# Rationale and design of the SafeHeart study: Development and testing of a mHealth tool for the prediction of arrhythmic events and implantable cardioverter-defibrillator therapy

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**BACKGROUND** Patients with an implantable cardioverter-defibrillator (ICD) are at a high risk of malignant ventricular arrhythmias. The use of remote ICD monitoring, wearable devices, and patient-reported outcomes generate large volumes of potential valuable data. Artificial intelligence–based methods can be used to develop personalized prediction models and improve early-warning systems.

**OBJECTIVE** The purpose of this study was to develop an integrated web-based personalized prediction engine for ICD therapy.

**METHODS** This international, multicenter, prospective, observational study consists of 2 phases: (1) a development study and (2) a feasibility study. We plan to enroll 400 participants with an ICD (with or without cardiac resynchronization therapy) on remote monitoring: 300 participants in the development study and 100 in the feasibility study. During 12-month follow-up, electronic health record data, remote monitoring data, accelerometry-assessed physical behavior data, and patient-reported data are collected. By using machine- and deep-learning approaches, a prediction engine is developed to assess the risk probability of ICD therapy (shock and antitachycardia pacing). The feasibility of the prediction engine as a clinical tool, the SafeHeart Platform, is assessed during the feasibility study.

**RESULTS** Development study recruitment commenced in 2021. The feasibility study starts in 2022.

**CONCLUSION** SafeHeart is the first study to prospectively collect a multimodal data set to construct a personalized prediction engine for ICD therapy. Moreover, SafeHeart explores the integration and added value of detailed objective accelerometer data in the prediction of clinical events. The translation of the SafeHeart Platform to clinical practice is examined during the feasibility study.

**KEYWORDS** Accelerometry; Artificial intelligence; Implantable cardioverter-defibrillator; Prediction model; Wearable

(Cardiovascular Digital Health Journal 2021;2:S11–S20) 

## Introduction

Implantable cardioverter-defibrillator (ICD) implantation is the cornerstone of the prevention of sudden cardiac death through the termination of ventricular arrhythmias for either primary prevention or secondary prevention.[1] Despite improvements in pharmacological and nonpharmacological treatments,[2,3] a meta-analysis of 5 clinical trials with 5516 participants showed that 18% received appropriate ICD therapy and 10% received inappropriate ICD therapy during an average follow-up time period of 2.4 years.[4] Aside from the potential harm related to ICD shock on the myocardium itself, ICD therapy has an adverse psychological impact

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 https://doi.org/10.1016/j.cvdhj.2021.10.002

and may reduce quality of life (QoL).[5] Also, ICD therapy—both appropriate and inappropriate—poses a burden on clinical staff and affects health care expenditure.[6] Several risk prediction and stratification models have been developed to assess the risk of ICD therapy (Online Supplemental Appendix Table A1). External validation of 3 previously developed risk stratification models for benefit of ICD implantation (ie, risk of death before first ICD intervention) rendered C statistics between 0.66 and 0.75.[2,7–9] The recently published Multicentre Autonomic Defibrillator Implantation Trial-ICD and The Dutch outcome in ICD therapy prediction scores have demonstrated similar discriminative performance; the external validation of both scores yielded C statistics of 0.75 and 0.60, respectively.[2,10] Although these models could aid in the risk stratification for ICD implantation, there are considerable differences in these models in terms of the included variables and predictive performance. Also, these aforementioned scores are merely based on clinical variables marked by significant collinearity and lack the ability for real-time prediction of arrhythmic events.

In addition to conventional patient data (eg, electrocardiography, imaging, laboratory biomarkers, and medical history), the digital health landscape is increasingly shaped by the continuous collection of health data through wearable devices and telehealth and mHealth apps. The increasing availability of and expertise in analytical techniques based on artificial intelligence (AI), such as machine learning and deep learning, enable the analysis of multiple time series data.[11] By leveraging these AI-based techniques and exploiting various novel data sources (eg, wearable devices, remote device monitoring, and patient-reported outcomes), we aim to develop a prediction algorithm for ICD therapy integrated into a web-based clinician's dashboard. Together with data from a patient app, wearable accelerometry, and remote ICD monitoring, this constitutes the SafeHeart Platform: an early warning system for the prediction of ICD therapy, alarming 30 days in advance; and a clinical decision support system that informs the clinician of the most important parameters affecting the likelihood of an event.

