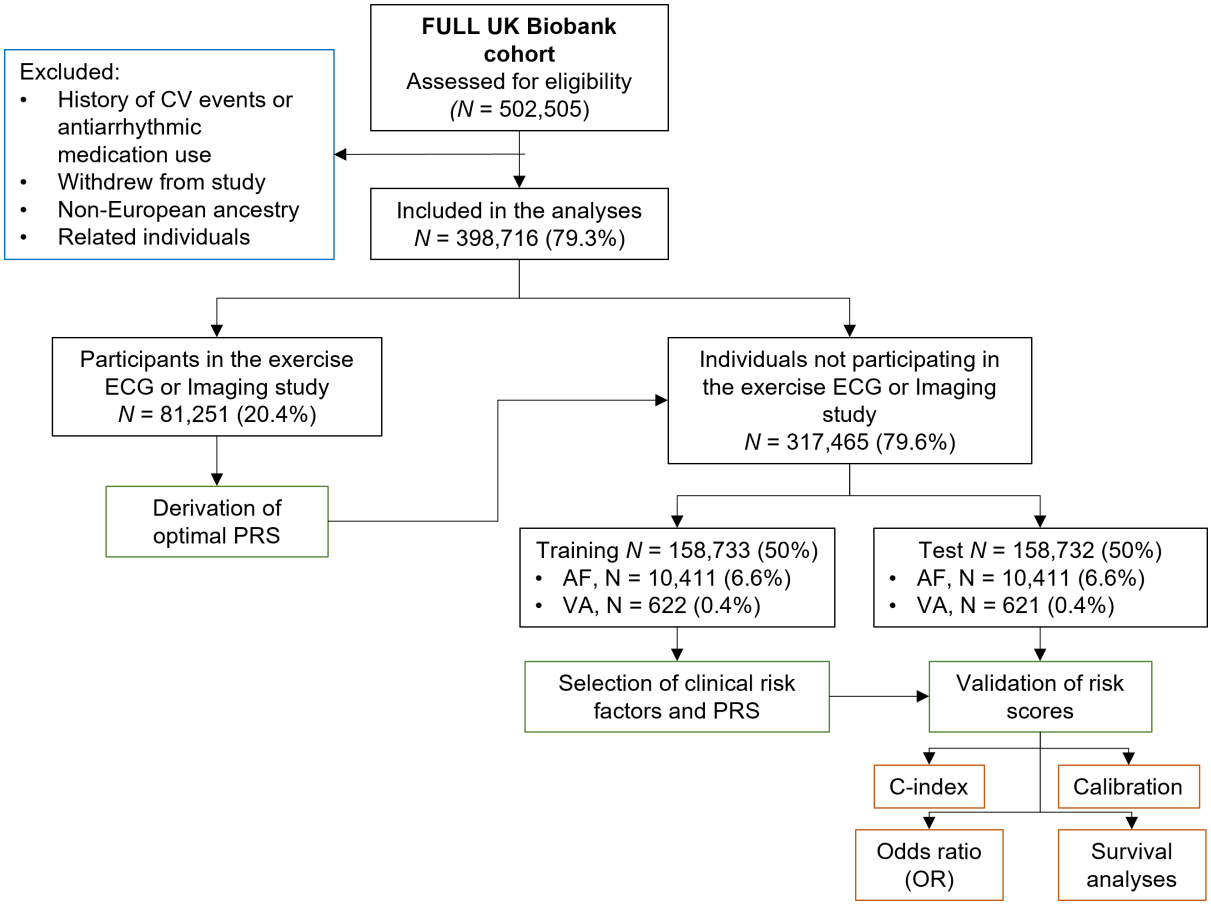
