Polygenic risk scores in atrial fibrillation: associations and clinical utility in disease prediction

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Short title: Polygenic risk scores in atrial fibrillation

Word count: 5,812 words

Disclosures: The authors have no conflicts of interest to disclose

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Abbreviations

AUC (Area under the receiver operating characteristic curve)

AF (Atrial fibrillation)

NT-proBNP (B Type Natriuretic peptide)

PRS (Polygenic risk scores)

GWAS (Genome-wide association studies)

SNP (Single-nucleotide polymorphisms)

Abstract

Atrial fibrillation (AF) is a common heart arrhythmia and a major cause of cardioembolic stroke. Therefore, accurate prediction is desirable to allow high-risk individuals to be identified early and their risk lowered before complications arise. Polygenic risk scores (PRS) have become a popular method of quantifying aggregated genetic risk from common variants, but their clinical value in atrial fibrillation remains uncertain. This literature review discusses the associations between PRS and AF risk, and the evidence for their clinical utility in AF prediction. Stroke risk in AF patients is also considered. Despite consistent associations between PRS and AF risk, the performance of PRS as a standalone tool for AF prediction was poor. However, addition of PRS to existing AF prediction models commonly increased predictive performance above that of the clinical models alone, including in cohorts with comorbid cardiovascular disease. Associations between PRS and cardioembolic stroke risk in AF patients have also been reported, but improvements to stroke prediction models from PRS have been minimal. PRS are likely to add value to existing clinical AF prediction models, however, standardisation of PRS across studies and populations will likely be required before they can be meaningfully adopted into routine clinical practice.

Keywords: Atrial fibrillation, stroke, risk factor, polygenic risk score, genetic risk score, CHARGE-AF

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is characterised by irregular beating of the atria.[1] The prevalence rises sharply with age and is approximately 2% for people in their 60s, almost 10% for people in their 70s, and 15-20% for people over 80.

Patients typically experience episodes of heart palpitations, shortness of breath, light-headedness, tiredness or chest pain, but many patients are asymptomatic.[2] While AF is not usually life threatening by itself, it does increase the risk of significant events such as heart failure or stroke.[3] Therefore, early and accurate identification of those at high-risk of AF is desirable in order that risk-lowering interventions can be introduced before its onset.

AF shares many risk factors with other cardiovascular diseases. These include older age, hypertension, diabetes, obesity, smoking and excessive alcohol use.[3] Family history and genetic predisposition have also been implicated. Additionally, other cardiovascular diseases (e.g. valvular heart disease) and diseases affecting other organ systems (e.g. chronic kidney disease) also increase risk.[4,5]

The CHARGE-AF model is one of the most widely used prediction tools for AF, and is used clinically to predict 5-year AF risk based on a range of clinical risk factors.[6] However, despite having relatively good discrimination for 5-year AF risk in the derivation cohort (C-index=0.765), in the validation cohorts the C-index ranged from 0.664 to 0.705, indicating modest discrimination overall. The model has also shown poor calibration in some external cohorts.[7] Additionally, its usefulness comes from its ability to predict relatively short-term AF risk in an older population, after other risk factors have already manifested. Thus, it does not

predict long-term risk in younger individuals currently without risk factors who may eventually go on to develop AF. The CHA_2DS_2-VASc score similarly uses clinical risk factors to predict stroke risk in patients who already have AF to inform anticoagulant use.[8]

In contrast with clinical risk factors which typically present later in life, genetic risk is established at conception and remains constant throughout life. Therefore, it may be possible to use genetic data to predict long-term risk of disease prior to the appearance of any clinical risk factors, when lifestyle changes may have greater impact. Polygenic risk scores (PRS) have become a popular method of quantifying aggregated genetic risk from common risk alleles identified from genome-wide association studies (GWAS).[9] Many PRS have been derived for AF, with studies demonstrating significant associations between PRS and AF risk. Despite this, the clinical utility of PRS in the prediction of AF remains undecided, and these scores are not yet used in routine clinical practice for AF management nor endorsed by any of the major cardiovascular society AF guidelines. This literature review summarises the associations between PRS and AF risk, and discusses the evidence for the clinical utility of PRS for AF prediction.

