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ECG-Based Deep Learning and Clinical Risk Factors to Predict Atrial Fibrillation

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BACKGROUND: Artificial intelligence (AI)–enabled analysis of 12-lead ECGs may facilitate efficient estimation of incident atrial fibrillation (AF) risk. However, it remains unclear whether AI provides meaningful and generalizable improvement in predictive accuracy beyond clinical risk factors for AF.

METHODS: We trained a convolutional neural network (ECG-AI) to infer 5-year incident AF risk using 12-lead ECGs in patients receiving longitudinal primary care at Massachusetts General Hospital (MGH). We then fit 3 Cox proportional hazards models, composed of ECG-AI 5-year AF probability, CHARGE-AF clinical risk score (Cohorts for Heart and Aging in Genomic Epidemiology–Atrial Fibrillation), and terms for both ECG-AI and CHARGE-AF (CH-AI), respectively. We assessed model performance by calculating discrimination (area under the receiver operating characteristic curve) and calibration in an internal test set and 2 external test sets (Brigham and Women's Hospital [BWH] and UK Biobank). Models were recalibrated to estimate 2-year AF risk in the UK Biobank given limited available follow-up. We used saliency mapping to identify ECG features most influential on ECG-AI risk predictions and assessed correlation between ECG-AI and CHARGE-AF linear predictors.

RESULTS: The training set comprised 45 770 individuals (age 55±17 years, 53% women, 2171 AF events) and the test sets comprised 83 162 individuals (age 59±13 years, 56% women, 2424 AF events). Area under the receiver operating characteristic curve was comparable using CHARGE-AF (MGH, 0.802 [95% CI, 0.767–0.836]; BWH, 0.752 [95% CI, 0.741–0.763]; UK Biobank, 0.732 [95% CI, 0.704–0.759]) and ECG-AI (MGH, 0.823 [95% CI, 0.790–0.856]; BWH, 0.747 [95% CI, 0.736–0.759]; UK Biobank, 0.705 [95% CI, 0.673–0.737]). Area under the receiver operating characteristic curve was highest using CH-AI (MGH, 0.838 [95% CI, 0.807 to 0.869]; BWH, 0.777 [95% CI, 0.766 to 0.788]; UK Biobank, 0.746 [95% CI, 0.716 to 0.776]). Calibration error was low using ECG-AI (MGH, 0.0212; BWH, 0.0129; UK Biobank, 0.0035) and CH-AI (MGH, 0.012; BWH, 0.0108; UK Biobank, 0.0001). In saliency analyses, the ECG P-wave had the greatest influence on AI model predictions. ECG-AI and CHARGE-AF linear predictors were correlated (Pearson *r*: MGH, 0.61; BWH, 0.66; UK Biobank, 0.41).

CONCLUSIONS: AI-based analysis of 12-lead ECGs has similar predictive usefulness to a clinical risk factor model for incident AF and the approaches are complementary. ECG-AI may enable efficient quantification of future AF risk.

Key Words: atrial fibrillation ■ deep learning ■ electronic health records

Atrial fibrillation (AF) is a common and morbid arrhythmia.[1–4] Identification of individuals at elevated AF risk is a clinical imperative because modifying lifestyle and behavioral factors may prevent AF[5,6] and cardiac rhythm monitoring may identify individuals with undiagnosed AF, thereby enabling prevention of strokes.[7–9]

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Clinical Perspective

What Is New?

- Artificial intelligence–based analysis of 12-lead ECGs has similar predictive usefulness as an established clinical risk factor model for incident atrial fibrillation (AF), and both are complementary.
- An ECG–artificial intelligence model for AF had predictive usefulness across independent study samples, discriminated risk in patients with heart failure and stroke, and was applicable to single-lead ECG tracings.

What Are the Clinical Implications?

- Artificial intelligence–based AF risk prediction models using 12-lead ECGs may enable efficient quantification of future AF risk.
- Prediction of AF can be performed using clinical risk factors or artificial intelligence–based analysis of ECGs, but the combination of both provides greatest predictive accuracy.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AI	artificial intelligence
AP	average precision
AUROC	area under the receiver operating characteristic curve
BWH	Brigham and Women's Hospital
CH-AI	CHARGE-AF (Cohorts for Aging Research and Genomic Epidemiology–Atrial Fibrillation) and ECG-AI
CHARGE-AF	Cohorts for Aging Research and Genomic Epidemiology–Atrial Fibrillation
EHR	electronic health record
HR	hazard ratio
ICI	integrated calibration index
MGB	Mass General Brigham
MGH	Massachusetts General Hospital
NRI	net reclassification improvement

Recent work highlights the potential for artificial intelligence (AI) to predict AF from a 12-lead ECG.[10–12] Yet several important knowledge gaps exist. First, existing models have not explicitly incorporated event-free survival or censoring, which is important for accurately estimating absolute risk.[11,12] Second, it is not clear whether AI complements, or extends, well-validated clinical risk factor models for AF that do not require ascertainment of an ECG for risk prediction, such as the CHARGE-AF score (Cohorts for Heart and Aging Research in Genomic Epidemiology–Atrial Fibrillation).[13–17] Third, it is unclear what ECG features influence AF risk estimates from ECG-based AI models, which is critical for assessing potential bias and promoting clinician confidence. Fourth, previous models are proprietary and have not been subjected to rigorous external validation.[11,12]

In the current study, we trained a convolutional neural network to explicitly predict time to incident AF (ECG-AI) within a sample of >40 000 individuals receiving longitudinal primary care at Massachusetts General Hospital (MGH). We validated this model in >80 000 individuals from 3 independent test sets including additional individuals from MGH, individuals receiving longitudinal primary care at a separate healthcare institution (the Brigham and Women's Hospital [BWH]), and participants from a prospective cohort study (UK Biobank). We then compared the predictive accuracy of ECG-AI with CHARGE-AF and examined the performance of a model including both ECG-AI and CHARGE-AF (CH-AI). We also examined what regions of the ECG most influenced ECG-AI model performance for predicting AF.

METHODS

Data Availability

UK Biobank data are publicly available by application (www.ukbiobank.ac.uk). MGH and BWH data contain protected health information and cannot be shared publicly. Data processing scripts used to perform the analyses described herein are available at https://github.com/shaankhurshid/ecg_ai.

Study Population

We trained and validated ECG-AI in the Community Care Cohort Project (C3PO), a dataset comprising patients aged 18 to 90 years who received longitudinal primary care within the Mass General Brigham (MGB) network between 2000 and 2019.[18] Individuals were included if they received ≥2 primary care visits that occurred between 1 and 3 years apart at any of 7 hospitals within the MGB network, all of which were linked to a common electronic health record (EHR) database.[19] Follow-up started after the inclusion window and comprised data ascertained from the EHR through August 31, 2019. ECG-AI was trained among individuals with ≥1 ECG performed at MGH within 3 years before start of follow-up (see below). ECG-AI was then evaluated in independent test sets comprising 4166 individuals from MGH (internal test set) and a separate set of 37 963 individuals with ≥1 ECG performed at BWH within the 3-year baseline period (Figure 1). There was no overlap between training and test sets.

