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Epidemiology of Atrial Fibrillation:

Modifiable Risk Factors and Concept of Atrial Fibrillation as a Systemic Illness

Usha B. Tedrow, MD MSc

Associate Professor, Harvard Medical School
Fellowship Director, Clinical Cardiac Electrophysiology Program

The Most Prevalent Arrhythmia: Atrial Fibrillation

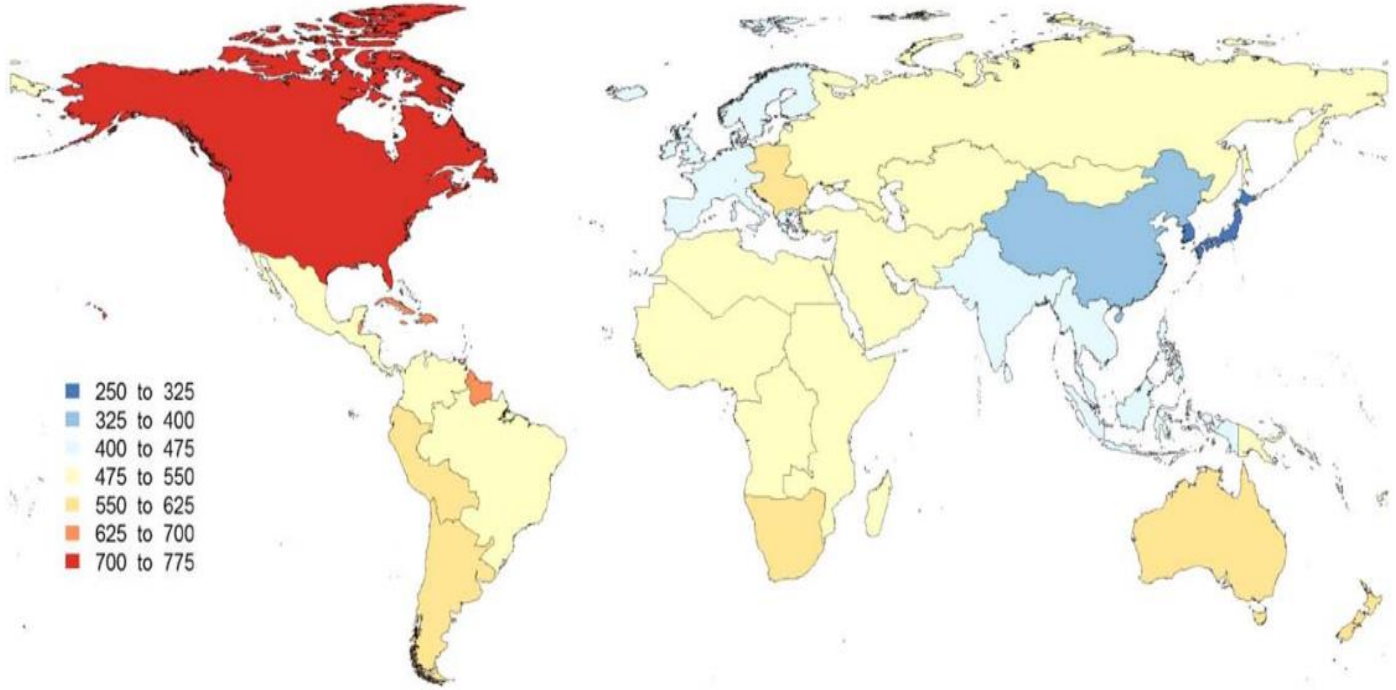


Figure 2. World map showing the age-adjusted prevalence rates (per 100 000 population) of atrial fibrillation in the 21 Global Burden of Disease regions, 2010.

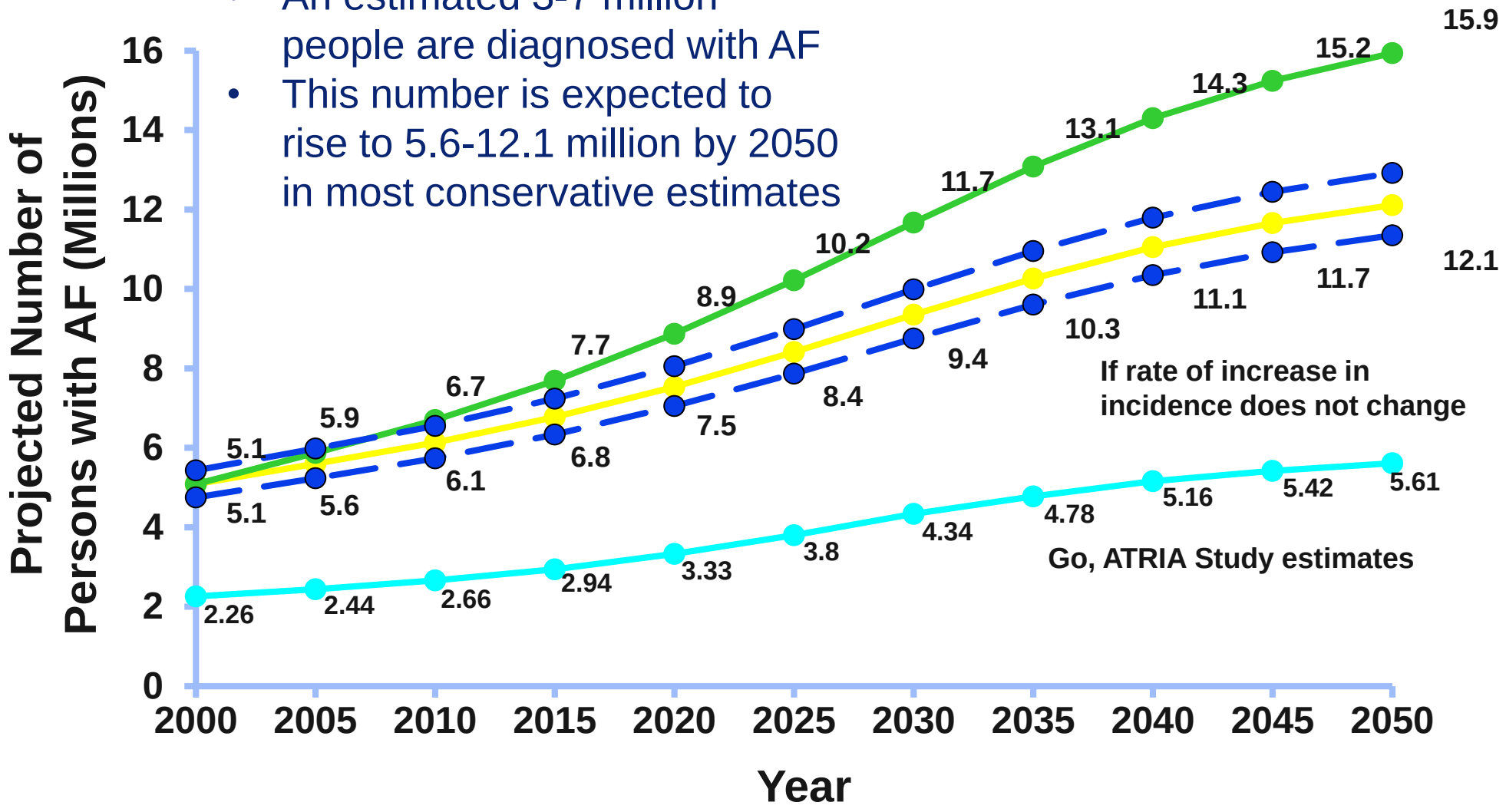
33.5 Million Worldwide have AF

(Screening?, Risk Factors? Life Expectancy? Genetics?)

Chugh SS et al. *Circulation* 2014;129:837-847

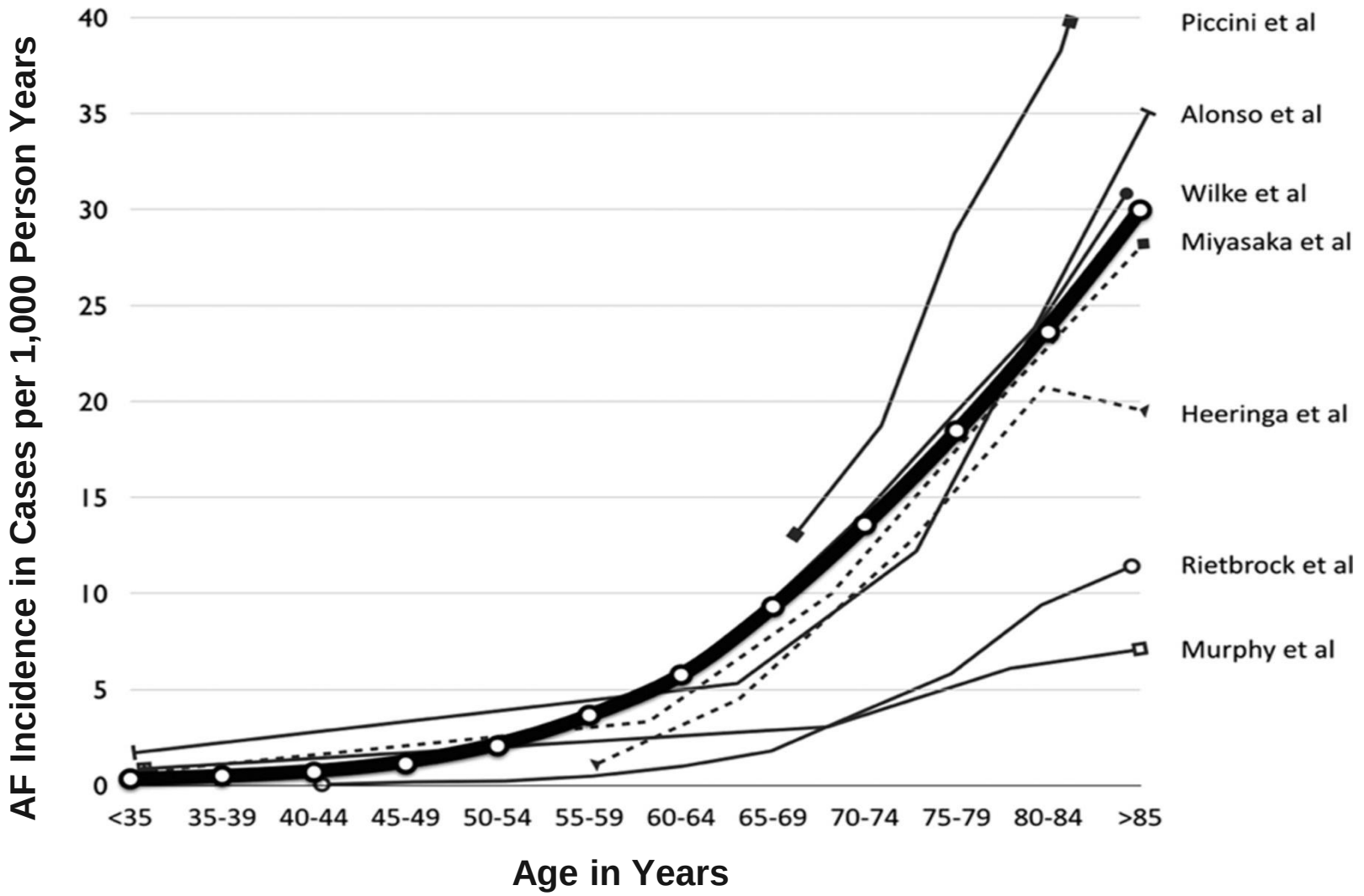
Projected Prevalence of Atrial Fibrillation (AF) (United States)

- An estimated 3-7 million people are diagnosed with AF
- This number is expected to rise to 5.6-12.1 million by 2050 in most conservative estimates



Go AS et al. JAMA 2001;285:2370
Miyasaka Y et al. Circulation 2006;11:119-125

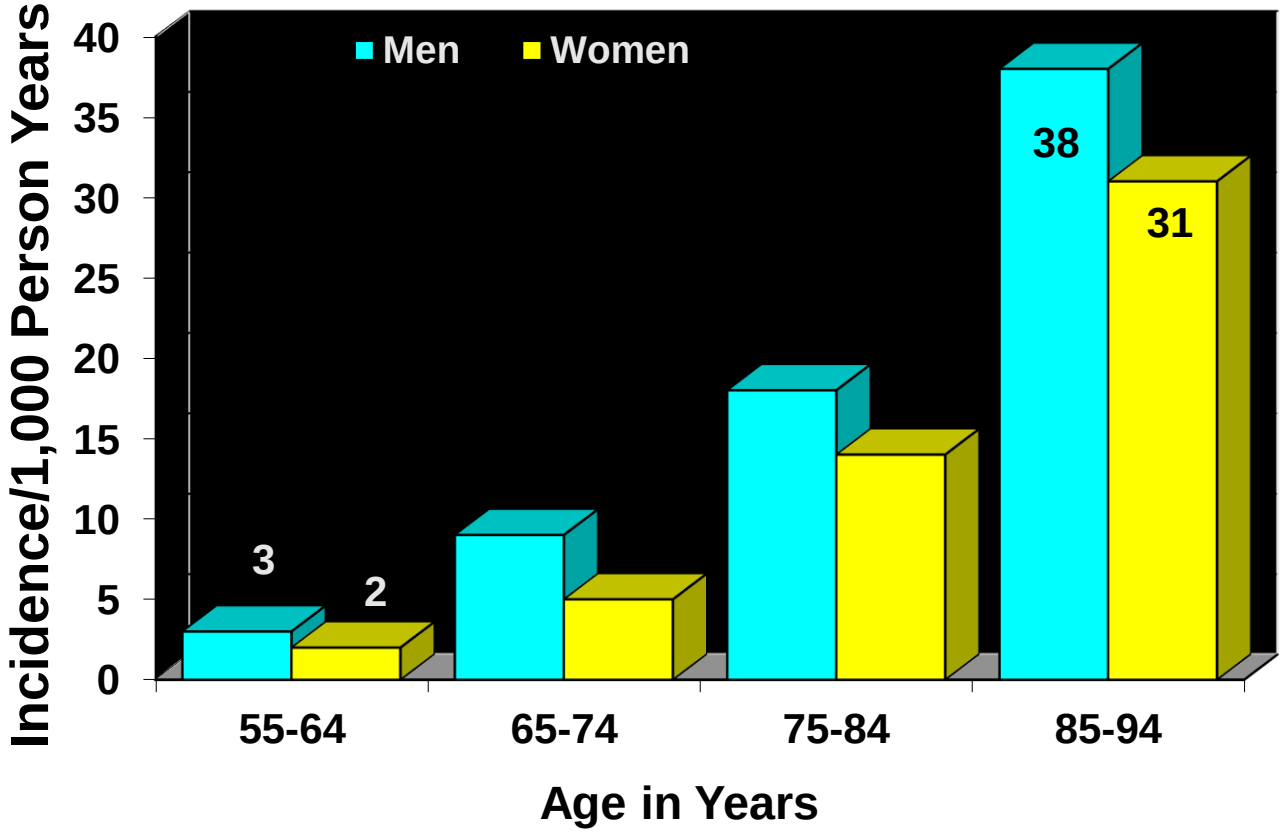
Atrial Fibrillation Incidence Rates by Age



Andrade J et al. Circulation Research 2014;114:1453-1468l

Atrial Fibrillation Incidence: Age and Sex Differences

- AF risk doubles for each advancing decade of life.
- Men have an adjusted 1.5 times risk of AF greater than women.



Benjamin EJ. JAMA 1994;271:840

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AF: Causes & Classification

Usha B. Tedrow, MD MSc

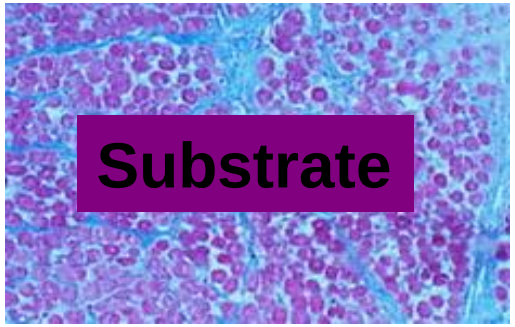
Associate Professor, Harvard Medical School
Fellowship Director, Clinical Cardiac Electrophysiology Program

What Causes AF?