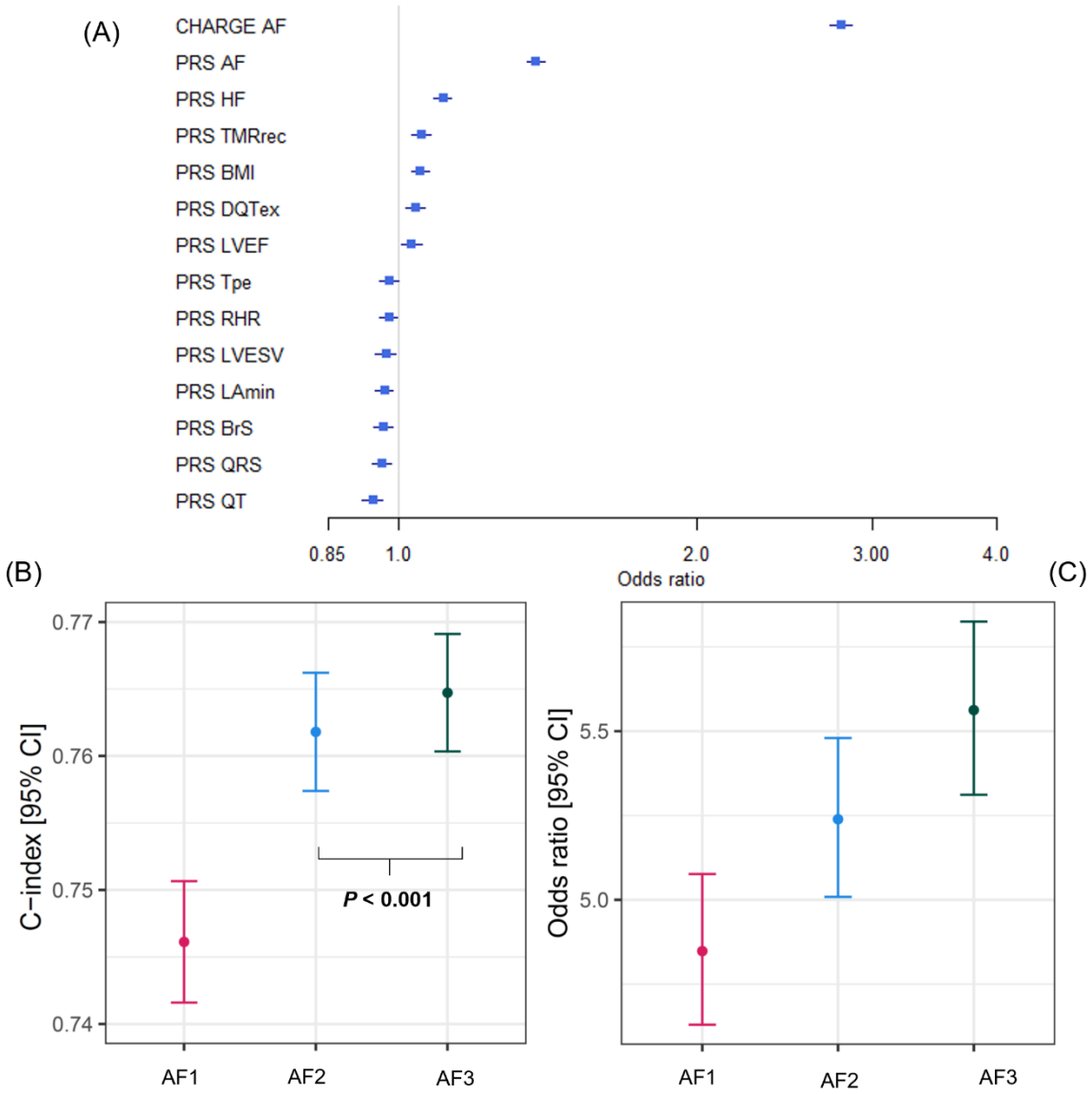