## Methods

### Study design

The SafeHeart study is an international, multicenter, prospective, observational study consisting of 2 phases: (1) a development study and (2) a feasibility study. A total of 400 participants with an ICD or cardiac resynchronization therapy with defibrillator (CRT-D) will be enrolled: 300 in the development study and 100 in the feasibility study. During the 12-month development study, data are collected from 4 sources: (1) electronic health records (EHRs), (2) remote ICD monitoring data, (3) wearable accelerometry, and (4) patient-reported outcome measures. The study flow chart can be seen in Figure 1. A prediction algorithm will be developed that provides the probability of impending ICD therapy (shock or antitachycardia pacing [ATP]) and displays the feature importance for each individual prediction trigger. Subsequently, during the 6-month feasibility study, the clinical utility, acceptability, safety, and feasibility of the SafeHeart Platform is assessed by exploiting both quantitative and qualitative methods from the perspectives of clinicians and participants. The feasibility study is not designed to specifically evaluate the outcome of interest—the prediction accuracy of the primary end point—but investigates the potential for the translation of the SafeHeart Platform to clinical practice (Figure 2).

### Study setting

The study is conducted at 2 cardiology departments at university hospitals in the Netherlands (Amsterdam University Medical Center location Academic Medical Center, University of Amsterdam) and Denmark (Copenhagen University Hospital-Rigshospitalet). Ethics approval was obtained at the 2 participating institutions, and the study is conducted in accordance with the Declaration of Helsinki as revised in 2013. The study is registered at the National Trial Registration in the Netherlands (Trial NL9218; https://www.trialregister.nl). Informed consent will be obtained for all participants.

### Participant selection

In order to have sufficient events in our patient cohort, we aim to target the ICD carriers that are at a high risk of therapy, that is, patients who have already experienced an arrhythmia event or received (in)appropriate therapy. Therefore, the following eligibility criteria are applied:

*Inclusion criteria*

- ICD or CRT-D implantation for either primary or secondary prevention less than 5 years before enrollment
- Having received appropriate or inappropriate ICD therapy or proof of ventricular arrhythmias in the last 8 years before enrollment
- Participation in the remote monitoring program
- Participant 18 years or older

*Exclusion criteria*

- Life expectancy of less than 1 year
- Participants with circumstances that prevent follow-up (emigration, change of hospital for follow-up, and dropping out of the remote monitoring program)
- Participants who are unable to wear the accelerometer wristband (eg, allergic to the material)
- Clinically unstable participants
- End stage of heart failure (New York Heart Association [NYHA] class IV)
- Participants unable to complete a questionnaire
- Participants who do not understand the local language (Dutch or Danish)
- Serious physical disability (eg, wheelchair bound)
- Planned ablation for ventricular tachycardia (VT)
- Significant movement disorder (ie, hemiplegia or Parkinson disease or similar)

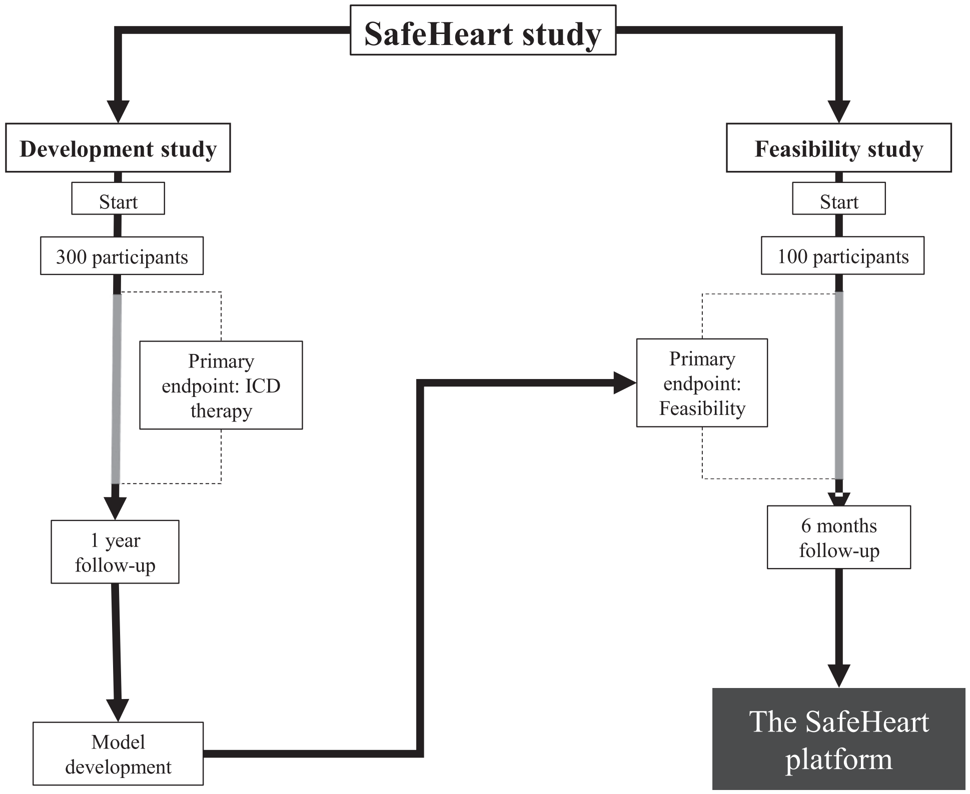


**Figure 1** Study flowchart of the SafeHeart study. ICD = implantable cardioverter-defibrillator.

- Unwillingness to participate

The study population for the development study and feasibility study is similar applying the same inclusion and exclusion criteria, but participants are allowed to take part in 1 of the 2 studies only.