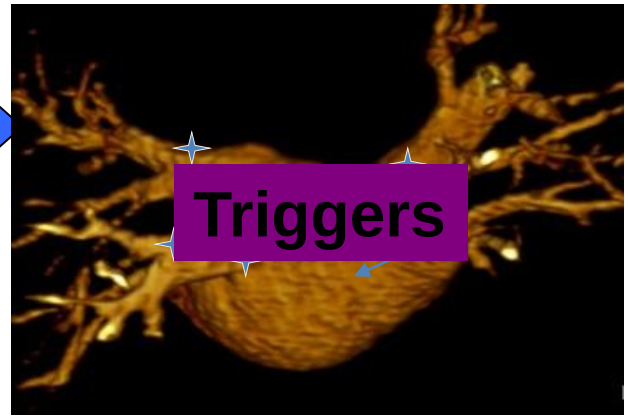
Increased Atrial Size and Pressure
- Ventricular hypertrophy
- Valvular Heart Disease
- Heart failure

- Genetic Predisposition

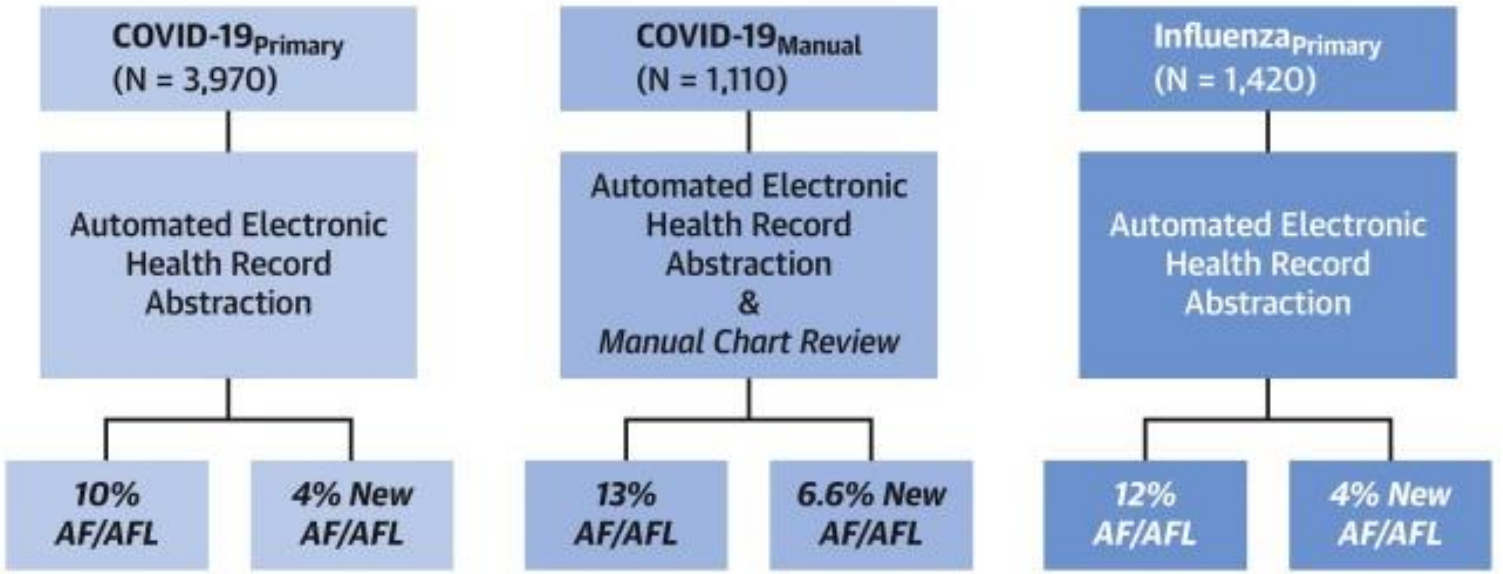
- Inflammation
- Neurohormonal influences



Atrial remodeling
And
Electrical Irritability

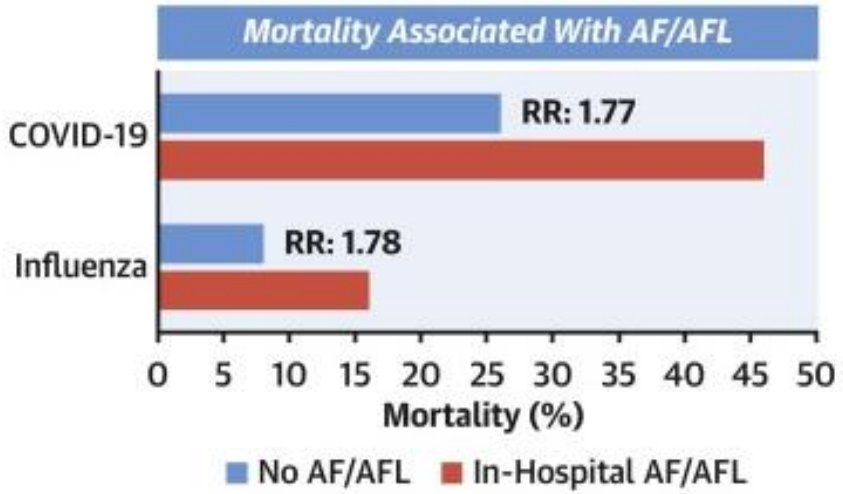


CENTRAL ILLUSTRATION: Incidence, Predictors, and Outcomes of Atrial Arrhythmias in Patients Admitted With COVID-19 Versus Influenza



Risk Factors for New AF/AFL in COVID-19Primary

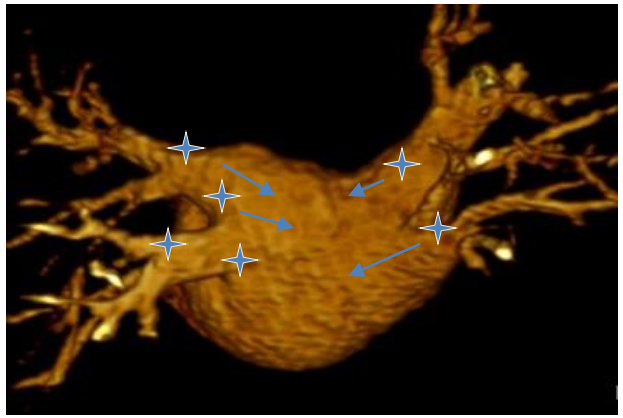
- ↑ Inflammatory markers
- ↑ Myocardial injury
- ↑ Intubation and vasopressor requirement
- ↑ Use of steroids



Musikantow, D.R. et al. J Am Coll Cardiol EP. 2021;7(9):1120-1130

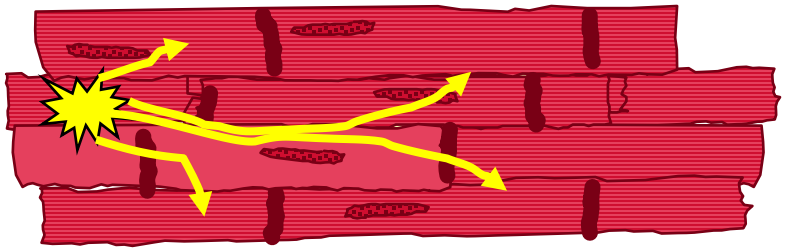
Types of AF

Paroxysmal AF



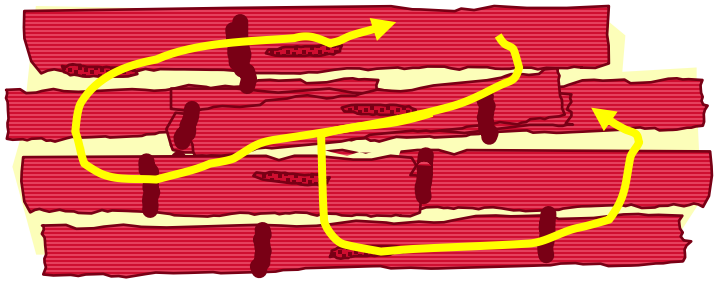
Triggers result in AF that starts and stops by itself

Persistent AF



Progression to longer episodes, days to weeks

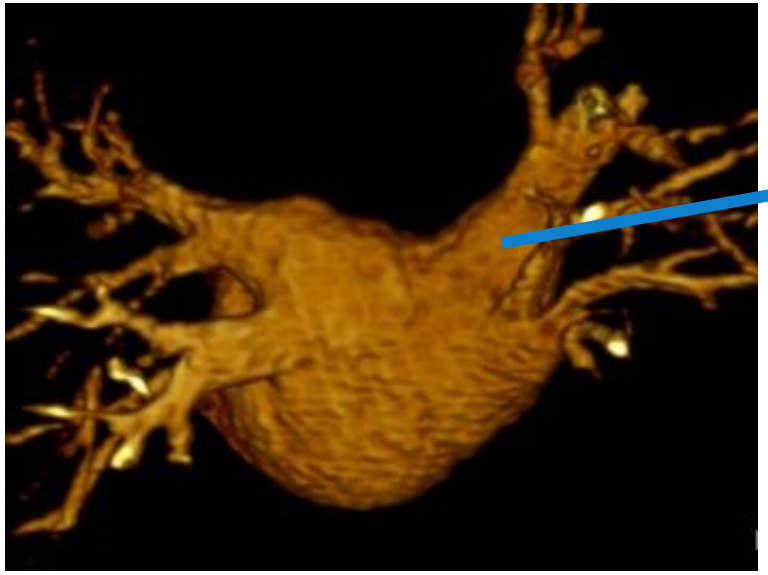
Permanent AF



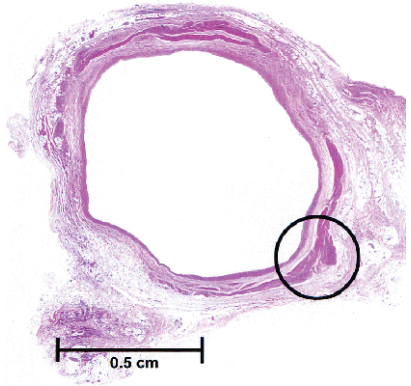
Fibrosis has progressed to the point where AF is continually present

Stambler et al JCE 2003
Li, Nattel et al. Circulation. 1999

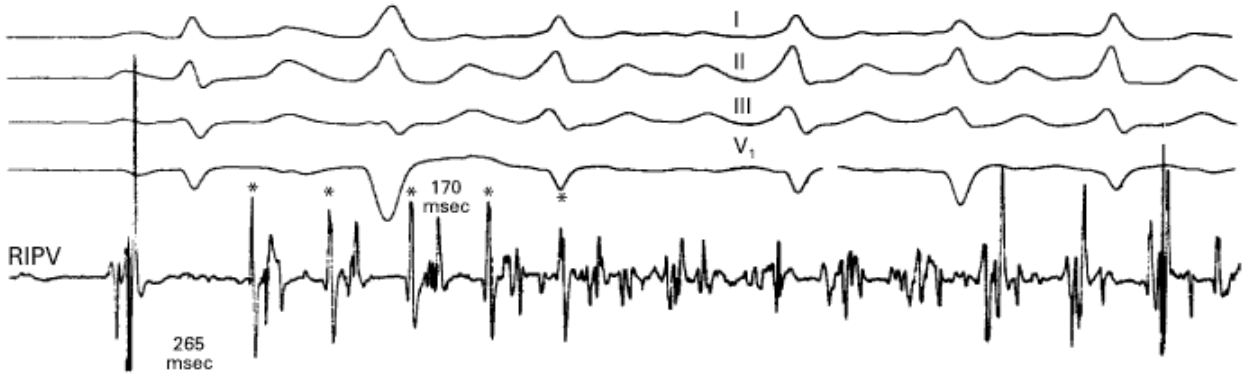
Pulmonary Vein Triggers



Myocardial sleeve around PV



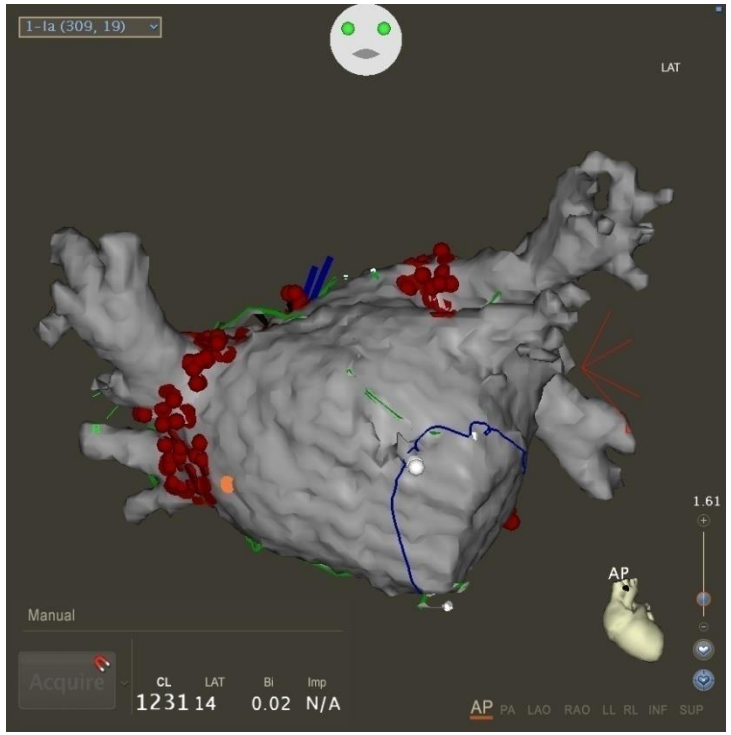
Initiation of AF by rapid firing in a PV

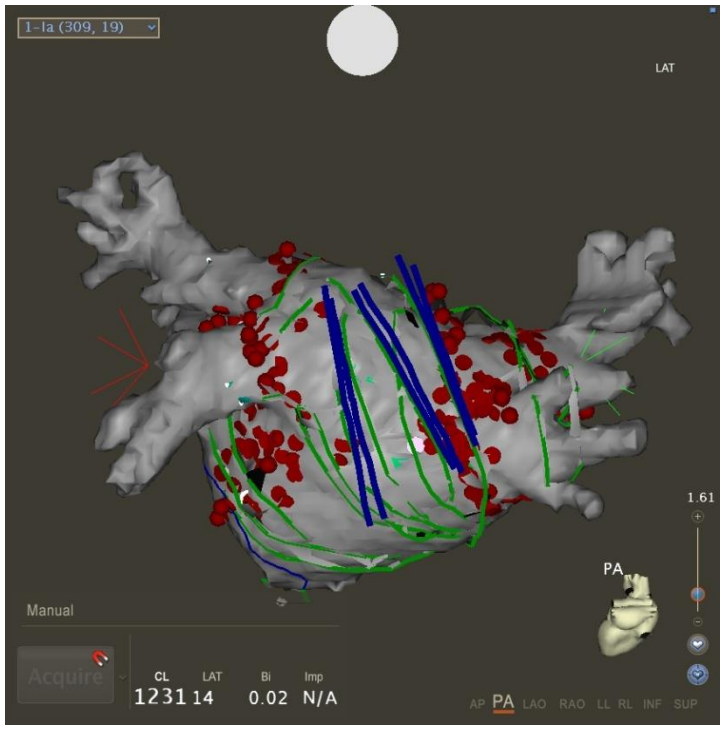


Haissaguerre M, et al. N Engl J Med 1998; 339:659-666

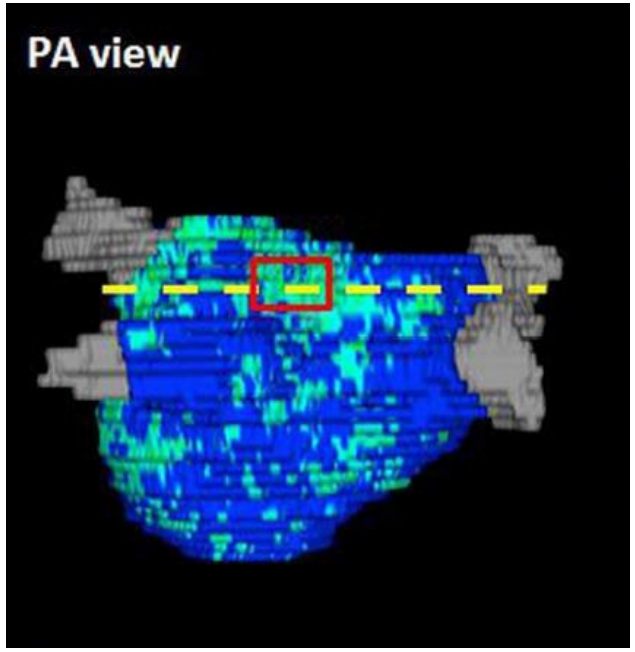
Perez-Lugones, et al. JCE 2003;14: 803

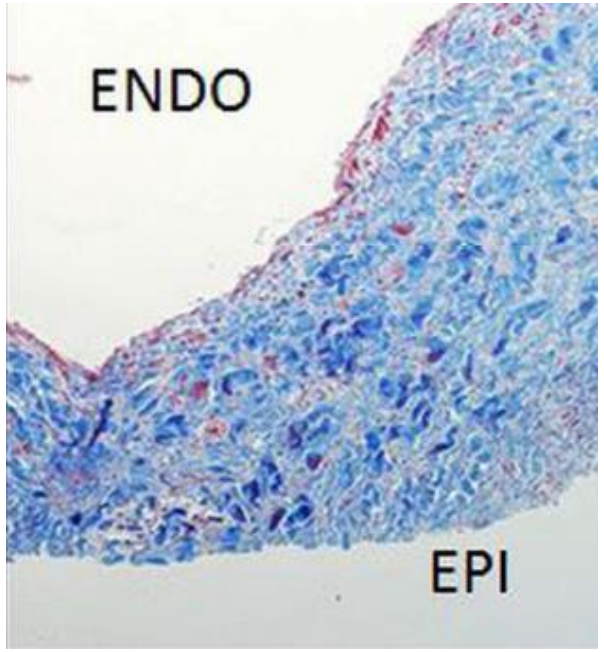
Pulmonary Vein Isolation with Substrate Modification





MRI Fibrosis and Histology in 84 yo F with AF and Severe MR

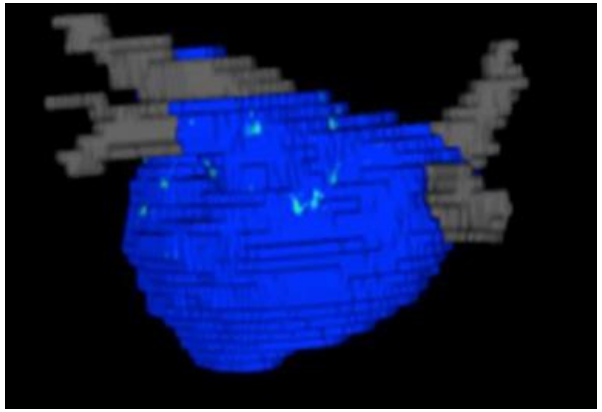


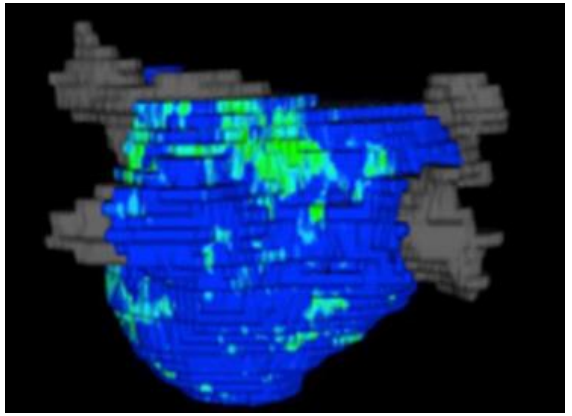


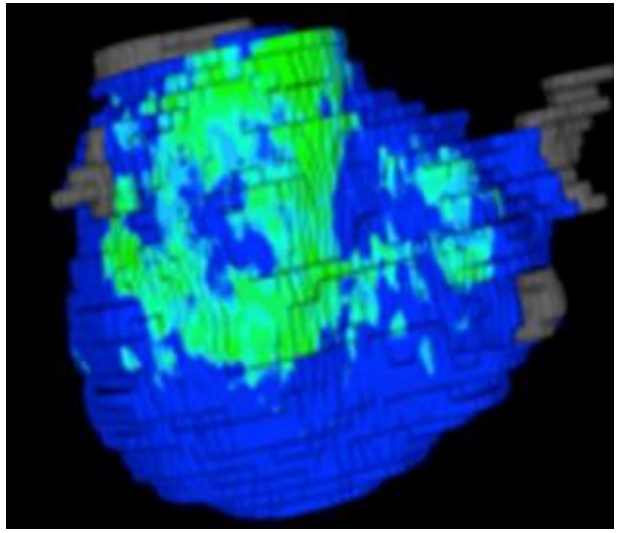
Higuchi K, et al. Heart 2014;100:590–596

Range of Atrial Fibrosis: Related to AF Severity?