Figure 2. Flowchart indicating the number of individuals included in the study and the partition into training and test for incident atrial fibrillation (AF) and ventricular arrhythmias (VA) risk prediction.



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592 **Figure 3: Prediction of incident AF risk.** (A) Forest plot illustrating the odds ratio of
593 CHARGE-AF score, the AF PRS and each PRS for cardiovascular risk factors and ECG or
594 MRI risk markers that remained significant in the adjusted model. Concordance indices and
595 odds ratios obtained for CHARGE-AF score (magenta), CHARGE-AF and the AF PRS (cyan)
596 and CHARGE-AF, the AF PRS and the PRS depicted in panel (A) (green) for incident AF risk
597 prediction are shown in panels (B) and (C).

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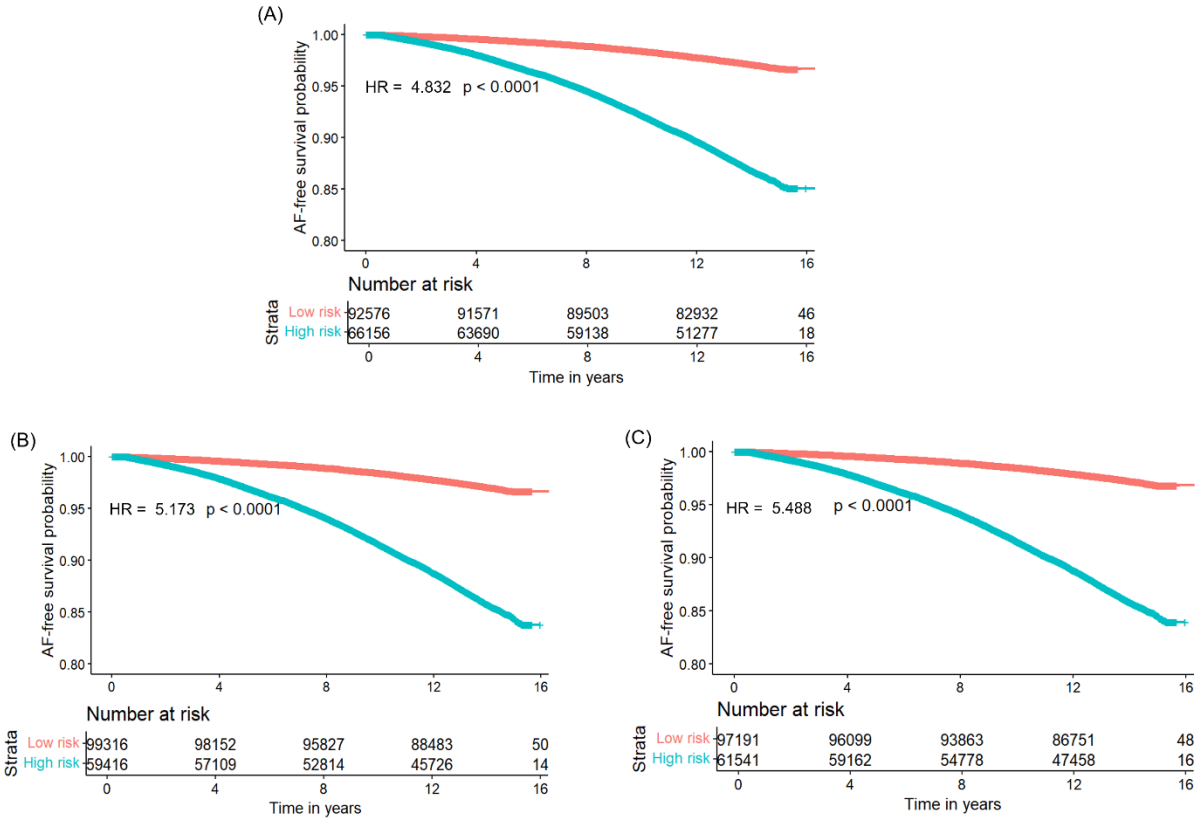

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601 **Figure 4:** Cumulative atrial fibrillation-free survival probability of individuals in the low- (red)

602 and high-risk (blue) groups for models AF1 (A), AF2 (B), AF3 (C).

