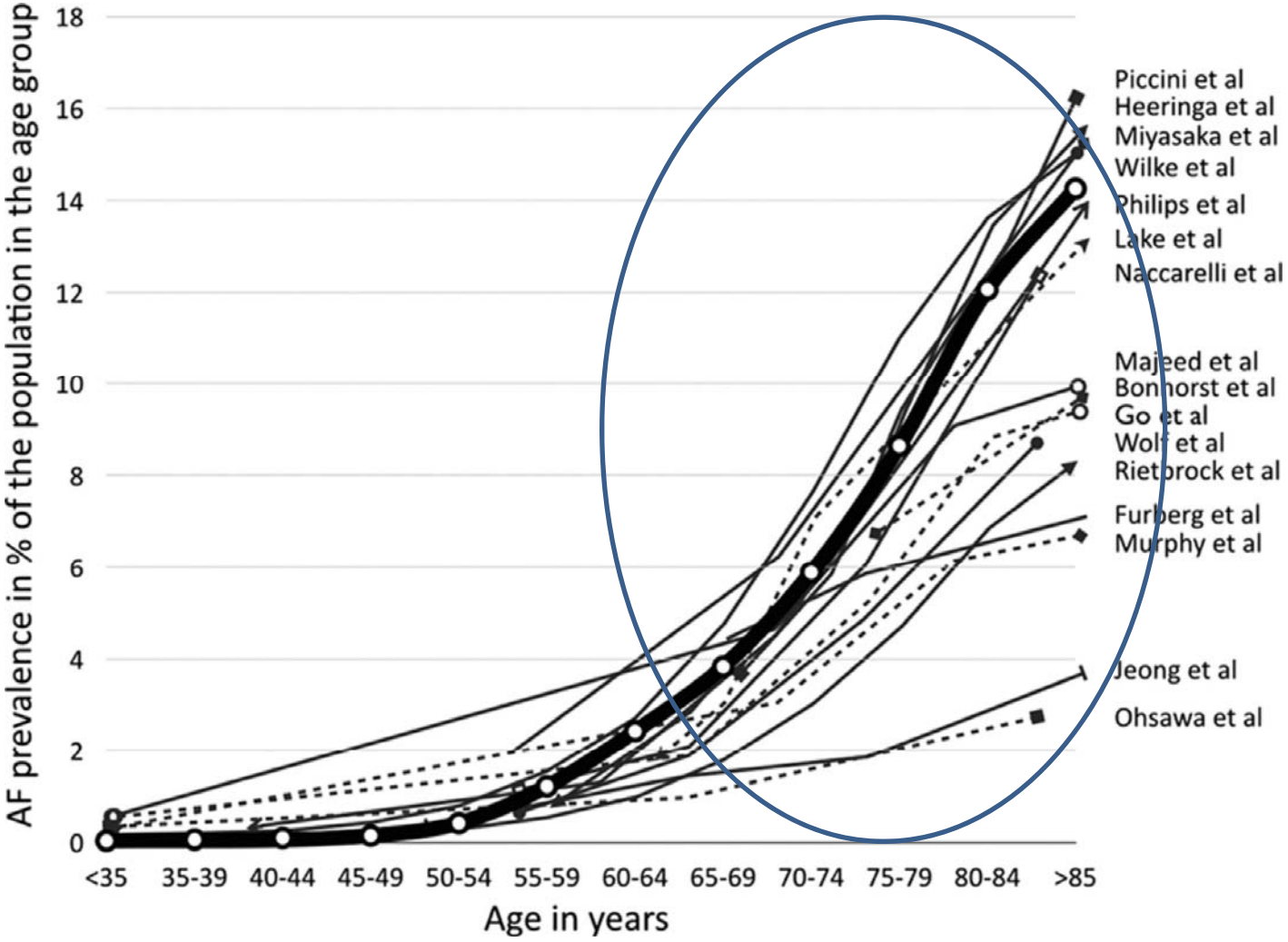
Aggressive Risk Factor Modification to Reduce Atrial Fibrillation: Is the Evidence Conclusive?