Not all AF Patients are equal







Higuchi K, et al. Heart 2014;100:590–596

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Risk Factors for AF

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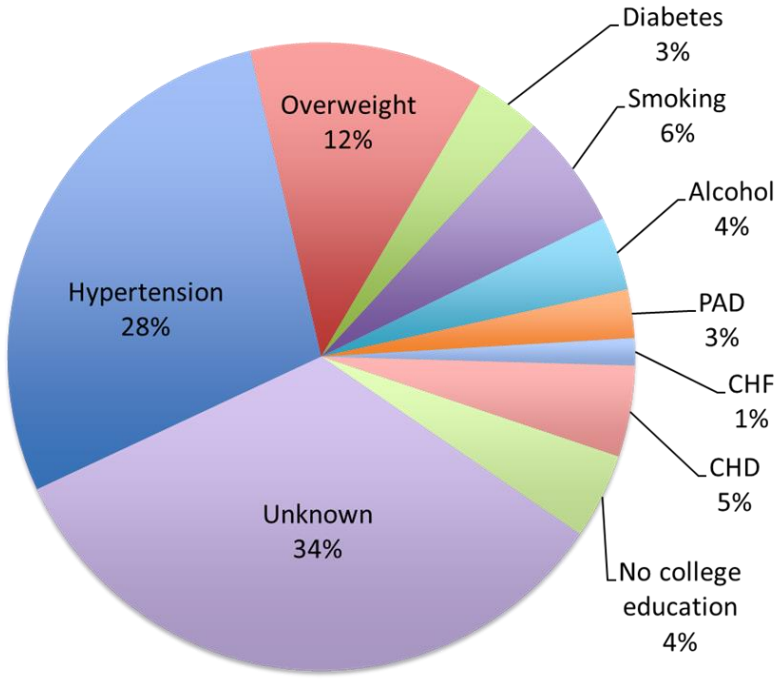
Modifiable Factors that Influence AF Risk

- Blood Pressure
- Weight
- Moderate Exercise
- Moderation of Alcohol
- Avoid Smoking
- Diabetes
- Sleep Apnea

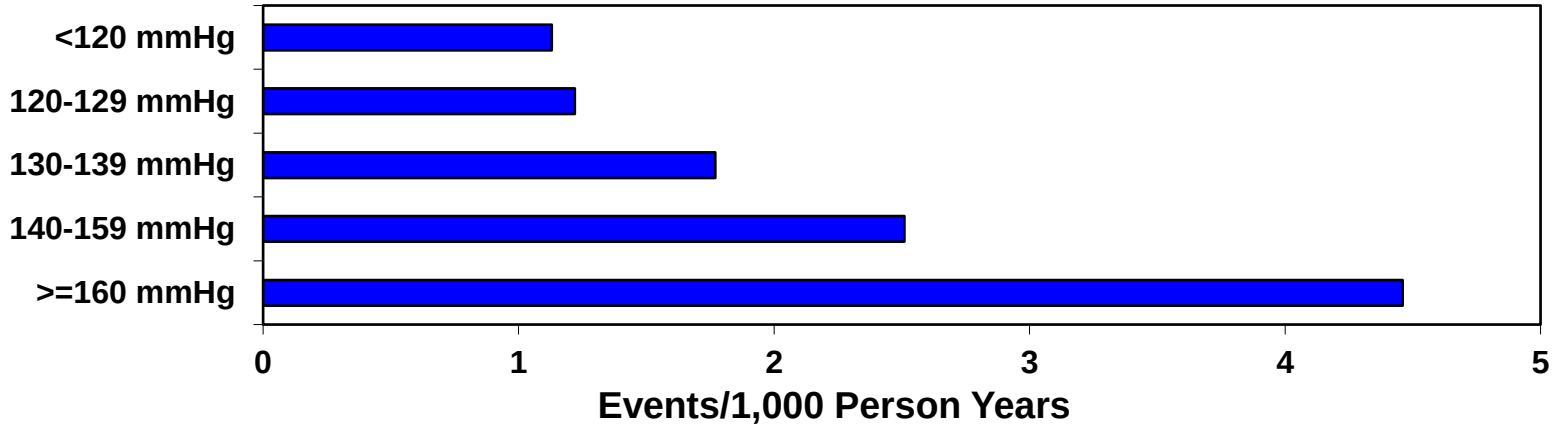


50-60% reductions in AF Risk associated with optimal AF risk factors

Perez MV et al. Heart 2013;99:1173-8

Systolic Blood Pressure and Risk of AF Among Apparently Healthy Women

Age-Adjusted AF Incidence by Baseline SBP:



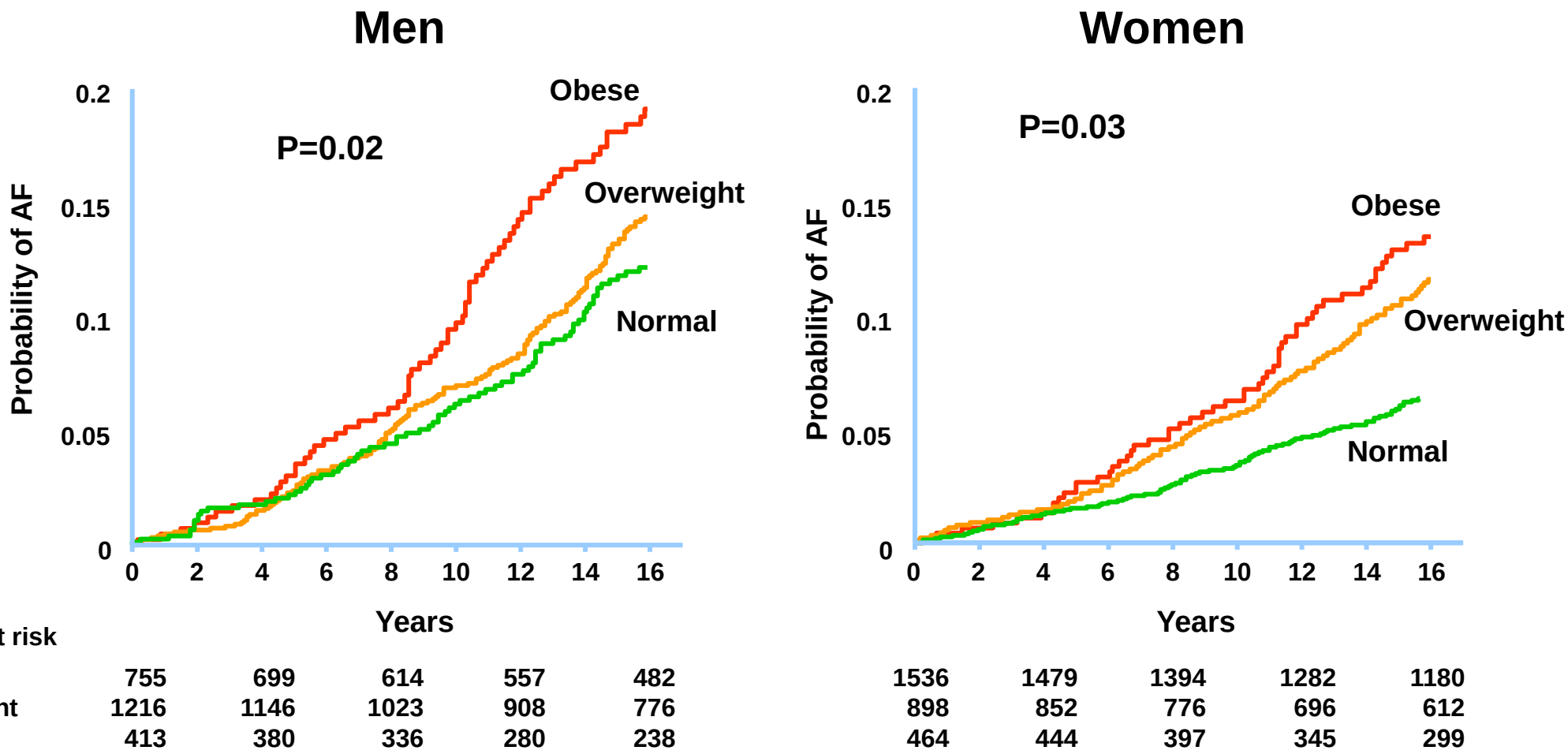
Updated BP Measurements:

Systolic BP	120-129 n=9,448	130-139 n=6,952	140-159 n=5,304	≥160 mmHg n=444
Incident AF	136	160	181	27
Multivariable	1.14 (0.89-1.46)	1.37 (1.07-1.76)	1.71 (1.33-2.21)	2.21 (1.45-3.36)
Combined with DBP	1.18 (0.91-1.51)	1.43 (1.09-1.87)	1.78 (1.34-2.38)	2.29 (1.45-3.63)

Conen D ....Albert CM. Circulation 2009;119:2146-2152

Atrial Fibrillation and Obesity

Framingham Heart Study



Number at risk					
Normal	755	699	614	557	482
Overweight	1216	1146	1023	908	776
Obese	413	380	336	280	238

1536	1479	1394	1282	1180
898	852	776	696	612
464	444	397	345	299

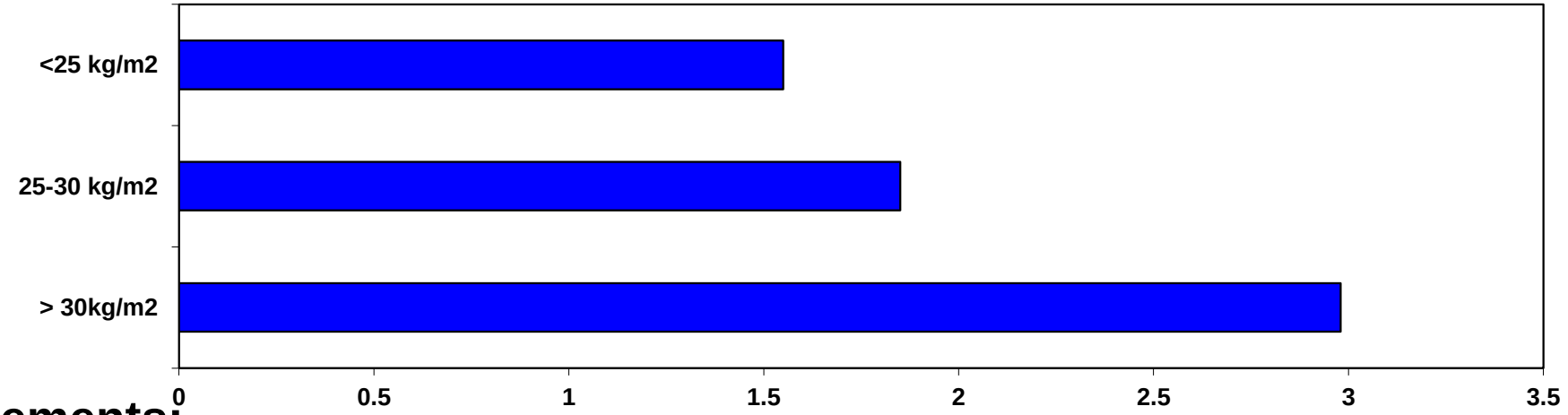
Obesity versus normal BMI: HR 1.5 (adjusted risk)

Mediated by left atrial enlargement

Wang TJ et al. JAMA 2004;292:2471

Dynamic BMI and Atrial Fibrillation Risk in WHS

Age adjusted AF Incidence by Baseline WHO Categories of BMI:



Updated BMI Measurements:

BMI N (%)	**<25 kg/m2** 17415 (51.1%)	**25-30 kg/m2** 10580 (30.8%)	**≥ 30kg/m2** 6185 (18.0%)	**Continuous** N=34,309
Incident AF	344	259	231	834
Age-adjusted	Referent	1.28 (1.09, 1.53)	1.98 (1.67, 2.36)	1.06 (1.05, 1.07)
Multivariable	Referent	1.22 (1.02, 1.45)	1.65 (1.36, 2.00)	1.04 (1.03-1.06)

Tedrow … Albert CM. JACC 2010;55:2319

BMI and AF: Meta-Analysis

Observational Estimates from 7 Prospective Cohorts

51 646 individuals, 4178 AF Cases

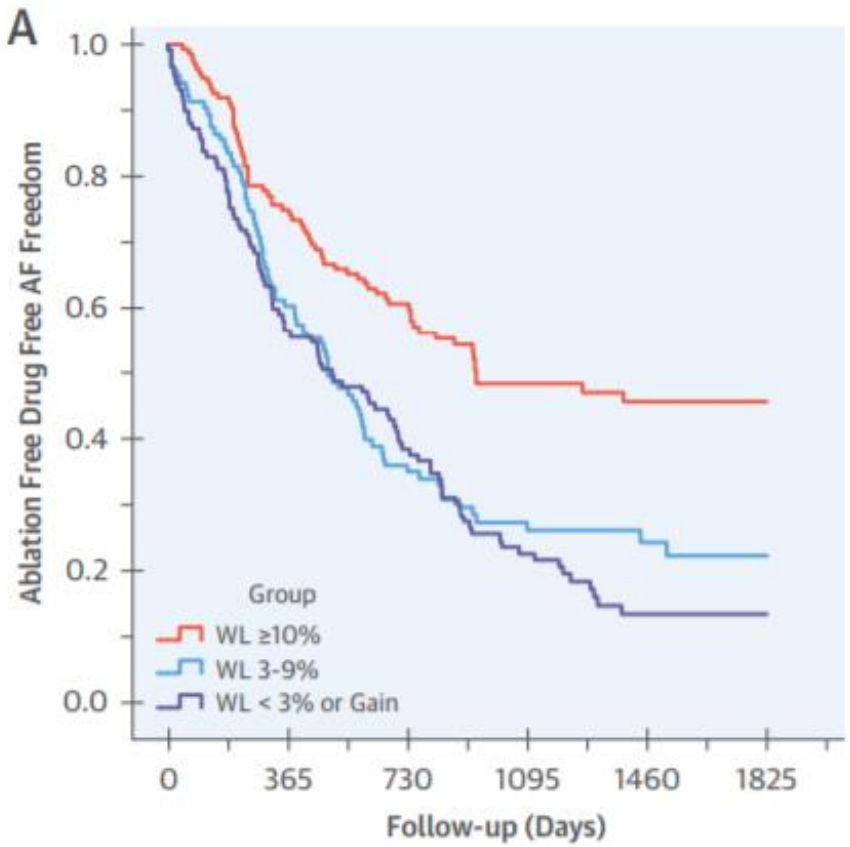
	Age, Sex Adjusted (HR, 95% CI)	+ Confounders (HR, 95% CI)	+ Mediators (HR, 95% CI)	+ Height (HR, 95% CI)
Per1 kg/m^2 ↑ BMI				
AGES	1.03 (1.01-1.05)	1.03 (1.01-1.06)	1.03 (1.01-1.05)	1.03 (1.01-1.05)
ARIC	1.06 (1.05-1.07)	1.07 (1.06-1.08)	1.05 (1.03-1.06)	1.05 (1.04-1.06)
FHS	1.05 (1.03-1.06)	1.05 (1.03-1.07)	1.04 (1.02-1.06)	1.04 (1.02-1.06)
PREVEND	1.06 (1.01-1.10)	1.05 (1.01-1.10)	1.05 (1.00-1.11)	1.06 (1.00-1.12)
RS-I	1.05 (1.03-1.07)	1.04 (1.02-1.07)	1.03 (1.00-1.05)	1.04 (1.01-1.06)
RS-II	1.05 (1.00-1.11)	1.05 (1.00-1.11)	1.03 (0.97-1.11)	1.03 (0.97-1.10)
WGHS	1.05 (1.04-1.06)	1.05 (1.04-1.06)	1.03 (1.02-1.05)	1.04 (1.03-1.05)
Meta-Analysis				
Observational estimate	**1.05 (1.04-1.06)**	**1.05 (1.04-1.06)**	**1.04 (1.03-1.05)**	**1.04 (1.03-1.05)**
Test for overall effect	p<0.001	p<0.001	p<0.001	p<0.001
Heterogeneity [I^2, Qp]	[24%, 0.37]	[47.5%, 0.10]	[5.1%, 0.68]	[0%, 0.78]

