Rationale and design of a large-scale, app-based study to identify cardiac arrhythmias using a smartwatch: The Apple Heart Study

Mintu P. Turakhia, MD, MAS,[a,b] Manisha Desai, PhD,[c] Haley Hedlin, PhD,[c] Amol Rajmane, MD, MBA,[d] Nisha Talati, MBA,[d] Todd Ferris, MD, MS,[e] Sumbul Desai, MD,[f] Divya Nag[f] Mithun Patel, MD,[f] Peter Kowey, MD,[g] John S. Rumsfeld, MD, PhD,[h] Andrea M. Russo, MD,[i] Mellanie True Hills, BS,[j] Christopher B. Granger, MD,[k] Kenneth W. Mahaffey, MD,[d] and Marco V. Perez, MD[l] *Stanford, Palo Alto, Cupertino, CA; Philadelphia PA; Denver Colorado; Camden NJ; Decatur TX; Durham NC*

Background Smartwatch and fitness band wearable consumer electronics can passively measure pulse rate from the wrist using photoplethysmography (PPG). Identification of pulse irregularity or variability from these data has the potential to identify atrial fibrillation or atrial flutter (AF, collectively). The rapidly expanding consumer base of these devices allows for detection of undiagnosed AF at scale.

Methods The Apple Heart Study is a prospective, single arm pragmatic study that has enrolled 419,093 participants (NCT03335800). The primary objective is to measure the proportion of participants with an irregular pulse detected by the Apple Watch (Apple Inc, Cupertino, CA) with AF on subsequent ambulatory ECG patch monitoring. The secondary objectives are to: 1) characterize the concordance of pulse irregularity notification episodes from the Apple Watch with simultaneously recorded ambulatory ECGs; 2) estimate the rate of initial contact with a health care provider within 3 months after notification of pulse irregularity. The study is conducted virtually, with screening, consent and data collection performed electronically from within an accompanying smartphone app. Study visits are performed by telehealth study physicians via video chat through the app, and ambulatory ECG patches are mailed to the participants.

Conclusions The results of this trial will provide initial evidence for the ability of a smartwatch algorithm to identify pulse irregularity and variability which may reflect previously unknown AF. The Apple Heart Study will help provide a foundation for how wearable technology can inform the clinical approach to AF identification and screening. (Am Heart J 2019;207:66-75.)

Atrial fibrillation and atrial flutter (AF, collectively) together represent the most common cardiac arrhythmia, currently affecting over 5 million people in the United States[1,2] with projected estimates up to 12 million persons by 2050.[3] AF increases the risk of stroke 5-fold[4] and is responsible for at least 15% to 25% of strokes in the United States.[5] Oral anticoagulation can substantially reduce the relative risk of stroke in patients with AF by 49% to 74%, with absolute risk reductions of 2.7% for primary stroke prevention and 8.4% for secondary prevention.[6] Unfortunately, 18% of AF-associated strokes present with AF that is newly detected at the time of stroke.[7]

AF can be subclinical due to minimal symptom severity, frank absence of symptoms, or paroxysmal nature, even in the presence of tachycardia during AF episodes. It is estimated that 700,000 people in the United States may have previously unknown AF, with an incremental cost burden of 3.2 billion dollars.[8,9] Asymptomatic AF is associated with similar risk of all-cause death, cardiovascular death, and stroke/thromboembolism compared to symptomatic AF.[10] Minimally symptomatic patients have been shown to derive significant symptom relief following rate or rhythm control of AF.[11] Undiagnosed or untreated AF can also lead to development of heart failure

From the [a]Center for Digital Health, Stanford University Stanford, CA, [b]VA Palo Alto Health Care System, Palo Alto, CA, [c]Quantitative Sciences Unit, Stanford University, Stanford, CA, [d]Stanford Center for Clinical Research, Stanford University, Stanford, CA, [e]Information Resources and Technology, Stanford University, Stanford, CA, [f]Apple Inc. Cupertino, CA, [g]Lankenau Heart Institute and Jefferson Medical College, Philadelphia, PA, [h]University of Colorado School of Medicine, Denver, CO, [i]Division of Cardiovascular Disease, Cooper Medical School of Rowan University, Camden, NJ, [j]StopAfib.org, American Foundation for Women's Health, Decatur, TX, [k]Duke Clinical Research Institute, Duke University, Durham, NC, and [l]Division of Cardiovascular Medicine, Stanford University, Stanford, CA.

Peter Alexander Noseworthy, MD served as guest editor for this article.
RCT# NCT03335800
Submitted August 13, 2018; accepted September 4, 2018.

Reprint requests: Mintu Turakhia, Marco Perez, Stanford Center for Clinical Research, Stanford University, 1070 Arastradero Rd., Palo Alto, CA, 94304.
E-mail: mintu@stanford.edu

0002-8703

https://doi.org/10.1016/j.ahj.2018.09.002

with reduced or preserved ejection fraction with much greater frequency,[12] and effective restoration of sinus rhythm may prevent or improve heart failure and LV dysfunction.[13,14]

Rationale for the Apple Heart Study

For these reasons, there is considerable public health interest in population-based screening for AF. Previously applied strategies include opportunistic physical examination for an irregular pulse, electrocardiogram,[15,16] ambulatory ECG monitoring of 2 to 14 days,[17,18] or episodic home-based monitoring over weeks or months.[19] These limited snapshots may fail to identify a substantial portion of subclinical paroxysmal AF. Technologies for continuous ECG monitoring, such as an insertable cardiac monitor, can identify AF with greater diagnostic yield in high-risk populations[20,21] but require implantation of a medical device and are costly. To our knowledge, large-scale screening with background monitoring using a commercially available consumer device in a broad-based population cohort has not been evaluated.

