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

Scripps Research

Atrial Fibrillation (AF)

- For adults >55, 37% lifetime risk of developing AF, which is associated with a 5-fold increase for stroke.
- In individuals with diagnosed AF, therapeutic anticoagulation can decrease the risk of stroke by >65% & mortality by 30%.
- 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.

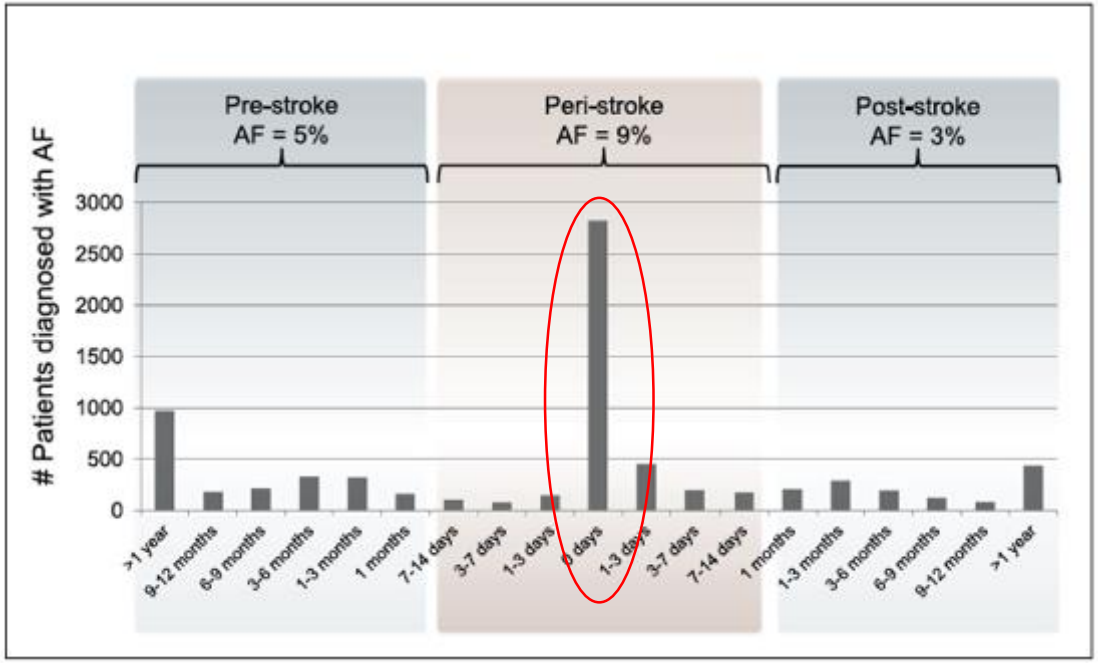
Weng L-C. Circulation 2017;CIRCULATIONAHA.117.031431 Lin HJ. Stroke 1995;26:1527-30
Aguilar MI. The Cochrane database of systematic reviews. 2005;3:Cd001927

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,*]

- ~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

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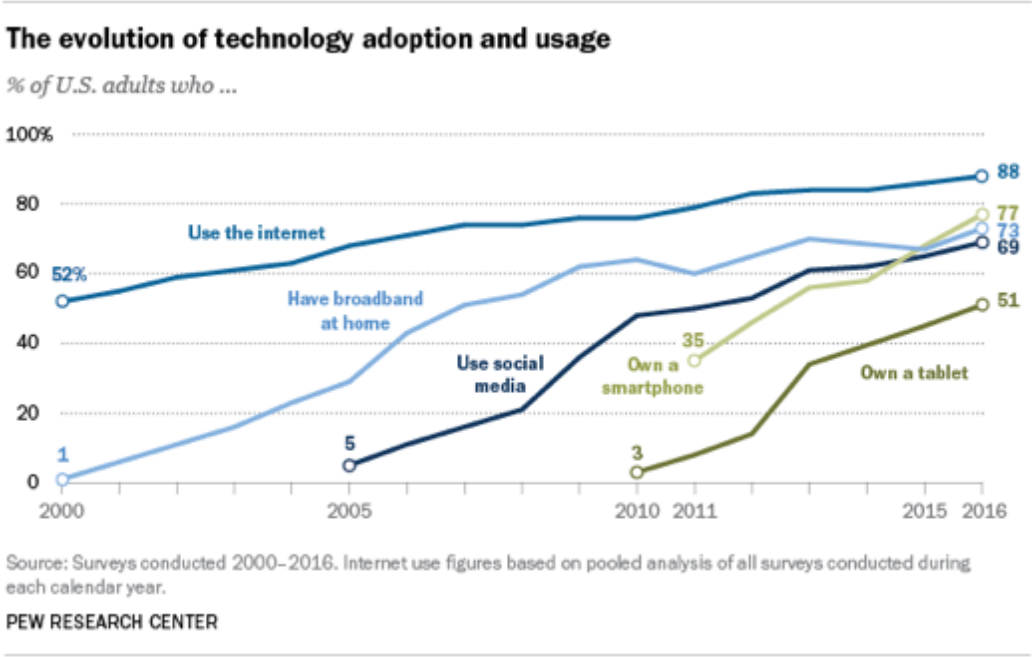
Transforming Clinical Trials

- 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



McDonald AM. Trials 2006;7:9 https://doi.org/10.1186/1745-6215-7-9

Murthy VH. JAMA 2004;291:2720-2726

Steinhubl SR. Lancet 2017;390:2135

mHealth Screening To Prevent Strokes

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

aetna® Members

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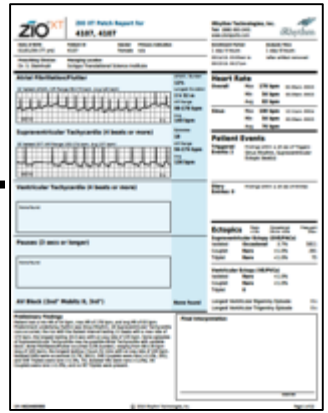

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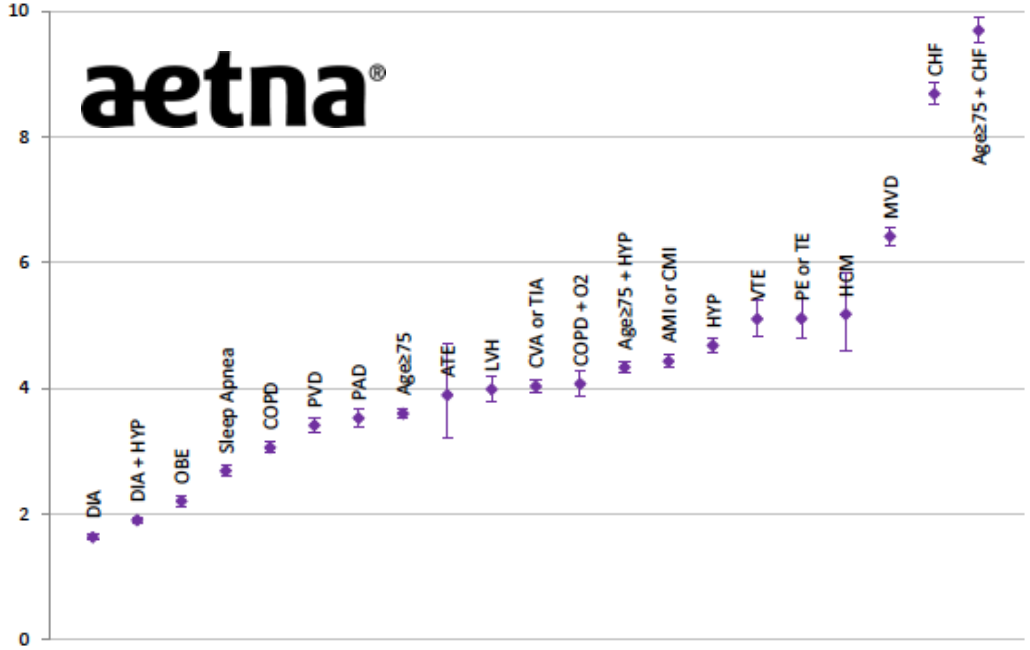
Population to be Based on Database Population Risk Factors