Multivariable adjustment included confounders (smoking, EtOH) and mediators (systolic and diastolic blood pressure, diabetes mellitus, history of coronary heart disease, history of heart failure)

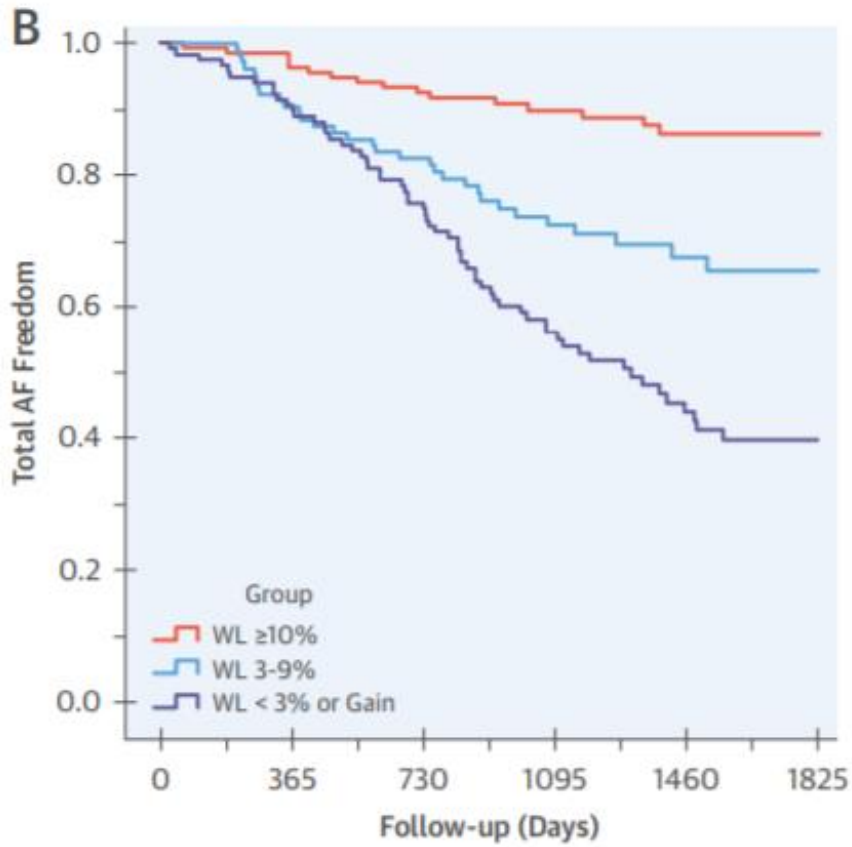
Each 1 kg/m^2 ↑ observed BMI associated with 4% ↑ risk of incident AF

Chatterjee et al….Albert CM. Circulation 2017

Goal-Directed Weight Management in AF



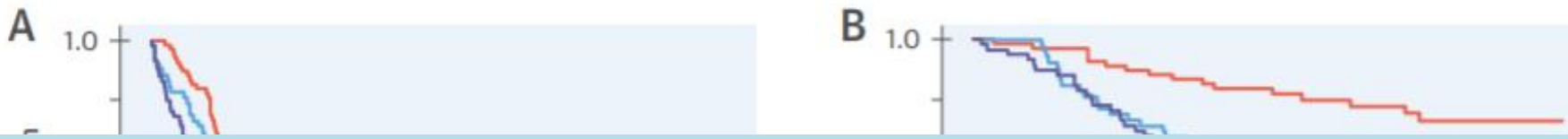
Time (Days)	0	365	730	1095	1460	1825
≥10 WL	135	101	72	42	31	18
3-9% WL	103	62	36	22	13	7
<3% WL or gain	117	66	44	22	11	9



0	365	730	1095	1460	1825
135	130	114	86	67	36
103	93	83	57	35	22
117	105	85	53	32	22

Pathak et. al. J Am Coll Cardiol 2015;65:2159–69

Goal-Directed Weight Management in AF



Weight loss ≥10% resulted in a 6-fold ($p < 0.001$) increased arrhythmia-free survival compared with the other 2 groups

A separate analysis of the same pts showed: Arrhythmia-free survival was greatest in those who gained "fitness," a gain of ≥ 2 METs compared to those with smaller gains in cardiorespiratory fitness ($p < 0.001$)

Time (Days)	0	365	730	1095	1460	1825
≥10 WL	135	101	72	42	31	18
3-9% WL	103	62	36	22	13	7
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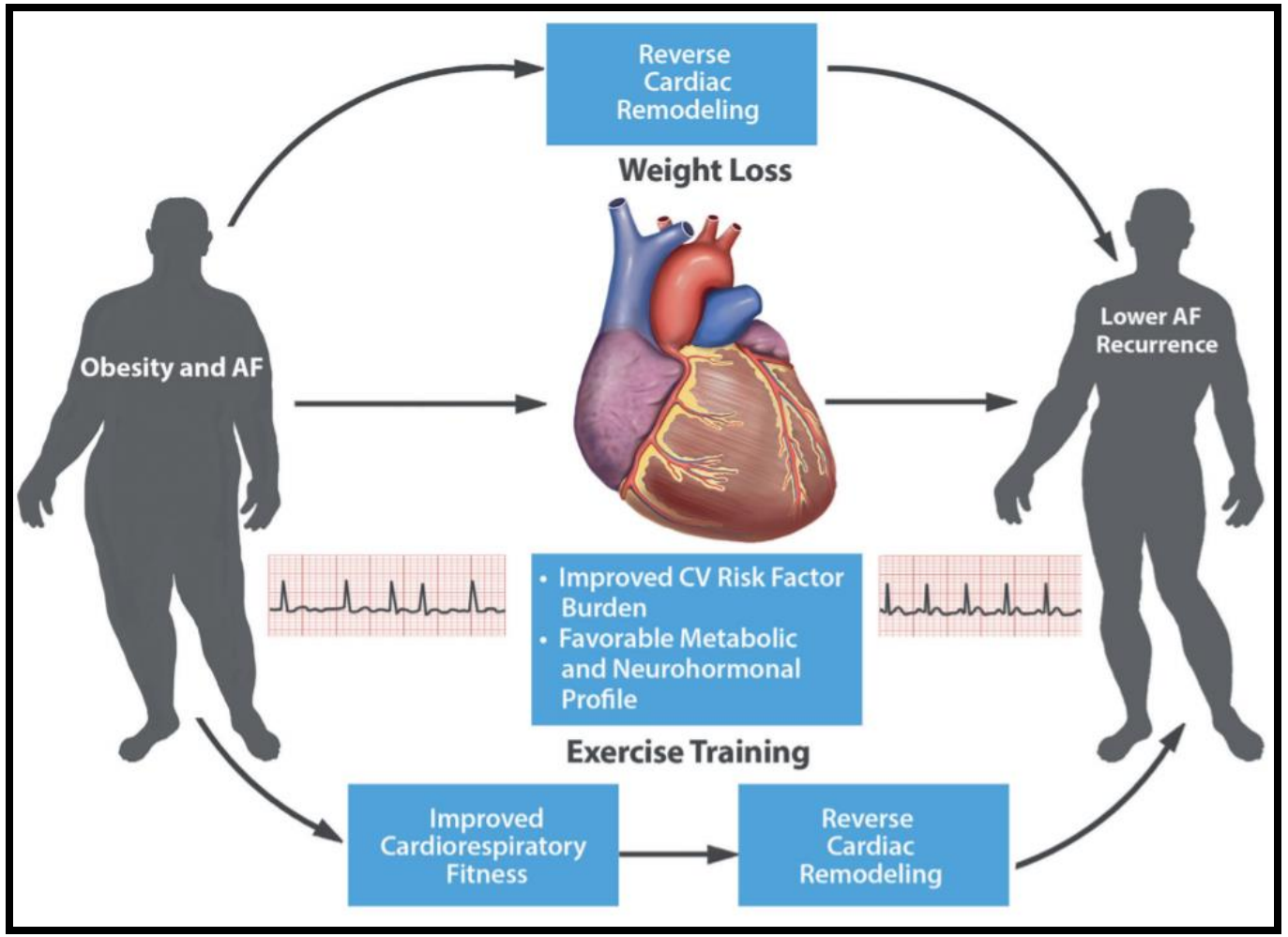
117	105	85	53	32	22

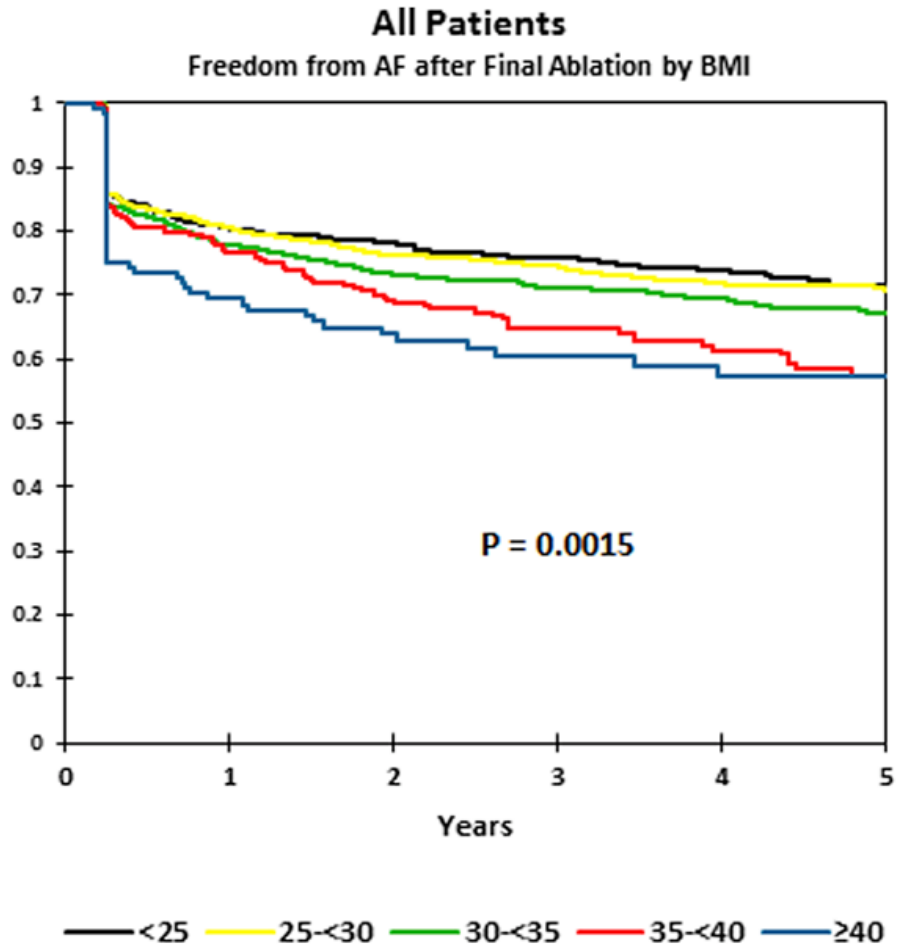
Pathak et. al. J Am Coll Cardiol 2015;65:2159–69
Pathak et al. J Am Coll Cardiol 2015;66:985–96

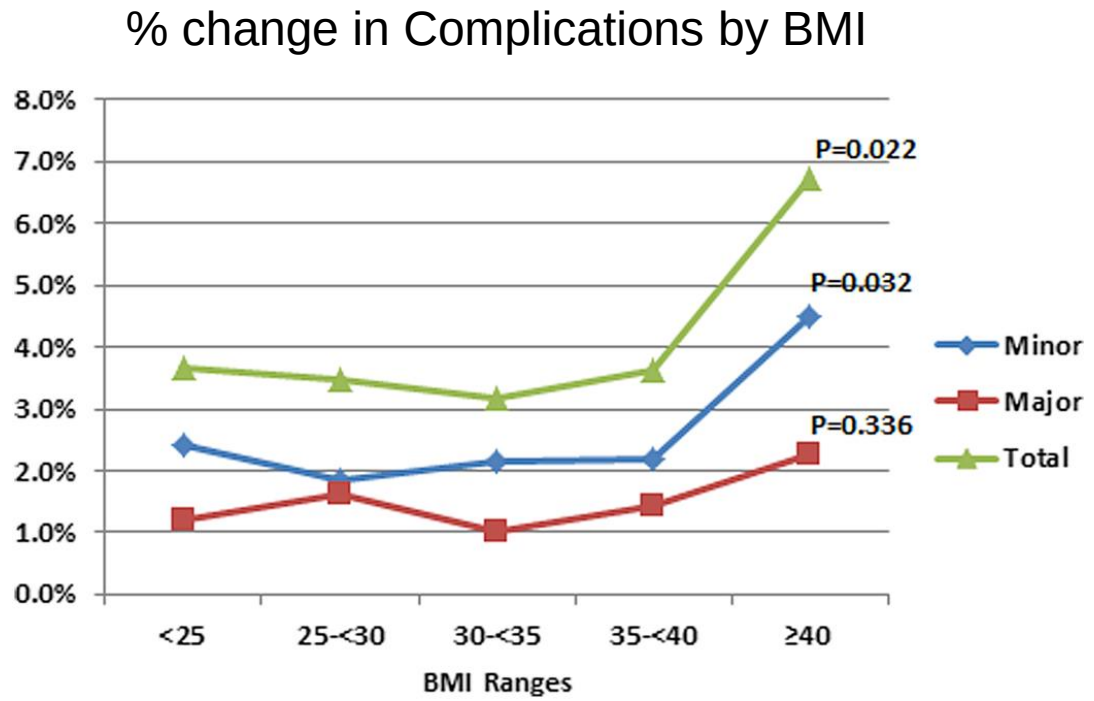
Proposed Mechanism of Weight Loss and AF Reduction



Lavie, C.J. et al. J Am Coll Cardiol.2017;70(16):2022-35

Particularly Important Because Catheter Ablation is Less Effective and More Risky in Obese Patients





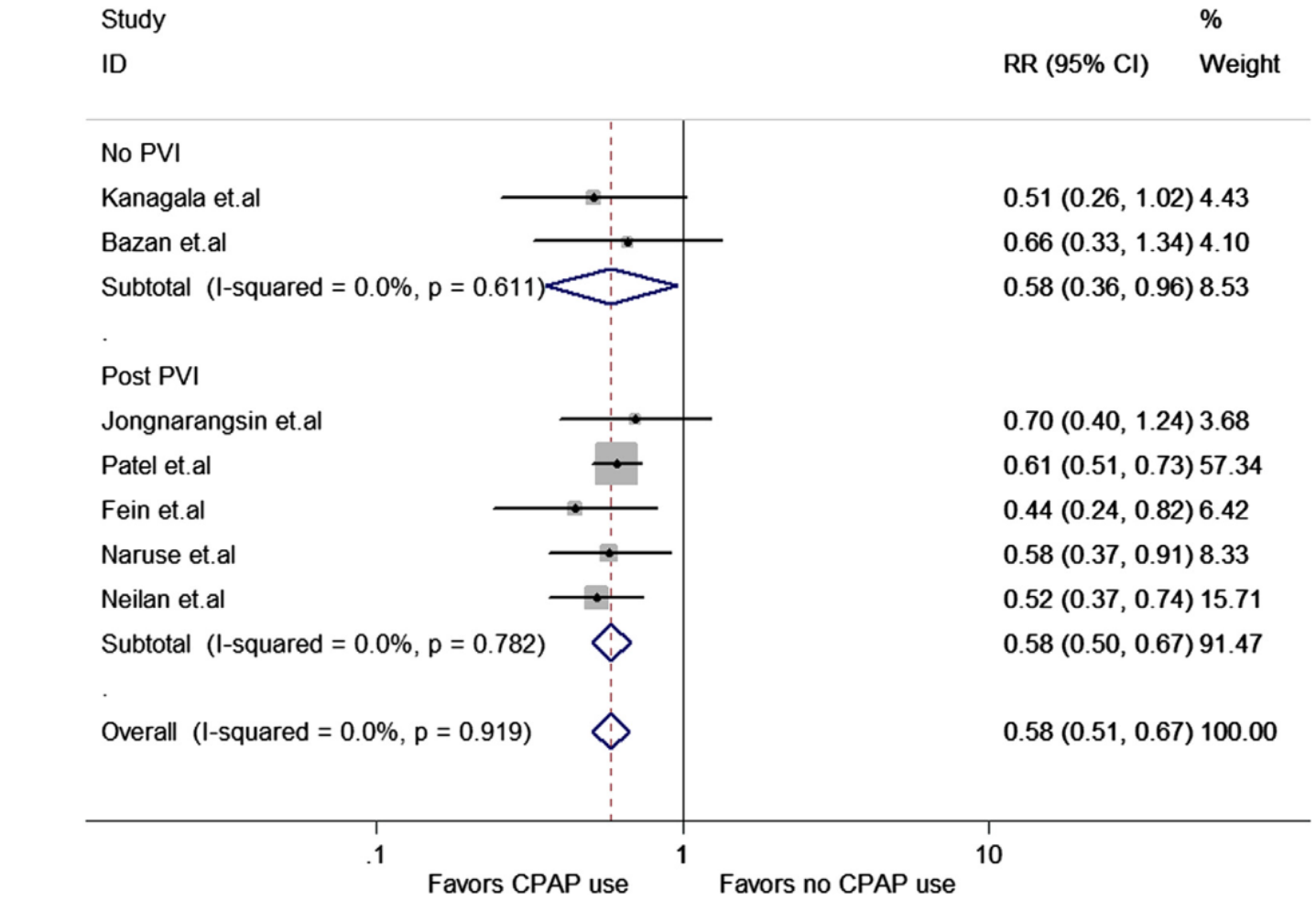
Winkle RA et al. Heart Rhythm 2017 14, 819-827

Sleep Apnea

- Obstructive sleep apnea (OSA) markedly increases the risk of both AF and stroke
- OSA pts are 5 times more likely to develop AF than those without sleep apnea
- Risk of AF is directly correlated with the severity of sleep apnea
- Mechanisms:
  - Autonomic: OSA stimulates excess vagal tone, while triggering activation of the sympathetic nervous system (Worsening of underlying hypertension)
  - Structural/hemodynamic: Upper airway obstruction during inhalation → negative intrathoracic pressure, increasing atrial blood volume → Left atrial enlargement

N. Gahungu et al. Sleep Medicine 57 (2019) 107e114

AF Recurrence in Users vs nonusers of CPAP in 2 groups of patients with OSA: PVI and Non-PVI groups



The forest plot exhibits effect size of each included study **(solid box)** with 95% confidence interval (CI) **(black lines through solid squares)**. The **diamond (and broken vertical line)** at the bottom represents pooled summary estimate with its CI given by its width. AF = atrial fibrillation; CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea; RR = relative risk ratio.

