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Artificial Intelligence–Enhanced Electrocardiography for Complete Heart Block Risk Stratification

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INTRODUCTION Complete heart block (CHB) is a life-threatening condition that can lead to ventricular standstill, syncopal injury, and sudden cardiac death, and current electrocardiography (ECG)-based risk stratification (presence of bifascicular block) is crude and has limited performance. Artificial intelligence–enhanced electrocardiography (AI-ECG) has been shown to identify a broad spectrum of subclinical disease and may be useful for CHB.

OBJECTIVE To develop an AI-ECG risk estimator for CHB (AIRE-CHB) to predict incident CHB.

DESIGN, SETTING, AND PARTICIPANTS This cohort study was a development and external validation prognostic study conducted at Beth Israel Deaconess Medical Center and validated externally in the UK Biobank volunteer cohort.

EXPOSURE Electrocardiogram.

MAIN OUTCOMES AND MEASURES A new diagnosis of CHB more than 31 days after the ECG. AIRE-CHB uses a residual convolutional neural network architecture with a discrete-time survival loss function and was trained to predict incident CHB.

RESULTS The Beth Israel Deaconess Medical Center cohort included 1 163 401 ECGs from 189 539 patients. AIRE-CHB predicted incident CHB with a C index of 0.836 (95% CI, 0.819-0.534) and area under the receiver operating characteristics curve (AUROC) for incident CHB within 1 year of 0.889 (95% CI, 0.863-0.916). In comparison, the presence of bifascicular block had an AUROC of 0.594 (95% CI, 0.567-0.620). Participants in the high-risk quartile had an adjusted hazard ratio (aHR) of 11.6 (95% CI, 7.62-17.7; $P < .001$) for development of incident CHB compared with the low-risk group. In the UKB UK Biobank cohort of 50 641 ECGs from 189 539 patients, the C index for incident CHB prediction was 0.936 (95% CI, 0.900-0.972) and aHR, 7.17 (95% CI, 1.67-30.81; $P < .001$).

CONCLUSIONS AND RELEVANCE In this study, a first-of-its-kind deep learning model identified the risk of incident CHB. AIRE-CHB could be used in diverse settings to aid in decision-making for individuals with syncope or at risk of high-grade atrioventricular block.

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Supplemental content

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Complete heart block (CHB) is a life-threatening condition resulting from advanced conduction system disease that can lead to ventricular standstill, syncopal injury, and sudden cardiac death. The prevalence of CHB increases with age, but the overall incidence is relatively low, affecting 0.04% of the general population.[1] The gold standard for diagnosis of CHB is an electrocardiogram (ECG) during CHB, and in the absence of reversible causes, the treatment is permanent pacemaker (PPM) implantation.[2]

The diagnostic challenge in CHB is that the ECG may not show evidence of high-grade atrioventricular (AV) block at the time of recording; the conduction system disease maybe intermittent. Ambulatory ECG recording has been recommended[2] in individuals presenting with syncope with suspected conduction disease; however, the sensitivity is low and represents limited health-economic value.[3] Prolonged monitoring with implantable loop recorders greatly improves diagnostic yield but is expensive, costing nearly the same as empirical PPM implantation.[4] Empirical PPM implantation in patients thought to have the highest risk can be considered and is advocated by international guidelines (eg, bifascicular block). However, this incurs the risk of complications at the time of implant and generator change, which is particularly concerning to patients who never go on to develop CHB.[5] An electro-

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physiology study can be undertaken to assess for infra-Hisian conduction delay. However, this procedure is invasive, carries risks, has limited sensitivity and specificity, and is costly.[6]

Furthermore, the first presentation of high-grade AV block may be syncope or sudden cardiac death. Asymptomatic (less severe) conduction system disease is commonly observed on routine ECG recordings, but it is unclear which individuals will eventually develop high-grade AV block.