Smartwatches and fitness bands, colloquially referred to as "wearables", can passively measure pulse rate from the wrist using photoplethysmography (PPG) from an optical sensor. Longitudinal pulse data could be analyzed in real-time to assess pulse irregularity and variability to identify potential irregular heart rhythms such as AF. However, the utilization of wearables or arrhythmia detection algorithms may not be without risks. Predictive value to detect AF must be measured against a gold standard and be acceptable if any technology is to be applied broadly. Accurate detection of an irregular pulse should trigger timely, evidence-based care when appropriate, such as anticoagulation and rate or rhythm control, while the absence of medical follow-up or inappropriate escalation of care could cause harm. The release of such a technology could trigger appropriate or inappropriate health care utilization, even if algorithm specificity is high, and it would be important to quantify. For these and other reasons, the U.S. Preventative Services Task Force has concluded that the evidence is insufficient to assess the balance of benefits and harms of screening for AF with an electrocardiogram.[22] A recent pragmatic study of AF screening using a 14-day ambulatory patch ECG in a high-risk population targeted from insurance claims data observed an increase in AF identification and use of anticoagulation. Screening, however, was also associated with greater cardiology health care utilization.[16]

In the United States, 77% of people have smartphones[23]; 13% have smartwatches, and an additional 40% of US consumers express interest in purchasing one.[24] The expanding consumer base of these devices allows for an opportunity to perform an irregular pulse detection study and to address many of the evidence gaps at scale. A collaboration was therefore developed to design and conduct a large, digital, pragmatic study to identify AF using a smartwatch, with an overarching goal of learning to responsibly release such a technology at scale, emphasizing participant safety, privacy, and protection of data.

Methods

Trial overview and objectives

The Apple Heart Study is a prospective, single arm study whose overall goal is to evaluate the ability of a smartwatch-based irregular pulse notification algorithm to identify AF (atrial fibrillation and atrial flutter) and guide subsequent clinical evaluation (ClinicalTrials.gov NCT03335800). The study design is illustrated in Figure 1. The primary objective of this study is to measure the proportion of participants with irregular pulse notifications who have atrial fibrillation or atrial flutter confirmed by subsequent ambulatory ECG patch monitoring for those aged ≥65 (Objective 1a) and for participants of all ages (Objective 1b).

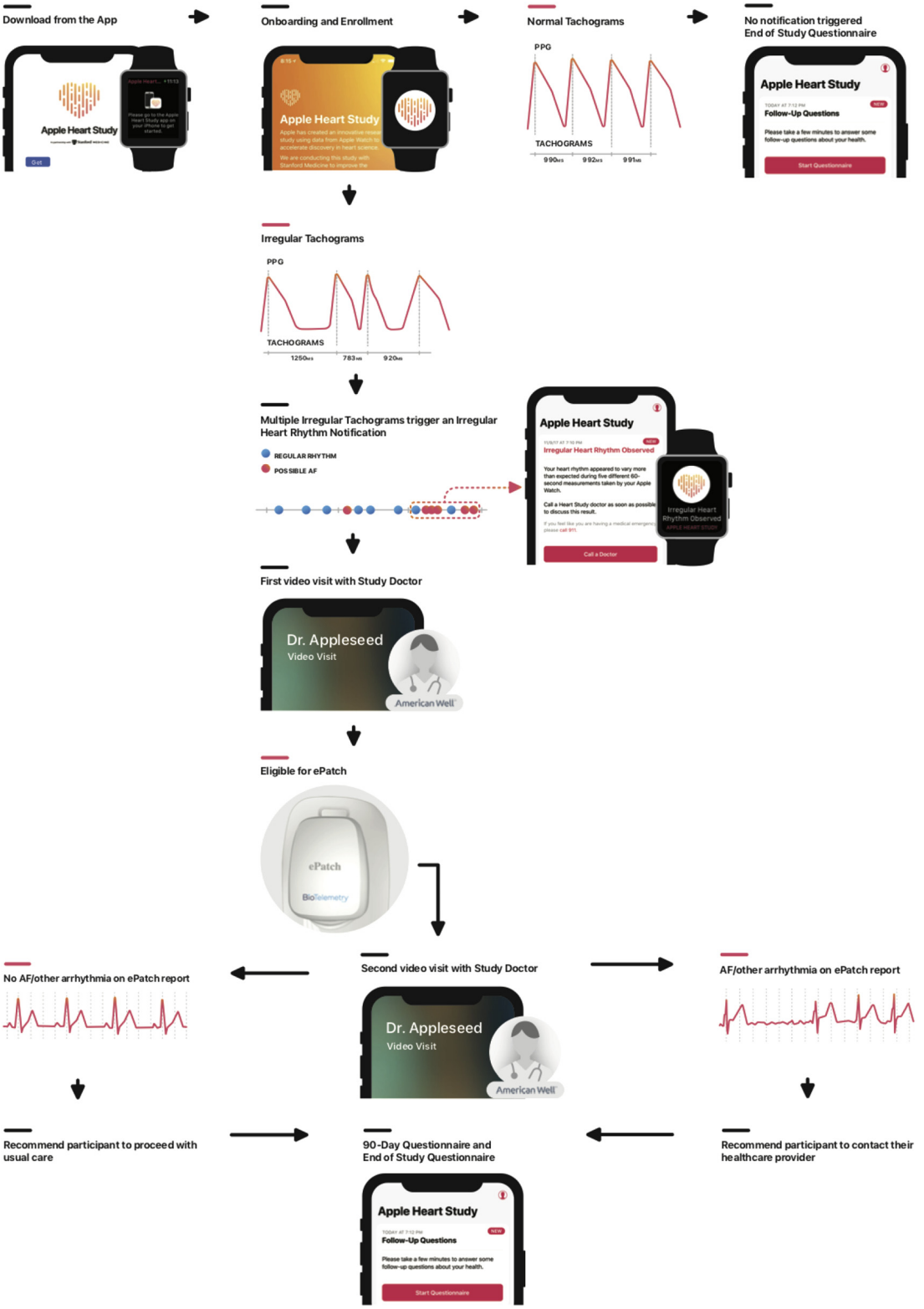
The second objective is to characterize the concordance of the irregular pulse notification algorithm on the Apple watch to simultaneously recorded ambulatory ECGs, specifically among participants who received a notification. This objective helps to validate the potential for real-time identification of changes in rhythm. The key measurement that will be made using these data is the positive predictive value of the irregular pulse notification for AF confirmed by the simultaneously recorded ambulatory ECG.

