A Digital, Pragmatic, Direct-to-Participant Clinical Trial for Identifying Undiagnosed Atrial Fibrillation in a Large Health Plan Population

Steven R. Steinhubl, MD
August 3, 2018
Atria

Fibrillation (AF)

• For adults >55, 37% lifetime risk of developing AF, which is associated with a 5-fold increase for stroke.

• In individuals with AF, therapeutic anticoagulation can decrease the risk of stroke by >65% and mortality by 30%. Anticoagulation can decrease the risk of stroke.

• Up to ~30% of individuals with AF are potentially asymptomatic and undiagnosed.

• The clinical value of, and optimal method for screening for AF is currently unknown.

Aguilar MI. The Cochrane database of systematic reviews. 2005;3:CD001927

Lin HJ. Stroke 1995;26:1527-30

Weng L-C. Circulation 2017;CIRCULATIONAHA.117.031431
Clinical Investigation

Risk of cardiovascular events and incident atrial fibrillation in patients without prior atrial fibrillation: Implications for expanding the indications for anticoagulation

Xiaoxi Yao, PhD a,b, Bernard J. Gersh, MB, ChB, DPhil, FRCP c, Lindsey R. Sangaralingham, MPH a, Nilay D. Shah, PhD a,b,d, Peter A. Noseworthy, MD a,c,e

- ~6.5M people OptumLabs
- Mean age 62.7 years
- Mean f/u 2.6 years

- 139,511 with new dx of AF (2.15%)
- ~7,407 of individuals with a stroke also had a new dx of AF (5.31% of all individuals with AF).
- 56% of people with a stroke and AF had their AF diagnosed in the days/weeks surrounding their stroke

Yao X. American Heart J 2018;199:137–143
• Only 1.7% of eligible patients are enrolled in clinical trials
• < 1/3 of RCTs meet their original recruitment targets.
• 88% of US adults use the internet and 77% own a smartphone
High-Level Objective

In the context of a digital clinical trial, determine if participant-generated data can improve the identification of AF relative to routine care.
Design Principles

• Make it as easy as possible for eligible people to participate in all aspects.
• No geographic limitations to enrollment
• 100% digital interactions with all participants as a primary focus
• All of a participant’s information will be returned to them.
Overview

Members

Scripps Translational Science Institute

Study consent

What is the Purpose of This Study?

The purpose of this study is to identify people with asymptomatic heart age acceleration. Your health is not guaranteed to improve because of this, but your participation will help others.
Population to be Based on Database Population Risk Factors

Afib Relative Risks – All Members
## Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 75 years old, OR</td>
<td>History of AF (fibrillation or flutter) or atrial tachycardia</td>
</tr>
<tr>
<td>Males age &gt;55, females &gt;65 AND</td>
<td>Chronic Anticoagulation</td>
</tr>
<tr>
<td>Prior CVA, OR</td>
<td>Implantable Pacemaker or Defibrillator</td>
</tr>
<tr>
<td>Heart Failure Diagnosis, OR</td>
<td>Metastatic Cancer</td>
</tr>
<tr>
<td>Diagnosis of Diabetes and HTN, OR</td>
<td>End Stage Renal Disease</td>
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<tr>
<td>Mitral Valve Disease, OR</td>
<td>Moderate or Greater Dementia</td>
</tr>
<tr>
<td>Left Ventricular Hypertrophy, OR</td>
<td>Hospice Care</td>
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<tr>
<td>Severe O2-Depended COPD, OR</td>
<td></td>
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<tr>
<td>Obstructive Sleep Apnea, OR</td>
<td></td>
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<tr>
<td>History of Pulmonary Embolism, OR</td>
<td></td>
</tr>
<tr>
<td>History of Myocardial Infarction, OR</td>
<td></td>
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<tr>
<td>Morbid Obesity</td>
<td></td>
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</tbody>
</table>
You can help with an important heart health study

You’re invited to join an important research study on how to better detect irregular heart rhythm. And you can do it from the comfort of your own home.