We performed additional external validation in the UK Biobank, a prospective cohort of 502 629 participants recruited between 2006 and 2010.[20] Approximately 9.2 million individuals 40 to 69 years of age living within 25 miles of the 22 assessment centers in England, Wales, and Scotland were invited and 5.4% participated in the baseline assessment. Questionnaires, physical measures, and biological samples were collected at recruitment, with diagnostic tests in a large subset. Participants are followed for health outcomes using national datasets

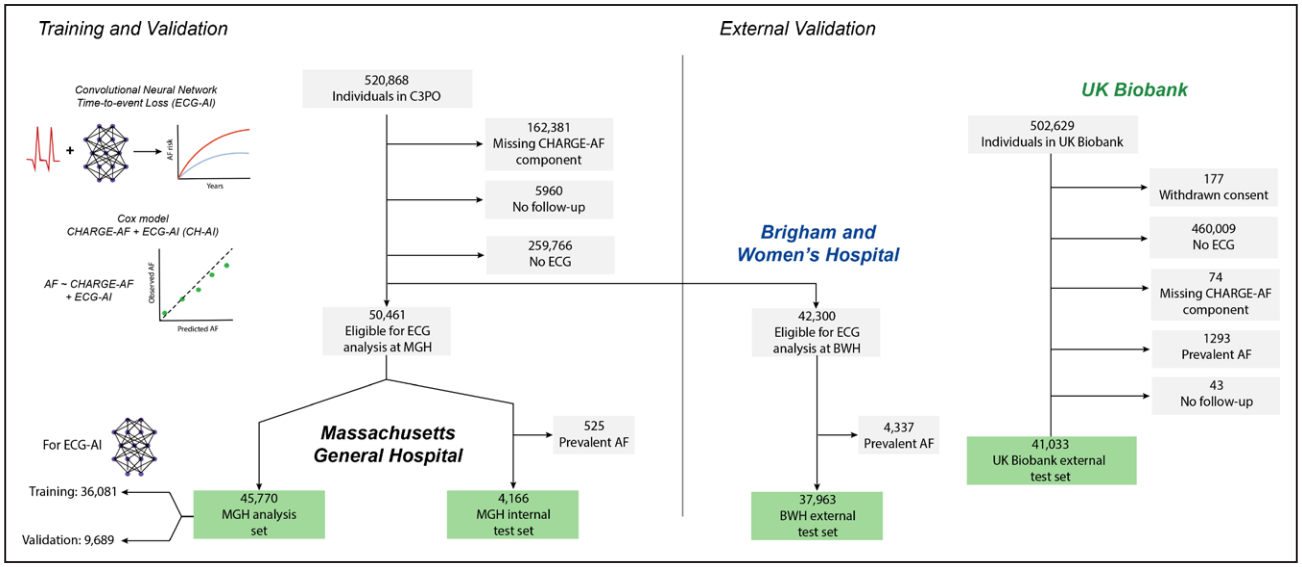

Figure 1. Study overview.

We trained a deep learning model to predict incident atrial fibrillation (AF; ECG–artificial intelligence [AI]) in Massachusetts General Hospital (MGH). We then developed a model combining ECG-AI and the CHARGE-AF (Cohorts for Aging Research and Genomic Epidemiology–Atrial Fibrillation) clinical risk score (CH-AI) in the same training population. We then validated ECG-AI and CH-AI in 3 test sets: MGH, individuals from a separate hospital (Brigham and Women's Hospital [BWH]), and the UK Biobank prospective cohort study. C3PO indicates Community Care Cohort Project.

(updated through March 31, 2021). We analyzed all individuals who underwent a standardized study-based 12-lead ECG. An overview of the analysis samples is shown in Figure 1.

The UK Biobank was approved by the UK Biobank Research Ethics Committee (reference 11/NW/0382). All UK Biobank participants provided written informed consent. Use of MGB and UK Biobank (application 7089) data were approved by the MGB institutional review board.

ECG Acquisition and ECG-AI Training

ECG-AI is a convolutional neural network trained to predict 5-year AF-free survival. The input to ECG-AI is a single 12-lead ECG containing a time series of 5000 voltage measurements for each of 12 leads sampled at 500 Hz and lasting 10 seconds. A minority of ECGs having lower sampling rates were linearly resampled up to 500 Hz and ECGs having shorter durations were 0-padded to contain 5000 measurements, resulting in a uniform input tensor of dimension 5000 x 12. The raw waveform data as well as tabular metadata including date, time, machine type, sampling frequency, and automated and physician reads were extracted from the MUSE Cardiology Information System (GE Healthcare), which stores data for all ECGs performed within MGB. All ECGs analyzed within MGH and BWH were performed for clinical purposes; ECGs in the UK Biobank sample were performed prospectively as part of the study protocol. No ECGs were excluded from the training or test sets on the basis of particular findings.

Rather than binary classification,[10,11] ECG-AI used an encoding and loss function[21] accounting for both time to outcome (ie, AF) and missingness introduced by censoring (defined as the earliest of death or loss to follow-up). To achieve this, the ECG-AI encoding divided time into discrete bins in which either an AF event or a censoring event could occur, and the loss function optimized the negative log likelihood of predicted AF occurring within each time bin. In this way, censored individuals do not contribute to the loss at time bins occurring after censoring (further details are supplied in the Supplemental Methods). For training, ECG-AI was exposed to all 12-lead ECGs performed within 3 years before start of follow-up. For evaluation, ECG-AI was tested using only the most recent ECG before start of follow-up in MGH/BWH, and the single study visit ECG in the UK Biobank. Because sinus rhythm ECGs among individuals with a diagnosis of AF may contain useful training signals (ie, they provide an example of AF-related changes in sinus rhythm),[10] we included individuals with a history of AF in model training. However, we evaluated ECG-AI only among individuals without a history of AF. In addition to incident AF prediction, we trained ECG-AI to perform three related tasks (estimation of age, classification of sex, and identification of AF in the tracing) because we observed that the multitask approach improved AF prediction performance compared with other model-building approaches we considered during model derivation (Table S1). Further details of ECG-AI training are described in the Supplemental Methods. ECG-AI architecture is summarized in Figure S1. Learning curves are shown in Figure S2. Performance of ECG-AI for secondary tasks is shown in Figure S3. ECG-AI performance varied modestly when training was performed using alternative training and validation splits (Table S2).