The third objective is to estimate the rate of initial contact with a health care provider within 3 months after notification of pulse irregularity. The study will help measure how likely someone who receives a message from a digital device is to take an action that may lead to appropriate medical care. The goals of this objective are to understand what care occurs as part of the participant journey after diagnosis, how this technology would be received by participants, how participants would interact with virtual study health providers, how effectively the information is conveyed to their primary physicians, and how real-world clinicians respond by measuring the healthcare resources that are ultimately utilized.

Study procedures

Screening, eligibility, and consent. Interested individuals who download and open the Apple Heart Study App and meet inclusion criteria (Table I) are invited to participate in the study. After self-verification of eligibility, participants are electronically presented the informed consent form and are asked to sign digitally on the iPhone touchscreen. Potential participants, as well as enrolled participants, are able to use a 24-hour study telephone number to ask questions, seek more information, and request clarifications at any time prior to or

Figure 1



Study design. Overview of study flow with example tachograms and screenshots. The tachograms are not visualized or provided to the participant, and analyses are run in the background.

Table I. Inclusion and exclusion criteria

Inclusion criteria
1. iPhone (5 s or later) with iOS version 11.0 or later
2. Apple Watch (Series 1 or later) with watchOS version 4.0 or later
3. Age ≥22 years at time of eligibility screening
4. US resident (50 states or D.C.)
5. Proficient in written and spoken English, defined by self-report
6. Valid phone number associated with iPhone, ascertained from self-report.
7. Valid email address, ascertained from self-report.

Exclusion criteria
1. Self-reported diagnosis or history of Atrial Fibrillation at the time of consent.
2. Self-reported diagnosis or history of Atrial Flutter at the time of consent.
3. Currently on anticoagulation therapy, as self-reported at the time of consent.

during the study. Participants are asked to answer a demographic and medical history questionnaire before monitoring begins.

Monitoring and study intervention. The Apple Heart Study App is the mobile application that is used to screen participants, electronically consent those who qualify, notify participants of an irregular pulse that is believed to be consistent with AF, and direct participants through study procedures (Data Supplement A, Data Supplement B). The Apple Watch (Apple Inc, Cupertino, CA) uses LED lights and light-sensitive photodiodes to measure the changes in blood volume (flow) passing through the wrist and generate a photoplethysmogram, which is then used to estimate the pulse. The time between photoplethysmography signal peaks that are observed during periods of minimal arm movement are recorded as intervals between pulses. These are used to create a tachogram (pulse rate over time). Intermittent spot tachograms are recorded while the participant is wearing the Apple Watch. Within the app, participants can view the number of days they have been in the study and the total number of tachograms recorded (Figure 2). The Irregular Pulse Notification Algorithm uses photoplethysmography waveforms to identify periods of an irregular pulse, which may indicate possible AF. If an initial tachogram meets irregularity criteria, then the algorithm will prospectively and opportunistically scan for photoplethysmography irregularity during periods of minimal arm movement. If 4 subsequent confirmations are obtained, then the participant is notified of the detected irregular pulse via a notification on the Apple Watch and Apple Heart Study app. The rationale for reconfirmation is to increase algorithm specificity for AF.

Once alerted, the participant is asked to use the iPhone to contact the telemedicine technology services company, American Well Corporation (Boston, MA), from within the Apple Heart Study application. If the participant fails to contact the Study Telehealth Provider after multiple reminders, the study team at the American Well Corporation attempts to contact participants to discuss their interest in contact.