About the study
Aetna is working with the Scripps Translational Science Institute on a research study to try to find new ways to identify people who might be at risk for a heart rhythm called atrial fibrillation. It’s an irregular heartbeat and can be associated with a higher risk of stroke. The study uses a new state-of-the-art wearable device that monitors your heart rhythm.

We are reaching out to tens of thousands of Aetna members like you. Please consider being a part of this study. We hope you’ll help make a difference to improve health care. Research like this can help enhance the lives of others by improving medical knowledge for future generations.

What’s involved in the study
The study is voluntary. You don’t have to join. If you do, there won’t be any interruption to your daily routine. No doctor visits are needed to participate in the study.
Informed Consent

Welcome To The Study

Schedule & Time Commitment

Risks

Confidentiality

You're Almost Done

Answer the following questions to complete the enrollment process.

We’ve mentioned it before and we will mention it again; your medical information is confidential and private.

Up to this point, you’ve been informed of the major sections of the consent process. We will send you the signed consent document for your reference. Please provide your email address below.

Email Address

Translational Institute
Lessons from a fully digital, direct-to-participant, randomized pragmatic trial:

Our first attempt at email-based recruitment: 0.07% enrollment rate
Eventually Achieved an ~20-fold Increase in Response Rate

Our final attempt with a 5 piece* redesigned campaign:
9.3% enrollment rate

*3 emails and 2 direct mail pieces
Recruitment Success:
Designing a Learning System That Allowed Ongoing Refinement and Improvement

![Projected vs Actual Recruitment Success Graph]

- **Projected** vs **Actual**
- Dates range from 28-Mar to 29-Aug
- The graph shows a comparison between the projected and actual recruitment success over the specified period.
359,161 Aetna members meeting eligibility criteria

- 52,553 invited by email
- 50,000 invited by direct mail
- 2,655 consented & confirmed eligible
359,161 Aetna members meeting eligibility criteria

- 52,553 invited by email
- 50,000 invited by direct mail

2,655 consented & confirmed eligible

- 1,364 randomized to immediate monitoring
- 1,291 randomized to delayed monitoring

456 never wore a patch

908 actively monitored

457 never wore a patch

Primary Endpoint
New Diagnosis of AF after 4 months
# Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Immediate n=1364</th>
<th>Delayed n=1291</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>73.5 (7.3)</td>
<td>73.1 (7.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>% Female</td>
<td>38.2</td>
<td>39.0</td>
<td>0.66</td>
</tr>
<tr>
<td>CHA$_2$DS$_2$-VASc (median, Q1-Q3)</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
<td>0.82</td>
</tr>
<tr>
<td>Prior Stroke (%)</td>
<td>13.7</td>
<td>14.0</td>
<td>0.82</td>
</tr>
<tr>
<td>Heart Failure (%)</td>
<td>5.1</td>
<td>4.6</td>
<td>0.56</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>77.1</td>
<td>76.8</td>
<td>0.86</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>38.7</td>
<td>36.5</td>
<td>0.24</td>
</tr>
<tr>
<td>Sleep Apnea (%)</td>
<td>24.9</td>
<td>29.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Hx of MI (%)</td>
<td>5.5</td>
<td>5.6</td>
<td>0.93</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>17.3</td>
<td>18.4</td>
<td>0.45</td>
</tr>
<tr>
<td>Chronic Renal Failure (%)</td>
<td>10.9</td>
<td>9.6</td>
<td>0.29</td>
</tr>
</tbody>
</table>
Primary 4-Month Endpoint – New Diagnosis AF

Definition of Atrial Fibrillation

• > 30 consecutive seconds of AF by ECG. (CEC adjudicated), or
• A new diagnosis of AF through claims data. (A single new ICD9 or ICD10 code)

For ITT population

OR 8.8
95%CI 3.5-22.4
P<0.0001

OR 9.0
95%CI 3.6-22.7
P<0.0001
2,655 consented & confirmed eligible

1,364 randomized to immediate monitoring
1,291 randomized to delayed monitoring

456 never wore a patch
457 never wore a patch

908 actively monitored
834 actively monitored

Primary Endpoint
New Diagnosis of AF after 4 months

1,738 actively monitored participants with 12 months follow-up
New Diagnosis of AF 12 months