An untapped resource in the prediction of CHB is the ECG. Simple human-identified morphologies have been deemed high risk, including bifascicular block, which is commonly defined as block within 2 of the 3 fascicles (therefore including left bundle-branch block [LBBB]).[7] Using bifascicular block as a risk stratification criterion is supported by international guidelines.[2,7] However, the presence of bifascicular block is not a sensitive or specific finding for CHB.[8]

Artificial intelligence–enhanced ECG (AI-ECG) has been recently shown to have significant potential to diagnose hidden cardiovascular disease and predict the risk of future disease.[9-11] Recently, we have developed the AI-ECG risk estimation platform (AIRE) capable of predicting mortality and cardiac events from 12 lead ECGs.[10] Here, we build on this platform to predict incident CHB and explore the underlying biology behind these predictions.

Key Points

Question Can artificial intelligence–enhanced electrocardiography (AI-ECG) be used to identify individuals with risk of incident complete heart block (CHB)?

Findings This cohort study demonstrated that an AI-ECG risk model can predict the risk of incident CHB and is superior to traditional, guideline-based, ECG risk markers.

Meaning The AI-ECG model termed *AIRE-CHB* could be used to risk-stratify patients at risk of CHB to guide treatment decisions such as rhythm monitoring or empirical pacemaker implantation.

Methods

This study complied with all relevant ethical regulations (eMethods in Supplement 1). The Beth Israel Deaconess Medical Center (BIDMC) cohort ethics review and approval was provided by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations, which granted a waiver of consent. The UK Biobank (UKB) has approval from the North West Multi-Centre Research Ethics Committee as a Research Tissue Bank; informed consent was obtained by all participants. This study is reported in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guideline for artificial intelligence (TRIPOD-AI).

Cohorts

We studied 2 cohorts. The BIDMC cohort was an unselected secondary care cohort consisting of routinely collected health record data. The UKB cohort is a longitudinal study of volunteers who were aged 40 to 69 years on joining during 2006 to 2010. A subset of these individuals who lived near an imaging assessment center were invited for the second follow-up visit and had an ECG performed. More information about these cohorts can be found in the eMethods in Supplement 1.

Data Preprocessing

ECG preprocessing is described in the eMethods in Supplement 1. The data were split at a ratio of 50%/10%/40% for training, tuning, and internal testing, respectively. Data were split by patient identifier stratified by presence of ECGs with paired 5-year life status. Therefore, ECGs from the same patient could only be in 1 of the training, tuning or internal test sets. ECGs were treated independently, and multiple ECGs per patient (where available) were used for training. ECG LBBB and right bundle-branch block (RBBB) morphology was determined using a previously described AI-ECG model that has been shown to outperform clinicians in this task.[12] Bifascicular block was defined as RBBB with axis deviation or LBBB.[7]

Model Development

We expanded the AIRE platform for diagnosis and prediction of CHB (AIRE-CHB). CHB outcomes were defined using diagnostic codes from the *International Classification of Diseases, Ninth Revision* (*ICD-9*), or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) recorded anywhere in the electronic health record (eMethods in Supplement 1). AIRE-CHB was developed by fine-tuning our previously described AIRE model.[10] Briefly, AIRE was developed using a previously described convolutional neural network architecture based on residual blocks,[12] which was modified so the final layer accommodated a discrete-time survival approach.[13] The same data splits (by patient identifier) were used as for training the original model. Fine-tuning was performed by loading the previous model and training using a low learning rate without freezing any layers.

The outputs of the AIRE-CHB model are termed the *AIRE-CHB score*. Higher values indicate higher risk of CHB. The model output at 5 years was used for prediction of incident CHB (irrespective of the duration of follow-up for that particular participant). Further details of hyperparameters and model training are in the eMethods in Supplement 1.

Outcome Definitions

Analysis used a single ECG per participant; where more than 1 ECG was available, the first ECG was used. Incident CHB was defined as a new diagnosis of CHB at a time greater than 31 days after the ECG (to exclude cases of CHB diagnosed at the time of hospital presentation). Participants with a pacemaker implanted or high-grade AV block (second degree or complete heart block) diagnosed before or within 31 days after the ECG were excluded. Participants with follow-up less than 31 days were also excluded.