Early work and proof-of-concept

Three early studies examined associations between PRS and AF risk, and laid the foundation for future work **(Supplementary Table 1)**.[10–12] In each study, small PRS were constructed using 12 single-nucleotide polymorphisms (SNPs) previously associated with AF at the genome-wide significance level. These included one SNP at each of the *KCNN3*, *PRRX1*, *CAV1*, *C9orf3*, *SYNPO2L*, *SYNE2*, *HCN4* and *ZFHX3* loci, and 4 SNPs at the *PITX2* locus. At

most loci, choice of lead SNP was the same between each study, with slight differences at the remaining loci. Both weighted and unweighted PRS were examined.

Across the three studies, an increase in both the weighted and unweighted PRS was associated with an increase in AF risk. One study reported that this association remained even after adjusting for age, sex, AF risk factors and cardiovascular history, with a 2-fold risk gradient between those in the highest and lowest PRS quintiles.[12] This same study also reported that the PRS was also associated with risk of ischaemic stroke. Another study reported that those with the highest unweighted PRS (15-16 risk alleles) had up to five times the risk of AF compared to those with the lowest PRS (3-4 risk alleles).[11]

Two of these studies also examined the clinical utility of PRS for AF prediction. One study reported that addition of the weighted PRS to a clinical model including age, height, weight, systolic blood pressure, smoking and alcohol use resulted in better predictive ability compared to the clinical model alone (C-index=0.741 (95% CI, 0.709 – 0.774), C-index=0.718 (95% CI, 0.684 – 0.753), respectively).[10] Reclassification and discrimination were also significant using the combined model (continuous net reclassification improvement (NRI)=0.490 (95% CI, 0.301 – 0.670), integrated discrimination improvement (IDI)=0.0053 (95% CI, 0.0033 – 0.0076)). Another study reported similar results, and further demonstrated that addition of the PRS to the $CHADS_2$ score improved reclassification of AF patients at risk of stroke (continuous NRI=0.166 (95% CI, 0.018 – 0.315)).[12]

Associations with atrial fibrillation risk

Following on from these early studies, many subsequent studies have similarly demonstrated a significant association between higher PRS and increased risk of AF **(Supplementary Table 1)**. For example, Weng et al. investigated AF risk in a European cohort of 4,606 AF-free individuals over a median 9-year follow-up period. Using a weighted PRS comprising 1,168 SNPs, the authors reported that the PRS was significantly associated with AF risk, even after adjusting for CHARGE-AF score (hazard ratio (HR)=1.14 (95% CI, 1.11 – 1.16) per unit increase in PRS).[13] A subsequent study reported that this same PRS developed by Weng et al. was consistently associated with 5-year AF risk across four independent cohorts in univariate analyses.[14] Comparable observations have been reported using other small to medium-sized PRS in a range of different populations, and adjusting for a range of different covariates.[15–21]

In addition to the relatively small PRS discussed above, a few studies have also developed much larger PRS comprising millions of SNPs across the whole genome. One influential study by Khera et al. developed a genome-wide PRS comprising 6,730,541 SNPs, demonstrating that those with a score in the top 1% of the cohort had almost 5 times the risk of AF compared to the rest of the cohort (OR=4.63 (95% CI, 3.96 – 5.39), adjusted by age, sex, genotyping array and 4 principal components of ancestry).[22] Another study used this same PRS with similar basic covariates and reported a 46% increase in AF risk per standard deviation (SD) increase in PRS.[23] Other studies have developed similar genome-wide scores, with comparable results.[24–26]

Associations with age at onset of atrial fibrillation

A number of studies have demonstrated an association between higher PRS and younger age at onset of AF **(Supplementary Table 2)**. One early Japanese study used an unweighted PRS of 6 SNPs and reported that those with 9-12 risk alleles were on average 5 years younger at onset of AF than those with 1-4 risk alleles.[27] A more recent Japanese study obtained similar results, showing that those in the top 1% of a larger PRS were on average 4 years younger at onset than the remainder of the cohort.[28] Similar observations have been reported in European cohorts.[29,30] A study of patients undergoing catheter ablation of AF found that those with a PRS in the top quintile were younger at time of ablation than those in the bottom quintile.[31]

Clinical utility for disease prediction

Despite many studies demonstrating a strong association between PRS and AF risk, the clinical utility of PRS as a standalone tool for AF prediction has had mixed results **(Supplementary Table 1)**. In particular, PRS derived from smaller numbers of SNPs tend to have a weaker performance. Using a weighted PRS comprising 6 SNPs, one Japanese study found that the predictive ability of the PRS alone was modest (area under the receiver operating characteristic curve (AUC)=0.641 (95% CI, 0.628 – 0.653).[27] This was despite a 4-fold risk gradient between those in the top and bottom PRS quartiles. Another study of participants from the UK Biobank reported similar findings using a PRS calculated using 181 SNPs.[32]