Afib Relative Risks – All Members



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Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Age ≥ 75 years old, OR	History of AF (fibrillation or flutter) or atrial tachycardia
Males age >55, females >65 AND	Chronic Anticoagulation
Prior CVA, OR	Implantable Pacemaker or Defibrillator
Heart Failure Diagnosis, OR	Metastatic Cancer
Diagnosis of Diabetes and HTN, OR	End Stage Renal Disease
Mitral Valve Disease, OR	Moderate or Greater Dementia
Left Ventricular Hypertrophy, OR	Hospice Care
Severe O2-Depenedent COPD, OR	
Obstructive Sleep Apnea, OR	
History of Pulmonary Embolism, OR	
History of Myocardial Infarction, OR	
Morbid Obesity	

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Outlook File Edit View Message Format Tools Window Help

Test - Invitation to an important heart health study - Temporary Items

Message

Delete Reply Reply All Forward Move Rul... Junk Unread Categorize Follow Up

Test - Invitation to an important heart health study

Aetna

Sent: Wednesday, November 4, 2015 at 5:00 AM

To: Tigre, Eduardo

aetna®

Quality health plans & benefits
Healthier living
Financial well-being
Intelligent solutions

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

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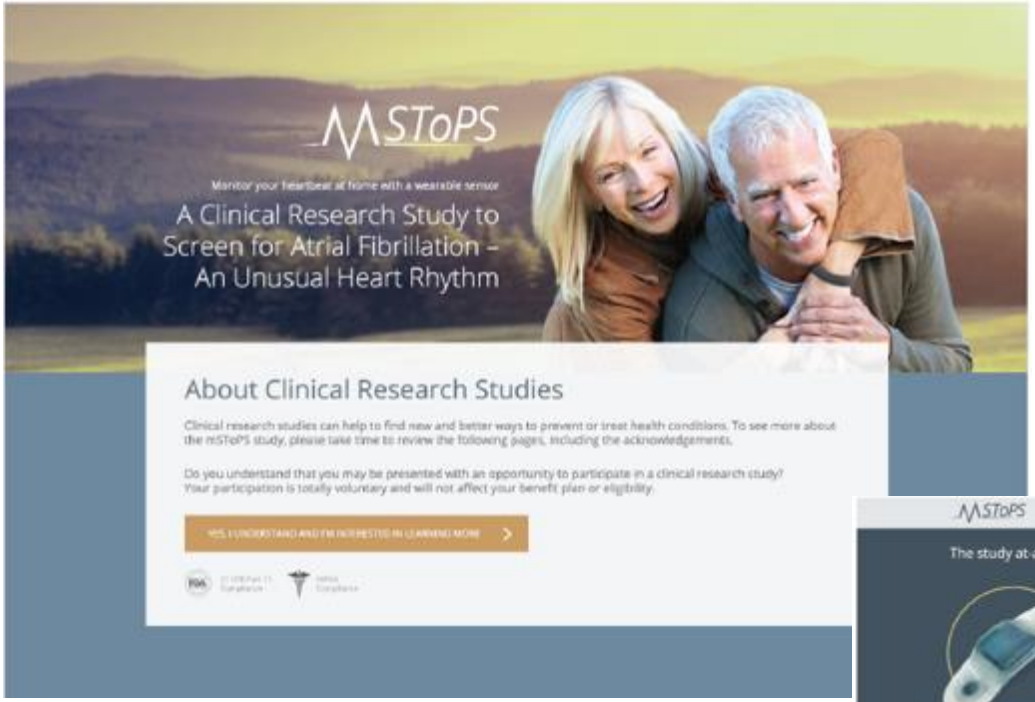
mSToPS Website



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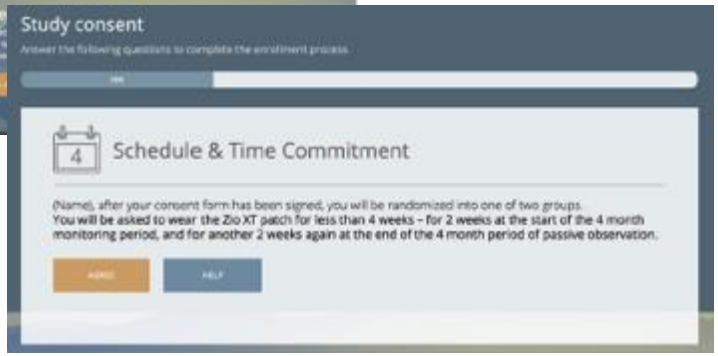
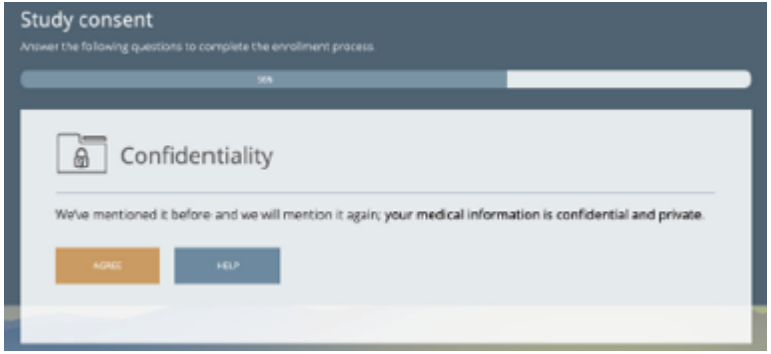
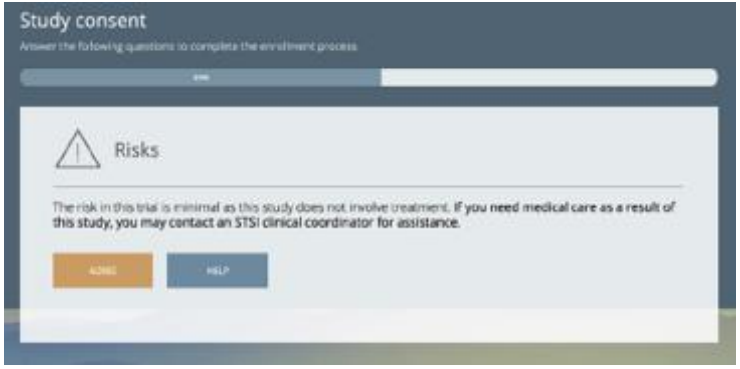
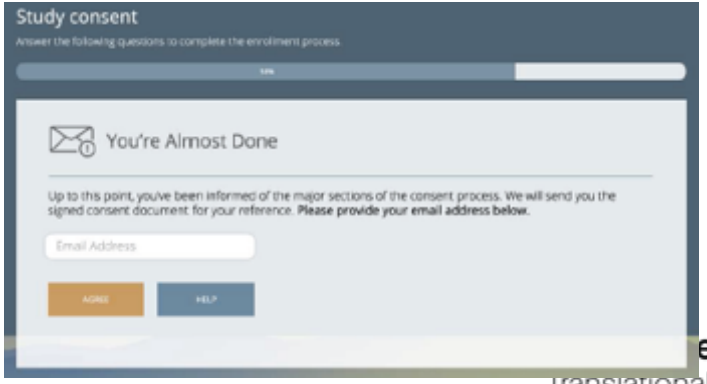
ed Consent









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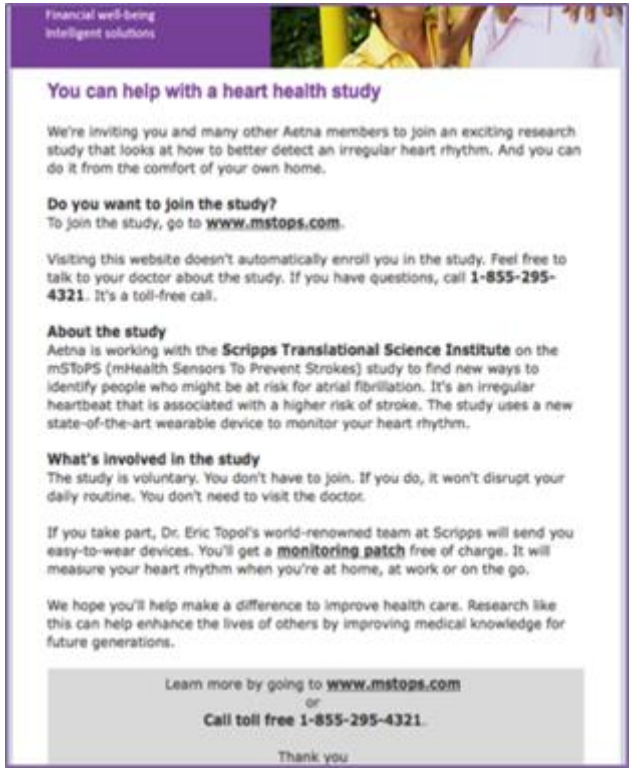
Lessons from a fully digital, direct-to-participant, randomized pragmatic trial:



Financial well-being
Intelligent solutions

You can help with a heart health study

We're inviting you and many other Aetna members to join an exciting research study that looks at how to better detect an irregular heart rhythm. And you can do it from the comfort of your own home.

