

Atrial Fibrillation in the WHI and WHISH STAR

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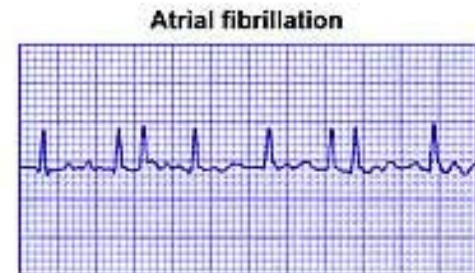
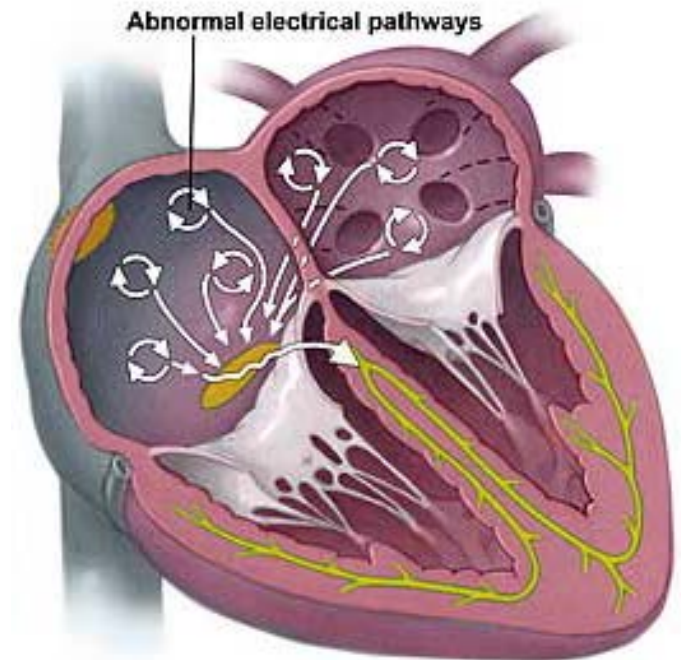
Stanford Division of Cardiovascular Medicine

WHI Investigator Meeting 2018



Atrial Fibrillation

- Disorganized Atrium
- Most Common Arrhyth.
 - 2.2M people
 - 1:4 after age 40
 - 75,000 strokes/yr
 - Increased risk of death
- Costly: \$6.5B / yr
- Treatments are Limited
 - Antiarrhythmics: Side Effects
 - Ablation: Select population, moderate risk.
- Pathophysiology complex and poorly understood.



AF Ascertainment

- Challenges:
 - AF can be paroxysmal (episodic), asymptomatic
 - Participants may be unaware of AF diagnosis
- WHI – AF ascertainment
 - ECGs (RCT), Yearly Self-report (OS)
 - Hospitalization Data (ICD-9 codes, incomplete, un-adjudicated)
- CMS (Centers for Medicare/Medicaid Services)
 - Linked to CMS via social security #, birth/death dates
 - 97% success rate in linking
 - ICD-9 coding to ascertain AF has been validated:
 - Specificity 99%, Positive Predictive Value 97%
 - Internal WHI validation:
 - 98% of subjects identified by ECG or hospitalized ICD-9 coding were successfully identified by CMS linkage.