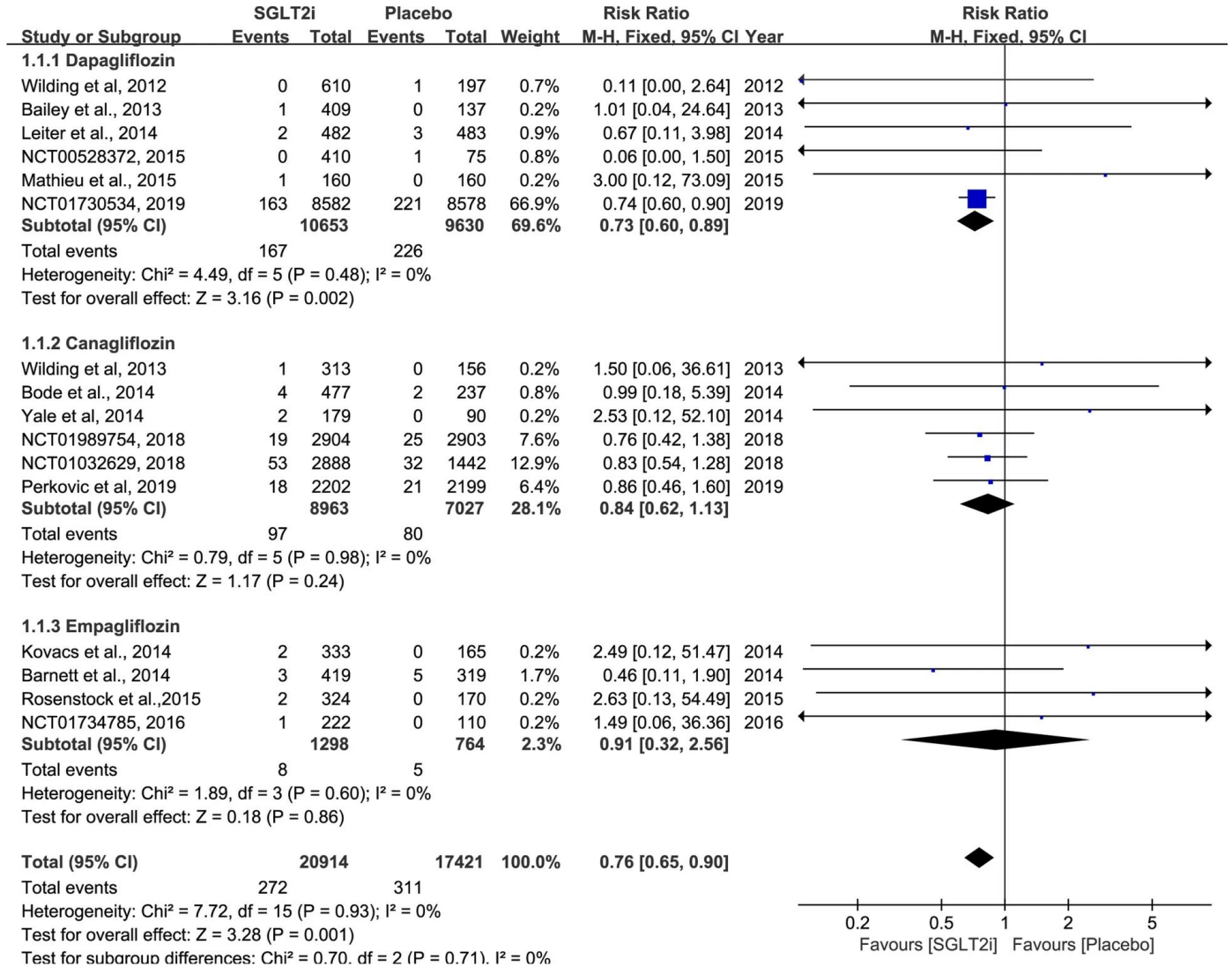
Shukla et al. J Am Coll Cardiol EP 2015;1-2:41–51

Type 2 Diabetes and AF, SGLT-2 Inhibitors

Patients with DM2 have a 35% higher risk of AF compared with age- and gender-matched control subjects

SGLT-2 inhibitors are a class of prescription medicines that are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes.

SGLT-2 inhibitor use can reduce AF risk by **19%**



Li WJ et al. Cardiovasc Diabetol 2020; 19: 130.

Frequency of Jogging and Atrial Fibrillation

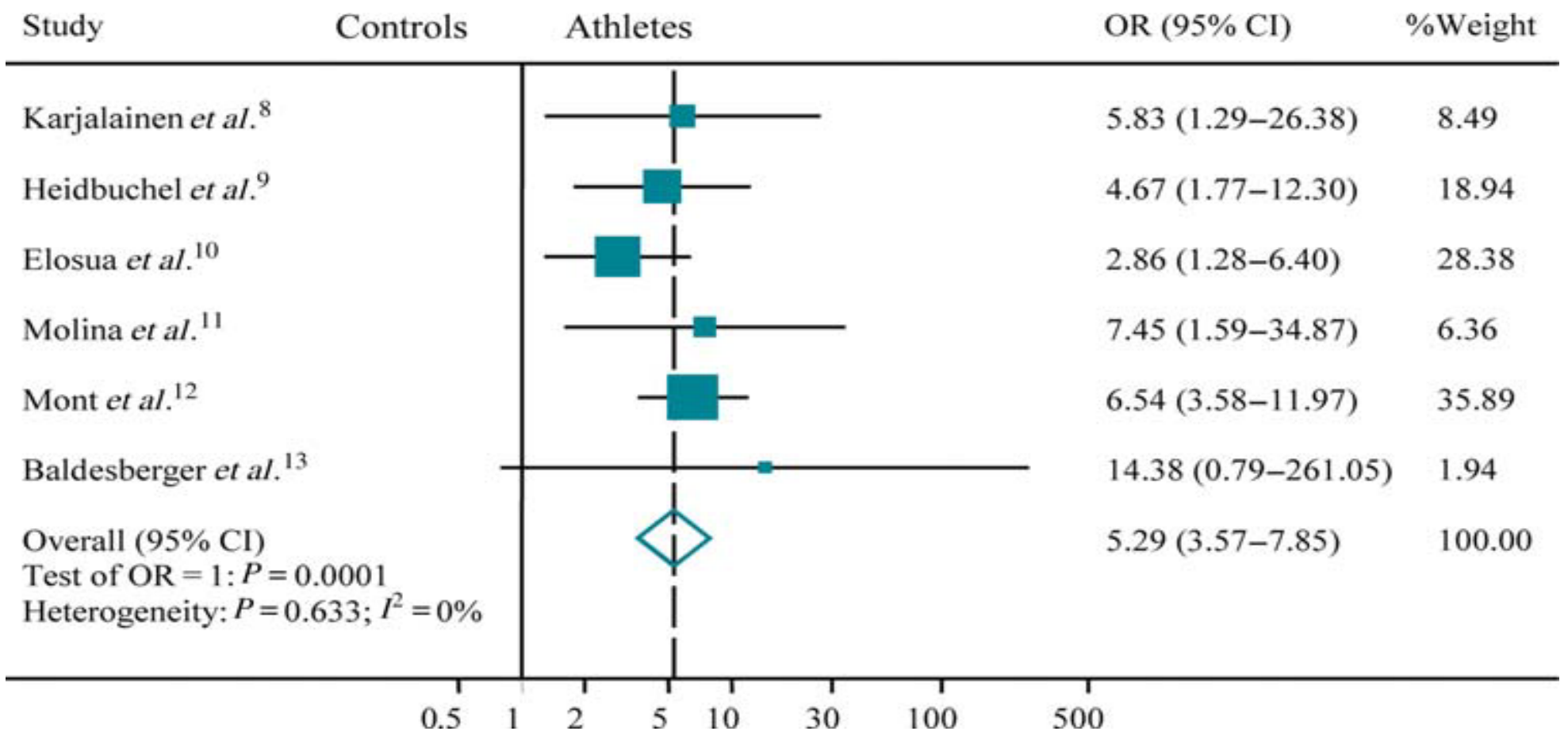
Physicians' Health Study

Frequency of Habitual Jogging	<1/Wk	1-2/Wk	3-4/Wk	5-7/Wk	P-Trend
Model 1*– Hazard Ratio	0.78	0.90	1.16	1.42	0.013
Multivariable Model 2†	0.91	1.03	1.30	1.53	<0.001
Multivariable Model 3‡	0.83	0.91	1.22	1.45	<0.01

* Model 1: age and treatment assignment.
† Model 2: age, treatment assignment, parental history of premature MI, alcohol, smoking, fish consumption, multivitamin, vitamin C and vitamin E intake, **BMI, DM, HTN, Hyperlipidemia, LVH, CHF, and CVD.**
‡ Model 3: age, treatment assignment , parental history of premature MI, alcohol, smoking, fish consumption, multivitamin, and vitamin C and vitamin E intake.

Aizer A et al. Am J Cardiol 2009;103:1572-1577

Meta-Analysis of AF Risk in Athletes Compared with Controls

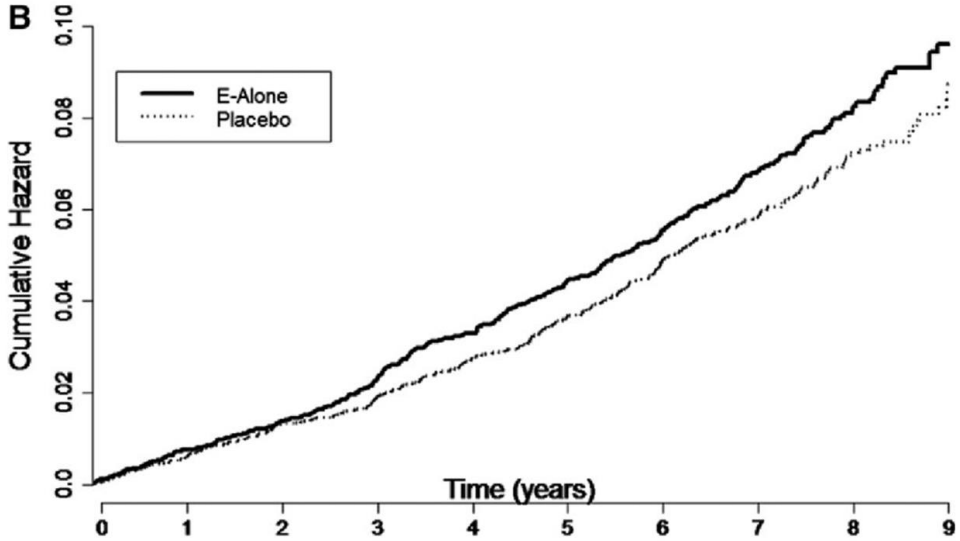


Abdulla J and Nielsen JR. Europace 2009;11:1156-1159

AF Risk Factors Specific to Women

Women's Health Initiative
10,739 Women with Prior Hysterectomy

Women randomized to Estrogen had 17% more AF

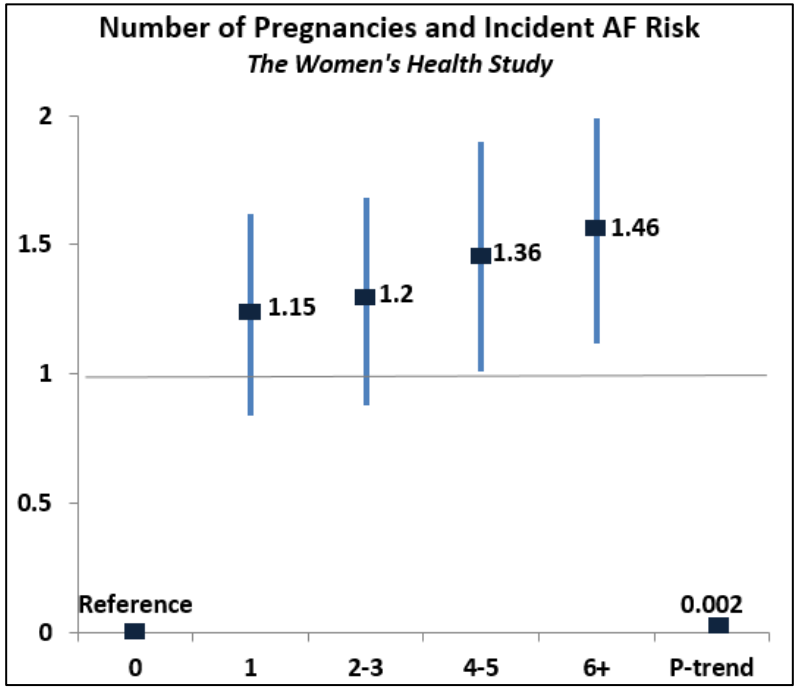


Hazard Ratio in Estrogen Alone Trial: 1.17 (P=0.045)

Women's Health Study
30,034 Women without TAH-BSO

Hazard Ratio for AF in Women on Estrogen Alone:
1.22 (P=0.035)

No Increased Risk associated Menopause beyond that associated with Age



Perez MV et al. Circ Arrhythm Electrophysiol 2012;5:1108-16
Wong JA et al. Heart 2017; 103:1954-1961
Wong JA et al. Circulation 2017; 135:622-624