## Study end points

The primary study end point during the development study is a composite of both appropriate and inappropriate ICD therapies (defibrillator shock or ATP). Secondary end points include appropriate ICD therapy alone, heart failure–related hospitalization, supraventricular arrhythmia onset, and

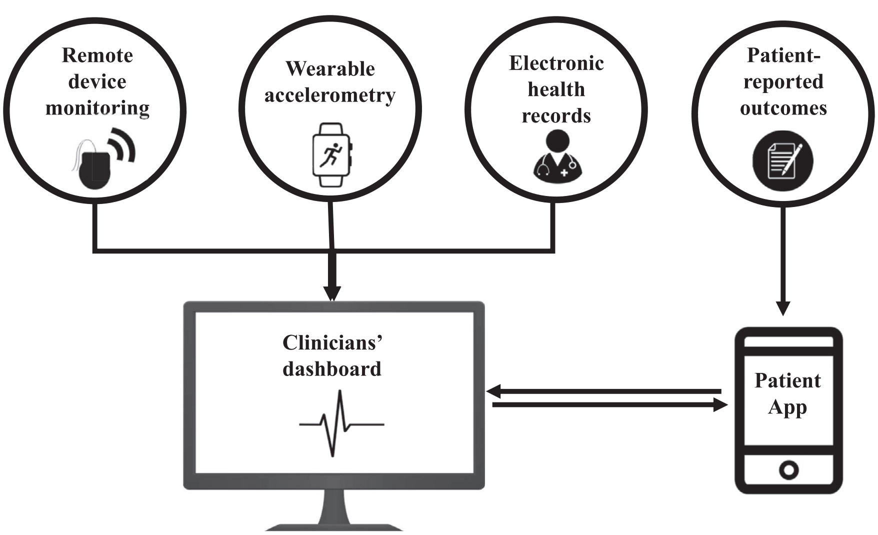


**Figure 2** The SafeHeart Platform.

**Table 1** Data sources and variables in the SafeHeart study

| Modality | Source | Baseline/time-varying data | |
|---|---|---|---|
| | | Baseline (static) | Dynamic (temporally varying) |
| Clinical data | Electronic health records | • Demographic variables<br>• Left ventricular functionality<br>• (Cardiac) history<br>• Comorbidities<br>• Medication usage<br>• Genetic predisposition<br>• Diagnostic imaging, ECG<br>• Laboratory examination | • Worsening of LV functionality<br>• Change in medication<br>• Heart failure hospitalization<br>• MACE<br>• Change in laboratory examinations |
| Remote monitoring | Research database (all vendors included) | N/A | • (Transient) ventricular arrhythmia<br>• Supraventricular arrhythmia onset/burden<br>• Pacing percentages<br>• Device diagnostics<br>o Device-measured activity<br>o Fluid index<br>o Heart rate variability* |
| Physical behavior | Wearable accelerometry | • N/A | • Worsening of functional capacity<br>• Lifestyle changes<br>• Change in rest-activity patterns<br>• Sleep behavior changes |
| • Patient-reported outcomes | • Participant diary<br>• Questionnaires (EQ5D-5L, KCCQ) | • NYHA class at baseline | • Symptomatic heart failure<br>• Quality of life over time |

ECG = electrocardiography; EQ5D-5L = European Quality of Life Scale- 5 Dimensions- 5 Levels; KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricular; MACE = major adverse cardiac events; N/A = not available; NYHA = New York Heart Association.
*Availability of these parameters differs per vendor.

mortality. During the feasibility study, the feasibility is assessed on the basis of clinical utility, acceptability, safety, and implementation of the SafeHeart Platform.

## Data collection

Data are collected from 4 data sources during both the development study and the feasibility study: (1) electronic health records, (2) remote ICD monitoring, (3) wearable accelerometry, and (4) patient-reported data as summarized in Table 1.

*Clinical data from EHRs*

Clinical data are collected prospectively from EHRs. Clinical data include demographic characteristics, comorbidities, cardiac history, cardiac imaging examinations, laboratory evaluations, and medications. These data are collected at the time of device implantation, study baseline, and end of follow-up.

*Remote ICD monitoring data*

The second type of data are prospectively collected remote ICD monitoring data, where information is communicated from the ICD or CRT-D device to the health care team in real time by using wireless technology and a Bluetooth-enabled device. Devices from all vendors are used. The metrics include, but are not limited to, the time of transmission, onset of an arrhythmic episode, heart rate, heart rhythm {ie, ventricular arrhythmia (VT, ventricular fibrillation [VF]) and supraventricular arrhythmia}, arrhythmia duration, therapy (shock, ATP, and aborted shocks), device function (lead impedance and battery), and other device-measured metrics (physical activity measured by the device and percentage of pacing). Transmissions sent from the device include scheduled routine device controls and participant-activated or device-activated transmissions.