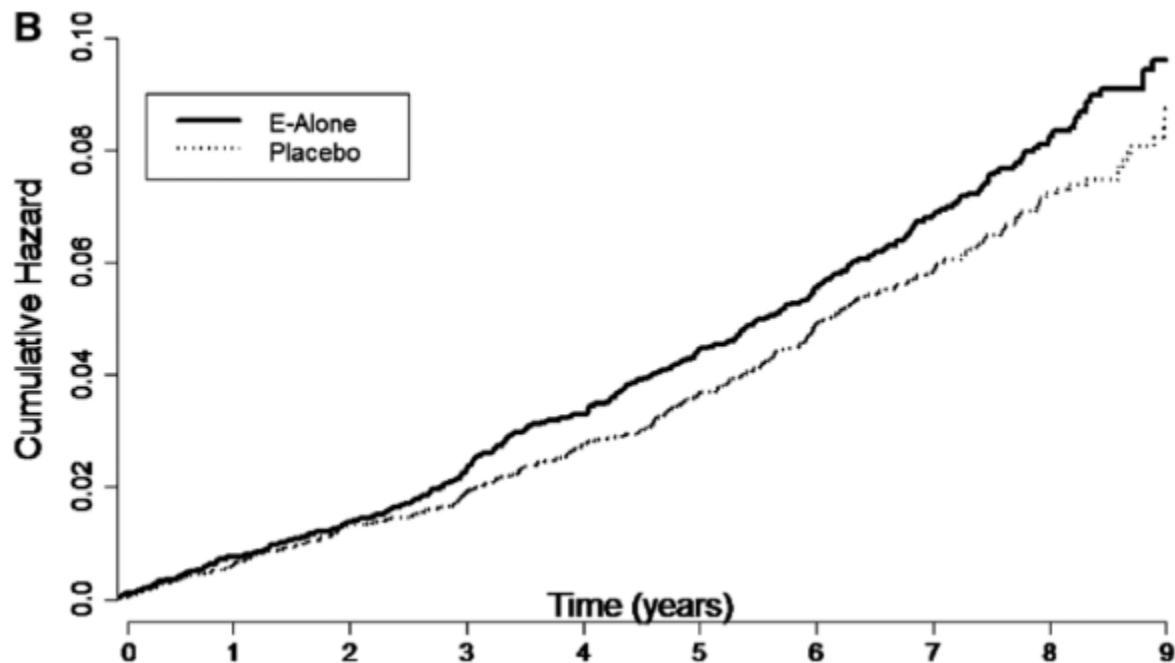
WHI OS and RCTs – AF by Race

Exclusion	White		African American		Hispanic		Asian	
	Total n	AF cases	Total n	AF cases	Total n	AF cases	Total n	AF cases
Original sample	133541	23297	14618	1452	6484	392	4190	279
Exclude baseline AF	127690	20328	13877	1270	6289	351	4051	246
Exclude missing data and lost f/u	114,083	18,015	11,876	1,084	5,174	292	3,803	232

Now: Limit ascertainment to CMS

- ~ 45,000 participants CMS baseline
- ~ 33,000 age INTO CMS
- 78,000 Participants from OS/RCTs
- ~ 610,000 Person Years
- ~ 15,200 incident cases of AF (About 20%)

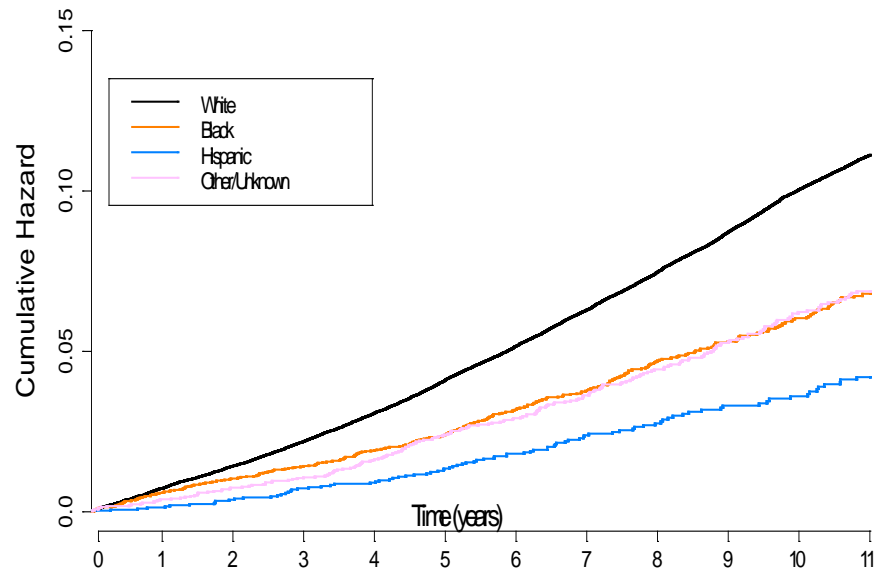
Incidence of AF in RCT



E-alone Trial

Model	Active Events (Ann%)	Placebo Events (Ann%)	HR	95% CI	P-value
Primary Model (427.31)	360 (1.03)	323 (0.90)	1.17	(1.00, 1.36)	0.045
Stricter AF ¹	295 (0.84)	259 (0.72)	1.19	(1.01, 1.41)	0.041
Any AF ²	361 (1.04)	324 (0.90)	1.17	(1.00, 1.36)	0.045
AF or Atrial Flutter ³	369 (1.06)	337 (0.94)	1.15	(0.99, 1.33)	0.073
CMS Enrollment at baseline	268 (1.77)	235 (1.47)	1.21	(1.01, 1.44)	0.035
WHI Data Alone ⁴	215 (0.61)	190 (0.52)	1.17	(0.97, 1.43)	0.107