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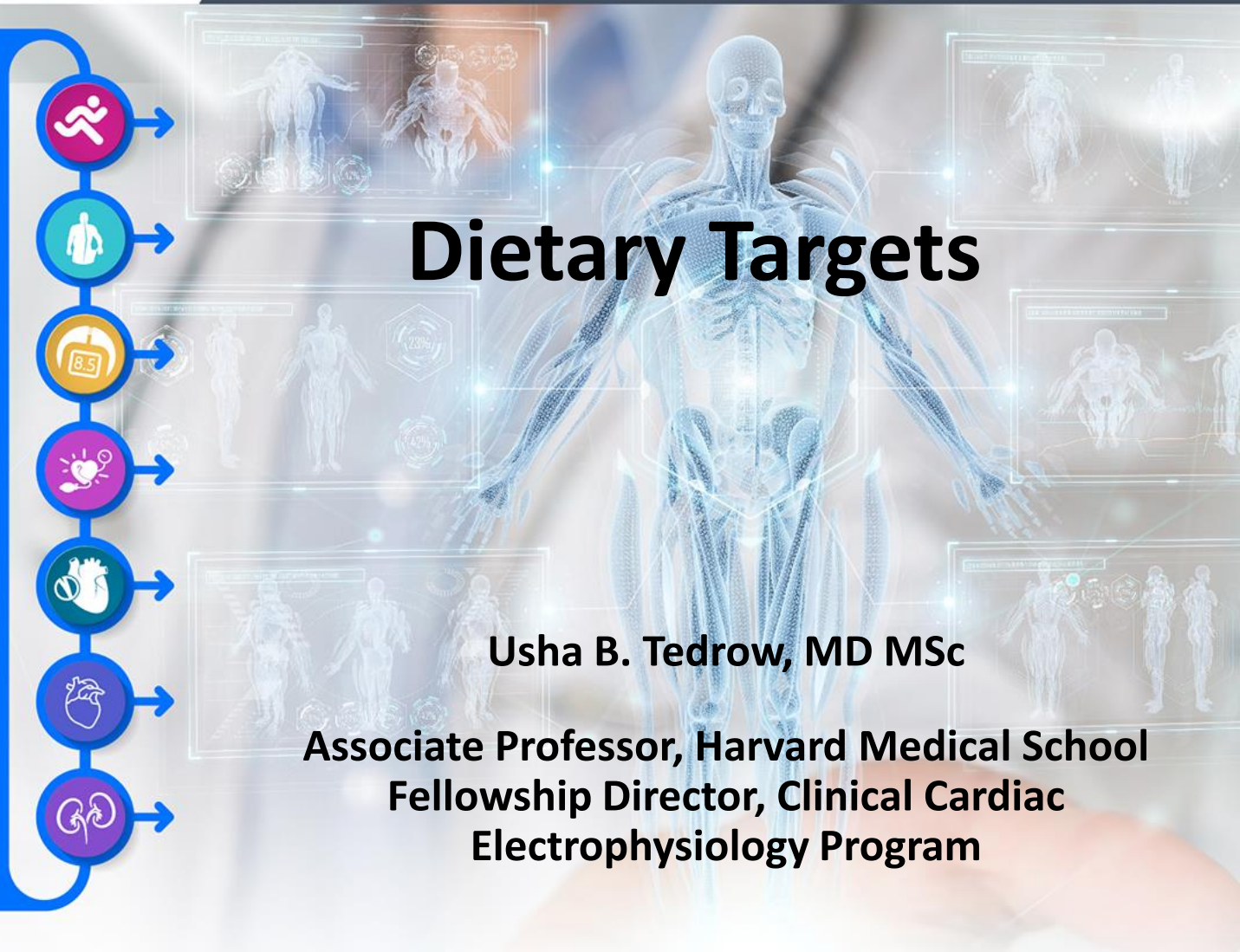
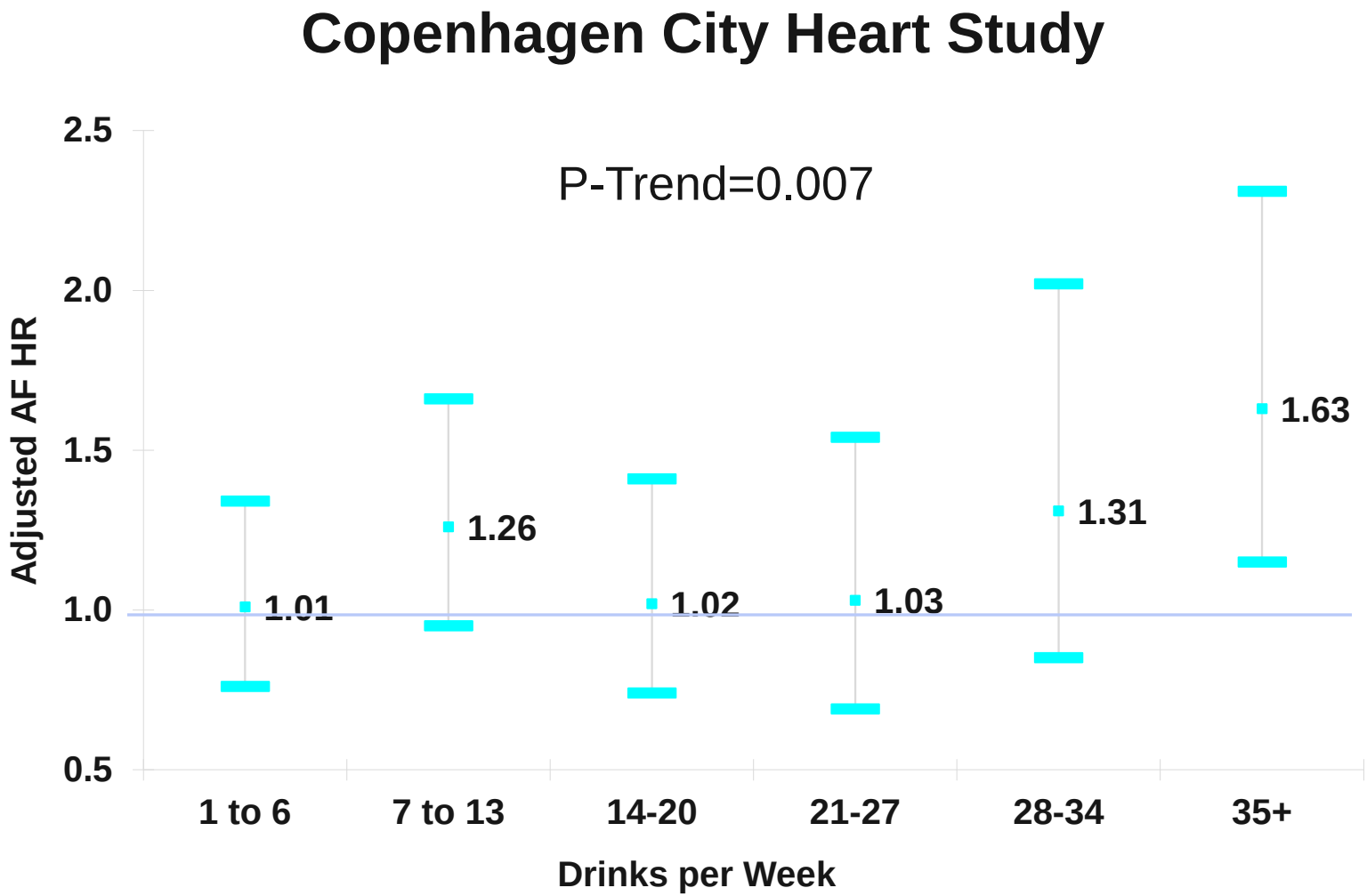


Dietary Targets

Usha B. Tedrow, MD MSc

Associate Professor, Harvard Medical School
Fellowship Director, Clinical Cardiac Electrophysiology Program

Risk of AF by Weekly Alcohol Consumption in Men

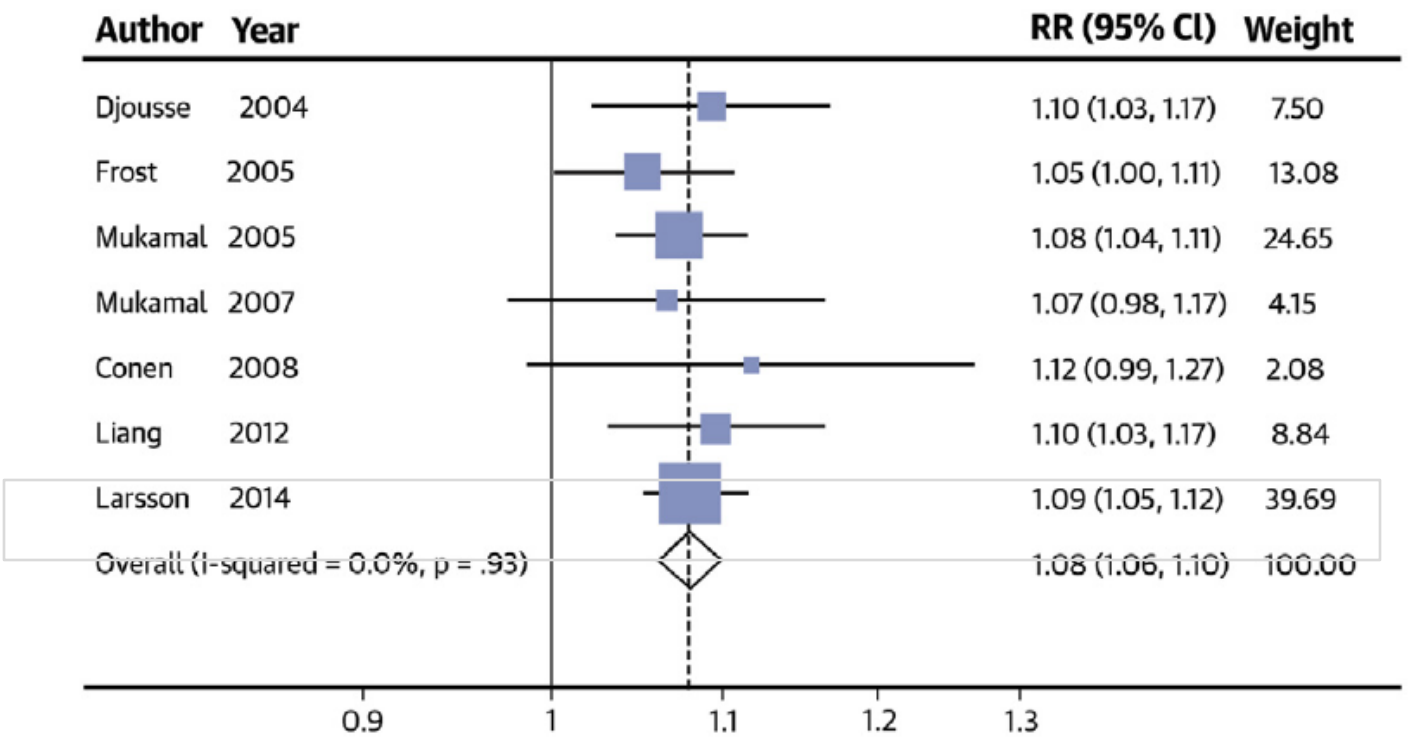


Heavy alcohol consumption in men associated with higher adjusted AF risk unexplained by CHD or BP
Risk not observed in women, but few drank heavily.

Mukamal KJ Circulation 2005;112:1736

Alcohol Intake and Risk of AF

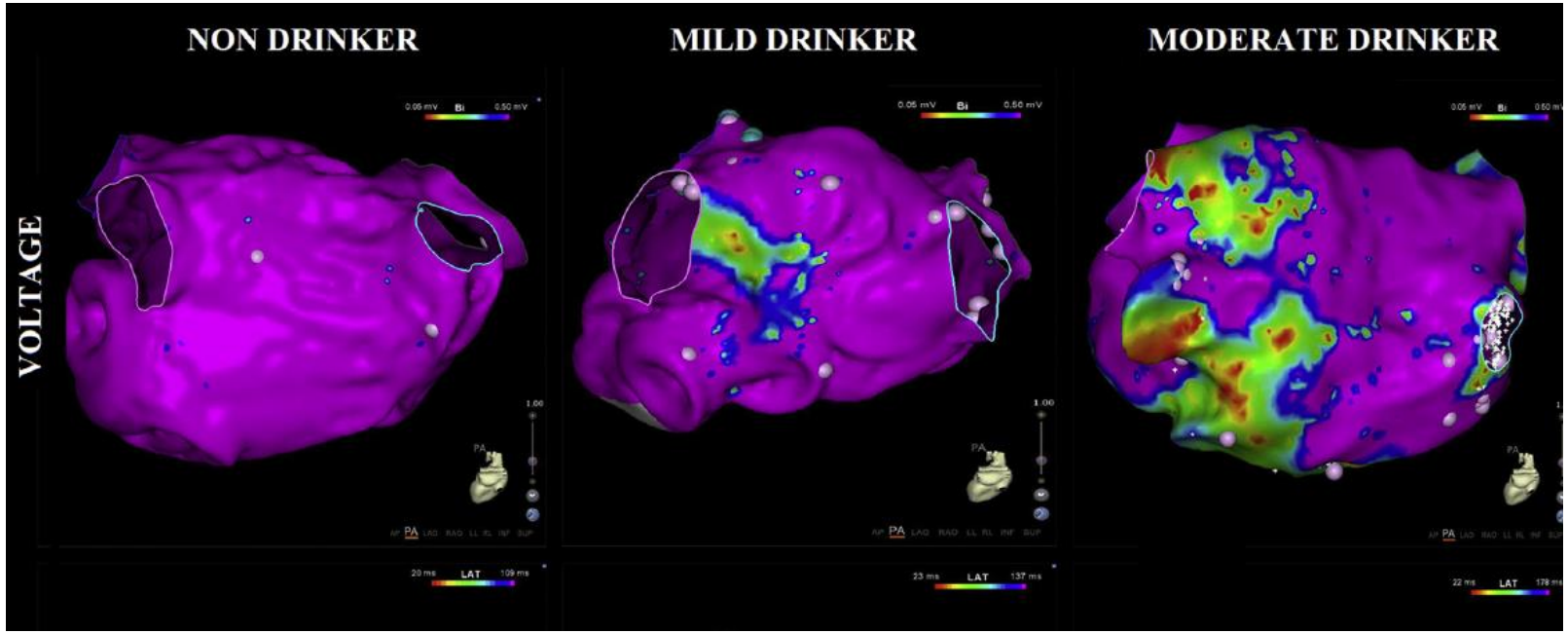
Meta-analysis of Prospective Studies



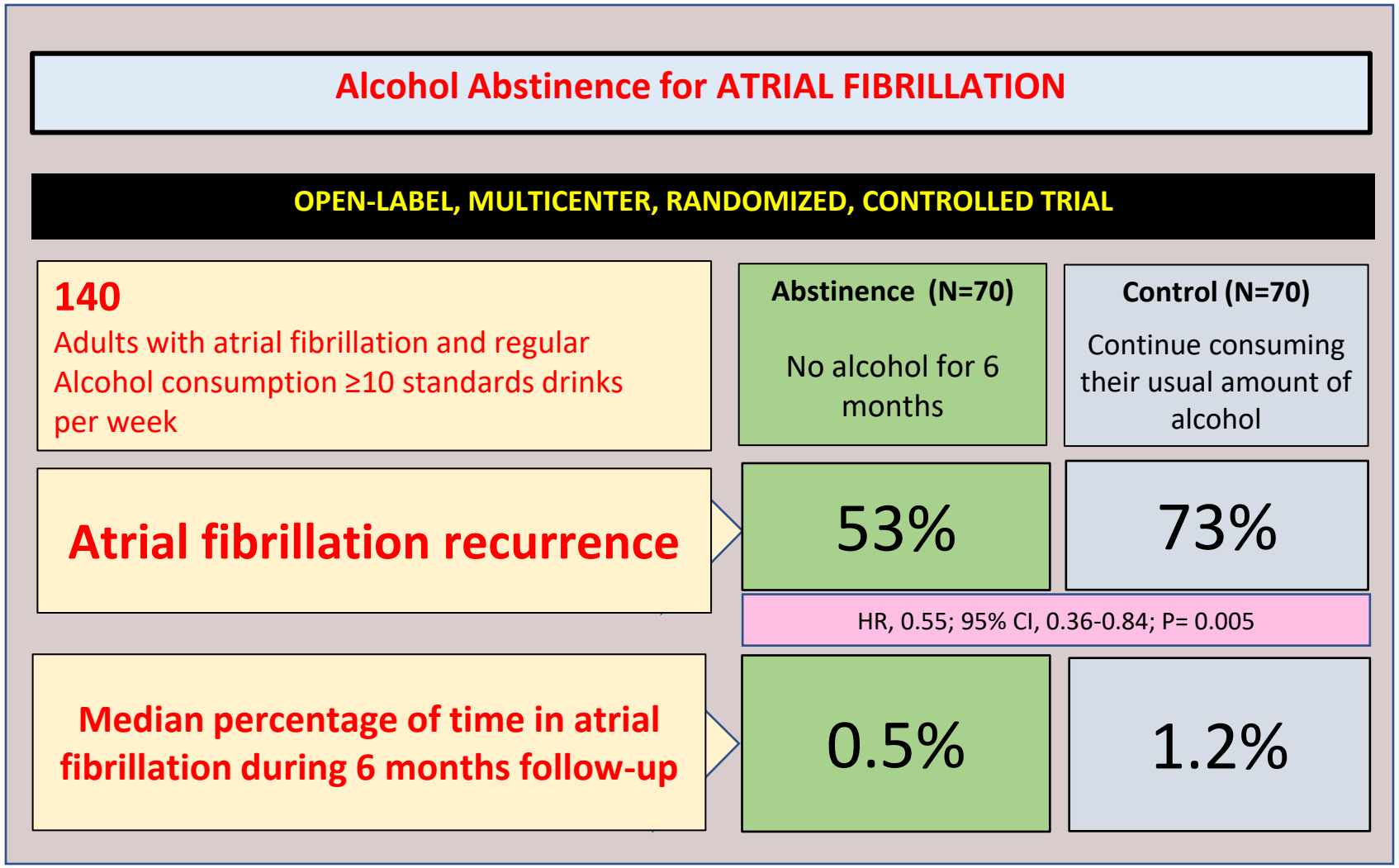
CENTRAL ILLUSTRATION **Forest Plot of Relative Risks of Atrial Fibrillation Per 1 Drink/Day Increment in Alcohol Consumption**