*Wearable accelerometry data*

Body-worn accelerometers are activity trackers that enable continuous measurement of long-term physical behavior in a free-living environment. Physical behavior encompasses an individual's behavior and activities throughout the day and night, including physical activity (intensity, frequency, volume, and type), gait, posture, sleep behavior, and rest-activity patterns.[12] Raw data are collected from the accelerometers, after which open and proprietary algorithms are applied for the conversion of raw data into specific metrics such as sleep time, sleep efficiency, sleep duration, time spent in moderate-to-vigorous physical activity, and sedentary time (Table 2). In this study, accelerometry data are collected through research-grade, wrist-worn, triaxial accelerometers: GENEActiv and Activinsights Band (Activinsights Ltd., Kimbolton, UK; specifications of both wearables are displayed in Table 3).[13] Unlike GENEActiv, the Activinsights Band accelerometer is compatible with a mobile application that will facilitate real-time data collection, making it suitable for integration within the SafeHeart Platform.

**Table 2** Taxonomy of digital clinical measures derived from wrist-worn accelerometry for the SafeHeart study

| Measure class and description | Digital clinical measures |
|---|---|
| *Seconds/minutes* | |
| Data characterization measures | |
| Statistical measures calculated from raw sensor data over short periods of time (events) | • Acceleration magnitude<br>• Principal frequency<br>• Arm elevation and wrist rotation (mean, variance, and MAD)<br>• Step interval<br>• Mean environment light<br>• Near body temperature |
| Behavioral and physiological classification measures | |
| Behavior measures inferred from characterized data events using models, heuristics, and meta-data | • Sleep, inactive, and sitting/lying<br>• Standing, active, walking, and exercising bouts |
| *<1 d (including nocturnal and diurnal separation)* | |
| Short-term summary measures | |
| Summaries of<br>• data characteristics or<br>• behavioral and physiological classifications | • Sit-to-stand transitions<br>• Mean activity intensity |
| Daily summary measures | |
| Summaries of<br>• data characteristics or<br>• behavioral and physiological classifications | • Sedentary/light/moderate/vigorous time<br>• Six-minute maximum intensity<br>• Daytime sleep<br>• Total steps per day<br>• High cadence steps<br>• Entropy<br>• Sleep onset and rise times<br>• Mid-sleep time<br>• Sleep duration and efficiency<br>• Sleep interruption and fragmentation<br>• Wear time |
| *Multiple days* | |
| Long-term summary measures | |
| Summaries of<br>• data characteristics or<br>• behavioral and physiological classifications | • Rest-activity rhythm (acrophase, mesor, amplitude, and robustness)<br>• Sleep and activity level trends<br>• Sleep duration variability |
| *Months* | |
| Population measures | |
| Statistics describing<br>• distribution of data characteristics<br>• behavioral and physiological classifications<br>• summary measures for a population | • Activity intensities<br>• Step cadence and sleep parameters by age, sex, clinical history, and self-reported quality of life |

Acrophase = time of peak activity; amplitude = range of activity; MAD = mean amplitude deviation; mesor = mean activity.

### *Patient-reported outcomes*

The fourth data type is patient-reported outcomes consisting of 2 questionnaires and participants' diaries. The questionnaires are the generic health-related European Quality of Life Scale- 5 dimensions-5 levels and the disease-specific Kansas City Cardiomyopathy Questionnaire filled out at baseline and at 6-month intervals.[14,15] The European Quality of Life Scale- 5 dimensions-5 levels questionnaire assesses the patient-reported health status and consists of 5 domains—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression—along with a visual analog scale where participants rate their health on a scale of 0 (worst score) to 100 (best score). The Kansas City Cardiomyopathy Questionnaire is a questionnaire specifically developed to assess the health-related QoL in participants diagnosed with cardiomyopathy. It consists of 23 items and domains (symptoms, physical limitations, self-efficacy, QoL, symptom stability, and social limitation). Participants' diaries concerning self-reported cardiac symptoms (eg, vertigo, palpitations, and chest pain), weight, and blood pressure (if available through private possession of a measuring device) will be collected together with the wearables biweekly during the development study and electronically retrieved during the feasibility study. A 2-week sleep diary is also completed by the participant at 3 time points during the development study.

## Follow-up

Follow-up is done periodically in the outpatient department or by telephone interview every 6 months. During these follow-ups, changes in medication use and NYHA class will be evaluated and participants will be asked to fill out QoL questionnaires. The primary and secondary end points are evaluated by the investigator through monitoring of EHRs (Table 4).