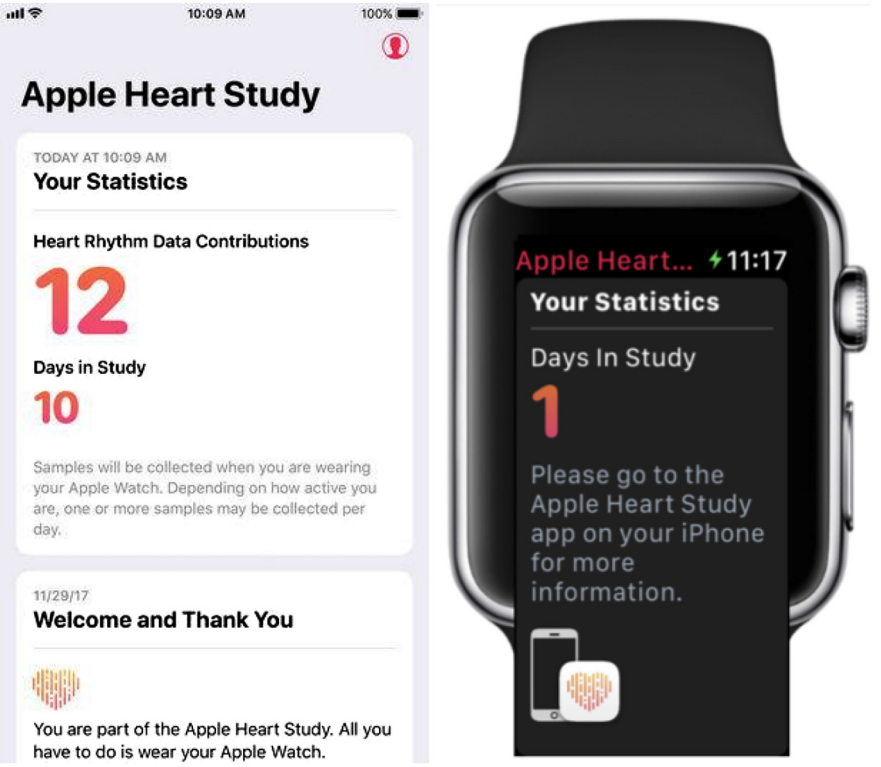
Initial Study Telehealth Visit. After an irregular pulse notification, participants have up to 30 days to contact the Study Telehealth Provider to initiate Study Visit #1 with a study physician. Access to a virtual study visit allowed for the nation-wide implementation of this study and gave participants access to medical attention if needed, helping ensure participant safety. During this visit, participants undergo a virtual study evaluation. The role of the study physician at this visit is to confirm the self-reported medical history that participants enter in the app at time of enrollment, obtain additional history (clinical/medical, medications, symptoms), evaluate the participant to ensure there are no serious or life-threatening conditions that would merit urgent or emergency care, and to counsel the participant on the next step in the study (ambulatory ECG patch).

Participants with urgent symptoms (chest pain, shortness of breath, fainting/losing consciousness) are directed to go to an urgent care clinic or emergency room for medical evaluation. Participants are then informed that they will receive no further irregular pulse notifications, even if pulse irregularity that meets Irregular Pulse Notification Algorithm notification threshold occurs at any time point until the study end. Participants without urgent symptoms who received a notification and who confirm that they are not currently on an anticoagulant therapy or are on an anticoagulant therapy that started after enrollment in the study are offered an ambulatory ECG monitor. The study physicians follow a study protocol and case report form script; they do not prescribe therapy or provide treatment.

Ambulatory ECG monitoring. The selection of the ambulatory ECG monitoring device was conducted after a thorough review of the landscape of approved devices, factoring in monitoring duration, signal fidelity and ability to ascertain AF, analyzable signal time, ease of use, and participant experience. The participants who qualify are mailed ePatches (BioTelemetry, Inc, Conshohocken, PA), ambulatory single-channel ECG patch monitors that the participants are requested to wear for up to 7 days. Although the ePatch can record a 3-channel ambulatory ECG for up to 5 days, we decided to use a single lead configuration in order to extend monitoring time and to simplify self-application for the user. In prior work, 96.6% of arrhythmias identified with a 14-day patch monitoring were identified by the end of the seventh day.[25]

If the initial technical read identifies abnormalities that require urgent attention (ventricular tachycardia or ventricular fibrillation, high-degree heart block, long pauses, or sustained and very rapid ventricular rates), then the participant is contacted immediately and directed to local emergency care or advised how to seek local emergency care. If no emergencies are identified, then the ambulatory ECG is adjudicated by a central, independent, trained committee of board-certified clinicians coordinated by the Stanford Center for Clinical Research (SCCR). After adjudication, a final report is then made available to the Study Telehealth

Figure 2



Participant study engagement screenshots. Number of days the participant has been in the study and total number of tachograms recorded for that participant as seen within the app on the phone (left) and watch (right).

Provider and the participant is instructed to contact the Study Telehealth Provider to conduct Study Visit #2.

Study Visit #2. The second study visit with the Study Telehealth Provider is also performed via the Apple Heart Study application. If AF or any other arrhythmias have been detected in reviewing the ambulatory ECG monitor data, or if there are other non-urgent symptom identified by the study physician during the video visit that may need further clinical evaluation, the Study Telehealth Provider directs the participant to his or her primary health care provider, or other health care provider as deemed appropriate by the study physician. Medical therapies or other interventions are not initiated by the study physician. For participants who do not have an established primary health care provider, the study physician will encourage and offer guidance in establishing a primary care provider. Participants are provided a copy of their study visit summaries and patch ECG report in a secure manner.

Adverse events description and ascertainment. All suspected adverse events (AEs) will be collected and reviewed by the Study Safety Monitoring Desk at SCCR to determine whether they are adverse device effects (ADEs), ie, AEs related to the use of the investigational medical device, the Apple Heart Study app. Anticipated ADEs include stress, anxiety, and their associated symptoms. Possible AEs related to participation in the study, but not related to use of the investigational device, include skin rash, skin itchiness, or blister due to wearing the ePatch and skin rash on the wrist or pressure artifacts on the wrist due to wearing the Apple Watch.

