

Is Atrial Fibrillation preventable?

The interplay between genetic and environmental factors in genesis of AF

Andrew Grace

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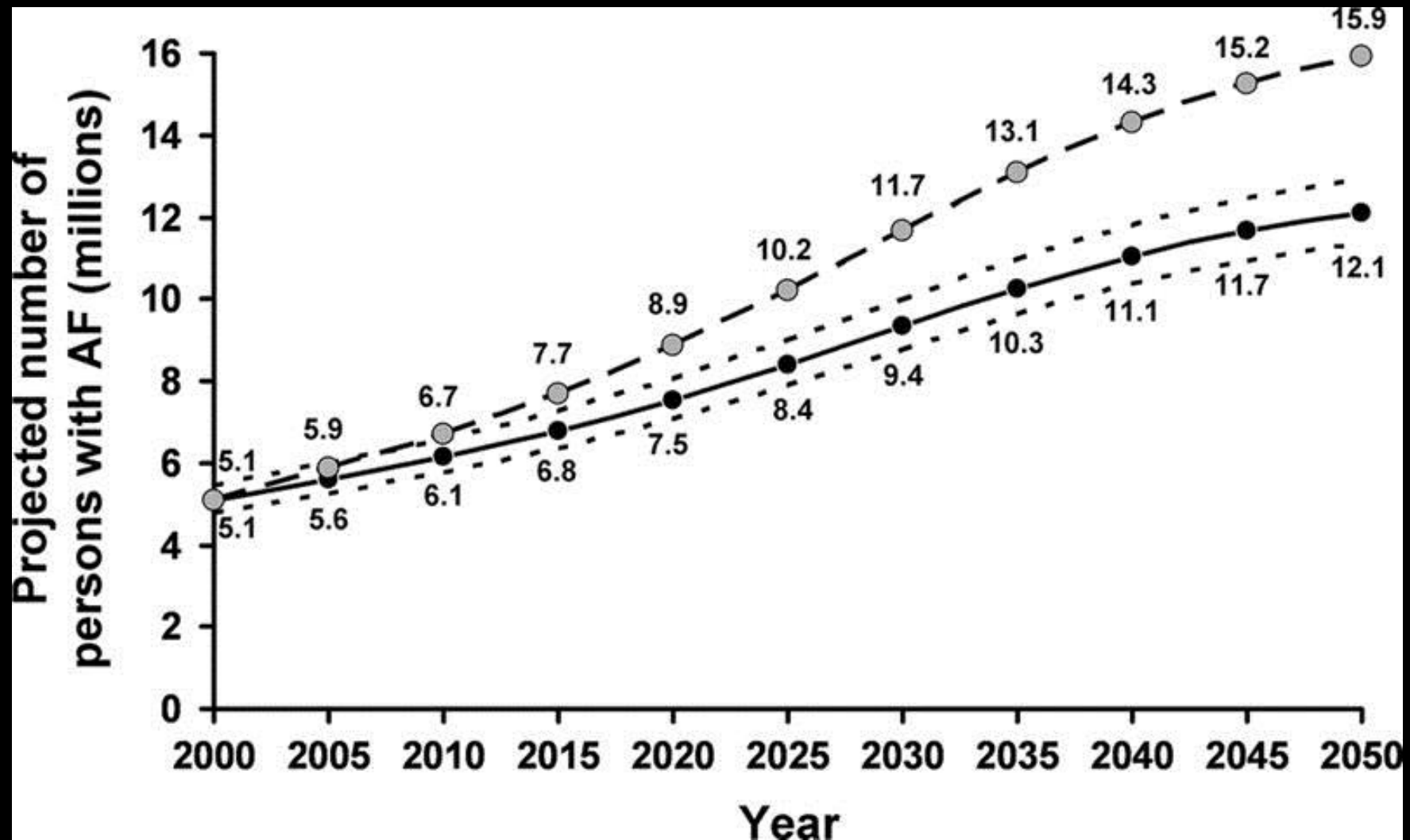
Consultant: Acutus Medical Inc., Bardy Diagnostics

Boston Scientific Inc. (member PSAB) and Founder, Electus Medical Inc.

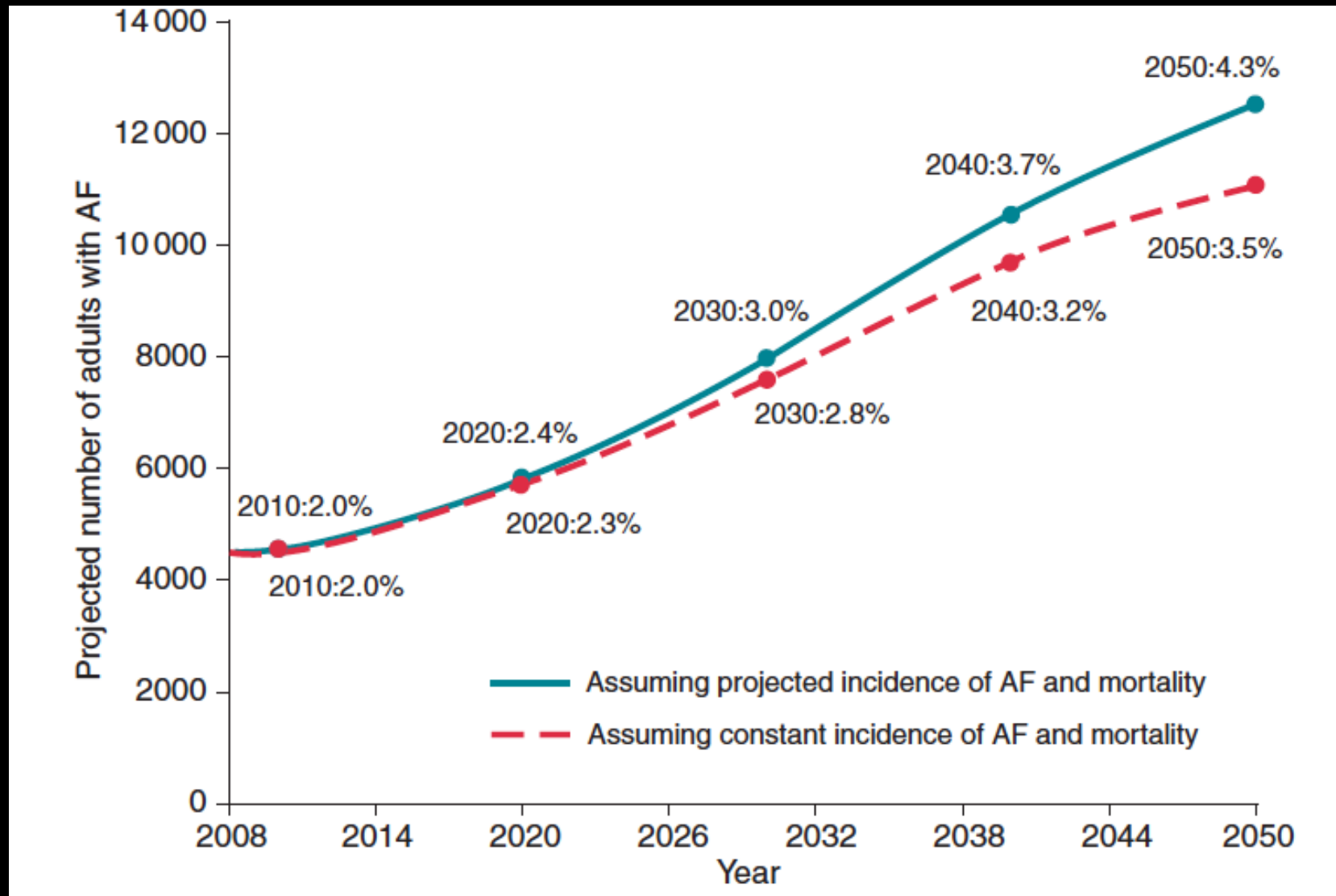
AF Demographics

Projected AF prevalence

Olmsted county data



Projected AF prevalence in Iceland



One 'typical' Atrial Fibrillation Patient

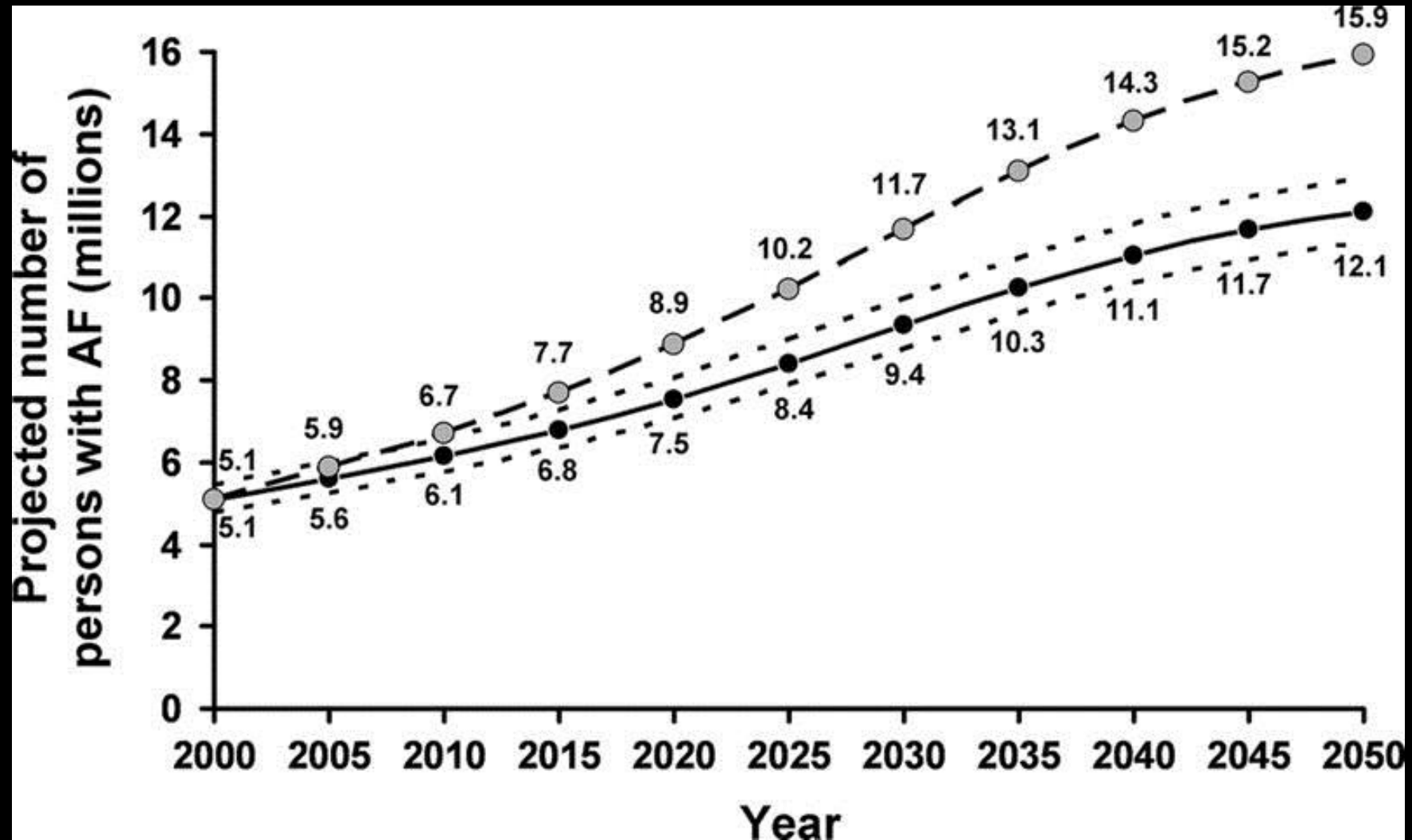
- Older
- Hypertension
- Coronary disease
- Heart Failure
- Metabolic disease
(diabetes)



'Any History of Physical Activity in Your Family'

Projected AF prevalence

Olmsted county data



WHERE ARE WE WITH GENETICS?

Familial AF

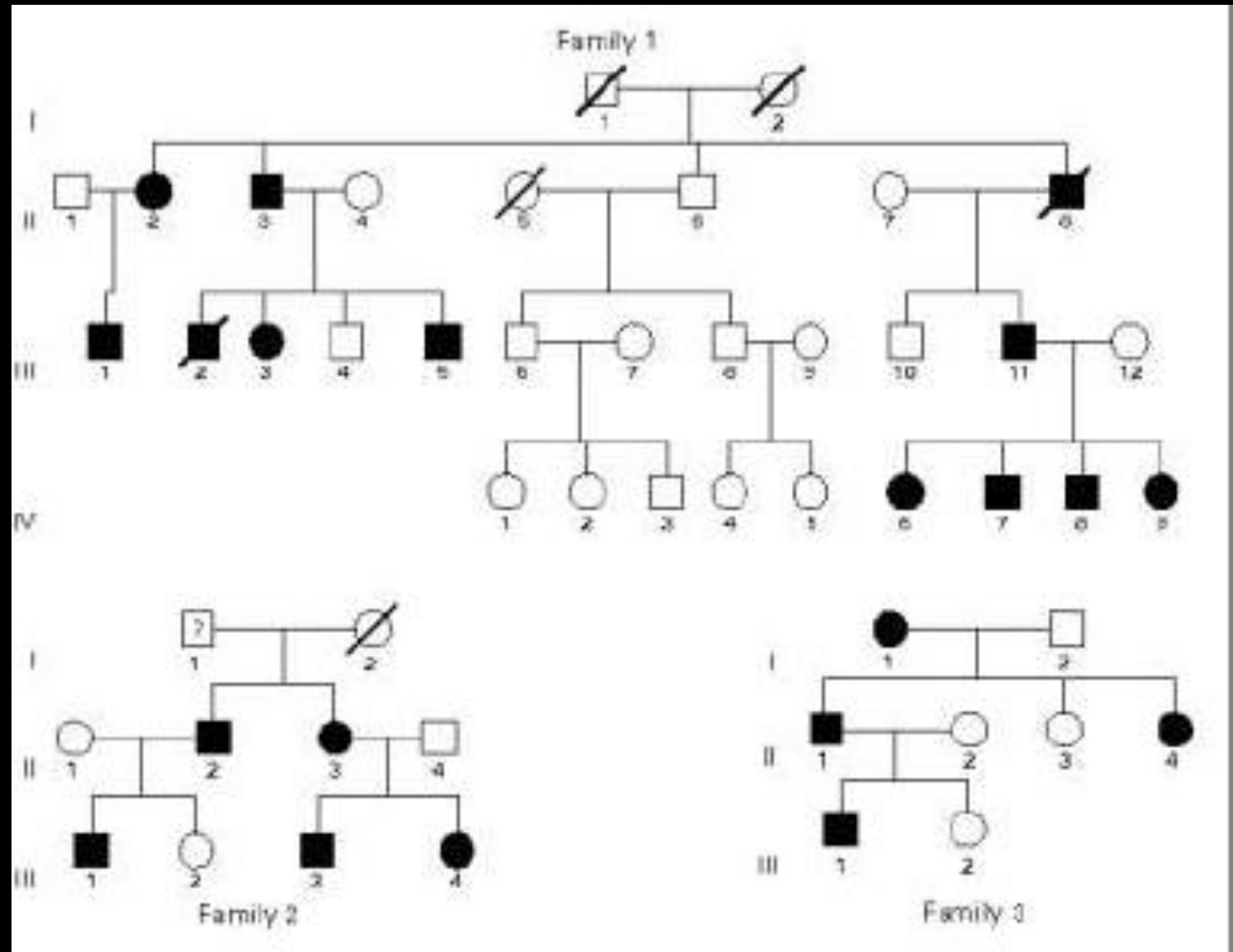
Original description of family with 3 brothers with AF dates to 1943

Wolff, L. NEJM 1943 229:396

3 families with AF have been mapped to locus on chromosome 10.