PRS derived from larger numbers of SNPs have also have varying levels of success as standalone prediction tools. For example, one study showed that the genome-wide PRS developed by Khera et al. had good predictive ability for lone AF, and outperformed the

smaller PRS developed by Weng et al. (C-index=0.76 (95% CI, 0.72 – 0.80), C-index=0.70 (95% CI, 0.65 – 0.75), respectively).[33] However, another study applied this same genome-wide PRS to a large cohort of over 11,500 participants and reported poor predictive performance for the PRS alone (AUC=0.57).[34]

Despite these mixed results, some studies have shown that including additional covariates alongside the PRS can improve the predictive performance of the model.[35] In the same study of 11,500 participants discussed above, even the simple addition of age and sex to the PRS model resulted in significantly better predictive ability compared to PRS alone (AUC=0.78, AUC=0.57, respectively).[34] Other studies have reported even greater predictive performances incorporating additional AF risk factors such as body mass index and hypertension.[36]

Several studies have examined the value of incorporating PRS into existing clinical prediction models. One study reported that addition of a PRS to a clinical model including age, sex, smoking status, body mass index, diabetes, hypertension and history of myocardial infarction or heart failure had better predictive ability for AF than the clinical model alone (C-index=0.719, C-index=0.687, respectively).[37] Other studies have demonstrated similar improvements using additional risk models.[15,38] Importantly, addition of PRS has been demonstrated to improve the predictive performance of the widely-used CHARGE-AF risk prediction model, with improvements seen across a range of different cohorts.[14,30,39,40] These findings all suggest that PRS may be a clinically useful addition to existing AF prediction models.

High-risk groups

In addition to studies examining PRS and AF risk in the general population, several studies have also examined cohorts of individuals already at high risk of AF **(Supplementary Table 3)**. This includes individuals with chronic kidney disease, heart failure and other cardiovascular diseases, as well as those who have undergone heart surgery. Establishing whether genetics contributes to AF risk in these high-risk groups would allow better patient stratification and management.

Chronic kidney disease

Only one study has examined PRS and AF risk in patients undergoing haemodialysis for end-stage kidney disease. The authors reported that the average PRS was significantly higher in those who developed AF compared to those who did not.[41] Furthermore, PRS was independently associated with AF risk, even after adjusting for cardiovascular history and risk factors (OR=1.24 (95% CI, 1.07 – 1.43) per 0.1 unit increase in PRS). In a post-hoc analysis, this model correctly classified 75% of patients with AF.

Heart failure

Using a multivariate analysis incorporating the CHARGE-AF model, one study found that a higher PRS in patients with heart failure was associated with increased risk of AF (OR=2.12 (95% CI, 1.84 – 2.45) per 1 unit increase in PRS).[42] Addition of the PRS to the CHARGE-AF model resulted in a higher predictive ability for AF (AUC=0.721 (95% CI, 0.704 – 0.737)) compared to the CHARGE-AF model alone (AUC=0.699 (95% CI, 0.682 – 0.716)). Interestingly, one other recent study used an unsupervised machine learning approach to identify a potential subtype of heart failure characterised by subsequent development of AF.[43] This

subtype was associated with an established PRS for atrial arrhythmias, suggesting that AF risk in patients with heart failure has a genetic basis.

Cardiac surgery

Post-operative AF is a common adverse outcome following coronary revascularisation procedures such as coronary artery bypass graft surgery. Using a cohort of post-cardiac surgery patients, one study found that a PRS was significantly associated with risk of post-operative AF, adjusting for age, sex and known predictors of AF (OR=1.92 (95% CI, 1.63 – 2.29) per SD increase in PRS).[44] Furthermore, addition of the PRS to standard clinical predictors significantly improved the predictive ability of the model (C-index=0.782 (95% CI, 0.742 – 0.804), C-index=0.742 (95% CI, 0.700 – 0.764), respectively). Addition of PRS also improved reclassification of intermediate-risk individuals into low and high-risk. Similar findings were reported by a larger Finnish study.[45]

Cardiovascular disease

In addition to heart failure and coronary revascularisation, one study examined AF risk across cardiovascular disease in general using the PRS developed by Khera et al. This PRS was associated with AF risk after adjusting for clinical AF risk factors (HR=1.40 (95% CI, 1.32 – 1.49) per 1 SD increase in PRS), even when stratifying by CHARGE-AF score.[46] Interestingly, a high PRS was a stronger predictor of AF than most other clinical risk factors except age. Addition of the PRS to a model incorporating the CHARGE-AF score and a clinical biomarker (NT-proBNP) improved the predictive performance and showed good reclassification.