The model was trained to predict CHB diagnoses (based on *ICD* codes), and this was the primary outcome for the study. Sensitivity analyses were performed using PPM implantation

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Table. Dataset Demographics

Characteristic	No. (%)	
	BIDMC cohort[a]	UK Biobank
No. of participants	189 539	50 641
Age, mean (SD), y	57.68 (18.69)	64.58 (7.88)
Follow up time, mean (SD), y	3.41 (4.08)	4.01 (2.16)
Sex		
Male	90 792 (47.9)	24 560 (48.5)
Female	98 747 (52.1)	26 081 (51.5)
Hypertension	74 409 (39.3)	15 601 (30.8)
Previous MI	11 788 (6.2)	1196 (2.4)
Smoker	23 343 (12.3)	1720 (3.4)
Diabetes	33 748 (17.8)	2859 (5.6)
Hyperlipidemia	67 087 (35.4)	11 736 (23.2)
Mortality	34 938 (18.4)	789 (1.6)

Abbreviations: BIDMC, Beth Israel Deaconess Medical Center; MI, myocardial infarction.

[a] Data at the time point of a randomly selected electrocardiogram per participant are shown for the BIDMC dataset.

(using *Current Procedural Terminology* codes in BIDMC and Office of Population Censuses and Surveys codes in UKB) and both CHB and PPM implantations as alternative end points. History of syncope in BIDMC was determined using *ICD* codes.

Statistical Analyses

AIRE-CHB score quartiles were defined using the distributions in the tuning set for Kaplan-Meier curves. The highest-risk quartile was compared with the lowest-risk quartile in Cox models to derive age- and sex-adjusted hazard ratios (HRs). AIRE-CHB score quartiles were plotted and statistical significance assessed using the log-rank test. C index, area under the receiver operating characteristics curve (AUROC), precision recall curve (AUPRC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the Brier score (a measure of calibration) are reported. The UKB cohort was used for external validation.

Statistical analyses were performed with R version 4.2.0 (R Core Team) or Python version 3.9 (Python Software Foundation).

Explainability Analysis

To explore the ECG morphologies and standard ECG metrics linked to the AIRE-CHB score, we used 3 approaches.

First, a variational autoencoder (VAE) was trained on median ECG beats. Median beats were derived using the BRAVEHEART ECG analysis software.[12] The latent features derived from the VAE were then fed into a linear regression model, aiming to predict the output of AIRE-CHB, a continuous range between 0 and 1 that relates to incident CHB risk. The VAE and median beats were used only for explainability analysis and not to create the AIRE-CHB model (which used an end-to-end neural network as described above, using a 10-second ECG input). We identified and visualized the top 3 most significant features, based on their *t* values, through a process known as latent feature traversal. Further details are available in eMethods in Supplement 1.

Second, we calculated the median waveform from the 10 000 ECGs with the lowest and highest AIRE-CHB scores to qualitatively explore the morphologies associated with risk. Third, we performed univariable correlation between AIRE-CHB and ECG parameters. Using linear regression, AIRE-CHB was adjusted for age, sex, and age squared.

Results

AIRE-CHB Prediction of Incident CHB

In the BIDMC cohort, 1 163 401 ECGs were available from 189 539 participants; 90 792 (47.9%) were male and 98 747 (52.1%) female. A total of 34 938 participants (18.4%) died during follow-up (**Table**). eFigure 1 in Supplement 1 depicts the ECGs used for training/tuning/testing in both cohorts.