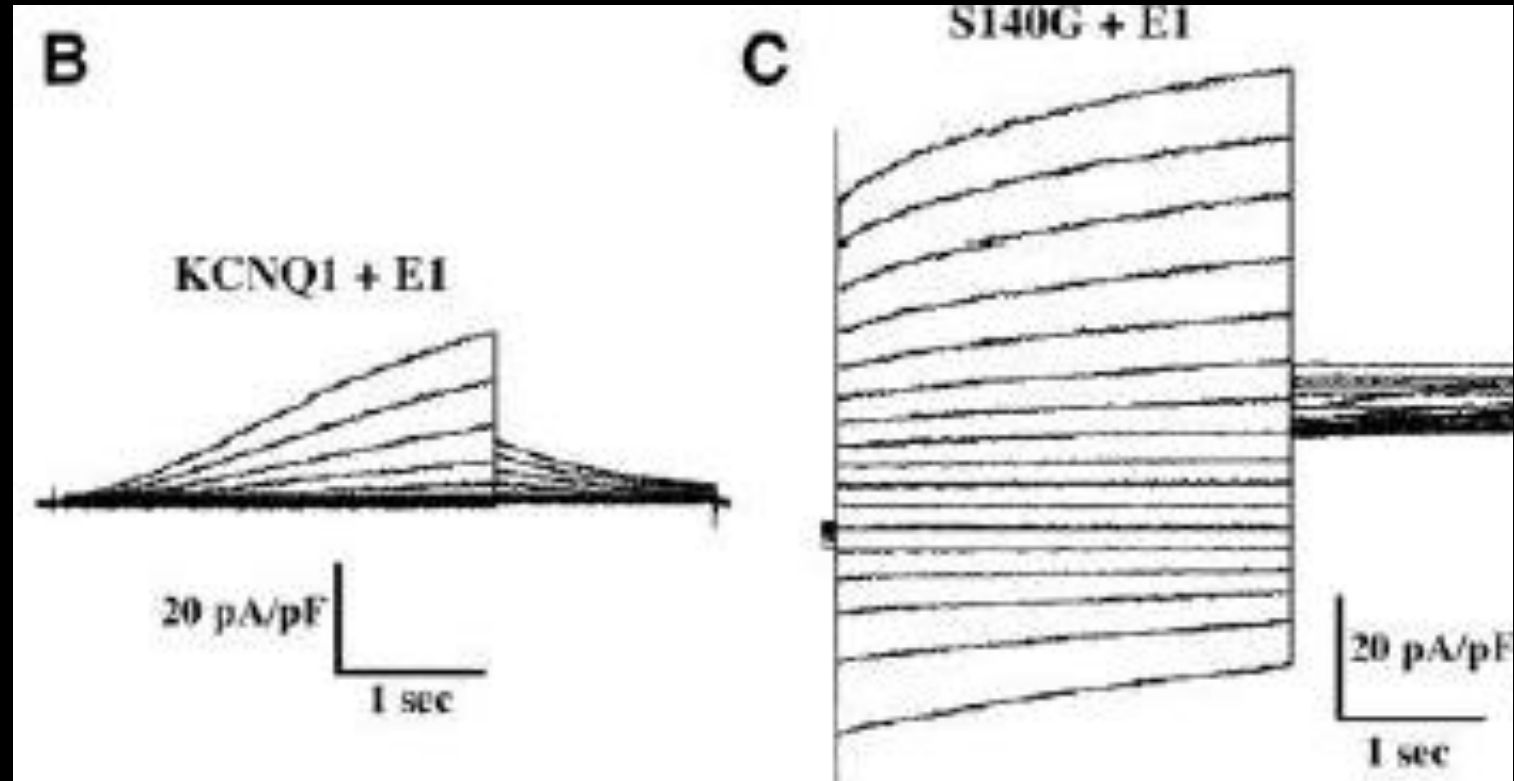
Brugada R *et al.*

NEJM 1997 336:905-11



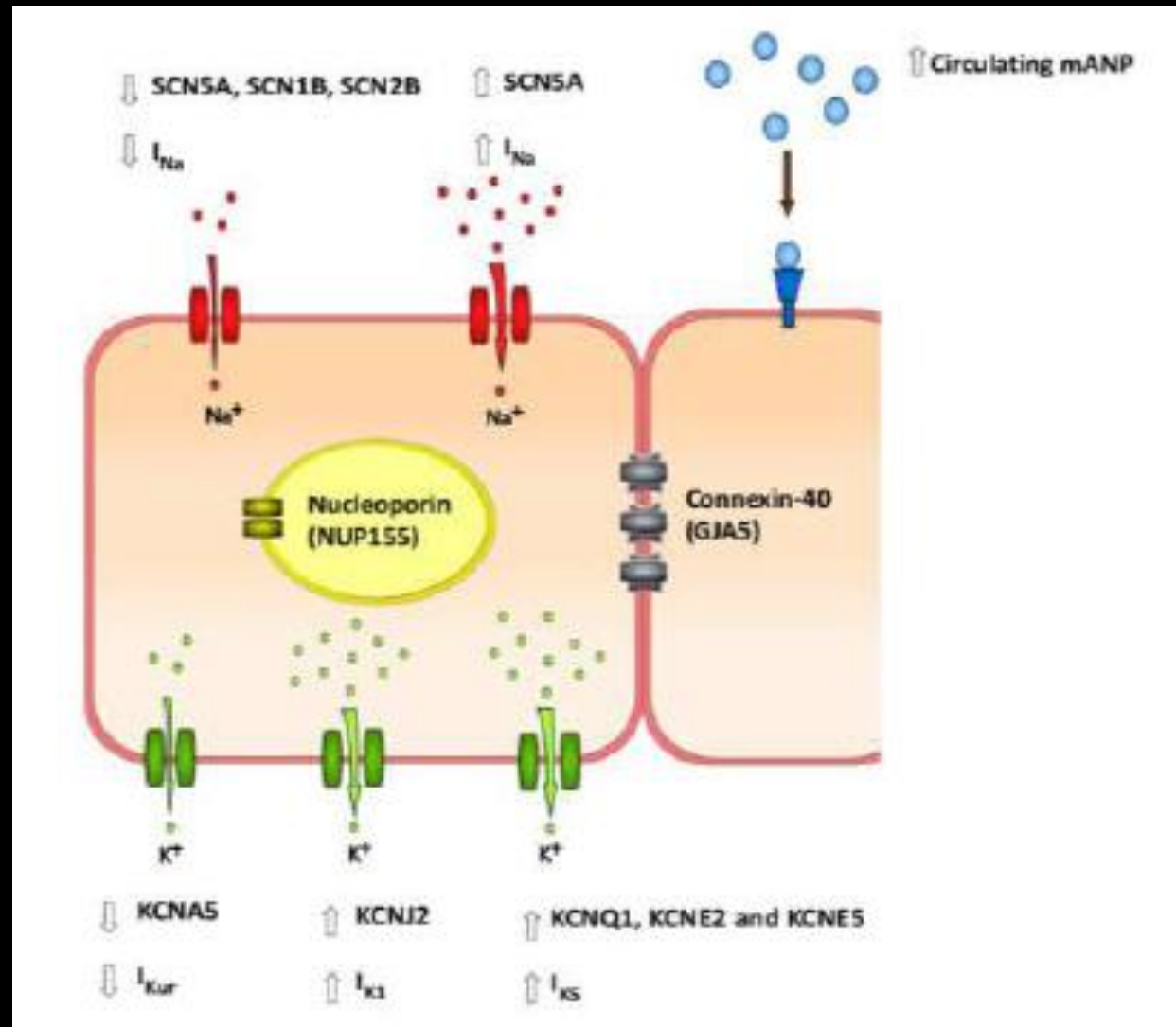
***KCNQ1* Mutation Leading to AF**

- 24 years mean onset
- Prolonged QT
- 3 patients develop DCM



Mutations in Ion Channels are rare causes of AF

- Few additional variants identified by sequencing
- Family-specific



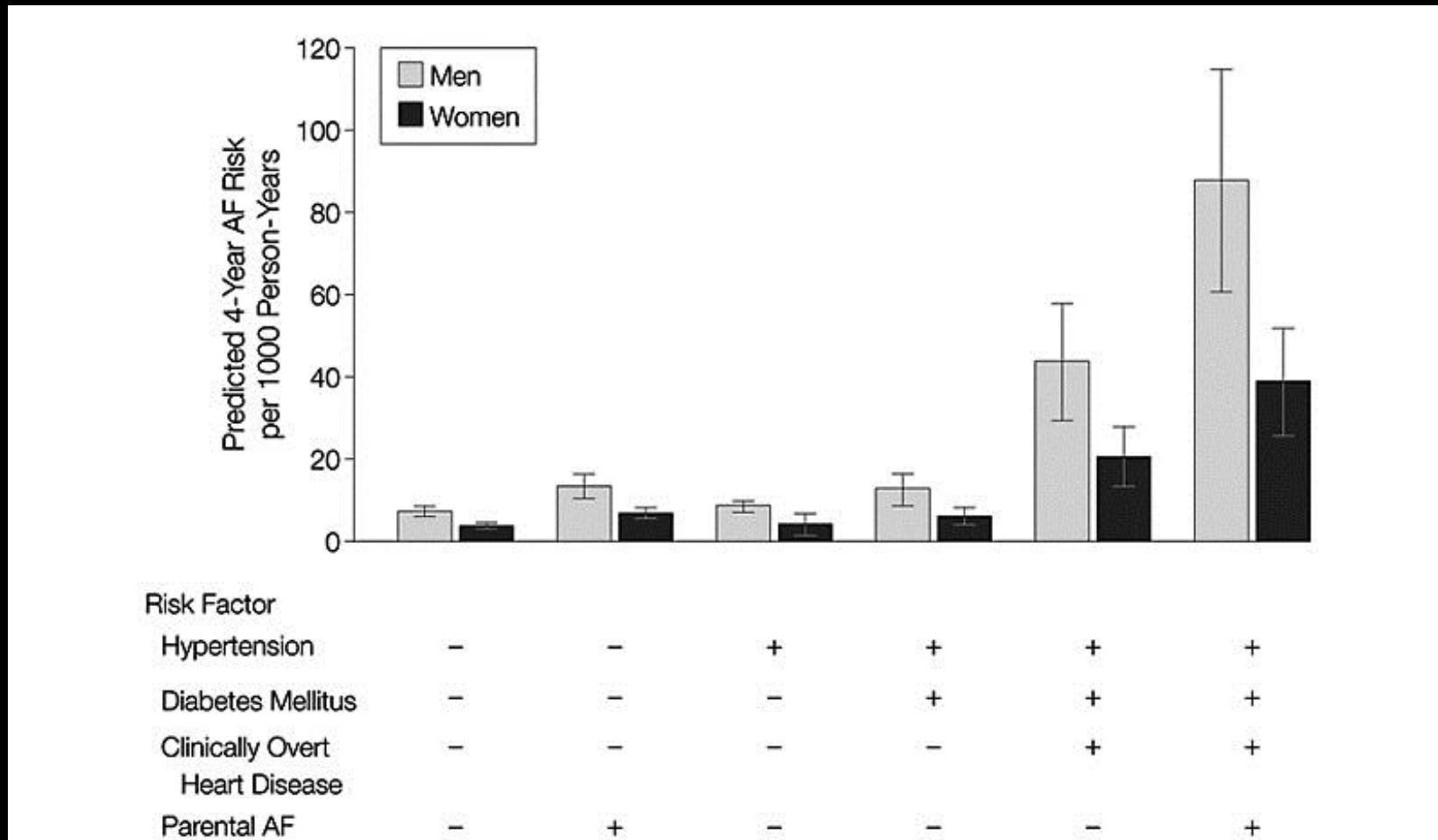
**AF IN YOUNGER PATIENTS IS
USUALLY GENETIC BUT COMPLEX**

Who Gets Atrial Fibrillation ..?