Clinical Factors

We calculated CHARGE-AF, a validated AF prediction tool, for all individuals.[13,14,17] Baseline age, sex, race, height, weight, and blood pressure values were obtained from the EHR.[18] Antihypertensive use was determined using medication lists.[14] Tobacco use was categorized as present or absent. Race was classified as White or non-White, as determined previously using CHARGE-AF.[14,22] The presence of heart failure, diabetes, and myocardial infarction were ascertained using previously

Table 1. Sample Characteristics

	MGH training set (n=45 770)*	MGH test set (n=4166)	BWH test set (n=37 963)	UK Biobank test set (n=41 033)
Age, y	54.9±16.6	53.5±16.2	53.8±15.3	64.5±7.7
Female	24 047 (52.5)	2300 (55.2)	23 211 (61.1)	21 426 (52.2)
Race/ethnicity				
White	35 629 (77.8)	3209 (77.0)	25 150 (66.2)	39 607 (96.5)
Black	2959 (6.5)	273 (6.6)	5283 (13.9)	300 (0.7)
Hispanic or Latino	1897 (4.1)	197 (4.7)	3240 (8.5)	–
Asian or Pacific Islander	2155 (4.7)	228 (5.5)	1082 (2.9)	587 (1.4)
Mixed	1 (0.002)	0 (0)	5 (0.01)	203 (0.5)
Other	1953 (4.3)	177 (4.2)	1673 (4.4)	226 (0.6)
Unknown	1176 (2.6)	82 (2.0)	1530 (4.0)	110 (0.3)
Current smoker	3616 (7.9)	337 (8.1)	3463 (9.1)	1495 (3.6)
Systolic blood pressure, mm Hg	126±17	126±18	126±18	138±19
Diastolic blood pressure, mm Hg	76±10	76±11	76±11	79±10
Antihypertensive medication use	25 187 (55.0)	2088 (50.1)	21 148 (55.7)	4374 (10.7)
Diabetes	8715 (19.0)	715 (17.2)	6656 (17.5)	1597 (3.9)
Heart failure	3255 (7.1)	170 (4.1)	1388 (3.7)	191 (0.5)
Myocardial infarction	3574 (7.8)	245 (5.9)	2643 (7.0)	933 (2.3)

Values are mean±SD or n (%). BWH indicates Brigham and Women's Hospital; and MGH, Massachusetts General Hospital.

*Includes 5183 individuals with prevalent atrial fibrillation who were used to train ECG artificial intelligence (ECG-AI) but not to fit CHARGE-AF (Cohorts for Aging Research and Genomic Epidemiology–Atrial Fibrillation) and ECG-AI (CH-AI) and 9689 individuals in an internal validation set for ECG-AI who were used to fit CH-AI.

published sets of diagnostic codes and medications (eg, antiglygemics), having a reported positive predictive value for each disease of ≥85% in MGH and BWH.[14,23] We used a complete case approach in all analyses (Figure 1).

Outcomes

The primary outcome was incident AF. Atrial flutter was considered equivalent to AF. In MGH and BWH, incident AF was defined using a previously published AF algorithm comprising combinations of diagnostic and procedural codes and ECG reports (modified AF algorithm) with a reported positive predictive value of 92% for AF.[24] In the UK Biobank, AF was defined using a previously published set of self-reported diagnoses, inpatient diagnosis codes, and procedure codes. Although direct validation is not possible in the UK Biobank, the AF definition was previously assessed in an external dataset with a reported positive predictive value of 92%.[25] The details of each AF definition are shown in Table S3.

Statistical Analysis

Consistent with previous work including the original CHARGE-AF derivation study,[13] we defined the outcome of incident AF at 5 years in the MGH and BWH datasets. Because of limited available follow-up (median, 2.8 years [quartile 1, 1.9; quartile 3, 4.3]) in the UK Biobank, we assessed 2-year AF as the outcome. ECG-AI was trained to generate 5-year AF risk estimates. We calculated 5-year AF risk estimates for CHARGE-AF using the equation $1-0.9718412736^{\exp(score-12.58156)}$,[13] where *score* is the individual's CHARGE-AF score. To compare ECG-AI with CHARGE-AF (a score derived as a Cox proportional hazards model), we fit Cox proportional hazards models in the MGH training set with incident AF as the outcome and (1) ECG-AI probability and (2) ECG-AI probability and CHARGE-AF as covariates (CH-AI). ECG-AI probability was logit-transformed to achieve an approximately linear relationship with the log hazard.[12] We also fit an analogous model including only age and sex. Although ECG-AI and CHARGE-AF were correlated in the training set, the strength of correlation was only moderate (Pearson r=0.68 [95% CI, 0.67–0.68]). We used the CHARGE-AF score rather than fitting the individual score components given that the score has been validated across multiple settings.[13,14,16,17] However, in secondary analyses, we also fit a version of CH-AI in which each CHARGE-AF component was included as an individual covariate. Given low death rates within the time window of interest (MGH training set, 4.6%; MGH test set, 3.2%; BWH, 2.8%; UK Biobank, 0.4%), we did not account for death as a competing risk. We compared the age and sex, CHARGE-AF, ECG-AI, and CH-AI models in each test set. The linear predictors of age and sex, ECG-AI, and CH-AI were converted to predicted probabilities of AF using the equation $1-s_0^{\exp(\sum\beta X-\sum\beta Y)}$, where s_0 is the average AF-free survival probability at the window of interest in the MGH training set, $\sum\beta X$ is the individual's score value, and $\sum\beta Y$ is the average score in the MGH training set. Values of s_0 and $\sum\beta Y$ are provided in Table S4.

Within each test set, we assessed AF discrimination using the area under the time-dependent receiver operating characteristic curve (AUROC).[26] Because AUROC may be misleading for relatively uncommon outcomes, we also assessed discrimination using time-dependent average precision (AP).[27] Both AUROC and AP estimates were calculated using

Table 2. Model Performance for Incident Atrial Fibrillation in Test Sets

MGH (n=4166)						BWH (n=37 963)	
Model	HR (per 1 SD)	5-year AUROC	5-year average precision	Calibration slope	ICI‡	HR (per 1 SD)	5-year AUROC
Deep learning architectures							
ECG-AI	–	0.823* (0.790–0.856)	0.27 (0.21–0.34)	–	0.0231	–	0.747* (0.736–0.759)
Cox proportional hazards models							
Age and sex	2.91 (2.44–3.47)	0.768 (0.732–0.805)	0.16 (0.13–0.20)	1.05 (0.88–1.23)	0.0074	2.48 (2.35–2.62)	0.730 (0.717–0.743)
CHARGE-AF	3.36 (2.98–4.30)	0.802* (0.767–0.836)	0.21* (0.17–0.26)	0.68 (0.58–0.77)	0.0320	2.78 (2.63–2.94)	0.752* (0.741–0.763)
ECG-AI	2.45 (2.23–2.69)	0.823* (0.790–0.856)	0.27* (0.21–0.34)	1.06 (0.95–1.17)	0.0212	2.05 (1.98–2.11)	0.747* (0.736–0.759)
CH-AI	3.74 (3.24–4.33)	0.838*† (0.807–0.869)	0.30*† (0.24–0.38)	1.13 (1.01–1.25)	0.0120	2.76 (2.64–2.88)	0.777*† (0.766–0.788)

(*Continued*)

inverse probability of censoring weights to account for potential bias introduced by censoring.[28,29] We calculated AUROC and AP in 1-year increments after ECG until the window of interest. Standard errors were estimated using 500-iteration bootstrapping, which were used to calculate 95% CIs and perform pairwise *Z* testing.