In the internal testing dataset for incident complete heart block (BIDMC, n = 61676; 791 events [1.3%]), AIRE-CHB predicted incident CHB with a C index of 0.836 (95% CI, 0.823-0.853) over a mean (SD) follow-up of 6.66 (5.78) years (**Figure 1**). Participants in the high-risk quartile had an age- and sex-adjusted HR of 11.6 (95% CI, 7.62-17.7; $P < .001$) for development of incident CHB compared with the low-risk group. The AUROC for prediction of incident CHB at 1 year was 0.889 (95% CI, 0.863-0.916). Additional metrics are reported in eTable 1 and eFigures 2 through 4 in Supplement 1. Sensitivity analyses for the prediction of PPM implantation and CHB or PPM implantation yielded similar results (C index, 0.799; 95% CI, 0.779-0.819, and C index, 0.814; 95% CI, 0.798-0.829, respectively). In comparison, the presence of bifascicular block had an AUROC of 0.594 (95% CI, 0.567-0.620; $P < .001$ for comparison with AIRE-CHB). We also evaluated additional existing high-risk ECG criteria including LBBB, RBBB with axis deviation, and bifascicular block with prolonged PR interval; these all had inferior discrimination compared with AIRE-CHB (eTable 2 in Supplement 1).

We performed external validation in the UKB (n = 50 641), in which 35 participants (0.07%) developed CHB during a mean (SD) follow-up of 4.01 (2.16) years. The C index for incident CHB prediction was 0.936 (95% CI, 0.899-0.972). Participants in the high-risk quartile had an age- and sex-adjusted HR of 7.17 (95% CI, 1.67-30.83; $P < .001$) for development of incident CHB compared with the low-risk group (Figure 1).

Evaluation of AI-ECG predictions over serial ECGs showed that for participants with CHB during follow-up, the average predictions of AIRE-CHB increased over time until CHB was diagnosed (**Figure 2**).

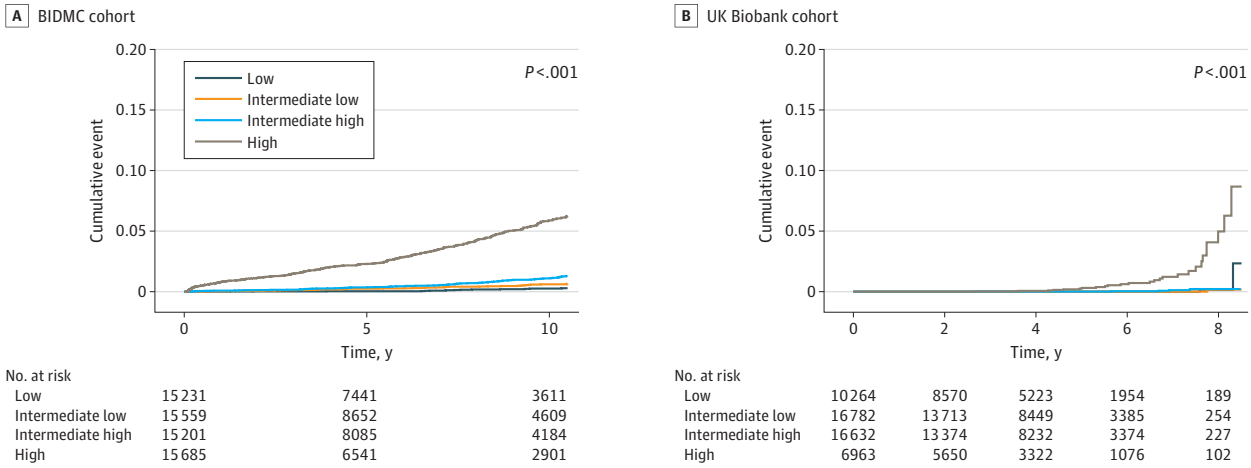
AIRE-CHB Compared With ECG Morphology for Prediction of Incident CHB

In Cox models, we compared AIRE-CHB with bifascicular block on the ECG with and without age and sex. AIRE-CHB alone was superior to the baseline models (**Figure 3** and eTable 3 in Supplement 1). Addition of the baseline variables to AIRE-CHB did not improve overall performance (eTable 3 in Supplement 1). In an exploratory analysis, we evaluated the performance of a Cox model using age, sex, PR interval, and QRS