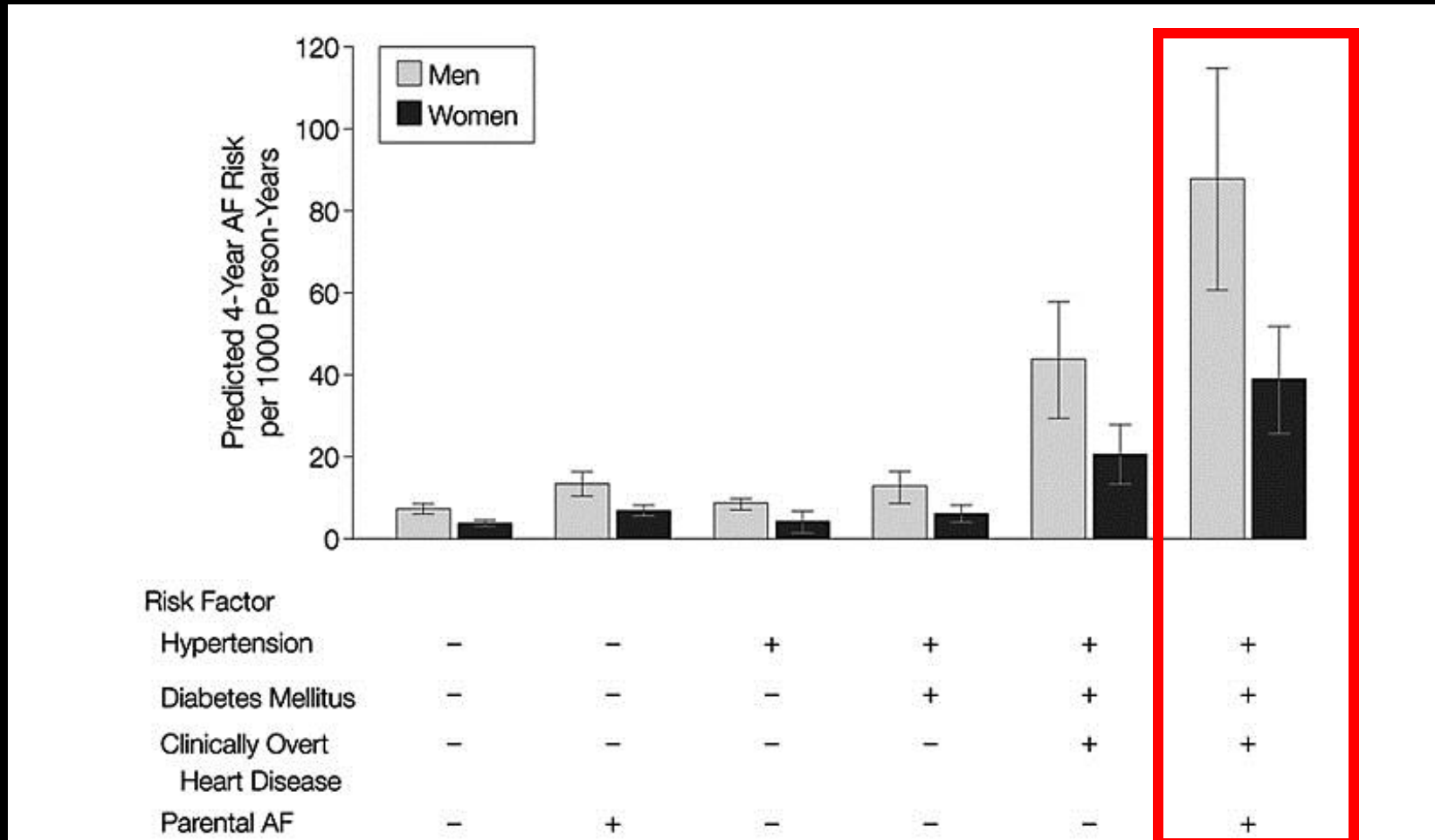


- Tend to be younger
- Structurally normal heart
- No other co-morbidity
- His brother has it
- His mother had a stroke

FAMILY HISTORY AS RISK FACTOR FOR AF



FAMILY HISTORY AS RISK FACTOR FOR AF



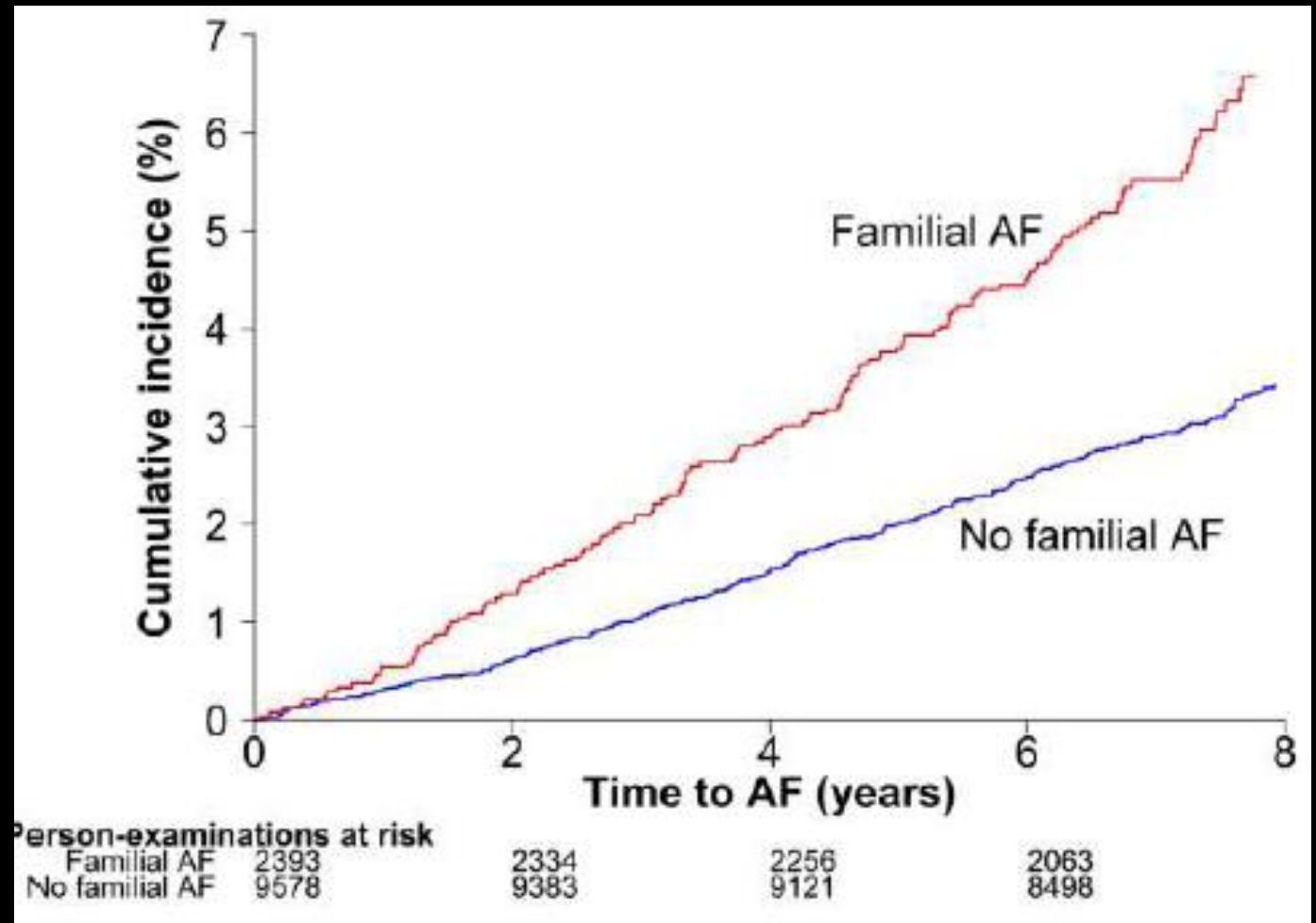
30% of AF patients have at least one parent with AF (OR 1.8)
 OR increased to 3.2 if both parents and offspring had AF at age < 75

AF in First Degree Relatives in associated with increased risk of AF

HR 1.39

(1.12-1.73)

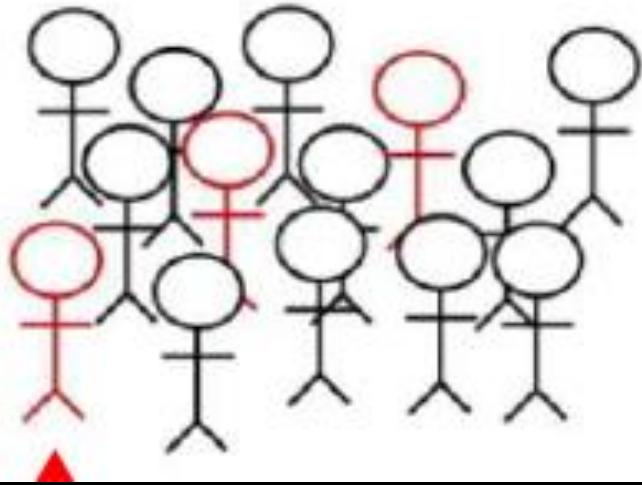
P=0.003



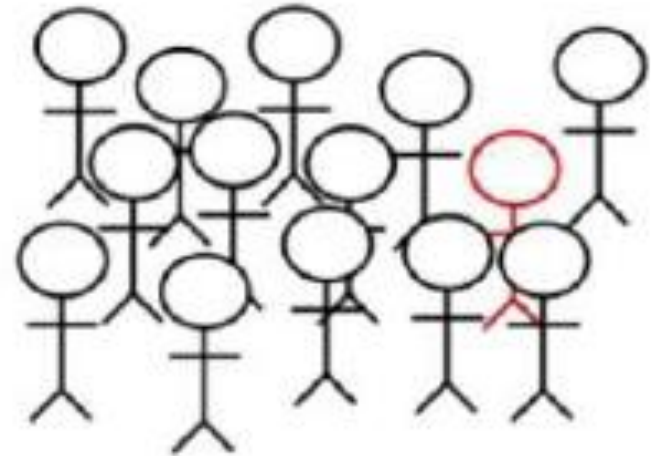
COMPLEX AF GENETICS

Genome Wide Association Study

AF



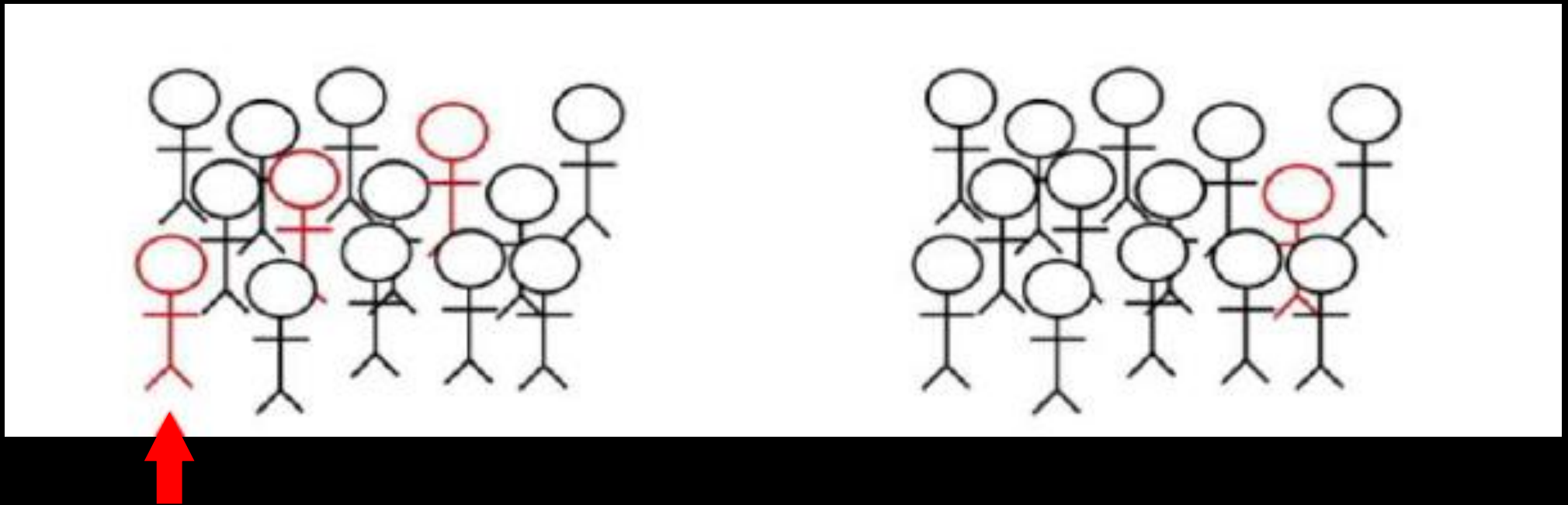
No AF



Genome Wide Association Study

AF

No AF



Genetic variant more common in those with AF

Variants conferring risk of atrial fibrillation on chromosome 4q25

Table 1 | Analysis of the association of rs2200733 and rs10033464 on chromosome 4q25 with AF/AFI

Sample (cases/controls)	rs2200733 T* Frequency§	OR (95% CI)	P	rs10033464 T*† Frequency§	OR (95% CI)
Iceland 					
Discovery (550/4,476)	0.191 (0.114)	1.84 (1.54–2.21)	2.0×10^{-11}	0.110 (0.080)	1.42 (1.13–1.77)
Replication (2,251/13,238)	0.166 (0.108)	1.64 (1.49–1.81)	2.7×10^{-23}	0.108 (0.080)	1.40 (1.24–1.58)
Combined (2,801/17,714)	0.171 (0.110)	1.68 (1.53–1.83)	1.9×10^{-30}	0.108 (0.080)	1.40 (1.25–1.55)
Other European ancestry					
Sweden (143/738)	0.179 (0.098)	2.01 (1.38–2.93)	0.00027	0.172 (0.111)	1.65 (1.14–2.41)
United States (636/804)	0.229 (0.139)	1.84 (1.51–2.23)	9.8×10^{-10}	0.105 (0.083)	1.30 (1.00–1.69)
Combined¶	– (–)	1.88 (1.58–2.23)	1.2×10^{-12}	– (–)	1.41 (1.13–1.75)
All European ancestry					
Combined¶	– (–)	1.72 (1.59–1.86)	3.3×10^{-41}	– (–)	1.39 (1.26–1.53)
Hong Kong					
Hong Kong (333/2,836)	0.605 (0.528)	1.42 (1.16–1.73)	0.00064	0.190 (0.218)	1.08 (0.84–1.39)

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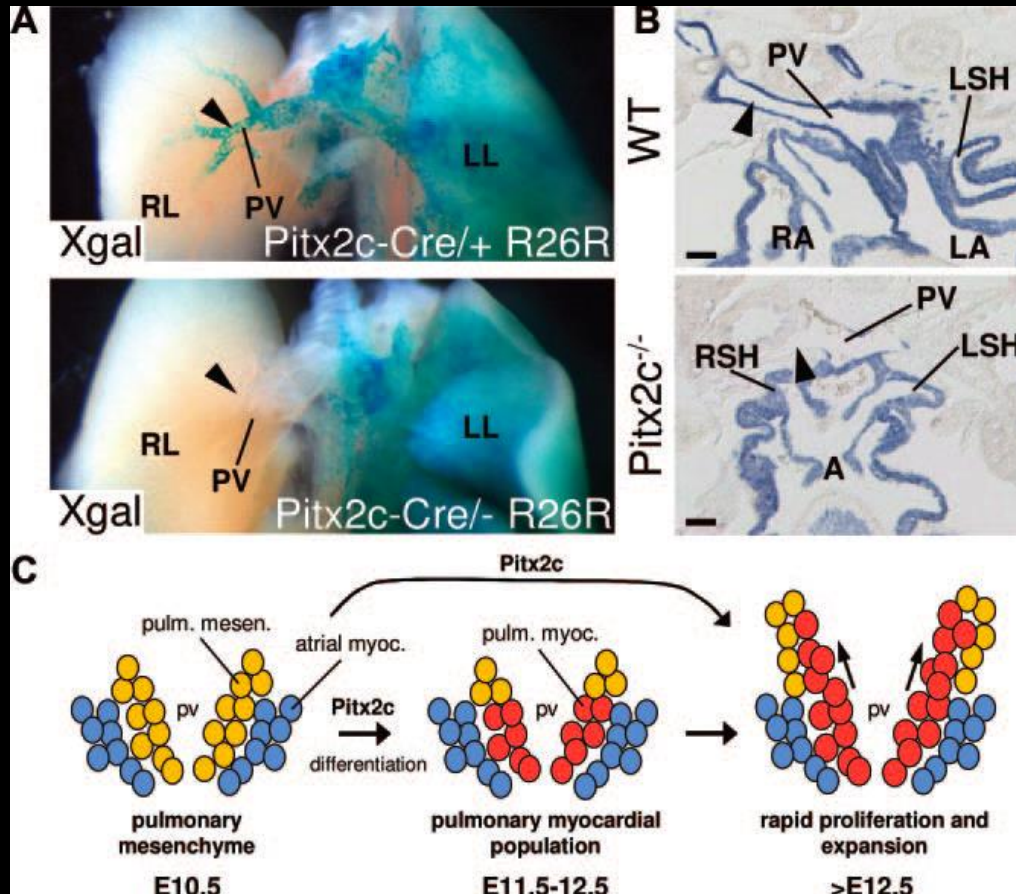
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- Genome-wide association scan with replication in other populations
- Variants adjacent to *PITX2* - critical function in left-right asymmetry in heart