## Prediction algorithm development

The SafeHeart prediction algorithm is an extension of a predecessor model developed from a larger data set that

**Table 3** Wrist-worn wearable accelerometers used in the SafeHeart study

| | Use during the SafeHeart study | Sensor output | Size and weight | Data analytics | Data extraction | Battery life |
|---|---|---|---|---|---|---|
|  | *GENEActiv*<br>Development study (0–6 mo) | Acceleration between 10 and 100 Hz, near body temperature, and light exposure | 40 mm wide × 13 mm deep, 27 g | Raw data measurement. Features and measures can be created with standard time-domain statistics, frequency domain approaches, pattern/structure detection, or dedicated algorithms | Via a USB connection | Can record data continuously for 1 wk and 1 mo depending on the sample frequency |
|  | *Activinsights Band*<br>Development (6–12 mo) and feasibility study | Behavioral event output (eg, sit, stand, walk, and sleep) | 23 mm wide × 13 mm deep, 25 g | Infer time spent in a range of behavioral states using algorithms | Wirelessly to a computer or phone | Can record and communicate data continuously for up to 1 y |

**Table 4** Overview of data collection during the SafeHeart study

| | Retrospective | Prospective | | | | |
|---|---|---|---|---|---|---|
| Variable | T1 (implantation) | T0 (baseline) | T1a (reaching of the study end point) | T1b (6-mo FU) | T1a (reaching of the study end point) | T2 (12-mo FU) |
| Informed consent | | ✓ | | | | |
| Demographic characteristics | | ✓ | | | | |
| Medication log | ✓ | ✓ | ✓ | | ✓ | ✓ |
| Clinical history | ✓ | ✓ | | | | |
| Blood samples | ✓ | | ✓ | | ✓ | |
| Cardiac imaging and diagnostics* | ✓ | | ✓ | | ✓ | |
| Implant characteristics† | ✓ | | | | | |
| Device characteristics (eg, model) | ✓ | | | | | |
| Device settings/programming | ✓ | ✓ | ✓ | | ✓ | ✓ |
| NYHA class | ✓ | ✓ | | | | ✓ |
| EQ5D-5L | | ✓ | | | | ✓ |
| Kansas City Cardiomyopathy Questionnaire | | ✓ | | ✓ | | ✓ |
| Patient-reported outcomes | | ✓ | | ✓ | | ✓ |
| Remote monitoring | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| GENEActiv wearable | | | ✓ | | | ✓ |
| Activinsights Band wearable | | | | ✓ | ✓ | ✓ |
| Clinical events | | ✓ | ✓ | ✓ | ✓ | ✓ |

EQ5D-5L = European Quality of Life Scale- 5 dimensions-5 levels; FU = follow-up; NYHA = New York Heart Association.

*For instance, electrocardiography, exercise electrocardiography, echocardiography, coronary angiography, and cardiac magnetic resonance imaging.

†Procedure times, adverse events, vitals, etc.

consisted of 11,921 transmissions from 1251 participants with an ICD, followed over a 4-year period from 2015 to 2019 at Copenhagen University Hospital-Rigshospitalet. This model was trained on transmission data from remote device monitoring to predict the risk of VT and VF. The data set contained 74,149 arrhythmia episodes, each characterized by 7 variables such as the type of arrhythmia (eg, VT, VF, supraventricular tachycardia, and atrial fibrillation), ICD treatment of the arrhythmia, duration of the episode, and maximum heart rate reached during the episode. The random forest machine learning prediction method provided optimal results compared with other classifier methods (supervised, unsupervised, and deep learning methods) when considering the trade-offs between model performance and explainability. Other models tested included KNeighborsClassifier, GradientBoostingClassifier, AdaBoostClassifier, SVC (Support Vector Classifier), and LSTM (Long Short-Term Memory) neural network. The algorithm was subsequently tested on 2342 of the transmissions, achieving an accuracy of 0.96 with a positive predictive value of 0.67 and a negative predictive value of 0.97 for the prediction of VT and VF 30 days in advance. In the SafeHeart study, this previously developed model is expanded with prospectively collected data during the development study to assess and improve the predictive performance. The aim is to fix the prediction model for the feasibility testing. In the present study, multiple models, including those previously examined, will be evaluated on the basis of several aspects: accuracy, explainability, and generalizability, and the best performing model will be used for the further development of the SafeHeart Platform. For the development of the SafeHeart prediction model, we will use data previously gathered from transmissions and enhance this with prospectively enriched data sources: accelerometry, the electronic health records, and patient-reported outcomes derived from questionnaires. This will allow the evaluation of the previous model using the new data as well as testing the new model on the original data containing only transmission data. The end product of the development study is a new prediction model. In case of a new testing and validation of the new data set during the development study, we will use repeated random splits of the data into training and test data sets.

After the development study, we will use the best performing model and validate it in a fixed feasibility study with 100 patients in total.