Ratika Parkash MD MS FRCPC FHRS

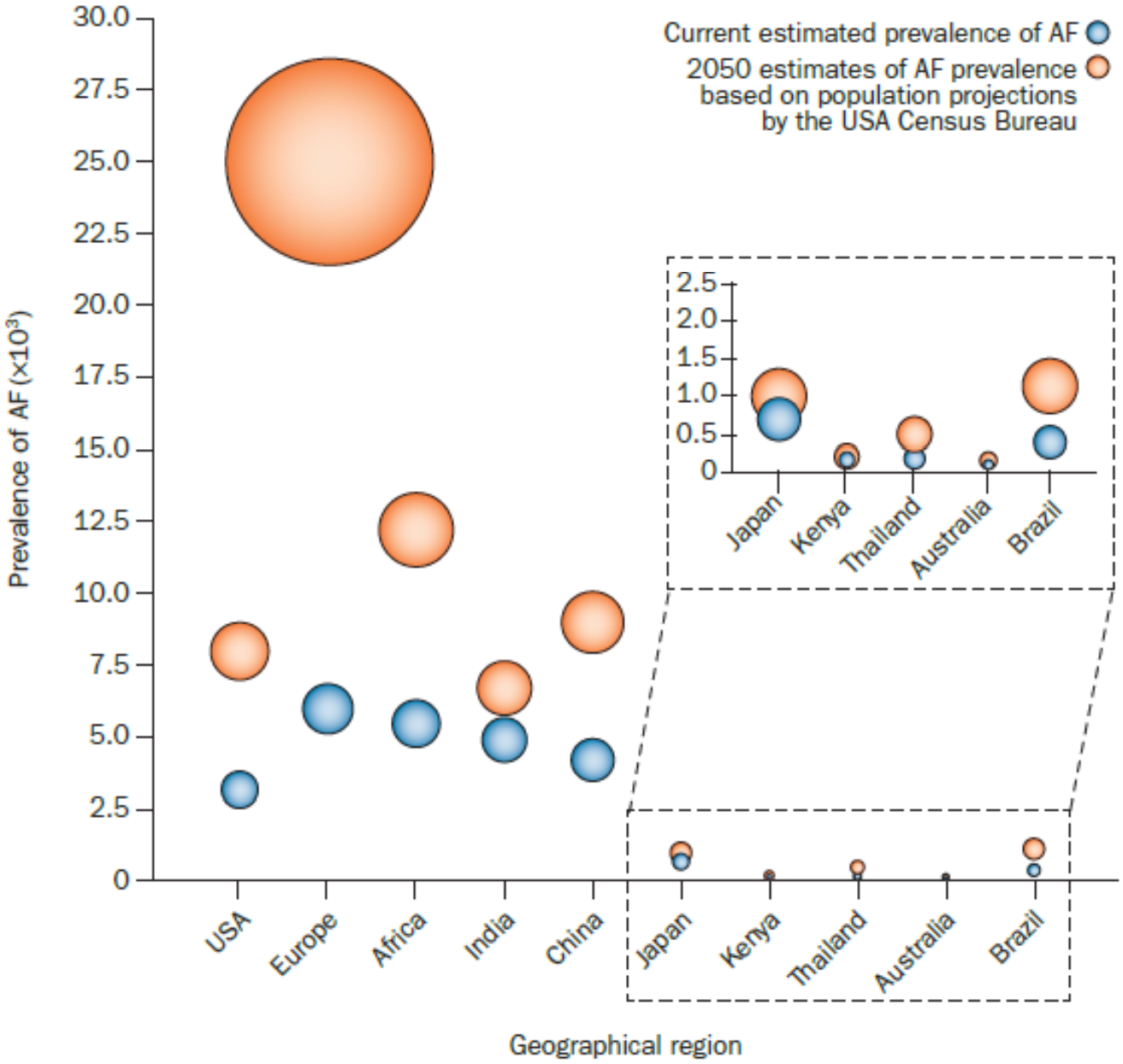
Professor, Dalhousie University
QEII Health Sciences Center