603 HR, hazard ratio.

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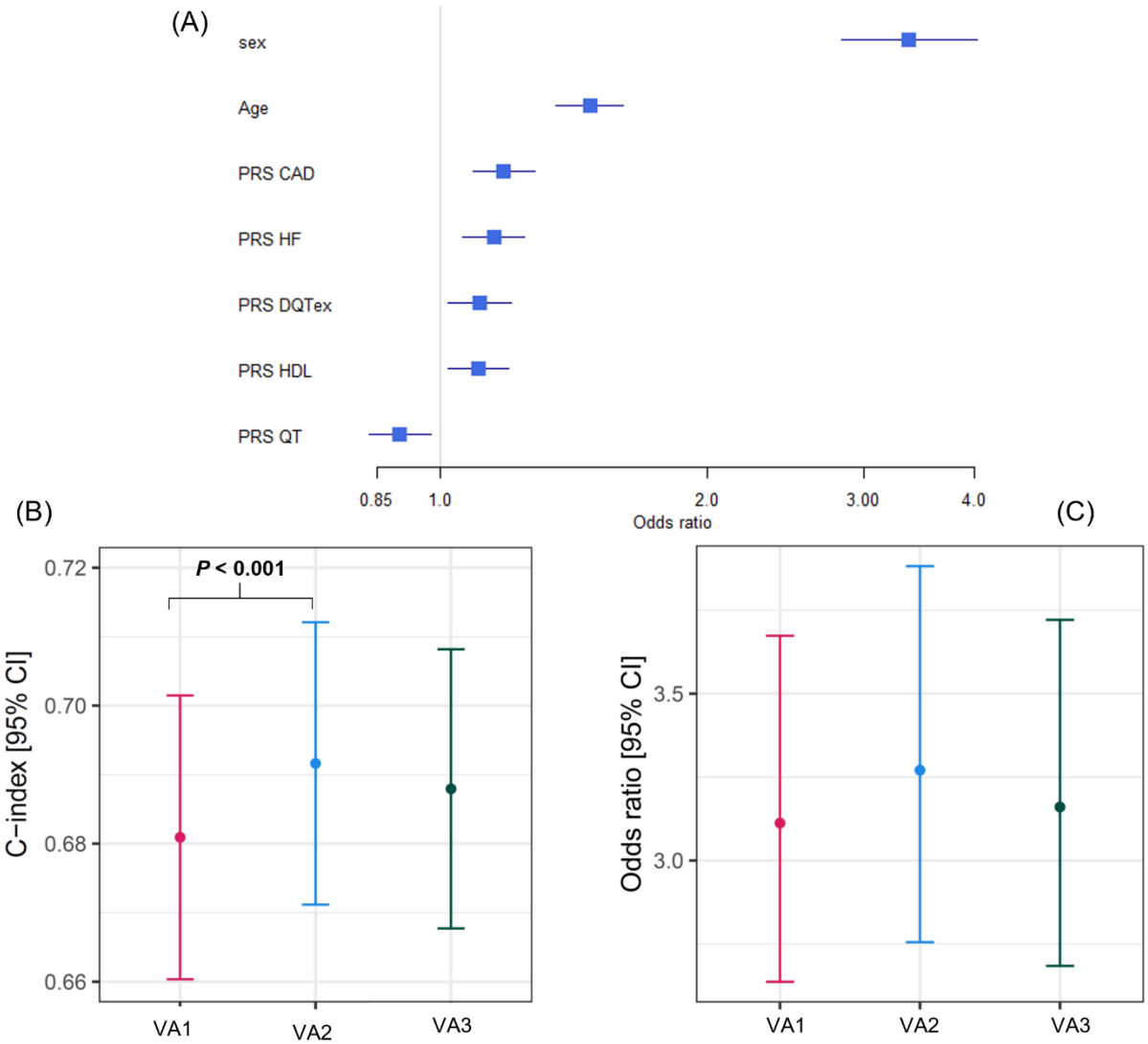