Participant-reported outcomes. Those participants who received an irregular pulse notification receive a separate app notification 90 days post irregular pulse notification to complete the 90-day participant-reported outcomes (PRO) questionnaire within the app. These participants are asked whether or not they contacted a health care provider and what additional treatments or diagnostic tests they underwent. They are also asked questions about symptoms during the monitoring period including palpitations, dizziness and fatigue. All enrolled participants, regardless of whether or not they received an irregular pulse notification, will receive an End of Study PRO questionnaire. This questionnaire will ask participants whether or not they were diagnosed with AF during the study period, and if so, what additional treatments or diagnostic tests they received. The PRO questionnaires also include an assessment of self-

Table II. Primary, secondary and tertiary endpoints

Primary
1. Atrial fibrillation or atrial flutter of greater than 30 seconds duration detected on subsequent ambulatory ECG monitoring for a participant who received an irregular pulse watch notification.
2. Simultaneous ambulatory ECG monitoring indicating an irregular rhythm consistent with atrial fibrillation or atrial flutter during time intervals when the spot tachogram is positive for an irregular pulse among those who received a notification.

Secondary
1. Simultaneous ambulatory ECG monitoring indicating an irregular rhythm consistent with atrial fibrillation or atrial flutter when the Irregular Pulse Notification Algorithm based on multiple tachograms is positive for an irregular pulse among those who received a notification
2. Self-reported contact with a health care provider within 3 months following an irregular pulse watch notification

Tertiary
1. Other arrhythmias detected on cardiac patch monitoring.
2. Different durations of atrial fibrillation (6 minutes, 1 hour, 6 hours, 24 hours)
3. Clinical Diagnosis of atrial fibrillation or atrial flutter
4. Therapies for atrial fibrillation or atrial flutter (anticoagulation, antiarrhythmics, rate-controlling meds)
5. Cardioversion by a health care provider.

perceived anxiety related to the possibility of receiving an irregular pulse notification (asked to all participants at the end of study) and the anxiety related to medical workup as a result of an irregular pulse notification (asked to participants that receive an irregular pulse notification at 90 days post notification).

Statistical considerations

Planned analyses. To address the first objective, the ability of the Irregular Pulse Notification Algorithm to identify those who will subsequently be found to have AF will be estimated as the number of participants who have AF confirmed via adjudication of the subsequent ambulatory ECG monitor divided by all participants who have analyzable ECG patch data, among those who initially received an irregular pulse notification.

In those who subsequently wear an ECG patch monitor, tachograms and markers of a positive irregular pulse notification algorithm are recorded and synchronized with the ECG recordings from the patch monitor, however, no further irregular pulse notifications are sent to participants. To address the second objective, the positive predictive value of irregular pulse identified by the spot tachograms will be estimated as the number of tachograms indicating an irregular rhythm where AF is present as confirmed via adjudication of the simultaneously worn ambulatory ECG monitoring divided by the number of tachograms indicating an irregular rhythm sampled from the period of time when the participant provides analyzable ECG patch data. Among those with irregular pulse notifications and analyzable ePatch data, an equal number of tachograms per participant will be randomly selected, but weighted to include representative samples of irregular tachograms, to ensure each participant contributes a comparable number of tachograms and to reduce the number of tachograms requiring adjudication. All tachograms will be used in participants who have fewer tachograms available than the number of tachograms to be sampled. We assume that each tachogram measured on a participant is independent of other intervals measured from that participant. The impact of this assumption will be assessed in sensitivity analyses.

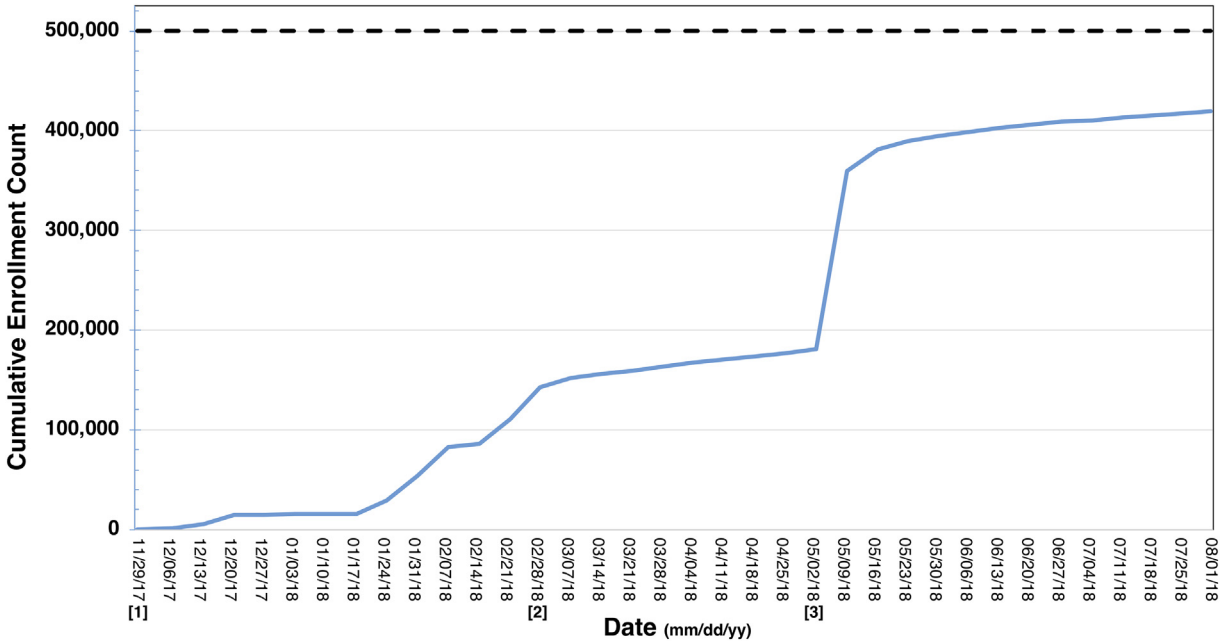
The Irregular Pulse Notification Algorithm will be considered to produce clinically meaningful alerts if the concordance with AF identified on simultaneous ECG patch monitoring is high. To that end, the ePatch will be considered the gold standard against which to gauge performance of the spot tachograms. The decision rule for concluding the Irregular Pulse Notification Algorithm is sufficiently concordant with simultaneously worn ePatch is that the lower bound of a 2-sided 97.5% confidence interval of the positive predictive value is greater than 0.70 and the upper bound is at least 0.75. The threshold for positive predictive value was determined based on what would be considered clinically meaningful. While there is no hypothesis testing for the co-primary objectives, 97.5% confidence intervals based on the Gaussian approximation are employed to account for having 2 primary objectives. Alternatively confidence intervals using the bias-corrected and accelerated method will be used for proportions when values cross boundary values of 0 and 1.[26]