Do you want to join the study?
To join the study, go to **www.mstops.com**.

Visiting this website doesn't automatically enroll you in the study. Feel free to talk to your doctor about the study. If you have questions, call **1-855-295-4321**. It's a toll-free call.

About the study
Aetna is working with the **Scripps Translational Science Institute** on the mSToPS (mHealth Sensors To Prevent Strokes) study to find new ways to identify people who might be at risk for atrial fibrillation. It's an irregular heartbeat that is associated with a higher risk of stroke. The study uses a new state-of-the-art wearable device to monitor your heart rhythm.

What's involved in the study
The study is voluntary. You don't have to join. If you do, it won't disrupt your daily routine. You don't need to visit the doctor.

If you take part, Dr. Eric Topol's world-renowned team at Scripps will send you easy-to-wear devices. You'll get a **monitoring patch** free of charge. It will measure your heart rhythm when you're at home, at work or on the go.

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.

Learn more by going to **www.mstops.com**
or
Call toll free 1-855-295-4321.

Thank you

Our first attempt at email-based recruitment:
0.07% enrollment rate

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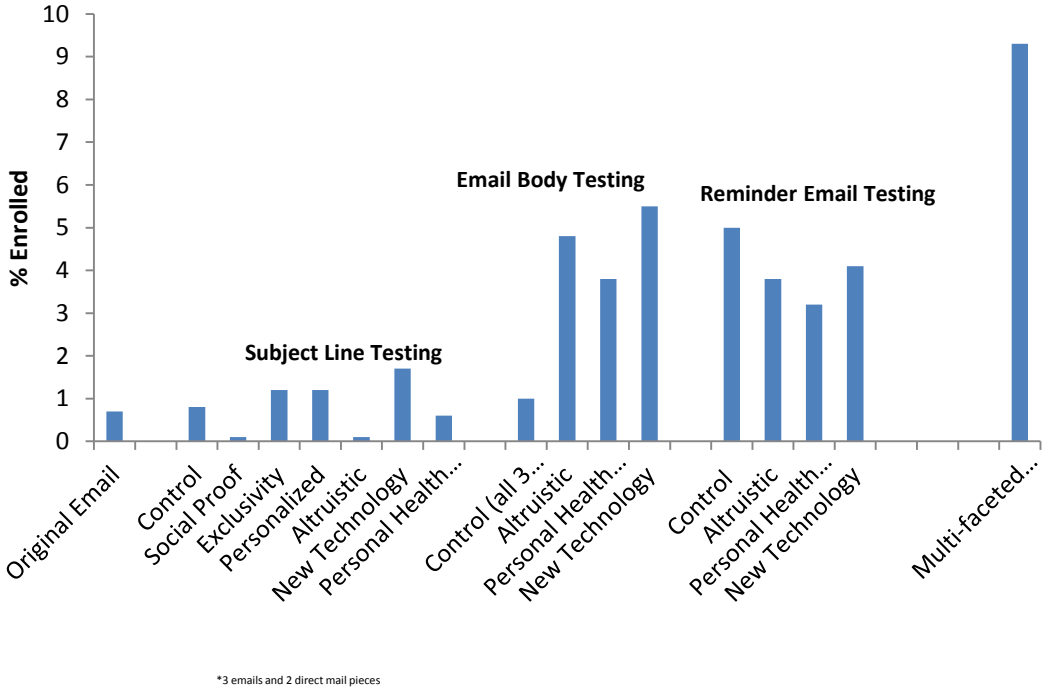
Eventually Achieved an ~20-fold Increase in Response Rate



*3 emails and 2 direct mail pieces

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

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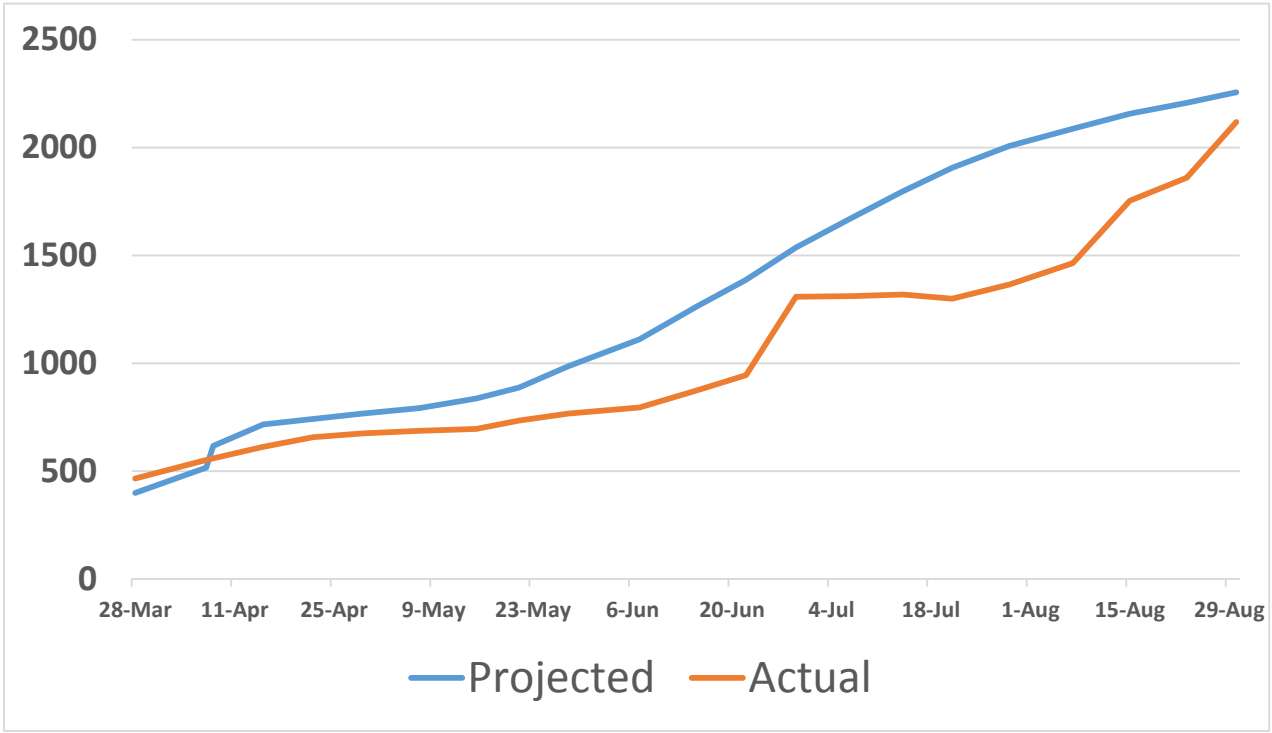
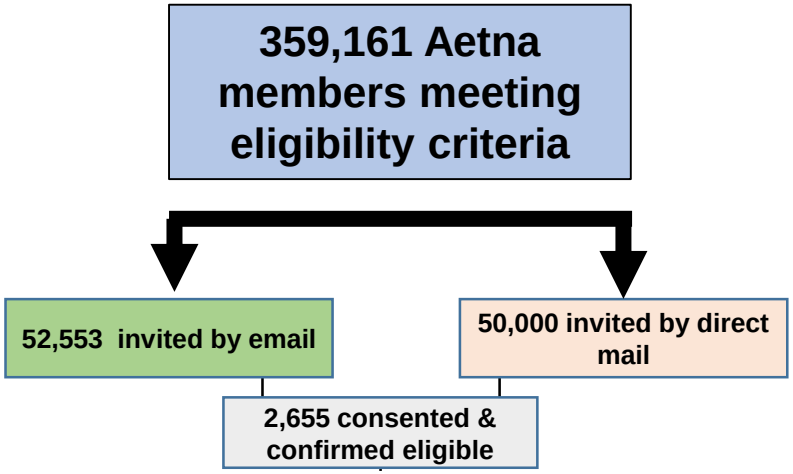
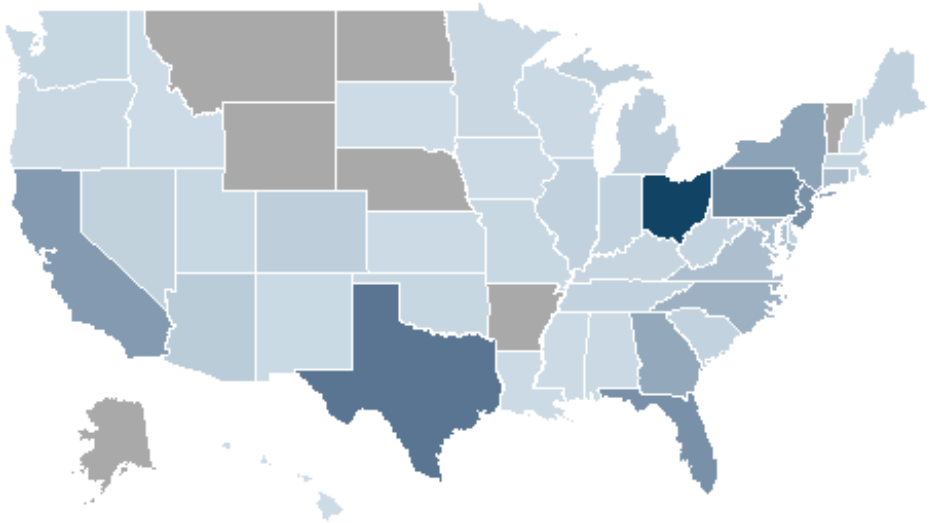
Recruitment Success:

Designing a Learning System That Allowed Ongoing Refinement and Improvement







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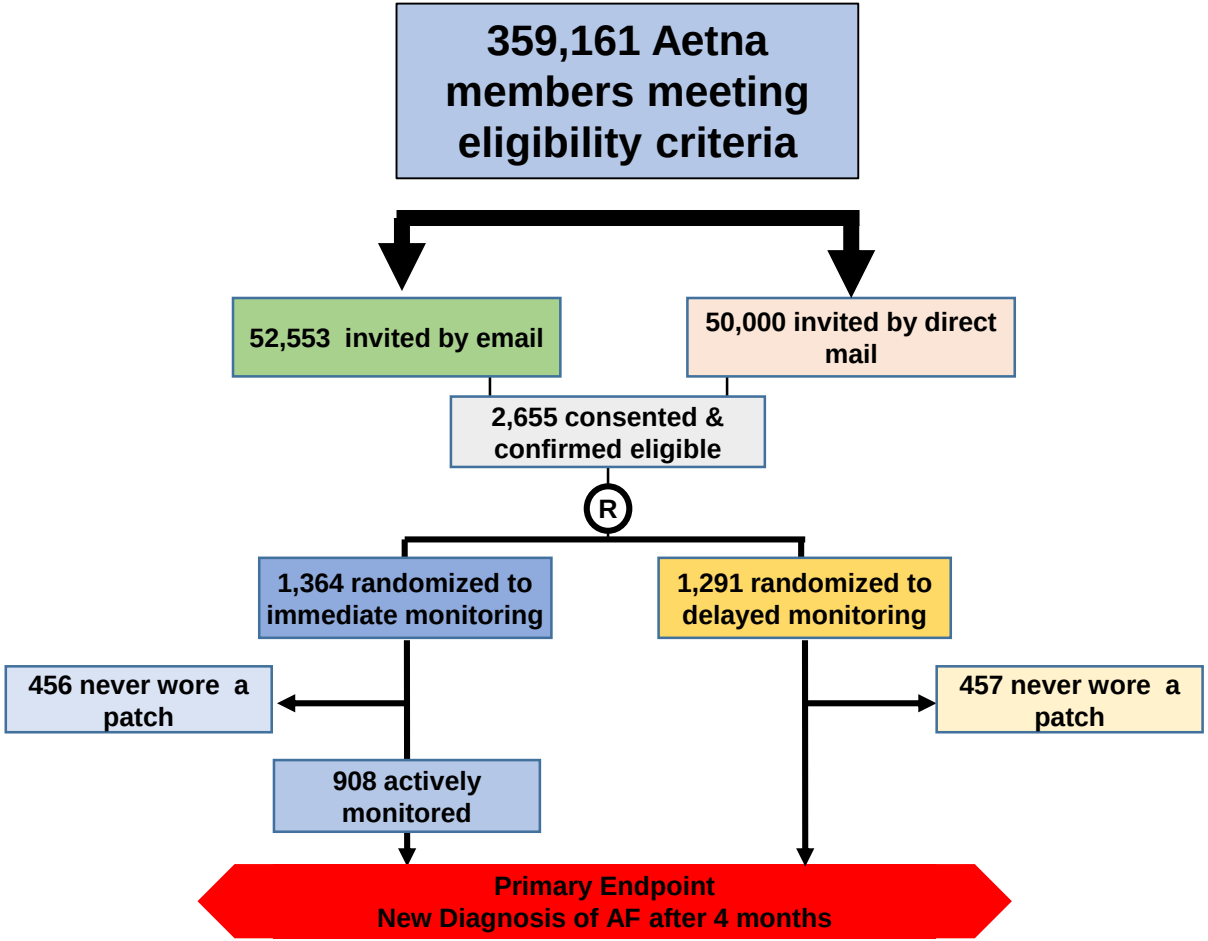

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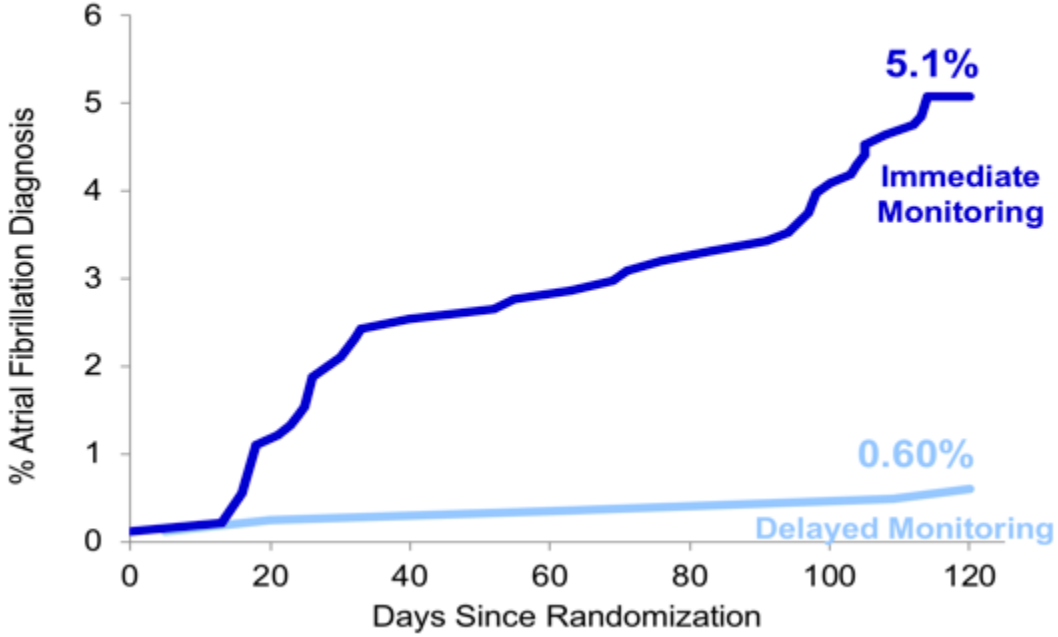
Baseline Demographics

	Immediate n=1364	Delayed n=1291	p-value
Age (mean, SD)	73.5 (7.3)	73.1 (7.1)	0.12
% Female	38.2	39.0	0.66
CHA_2DS_2-VASc (median, Q1-Q3))	3 (2-4)	3 (2-4)	0.82
Prior Stroke (%)	13.7	14.0	0.82
Heart Failure (%)	5.1	4.6	0.56
Hypertension (%)	77.1	76.8	0.86
Diabetes (%)	38.7	36.5	0.24
Sleep Apnea (%)	24.9	29.0	0.02
Hx of MI (%)	5.5	5.6	0.93
Obesity (%)	17.3	18.4	0.45
Chronic Renal Failure (%)	10.9	9.6	0.29