We assessed calibration using adaptive hazard regression[30] curves of predicted versus observed AF risk; calibration slopes, where a value of 1 indicates optimal calibration[31]; and integrated calibration index (ICI), the average prediction error weighted by the empirical risk distribution.[30] Because initial 2-year AF estimates from ECG-AI and CH-AI substantially overestimated risk in the UK Biobank (Figure S4), and because the CHARGE-AF score was designed to predict 5-year AF,[13] we recalibrated each score on the basis of the observed 2-year AF incidence in the UK Biobank.[32]

We then quantified time-dependent net reclassification improvement (NRI).[33] We assessed reclassification at standard risk thresholds (ie, 5-year AF risk <2.5%, 2.5% to 5%, and ≥5% in MGH/BWH and 2-year AF risk <0.5%, 0.5% to 1%, and ≥1% in the UK Biobank), at high risk thresholds (ie, 5-year AF risk <20% versus ≥20% in MGH/BWH and 2-year AF risk <2% versus ≥2% in UK Biobank), and using continuous risk values. Standard risk thresholds were chosen to mirror previous thresholds used when deriving the CHARGE-AF score,[13] and high risk thresholds were chosen to reflect higher levels of AF risk, which may be more clinically actionable. Before estimating NRI, models were recalibrated using the methods described, with or without additional adjustment for the calibration slope as required,[32] to obtain well-calibrated scores (ICI range: 7.1×10^{-5} to 0.0129). We then plotted the cumulative risk of AF across high risk strata defined using ECG-AI and CHARGE-AF. To assess ECG-AI behavior, we produced saliency maps depicting areas of the ECG in which changes in voltage had the greatest influence on ECG-AI predicted risk estimates. We also plotted the median ECG waveforms for individuals at high estimated AF risk (≥5%) versus low estimated AF risk (<2.5%) for 1000 randomly selected individuals within each stratum from the BWH test set, with cutoffs mirroring our standard risk thresholds.[13] Further details of saliency map and median waveform analysis are described in the Supplemental Methods.

We performed several secondary analyses, described in detail in the Supplemental Methods. We considered 2-sided *P* values <0.05 statistically significant. Analyses were performed using Python v3.8[34] and R v4.0.[35]

RESULTS

Training and Validation Samples

Overall, 45 770 individuals in the MGH sample were eligible for analysis (mean age 55 years, 53% female), and were divided into training (n=36 081) and validation (n=9689) sets for ECG-AI. Characteristics of participants are displayed in Table 1. The training set included 100 954 12-lead ECGs (median ECGs per individual, 1 [quartile 1, 1; quartile 3, 3]). After ECG-AI training, we fit Cox proportional hazards models in the full MGH sample of 45 770 individuals. When fitting CH-AI, both ECG-AI probability (hazard ratio [HR], 1.85 per 1-SD increase [95% CI, 1.75–1.95]) and CHARGE-AF score (HR, 1.97 per 1-SD increase [95% CI, 1.84–2.11]) were associated with incident AF, without interaction (*P*=0.60).

We assessed each model in 3 independent test sets: MGH (n=4166), BWH (n=37 963), and UK Biobank (n=41 033). AF incidence rates were substantially higher in MGH (12.8 per 1000 person-years [95% CI, 11.0–14.5]) and BWH (12.9 [95% CI, 12.3–13.4]) as compared with the UK Biobank (4.2 [95% CI, 3.7–4.7]). Median follow-up for analysis was 5.0 years (quartile 1, 2.6; quartile 3, 5.0) in MGH, 5.0 years (2.6, 5.0) in BWH, and 2.0 years (1.9, 2.0) in the UK Biobank. A sample overview is depicted in Figure 1 and baseline characteristics are shown in Table 1. Predicted AF risk distributions are shown in Figure S5.

Discrimination

ECG-AI demonstrated moderate AF discrimination (AUROC: MGH, 0.823; BWH, 0.743; UK Biobank, 0.705), comparable to the full CHARGE-AF score (Table 2; 0.802, 0.752, 0.732). Compared with CHARGE-AF, AUROC point estimates for CH-AI were consistently higher (0.838, 0.777, 0.746), although the difference was

Table 2. Continued

BWH (n=37 963)			UK Biobank (n=41 033)				
5-year average precision	Calibration slope	ICI	HR (per 1 SD)	2-year AUROC	2-year average precision	Calibration slope	ICI
0.19*† (0.17–0.20)	–	0.0124	–	0.705 (0.659–0.724)	0.060* (0.043–0.087)	–	0.0768
0.14 (0.13–0.15)	0.94 (0.88–1.00)	0.0072	2.21 (1.96–2.50)	0.728 (0.702–0.755)	0.018 (0.015–0.024)	1.48 (1.25–1.71)	0.0019§
0.17* (0.15–0.18)	0.57 (0.53–0.60)	0.0344	2.26 (2.00–2.55)	0.732 (0.704–0.759)	0.020 (0.016–0.026)	0.87 (0.75–1.00)	0.0011§
0.19*† (0.17–0.20)	0.81 (0.77–0.84)	0.0129	2.01 (1.88–2.14)	0.705 (0.673–0.737)	0.060*† (0.044–0.090)	0.75 (0.68–0.82)	0.0035§
0.21*† (0.19–0.23)	0.77 (0.74–0.81)	0.0108	2.27 (2.11–2.44)	0.746 (0.716–0.776)	0.059*† (0.042–0.083)	1.01 (0.92–1.10)	0.0001§

Difference in *c* index for CHARGE-AF (Cohorts for Aging Research and Genomic Epidemiology–Atrial Fibrillation) and ECG artificial intelligence (CH-AI) vs ECG artificial intelligence (ECG-AI): area under the receiver operating characteristic curve (AUROC): Massachusetts General Hospital (MGH), *P*=not significant (NS); Brigham and Women's Hospital (BWH), *P*<0.05; UK Biobank, *P*<0.05; average precision: MGH, *P*<0.05; BWH, *P*<0.05; *P*=NS. HR indicates hazard ratio.

*$P<0.05$ for comparison against age and sex.

†$P<0.05$ for comparison against CHARGE-AF.

‡Integrated calibration index (ICI) is a quantitative measure of the average difference between predicted event risk and observed event incidence, weighted by the empirical distribution of event risk.[30] Smaller values indicate better calibration.