Larsson SC et al. JACC 2014;64:281-289

Alcohol Intake and Atrial Fibrosis



Voskoboinik et al. Heart Rhythm 2019;16:251–259



Adapted from: A. Voskoboinik et al. 10.1056/NEJMoa1817591

Caffeine Intake and AF Risk in Women in WHS

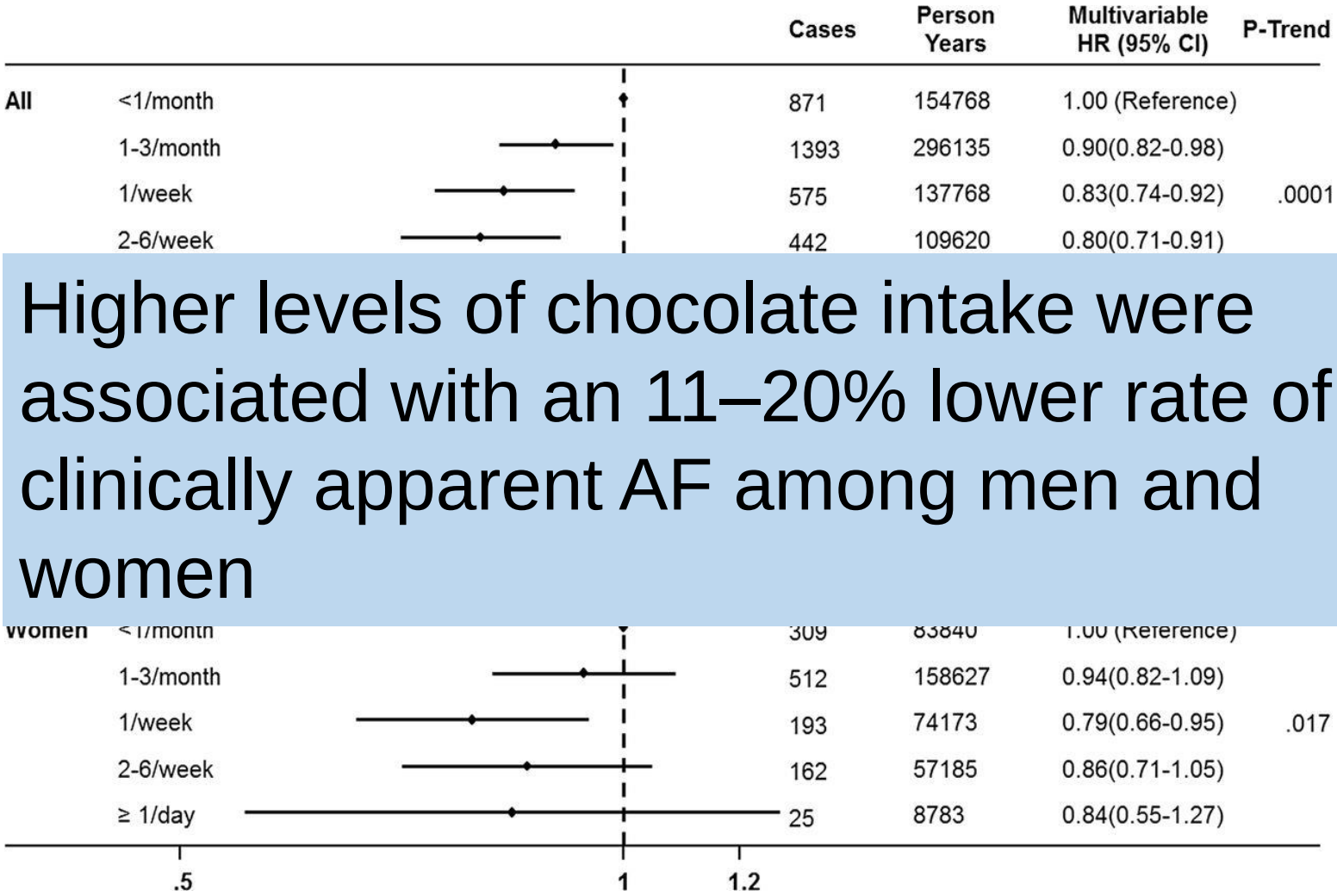
	Quintile of Caffeine Intake					
	1	**2**	**3**	**4**	**5**	**P, Linear**
Number of events	203	172	184	208	178	
Age-adjusted incidence rate	2.15	1.89	2.01	2.24	2.04	
Age-adjusted relative risk	**Referent**	**0.89 (0.74-1.08)**	**0.97 (0.77-1.22)**	**0.97 (0.81-1.18)**	**0.90 (0.73-1.10)**	**0.44**
Multivariable* relative risk	**Referent**	**0.88 (0.72-1.06)**	**0.78 (0.64-0.95)**	**0.96 (0.79-1.16)**	**0.89 (0.73-1.09)**	**0.45**

* Adjusted for age, systolic blood pressure, body mass index, hypertension, diabetes, hypercholesterolemia, smoking, exercise, alcohol consumption, parental history of myocardial infarction, treatment group, fish intake, and race/ethnicity.

Conen D et al. Am J Clin Nutr 2010;92:509-514

Chocolate Intake and Atrial Fibrillation

Danish Diet, Cancer, and Health Study

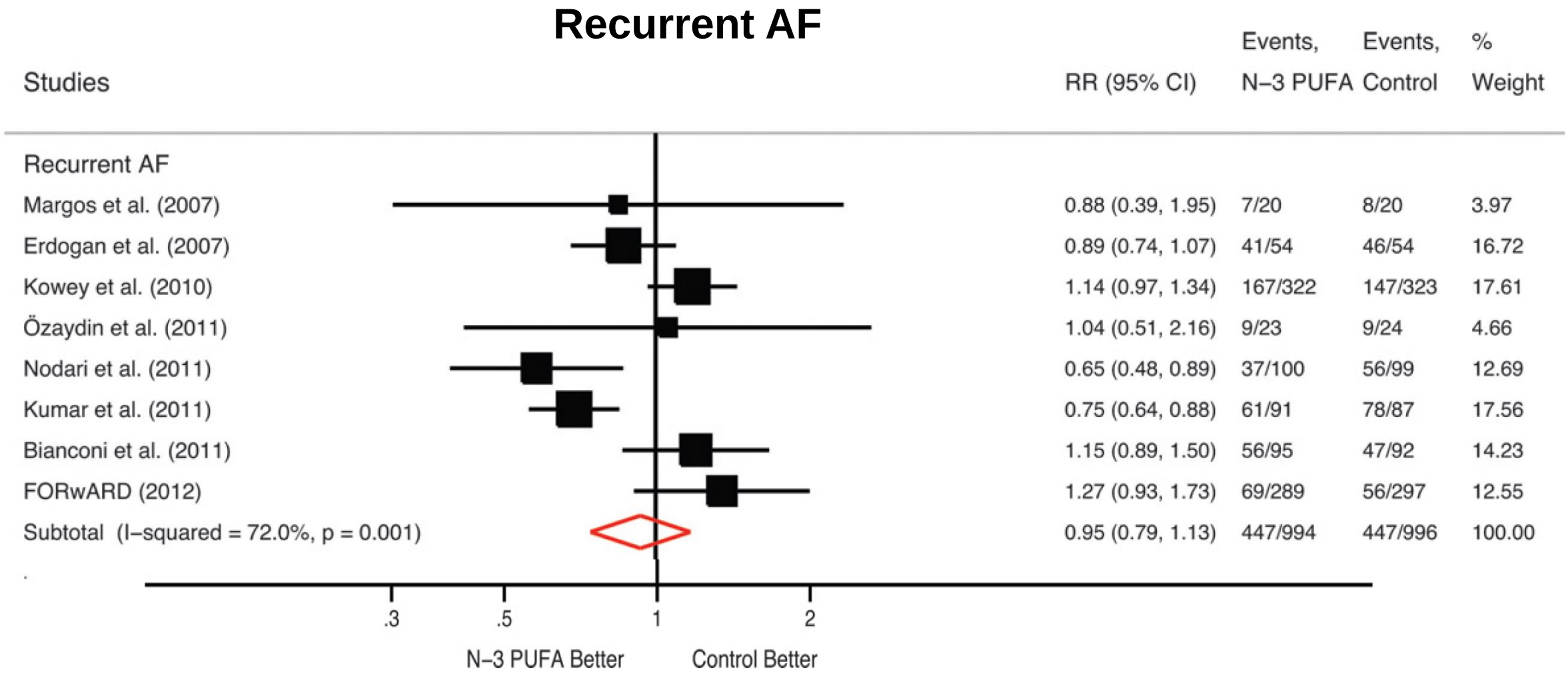


Higher levels of chocolate intake were associated with an 11–20% lower rate of clinically apparent AF among men and women

Elizabeth Mostofsky et al. Heart 2017;103:1163-1167

Early Clinical Trials of Omega-3 Fatty Acids in Secondary Prevention of Atrial Fibrillation

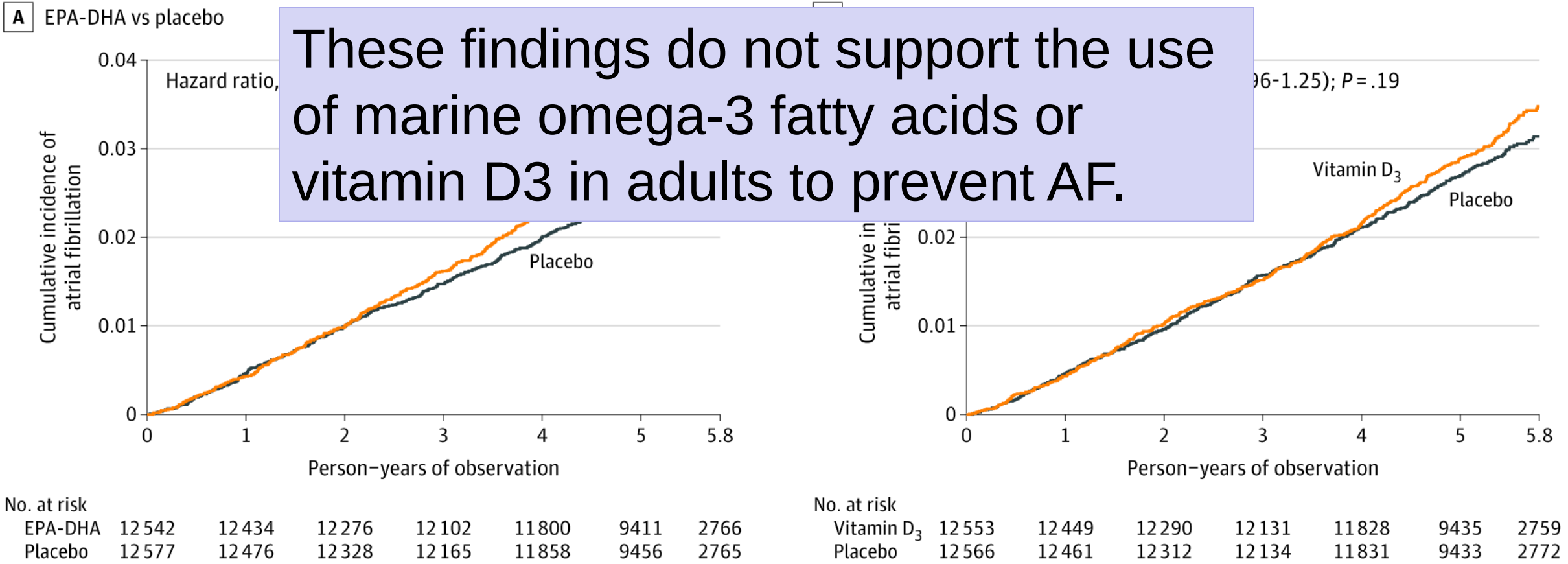
Recurrent AF



Mariani J et al. J Am Heart Assoc 2013;2:e005033

Marine Omega-3 Fatty Acid and Vitamin D Supplementation and Incidence of Atrial Fibrillation

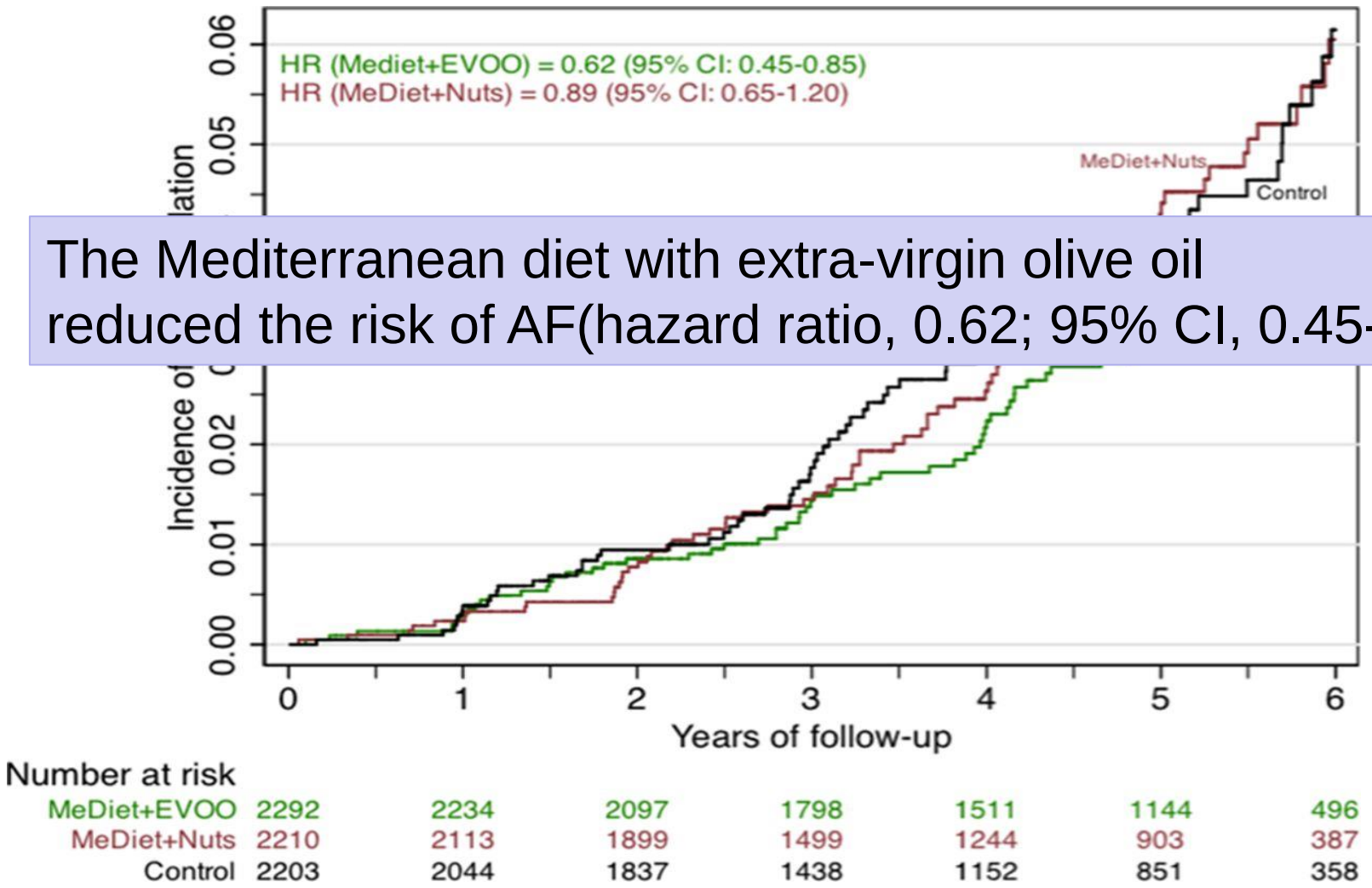
These findings do not support the use of marine omega-3 fatty acids or vitamin D3 in adults to prevent AF.



Albert, CM et al JAMA. 2021;325(11):1061-1073.

Mediterranean Diet and Olive Oil and AF:

The PREDIMED(Prevención con Dieta Mediterráne) Study



The Mediterranean diet with extra-virgin olive oil reduced the risk of AF(hazard ratio, 0.62; 95% CI, 0.45-0.85)

Martínez-González MÁ et al. Circulation 2014;130:18-26l

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Identification of Patients at High-Risk for AF

Usha B. Tedrow, MD MSc

Associate Professor, Harvard Medical School
Fellowship Director, Clinical Cardiac Electrophysiology Program

Combination of Risk Factors

Atrial Fibrillation Risk Scores:
Identification of Patients at High Risk

AF Risk Prediction in Individuals without Cardiovascular Disease

Women's Health Study

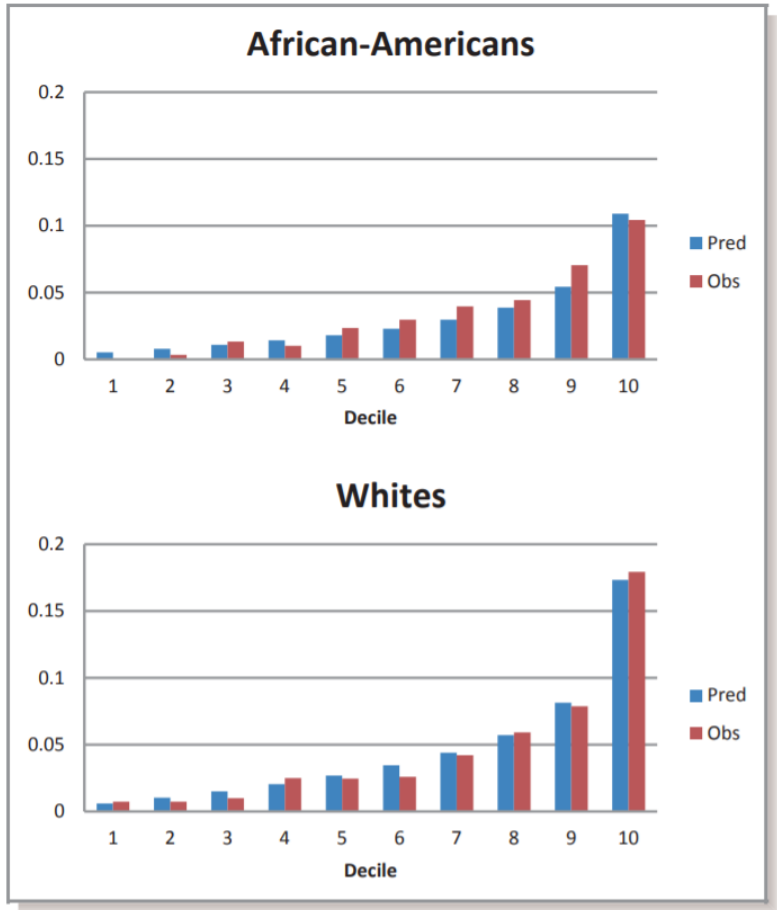
Base Model Covariables	Beta (SE)	Adjusted HR (95% CI)	χ^2	P-Value
Ln (age)	5.475 (0.40)	238.65 (109.46-520.30)	189.6	<0.0001
Weight (per 10 kg)	0.157 (0.035)	1.17 (1.09-1.25)	20.0	<0.0001
Height (per 10 cm)	0.306 (0.082)	1.36 (1.16-1.60)	13.8	0.0002
Systolic blood pressure (per 10 mmHg)	0.155 (0.037)	1.17 (1.09-1.25)	17.7	<0.0001
2+ drinks per day	0.494 (0.20)	1.64 (1.10-2.44)	6.0	0.01
Ever smoker	0.254 (0.10)	1.29 (1.06-1.57)	6.3	0.01

