N-of-1 Randomized Trials: CRAVE and I-STOP-AFib as Examples

Gregory M Marcus, MD, MAS
Professor of Medicine
Endowed Professor of Atrial Fibrillation Research
Associate Chief of Cardiology for Research

UCSF
University of California
San Francisco

Disclosures

- Research
  - NIH (NIBIB, NCI, NHLBI)
  - PCORI
  - TRDRP
  - Baylis
- Consulting
  - InCarda Therapeutics
  - Johnson and Johnson
- Equity
  - InCarda Therapeutics (as co-founder)

The Individualized Studies of Triggers of Paroxysmal Atrial Fibrillation Trial

Gregory M Marcus, MD, MAS, Madelaine Faulkner Modrow, MPH, Christopher H Schmid, PhD, Kathi Sigona, MA, Gregory Nah, MA, Jiabei Yang, MS, Tzu-Chun Chu, MPH, Sean Joyce, BS, Shiffen Gettabecha, MPH, Kelsey Ogomori, Vivian Yang, Xochitl Butcher, Mellanie True Hills, BS, Debbe McCall, MBA, Kathleen Sciarappa, EdD, Ida Sim, MD, PhD, Mark J Pletcher, MD, MPH, Jeffrey E Olgin, MD

UCSF
University of California
San Francisco

Risk Factors for Atrial Fibrillation

- Age, Male sex, European ancestry, hypertension, diabetes, increased BMI, heart failure, coronary disease, obstructive sleep apnea
  - Fairly static, chronic, and often immutable

Lifestyle and Atrial Fibrillation: Body Weight

Original Investigation

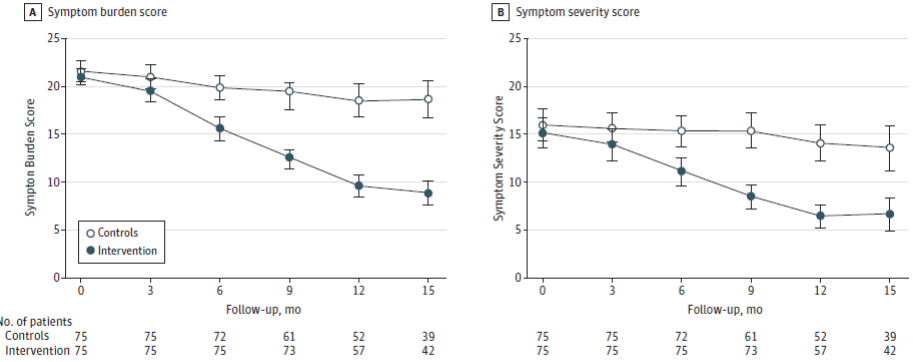
Effect of Weight Reduction and Cardiometabolic Risk Factor Management on Symptom Burden and Severity in Patients With Atrial Fibrillation

A Randomized Clinical Trial

Hany S. Abed, BPharm, MBBS; Gary A. Wittert, MBBch, MD; Darryl P. Leong, MBBS, MPH, PhD; Masoumeh G. Shirazi, MD; Bobak Bahrami, MBBS; Melissa E. Middeldorp; Michelle F. Lorimer, BSc; Dennis H. Lau, MBBS, PhD; Nicholas A. Antic, MBBS, PhD; Anthony G. Brooks, PhD; Walter P. Abhayaratna, MBBS, PhD; Jonathan M. Kalman, MBBS, PhD; Prashanthan Sanders, MBBS, PhD

JAMA November 20, 2013 Volume 310, Number 19

Figure 3. Changes in Atrial Fibrillation Symptom Scale (AFSS) Scores Over Study Follow-up



Error bars indicate 95% confidence intervals. A, Between-group level of significance: $P = .41$ at time 0, $P = .12$ at 3 months, $P < .001$ at 6, 9, 12, and 15 months. B, Between-group level of significance: $P = .49$ at time 0, $P = .17$ at 3 months, $P < .001$ at 6, 9, 12, and 15 months.

UCSF

Lifestyle and Atrial Fibrillation: Alcohol

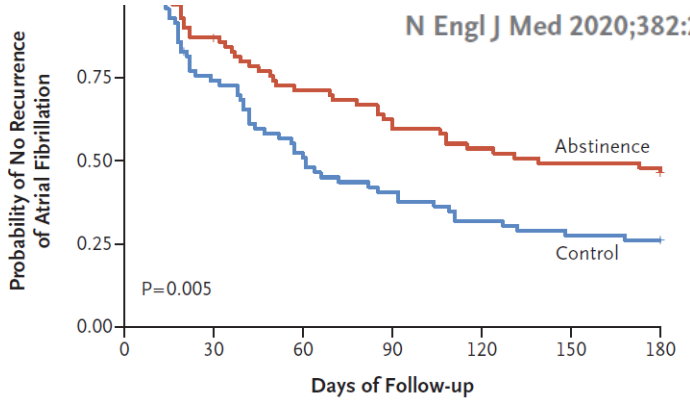
ORIGINAL ARTICLE

Alcohol Abstinence in Drinkers with Atrial Fibrillation

Aleksandr Voskoboinik. M.B.. B.S.. Ph.D.. Ionathan M. Kalman. M.B.. B.S.. Ph.D..

Andrew J. Taylor, M.B., B.S., Ph.D., and Peter M. Kistler, M.B., B.S., Ph.D.

N Engl J Med 2020;382:20-8.



No. at Risk							
Abstinence	70	61	49	43	37	34	33
Control	70	51	36	28	22	19	18

UCSF

What about acute effects?

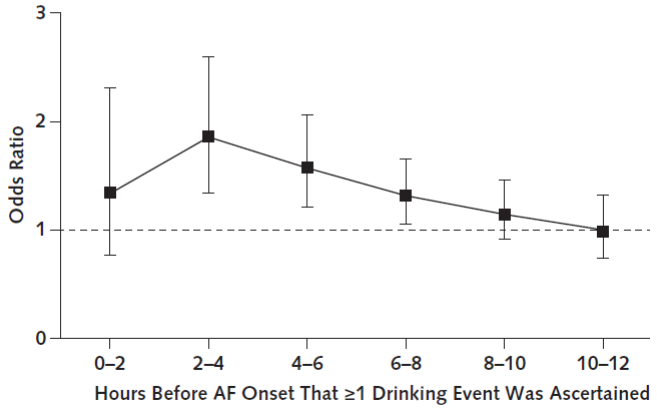
- Can we, or our patients, influence the chance a discrete episode of AF will occur?

Annals of Internal Medicine ORIGINAL RESEARCH

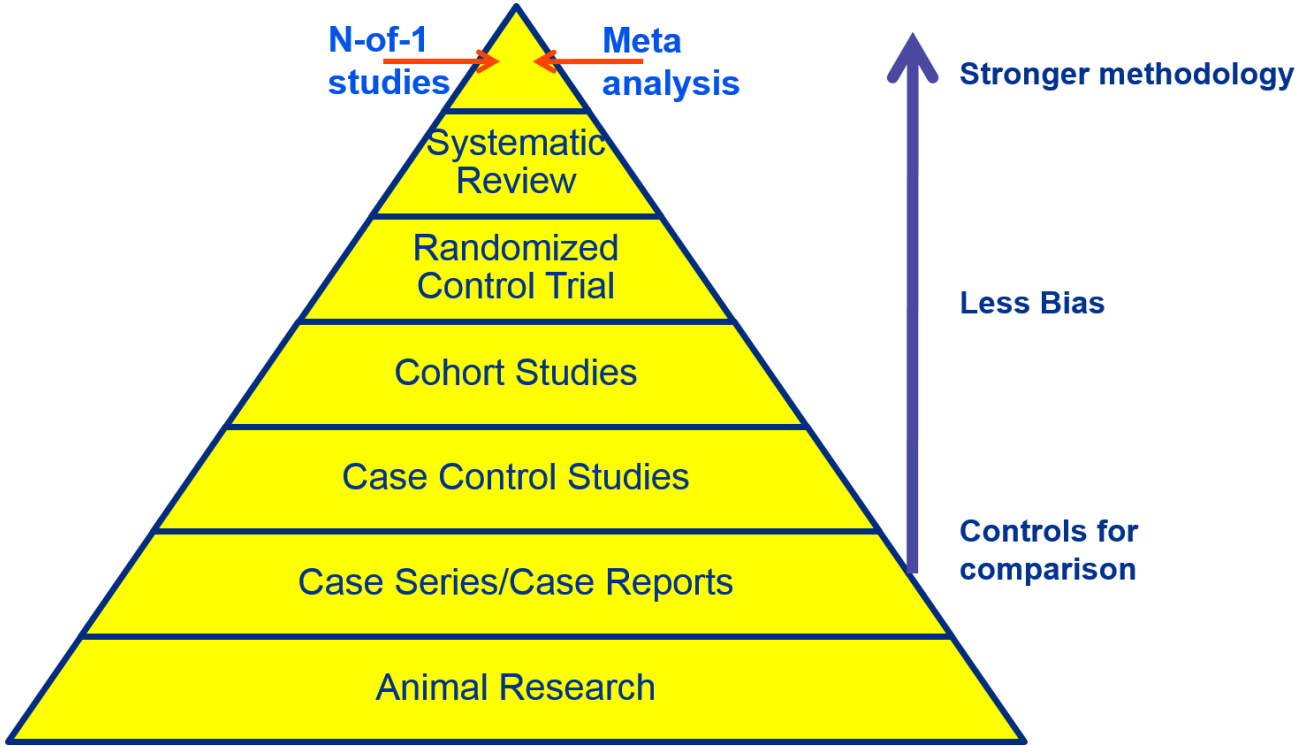
Acute Consumption of Alcohol and Discrete Atrial Fibrillation Events

Gregory M. Marcus, MD, MAS; Eric Vittinghoff, PhD; Isaac R. Whitman, MD; Sean Joyce, BS; Vivian Yang, BA; Gregory Nah, MA; Edward P. Gerstenfeld, MD; Joshua D. Moss, MD; Randall J. Lee, MD, PhD; Byron K. Lee, MD; Zian H. Tseng, MD, MAS; Vasanth Vedantham, MD, PhD; Jeffrey E. Olgin, MD; Melvin M. Scheinman, MD; Henry Hsia, MD; Rachel Gladstone, BA; Shannon Fan, BA; Emily Lee, BS; Christina Fang, BA; Kelsey Ogomori, BA; Robin Fatch, MPH; and Judith A. Hahn, PhD, MA

Figure 2. Odds of any real-time, self-reported drinking event restricted to 2-hour increments before an AF episode.