Incident AF by Race/Ethnicity



Perez et. al., Heart 2013; 99:117-1178

Table II. Attributable risk (%) of traditional AF risk factors

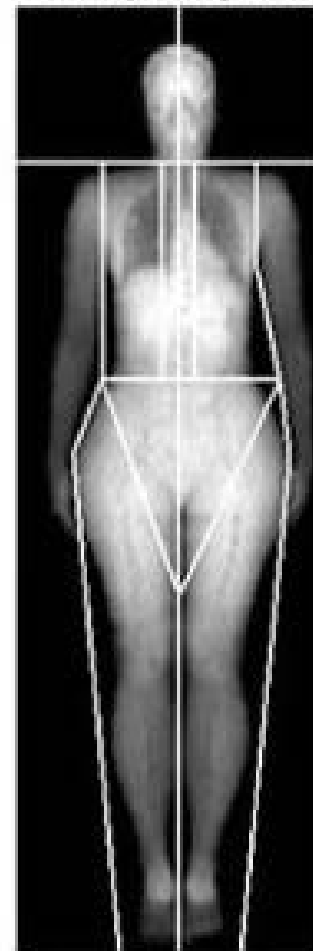
Characteristic	Level of interest	NHW	African American	Hispanic	Asian
Hypertension	Yes	24.3	38.3	29.2	18.3
BMI	>25 kg/m ²	13.1	18.9	15.7	6.9
Diabetes	Yes	2.6	8.7	3.6	4.9
Smoking	Past/Current	4.3	5.4	9.1	4.2
PAD	Yes	1.6	3.4	1.6	0.2
Heart failure	Yes	0.9	2.9	2.0	1.1
Coronary heart disease	Yes	3.5	5.5	4.4	1.8
Total		50.3	83.1	65.6	37.4

Fatima Rodriguez et al., American Heart Journal 2016 Jun;176:70-7

Lean Body Mass and AF in WHI

- Dual-energy X-ray absorptiometry
- Measures: Bone Mineral Density, total body composition (lean mass and fat content).
- 3 Sites, ~10,000 women ~1,035 incident AF

Total Body Tissue Quantitation



Characteristic	Multivariate Model		Multivariate Model + BMI	
	HR (95% CI)	p-value	HR (95% CI)	p-value
BMI (5 kg/m ²)	1.07 (1.01, 1.13)	0.019		
Fat Percentage				
Central fat 5% (of total central mass)	0.98 (0.94, 1.03)	0.406	0.89 (0.84, 0.95)	<0.001
Central fat 5% (out of total fat mass)	0.95 (0.90, 0.99)	0.028	0.92 (0.88, 0.97)	0.002
Percentage body fat (5%)	1.00 (0.95, 1.04)	0.839	0.92 (0.86, 0.98)	0.006
Fat Mass				
Central fat mass (5 kg)	1.05 (1.00, 1.11)	0.073	0.99 (0.90, 1.09)	0.781
Peripheral fat mass (5 kg)	1.09 (1.03, 1.16)	0.002	1.12 (1.01, 1.24)	0.038
Whole-body fat mass (5 kg)	1.04 (1.01, 1.07)	0.010	1.04 (0.97, 1.10)	0.282
Lean Mass				
Central lean mass (5 kg)	1.46 (1.29, 1.66)	<0.001	1.49 (1.29, 1.71)	<0.001
Peripheral lean mass (5 kg)	1.33 (1.18, 1.51)	<0.001	1.36 (1.16, 1.58)	<0.001
Whole-body lean mass (5 kg)	1.19 (1.12, 1.27)	<0.001	1.22 (1.13, 1.32)	<0.001

WHISH Trial

- Women's Health Initiative Strong and Healthy
- Pragmatic trial of PA Intervention: Randomize to Consent

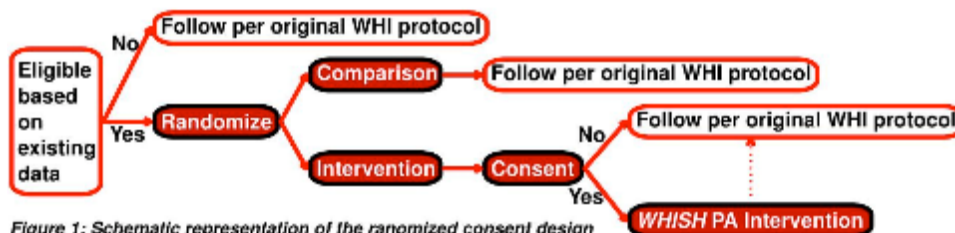


Figure 1: Schematic representation of the randomized consent design for the WHISH trial (based on Zelen, *N Eng J Med* 1979, 300: 1242–1245)

- PA Intervention:
 - Department of Health and Human Services Exercise Recommendations
 - Aerobic, muscle strengthening, and flexibility
 - Go4Life and other print/online material/Interactive voice response
- Inclusion
 - WHI Extension study (MRC + CMS)
 - Randomized 49,347 women