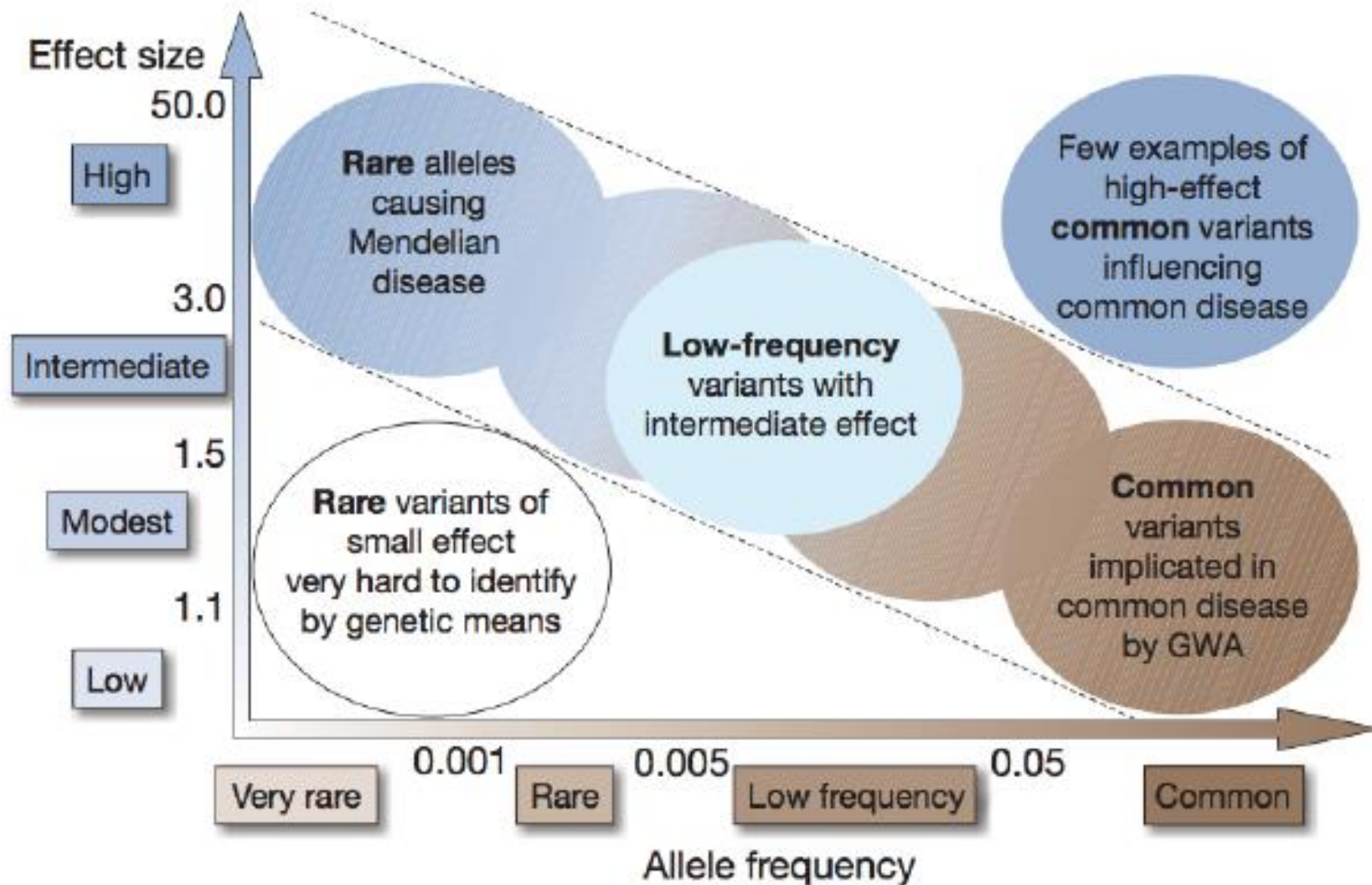
PITX2c is required for the development of the pulmonary vein myocardium



Mommersteeg et al. Circ Res 2007 101:902-9

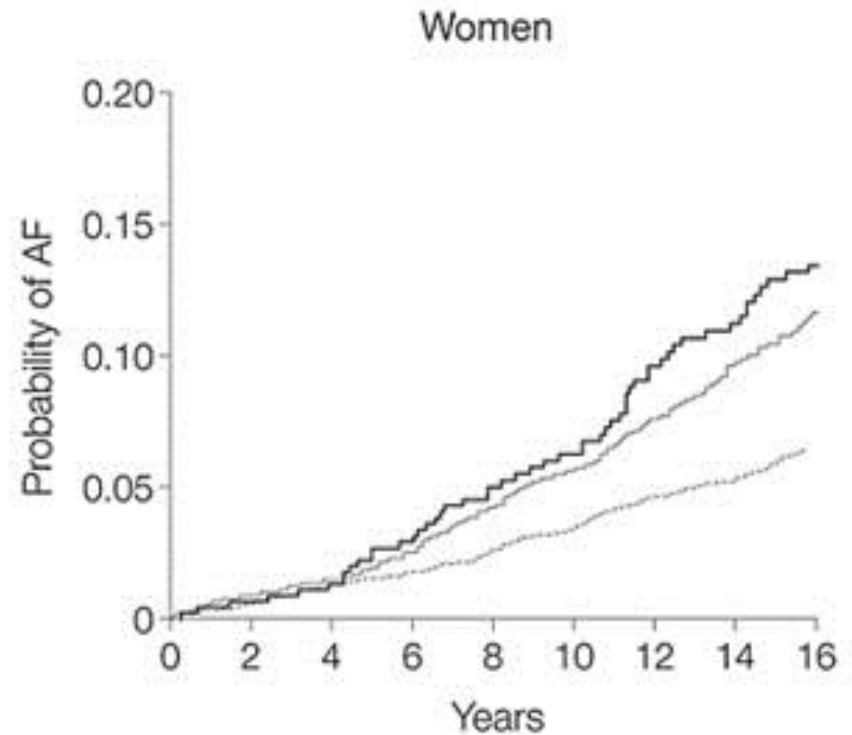
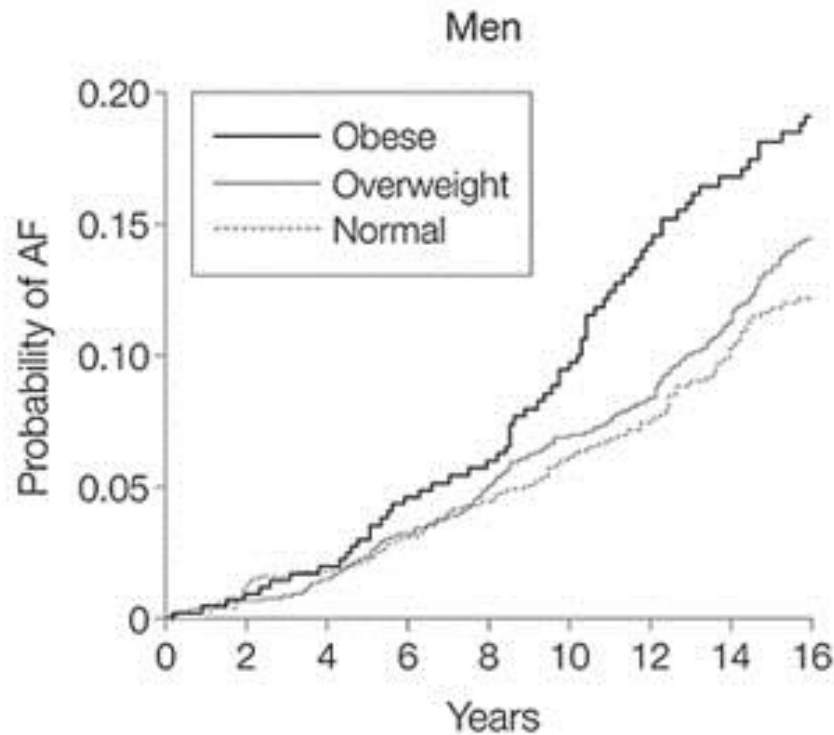
Haissaguerre et al. N Engl J Med 1998; 339:659

Feasibility of Identifying Disease Loci



Impact Metabolic Disease

Obesity and AF risk



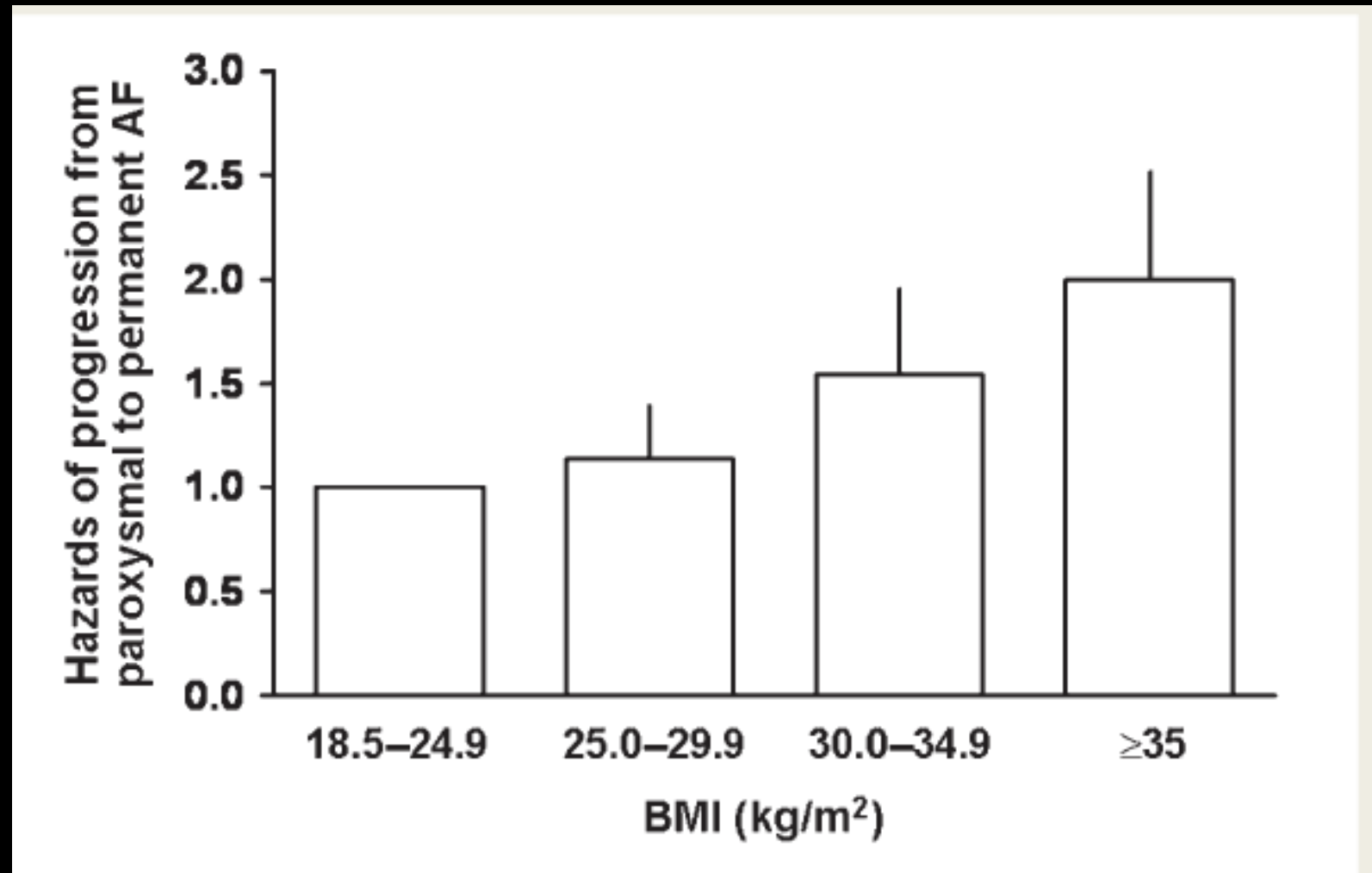
No. at Risk					
Obese	413	380	336	280	238
Overweight	1216	1143	1023	908	776
Normal	755	699	614	557	482

464	444	397	345	299
898	852	776	696	614
1536	1476	1394	1282	1180

Adjusted HR 1.5 with obesity

Age and sex-adjusted hazards of progression from paroxysmal to persistent AF by BMI