C-Index = 0.75 in derivation and 0.72 in validation

Everett BM et al. Eur Heart J 2013;34:2243-2251

CHARGE-AF Risk Score
Derived in ARIC, CHS, and FHS

Final Multivariate Model for 5-year Risk of AF Derived in ARIC, CHS, and FHS

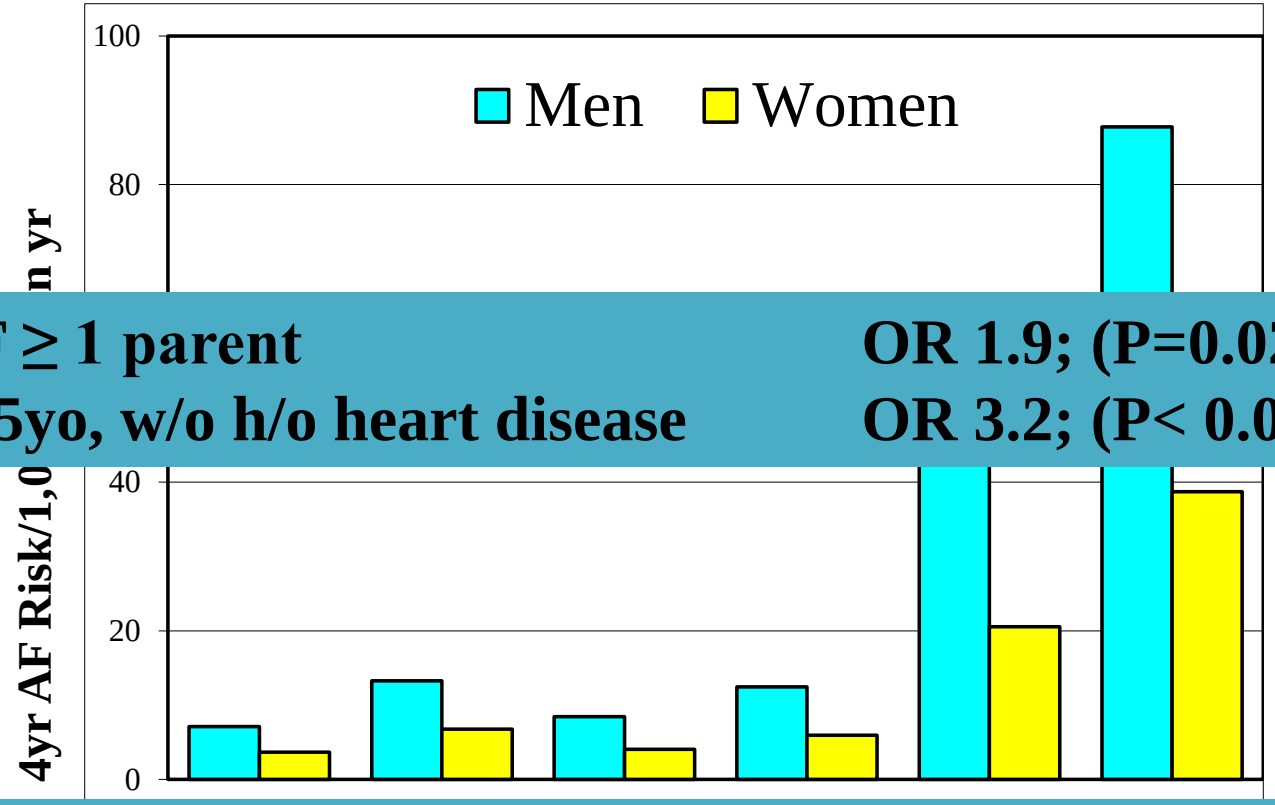


Variable					
Age (5 years)					
Race (white)					
Height (10 cm)					
Weight (15 kg)					
Systolic BP (20 mm Hg)					
Diastolic BP (10 mm Hg)					
Smoking (current)					
Antihypertensive medication				1.60)	0.341 (0.063)	1.41 (1.24, 1.59)
Diabetes (Yes)				1.46)	0.242 (0.073)	1.27 (1.10, 1.47)
Heart failure (Yes)				2.48)	0.678 (0.107)	1.97 (1.60, 2.43)
Myocardial infarction (Yes)				1.96)	0.469 (0.090)	1.60 (1.34, 1.91)
LVH by electrocardiogram (Y					0.401 (0.129)	1.49 (1.16, 1.92)
PR Interval (<120 vs 120 to 199)	—	—			0.645 (0.200)	1.91 (1.29, 2.82)
PR Interval (>199 vs 120 to 199)	—	—			0.118 (0.077)	1.13 (0.97, 1.31)

- Evaluate putative novel clinical factors to reclassify an individual's risk of developing AF.
- Select high-risk individuals for trials of primary prevention or of intensive monitoring for AF detection

Alonso A et al. J Am Heart Assoc 2013;2:e000102

Offspring AF risk by Parental h/o AF



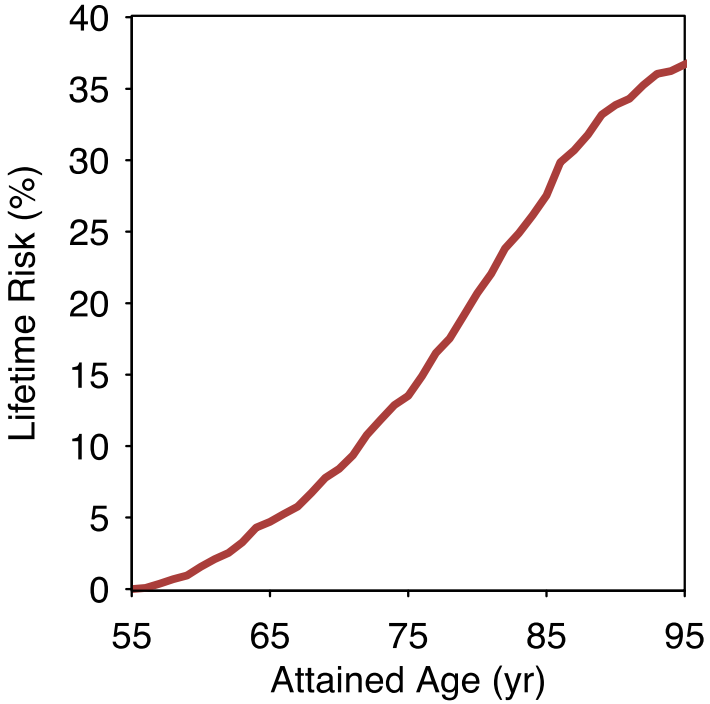
- **AF ≥ 1 parent** — **OR 1.9; (P=0.02)**
- **<75yo, w/o h/o heart disease** — **OR 3.2; (P< 0.001)**

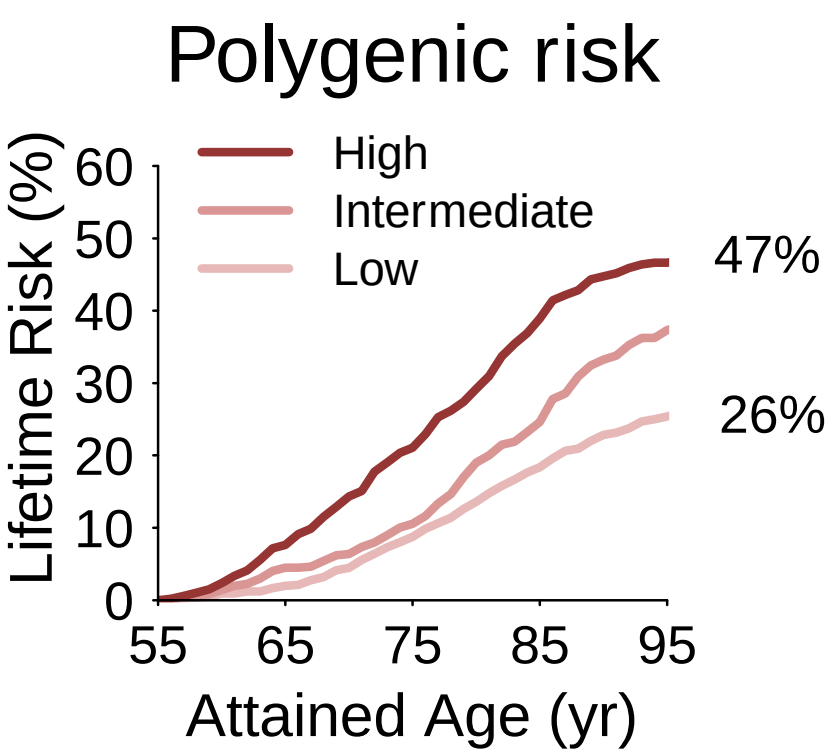
HTN	-	-	+	+	+	+
Diabetes	-	-	-	+	+	+
Heart Disease	-	-	-	-	+	+
Parent hx AF	-	+	-	-	-	+

Fox et al. JAMA 2004;291:2851

Lifetime Risk of Developing Clinical AF

Genetic risk can stratify lifetime risk of AF





Weng LC et al. Circulation 2018;137:1027-1038

AF Genetic Risk Scores

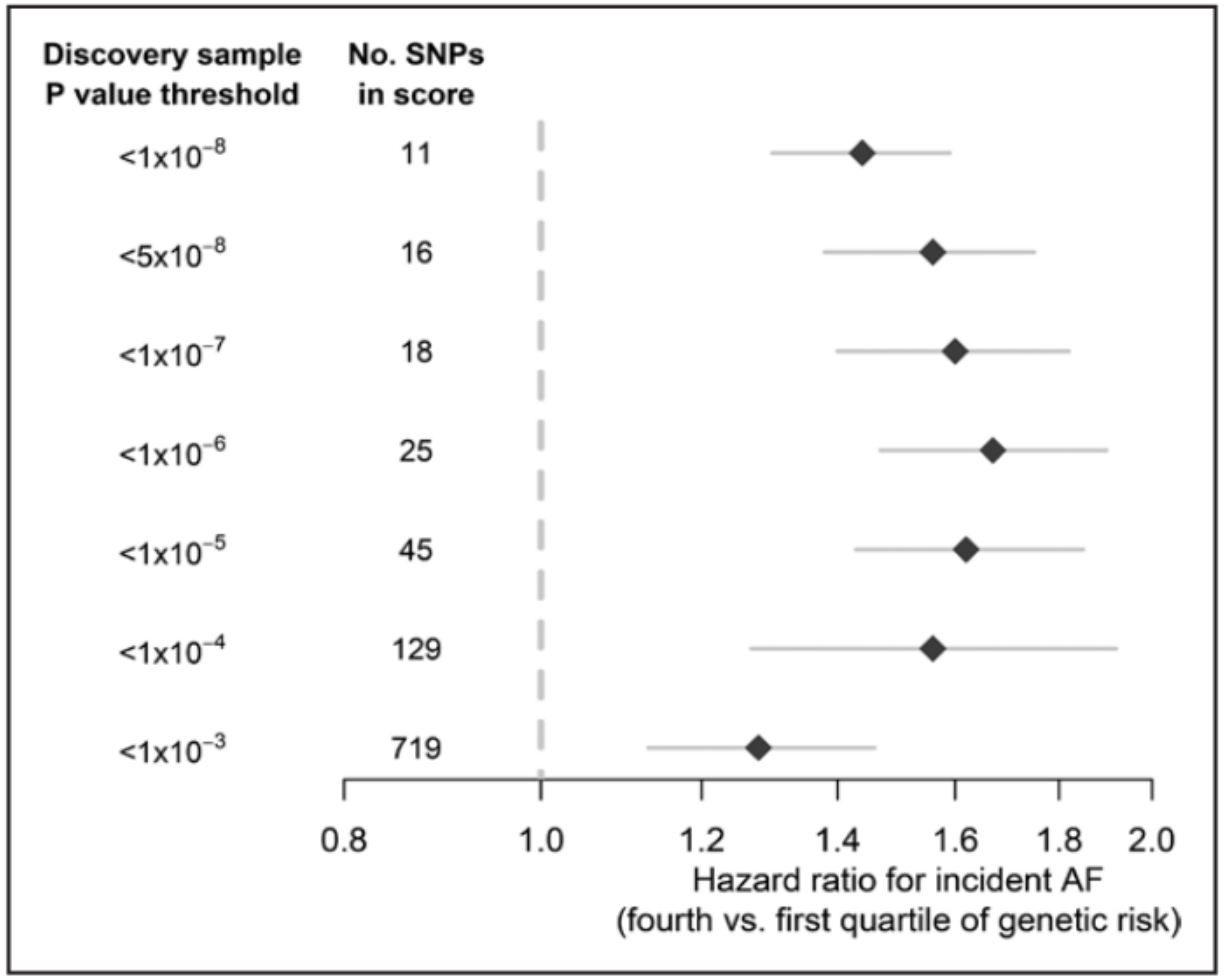
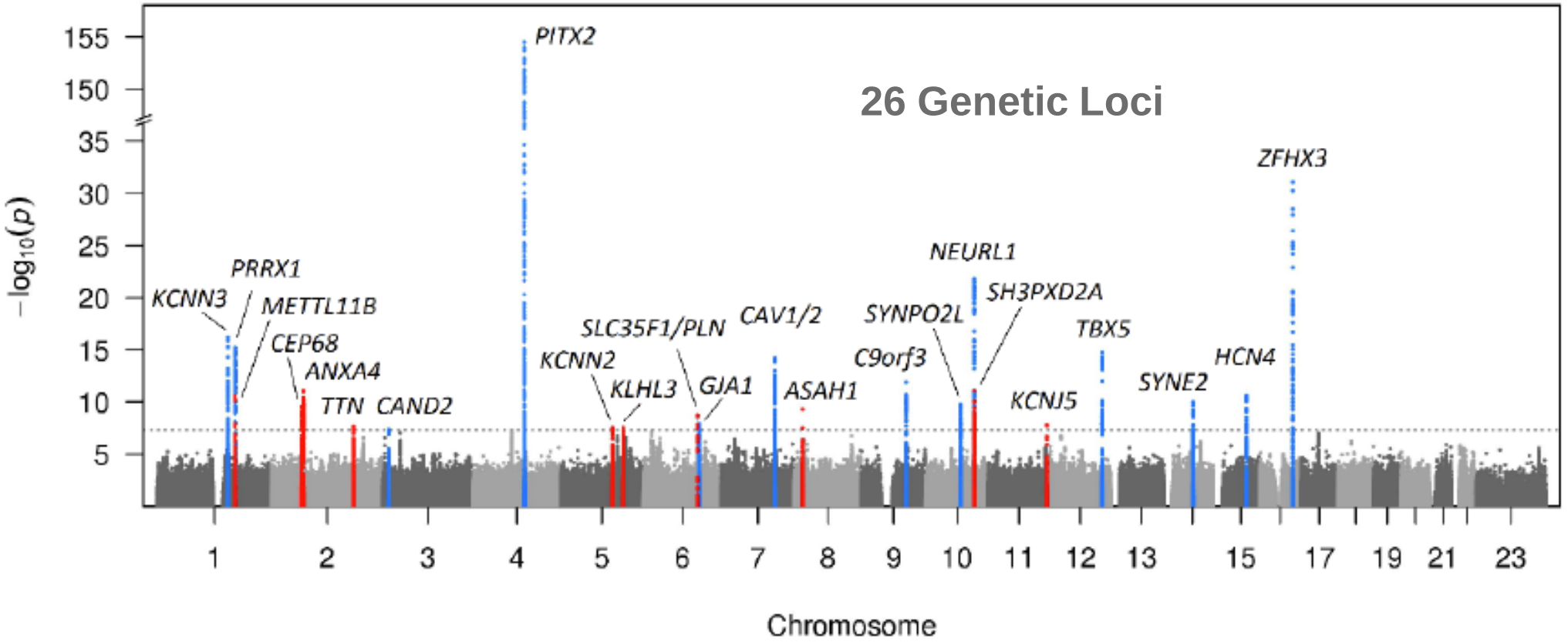


Figure 1. Pooled 5-year relative hazard of incident atrial fibrillation (AF) among individuals in the highest quartile of AF genetic risk relative to those in the lowest quartile.

Lubitz SA et al. Circulation 2017; 135:1311-1320

Atrial Fibrillation Genetics:

Beyond Risk Prediction:



Personalized Medicine Approaches:

- *AF sub-classification: Beyond Paroxysmal, Persistent, Permanent*
- *Outcome Prognostication*
- *Response to Therapy*

New Targets for Therapy

Christophersen I.E. et al Nature Genetics 2017:49, 946–952 ,

Conclusions

- The reasons for the AF epidemic are not entirely clear, but partly related to aging of the population, improved longevity from CVD, improved detection, and rising obesity rates.
- There are several currently several potentially-modifiable risk factors for AF that may provide strategies for AF prevention
    - Blood pressure control
    - Weight loss
    - Moderate physical activity
    - Smoking avoidance
    - Minimization of alcohol intake.
- There are also reproductive and hormonal AF risk factors unique to women suggesting a possible impact of multiple pregnancies and estrogen on AF risk.
- Combinations of AF clinical and genetic risk factors can be utilized to identify high risk patients for targeted AF screening and future intervention trials.