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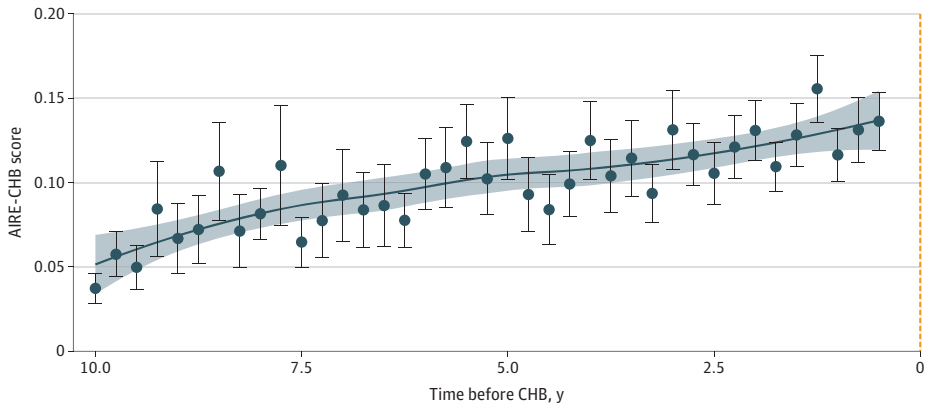
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Figure 1. Artificial Intelligence–Enhanced Electrocardiography Risk Estimator for Complete Heart Block (AIRE-CHB) Prediction of Incident CHB



AIRE-CHB stratified risk of incident CHB in the Beth Israel Deaconess Medical Center (BIDMC) (A) and UK Biobank (B) cohorts. Kaplan-Meier curves show cumulative probabilities of complete heart block for the 4 quartiles of risk defined by AIRE-CHB predictions using a single ECG.

Figure 2. Change in Artificial Intelligence–Enhanced Electrocardiography Risk Estimator for Complete Heart Block (AIRE-CHB) Scores Before the Development of CHB



The AIRE-CHB score is a continuous value denoting risk of AI-ECG predicted risk of CHB. The dashed line indicates the first time of CHB diagnosis. The AIRE-CHB scores with 95% CIs are presented in bins of 90 days. AIRE-CHB scores increase on average over time before the diagnosis of CHB.

duration (eTable 4 in Supplement 1) and found reduced performance compared with AIRE-CHB, particularly in participants 65 years or younger.

AIRE-CHB and Incident Complete Heart Block in Participants With Syncope

We studied a group of patients from the BIDMC test set who had ECGs performed in the emergency department and a history of syncope in the preceding 30 days (n = 2417). In individuals with an event (n = 17) or at least 1 year of follow-up, AIRE-CHB discriminated risk of a diagnosis of CHB within 1 year with an AUROC of 0.832 (95% CI, 0.743-0.908). Using binary AIRE-CHB predictions, sensitivity and specificity were 0.706 (95% CI, 0.440-0.897) and 0.835 (95% CI, 0.819-0.849), respectively. In contrast, the presence of bifascicular block (n = 108) had an AUROC of 0.626 (95% CI, 0.515-0.734) and sensitivity and specificity of 0.294 (95% CI, 0.103-0.560) and 0.957 (95% CI, 0.948-0.965) respectively. Further comparisons and metrics, including AUPRC, PPV, NPV, and Brier score, are reported in eTable 5 in Supplement 1.

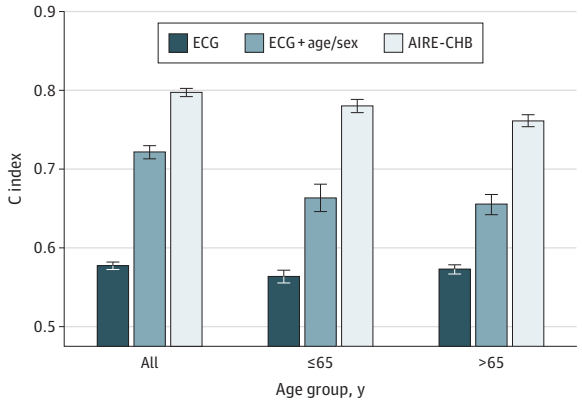
Association of Explainable ECG Morphologies With AIRE-CHB Predictions

We used 3 approaches to explore ECG morphologies associated with AIRE-CHB scores. First, using a VAE, we visualized the ECG morphologies most strongly associated with AIRE-CHB scores (**Figure 4**A). Second, we visualized using median beats the 10 000 ECGs with the highest and lowest AIRE-CHB predictions (Figure 4B). Third, we used linear regression of standard ECG parameters and morphologies (PR interval, QRS duration, QTc interval, and LBBB and RBBB morphologies) to predict AIRE-CHB scores (eFigure 5 in Supplement 1).