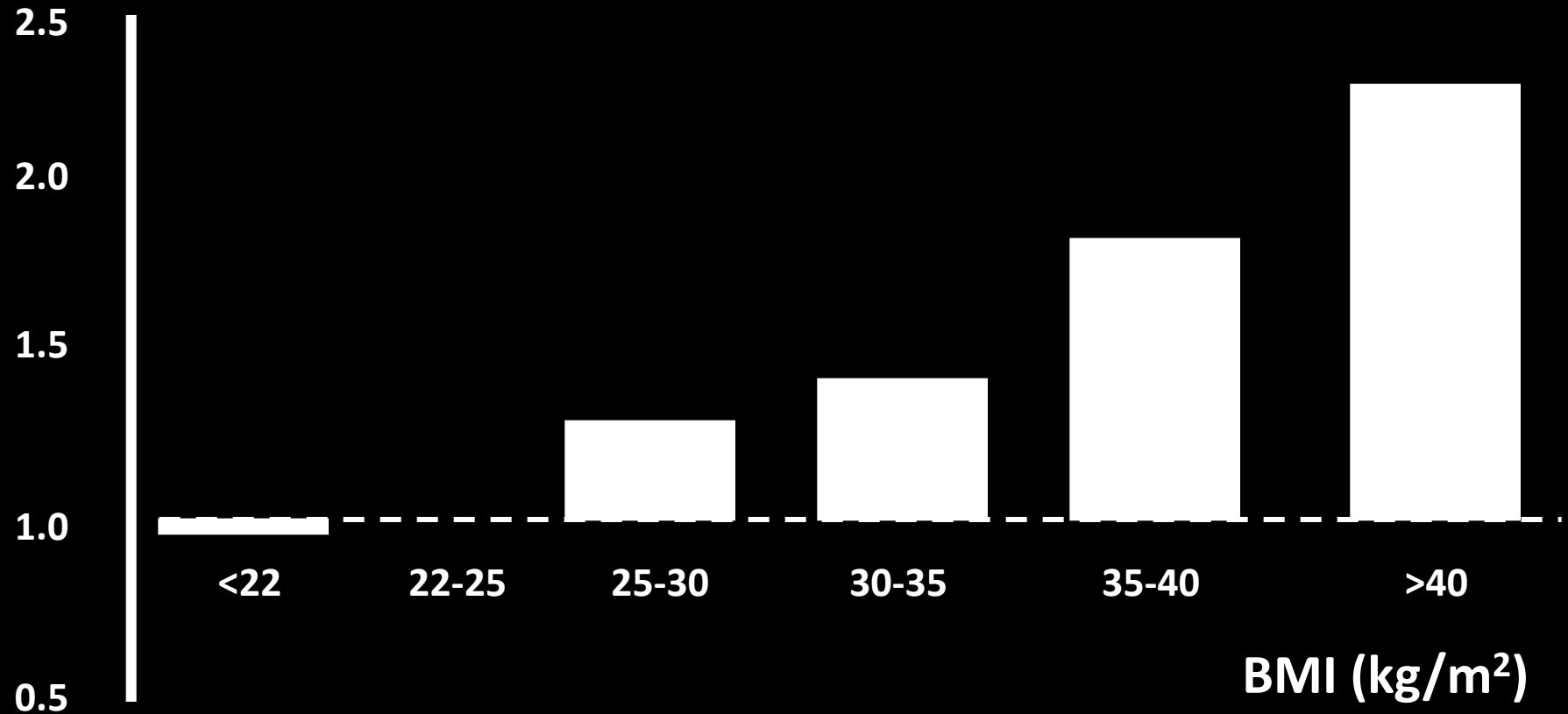
(Olmsted county data)



Obesity and post-operative AF risk

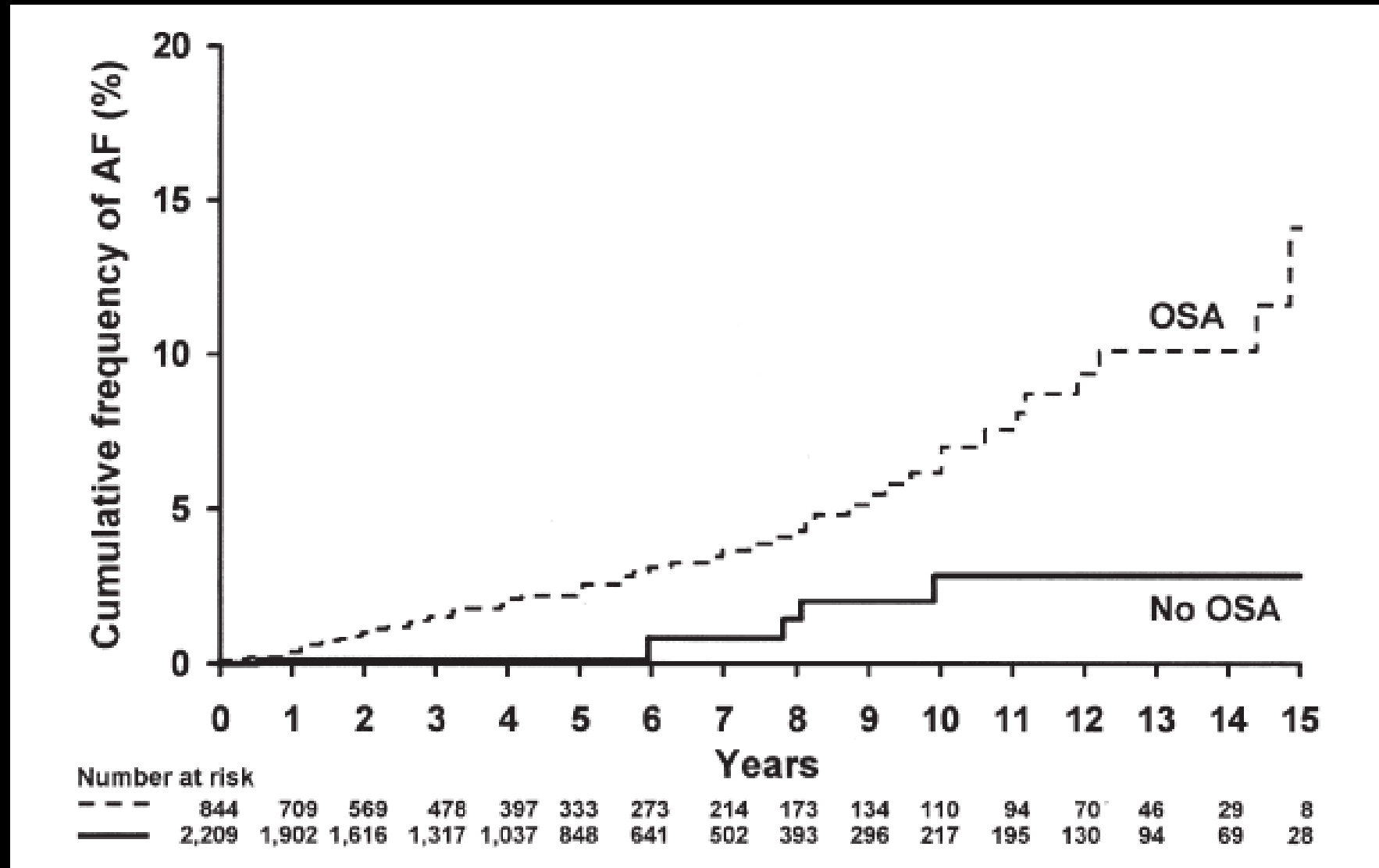
Adjusted OR AF

Retrospective
n = 8051
Obese = 3164



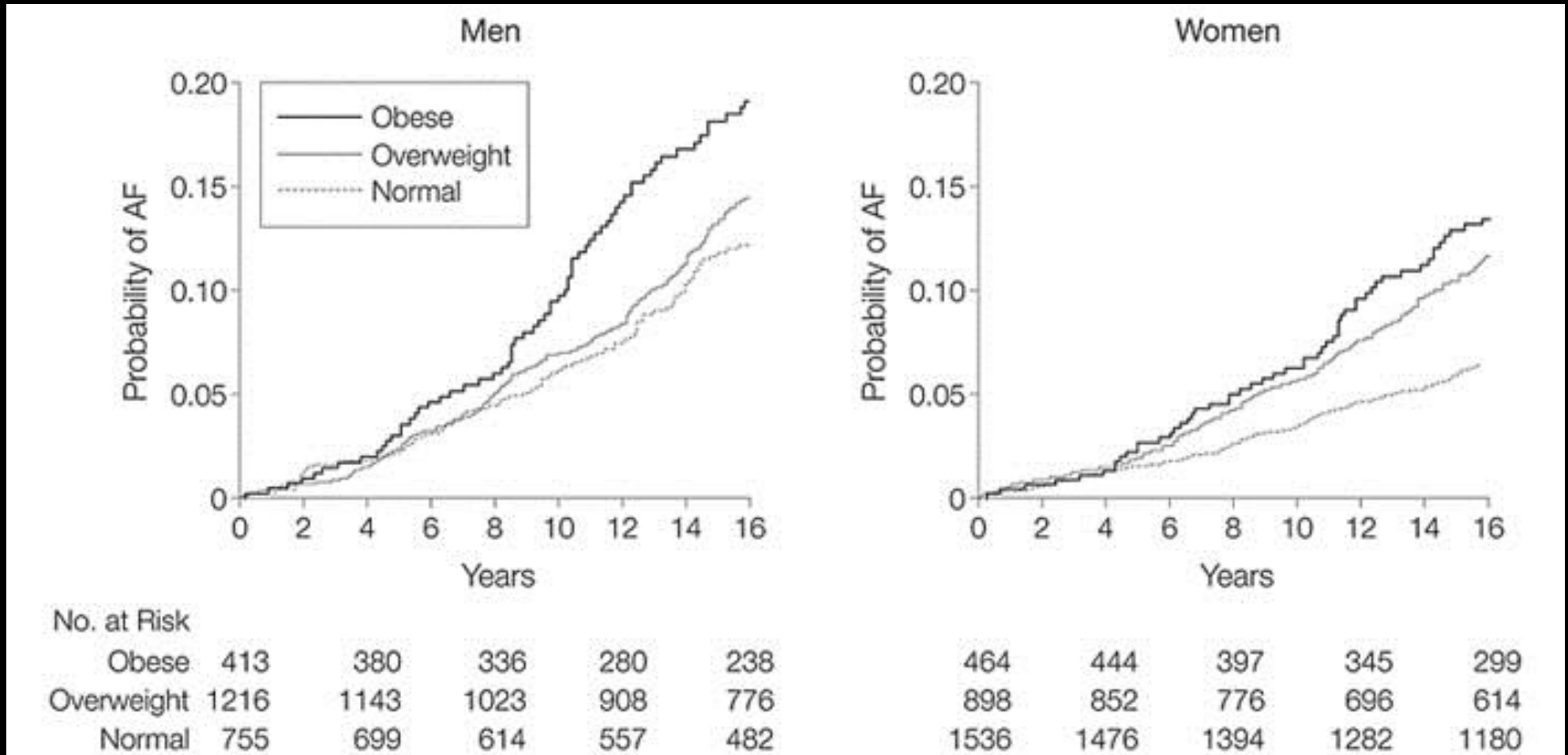
Obstructive Sleep Apnoea and AF risk

(Olmsted county data)