## Sample size

As proposed by Figueroa et al,[16] the sample size calculation for prediction algorithms can be estimated using weighted fitting of learning curves on a smaller annotated training set. However, in this early exploratory study where novel data are added to an existing model of which the predictive value is uncertain, it is unrealistic to accurately define the required sample size. With regard to the primary end point (ICD therapy), the number of days of accelerometer data collection is critical for sample size estimation. A prior study by Almehmadi et al[17] demonstrated a cumulative incidence of appropriate ICD therapy (ATP and shock) of 28.5% at 1 year after de novo ICD implantation for secondary prevention. With respect to inappropriate ICD therapy, in a combined primary and secondary prevention ICD patient cohort, a cumulative incidence of 7% was seen for inappropriate ICD shock in the first year after implantation.[18] Therefore, we assume an incidence of the primary end point of total ICD therapy—both appropriate and inappropriate ICD therapies—of 25% (equivalent to a daily incidence of 0.0685%). With a targeted sensitivity of 95%, a total of 106,580 days of accelerometer data is required, met by following 292 patients for a year. Considering the 300 patients included in the development study alone, we exceed the minimum required sample size. In addition to accelerometry data, we expect to collect up to 3000 transmissions from remote device monitoring, 900 patient-reported outcome data points, and a minimum of 40 clinical variables from the EHR (eg, sociodemographic, medication usage, and comorbidities).

### Statistical analysis and covariates

The model performance is evaluated on the basis of the accuracy, sensitivity (recall), specificity, positive predictive value (precision), negative predictive value, and the area under the curve. The accuracy of the models is compared using a 2-sided McNemar test, and a 1-sided binomial test is used to test model performance compared to baseline class probabilities. The significance level is initially set to .01. The covariates added to the models include demographic characteristics (eg, age and sex), medication usage (eg, digoxin, angiotensin receptor blocker/angiotensin-converting enzyme inhibitor, β-blocker, and aldosterone), severity of heart failure (eg, NYHA class, left ventricular ejection fraction [LVEF], and number of hospitalizations per year), comorbidities (eg, hypertension, renal disease, frequency of nonsustained VTs, atrial fibrillation, peripheral artery disease, and diabetes mellitus), left ventricular functionality (eg, LVEF and synchronicity of myocardial contraction), presence of cardiomyopathy, presence of late gadolinium enhancement, vital parameters (eg, blood pressure, weight, and heart rate), laboratory findings (eg, estimated glomerular function rate, sodium, and potassium), and accelerometry-assessed physical behavior.[19,20]

## Results

Ethics approval was obtained on December 18, 2020, and recruitment commenced in 2021. Complete recruitment for the development study is believed to be reached by 2022. Initiation of the feasibility study will begin thereafter.

## Discussion

This article outlines the rationale and design of a prospective international study aimed to develop a multimodal prediction algorithm facilitating real-time personalized prediction of ICD therapy. The integration of the prediction algorithm in a web-based clinician's dashboard (SafeHeart Platform) serves as an early warning system and clinical decision support system that identifies participants at risk of developing life-threatening arrhythmia in time to enable preventive intervention such as medicine alterations or device (re)programming. Also, clinical decision support is achieved through display of critical factors that increase the participant's risk of ICD therapy and prioritization of incoming participants' data from the remote ICD monitoring system. Over the past decade, there has been a steep increase in the number of AI studies, albeit prospective validation of the actual benefit of these AI tools is often lacking.[21,22] Instead, the focus has predominantly been on accuracy and validation, without answering the question of whether the AI tools have achieved an expected change in clinical practice.[23] The choice of a 2-phased prospective study combining algorithm development and clinical feasibility testing was therefore designed in order to safeguard the clinical applicability of the SafeHeart Platform.

Accelerated by the wide implementation of telemonitoring and the increasing popularity of consumer-lead and research-grade wearable devices over the past decade, novel data streams have become available for the prediction of clinical events. In addition, contemporary ICD devices are equipped with sensors that can capture specific metrics (eg, thoracic impedance, respiration, and heart sounds), including an accelerometer capable of capturing physical activity.[24] Several studies have demonstrated the potential of algorithms on the basis of remote ICD monitoring data for the prediction of heart failure events.[24–26] Exploiting a combination of both static and dynamic variables as input to an AI-based prediction algorithm for ICD therapy has been examined by Wu et al,[27] who showed that the incorporation of both baseline and dynamic (temporally varying) parameters in a random forest statistical method for the prediction of appropriate ICD therapy rendered better model performance compared to a model based on baseline predictors alone. Regarding the predictive value of accelerometry data specifically, a random forest model for the prediction of impending electrical storms by Shakibfar et al[28] demonstrated ICD-measured physical activity to be among the most relevant features. However, ICD-embedded accelerometers are limited by their ability to capture only "time being active" as a sole parameter, instead of the broader concept of short-term and long-term physical behaviors (eg, sit-to-stand transitions, rest-activity patterns, sleep and activity level trends, and sleep duration variability) captured by wearable accelerometers. Prior studies have shown that wearable accelerometer–derived metrics correlate with LVEF,[29] QoL,[30] and an increased risk of hospitalization and mortality in patients with advanced heart failure.[31] Amplified by advances in the field of AI, SafeHeart aims to expedite and improve real-time prediction of ICD therapy by using static and dynamic variables including both high-quality accelerometer-derived metrics and remote ICD monitoring data on top of clinical and patient-reported outcomes.