UCSF


N-of-1 studies
Meta analysis
Systematic Review
Randomized Control Trial
Cohort Studies
Case Control Studies
Case Series/Case Reports
Animal Research
Stronger methodology
Less Bias
Controls for comparison

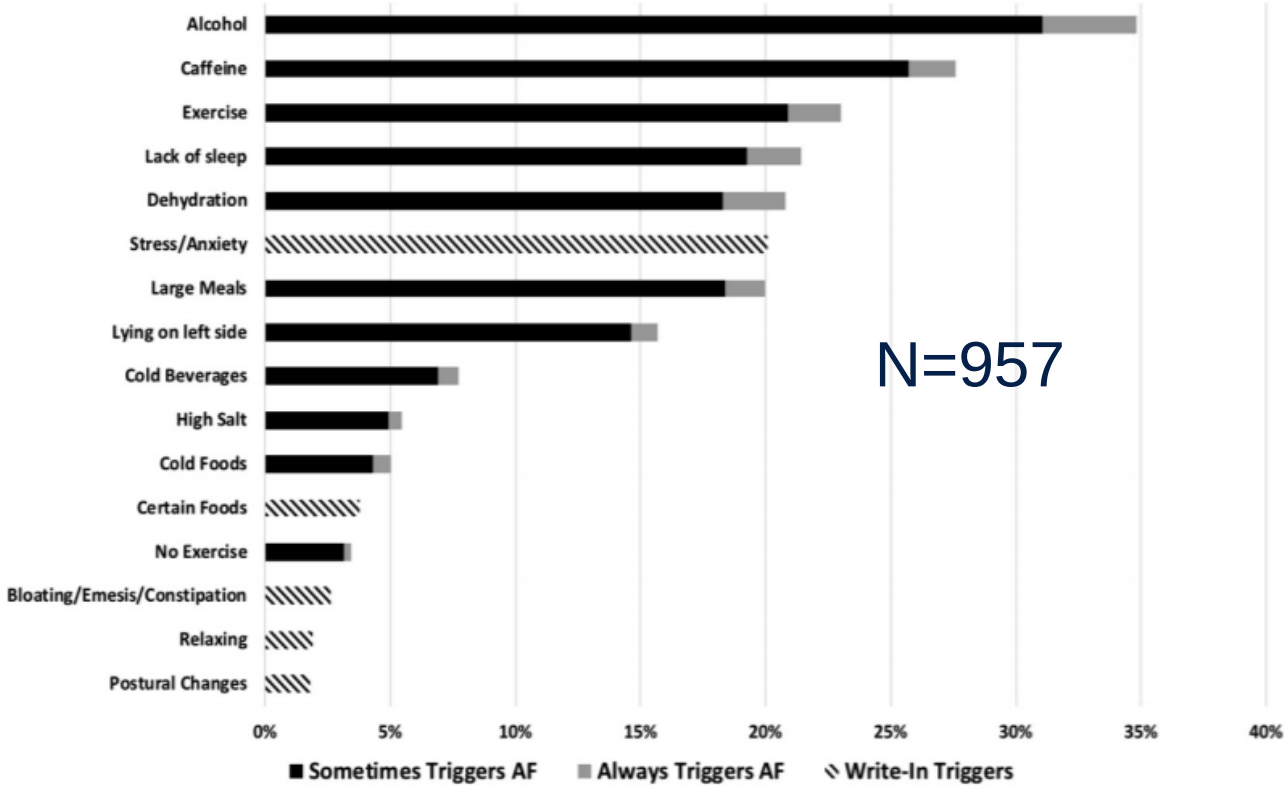
N-of-1 Studies

- Conventional trials can only describe average differences between groups
- Only an “N-of-1 study” can demonstrate how any given individual will react to a particular intervention

N-of-1 Studies

- To conduct an N-of-1 Study (or studies), you need:
  - An exposure and outcome that are:
    - Repeated
    - And have near-term effects
  - An exposure that is modifiable (can introduce or withhold)
  - An outcome that is not catastrophic

We needed a "menu" of potential AF triggers



Groh et al. *Heart Rhythm* 2019

UCSF

Methods

The Health *e*Heart Study

StopAfib.org

AF event tracking only

N-of-1 Trials to Test Triggers and Receive Results

Assess quality of life

Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

UCSF

Methods

KardiaMobile (AliveCor, San Francisco, CA)

Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

UCSF

Methods: Inclusion Criteria

- Adult symptomatic AF patients
- Owned a smartphone (either Android or iOS)
- Interested in testing a presumed AF trigger they could readily introduce or withhold

Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

Methods: Exclusion Criteria

- Those who planned to change their AF management (e.g., with catheter ablation or medication changes) in the subsequent 6 months
- Did not speak English
- A history of an AV junction ablation

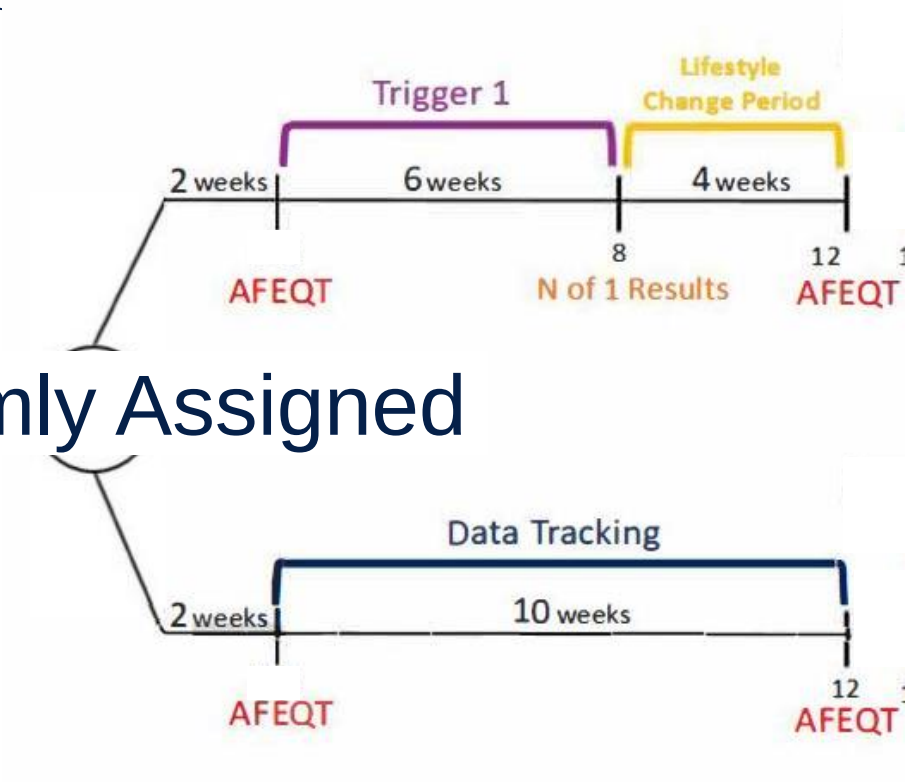
Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

Methods

- Recruited via Health eHeart Study, StopAfib.org, social media, word of mouth, and healthcare providers
- Interested participants downloaded the Eureka mobile app
  - Eureka is an NIH-funded digital research platform housed at UCSF
- Eligibility was determined on the mobile app
- Eligible participants were consented on the mobile app
- Those who already owned a KardiaMobile could integrate their device
  - Otherwise participants were sent a device

Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

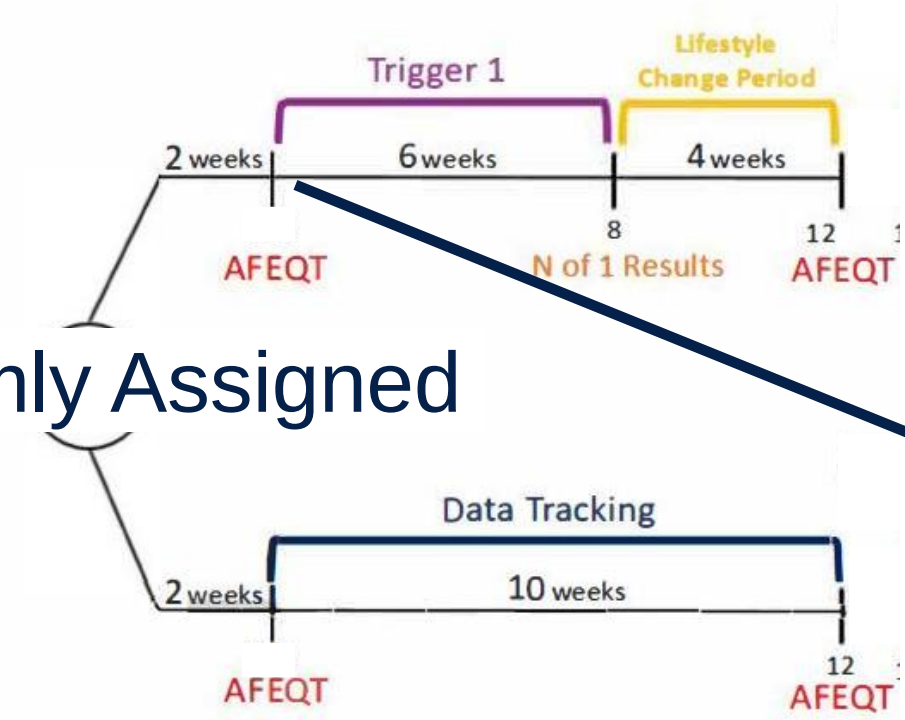
Methods



Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

UCSF

Methods

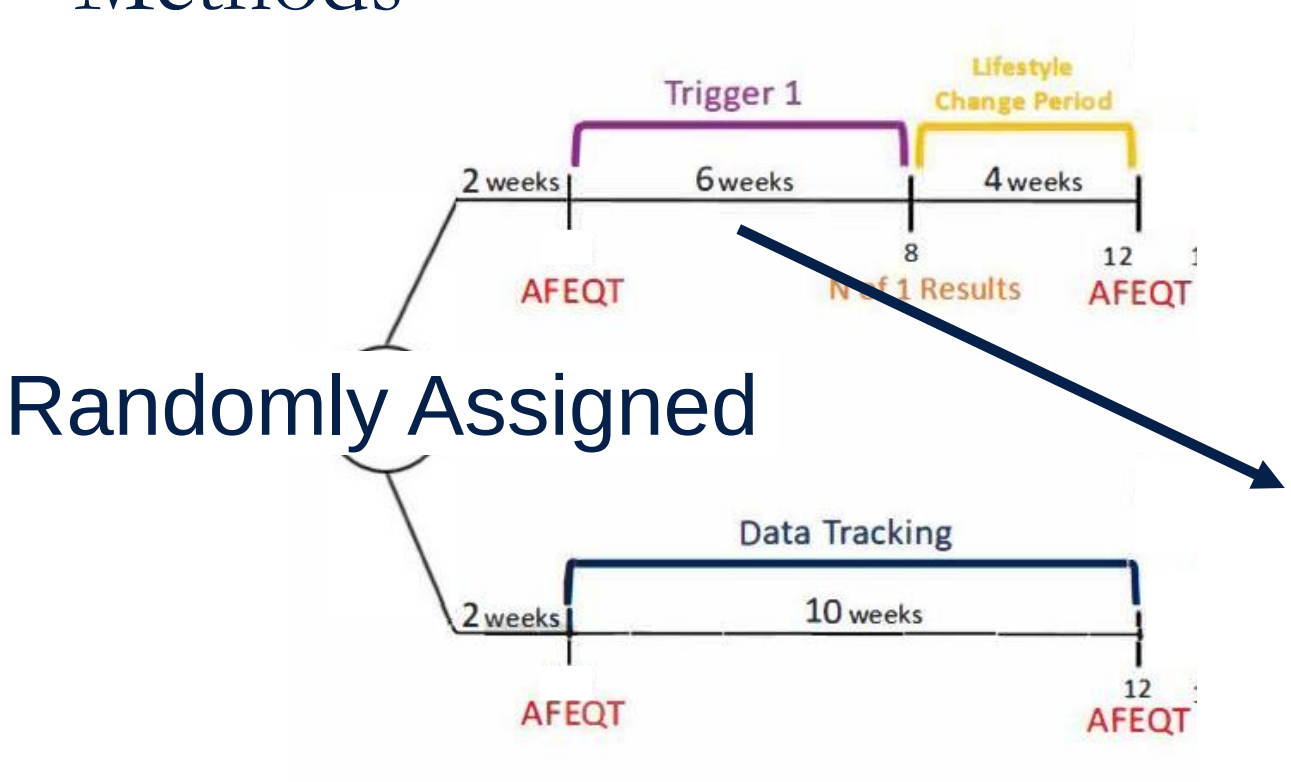


- Participants selected from a menu of triggers
  - Could write-in “custom” triggers to test

Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

UCSF

Methods

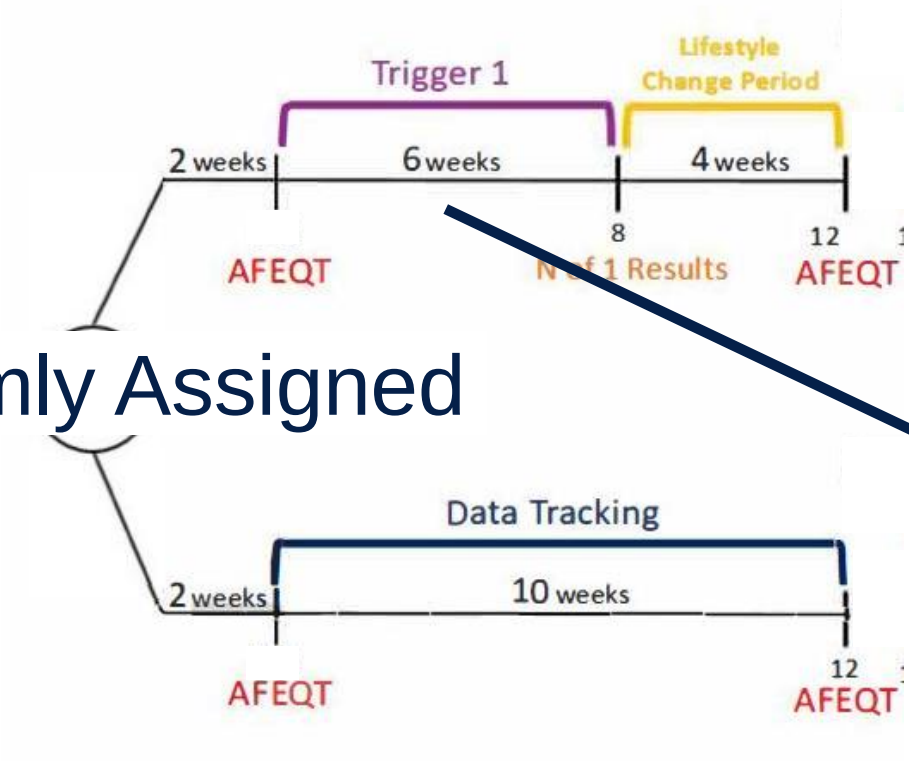


- Randomly assigned in one-week blocks with daily text-based instructions to expose to a given trigger at some point during that week versus avoid their trigger for the entire week

Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

UCSF

Methods

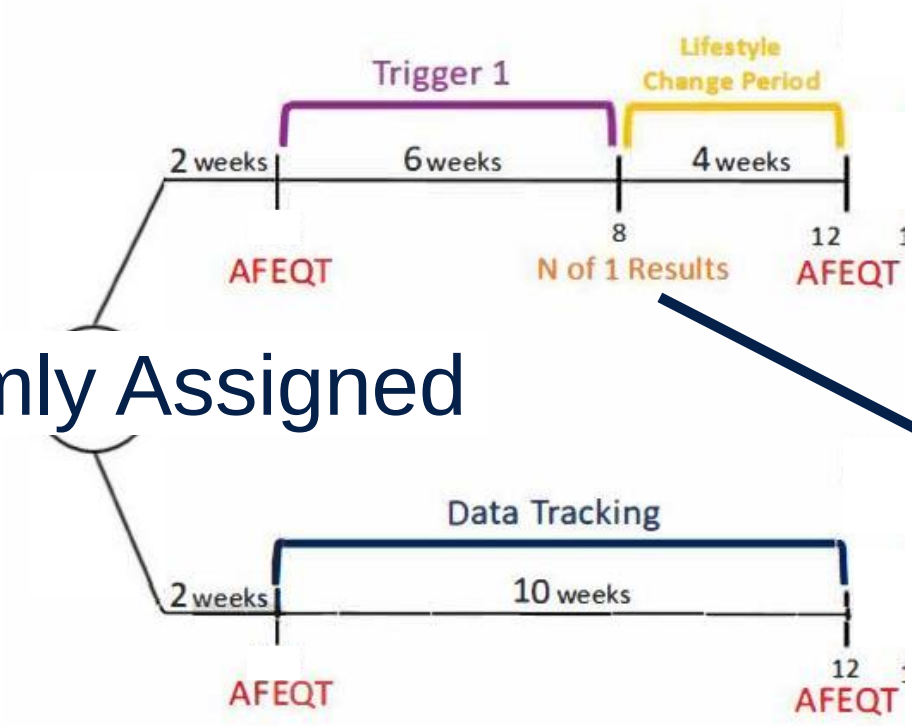


- Trigger compliance was assessed with daily questionnaires

Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

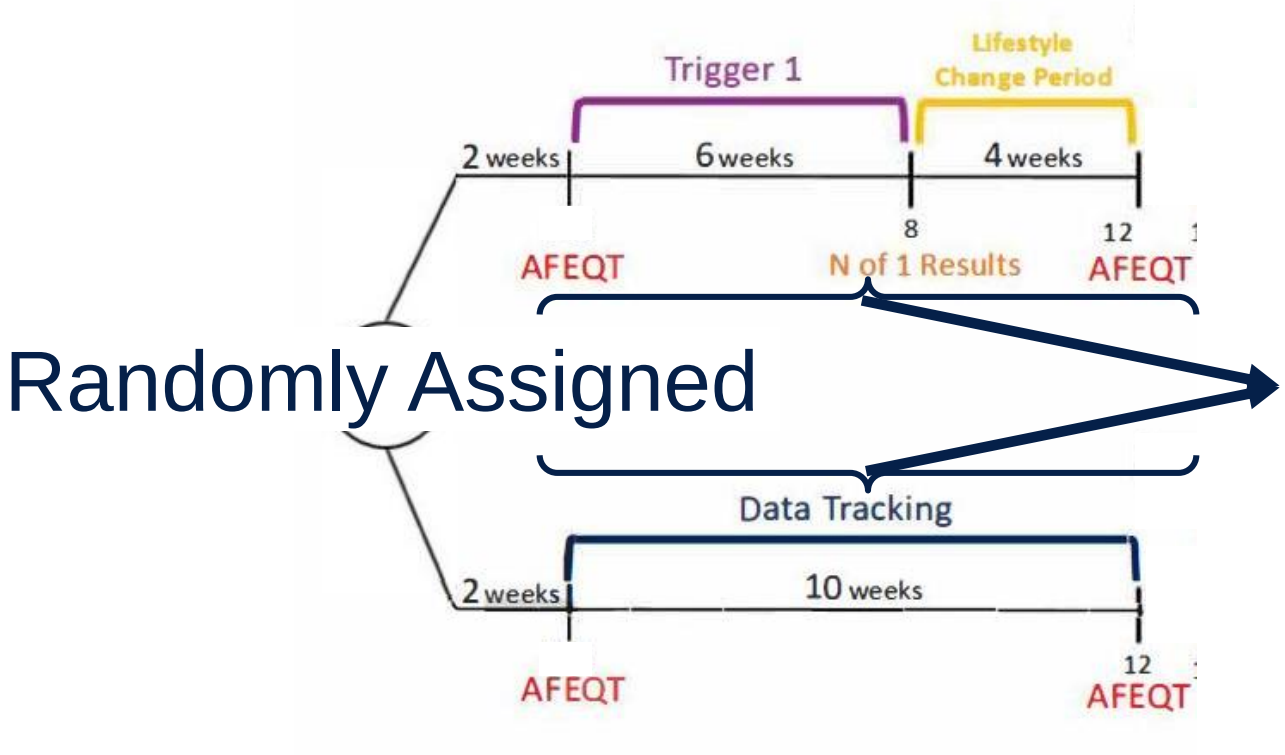
UCSF

Methods



Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

Methods

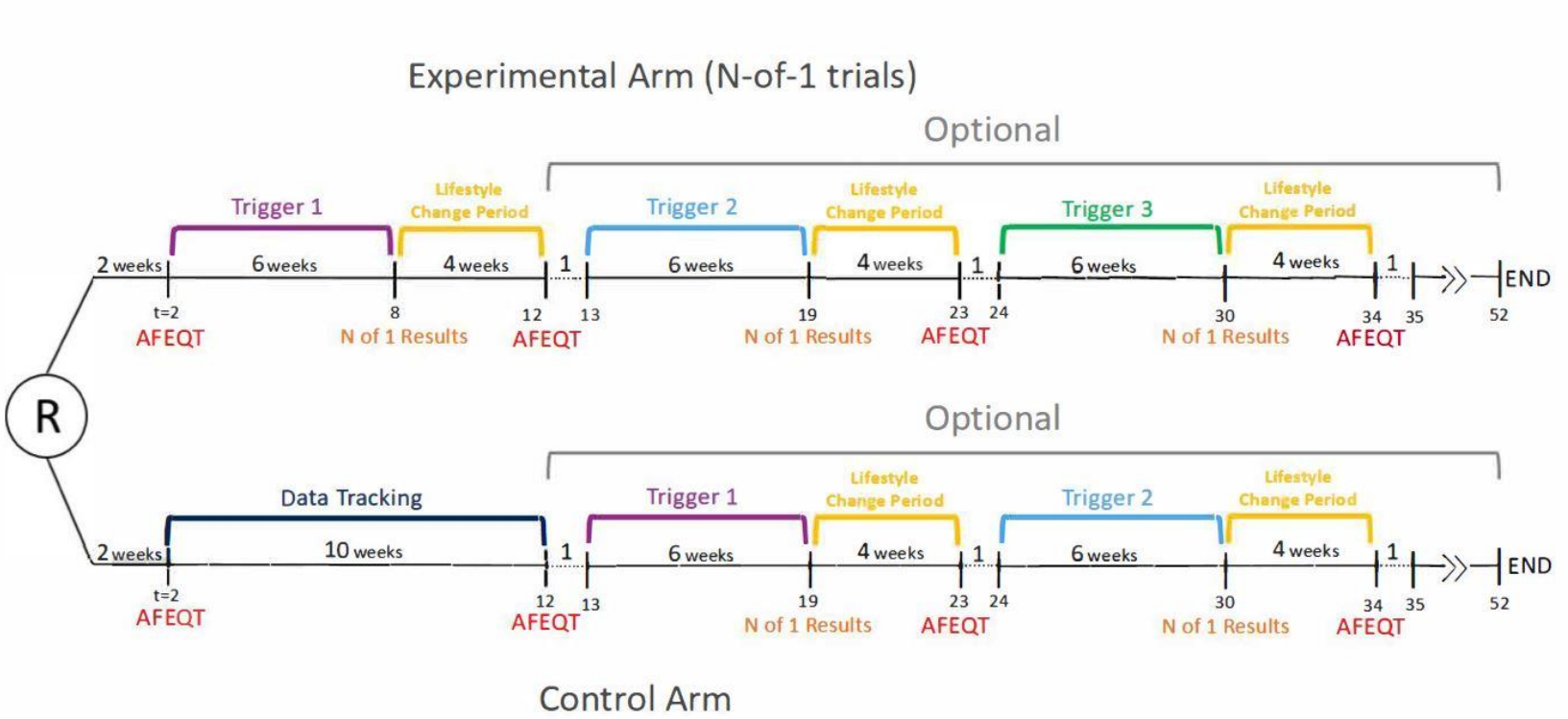


- All participants received daily text-based queries regarding the presence or absence of AF the previous day

Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

UCSF

Methods



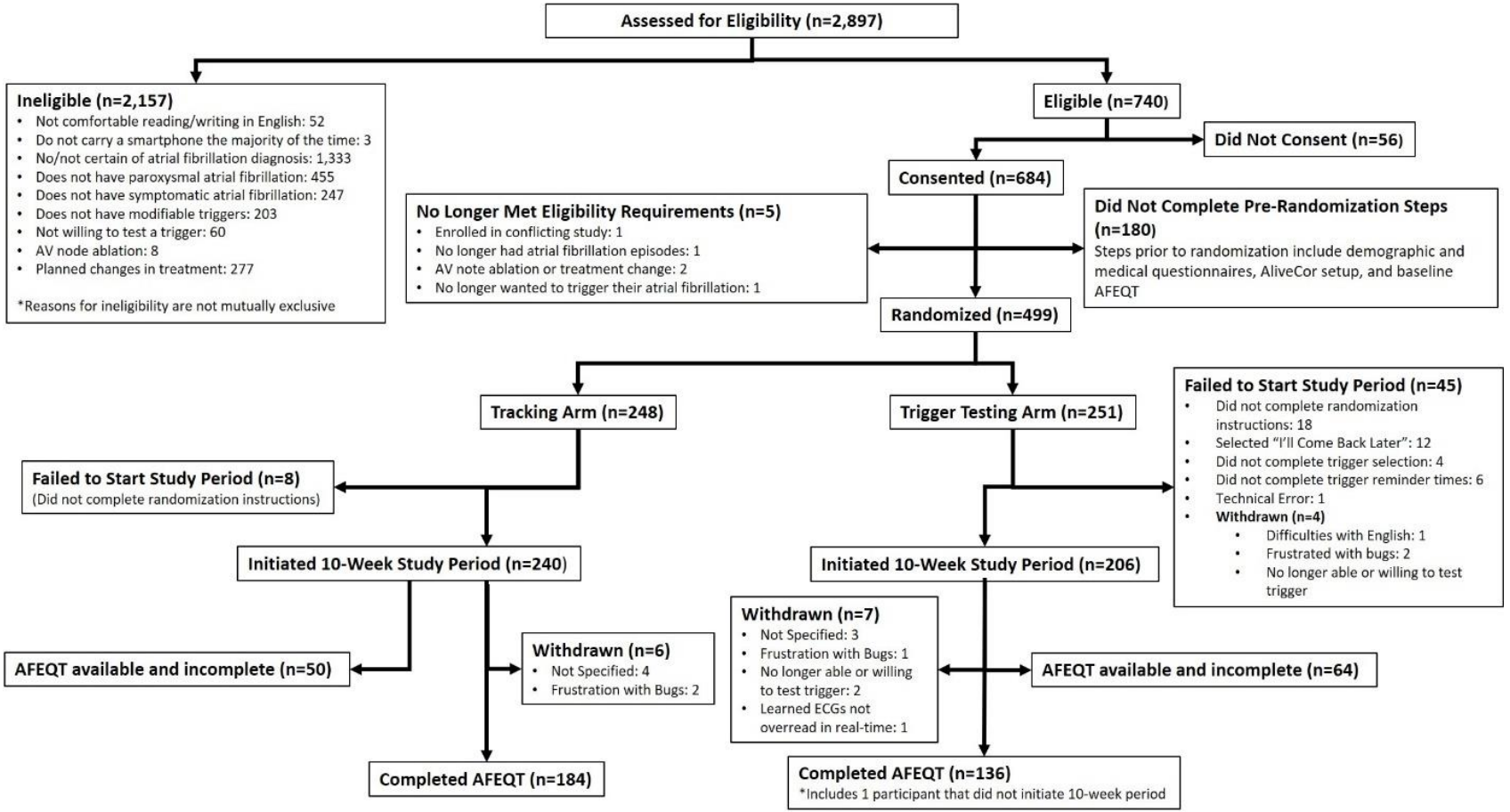
Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

UCSF

Methods: Outcomes

- The primary outcome was the follow-up AFEQT using intention to treat
- Second outcomes included:
  - The number of daily AF episodes recorded in the final 4 weeks of the primary study period
  - Analyses of N-of-1 trials analyzed as intention-to-treat and “per-protocol”
    - Meta-analyses and network meta-analyses of the relationships between specific triggers and the risk of an AF event
    - Utilized Bayesian methods where findings were considered significant if he credible confidence interval did not cross 1 (one-sided posterior probability >97.5%).

Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021



Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

Results

- Triggers selected during the initial N-of-1 assessment period included caffeine (n=53), alcohol (n=43), reduced sleep (n=31), exercise (n=30), laying on left side (n=17), dehydration (n=10), large meals (n=7), cold food or drink (n=5), specific diets (n=6) and customized triggers (n=4)

Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

Results

	Participants		Mean	SD
Trigger-Testing Arm	136	**Baseline AFEQT**	76.1	16.8
		10-week AFEQT	77.9	19.6
		AFEQT Difference	1.7	13.0
Monitoring Only Arm	184	**Baseline AFEQT**	72.4	19.1
		10-week AFEQT	72.9	18.7
		AFEQT Difference	0.5	14.1
	Average difference in 10-week AFEQT between Arms	**95% CI**	**P value**	
***Adjusted for baseline AFEQT and education**	2.1	-0.9 to 5.0	0.17	
†Adjusted for baseline AFEQT, age and race	2.1	-0.0 to 5.0	0.17	

Results

- Those randomized to N-of-1 testing self-reported 40% fewer AF events in the 4 weeks following receiving the results of their N-of-1 study compared to monitoring-only participants during the same time frame (adjusted RR 0.60, 95% CI 0.43-0.83, p<0.0001).
  - Driven by those testing alcohol, dehydration, and exercise (each alone was associated with significantly less AF in the last 4 weeks)

Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

Results: N-of-1 Trials

- No significant differences examining exposures in intention-to-treat were observed
- No significant relationships were observed when analyses were restricted to the first treatment period
  - KardiaMobile over-reads were only available for the first treatment period
- Of all study periods: 326 participants conducted 474 trials testing various triggers: caffeine (n=100), alcohol (n=82), exercise (n=75), reduced sleep (n=66), laying on left side (n=42), dehydration (n=37), cold food or drink (n=9), large meals (n=29), specific diets (n=17) and customized triggers (n=17)

Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

Meta-analyses of all treatment periods

	Odds of Self-reported AF			
	Intention-to-Treat		Per protocol	
	OR (95% CrI) ††	Pr(OR > 1) †††	OR (95% CrI) ††	Pr(OR > 1) †††
Alcohol	1.17 (0.81-1.72)	0.81	1.77 (1.20-2.69)	1.00
Caffeine	1.01 (0.68-1.45)	0.51	0.95 (0.58-1.55)	0.42
Lack of sleep	1.03 (0.71-1.53)	0.55	N/A†	
Exercise	1.05 (0.64-1.68)	0.57	1.02 (0.50-1.95)	0.52
Dehydration	1.73 (0.61-4.06)	0.87	N/A†	
Cold food or drink	0.53 (0.14-2.03)	0.14	0.85 (0.08-10.27)	0.43
Laying on left side	1.00 (0.51-2.09)	0.51	0.81 (0.38-1.63)	0.29
Large meals	0.92 (0.51-1.65)	0.39	0.63 (0.22-1.40)	0.12
Custom	1.01 (0.22-3.49)	0.51	6.30 (0.83-23.90)	0.97
Diet	1.34 (0.28-5.49)	0.65	3.46 (0.68-12.13)	0.94

Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

Limitations

- Although target enrollment numbers were achieved, there was substantial attrition
  - Likely bias introduced by the nature of those lost-to follow-up
- Continuous ECG monitoring was not employed
- Self-reported AF may not be accurate
- Trigger selection was based on individual presumptions
- The population studied may not represent the general population with AF

Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

Conclusions from I-STOP-AFib

- Randomized assignment to individual trigger testing did not result in improved AF-related quality of life
- Those randomized to trigger testing subsequently reported less AF episodes
  - Perhaps less prone to recall bias than the AFEQT
  - Perhaps AFEQT captured experiences more broadly pertinent to AF severity
- Although caffeine was the most common trigger selected for testing, only alcohol exhibited consistent evidence of a near-term effect on self-reported AF episodes

Marcus et al. AHA 2021 Late Breaking Clinical Trial; JAMA Cardiol 2021

The Coffee And Real-time Atrial And Ventricular Ectopy (CRAVE) Trial

Gregory M Marcus, MD, MAS, David G Rosenthal, MD, Gregory Nah, MS, Eric Vittinghoff, PhD, Christina Fang, Kelsey Ogomori, Sean Joyce, Defne Yilmaz, MS, Vivian Yang, Tara Kessedjian, Dolkun Rahmutula, PhD, Emily Wilson, Michelle Yang, Kathleen Chang, Grace Wall, Jeffrey E Olgin MD

UCSF

University of California
San Francisco

Conventional Wisdom

- Coffee leads to arrhythmias
- Professional society guidelines warn against caffeine consumption to avoid arrhythmias[1,2]

1. AHA/ ACC/ ESC SVT Guidelines
2. AHA/ ACC/ HRS Ventricular Arrhythmia Guidelines .

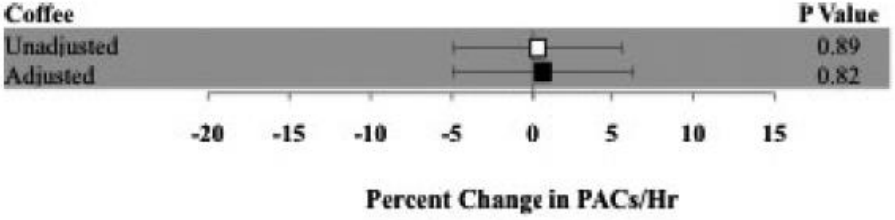
ORIGINAL RESEARCH

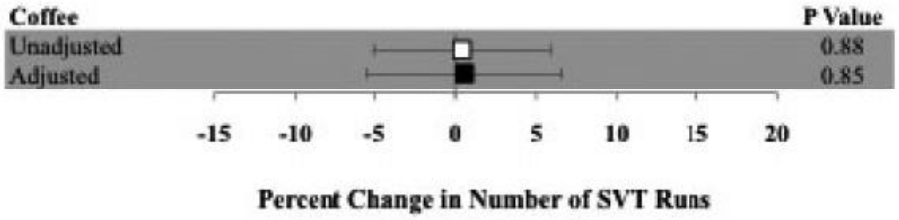
American Heart Association | American Stroke Association