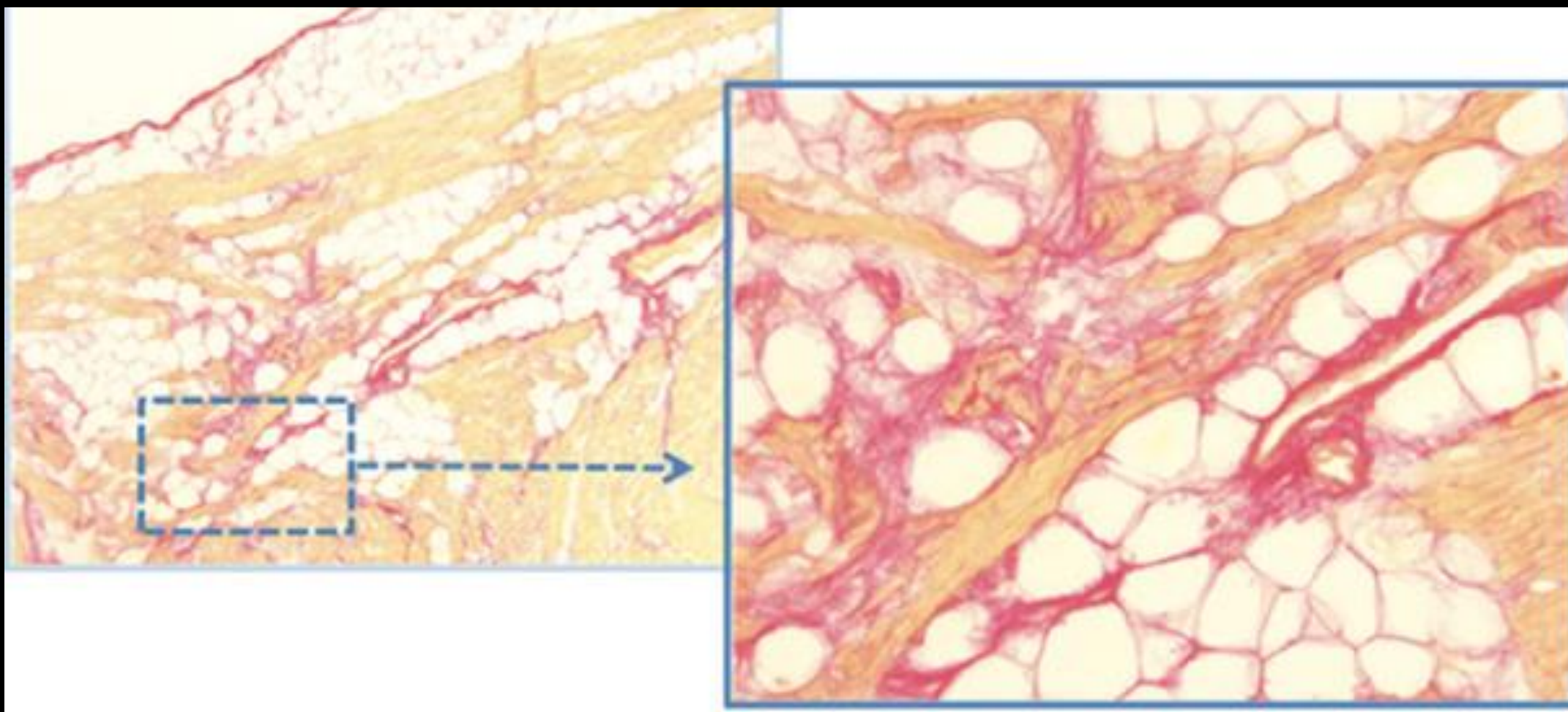
Possible Mechanisms

Obesity and AF risk

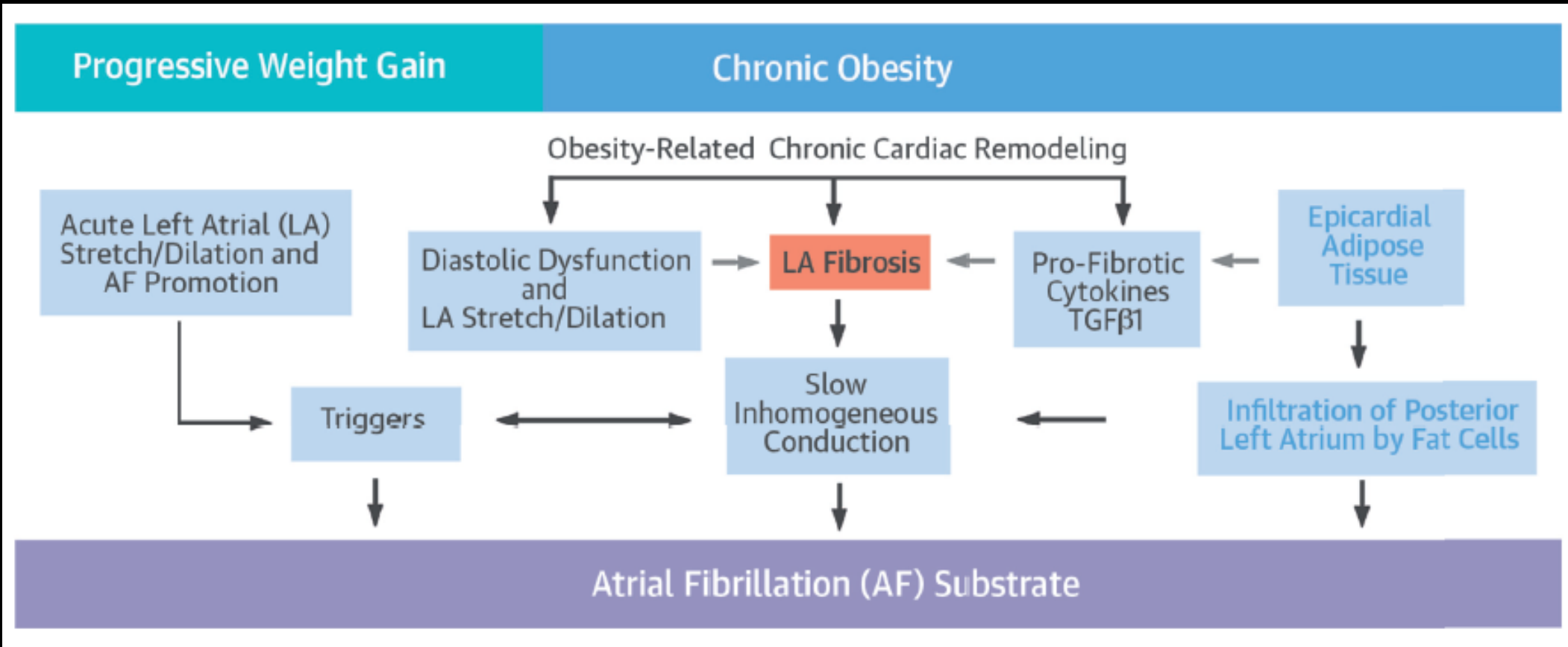


Adjusted HR 1.5 with obesity, attributable to increased LA size

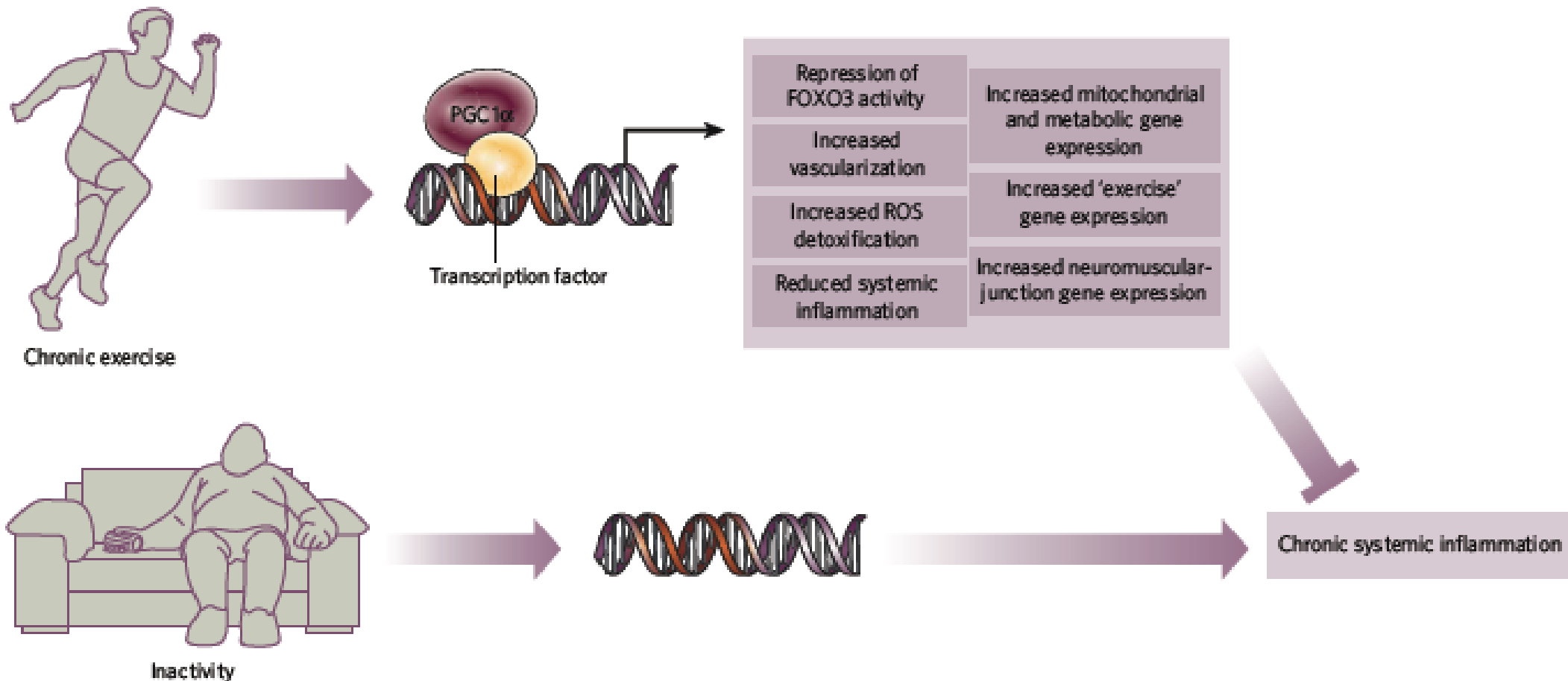
Epicardial fat – adipocyte infiltration - fibrosis



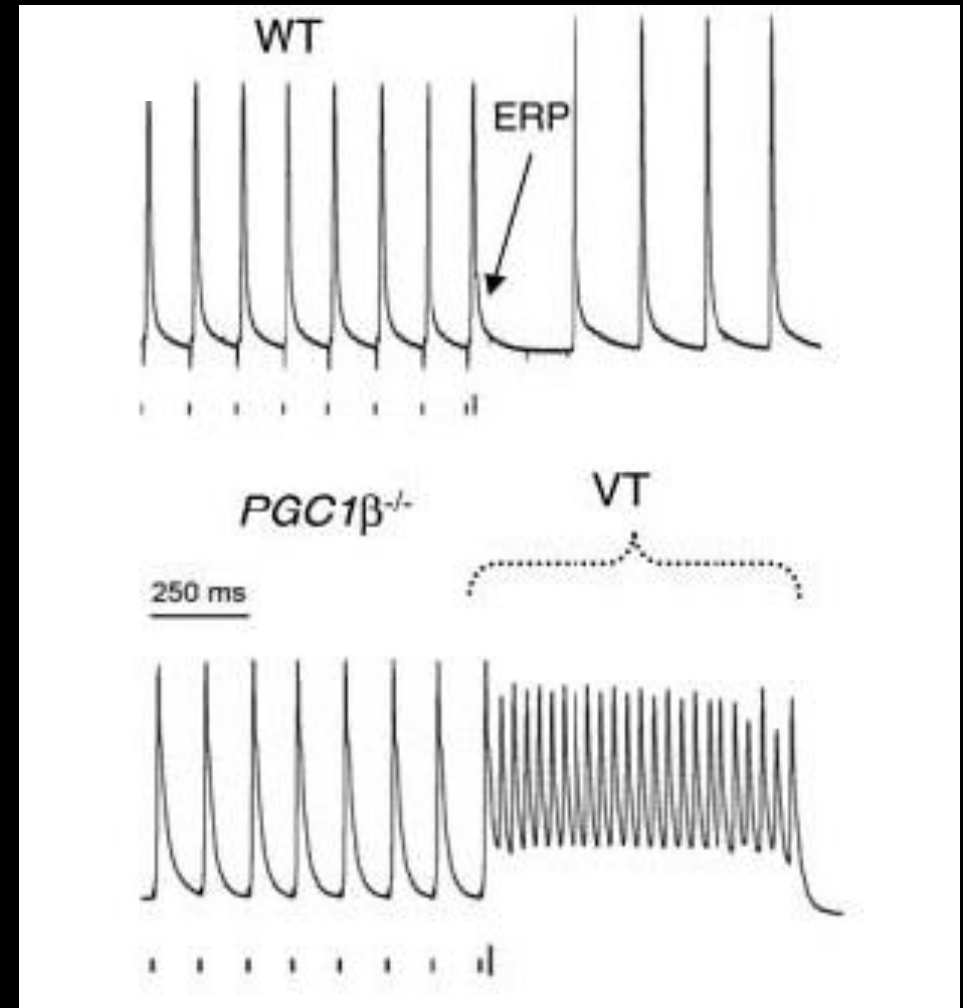
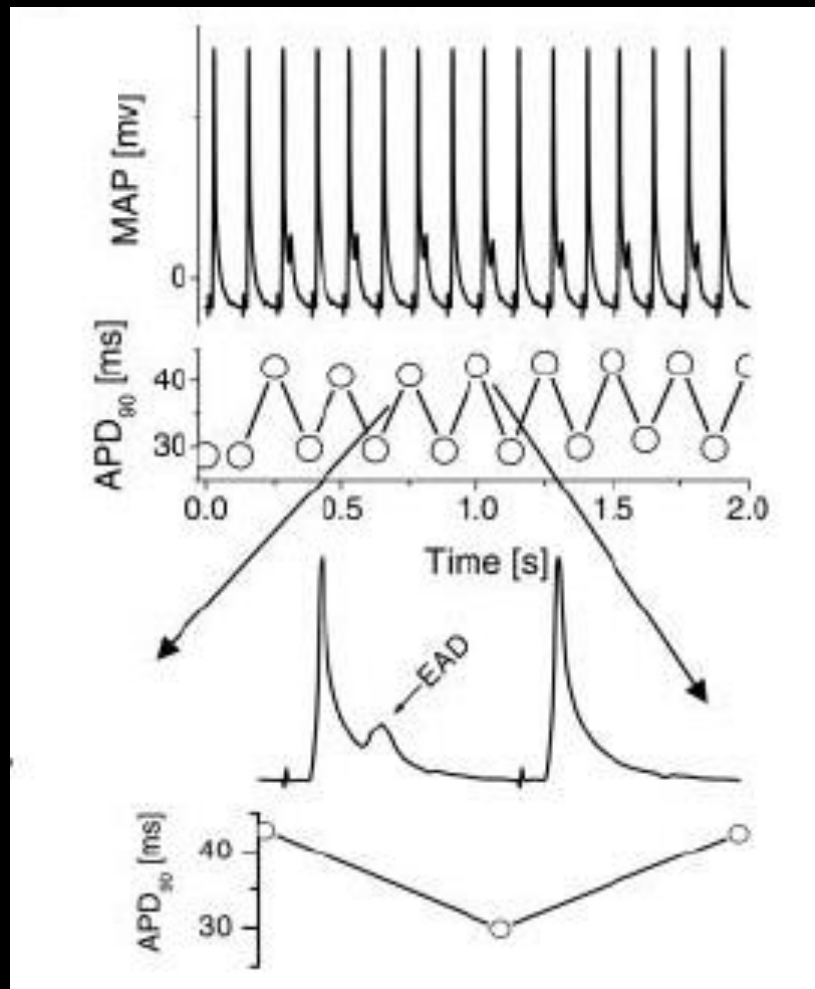
Atrial functional consequences chronic obesity in sheep