### Strengths and limitations

SafeHeart is the first study to predict ICD therapy by applying AI on multimodal data in a live clinical setting. Apart from clinical expertise, third-party expert knowledge in the field of wearable accelerometry and digital health technology development is used. An important limitation to the study could be suboptimal compliance with the wearables; however, prior studies have indicated high compliance with accelerometers when used for shorter time periods than in our study.[32] It is yet uncertain what noncompliance rate generally applies specifically to a population with an ICD. Furthermore, SafeHeart examines a high-risk population, potentially limiting the generalizability to primary prevention patients or lower risk patients. Related to this, the power to predict arrhythmia is dependent on the occurrence and distribution of clinical end points between participants in this specific patient population. A sample size calculation was made on the basis of expected event rates, but the risk remains of receiving few end points aggregated in the same few participants affecting the generalizability of the results. Last, although AI-based prediction tools have clear advantages over more classical statistical models in terms of accuracy, these "black-box algorithms" are limited in their interpretability, which hinders clinical application. Through the display of feature relevance, presenting reasons for an alarm being triggered and use of the local interpretable model-agnostic explanation procedure, more insight into the algorithm is given.

## Conclusion

The SafeHeart study is the first to prospectively develop a platform consisting of a patient app, remote device monitoring, wearable accelerometry, and a clinician's dashboard. The prediction algorithm for ICD therapy is based on a multimodal data set integrating clinical data, remote monitoring, high-resolution accelerometer data, and patient-reported outcomes. Clinical implementation of the results will be facilitated by combining a development and a feasibility study in 1 prospective study design. With the SafeHeart study we aim to provide clinicians with a clinical decision support system that assists in follow-up care for ICD carriers. The SafeHeart study will inform the design of a future randomized controlled trial that compares standard of care to the SafeHeart Platform.

## Acknowledgments

We thank Merijn Hofland, Bsc, clinical automation specialist at Amsterdam UMC, for his help in building the research data infrastructure. We thank the participants of the study. Furthermore, we thank the European Union funding program for research and innovation for the Horizon 2020 (grant number: Eurostars project E!113994- SafeHeart).

## Funding Sources

This research received the specific grant Horizon 2020 from the European Union funding program for research and innovation (grant number: Eurostars project E!113994- SafeHeart; to Drs Tan, Knops, Andersen, Svendsen, and Tjong and Mr Langford). The funding source is not involved in study design; collection, analysis, and interpretation of data; nor writing or publishing of the study.

## Disclosures

Dr Andersen is cofounder of Vital Beats and has stock ownership. He is coauthor of a pending patent application that is within the field of this study. Mr Langford is an employee and shareholder of Activinsights Ltd, the manufacturers of the behavioral assessment wearable used in the study. The rest of the authors report no conflicts of interest.

## Authorship

All authors attest they meet the current International Committee of Medical Journal Editors criteria for authorship.

### Patient Consent

All patients provide written informed consent before inclusion.

### Ethics Statement

The authors designed the study and gathered and analyzed the data according to the Helsinki Declaration guidelines on human research. The research protocol used in this study was reviewed and approved by the institutional review board.

## Appendix

### Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.cvdhj.2021.10.002.

## References

1. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2013; 61:e6–e75.
2. Verstraelen TE, van Barreveld M, van Dessel PHFM, et al. Development and external validation of prediction models to predict implantable cardioverter-defibrillator efficacy in primary prevention of sudden cardiac death. EP Europace 2021;23:887–897.
3. Knops RE, Olde Nordkamp LRA, Delnoy PPHM, et al. Subcutaneous or transvenous defibrillator therapy. N Engl J Med 2020;383:526–536.
4. Aktaş MK, Younis A, Zareba W, et al. survival after implantable cardioverter-defibrillator shocks. J Am Coll Cardiol 2021;77:2453–2462.
5. da Silva KR, Costa R, Rodrigues CG, et al. Quality of life in patients with implantable cardioverter-defibrillator: systematic review of randomized controlled trials. Eur J Cardiovasc Nurs 2018;17:196–206.
6. Sanders P, Connolly AT, Nabutovsky Y, Fischer A, Saeed M. Increased hospitalizations and overall healthcare utilization in patients receiving implantable cardioverter-defibrillator shocks compared with antitachycardia pacing. JACC Clin Electrophysiol 2018;4:243–253.
7. van Rees JB, Borleffs CJW, van Welsenes GH, et al. Clinical prediction model for death prior to appropriate therapy in primary prevention implantable cardioverter defibrillator patients with ischaemic heart disease: the FADES risk score. Heart 2012;98:872–877.
8. Barsheshet A, Moss AJ, Huang DT, McNitt S, Zareba W, Goldenberg I. Applicability of a risk score for prediction of the long-term (8-year) benefit of the implantable cardioverter-defibrillator. J Am Coll Cardiol 2012; 59:2075–2079.
9. Levy WC, Lee KL, Hellkamp AS, et al. Maximizing Survival benefit with primary prevention ICD therapy in a heart failure population. Circulation 2009; 120:835–842.
10. Younis A, Goldberger JJ, Kutyifa V, et al. Predicted benefit of an implantable cardioverter-defibrillator: the MADIT-ICD benefit score. Eur Heart J 2021; 42:1676–1684.