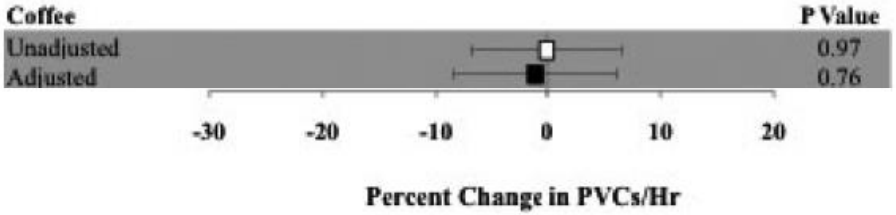
Consumption of Caffeinated Products and Cardiac Ectopy

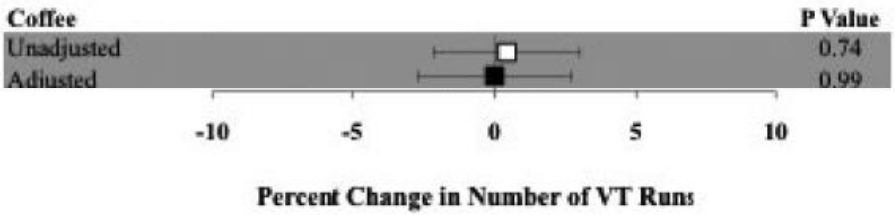
Shalini Dixit, BA; Phyllis K. Stein, PhD; Thomas A. Dewland, MD; Jonathan W. Dukes, MD; Eric Vittinghoff, PhD; Susan R. Heckbert, MD, PhD; Gregory M. Marcus, MD, MAS

J Am Heart Assoc. 2016;5:e002503









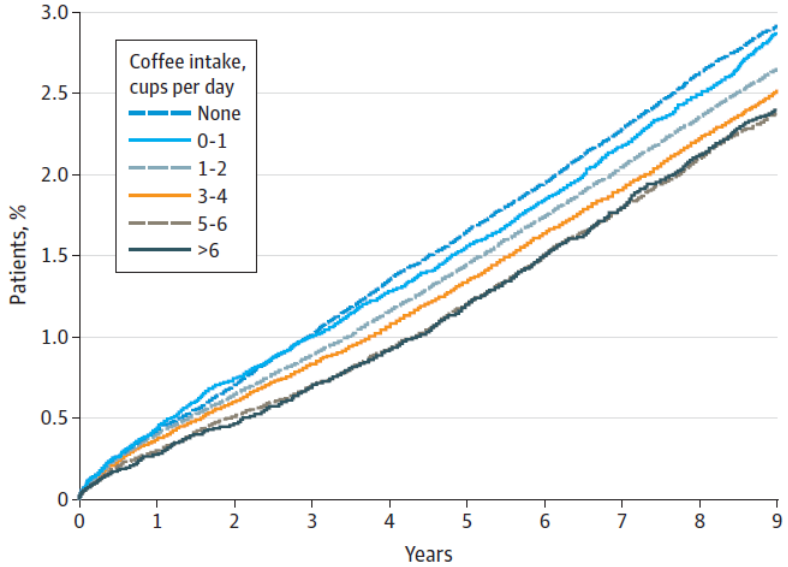
UCSF

JAMA Internal Medicine | Original Investigation

Coffee Consumption and Incident Tachyarrhythmias

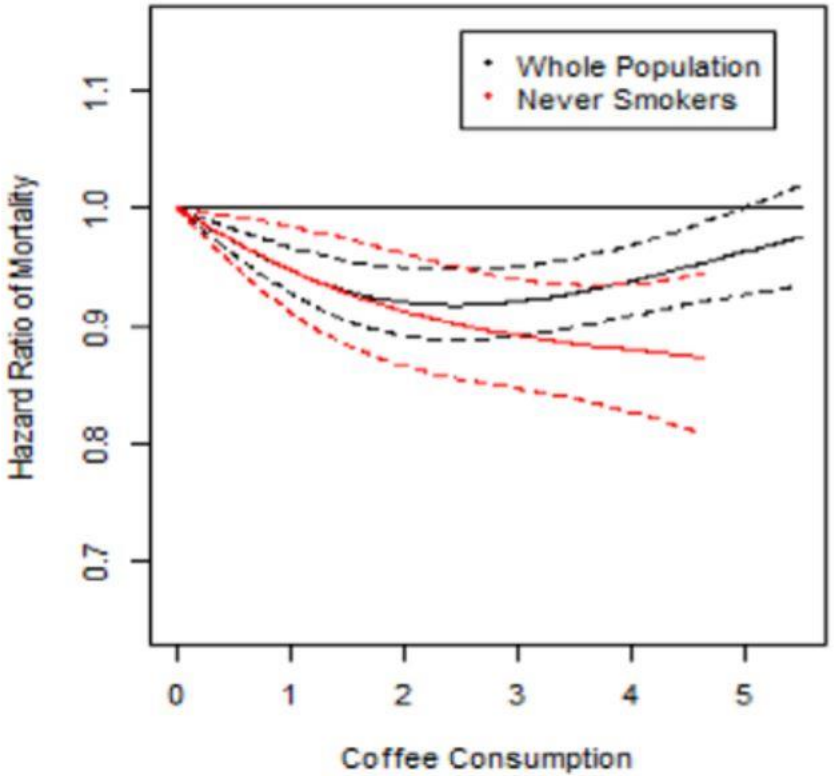
Reported Behavior, Mendelian Randomization, and Their Interactions

Eun-jeong Kim, MD; Thomas J. Hoffmann, PhD; Gregory Nah, MA; Eric Vittinghoff, PhD; Francesca Delling, MD; Gregory M. Marcus, MD, MAS



Cumulative Risk of Arrhythmia

Overall Mortality



Ding et al. *Circulation* 2015

UCSF

Why Reduced Mortality with Coffee Consumption?

- Large epidemiologic studies reveal lower risks of diabetes[1]
- Perhaps coffee consumption motivates physical activity
  - Coffee increases exercise performance[2]
  - Associated with lower BMI[3]
- Observational studies are prone to confounding

1. Poole et al. *BMJ* 2017
2. Clarke et al. *Nurtients* 2019
3.. Tabrizi et al. *Crit Rev Food Sci Nutr* 2019;

Sleep Disruption?

- Poor sleep associated with worsening:
  - Cardiovascular health
  - Metabolic health
  - Mental and neurologic health
  - Overall mortality

Gradner et al. Sleep Med Clin 2020

Limitations Common to Coffee Studies

- Observational
  - Prone to confounding
- Rely on self-report
- Long-term effects
- Outcomes ascertained in snap-shots in artificial environments

- Purpose:
  - To assess real-time relationships between random assignment to consume versus avoid coffee and cardiac ectopy, physical activity, sleep, and glucose levels
  - To assess for interactions by genetic variants affecting caffeine metabolism

Methods: Inclusion Criteria

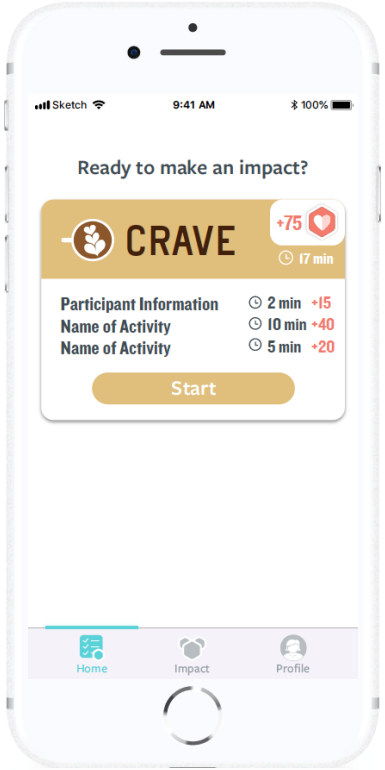
- Enrolled healthy volunteer adults who consumed coffee
  - Willing to go without coffee for now more than 2 consecutive days
  - English speakers
  - Owned a smartphone (iOS or Android)

Methods: Exclusion Criteria

- A history of atrial fibrillation
- A history of heart failure
- Presence of an ICD or pacemaker
- Treated with beta blockers, non-dihydropyridine calcium channel blockers, or Vaughn-Williams class 1 or 3 antiarrhythmic medications
- Have a medical reason to avoid coffee

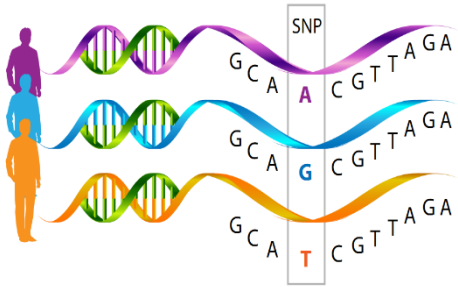
Fitbit Flex 2

(Step counts + sleep duration)

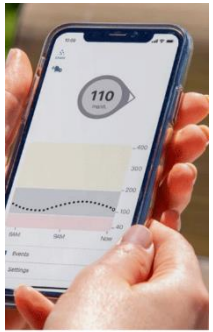


Eureka

Continuous ECG



Polygenic Score



Continuous Glucose

Methods: Intervention

- Daily random assignment to:
  - Consume coffee (at least one drink)
  - Versus avoid all caffeinated products
- Assignments communicated by text 8 PM the evening prior
  - Reminder 8 AM the following morning
- Randomized in “on-off” versus “off-on” pairs
  - Assuring there were never more than 2 consecutive days of one assignment

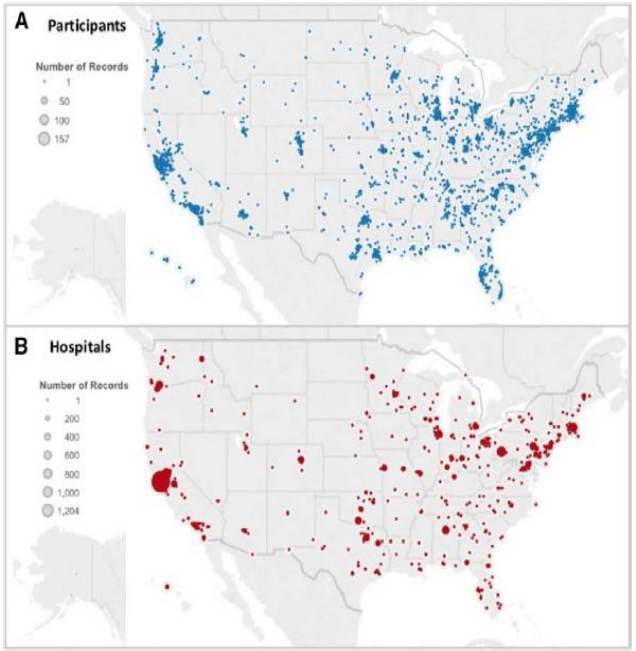
Methods: Compliance Assessment

- Participants instructed to press the button on the Zio patch for every coffee drink (or per shot of espresso)
- Participants were queried via text regarding actual coffee consumption the previous day