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)



OR 8.8
95%CI 3.5-22.4
P<0.0001

For ITT population

OR 9.0

95%CI 3.6-22.7
P<0.0001

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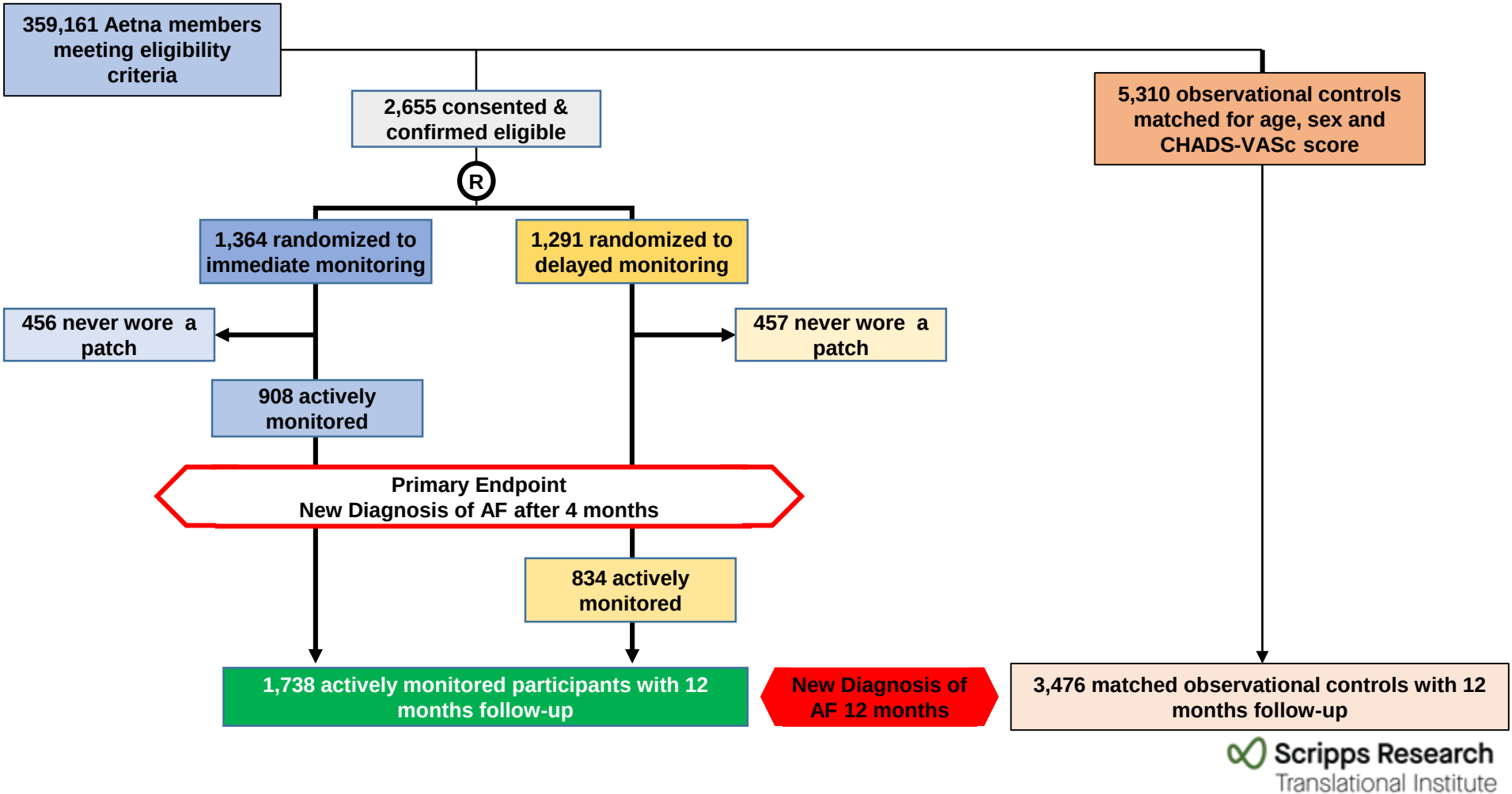
359,161 Aetna members meeting eligibility criteria
2,655 consented & confirmed eligible
R
5,310 observational controls matched for age, sex and CHADS-VASc score
1,364 randomized to immediate monitoring
1,291 randomized to delayed monitoring
456 never wore a patch
457 never wore a patch
908 actively monitored
Primary Endpoint
New Diagnosis of AF after 4 months
834 actively monitored
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
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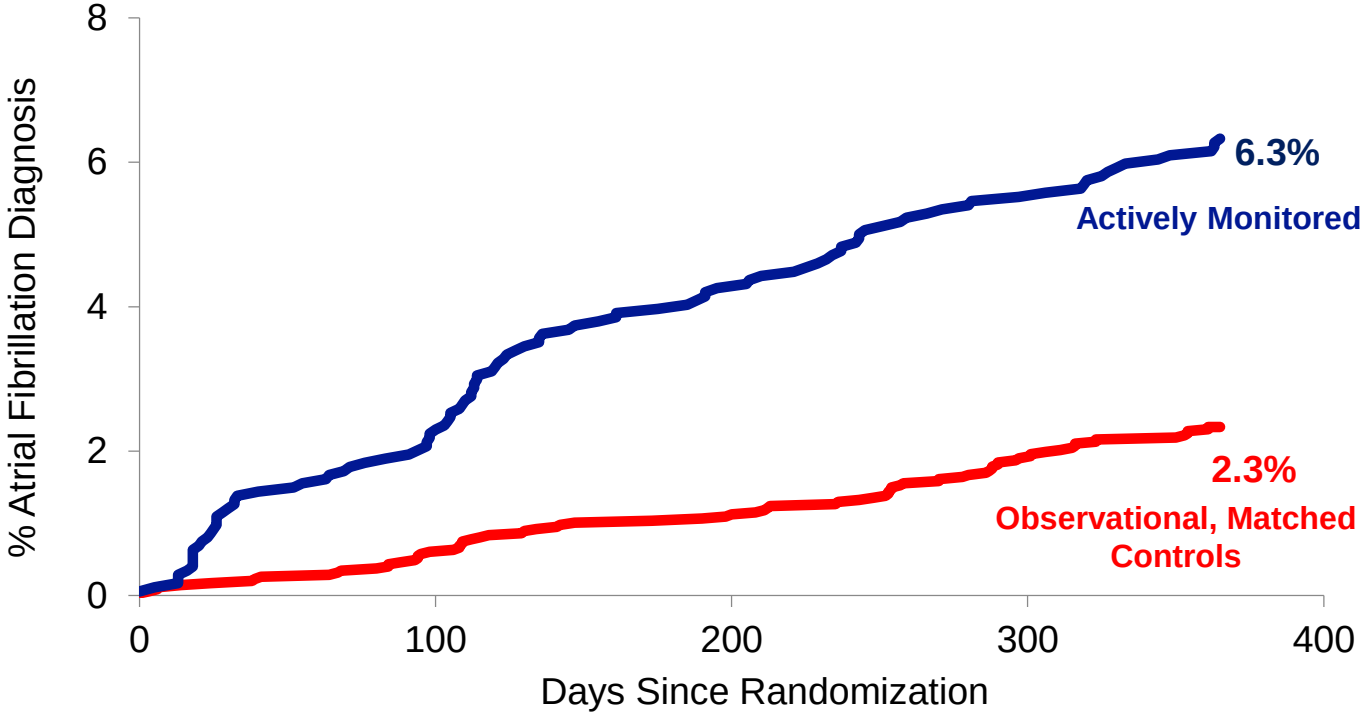
1-Year New Diagnosis of AF