§Values reflect ICI after recalibration to the baseline 2-year atrial fibrillation risk in the UK Biobank.

not statistically significant in the UK Biobank ($P<0.05$ for MGH and BWH; $P=0.28$ for UK Biobank; Table 2). Improvements in discrimination were more prominent according to AP, where ECG-AI (0.27, 0.19, 0.06) and CH-AI (0.30, 0.21, 0.06) were favorable compared with CHARGE-AF (0.21, 0.17, 0.02; ECG-AI: $P=0.06$, $P<0.05$, $P<0.05$, respectively; CH-AI: $P<0.05$ for all). Overall patterns in model discrimination were generally consistent for events occurring between 1 and 5 years, although discrimination for CH-AI and CHARGE-AF tended to increase with longer prediction windows whereas that using ECG-AI tended to remain constant (Figure 2 and Table S5). When assessed at specific thresholds, ECG-AI and CH-AI tended to provide greater precision at higher specificity. For example, at 95% specificity, precision was substantially greater using ECG-AI (MGH, 17.3%; BWH, 12.6%; UK Biobank, 4.12%) and CH-AI (17.9%, 14.6%, 4.85%) versus CHARGE-AF (11.0%, 12.0%, 3.28%; Table S6).

Calibration

CH-AI was well-calibrated in MGH (integrated calibration index 0.012) and BWH (0.019), but overestimated risk in the UK Biobank (0.068; Figure S4). Given a near-optimal calibration slope (1.01 [95% CI, 0.92–1.10]), overestimation was likely attributable to a greater average 2-year AF risk in the MGH training set (1.48%) versus UK Biobank (0.56%). Accordingly, calibration of CH-AI in the UK Biobank was excellent after recalibration to the average 2-year AF hazard in the UK Biobank (integrated calibration index 7.1×10^{-5}; Figure 3). Cumulative risk of AF was greatest among individuals classified as high risk using both CHARGE-AF and ECG-AI, lowest among individuals classified as low risk using both CHARGE-AF and ECG-AI, and intermediate among individuals classified as high risk using CHARGE-AF alone or ECG-AI alone (Figure 4). Cumulative risk of AF stratified by estimated risk using CH-AI is shown in Figure S6.

Model Behavior

Saliency maps demonstrated that the P wave and surrounding regions had the greatest effect on ECG-AI AF risk (Figure 5). Median waveform analysis demonstrated specifically that individuals with high estimated AF risk tended to have a longer P wave duration, as well as slightly wider QRS and a flatter ST segment (Figure 5).

Reclassification and Subgroup Analyses

Compared with CHARGE-AF, CH-AI demonstrated favorable NRI using standard risk thresholds, high risk thresholds, and continuous risk values (Tables S7–S9 and Figure S7). Use of ECG-AI compared with CHARGE-AF did not result in favorable NRI using standard risk thresholds or continuous risk values, but did result in favorable reclassification at high risk thresholds (Tables S7–S9 and Figure S7). Receiver operating characteristic and precision recall curves are shown in Figure S8.

Improvements in model performance using CH-AI versus CHARGE-AF were generally consistent among individuals with prevalent heart failure and stroke (Table S10), and were more prominent within subgroups of age (Figure S9). Using models developed using only lead I, and separately lead II—vectors typical for single-lead ECGs—CH-AI continued to provide greater discrimination than CHARGE-AF, although discrimination using ECG-AI was lower (Table S11). Performance of CH-AI and ECG-AI for 2-year AF risk in MGH and BWH were similar to that

observed for 5-year AF risk (Table S12). When ECG-AI was fit sequentially along with covariate terms for sex and individual components of the CHARGE-AF score, we observed that inclusion of age and sex improved discrimination over ECG-AI alone, with further improvement observed when additional CHARGE-AF components were added (Table S13). A model fit using ECG-AI, sex, and each individual component of the CHARGE-AF score resulted in nearly identical discrimination to CH-AI, with worse calibration in the UK Biobank (Table S13). Saliency maps across strata of CHARGE-AF and ECG-AI risk are shown in Figure S10. The linear predictors of ECG-AI and CHARGE-AF were consistently correlated (Pearson *r*: MGH, 0.61; BWH, 0.66; UK Biobank, 0.41; $P<0.01$ for all).

DISCUSSION

We developed ECG-AI, a deep learning model that explicitly predicts time to incident AF using 12-lead ECG data. ECG-AI was trained using roughly 100 000 ECGs from >40 000 individuals within a primary care cohort. CH-AI, a model that combined both ECG-AI and CHARGE-AF, demonstrated improved performance across multiple prognostic model metrics as compared with CHARGE-AF within 3 independent test sets including >80 000 individuals whose clinical characteristics varied substantially. AF risk estimates from ECG-AI alone demonstrated comparable discrimination when compared with the 11-component CHARGE-AF score. We further observed that ECG-AI and CHARGE-AF were highly correlated, suggesting that much of the predictive usefulness of ECG-AI may reflect electrocardiographic manifestations of established clinical risk factors for AF. On balance, our findings suggest that deep learning–derived ECG-based risk provides comparable predictive usefulness to a clinical risk model for predicting incident AF. Moreover, our results indicate that ECG-AI and clinical risk factors provide complementary information that augments AF prediction.

Attia et al[10] developed a deep learning model that was 80% accurate in the classification of a patient's AF status among those in normal sinus rhythm. Raghunath et al[11] subsequently developed a neural network to predict incident AF using 12-lead ECGs, demonstrating good discrimination at 1 year, and modestly improved performance when compared with CHARGE-AF in a subset analysis. Our findings add substantively to previous work by introducing a deep learning model that explicitly incorporates survival time and performing a rigorous epidemiologic assessment including quantification of discrimination, calibration, reclassification, and a broad external validation. We are unable to directly compare our approach with previous models given that the models are not available for application to our data. Even if previous models were available, important differences in model design (eg, a standard *c* statistic cannot be calculated for time-to-event models) would likely preclude direct comparison of our model metrics with previous models. Nevertheless, our results broadly support the notion that deep learning models using 12-lead ECG provide important predictive usefulness for determining AF risk. Our results also provide new evidence that ECG-derived risk estimates are generalizable, with predictive value maintained up to 5 years after an ECG is performed. The ability to predict incident AF up to 5 years in the future may facilitate implementation of preventive interventions (eg, alcohol cessation,[5] achievement of healthy weight,[6] control of high blood pressure[36]) designed to reduce risk of AF and associated complications.