Smartphone-Based Geofencing to Ascertain Hospitalizations

Kaylin T. Nguyen, BS; Jeffrey E. Olgin, MD; Mark J. Pletcher, MD, MPH;
Madelena Ng, MPH; Leanne Kaye, PhD, MPH; Sai Moturu, PhD; Rachel A. Gladstone, BA;
Chaitanya Malladi, BS; Amy H. Fann; Carol Maguire, RN; Laura Bettencourt, BS;
Matthew A. Christensen, BS; Gregory M. Marcus, MD, MAS

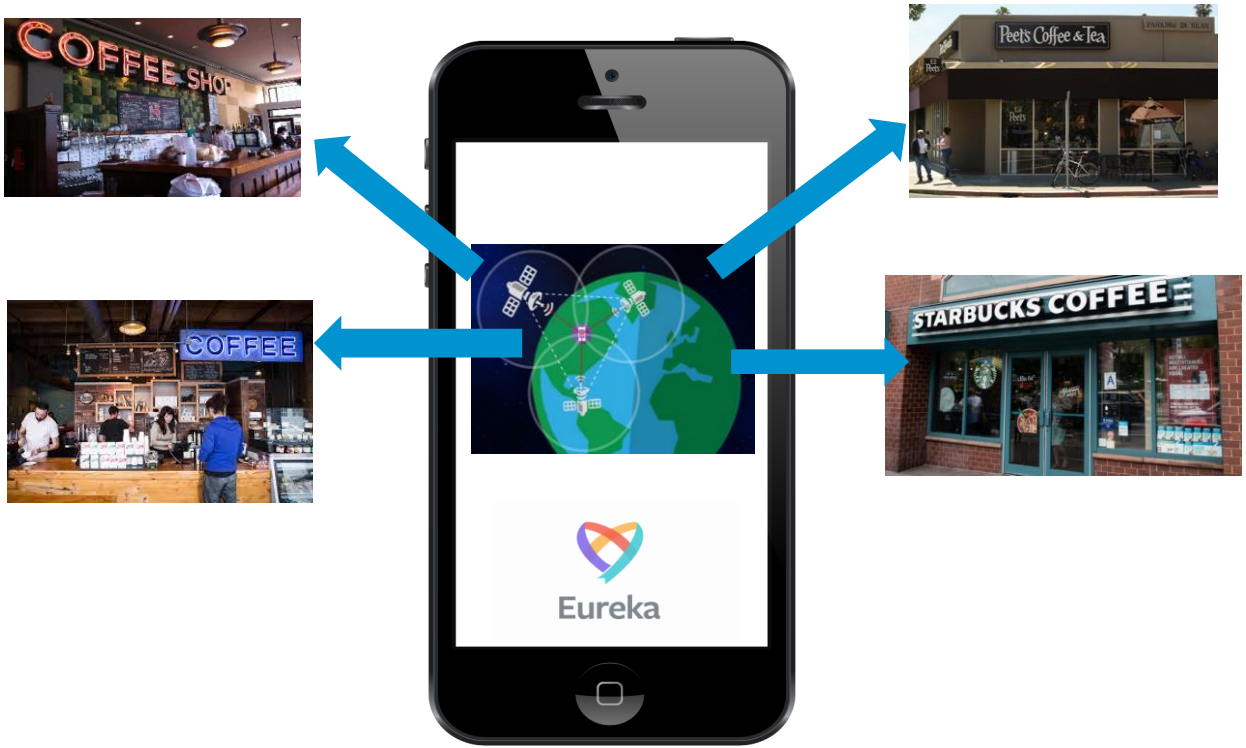
Circ Cardiovasc Qual Outcomes. 2017;10:e003326.



- In-person pilot (n=22): 77% sensitivity (95%CI 55-92)
- Remote:
  - 3,443 participants in all 50 US states
  - 243 hospitalizations detected over ~1 year
  - PPV 65%

UCSF

Smartphone-Based Geofencing to Ascertain




11-11-2016
8:17 AM
TRANS 00A8EC
AUTH 04739C3
AMEX ********3928
Enjoy your coffee.
PRICE: 17.21
Subtotal 17.21
Tip 3.50

Methods: Outcomes

- Primary outcomes:
  - Daily PAC counts
  - Daily PVC counts
- Secondary outcomes:
  - Daily SVT counts
  - Daily VT counts
  - Daily mean step counts
  - Nightly mean sleep duration
  - Daily mean daily glucose

Why Cardiac Ectopy? Everyone has Some

Why Cardiac Ectopy? Clinically Relevant

Atrial Ectopy as a Predictor of Incident Atrial Fibrillation

A Cohort Study

Thomas A. Dewland, MD; Eric Vittinghoff, PhD, MPH; Mala C. Mandyam, MD; Susan R. Heckbert, MD, PhD; David S. Siscovick, MD, MPH; Phyllis K. Stein, PhD; Bruce M. Psaty, MD, PhD; Nona Sotoodehnia, MD; John S. Gottdiener, MD; and Gregory M. Marcus, MD, MAS

Figure 1. Observed versus predicted 10-year AF risk.

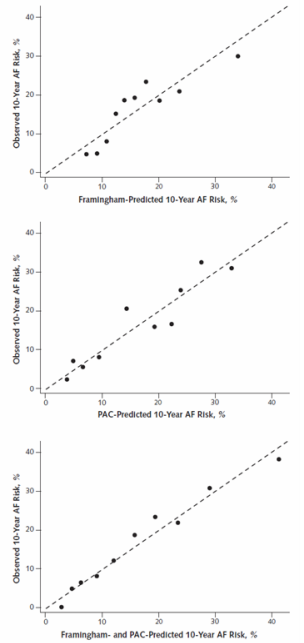
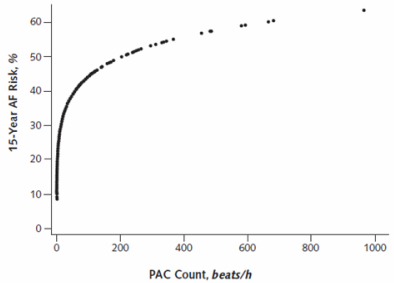


Figure 2. Predicted AF risk and PAC count.



PAC Count, *beats/h*	Sensitivity, %	Specificity, %
0.1	99.7	2.7
1	86.9	35.0
5	51.9	71.0
10	39.1	81.2
50	12.0	92.6
100	4.7	95.7
200	2.3	98.1
400	1.2	99.7

Model	C-Stat for 5 year AF risk	95% CI
Framingham	0.68	0.62-0.72
PACs	0.73	0.68-0.77
Combined	0.76	0.72-0.79

UCSF

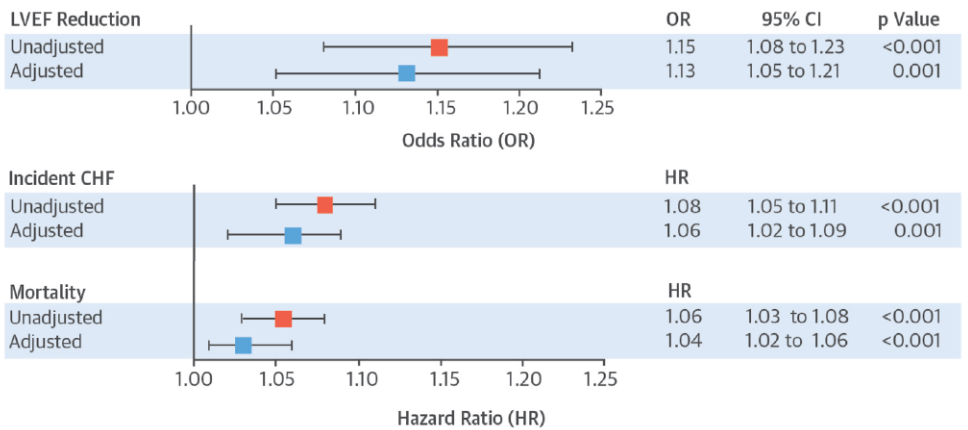
Why Cardiac Ectopy? Clinically Relevant

Ventricular Ectopy as a Predictor of Heart Failure and Death

(J Am Coll Cardiol 2015;66:101–9)

Jonathan W. Dukes, MD,* Thomas A. Dewland, MD,† Eric Vittinghoff, PhD, MPH,‡ Mala C. Mandyam, MD,§ Susan R. Heckbert, MD, PhD,‖ David S. Siscovick, MD, MPH,‖¶ Phyllis K. Stein, PhD,# Bruce M. Psaty, MD, PhD,‖**†† Nona Sotoodehnia, MD,‖‡‡ John S. Gottdiener, MD,§§ Gregory M. Marcus, MD, MAS*

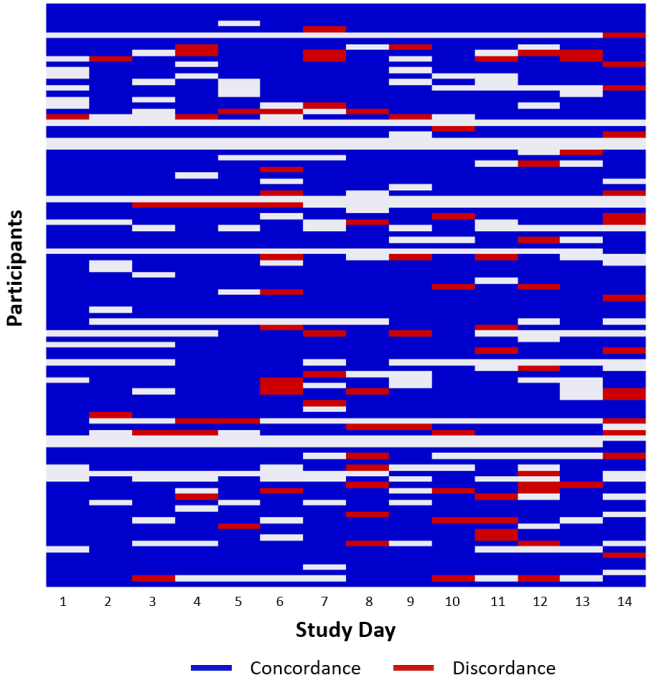
CENTRAL ILLUSTRATION Associations Between Baseline Percent PVCs and 5-Year Reduction in LVEF, Incident CHF, and Mortality



Results

Mean Age (years)	38 ± 13
Median BMI (kg/ m2), IQR	24, 22-26
Female	51%
Race	
White	51%
Black	8%
Asian	34%
Pacific Islander	1%
Other	6%
Hispanic Ethnicity	8%
Hypertension	5%
Diabetes	1%
Baseline Coffee Drink Frequency	
Less than one cup per month	5%
1-3 cups per months	6%
2-5 cups per month	14%
6-7 cups per month	21%
1 cup per day	29%
2-3 cups per day	21%
4-5 cups per day	3%

Compliance



Date-stamped receipts for coffee purchase

	Median	Interquartile Range
Proportion of days randomized to consume coffee	1.00	0.86 – 1.00
Proportion of days randomized to avoid caffeine	0.00	0.00 – 0.14

N=61, p< 0.001

Geofenced coffee shops among those who reported a location where they purchase the majority of coffee consumed