These analyses demonstrate broader, more LBBB morphology QRS complexes as important factors in AIRE-CHB predictions. The PR interval was also an important factor. The

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Figure 3. Artificial Intelligence–Enhanced Electrocardiography Risk Estimator for Complete Heart Block (AIRE-CHB) Compared With Baseline Models in Predicting Incident CHB



AIRE-CHB was compared with Cox models including ECG criteria for bifascicular block and with age and sex. Subgroups of patients 65 years and younger and those older than 65 years were also compared. AIRE-CHB had higher C indexes in all groups. Error bars indicate 95% CI.

linear regression of standard ECG parameters and morphology had limited ability to predict AIRE-CHB (R^2 = 0.351).

Discussion

In this article, we describe AIRE-CHB, a novel AI-ECG model for detection of incident CHB. AIRE-CHB is superior to ECG risk markers used in current practice for risk stratification of CHB. Through comprehensive explainability analyses, we have demonstrated the physiological plausibility of our findings.

Clinical Applications

Current international guidelines offer limited guidance for risk stratification of patients at risk of CHB. Bifascicular block is recognized as a higher-risk phenomenon, but current clinical guidelines allow for a range of management strategies, including clinical observation, electrophysiology study, implantable loop recorders, or empirical PPM, with limited guidance on choosing between these potential options.[7] Bifascicular block also has limited performance as a risk-stratification criterion.[14] Existing ECG-based risk stratification is built on crude human-crafted morphological assessment and likely misses the substantial information on the conduction system contained in the ECG. Clinical risk factors for AV block have been identified,[15-21] but only limited work has been done using the ECG[22,23] and clinically useful risk scores have not been developed.

We have shown AIRE-CHB has the ability to risk stratify individuals, both on a population level and more selected populations, including those with syncope. The AIRE platform, including AIRE-CHB, could be applied to patients presenting with syncope to identify those most likely to have intermittent CHB. For example, where AIRE-CHB predicts very high risk, an electrophysiologic study for PPM consideration could be recommended, moderate risk could warrant an electrophysiologic study or prolonged rhythm monitoring, and the lowest-risk cases could have conservative management. In this way, a more objective risk stratification–guided approach could be adopted.

Additionally, AIRE-CHB could be applied opportunistically in individuals having an ECG for any reason. In participants identified as having a very high risk of atrioventricular block, further investigation with ambulatory monitoring, an implantable loop recorder, or an electrophysiology study could be recommended to facilitate early PPM implantation where appropriate. This approach requires prospective evaluation but has the potential to prevent cases of significant injury or death due to CHB or ventricular standstill.

AIRE-CHB Score Is a Biomarker of Conduction Disease

Our analyses demonstrate increasing AIRE-CHB score in participants who go on to develop CHB. This suggests AIRE-CHB score is a biomarker of underlying conduction disease that could be tracked over time. For example, in individuals with a stable AIRE-CHB score, a conservative approach may be favored, while progression may suggest further intervention such as an implantable loop recorders or empirical PPM implantation could be beneficial. Additionally, given the associations between obesity, diabetes and blood pressure, and AV block, elevated AIRE-CHB scores could prompt lifestyle changes that may slow or halt progression to high-grade AV block. Furthermore, physical activity has been shown to be protective for AV block.[16] Recent work has shown the value of communicating cardiovascular risk to patients to motivate lifestyle change[24]; similarly AIRE-CHB scores could be used to motivate patients to increase physical activity and improve lifestyle.