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

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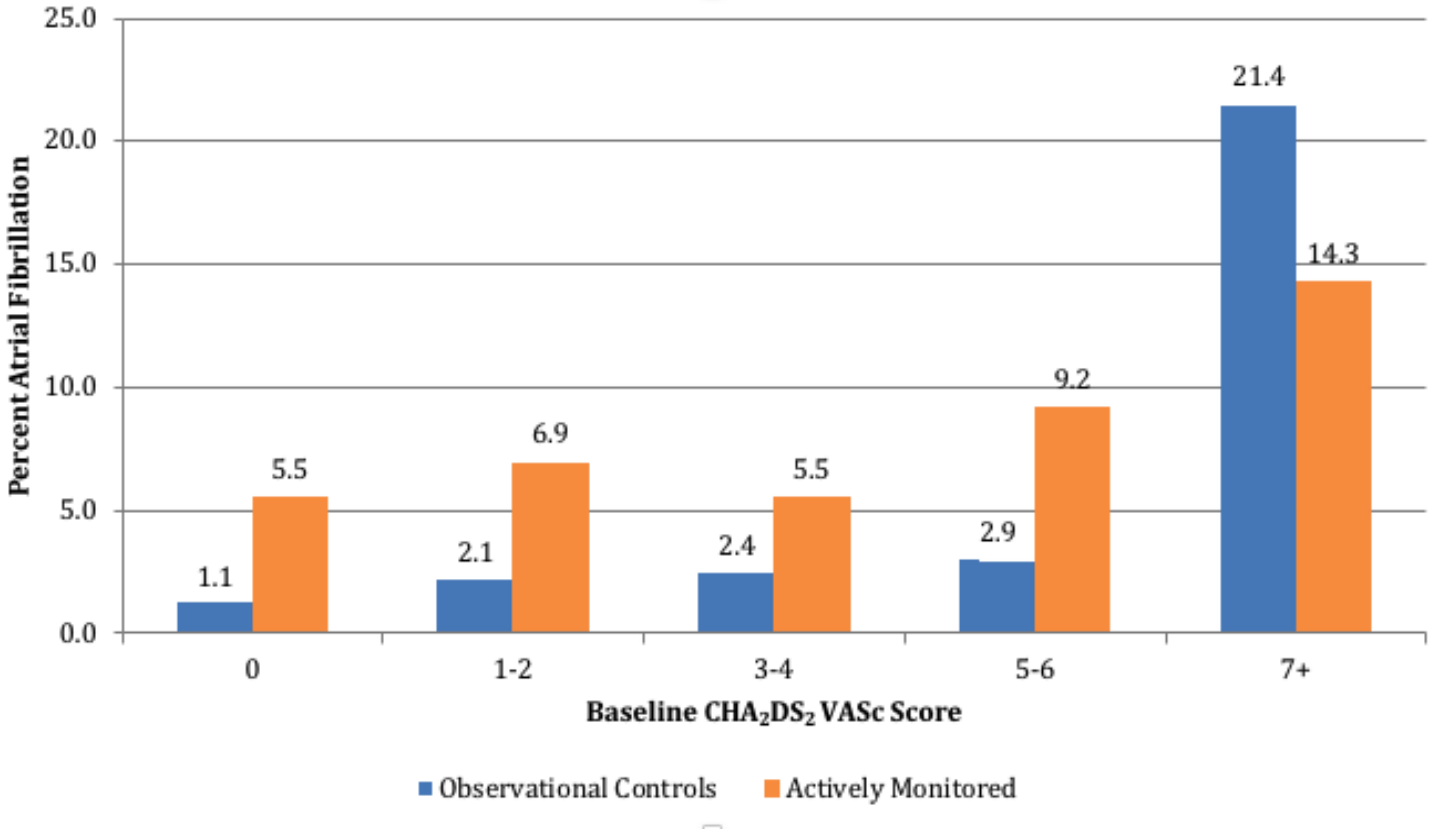
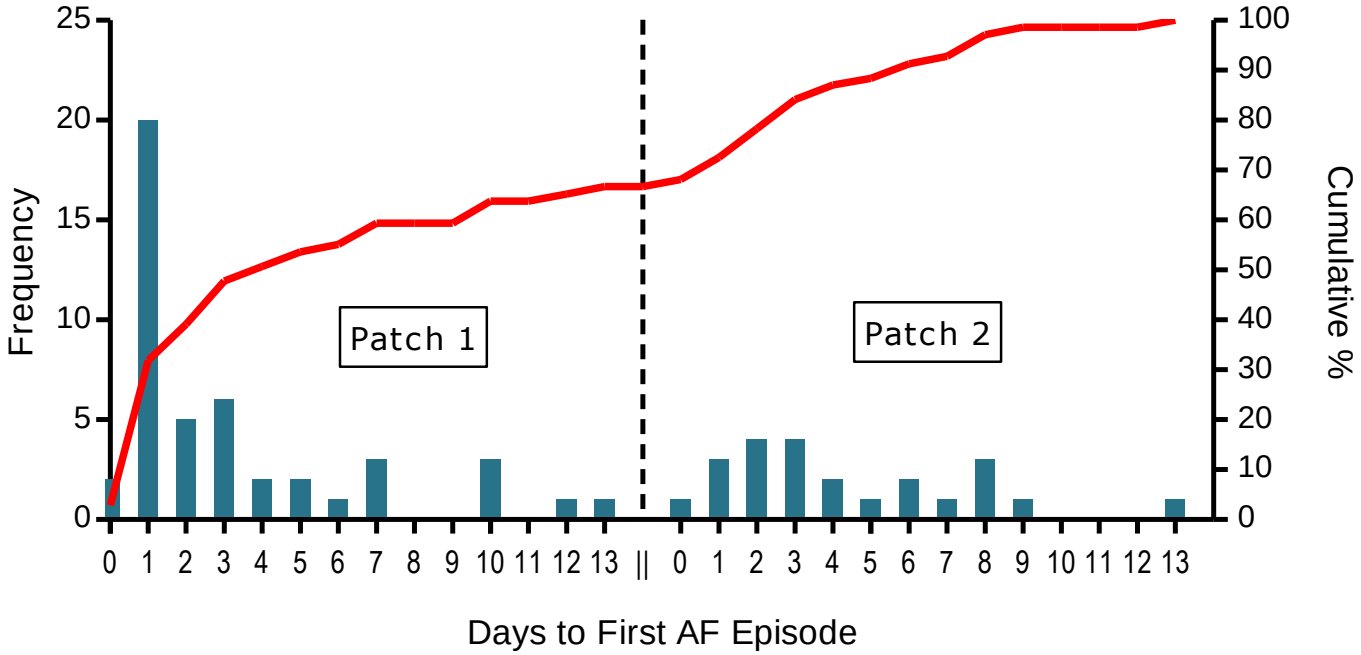
CHA_2DS_2-VASc Score & New Diagnosis of AF – Monitored vs Controls



Characteristics of Sensor-Detected AF

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



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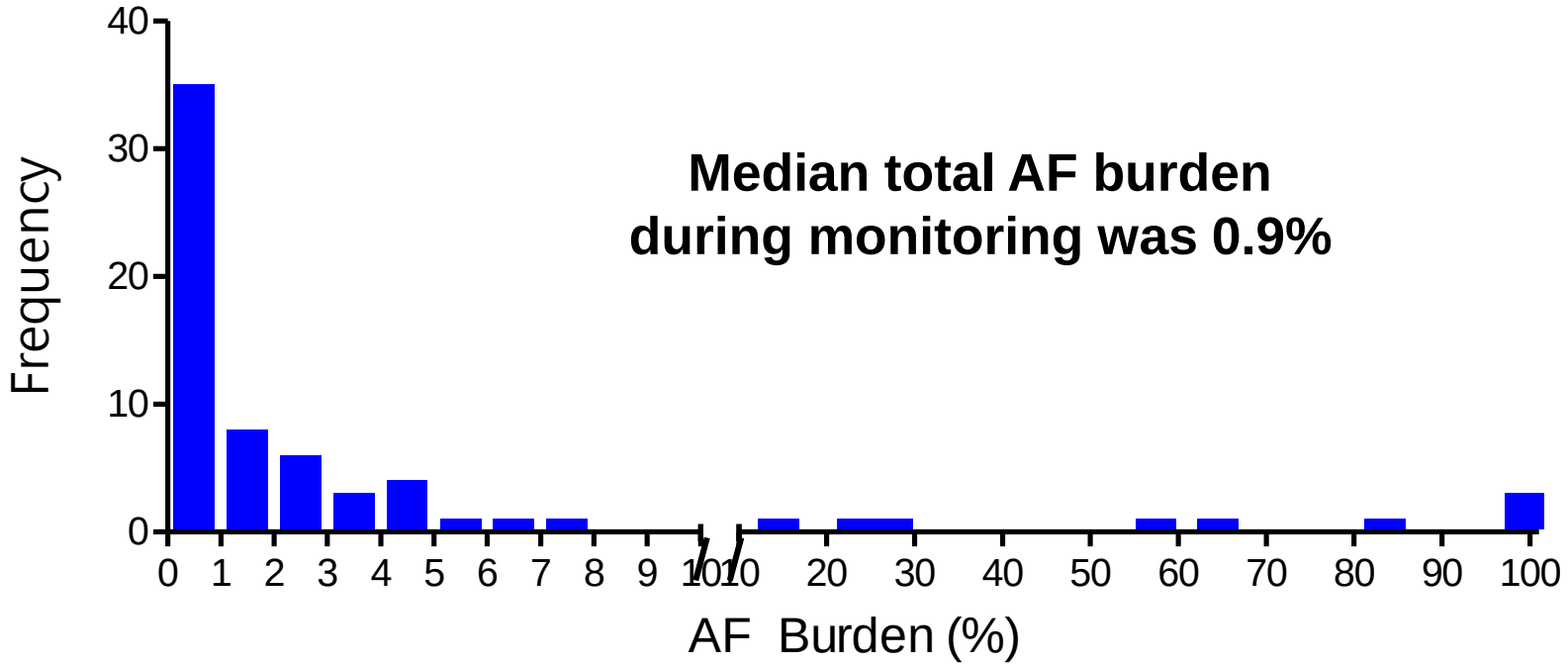
Characteristics of Sensor-Detected AF