AF and Exercise: Complex Relationship

- 1. Karjalainen J, Kujala UM, Kaprio J, Sarna S and Viitasalo M. Lone atrial fibrillation in vigorously exercising middle aged men: case-control study. *BMJ*. 1998;316:1784-5.
- 2. Furlanello F, Bertoldi A, Dallago M, Galassi A, Fernando F, Biffi A, Mazzone P, Pappone C and Chierchia S. Atrial fibrillation in elite athletes. *J Cardiovasc Electrophysiol*. 1998;9:S63-8.
- 3. Hoogsteen J, Schep G, Van Hemel NM and Van Der Wall EE. Paroxysmal atrial fibrillation in male endurance athletes. A 9-year follow up. *Europace*. 2004;6:222-8.
- 4. Heidbüchel H, Anné W, Willems R, Adriaenssens B, Van de Werf F and Ector H. Endurance sports is a risk factor for atrial fibrillation after ablation for atrial flutter. *Int J Cardiol*. 2006;107:67-72.
- 5. Molina L, Mont L, Marrugat J, Berruezo A, Brugada J, Bruguera J, Rebato C and Elosua R. Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study. *Europace*. 2008;10:618-23.
- 6. Mont L, Tamborero D, Elosua R, Molina I, Coll-Vinent B, Sitges M, Vidal B, Scalise A, Tejeira A, Berruezo A, Brugada J and Investigators GGIReF-IA. Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individuals. *Europace*. 2008;10:15-20.
- 7. Aizer A, Gaziano JM, Cook NR, Manson JE, Buring JE and Albert CM. Relation of vigorous exercise to risk of atrial fibrillation. *Am J Cardiol*. 2009;103:1572-7.



Physical Activity, Obesity and AF

Characteristic	Hazard Ratio*	P-value
Age	1.47 (1.44, 1.49)	<0.001
Race/ethnicity		<0.001
White	1.00 (ref)	
African-American	0.61 (0.55, 0.67)	
Hispanic	0.61 (0.51, 0.72)	
Education		0.039
≤High school/GED	1.00 (ref)	
Some college	0.97 (0.92, 1.03)	
≥College degree	0.94 (0.89, 0.99)	
BMI (5 kg/m² increase)	1.12 (1.10, 1.14)	<0.001
Hypertension	1.41 (1.35, 1.47)	<0.001
Diabetes	1.50 (1.38, 1.64)	<0.001
Hyperlipidemia	0.96 (0.91, 1.02)	0.188
Coronary artery disease (MI/CABG/PTCA)	1.79 (1.65, 1.95)	<0.001
Heart Failure	2.12 (1.80, 2.49)	<0.001
Peripheral artery disease	1.54 (1.39, 1.71)	<0.001
Current Smoking	1.25 (1.15, 1.37)	<0.001
Physical Activity		0.003
No Activity	1.00 (ref)	
>0 – 3 MET-h/wk	0.98 (0.91, 1.06)	
>3 – 9 MET-h/wk	0.94 (0.88, 1.01)	
>9 MET-h/wk	0.90 (0.85, 0.96)	

n > 80K women

*multivariate analysis adjusted for all variables present

- Women with highest intensity (top 10%) still protected
- Endurance athletes not assessed

WHISH STAR

- WHISH SilenT Atrial fibrillation Recording
 - NIH/NHLBI 1R01HL136390-01
- Goal: Study Effect of PA on incident AF
 - Inclusion: 49,347 WHISH Participants
 - Exclusion:
 - 11,541 (23.4%) with AF at WHISH enrollment
 - AF by any means (ECG, self-report, CMS, Med records)
 - Will be followed for secondary events
 - 9,796 not enrolled in CMS
 - Total: 28,010
- Primary Outcome:
 - Incident AF, ascertained by CMS
 - Outpatient AF events will be adjudicated