Atrial fibrillation recurrence following treatment

Given the high rate of AF recurrence following cardioversion or ablation therapy, some studies have examined whether recurrence is influenced by genetic factors **(Supplementary Table 4)**. One South Korean study followed up patients for approximately 2 years following radiofrequency catheter ablation and reported that a higher PRS was associated with a higher risk of recurrence (HR=1.13 (95% CI, 1.03 – 1.24) per risk allele, adjusted for clinical risk factors).[47] Smaller studies have reported similar findings following both catheter ablation and direct current cardioversion.[48,49] In contrast, a larger European study failed to find any association between the PRS developed by Weng et al. and time to AF recurrence following ablation.[31]

Only one study has examined treatment timing and AF recurrence. Using the PRS developed by Khera et al. and adjusting for treatment group, the authors reported that a higher PRS was associated with increased risk of AF recurrence over a mean 5-year follow-up (HR=1.08 (95% CI, 1.0 – 1.16)).[50] Compared to the typical standard of care, early rhythm control significantly reduced risk of AF recurrence, however no interaction was found between PRS and treatment strategy. This suggests that early rhythm control may be effective across all levels of genetic risk.

Stroke risk in atrial fibrillation patients

Stroke is one of the most significant complications of AF. However, this risk can be lowered through use of anticoagulants such as warfarin.[51] Therefore, accurate identification of AF patients at high risk of stroke is essential for appropriate patient management and treatment selection. Several studies have examined the potential of PRS for stroke prediction in AF patients with mixed results **(Supplementary Table 5)**. Some studies have

used PRS derived from SNPs associated with AF (PRS-AF), while others have used PRS derived from SNPs associated with stroke itself (PRS-stroke). Both are considered here.

Several studies have reported an association between PRS-AF and ischaemic stroke. This appears to be driven by cardioembolic stroke, which is the major subtype implicated in AF.[52] One study reported that a higher PRS-AF was associated with an increased risk of cardioembolic stroke after adjusting for age, sex, genotyping platform and principal components of ancestry (OR=1.45 (95% CI, 1.16 – 1.83) per SD increase in PRS).[39] Another study reported similar results, even after adjusting for known AF risk factors.[53] Interestingly, associations with PRS-AF were not observed for other ischaemic stroke subtypes such as atherothrombotic stroke or lacunar infarction, or for stroke overall, suggesting that PRS-AF is highly specific to cardioembolic stroke risk.[14,28]

In addition to PRS-AF, some studies have examined PRS-stroke for stroke prediction in AF patients. In a multivariate analysis including the CHA_2DS_2-VASc model, one study demonstrated that AF patients with a PRS-stroke in the highest tertile had a significantly higher stroke risk than those in the lowest tertile (OR=1.29 (95% CI, 1.01 – 1.64)).[54] Interestingly, the predictive performance of the PRS was greatest in those with a lower CHA_2DS_2-VASc score, suggesting that PRS may provide better risk stratification in AF patients without high clinical risk of stroke. Despite this, another study reported that addition of a PRS to the CHA_2DS_2-VASc model had minimal impact on the predictive ability compared to the clinical model alone (C-index=0.61, C-index=0.60, respectively).[55]

Only one study has used a multi-trait analysis to combine summary statistics for both AF and cardioembolic stroke GWAS. While the predictive ability of the resulting PRS alone was poorer than a basic clinical model including age, sex and hypertension (AUC=0.581, AUC=0.947, respectively), addition of the PRS to the clinical model significantly improved discrimination (AUC=0.950) and reclassification.[56]

Discussion

Many recent studies have examined the potential for PRS to be used in AF prediction, and evidence for its clinical value is growing. Following early success in the field, associations between PRS and AF risk have been repeatedly found, with some studies reporting over a 3-fold risk gradient between those with scores in the top and bottom quintiles of the population. Importantly, these associations have persisted across a range of different cohort sizes, ancestral groups and methods for PRS derivation, albeit with different effect sizes. A few studies have also reported younger ages at AF onset in those with higher PRS.