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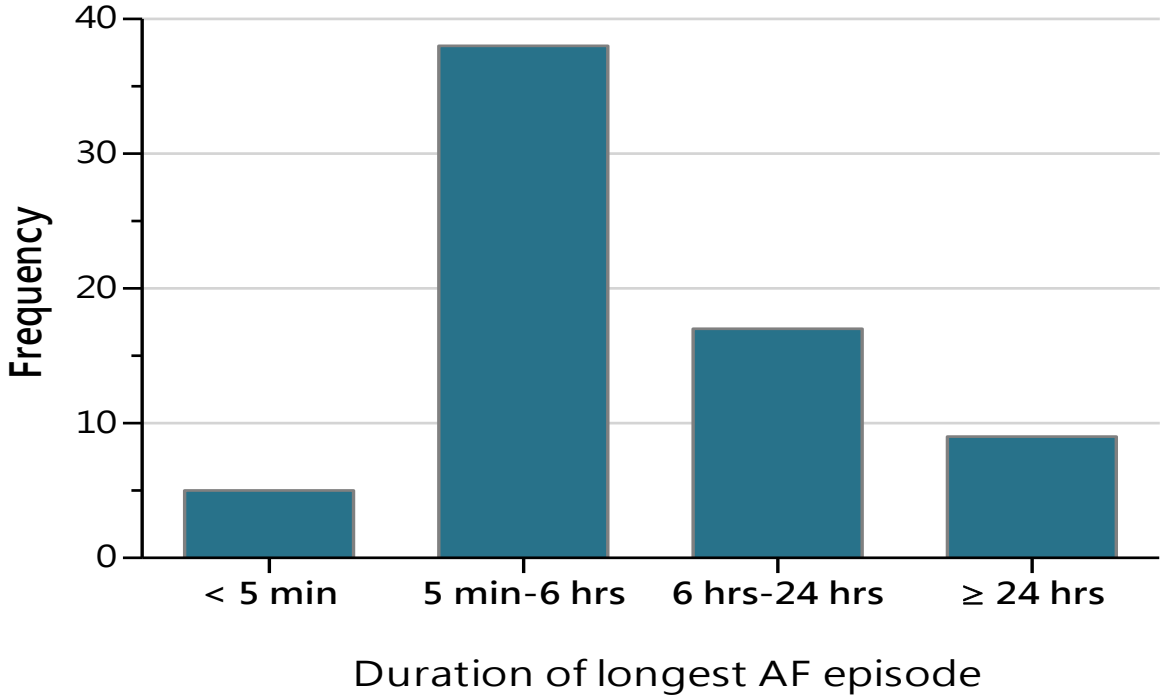
Characteristics of Sensor-Detected AF



Median duration of longest AF episode 185.5 minutes

- 92.8% > 5 minutes
- 37.7% > 6 hours

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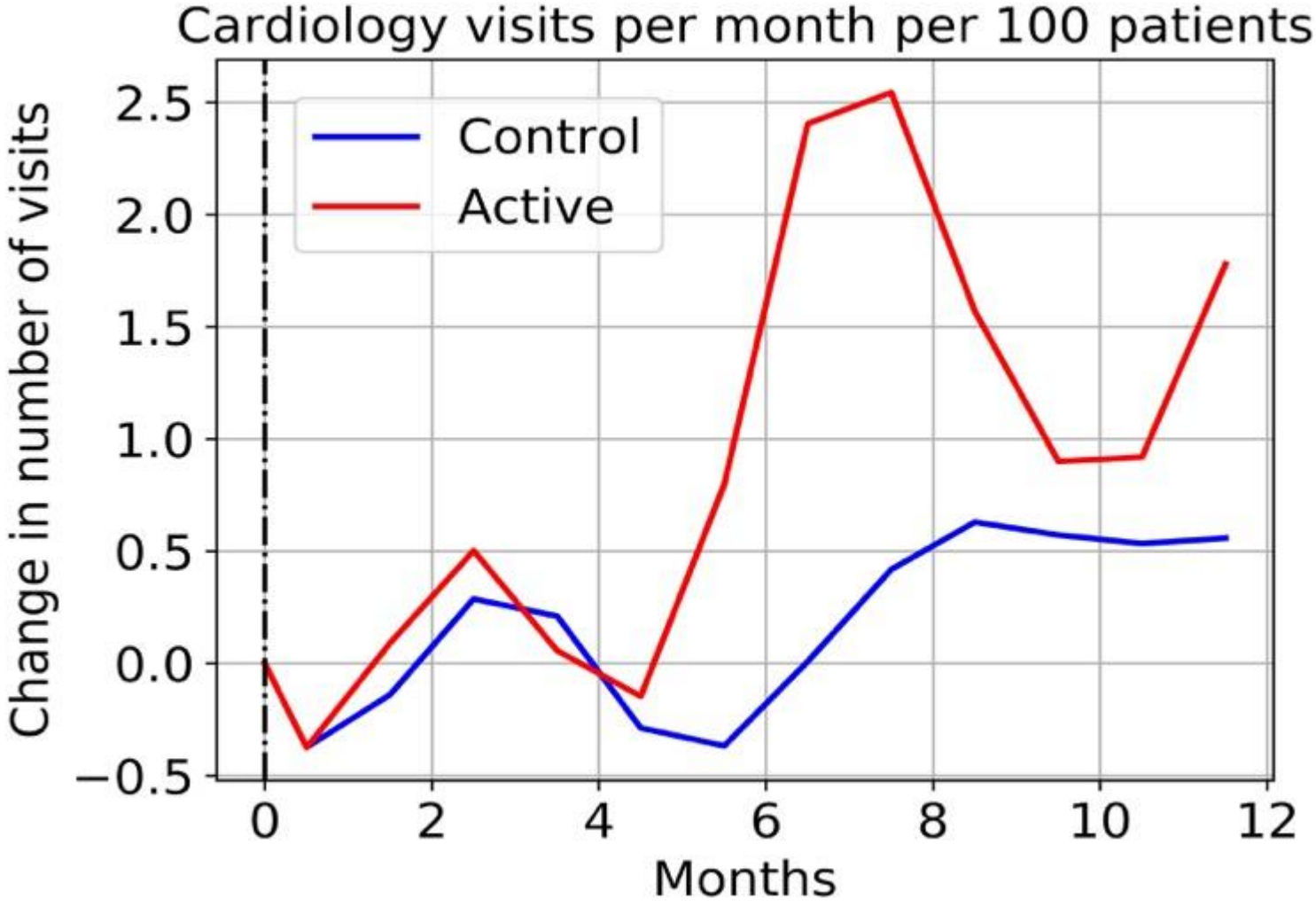
Table 4. Clinical Utilization Over 1 Year in Those Actively Monitored and Their Matched Observational Controls

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



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JAMA | Original Investigation

Effect of a Home-Based Wearable Continuous ECG Monitoring Patch on Detection of Undiagnosed Atrial Fibrillation

The mSToPS Randomized Clinical Trial

Steven R. Steinhubl, MD; Jill Waalen, MD, MPH; Alison M. Edwards, MStat; Lauren M. Ariniello, BS; Rajesh R. Mehta, BPh, MS; Gail S. Ebner, BS; Chureen Carter, PharmD, MS; Katie Baca-Motes, MBA; Elise Felicione, MPH, MBA; Troy Sarich, PhD; Eric J. Topol, MD

Editorial pages 137 and 139
Video and Supplemental content
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IMPORTANCE Opportunistic screening for atrial fibrillation (AF) is recommended, and improved methods of early identification could allow for the initiation of appropriate therapies to prevent the adverse health outcomes associated with AF.