Silent Atrial Fibrillation – CRYSTAL AF

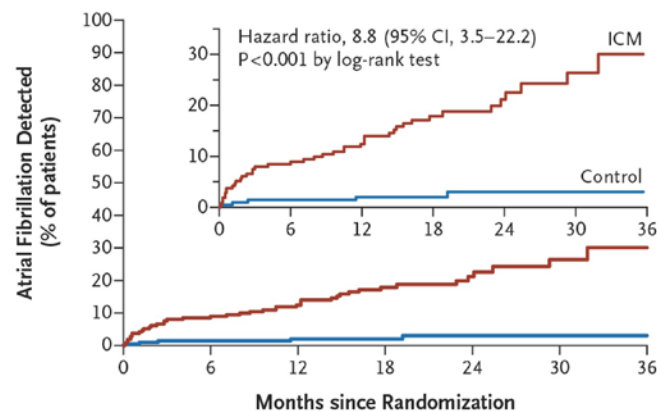
ORIGINAL ARTICLE

Cryptogenic Stroke and Underlying Atrial Fibrillation

Tommaso Sanna, M.D., Hans-Christoph Diener, M.D., Ph.D.,
Rod S. Passman, M.D., M.S.C.E., Vincenzo Di Lazzaro, M.D.,
Richard A. Bernstein, M.D., Ph.D., Carlos A. Morillo, M.D.,
Marilyn Mollman Rymer, M.D., Vincent Thijs, M.D., Ph.D.,
Tyson Rogers, M.S., Frank Beckers, Ph.D., Kate Lindborg, Ph.D.,
and Johannes Brachmann, M.D., for the CRYSTAL AF Investigators*



C Detection of Atrial Fibrillation by 36 Months



No. at Risk

Control	220	194	167	114	72	36	7
ICM	221	191	173	102	57	29	8

Sanna et al., *N Engl J Med* 2014;370:2478-86.

Ongoing studies in silent AF: mSTOPS, ARTESIA, NOAH

Cardiac Patch Monitor

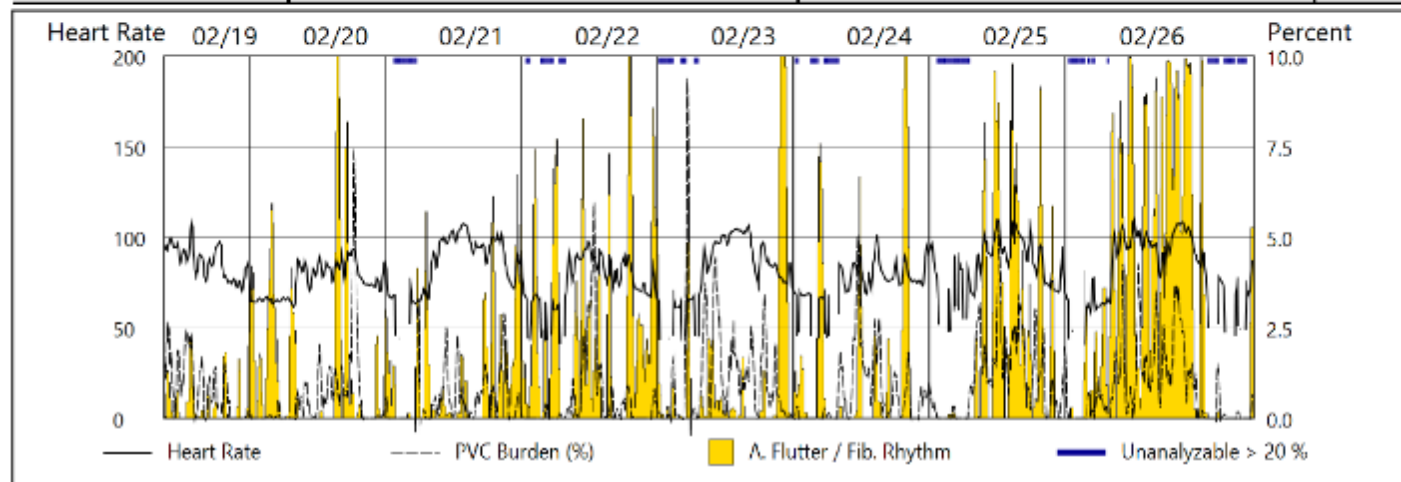
- Cardea Solo (Cardiac Insight)