Our findings demonstrate that deep learning models using ECG to estimate AF risk are robust and valid across contrasting populations when assessed using rigorous epidemiologic metrics. We assessed ECG-AI in test sets comprising independent individuals from the same institution as the training set, a separate institution within the same health care network, and a prospective research cohort from a different continent in which AF risk was substantially lower. Consistent with previous findings,[17] ECG-AI performed best in populations most closely resembling the training set, with decreasing discrimination across progressively different samples, underscoring the importance of widespread external validation of AI models for assessing clinical usefulness. Ultimately, we suspect that differences in discrimination may be related to differing sample characteristics (eg, age, baseline AF risk) leading to varying relationships between specific ECG features and future AF risk. Nevertheless, CH-AI consistently outperformed CHARGE-AF, and ECG-AI alone consistently demonstrated at least moderate discrimination. We observed substantial overestimation in AF risk estimates using CH-AI in the UK Biobank, a low risk sample. However, simple recalibration to the baseline hazard—a process commonly required for traditional prognostic models[37]—resulted in excellent calibration. CHARGE-AF had worse calibration than CH-AI even after recalibration, suggesting that deep learned AF risk may contribute directly to more calibrated estimates.

We note 2 important implications of our results on the relations between deep learning–based ECG risk signals and traditional clinical risk factors for AF. First, clinical risk factors appear to manifest on the ECG in ways that are perceptible to deep learning models. ECG-AI probability and CHARGE-AF score were moderately correlated within each test set. Using saliency mapping and median waveform analysis, we observed that ECG-AI probability was critically influenced by the period of atrial depolarization and repolarization (ie, P wave and surrounding period), a reflection of atrial structure and function that may be affected by age and chronic conditions such as hypertension.[38,39]

Second, deep learning models appear to extract elements of AF risk that are complementary to clinical risk

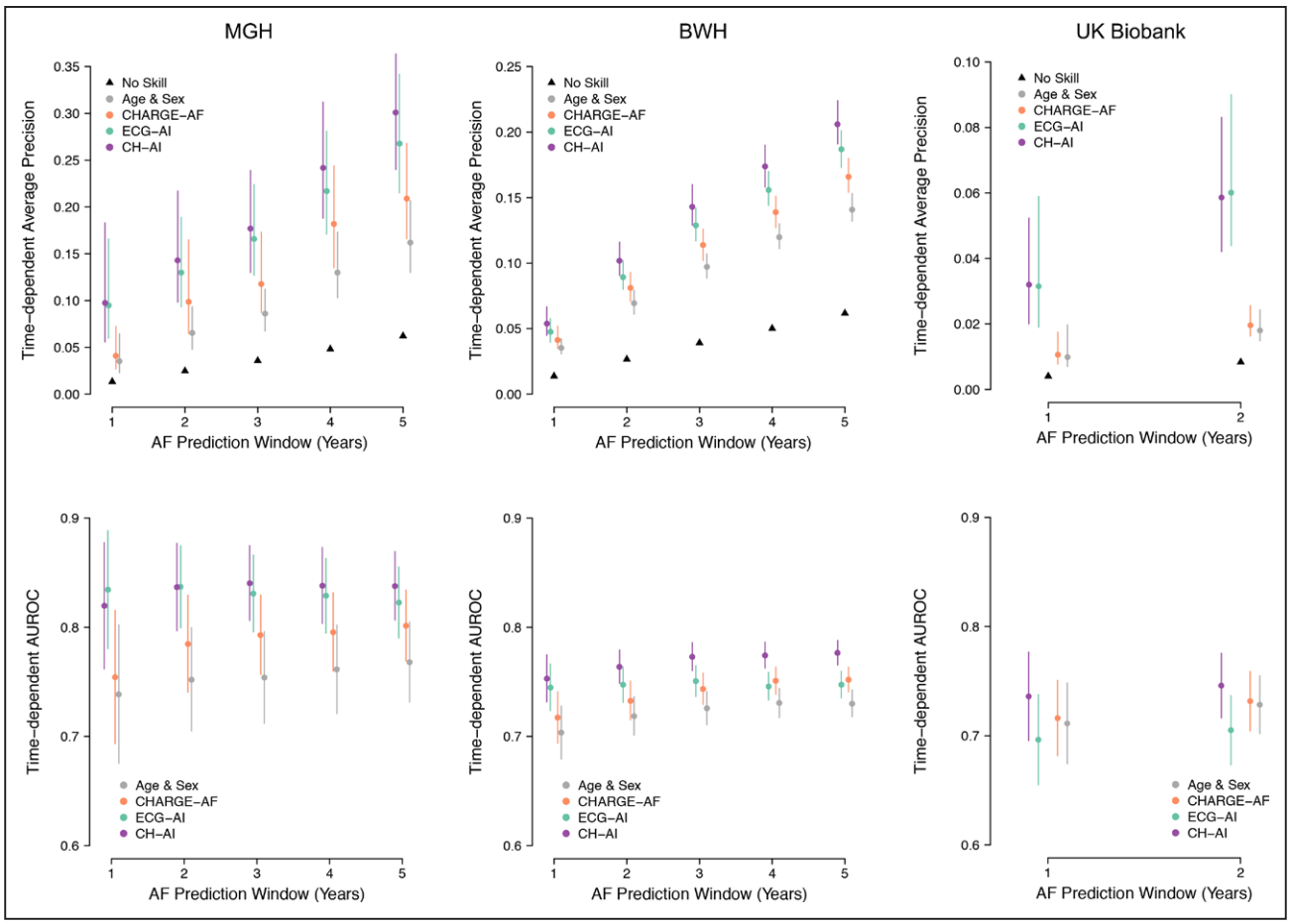

Figure 2. Discrimination of incident atrial fibrillation.
Discrimination of age and sex (gray), CHARGE-AF (Cohorts for Aging Research and Genomic Epidemiology–Atrial Fibrillation; orange), ECG–artificial intelligence (AI; green), and a model combining ECG-AI and CHARGE-AF (CH-AI; purple) in the Massachusetts General Hospital (MGH) test set (**left**), Brigham and Women's Hospital (BWH) test set (**middle**), and UK Biobank test set (**right**). **Top** panels plot the average precision and bottom panels plot the area under the receiver operating characteristic curve (AUROC) across increasing length of the prediction window (*x* axis). In the **top** panels, the black triangles represent the cumulative event rate (ie, the precision of a randomly guessing model). AF indicates atrial fibrillation.

factors. CH-AI—a model combining CHARGE-AF and ECG-AI—consistently demonstrated superior AF discrimination, calibration, and reclassification as compared with either ECG-AI or CHARGE-AF alone, suggesting meaningful improvement in predictive usefulness when combining clinical risk information with AI-enabled ECG risk stratification. AF risk was substantially higher among individuals classified as high risk according to both ECG-AI and CHARGE-AF as opposed to either model alone. Discrimination using CH-AI and CHARGE-AF tended to increase with longer prediction windows, likely relating to the cumulative effect of clinical risk factors over time, whereas discrimination using ECG-AI tended to remain relatively constant, suggesting that the relative contribution of ECG-based AF risk may be greatest for predicting AF events in the shorter term. Future work is needed to better characterize the biological correlates of increased AF risk as indicated by deep learning on ECG independent of clinical risk factors.