The primary analyses for the co-primary endpoints will be performed in participants 65 years of age or older who return an ePatch with at least 1 hour of wear time. The analyses will be repeated in participants of all ages to address secondary objectives of assessing PPV.

Secondary and tertiary endpoints (Table II) will be analyzed as proportions with 95% confidence intervals. Endpoints measured using data collected from the ambulatory ECG monitoring will be analyzed in participants who return an ePatch with at least 1 hour of wear time while self-reported contact with a health care provider and initiation of therapies such as anticoagulation and antiarrhythmic medication use or cardioversion will be analyzed in all participants who receive an irregular pulse notification. Generalized linear regression techniques will be employed to evaluate the variation observed in secondary and tertiary endpoints by subgroups described by age, race, gender, and family history.

Sample size considerations. A minimum number of 503 ePatches in each age group of interest (<65 and ≥ 65) was planned to support the primary objectives. More specifically, for the first primary endpoint, the study was

Figure 3



Cumulative participant enrollment per week based on operational metrics. [1] Study launch with media promotion (Apple press release, App store feature). [2] Waiting room eliminated. All individuals that had been in the waiting room were invited into the study. Enrollment metering ceased. [3] Single recruitment email sent.

designed to ensure a confidence interval width no wider than 0.10 with 250 patches in an age group when the PPV is >0.80 or <0.20. Regardless of the true PPV, with only 200 patches in each age group, the confidence interval width will be less than 0.15. The calculations rely on an asymptotic Gaussian approximation in the construction of the 97.5% confidence intervals. For the purpose of addressing the second primary objective, if 10 tachograms from each participant returning an ePatch are randomly sampled, we require only 300 participants with ePatches to provide 3,000 tachograms for the observed intervals, well below the 503 participants planned to address the first primary objective.

To achieve this number of tachograms, approximately 75,000 participants above the age of 65 and 425,000 participants below the age of 65 were targeted for enrollment. The targeted enrollment will further enable evaluation of the necessary number of tachograms to address the second primary objective to evaluate the PPV at the tachogram level.

Study organization

The study was funded by Apple, Inc, the software and hardware manufacturer, and performed in partnership with Stanford School of Medicine, including the Stanford Center for Clinical Research (SCCR) and the Quantitative Sciences Unit (QSU). Stanford SCCR and QSU are responsible for recruitment, data management, analysis, interpretation, safety monitoring, and ePatch adjudication. An independent data safety monitoring board was created. A steering committee was formed, consisting of representatives from Stanford University, the sponsor, and 5 external members, including one who is a patient with atrial fibrillation and patient advocate. The study was approved by the central IRB Advarra (Columbia, MD) with ethics, information security, and privacy approval from Stanford University. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the, manuscript, and its final contents.

Data flow, privacy, and security

The study has multiple streams of data generated in different sources. These data are aggregated to form the study dataset. Data sources include the participant smartwatch, phone, telehealth study visits, ambulatory ECG patch, participant reported outcome surveys, research adjudication portal, and study safety desk. These data are stored on multiple cloud systems, with privacy and security protections in place, including compliance with Title 21 Part 11 of the Code of Federal Regulations where appropriate. Protected health information is stored only in a subset of data streams, with linkages of data performed by non-PHI unique

identifiers. The sponsor, who is also the watch, phone, and algorithm manufacturer, did not have access to any PHI.

Study launch and enrollment

The Apple Heart Study was launched on November 29, 2017, with media promotion, at which time the study app was made available on the U.S. app store. During the first 2 weeks after study launch, participants were invited into the study on a metered basis, with a maximum of 1700 participants enrolled per week while others were kept in a virtual waiting room to ensure that study infrastructure was sufficiently robust. After evaluation of study operational and quality metrics, study enrollment proceeded without any further metering and ended on July 31, 2018. Based on operational metrics, there were 419,093 enrolled participants as of October 1, 2018, (Figure 3).

Discussion

The Apple Heart Study is one of the largest AF identification studies to date. It is also the first study to evaluate the use of photoplethysmography to screen for pulse irregularity which may reveal previously unknown AF in a broad population cohort. While other studies have examined algorithms using photoplethysmography signals and the Apple Watch,[27] this study is the first to do so in the general population, at large scale and to use a photoplethysmography algorithm designed to minimize false positive rates.

The study has several unique features in design and execution. One innovative aspect of this trial is the completely virtual nature of the design, with no in-person visits for participants. From enrollment and consent, to study visits and patch monitoring, all aspects of the study are performed without the need for participants to be physically present. This design allowed the implementation of a massive recruitment strategy in a relatively short period of time. Importantly, private health information (PHI) was carefully protected, with no PHI accessible to the study sponsor (Apple Inc).