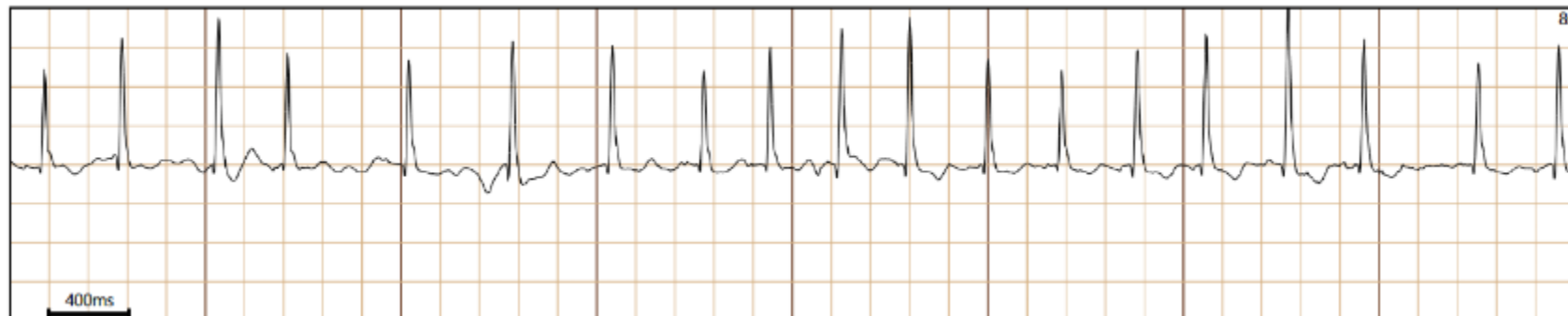
WHISH STAR – Monitoring Arm

- Aim 2: Study effect of PA on silent AF
- Inclusion:
 - WHISH trial in CMS
 - High risk of AF (5-year risk of AF > 5%)
 - Over-sampling for URM
- Exclusion
 - Baseline AF
 - OPACH
- Target Enrollment: 1,100
- Plan: Three 7-day patches - baseline, 6 months, 1 year
 - All done remotely
 - Consent to contact via mail, then consent via telephone
 - Patches are mailed to participant, then mailed back
 - Data processed at Stanford.
 - Raw data, technical data extraction, double-adjudication of AF

Sinus Rhythm: 80.4%			Awake (123h 52m)			Sleep (40h 10m) [11:00 PM - 07:00 AM]			Total
Avg HR	Range		HR < 50 (%)	HR > 100 (%)	PVC (%)	HR < 50 (%)	HR > 100 (%)	PVC (%)	PAC
Total	81	57 - 153	-	12	1	-	1	0	2.2%
Awake	84	66 - 153	PAC (%) VBi/Trigem (%) Pause (# - Max)			PAC (%) VBi/Trigem (%) Pause (# - Max)			PVC
Sleep	69	57 - 98	2	0	-	2	0	-	0.8%
Runs (>3 Beats)			Count	Avg HR	Avg Dur(sec)	Count	Avg HR	Avg Dur(sec)	
Supraventricular:			20	131	2	-	-	-	0.0%
Ventricular:			-	-	-	-	-	-	-
Atrial Flutter / Fibrillation: 19.6% (1d 8h 6m)			HR < 50 (%)	HR > 100 (%)	PVC (%)	HR < 50 (%)	HR > 100 (%)	PVC (%)	PVC
Total	89	53 - 148		7	0		1	0	0.2%
Awake	92	64 - 148	Pause (# - Max)			Pause (# - Max)			
Sleep	72	53 - 101	-			-			



02/25/2018 02:48:33 PM 218 1m 40s 129 bpm 120-153 bpm NO



Supraventricular tachycardia graphs

SVT With Fastest Heart Rate

Beats

Duration

Episode Average

Range

Pt Trig?

03/29/2018 08:18:26 PM

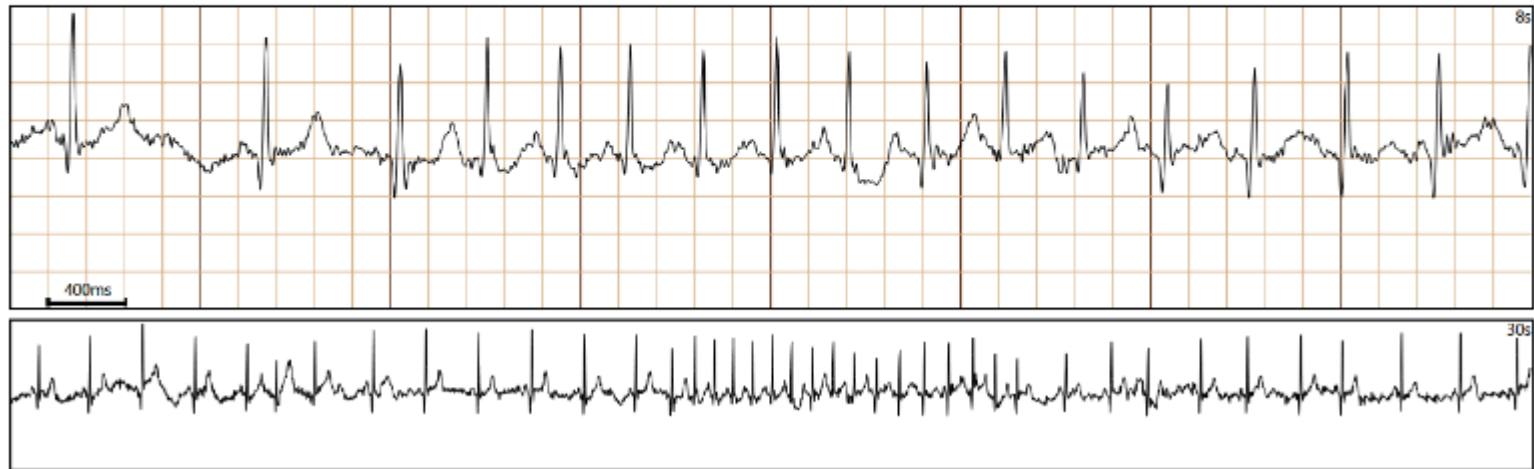
16

7s

136 bpm

128-145 bpm

NO



VT Episodes

VT With Fastest Heart Rate

Beats

Duration

Average

Range

Pt Trig?