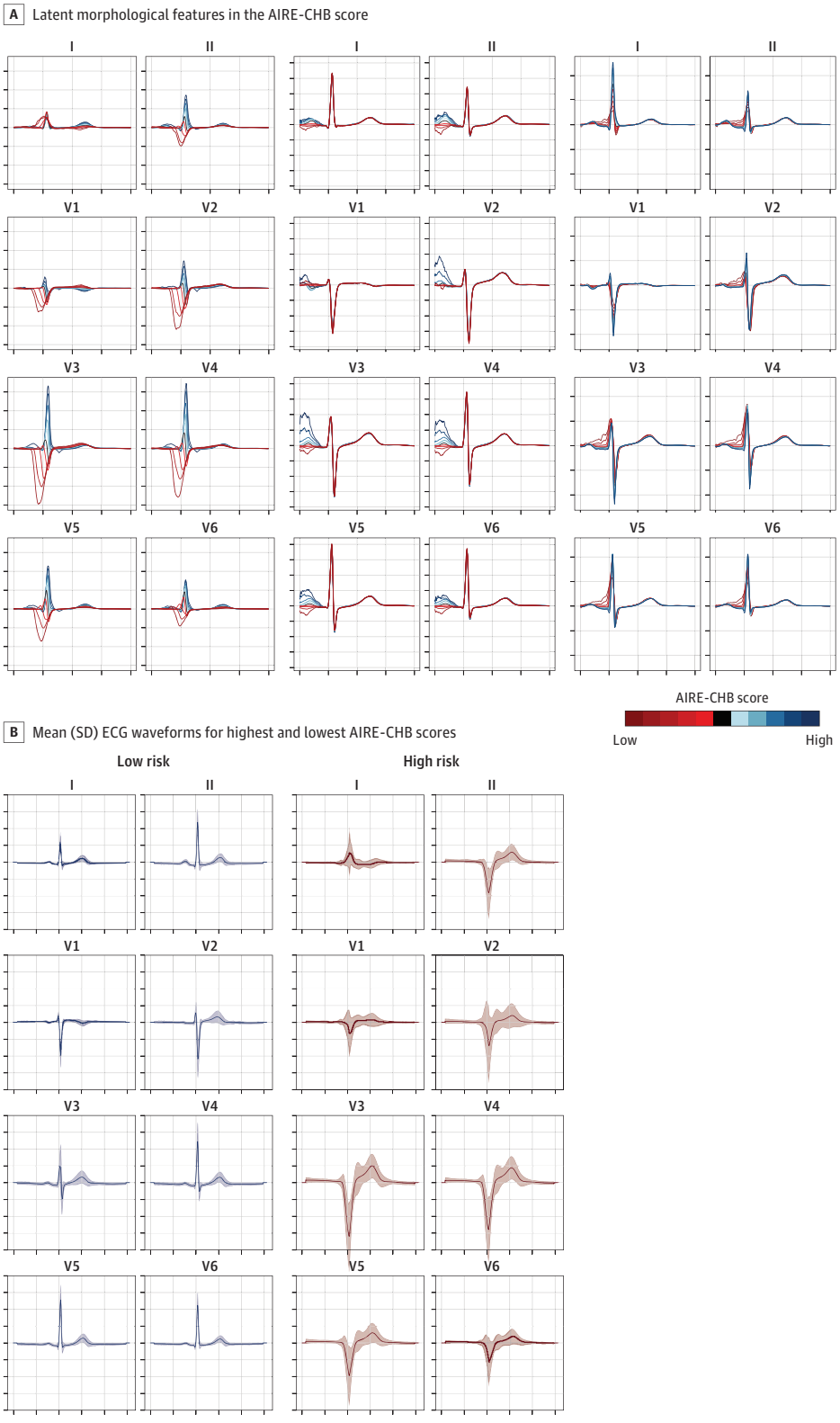
Detailed explainability analyses have highlighted plausible ECG features associated with AIRE-CHB predictions. Our findings are consistent with the literature and show the importance of QRS duration and morphology as well as PR interval.[25] Importantly, simple linear combinations of established ECG parameters and morphology had limited ability to predict the AIRE-CHB score.