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607 **Figure 5: Prediction of incident VA risk.** (A) Forest plot illustrating the odds ratio of sex,
608 age, the CAD PRS and each PRS for cardiovascular risk factors and ECG or MRI risk markers
609 that remained significant in the adjusted model. Concordance indices and odds ratios obtained
610 for sex and age score (magenta), sex, age and the CAD PRS (cyan) and sex, age, the CAD
611 PRS and the PRS depicted in panel (A) (green) for incident VA risk prediction are shown in
612 panels (B) and (C).

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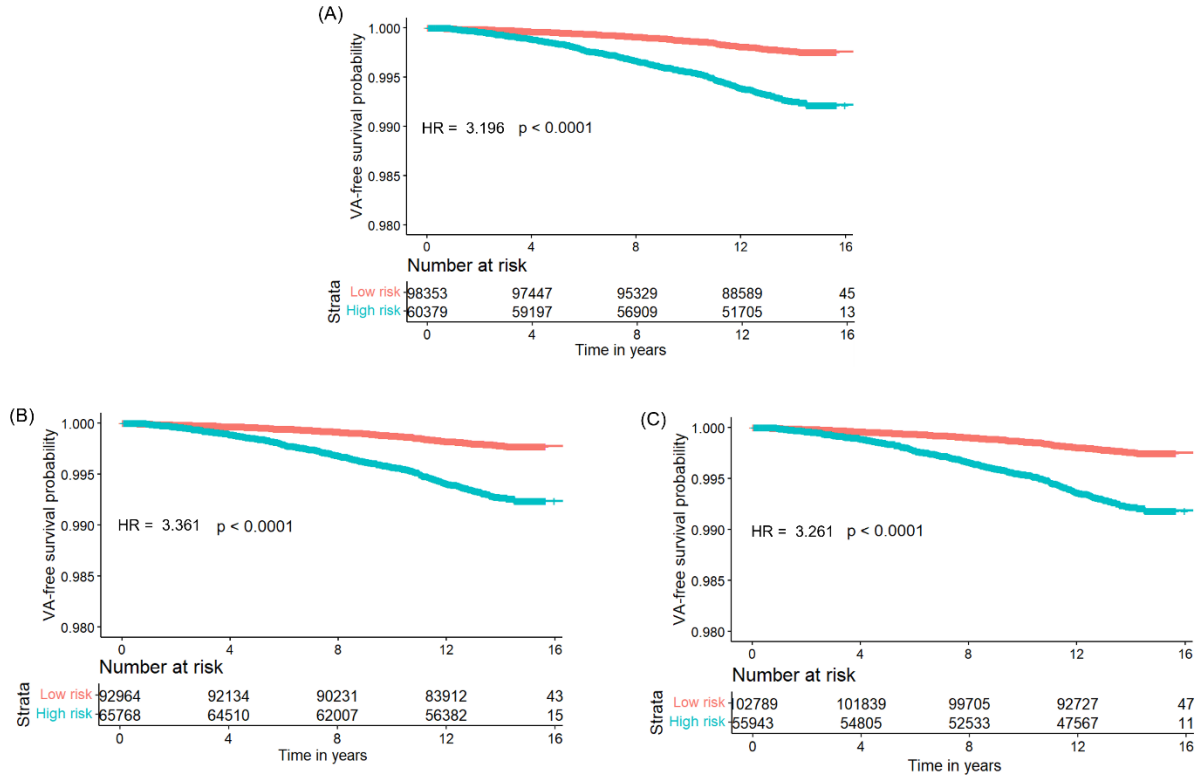

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617 **Figure 6:** Cumulative ventricular arrhythmia-free survival probability of individuals in the low-

618 (red) and high-risk (blue) groups for models VA1 (A), VA2 (B) and VA3 (C).

619 HR, hazard ratio.

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