Despite this strong foundation, the clinical utility of PRS as a standalone tool for AF prediction has not been consistently demonstrated. This is perhaps understandable, given one study found that PRS only explained 4.7% of the variance in AF risk in the general population.[57] More promising results have been reported using PRS alongside age, sex and other traditional AF risk factors, with many studies demonstrating improved predictive performance over clinical factors alone. Therefore, the clinical value of PRS will most likely come from their inclusion in established clinical risk models such as CHARGE-AF, which at present does not incorporate a genetic risk component. This may also improve AF prediction in those already at high risk, particularly those with heart failure or following heart surgery.

Interestingly, the predictive ability of PRS for lone AF (typically younger AF patients without known risk factors) was quite good.[33] Furthermore, another study observed that reclassification following addition of PRS to the CHARGE-AF model was greatest in those under 65 years.[14] Even with the PRS for stroke, predictive performance in AF patients was greater in those with a low CHA_2DS_2-VASc score.[54] Taken together, these suggest that PRS may be more useful in younger individuals, prior to the appearance of other clinical risk factors. Therefore, one potential application of PRS is in healthy individuals with a known family history who may wish to better understand their own future AF risk (PRS has been shown to capture AF risk information independent of that provided by family history).[26] It may also be informative to clinically-low risk individuals with only one or two other AF risk factors as an additional incentive to make healthier lifestyle changes before further comorbidities develop. Such testing of premorbid populations may become increasingly feasible as sequencing time and costs continue to drop, and as more people are likely to have already had their genomes sequenced at some point in their lives.

Despite many studies supporting the use of PRS for the prediction of AF, further work is still required prior to the adoption of PRS into routine care. While inclusion of PRS in clinical models may enhance predictive performance, studies examining the extent to which patient outcomes are improved are still necessary to determine whether this is worthwhile. This could include randomised controlled trials assigning people to either PRS-based screening or standard care to establish whether knowledge of one's PRS leads to earlier AF diagnosis, better adherence to preventative treatments, or reduced AF complications. These could also examine whether PRS-guided care (such as earlier/more aggressive rhythm control

treatment or closer monitoring for those with a high PRS) improves patient outcomes compared to standard care. Furthermore, no consistent definition of 'high' and 'low' PRS exists, leading to inconsistent risk stratification of individuals. Therefore, studies evaluating different PRS risk thresholds are needed to optimise identification of individuals most likely to benefit from early intervention. Finally, many different PRS for AF have been developed using different methods and comprising different SNPs and SNP weightings. However, no consensus exists as to which specific PRS will be the most suitable for clinical use. Thus, benchmarking studies to identify the best-performing PRS in each ancestral group may be desirable to allow for more robust comparisons of risk between individuals.

One major ethical issue in the clinical implementation of PRS in general is that the majority of GWAS are carried out using primarily European cohorts.[58] However, allele frequencies can differ drastically between different ancestral groups, potentially leading to differences in linkage disequilibrium and tagging of causal variants. This means that PRS derived from European GWAS will have the greatest clinical benefit in European individuals, with those of non-European ancestry receiving a poorer service due to less accurate risk predictions. This will inevitably lead to poorer patient management in those populations, further widening health inequalities. This is an important point to consider here, as the large majority of AF PRS have been both derived and tested using only European cohorts **(Supplementary Table 1)**. Such scores have limited transferability to other populations, with one study demonstrating very poor predictive performance when applied to African, East Asian and South Asian cohorts (all AUCs < 0.6).[59] Two other studies also reported that PRS derived from European GWAS had poorer performance in their Japanese/Korean cohorts compared to PRS derived from Japanese GWAS.[28,60] Interestingly, in both studies the highest performance

was obtained from PRS derived from cross-ancestral data, highlighting the need for more genetically-diverse training datasets to overcome some of these biases.

Conclusion

Associations between PRS and AF risk are strong, but as a standalone tool PRS will probably have little clinical value. The utility of PRS will likely come from their addition to existing clinical prediction tools, with several studies reporting modest but significant improvements in both predictive ability and reclassification. This has the potential to provide better AF risk stratification in the general population, in particular high-risk groups, as well as in younger individuals without current AF risk factors or comorbidities. Identification of AF patients at high risk of stroke may also be improved using PRS to better inform treatment selection.

Author Contributions

JTG: Study design, literature search, review and critical analysis of manuscripts, writing – original draft. **JHFR:** Study design, supervision, writing – review & editing. JTG undertook this work while a student at the University of Cambridge.

Funding

JHFR is part-supported by the NIHR Cambridge Biomedical Research Centre, the British Heart Foundation, HEFCE, the EPSRC and the Wellcome Trust.

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