Limitations

The inherent limitations to epidemiological real-world studies are the accuracy of coded outcomes within the clinical datasets. CHB was defined using *ICD* codes, which may lack granularity, and we were not able to evaluate the sensitivity and specificity of the *ICD* codes for CHB in the study cohort. Because of this lack of granularity, we chose to evaluate model performance at predicting CHB and not other forms of high-grade AV block (eg, Mobitz II), which may also warrant pacemaker implantation. Reassuringly, sensitivity analyses using CHB or PPM implantation (using procedure codes) as the outcome of interest yielded similar results. Model PPV was modest, which is unsurprising given the very low event rate and the dependence of PPV on disease prevalence, or in this case incidence.[26] The very high NPV would support reassurance for a large number of low-risk individuals. While AIRE-CHB has been internally and externally validated in a significant number of participants, its

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Figure 4. Explainability Analyses



A, A variational autoencoder was used to identify the most important morphological features in Artificial Intelligence–Enhanced Electrocardiography Risk Estimator for Complete Heart Block (AIRE-CHB) score; each subpanel shows 1 of 2 latent features. B, Mean (SD) ECG waveforms for the 10 000 highest and lowest AIRE-CHB scores from the Beth Israel Deaconess Medical Center test set.

performance across diverse populations and clinical settings remains to be fully explored. Despite these limitations, we have demonstrated that AIRE CHB is effective at predicting incident CHB.

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Conclusions

In this study, a first-of-its-kind deep learning model identified the risk of developing incident CHB. Through detailed explainability and biological plausibility analyses, we demonstrated the model is credible. AIRE-CHB could be used in diverse settings to aid in decision-making for participants with syncope or at risk of high-grade AV block.

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Author Contributions: Drs Sau and Ng had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Sau, Zhang, Barker, Pastika, El-Medany, Khattak, Kramer, Ng.
Acquisition, analysis, or interpretation of data: Sau, Zhang, Barker, Pastika, Patlatzoglou, Zeidaabadi, El-Medany, McGurk, Sieliwonczyk, Ware, Peters, Kramer, Waks.
Drafting of the manuscript: Sau, Zhang, Barker, El-Medany, Ng.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Sau, Zhang, Pastika, Patlatzoglou, Zeidaabadi, Sieliwonczyk.
Obtained funding: Sau, Pastika, Ware, Peters, Ng.
Administrative, technical, or material support: Sau, Barker, Pastika, Ware, Kramer, Waks.
Supervision: Ware, Peters, Kramer, Ng.

Conflict of Interest Disclosures: Dr Sau reported a patent for AI-ECG methods pending. Dr Pastika reported a patent for AI methods pending. Dr Zeidaabadi reported a patent for AI-ECG methods pending. Dr El-Medany reported a clinical research fellowship from Chelsea and Westminster NHS Foundation Trust during the conduct of the study. Dr Ware reported consulting for MyoKardia, Pfizer, Foresite Labs, Health Lumen, and Tenaya; research support from Bristol Myers Squibb; and being a founder with equity from Saturnus Bio outside the submitted work. Dr Kramer reported previously serving on the advisory board for HeartcoR Solutions, for whom they remain an independent consultant. Dr Waks reported fees from HeartcoR Solutions for core lab work and as a former member of their advisory board, grants from Anumana for research funding, and consultant fees from Heartbeam outside the submitted work. Dr Ng reported speaking fees from GE Healthcare and consulting fees from Astra-Zeneca during the conduct of the study and having a patent for AI-ECG methods pending. No other disclosures were reported.

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Data Sharing Statement: See Supplement 2.

Additional Contributions: This research has been conducted using the UK Biobank resource under application numbers 48666 and 47602. We thank the InSIGHT Core in the Center for Healthcare Delivery Science at Beth Israel Deaconess Medical Center for assistance in obtaining primary data.

Additional Information: The programming code relating to these analyses will be made available on request to the corresponding author.

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