03/23/2018 02:01:45 AM

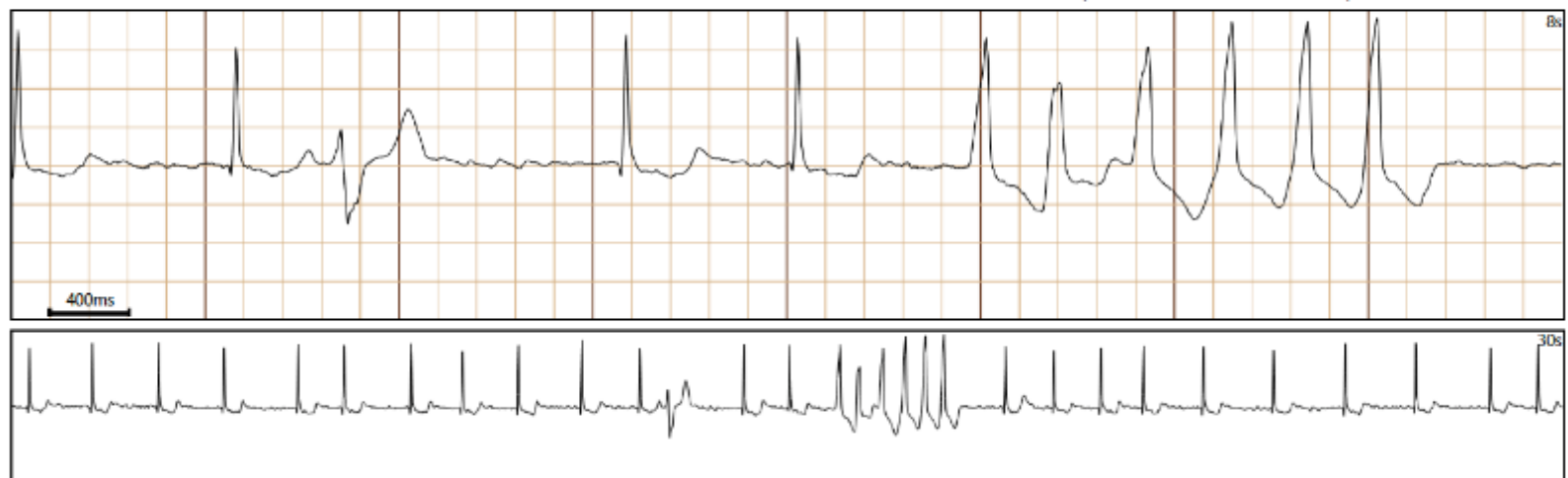
6

4.1 s

153 bpm

125-153 bpm

NO



Summary + Future Directions

- AF is very common and a/w strokes and morbidity
- Approximately 20% of women in WHI have incident AF
- WHISH STAR Aims to study effect of PA on AF
- Aiming for 1,100 participants x 3 monitors each
- Preliminary rate of AF at baseline patch: 3.1%

- Future Directions
 - Several AF Projects (sedentary state, pollution, VitD, dietary effects)
 - WHISH STAR secondary endpoints
 - ? Accelerometers in subset of patch participants
 - Baseline CVD/CHF/AF cohort

- Ignite Ideas:
 - AF Resilience
 - Ethnic enclaves to learn about environmental risk and AF
 - Using 24h Holter data from 10 years ago