The study is also a pragmatic study that informs decision-makers regarding the benefits, burdens, and risks at the individual and population level.[28] In contrast to typical pragmatic trials that take place in the setting where patients receive clinical care, the present study aims to take place in the general sphere of the patient's daily life and their use and interaction with personal consumer technologies. Further, because screening and enrollment are done via downloading and interacting with the study app, the study can be administered at scale and with relatively minimal incremental cost and resources. Without this approach, recruitment of over 400,000 participants in 9 months would not have been possible.

While this approach is attractive for scale, it presents operational challenges. The study requires fairly extensive strategies for data management and compliance with privacy and security best practices and requirements. There is particular emphasis on mechanisms to ensure that private participant data are in no manner accessible to the sponsor. Data are managed across multiple cloud platforms with unique identifiers for each participant. Adequate data protections are required for participants requiring study withdrawal, while also ensuring that smartwatch and phone hardware were tied to only a single enrollment of a single participant. Merging the data types presents further challenges as both the watch and the ePatch generate different types of longitudinal time series data that need to be thoughtfully aligned prior to assessing concordance.

Limitations

There are potential tradeoffs and limitations due to the study design. The study is observational and, thus, is not designed to evaluate the efficacy of a smartwatch-guided screening strategy for clinical outcomes such as stroke. Rather, the goal of the study is to understand the test characteristics of a smartwatch algorithm for photoplethysmography-based detection for AF and to estimate the diagnostic yield in a large, US-based population. The study is designed to perform ambulatory ECG monitoring only in participants receiving irregular pulse notifications, not in participants without notifications. We therefore are unable to evaluate negative predictive value or likelihood ratios.

Second, the initial Irregular Pulse Notification Algorithm alert that triggers subsequent evaluation and ambulatory ECG monitoring does not have any simultaneous ECG data. Doing so would have required continuous ECG monitoring for the entire observation period of all participants, which would not be feasible at scale. Therefore, the concordance of the initial alert of an irregular pulse with subsequent AF on ECG monitoring could vary across different temporal patterns and burdens of atrial fibrillation. Third, patch wear time could also affect Irregular Pulse Notification Algorithm PPV such that our estimates are more relevant for those with a higher burden. Fourth, the “site-less” workflow may be more dependent on participant initiation for study visits than traditional site-based research, which may affect engagement, adherence to study procedures, completeness of follow-up and reliance on participant reported outcomes on line. The participants who have irregular pulse notifications and complete the ECG monitoring therefore will be a smaller subset of those who would have qualified for ECG monitoring. Finally, the participants in this study were smartwatch users and may not be representative of the general population or those that met exclusion criteria. There may be a bias for a younger and possibly healthier cohort with a lower risk for AF.

Summary

The results of the Apple Heart Study of over 400,000 participants will provide initial evaluation of the ability of a smartwatch algorithm to identify an irregular pulse consistent with previously unknown AF. It will provide estimates of irregular pulse consistent with AF in a broad population, which has not been studied at this scale. If successful, this study may form the framework on which future studies using wearable technology to detect AF will be based. The study will also appraise practicability and scalability of pragmatic clinical trials using virtual and telehealth study designs.

Acknowledgements

The authors acknowledge Alex Perino M.D., Connor O'Brien M.D., Christoph Olivier M.D., and Justin Parizo M.D. for their assistance with the study and Mariam Askari M.S. for her editorial assistance with the manuscript.

Disclosures

Outside of the submitted work the authors disclose the following: Mintu Turakhia reports grants from Janssen Inc, Boehringer Ingelheim, Cardiva Medical, Bristol Myers Squibb, Astra Zeneca, American Heart Association; consulting fees from Medtronic, Precision Health Economics, iBeat, Abbott, iRhythm, Myokardia, Biotronik; equity from AliveCor; and member of the editorial board of the American Heart Journal. Dr. Manisha Desai reports research support from National Institutes of Health, Ferring Pharmaceuticals A/S, Merck Sharp & Dohme Corp, Cardiva Medical Inc., Duke Clinical Research Institute, CSL Behring LLC, Luitpold Pharmaceuticals Inc., and ACIST Medical Systems Inc. Dr. Haley Hedlin reports research support from National Institutes of Health, Ferring Pharmaceuticals A/S, Merck Sharp & Dohme Corp, Cardiva Medical Inc., Astra Zeneca, Duke University, Duke Clinical Research Institute, CSL Behring LLC, and Luitpold Pharmaceuticals Inc. Dr. Amol Rajmane and Nisha Talati are employees of Stanford School of Medicine. Todd Ferris is an employee of the Leland Stanford Junior University. Sumbul Desai is an employee of Apple Inc., reports equity from Apple Inc., and is faculty member of Stanford School of Medicine. Divya Nag is an employee of Apple Inc. and reports equity from Apple Inc. Mithun Patel is an employee of Apple Inc. Dr. Peter Kowey reports having been an ad hoc consultant to Medtronic and holder of equity interest with Biotelemetry. John Rumsfeld has no grants, consulting fees, or other forms of payment from any entity to report. Andrea M. Russo reports research support from Boston Scientific, Boehringer Ingelheim, and Medtronic; honoraria or consulting fees from Biotronik, Boston Scientific, and Medtronic. Mellanie True Hills is an employee of the American Foundation for Women's Health and True Hills, Inc., and receives no personal speaking or consulting fees. In 2017 and 2018, the American Foundation for Women's Health received unrestricted educational grants, patient conference sponsorships, and memberships from Abbott, AtriCure, Bayer, Biosense Webster, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb-Pfizer Alliance, Janssen, Medtronic, Sanofi, and SentreHEART. The foundation also received collaborative funding from the American Heart Association. In 2017 and 2018, True Hills, Inc. received speaking fees from Bristol-Myers Squibb and Pfizer. Dr. Christopher Granger reports grants from Apple, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Glaxo SmithKline, Janssen, Medtronic Foundation, Novartis, Pfizer; personal fees from Abbvie, Astra Zeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Gilead, Glaxo SmithKline, Janssen, Medscape, Medtronic Inc., Merck, Novo Nordisk, Novartis, Pfizer, Roche, Rho Pharmaceuticals, Sirtex, Verseon. Dr. Kenneth W. Mahaffey's financial disclosures can be viewed at http://med.stanford.edu/profiles/kenneth-mahaffey. Dr. Marco Perez reports grants from the NIH/NHLBI (major, >10K/year) and consulting fees from Apple, Inc. (minor, <10K/year).