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

DESIGN, SETTING, AND PARTICIPANTS A direct-to-participant randomized clinical trial and prospective matched observational cohort study were conducted among members of a large national health plan. Recruitment began November 17, 2015, and was completed on October 4, 2016, and 1-year claims-based follow-up concluded in January 2018. For the clinical trial, 2659 individuals were randomized to active home-based monitoring to start immediately or delayed by 4 months. For the observational study, 2 deidentified age-, sex- and CHA_2DS_2-VASc–matched controls were selected for each actively monitored individual.

INTERVENTIONS The actively monitored cohort wore a self-applied continuous ECG monitoring patch at home during routine activities for up to 4 weeks, initiated either immediately after enrolling (n = 1364) or delayed for 4 months after enrollment (n = 1291).

MAIN OUTCOMES AND MEASURES The primary end point was the incidence of a new diagnosis of AF at 4 months among those randomized to immediate monitoring vs delayed monitoring. A secondary end point was new AF diagnosis at 1 year in the combined actively monitored groups vs matched observational controls. Other outcomes included new prescriptions for anticoagulants and health care utilization (outpatient cardiology visits, primary care visits, or AF-related emergency department visits and hospitalizations) at 1 year.

RESULTS The randomized groups included 2659 participants (mean [SD] age, 72.4 [7.3] years; 38.6% women), of whom 1738 (65.4%) completed active monitoring. The observational study comprised 5214 (mean [SD] age, 73.7 [7.0] years; 40.5% women; median CHA_2DS_2-VASc score, 3.0), including 1738 actively monitored individuals from the randomized trial and 3476 matched controls. In the randomized study, new AF was identified by 4 months in 3.9% (53/1366) of the immediate group vs 0.9% (12/1293) in the delayed group (absolute difference, 3.0% [95% CI, 1.8%-4.1%]). At 1 year, AF was newly diagnosed in 10.9 monitored (5.7 per 100 person-years) and 81 unmonitored (2.6 per 100 person-years; difference, 4.1 [95% CI, 3.0-4.2]) individuals. Active monitoring was associated with increased initiation of anticoagulants (5.7 vs 3.7 per 100 person-years; difference, 2.0 [95% CI, 1.0-2.7]), outpatient cardiology visits (13.5 vs 26.0 per 100 person-years; difference, 7.5 [95% CI, 7.2-7.9]), and primary care visits (83.5 vs 82.6 per 100 person-years; difference, 0.9 [95% CI, 0.4-1.5]). There was no difference in AF-related emergency department visits and hospitalizations (1.3 vs 1.4 per 100 person-years; difference, 0.1 [95% CI, −0.1 to 0]).

CONCLUSIONS AND RELEVANCE Among individuals at high risk for AF, immediate monitoring with a home-based wearable ECG sensor patch, compared with delayed monitoring, resulted in a higher rate of AF diagnosis after 4 months. Monitored individuals, compared with nonmonitored controls, had higher rates of AF diagnosis, greater initiation of anticoagulants, but also increased health care resource utilization at 1 year.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02506244

JAMA. 2018;320(2):146-155. doi:10.1001/jama.2018.8102

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Wearable mHealth Device Detects Abnormal Heart Rhythms Earlier

Posted on July 17th, 2018 by Dr. Francis Collins

Caption: Woman wearing a Zio patch
Credit: Adapted from JAMA Network Summary Video

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

Recent Posts

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- Watching Cancer Cells Play Ball July 12, 2018
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- How the Brain Regulates Vocal Pitch July 10, 2018
- Celebrating Our Nation's Birth and What It Means for All of Us July 3, 2018

Post Archives

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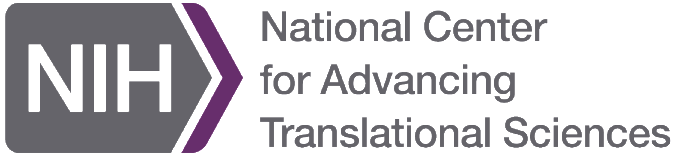
Thank you!

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



UL1TR001114

ESC European Society of Cardiology
European Heart Journal (2018) 39, 1407–1415
doi:10.1093/eurheartj/ehx731

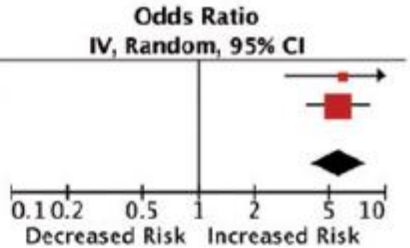
META-ANALYSIS

Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis

Association between Sub-clinical AF & Clinical AF

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Ancillary MOST	1.78	0.3685	22.5%	5.93 [2.88, 12.21]
ASSERT	1.7192	0.1987	77.5%	5.58 [3.78, 8.24]
Total (95% CI)			**100.0%**	**5.66 [4.02, 7.97]**

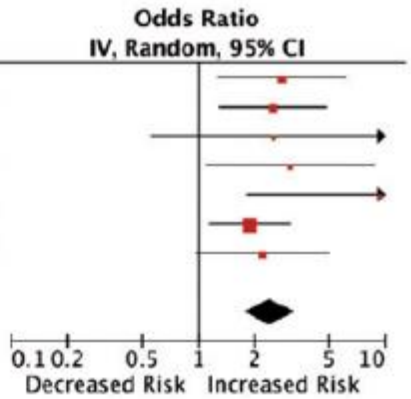
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.88); $I^2 = 0\%$
Test for overall effect: Z = 9.91 (P < 0.00001)



Sub-clinical AF & Stroke

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

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.91$, df = 6 (P = 0.69); $I^2 = 0\%$
Test for overall effect: Z = 5.68 (P < 0.00001)



Mahajan R. European Heart Journal (2018) 39, 1407–1415

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RESEARCH ARTICLE

Validation of a genetic risk score for atrial fibrillation: A prospective multicenter cohort study

Evan D. Muse[1,2], Nathan E. Wineinger[1], Emily G. Spencer[1], Melissa Peters[1], Riley Henderson[1], Yunyue Zhang[1], Paddy M. Barrett[1], Steven P. Rivera[3], Jay G. Wohlgemuth[3], James J. Devlin[3], Dov Shiffman[3], Eric J. Topol[1,2]*

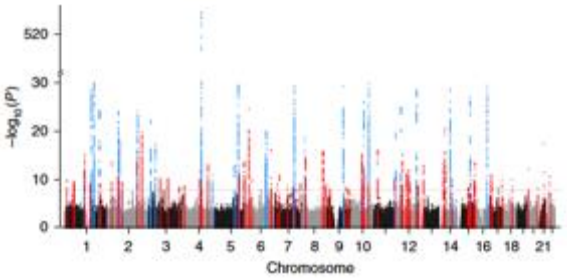

Table 3. Risk estimates of AF events according to AF GRS quintile (12 SNPs).

AF GRS quintile	Unadjusted OR (95% CI)	*p*-Value	Adjusted* OR (95% CI)	*p*-Value
1 (*n* = 187)	Reference	—	Reference	—
2 (*n* = 177)	2.35 (0.94–5.87)	0.07	2.37 (0.89–6.30)	0.08
3 (*n* = 180)	2.48 (1.05–5.87)	0.04	2.47 (0.98–6.22)	0.054
4 (*n* = 182)	3.40 (1.48–7.78)	0.004	3.49 (1.48–8.23)	0.005
5 (*n* = 178)	2.83 (1.21–6.61)	0.02	3.11 (1.27–7.58)	0.013

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.

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