Transcriptional co-activators (PGCs) as plausible candidates

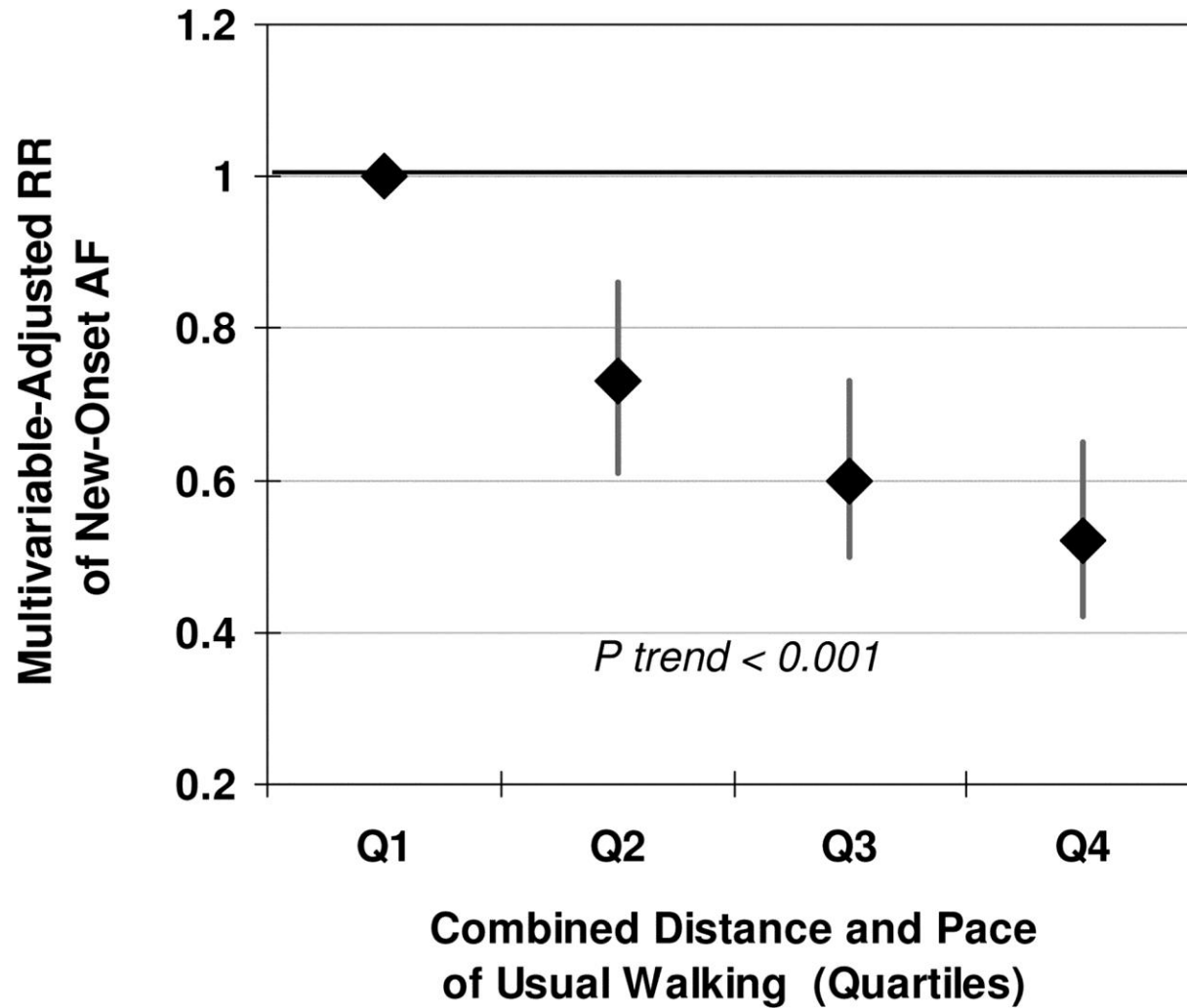


Cardiac Arrhythmia in PGC-1 β $-/-$ gene-targeted mice

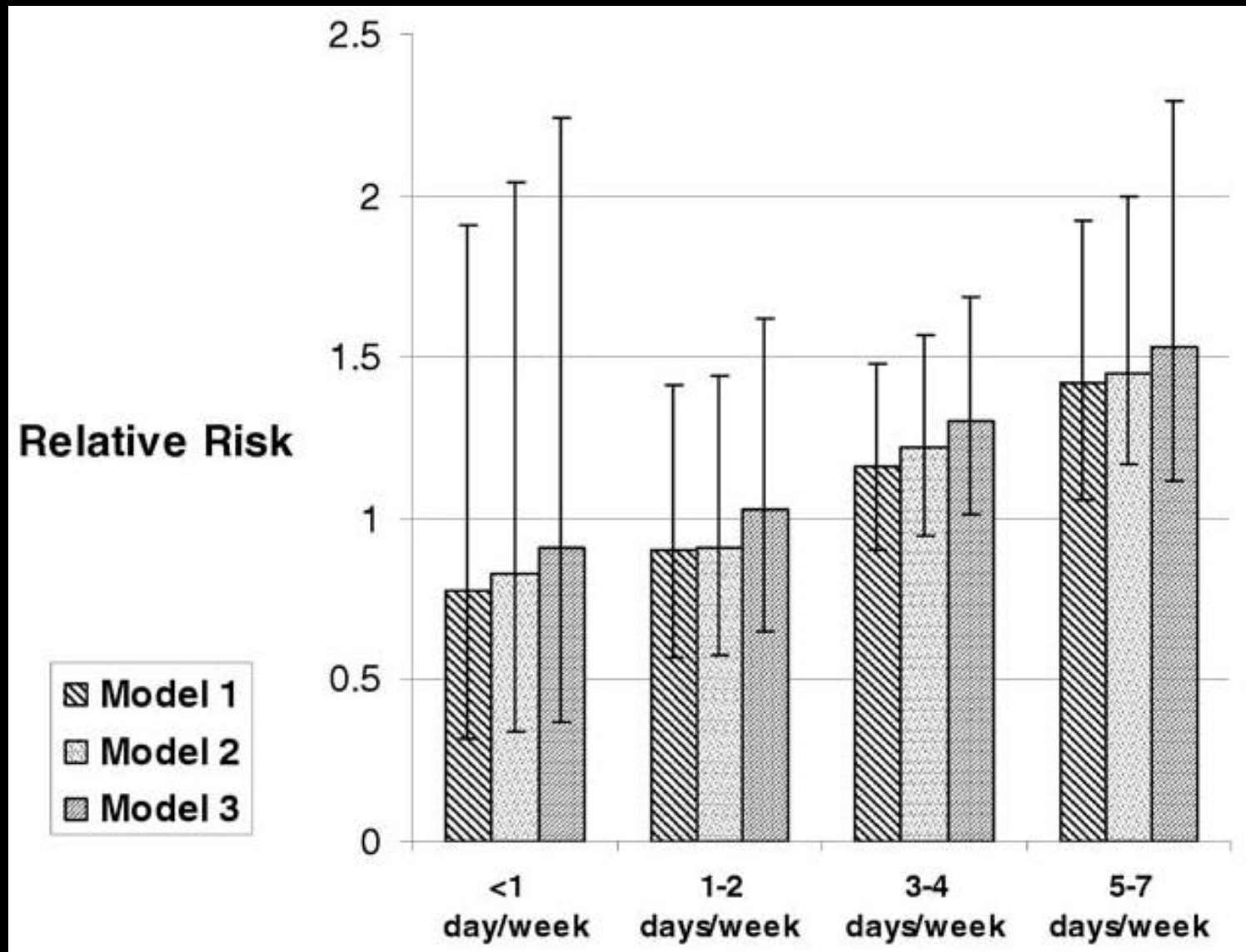


Prevention – Exercise/fitness

Physical activity and AF risk in Older Adults

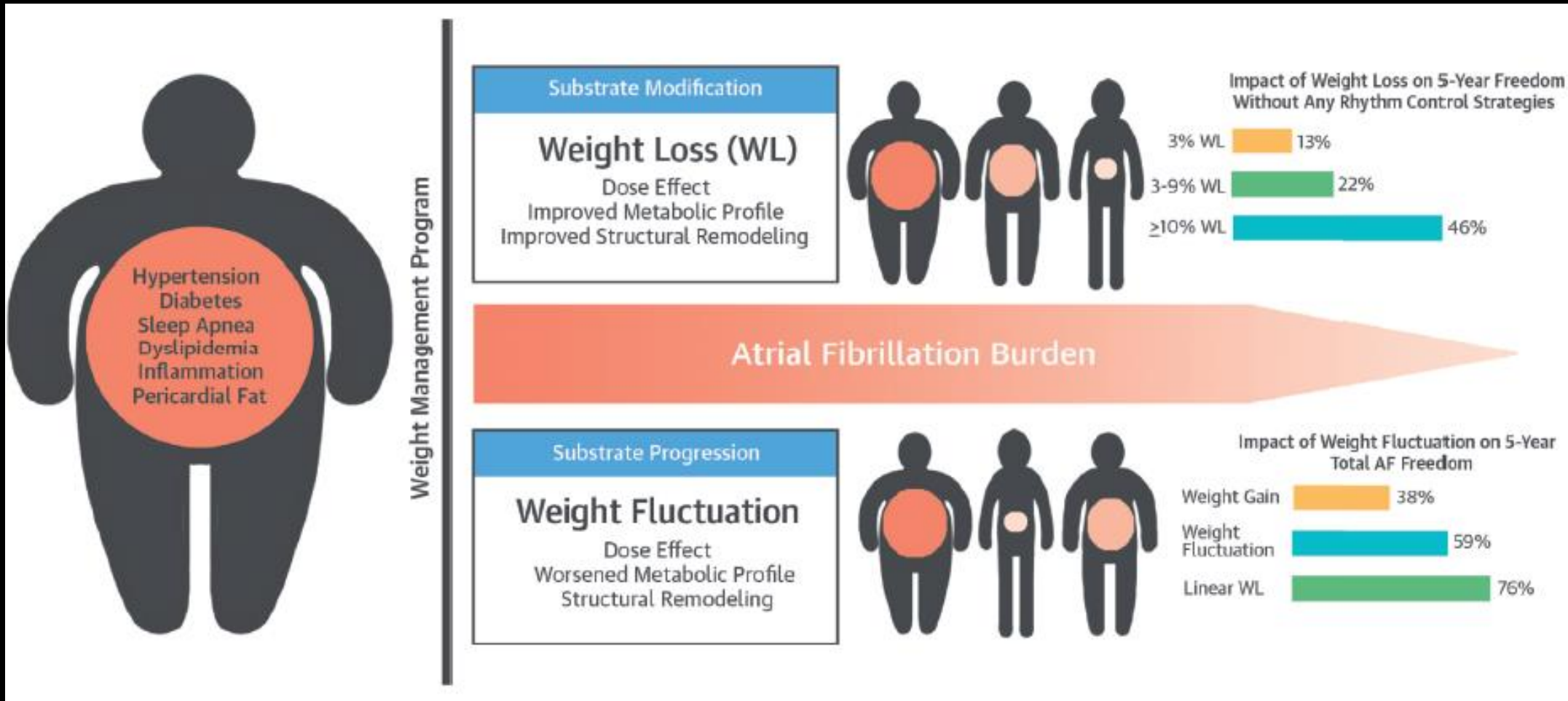


Relation of Vigorous exercise to risk of AF

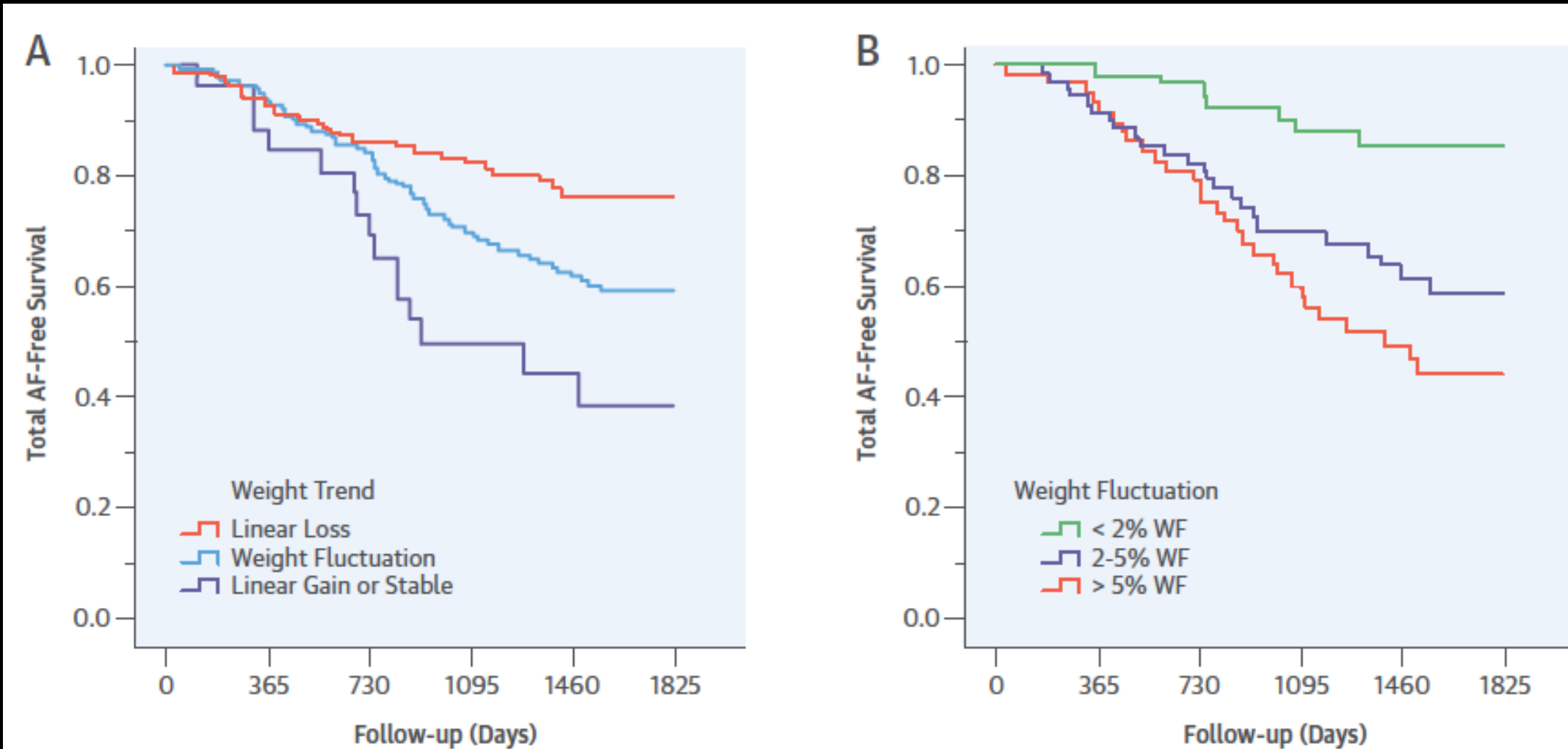


Prevention – weight control

Long term effects weight management (LEGACY trial)



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Case Study

Male b. 1970 - Persistent AF – 180.9 Kg (BMI 49.3)

Referred 10.2010 – unsuccessful DCC (amiodarone /metoprolol)

DCC (failed internal) success 12.2010 continued on amiodarone

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Bariatric surgery 01.2012

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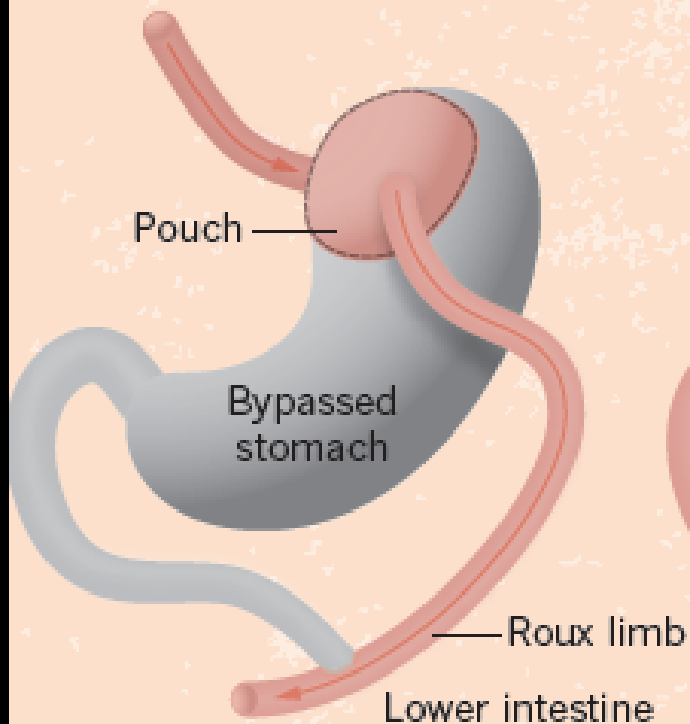
12.2012 – 86kg – stop amiodarone

09.2015 – first episode recurrent AF + PV Isolation

Bariatric Surgery

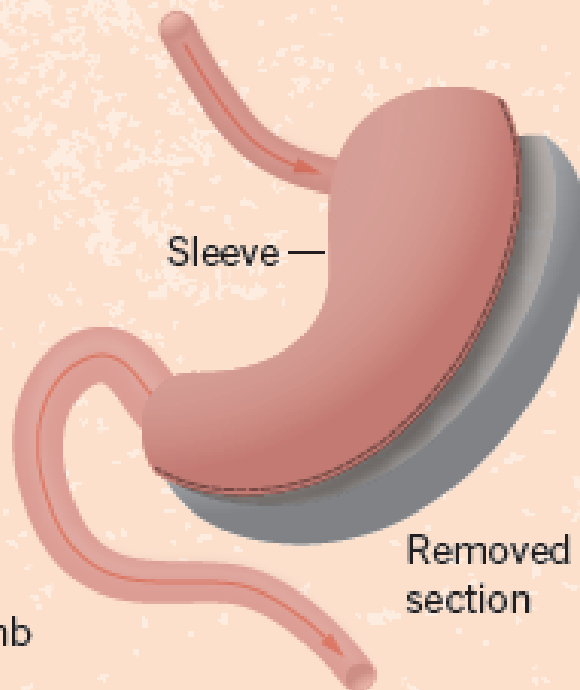
Roux-en-Y gastric bypass

The stomach is reduced to a small pouch and connected directly to the intestine.