3,476 matched observational controls with 12 months follow-up

5,310 observational controls matched for age, sex and CHADS-VASc score

359,161 Aetna members meeting eligibility criteria
1-Year New Diagnosis of AF

- Unadjusted OR 2.8, 95%CI 2.1 – 3.7, P<0.0001
- Adjusted OR 3.0, 95%CI 2.2 – 4.0, P<0.0001

Days Since Randomization vs. % Atrial Fibrillation Diagnosis

- Actively Monitored
- Observational, Matched Controls
CHA$_2$DS$_2$-VASc Score & New Diagnosis of AF – Monitored vs Controls
Characteristics of Sensor-Detected AF

- Average patch wear time 11.7 days
- Median time until first AF detection 2 days (IQR 1-5)
Characteristics of Sensor-Detected AF

Median total AF burden during monitoring was 0.9%
Characteristics of Sensor-Detected AF

- Median duration of longest AF episode: 185.5 minutes
- 92.8% > 5 minutes
- 37.7% > 6 hours
<table>
<thead>
<tr>
<th></th>
<th>Actively Monitored Group (n = 1738)</th>
<th>Matched Control Group (n = 3476)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AF-related therapeutic interventions, No./100 person-years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacy fill for an anticoagulant</td>
<td>5.7</td>
<td>3.7</td>
<td>2.0 (1.9 to 2.2)</td>
</tr>
<tr>
<td>Pharmacy fill for an anticoagulant for individuals with AF</td>
<td>2.4</td>
<td>1.3</td>
<td>1.1 (1.0 to 1.2)</td>
</tr>
<tr>
<td>Pharmacy fill for an antiarrhythmic medication</td>
<td>0.8</td>
<td>0.3</td>
<td>0.5 (0.4 to 0.5)</td>
</tr>
<tr>
<td>Cardioversion procedures</td>
<td>0.24</td>
<td>0.19</td>
<td>0.05 (0.03 to 0.08)</td>
</tr>
<tr>
<td>Cardiac ablation</td>
<td>0.3</td>
<td>0.1</td>
<td>0.2 (0.18 to 0.24)</td>
</tr>
<tr>
<td>ED visit or inpatient stays with an AF diagnosis</td>
<td>1.3</td>
<td>1.4</td>
<td>0.1 (-0.1 to 0)</td>
</tr>
<tr>
<td><strong>Clinical use (No./100 person-years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placement of a pacemaker or defibrillator</td>
<td>0.79</td>
<td>0</td>
<td>0.79 (0.75 to 0.84)</td>
</tr>
<tr>
<td>Any cause ED visit or inpatient stays</td>
<td>22.5</td>
<td>23.7</td>
<td>-1.2 (-1.5 to -0.9)</td>
</tr>
<tr>
<td>Participants with at least 1 all-cause outpatient office visit to a primary care clinician</td>
<td>83.5</td>
<td>82.6</td>
<td>0.9 (0.4 to 1.5)</td>
</tr>
<tr>
<td>Participants with at least 1 all-cause outpatient office visit to a cardiologist</td>
<td>33.5</td>
<td>26.0</td>
<td>7.5 (7.2 to 7.9)</td>
</tr>
<tr>
<td>Participants with at least 1 all-cause outpatient office visit to a cardiologist or primary care clinician</td>
<td>89.2</td>
<td>88.1</td>
<td>1.1 (0.5 to 1.7)</td>
</tr>
<tr>
<td><strong>Clinical use (No./person-year)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary care visits</td>
<td>2.78</td>
<td>2.84</td>
<td>-0.07 (-0.17 to -0.03)</td>
</tr>
<tr>
<td>Cardiology visits</td>
<td>0.67</td>
<td>0.48</td>
<td>0.19 (0.15 to 0.24)</td>
</tr>
<tr>
<td>Cardiology or primary care visits</td>
<td>3.45</td>
<td>3.32</td>
<td>0.12 (0.01 to 0.23)</td>
</tr>
</tbody>
</table>
Cardiology visits per month per 100 patients

- Control
- Active

Change in number of visits vs. Months

pps Research
slational Institute
Effect of a Home-Based Wearable Continuous ECG Monitoring Patch on Detection of Undiagnosed Atrial Fibrillation: The mStoPS Randomized Clinical Trial


OBJECTIVE To determine the effect of a self-applied wearable electrocardiogram (ECG) patch in detecting atrial fibrillation (AF) and the clinical consequences associated with such a detection strategy.