	Median	Interquartile Range
Proportion of days randomized to consume coffee	1.00	0.6 – 1.00
Proportion of days randomized to avoid caffeine	0.00	0.00 – 0.4

N=14, p=0.0063

Results: Zio Patch

- Median 13.3 days (IQR 12.2-13.8)

	Median	Interquartile Range
PACs	12.8	4.0-29.5
PVCs	7.5	3.0-37.0
Non-sustained SVT episodes*	1	1-2
Non-sustained VT episodes†	1	1-1

*At least one SVT episode observed in 55 participants (range 1-176)
†At least one VT episode observed in 13 participants (range 1-14)

Results: Zio Patch

- Premature Atrial Contractions

	RR*	95% CI	P value
Intention to Treat	1.09	0.98-1.20	0.10
Number of drinks			
0	Reference		
1	0.76	0.41-1.40	0.38
>1	0.81	0.51-1.29	0.38

*Adjusted for day of the week

Results: Zio Patch

- Premature Ventricular Contractions

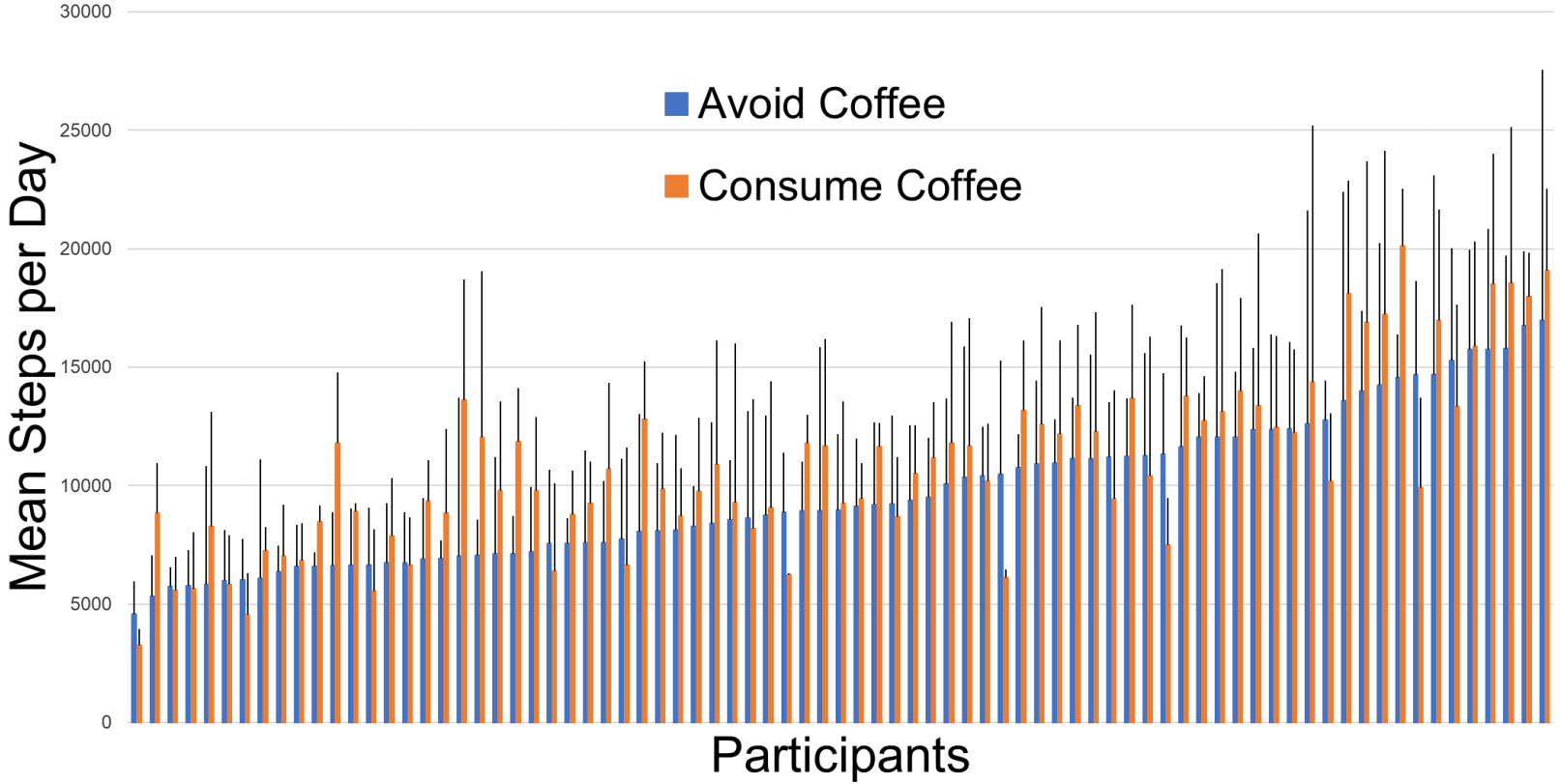
	RR*	95% CI	P value
Intention to Treat	1.54	1.19-2.00	0.001
Number of drinks			
0	Reference		
1	2.31	0.57-9.40	0.24
>1	2.20	1.24-3.92	0.007

*Adjusted for day of the week

Results: Zio Patch

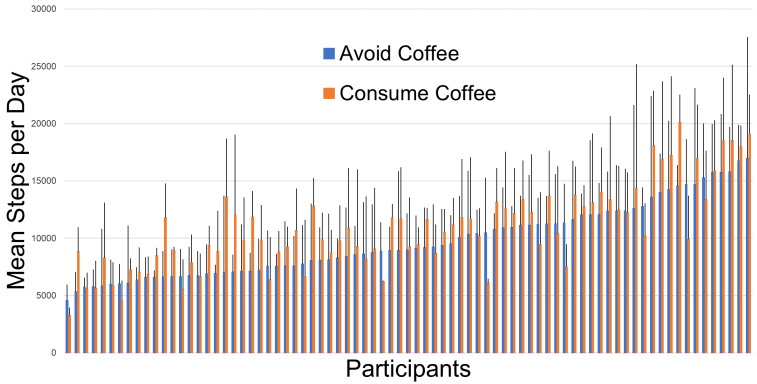
- SVT and VT episodes
  - No significant relationships were observed

Results: Step Counts

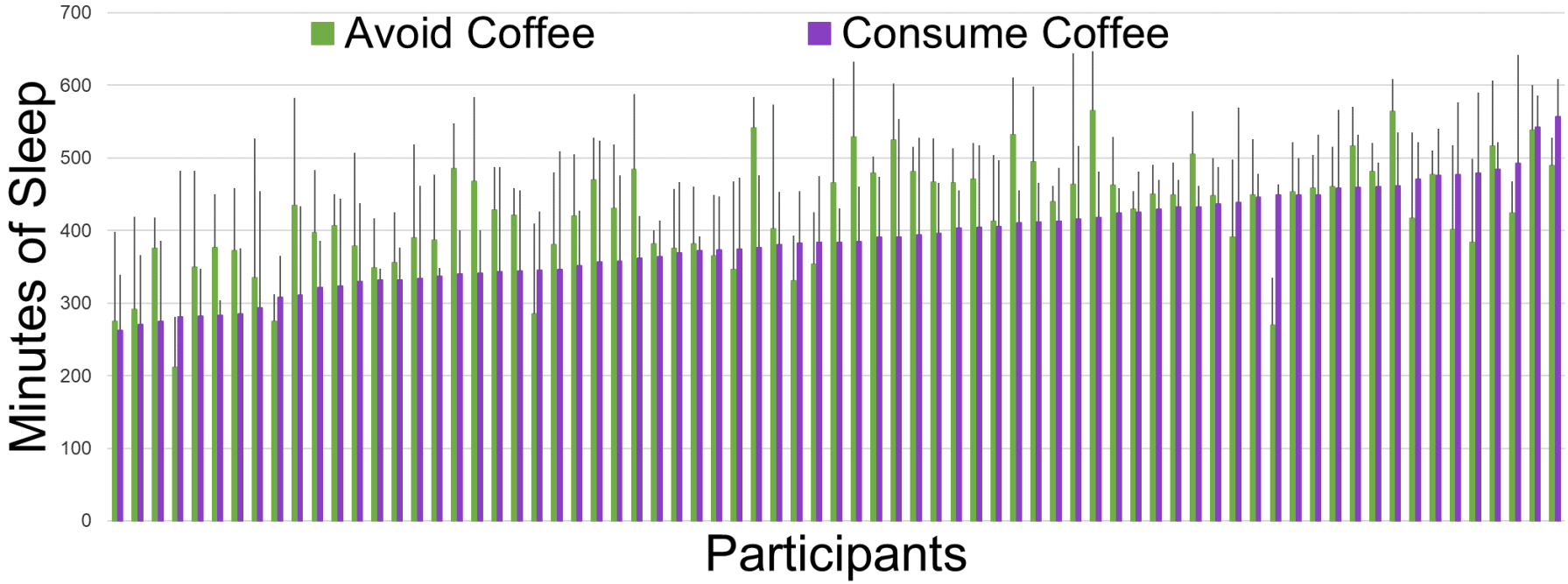


Results: Step Counts

- After adjusting for day of week:
  - Intention to treat: random assignment to coffee was associated with 1,058 more steps per day (95% CI 441-1675, p=0.0010).
  - Per protocol: every additional coffee drink consumed was associated with 587 more steps per day (95% CI 355-820, p<0.001).

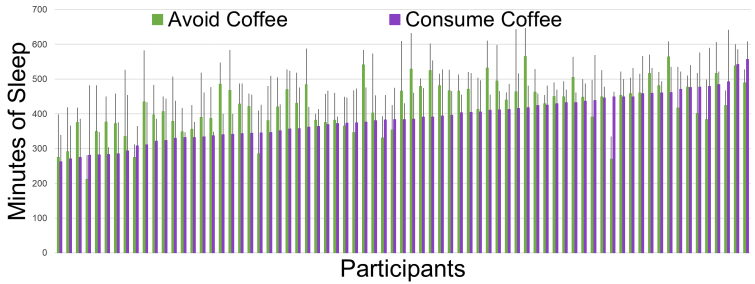


Results: Minutes Asleep



Results: Minutes Asleep

- After adjusting for day of week:
  - Intention to treat: random assignment to coffee was associated with 36 less minutes sleep per night (95% CI 22-50, p<0.001).
  - Per protocol: every additional coffee drink consumed was associated with 18 minutes less sleep per night (95% CI 13-23, p<0.001).

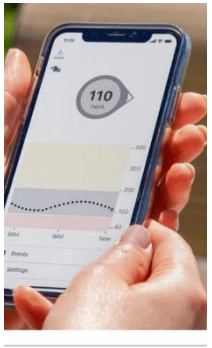


AHA 2021 Late Breaking Clinical Trial

UCSF

Results: Daily Average Glucose

- No statistically significant relationships between randomization assignment or per-protocol coffee consumption and daily average glucose levels were observed.