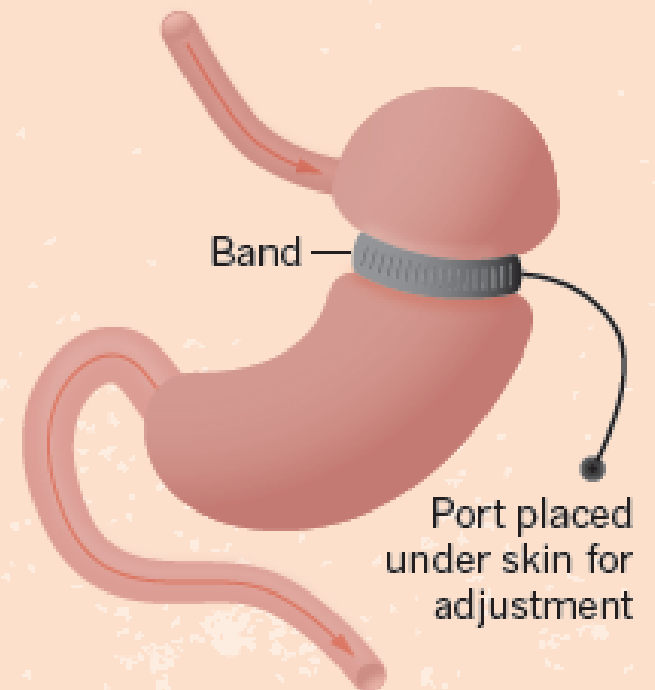
Vertical sleeve gastrectomy

Most of the stomach is removed and the part that remains is stapled back together.



Gastric banding

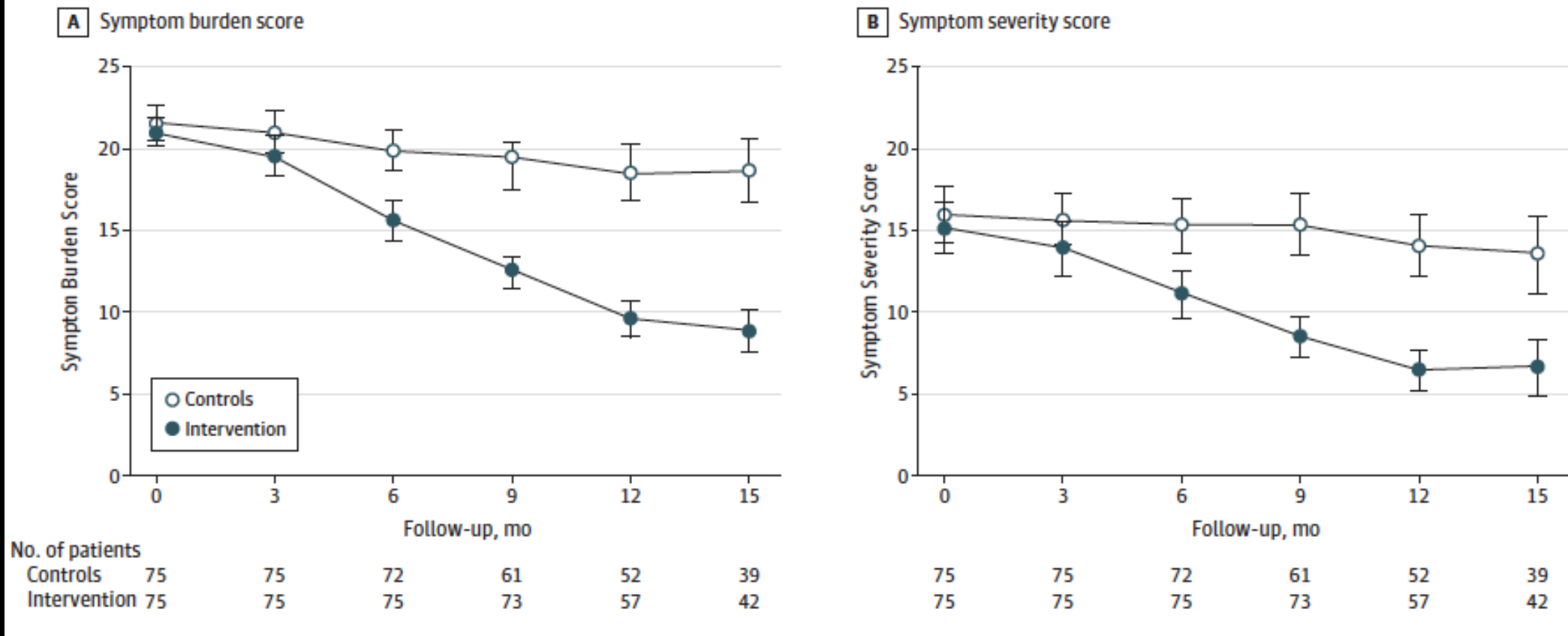
An adjustable silicone band controls how much food the stomach can hold.



Risk Factor Reduction in AF

Effect of weight reduction/risk factor control on AF symptoms

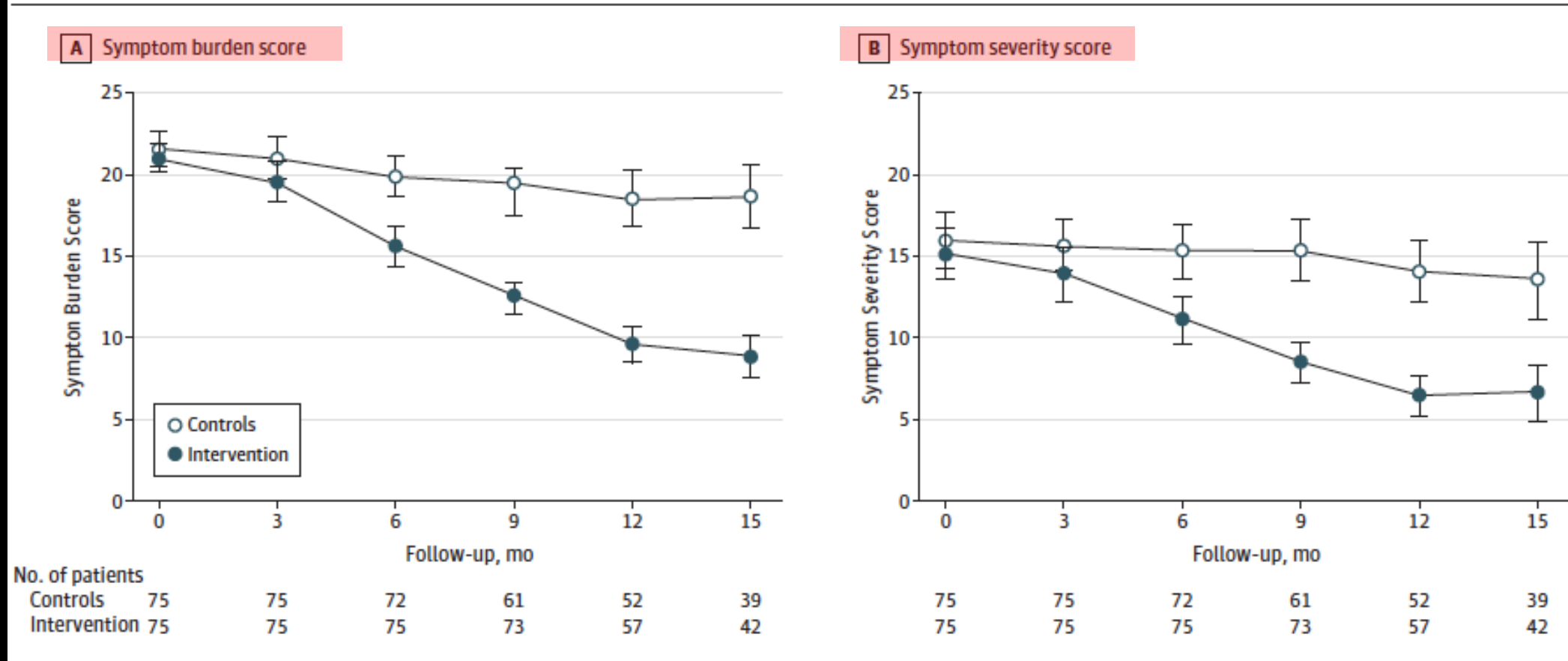
Figure 3. Changes in Atrial Fibrillation Symptom Scale (AFSS) Scores Over Study Follow-up



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.

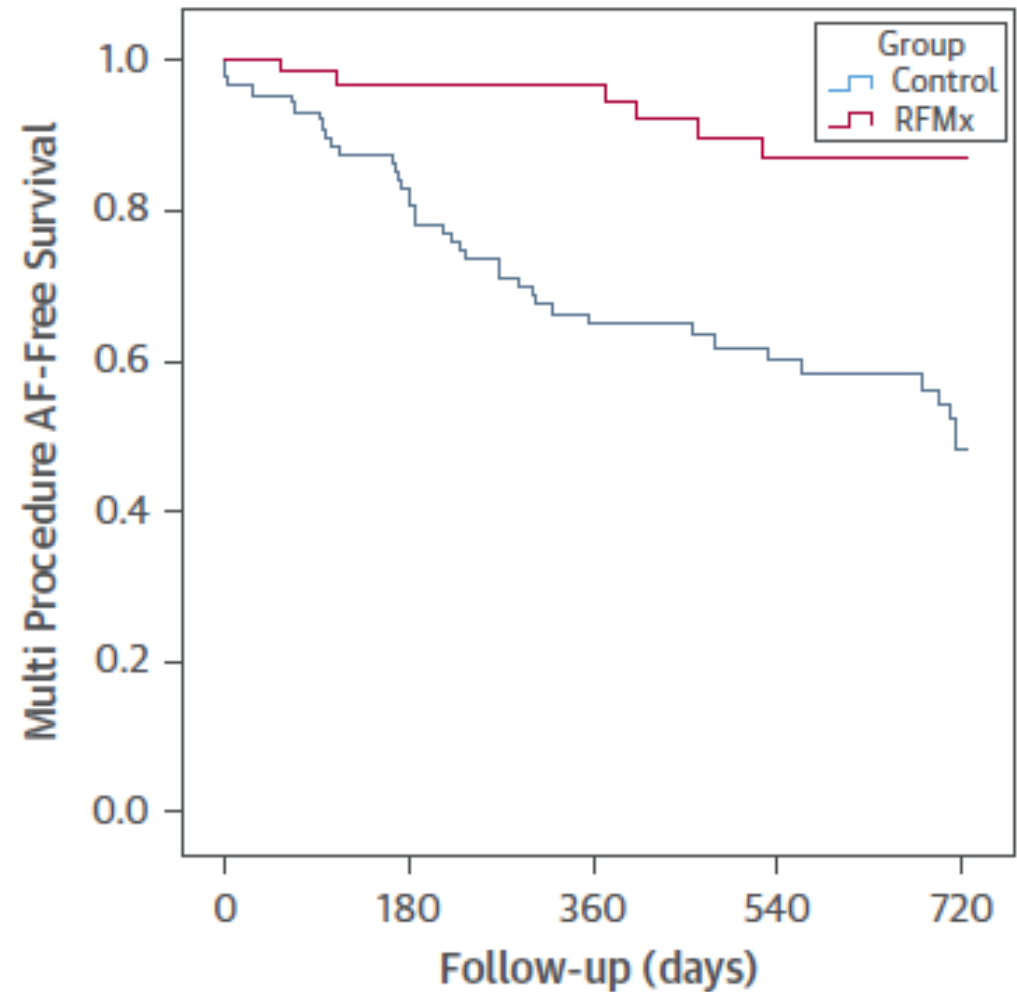
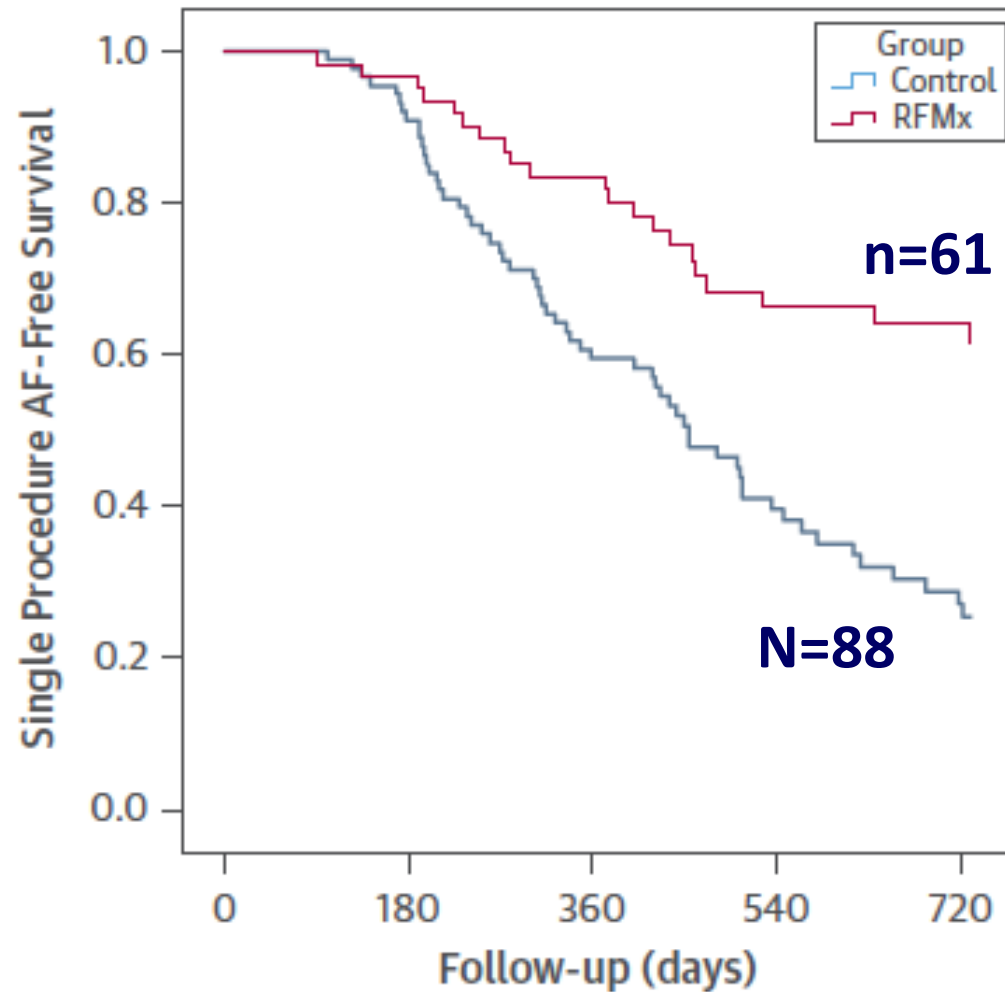
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Risk factor reduction and Ablation outcomes (ARREST-AF trial)



How hard should we try

- Genetic referral of no current clinical value (rare exceptions)
- Atrial fibrillation strong metabolic determination
- Prevention – public health message – ‘metabolic syndrome’
- Ideally integrated approaches (metabolic/sleep physicians)
- Consider bariatric surgery