METHODS AND PARTICIPANTS A self-applied wearable electrocardiogram (ECG) patch was used to monitor 2,650 participants for 4 months. The primary endpoint was the incidence of new episodes of AF within 30 days of patch start.

RESULTS The primary endpoint was met in 6% of participants.

CONCLUSIONS AND RELEVANCE Among individuals at high risk for AF, immediate monitoring with a home-based wearable ECG patch was associated with increased detection of AF episodes compared with delayed monitoring and lower rates of AF-related hospitalizations and emergency department visits.

NIH Director's Blog

Wearable mHealth Device Detects Abnormal Heart Rhythms Earlier

Posted on July 12th, 2018 by Dr. Francis Collins

As many as 6 million Americans experience a common type of irregular heartbeat, called atrial fibrillation (AFib).
Thank you!

To all of the mSToPS participants

& co-investigators:  Jill Waalen, Alison M. Edwards, Lauren M. Ariniello, Rajesh R. Mehta, Gail S. Ebner, Chureen Carter, Katie Baca-Motes, Elise Felicione, Troy Sarich, Eric J. Topol
### Association between Sub-clinical AF & Clinical AF

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancillary MOST</td>
<td>1.78</td>
<td>0.3685</td>
<td>22.5%</td>
<td>5.93 [2.88, 12.21]</td>
<td>5.93 [2.88, 12.21]</td>
</tr>
<tr>
<td>ASSERT</td>
<td>1.7192</td>
<td>0.1987</td>
<td>77.5%</td>
<td>5.58 [3.78, 8.24]</td>
<td>5.58 [3.78, 8.24]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>5.66 [4.02, 7.97]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 9.91 (P < 0.00001)

### Sub-clinical AF & Stroke

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancillary MOST</td>
<td>1.026</td>
<td>0.4096</td>
<td>14.2%</td>
<td>2.79 [1.25, 6.23]</td>
<td>2.79 [1.25, 6.23]</td>
</tr>
<tr>
<td>ASSERT</td>
<td>0.9163</td>
<td>0.3416</td>
<td>20.5%</td>
<td>2.50 [1.28, 4.88]</td>
<td>2.50 [1.28, 4.88]</td>
</tr>
<tr>
<td>Botto et al</td>
<td>0.9243</td>
<td>0.7674</td>
<td>4.1%</td>
<td>2.52 [0.56, 11.34]</td>
<td>2.52 [0.56, 11.34]</td>
</tr>
<tr>
<td>Capucci et al</td>
<td>1.1314</td>
<td>0.5286</td>
<td>8.6%</td>
<td>3.10 [1.10, 8.74]</td>
<td>3.10 [1.10, 8.74]</td>
</tr>
<tr>
<td>Shanmugam et al</td>
<td>2.2407</td>
<td>0.8433</td>
<td>3.4%</td>
<td>9.40 [1.80, 49.08]</td>
<td>9.40 [1.80, 49.08]</td>
</tr>
<tr>
<td>SOS AF</td>
<td>0.6366</td>
<td>0.2579</td>
<td>35.9%</td>
<td>1.89 [1.14, 3.13]</td>
<td>1.89 [1.14, 3.13]</td>
</tr>
<tr>
<td>TRENDS</td>
<td>0.7885</td>
<td>0.4231</td>
<td>13.4%</td>
<td>2.20 [0.96, 5.04]</td>
<td>2.20 [0.96, 5.04]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>2.41 [1.78, 3.26]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 3.91, df = 6 (P = 0.69); I² = 0%
Test for overall effect: Z = 5.68 (P < 0.00001)
Participants in the highest quintile of AF GRS were more likely (odds ratio 3.11; p = 0.01) to have had an AF event than participants in the lowest quintile after adjusting for clinical factors.