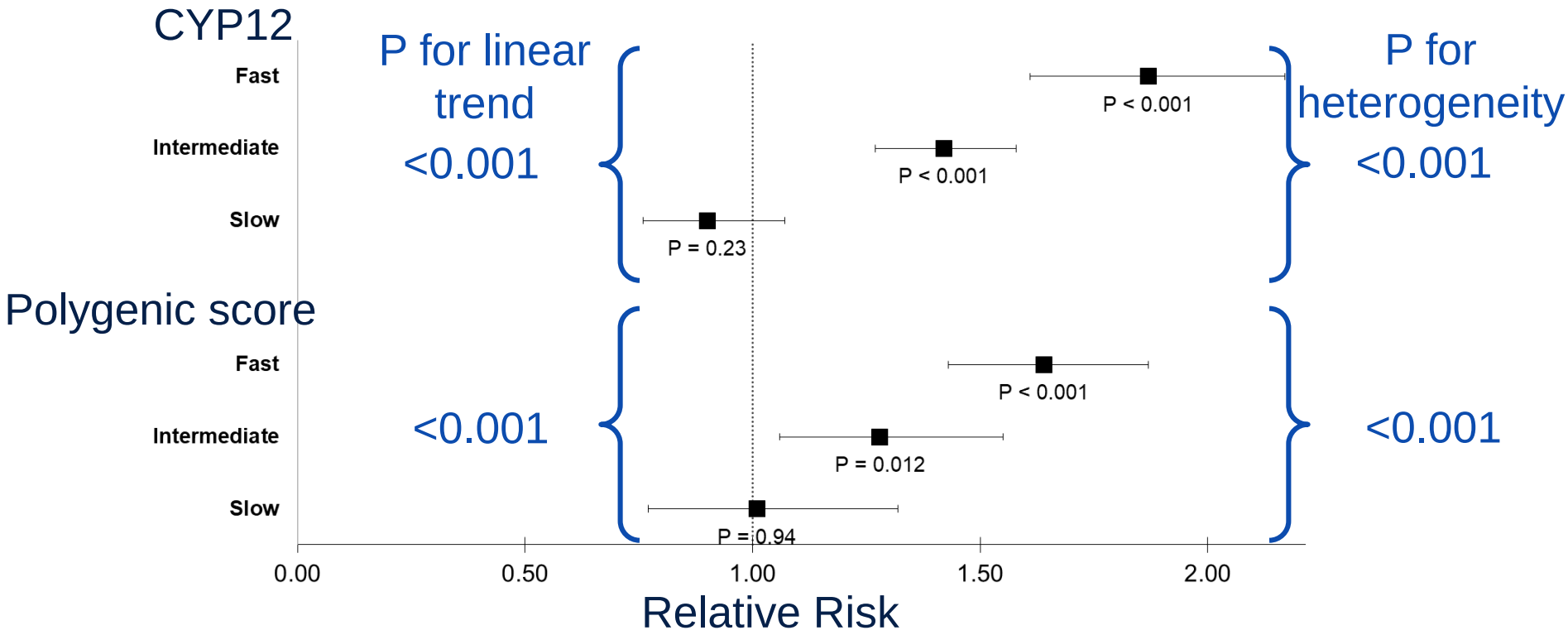


Results: Mediation Analyses

- No evidence that reduced sleep or enhanced step count mediated relationships between coffee and either SVT episode or PVC counts

Results: Interaction Analyses by Genotype

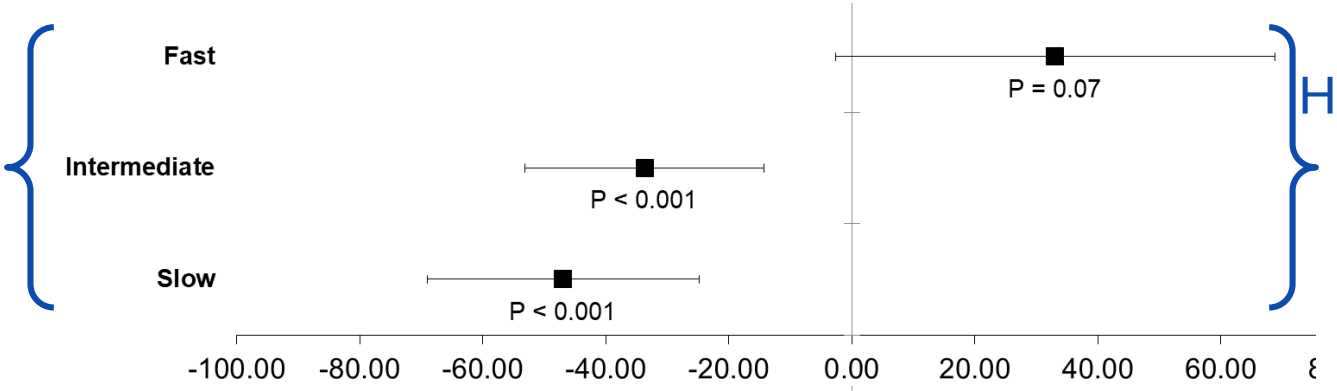
Coffee Randomization and PVC counts



UCSF

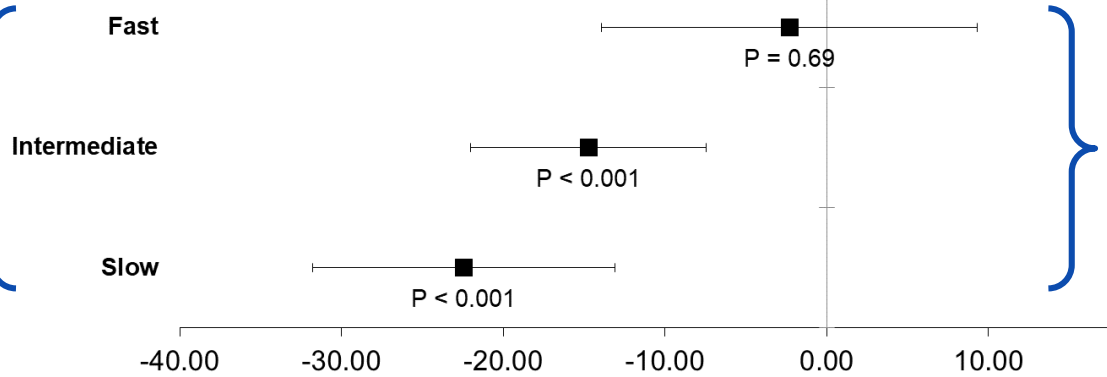
Interaction by Genotype, Coffee and Sleep

ITT Polygenic



P for Heterogeneity/ trend 0.001/ <0.001

Per-protocol Polygenic

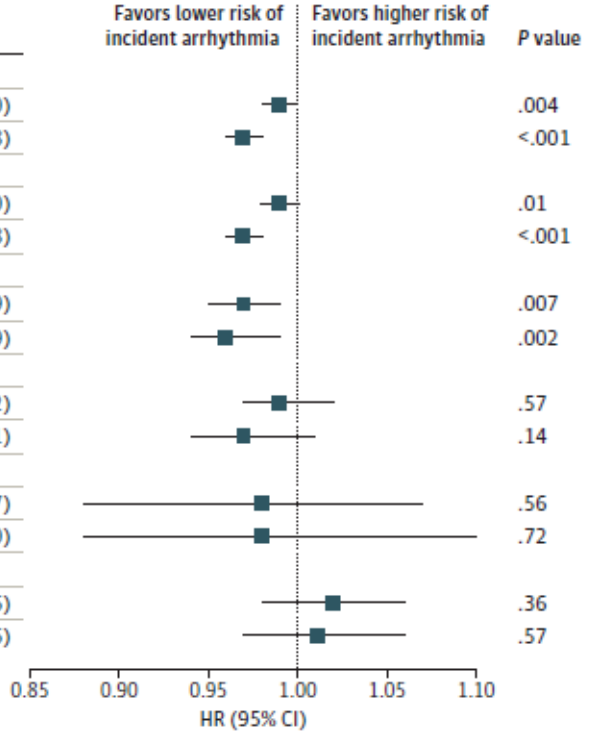


0.032/ 0.009

Brief Discussion

- Incongruity between atrial and ventricular arrhythmias?

Group	HR (95% CI)	P value
All arrhythmia (n = 16 979)		
Unadjusted	0.99 (0.98-1.00)	.004
Adjusted	0.97 (0.96-0.98)	<.001
Atrial fibrillation/flutter (n = 12 811)		
Unadjusted	0.99 (0.98-1.00)	.01
Adjusted	0.97 (0.96-0.98)	<.001
Supraventricular tachycardia (n = 1920)		
Unadjusted	0.97 (0.95-0.99)	.007
Adjusted	0.96 (0.94-0.99)	.002
Ventricular tachycardia (n = 909)		
Unadjusted	0.99 (0.96-1.02)	.57
Adjusted	0.97 (0.94-1.01)	.14
Premature atrial complex (n = 97)		
Unadjusted	0.97 (0.88-1.07)	.56
Adjusted	0.98 (0.88-1.10)	.72
Premature ventricular complex (n = 632)		
Unadjusted	1.02 (0.98-1.06)	.36
Adjusted	1.01 (0.97-1.06)	.57



Kim et al. *JAMA Intern Med* 2021

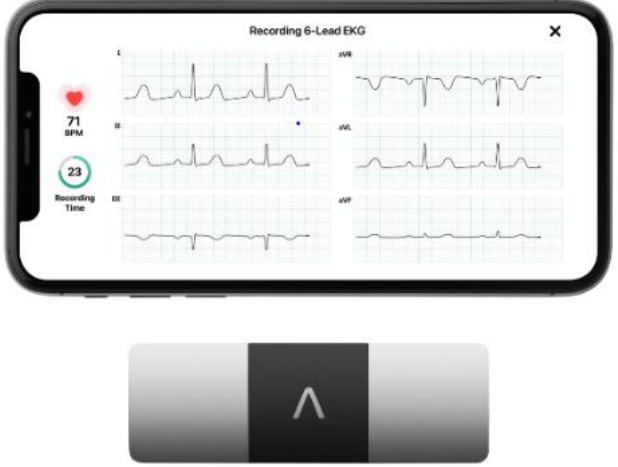
UCSF

Limitations

- Studied acute effects
- Included healthy volunteers, not arrhythmia patients
- Participants were not blinded to the intervention
  - Did not know what their continuous ECG rhythms were
  - The whole coffee experience was captured
- Other genetic variants or other behaviors may modify the observed effects

Conclusions from CRAVE: Coffee Consumption Resulted in…

- No increase in atrial arrhythmias
  - Less SVT in per-protocol analyses
- More PVCs
  - Faster caffeine metabolizers experienced a heightened response
- More physical activity recorded by step counts
  - A clinically relevant magnitude of effect
- Less sleep
  - A clinically relevant magnitude of effect
  - Slower caffeine metabolizers experienced a more potent effect
- No differences in serum glucose



- There is reasonable consternation and uncertainty about “screening” for AF
  - Largely driven by low prevalence→ low positive predictive value
- May be especially fruitful among patients with established AF
  - Particularly to engage in N-of-1 studies
  - How to engage them in “randomization?”

Conclusions

- N-of-1 trials are ultimately the most relevant to each of our individual patients
- This method is most amenable to repeated-measures, which is well-suited to many (but not necessary all) arrhythmias
- In addition to customizing idiosyncratic relationships, combining trials can enhance power using the same number of individuals
- Readily accessible technology now makes such studies more feasible
- Next steps will involve moving beyond simple technology access to method implementation on a large scale
  - Optimal approaches here themselves worthy of study

Thank You