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.09.002.

References

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation 2018;137(12):e67-492.
2. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64(21):e1-76.
3. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006 Jul 11;114(2):119-25.
4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22(8):983-8.
5. Marini C, De Santis F, Sacco S, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke 2005;36(6):1115-9.
6. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146(12):857-67.
7. Lin HJ, Wolf PA, Benjamin EJ, et al. Newly diagnosed atrial fibrillation and acute stroke. The Framingham Study. Stroke 1995 Sep;26(9):1527-30.

8. Turakhia MP, Shafrin J, Bognar K, et al. Estimated prevalence of undiagnosed atrial fibrillation in the United States. PLoS ONE 2018;13(4), e0195088.
9. Turakhia MP, Shafrin J, Bognar K, et al. Economic Burden of Undiagnosed Nonvalvular Atrial Fibrillation in the United States. Am J Cardiol 2015;116(5):733-9.
10. Xiong Q, Proietti M, Senoo K, et al. Asymptomatic versus symptomatic atrial fibrillation: A systematic review of age/gender differences and cardiovascular outcomes. Int J Cardiol 2015;191:172-7.
11. King DR, Mehta ND, Gehi AK, et al. Minimally symptomatic atrial fibrillation patients derive significant symptom relief following rate control or rhythm control therapy. J Clin Med Res 2015;7(9):690-3.
12. Wong JA, Conen D, Van Gelder IC, et al. Progression of device-detected subclinical atrial fibrillation and the risk of heart failure. J Am Coll Cardiol 2018;71(23):2603-11.
13. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018;378(5):417-27.
14. Di Biase L, Mohanty P, Mohanty S, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. Circulation 2016;133(17):1637-44.
15. Freedman B, Camm J, Calkins H, et al. Screening for atrial fibrillation: a report of the AF-SCREEN International Collaboration. Circulation 2017;135(19):1851-67.
16. Lowres N, Neubeck L, Salkeld G, et al. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. Thromb Haemost 2014;111(6):1167-76.
17. Turakhia MP, Ullal AJ, Hoang DD, et al. Feasibility of extended ambulatory electrocardiogram monitoring to identify silent atrial fibrillation in high-risk patients: the Screening Study for Undiagnosed Atrial Fibrillation (STUDY-AF). Clin Cardiol 2015;38(5):285-92.
18. Steinhubl SR, Waalen J, Edwards AM, et al. Effect of a home-based wearable continuous ECG monitoring patch on detection of undiagnosed atrial fibrillation: The mSToPS randomized clinical trial. JAMA 2018;320(2):146-55.
19. Svennberg E, Engdahl J, Al-Khalili F, et al. Mass screening for untreated atrial fibrillation: the STROKESTOP Study. Circulation 2015;131(25):2176-84.
20. Reiffel JA, Verma A, Kowey PR, et al. Incidence of previously undiagnosed atrial fibrillation using insertable cardiac monitors in a high-risk population: The REVEAL AF study. JAMA Cardiol 2017;2(10):1120-7.
21. Sanna T, Diener H-C, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370(26):2478-86.
22. US Preventive Services Task Force. Screening for atrial fibrillation with electrocardiography: Us preventive services task force recommendation statement. JAMA 2018;320(5):478-84.
23. Smith A. Record shares of Americans now own smartphones, have home broadband [Internet]. Available from: Pew Research Center, http://www.pewresearch.org/fact-tank/2017/01/12/evolution-of-technology/ 2017.
24. Lamkin P. Smartwatch popularity booms with fitness trackers on the slide. Forbes.[Internet]. Available from: https://www.forbes.com/sites/paullamkin/2018/02/22/smartwatch-popularity-booms-with-fitness-trackers-on-the-slide/#6ebca2b97d96 2018.
25. Turakhia MP, Hoang DD, Zimetbaum P, et al. Diagnostic utility of a novel leadless arrhythmia monitoring device. Am J Cardiol 2013;112(4):520-4.
26. Sun J, Chernick MR, LaBudde RA. A bootstrap test for comparing two variances: simulation of size and power in small samples. J Biopharm Stat 2011;21(6):1079-93.
27. Tison GH, Sanchez JM, Ballinger B, et al. Passive detection of atrial fibrillation using a commercially available smartwatch. JAMA Cardiol 2018;3(5):409-16.
28. Califf RM, Sugarman J. Exploring the ethical and regulatory issues in pragmatic clinical trials. Clin Trials 2015;12(5):436-41.