The convenience and external validity of estimating AF risk using a single modality rather than a complex clinical score suggests that deep learning models may be useful for clinical application. Although clinical factors are increasingly available, risk score functions remain challenging to implement given requirements for user interaction and susceptibility to misclassification of inputs. In contrast, models like ECG-AI may enable instantaneous AF risk estimation, which may facilitate rapid identification of individuals at elevated AF risk to guide preventive efforts and increase the efficiency of AF screening by targeting individuals most likely to have AF identified with diagnostic testing.[40] To this end, ECG-AI retained predictive usefulness in 2 populations of particular clinical interest—HF and stroke—in which AF risk assessment may have particular relevance considering the associated morbidity and high risk of stroke associated with AF. Furthermore, ECG-AI also had stable performance in models using only a single ECG lead, suggesting that deep learning may facilitate AF risk estimation using wearable devices, which are commonly equipped with single-lead ECG capability. Future work is warranted to validate and assess prospectively the

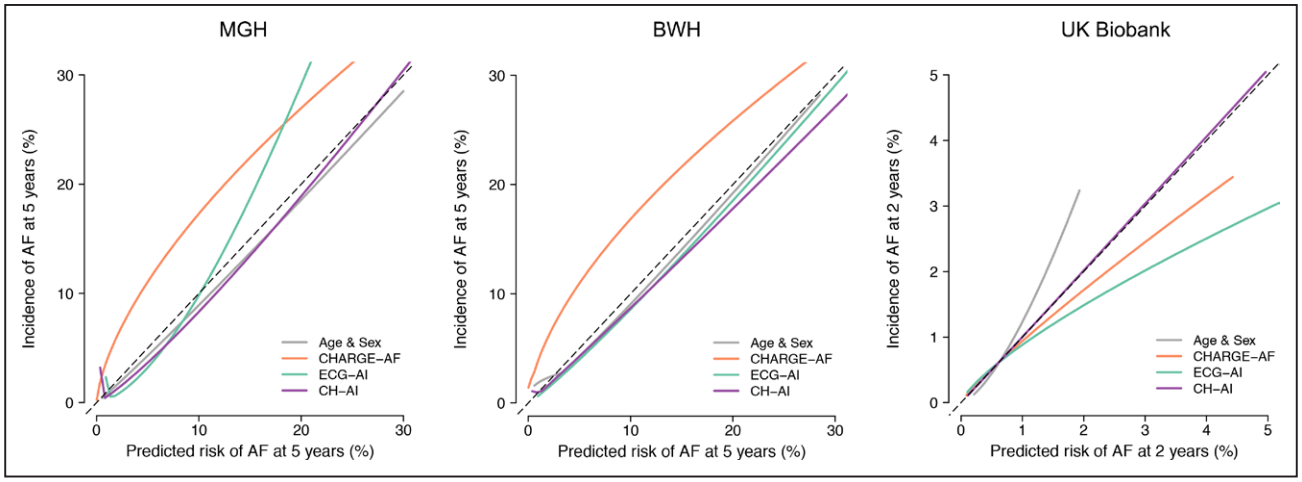

Figure 3. Calibration for incident atrial fibrillation.
Fitted calibration curves demonstrating the relationship between predicted event risk (*x* axis) and observed cumulative event incidence (*y* axis) for and age and sex (gray), CHARGE-AF (Cohorts for Aging Research and Genomic Epidemiology–Atrial Fibrillation; orange), ECG–artificial intelligence (AI; green), and a model combining ECG-AI and CHARGE-AF (CH-AI; purple). Perfect calibration is indicated by the hashed diagonal line, denoting perfect correspondence between predicted and observed risk. Curves were obtained using adaptive hazard regression[30] relating predicted risk and observed event risk. AF indicates atrial fibrillation.

predictive usefulness of ECG-AI in different clinical settings and as applied to wearable ECGs.

Our study should be interpreted in the context of the design. First, we trained ECG-AI on individuals with at least 1 ECG performed for clinical purposes. We also required that individuals have each component of the CHARGE-AF score available at baseline. Both of these requirements introduce potential selection bias. However, analyzing an EHR sample comprising individuals receiving longitudinal primary care is likely to reduce bias,[18] and our models continued to discriminate AF in a completely independent prospective cohort study. Second, our training set represented individuals from a single institution. Training on larger samples across multiple institutions may lead to more accurate and generalizable models. Third, given limited follow-up in the UK Biobank, we assessed a shorter prediction window of 2 years, as opposed to 5 years in MGH and BWH. Fourth, ECG-AI is a black box model. However, in contrast to previous AF prediction models,[10–12] we use saliency maps and median waveform analysis to demonstrate that biologically plausible ECG changes (eg, longer P wave duration) had greatest influence on AF risk estimates. Fifth, a 5-year prediction window may represent AF risk that is less immediately actionable. However, our models had consistent discrimination across shorter time windows as well. We cannot exclude that ECG-AI identifies individuals with preexisting undiagnosed AF. Sixth, ECG-AI

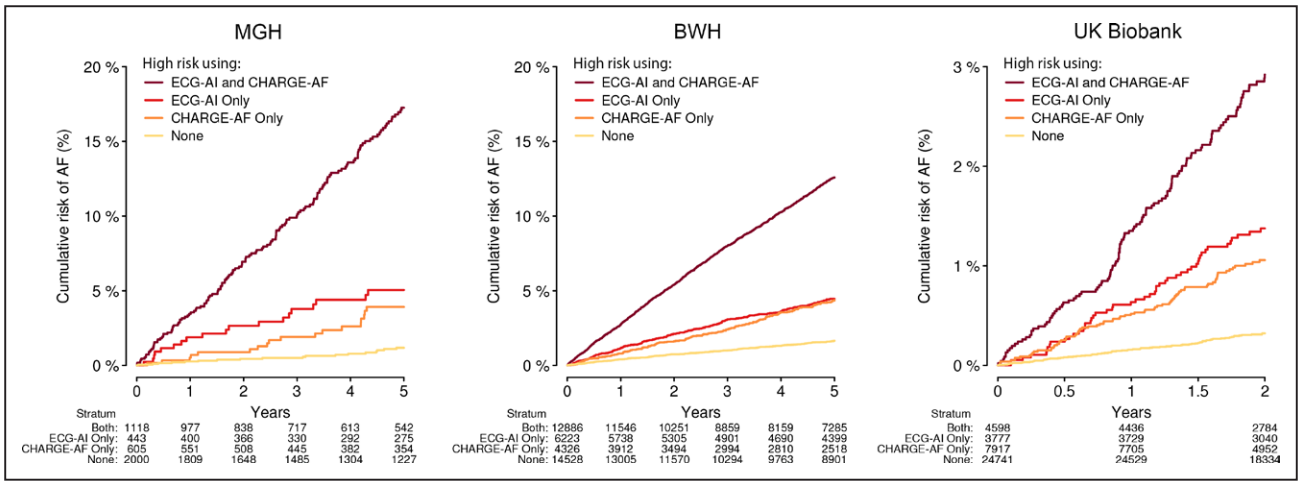

Figure 4. Cumulative risk of atrial fibrillation stratified by predicted atrial fibrillation risk.
Cumulative risk of atrial fibrillation (AF) stratified by high predicted risk of AF as determined using both ECG–artificial intelligence (AI) and CHARGE-AF (Cohorts for Aging Research and Genomic Epidemiology–Atrial Fibrillation; dark red), ECG-AI only (red), CHARGE-AF only (orange), or neither model (yellow). High AF risk was defined as 5-year AF risk ≥5% in Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH; as performed in the original CHARGE-AF derivation study)[13] and 2-year AF risk ≥1% in the UK Biobank (approximating the top tertile of risk). The number at risk across each stratum over time is depicted below each plot.