11. Patel B, Sengupta P. Machine learning for predicting cardiac events: what does the future hold? Expert Rev Cardiovasc Ther 2020;18:77–84.
12. Yang CC, Hsu YL. A review of accelerometry-based wearable motion detectors for physical activity monitoring. Sensors (Basel) 2010;10:7772–7788.
13. Professional wearables & accelerometer research watches. Activinsights Web site, https://www.activinsights.com/. Accessed February 24, 2021.
14. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245–1255.
15. Spertus J, Peterson E, Conard MW, et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J 2005;150:707–715.
16. Figueroa RL, Zeng-Treitler Q, Kandula S, Ngo LH. Predicting sample size required for classification performance. BMC Med Inform Decis Mak 2012;12:8.
17. Almehmadi F, Porta-Sánchez A, Ha ACT, et al. Mortality implications of appropriate implantable cardioverter defibrillator therapy in secondary prevention patients: contrasting mortality in primary prevention patients from a prospective population-based registry. J Am Heart Assoc 2017;6:e006220.
18. van Welsenes GH, van Rees JB, Borleffs CJW, et al. Long-term follow-up of primary and secondary prevention implantable cardioverter defibrillator patients. Europace 2011;13:389–394.
19. Bergau L, Tichelbäcker T, Kessel B, et al. Predictors of mortality and ICD shock therapy in primary prophylactic ICD patients—a systematic review and meta-analysis. PLoS One 2017;12:e0186387.
20. Kawakami H, Nerlekar N, Haugaa KH, Edvardsen T, Marwick TH. Prediction of ventricular arrhythmias with left ventricular mechanical dispersion: a systematic review and meta-analysis. JACC Cardiovasc Imaging 2020;13:562–572.
21. Meskó B, Görög M. A short guide for medical professionals in the era of artificial intelligence. NPJ Digit Med 2020;3:126.
22. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med 2019;25:44–56.
23. Lindsell CJ, Stead WW, Johnson KB. Action-informed artificial intelligence—matching the algorithm to the problem. JAMA 2020;323:2141–2142.
24. Whellan DJ, Ousdigian KT, Al-Khatib SM, et al. Combined heart failure device diagnostics identify patients at higher risk of subsequent heart failure hospitalizations: results from PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure) study. J Am Coll Cardiol 2010;55:1803–1810.
25. Auricchio A, Gold MR, Brugada J, et al. Long-term effectiveness of the combined minute ventilation and patient activity sensors as predictor of heart failure events in patients treated with cardiac resynchronization therapy: results of the Clinical Evaluation of the Physiological Diagnosis Function in the PARADYM CRT device Trial (CLEPSYDRA) study. Eur J Heart Fail 2014;16:663–670.
26. Boehmer JP, Hariharan R, Devecchi FG, et al. A multisensor algorithm predicts heart failure events in patients with implanted devices. JACC Heart Fail 2017; 5:216–225.
27. Wu KC, Wongvibulsin S, Tao S, et al. Baseline and dynamic risk predictors of appropriate implantable cardioverter defibrillator therapy. J Am Heart Assoc 2020;9:e017002.
28. Shakibfar S, Krause O, Lund-Andersen C, et al. Predicting electrical storms by remote monitoring of implantable cardioverter-defibrillator patients using machine learning. EP Europace 2019;21:268–274.
29. Baril J-F, Bromberg S, Moayedi Y, et al. Use of free-living step count monitoring for heart failure functional classification: validation study. JMIR Cardio 2019; 3:e12122.
30. Evangelista LS, Hamilton MA, Fonarow GC, Dracup K. Is exercise adherence associated with clinical outcomes in patients with advanced heart failure? Phys Sportsmed 2010;38:28–36.
31. Melin M, Hagerman I, Gonon A, Gustafsson T, Rullman E. Variability in physical activity assessed with accelerometer is an independent predictor of mortality in CHF patients. PLoS One 2016;11:e0153036.
32. Doherty A, Jackson D, Hammerla N, et al. Large scale population assessment of physical activity using wrist worn accelerometers: the UK Biobank study. PLoS One 2017;12:e0169649.