Thank You

WHI Central Coordinating Center

Lesley Tinker
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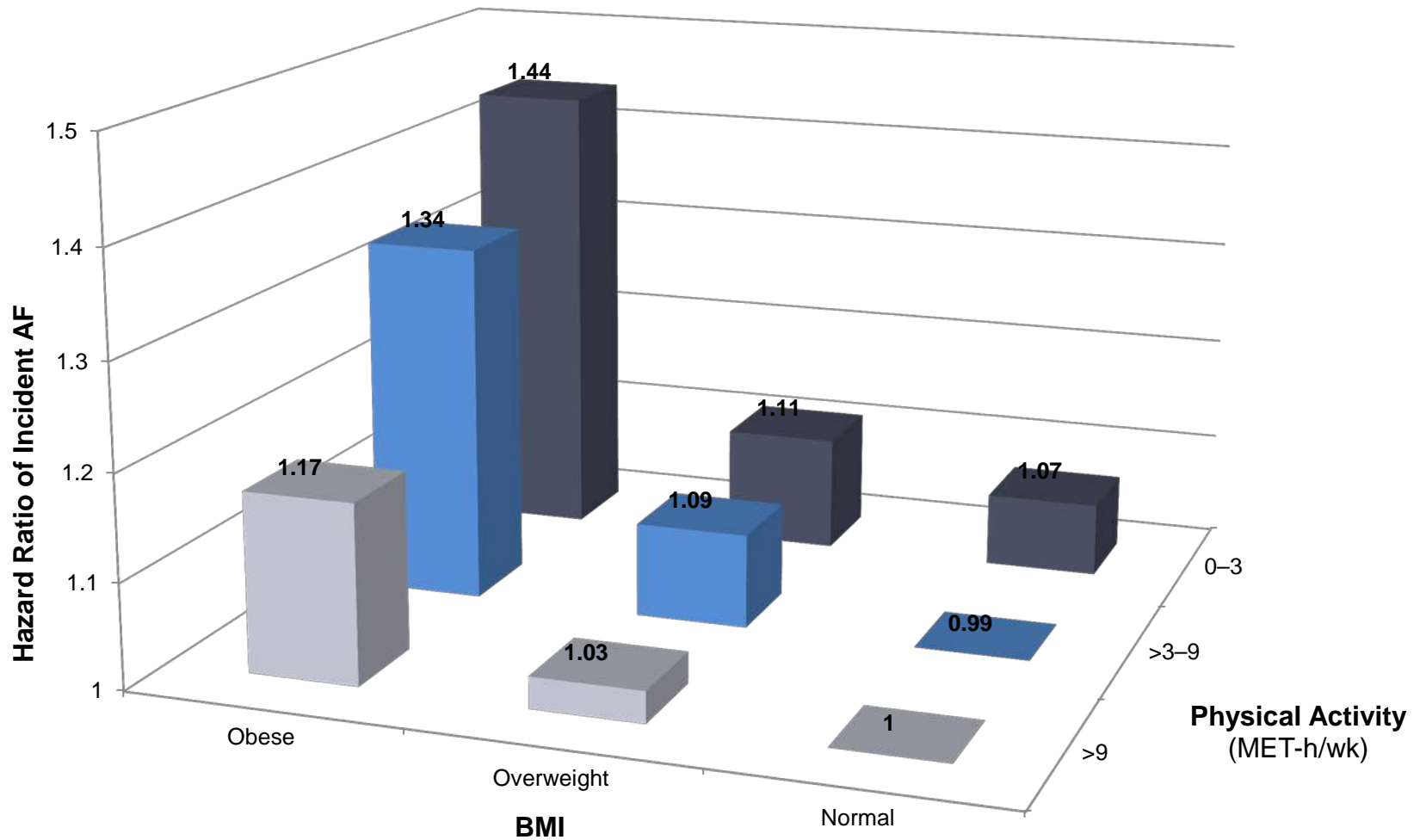
Robert Wood Johnson Foundation Career Development

Stanford Cardiovascular Institute Seed Grant

Contact: mvperez@stanford.edu



Physical Activity & Obesity Interaction



Interaction p -value = 0.033

Adipokines and Incident AF in WHI

Characteristic	Age / Race Adjusted		Multivariate Adjusted Excluding BMI		Multivariate Adjusted ¹ Including BMI	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Adiponectin per 1 log(ug/mL) increase	0.98 (0.76, 1.26)	0.87	1.08 (0.83, 1.40)	0.56	1.17 (0.89, 1.54)	0.25
Leptin per 1 log(ng/mL) increase	1.13 (0.99, 1.30)	0.06	1.08 (0.94, 1.23)	0.28	0.95 (0.81, 1.11)	0.53
Resistin per 1 log(ng/mL) increase	1.74 (1.27, 2.38)	<0.001	1.63 (1.19, 2.24)	0.003	1.55 (1.12, 2.14)	0.008
CRP Per 1 log(mg/L) increase	1.23 (1.09, 1.39)	< 0.001	1.20 (1.06, 1.35)	0.005	1.17 (1.01, 1.34)	0.03

Multivariate models are adjusted for age, race, education, hypertension, diabetes, hyperlipidemia, hx of CHD (MI/CABG/PTCA), hx of CHF, hx of PAD, current smoking, and BMI.

All models are weighted to the WHI OS using IPW weighting