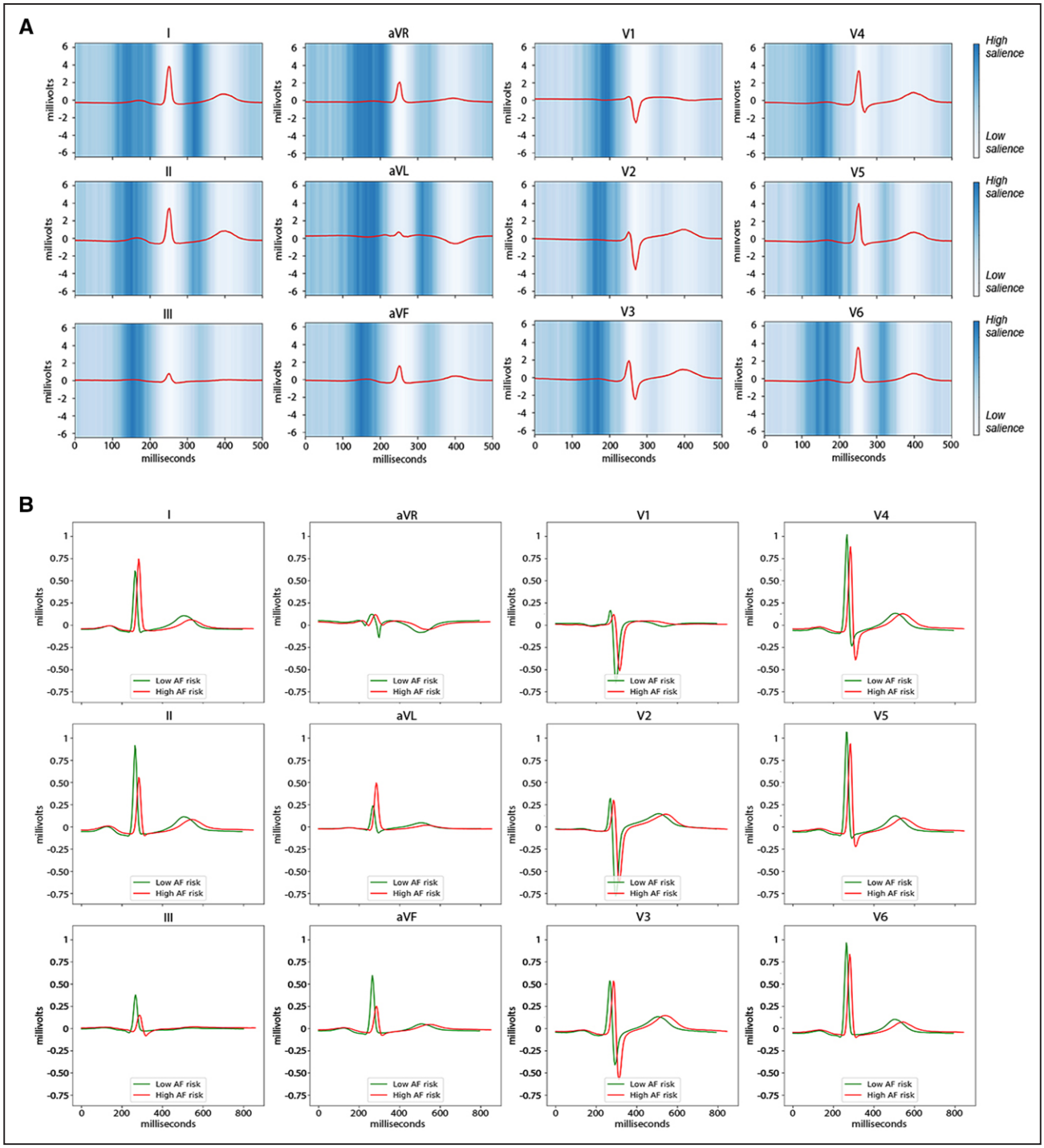

Figure 5. Representations of ECG–artificial intelligence behavior.
Two forms of visualizing the behavior of the ECG–artificial intelligence (AI) deep learning model. **A**, Saliency map of ECG-AI demarcating regions of the ECG waveform having the greatest influence on atrial fibrillation (AF) risk predictions. Blue shades depict the magnitude of the gradient of predicted AF risk with respect to the ECG waveform amplitude, where darker shades illustrate regions of the waveform exerting greater salience, or influence on AF risk predictions. Saliency was averaged over a random sample of 4096 individuals in the Brigham and Women's Hospital (BWH) test set. The red waveform depicts the median waveform in each lead among the 4096 individuals. **B**, Median waveform of a random sample of 1000 individuals in the BWH test set with low predicted AF risk (ie, 5-year AF risk <2.5%, green) vs the median waveform of a random sample of 1000 individuals in the BWH test set with high predicted AF risk (ie, 5-year AF risk >5%, red).

and CH-AI required recalibration in the UK Biobank. Recalibration is frequently necessary when transferring prognostic models across populations,[37] and simple recalibration to the observed AF incidence in the UK Biobank resulted in very well-calibrated estimates, suggesting that initial miscalibration was attributable to a baseline AF incidence in the UK Biobank that was roughly one-third that in MGH and BWH. Furthermore,

CH-AI had better calibration than CHARGE-AF even though CHARGE-AF was similarly recalibrated in the UK Biobank.

Across 3 independent test sets spanning >80 000 individuals, ECG-AI, a deep learning model that explicitly predicts time to incident AF using 12-lead ECG, offers comparable discrimination of 5-year AF risk when compared with the 11-component CHARGE-AF clinical risk score. CH-AI—a model integrating CHARGE-AF and ECG-AI—offers consistently superior discrimination, calibration, and reclassification. Deep learned ECG-based AF risk signals have the potential for broad deployment to provide accurate and generalizable absolute AF risk estimates up to several years after an ECG is performed.

ARTICLE INFORMATION

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