Halifax, Nova Scotia

Prevalence of Atrial Fibrillation

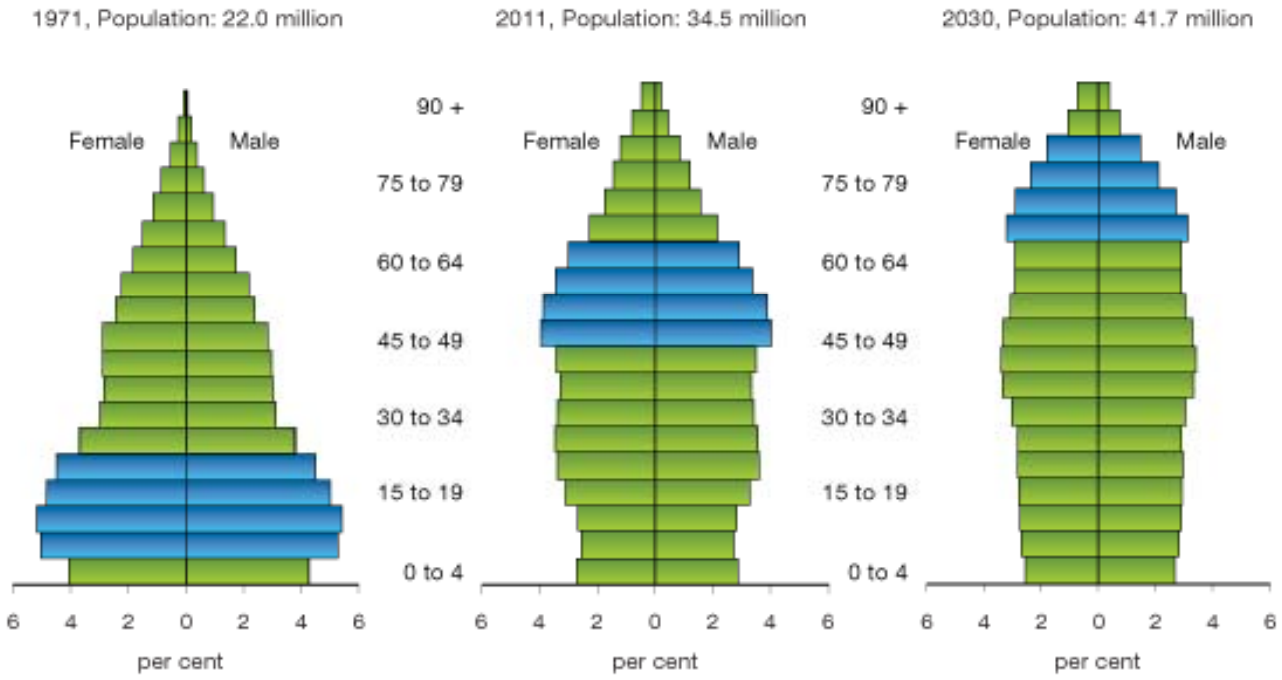


Jason Andrade et al. Circulation Research. 2014;114:1453-1468

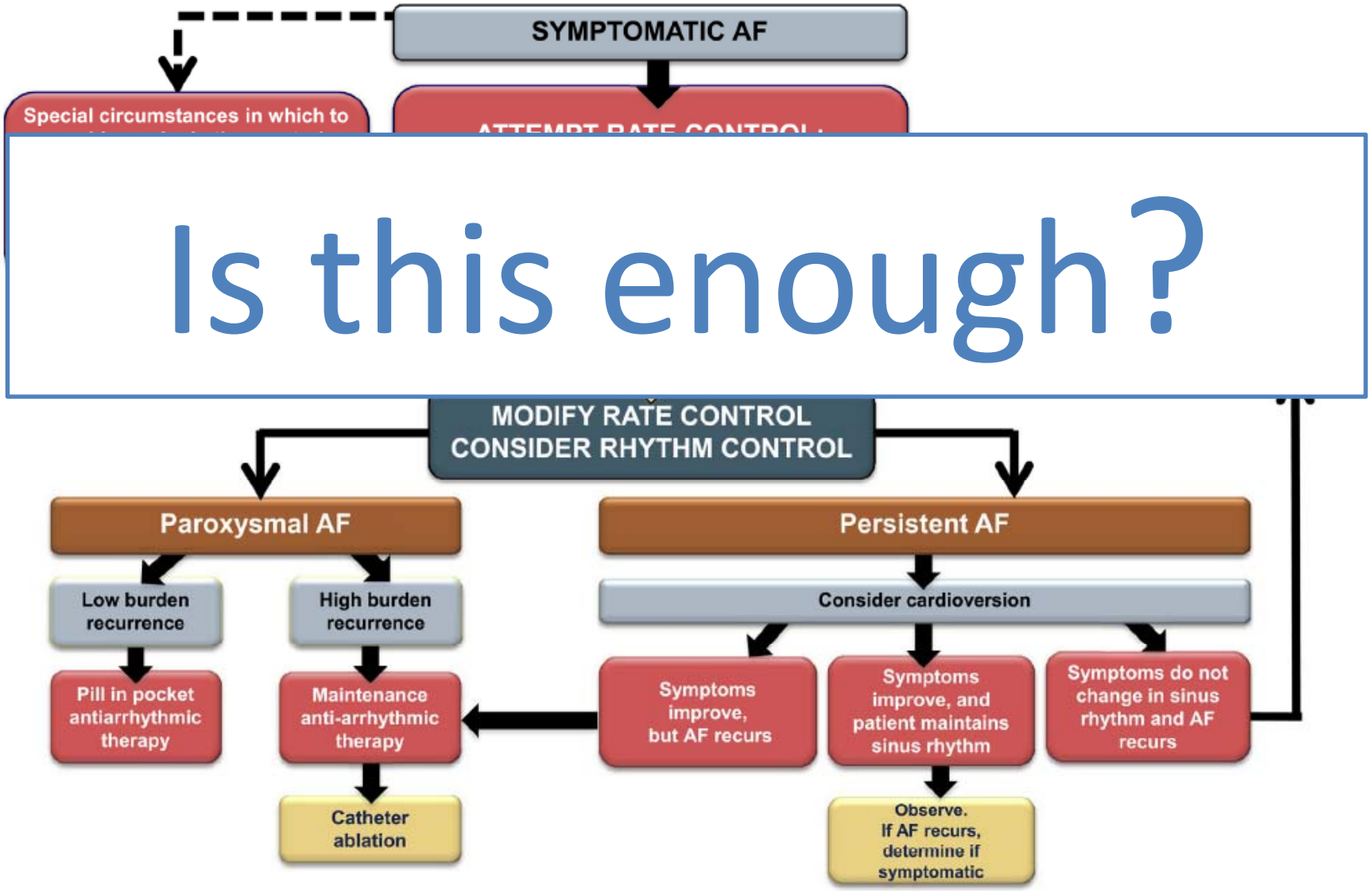


Rahman et al Nat Rev Card 2014; 639-54

*In 2011, an estimated **5.0 million** Canadians were 65 years of age or older, a number that is expected to double in the next 25 years to reach **10.4 million** seniors by 2036. By 2051, about one in four Canadians is expected to be 65 or over.*

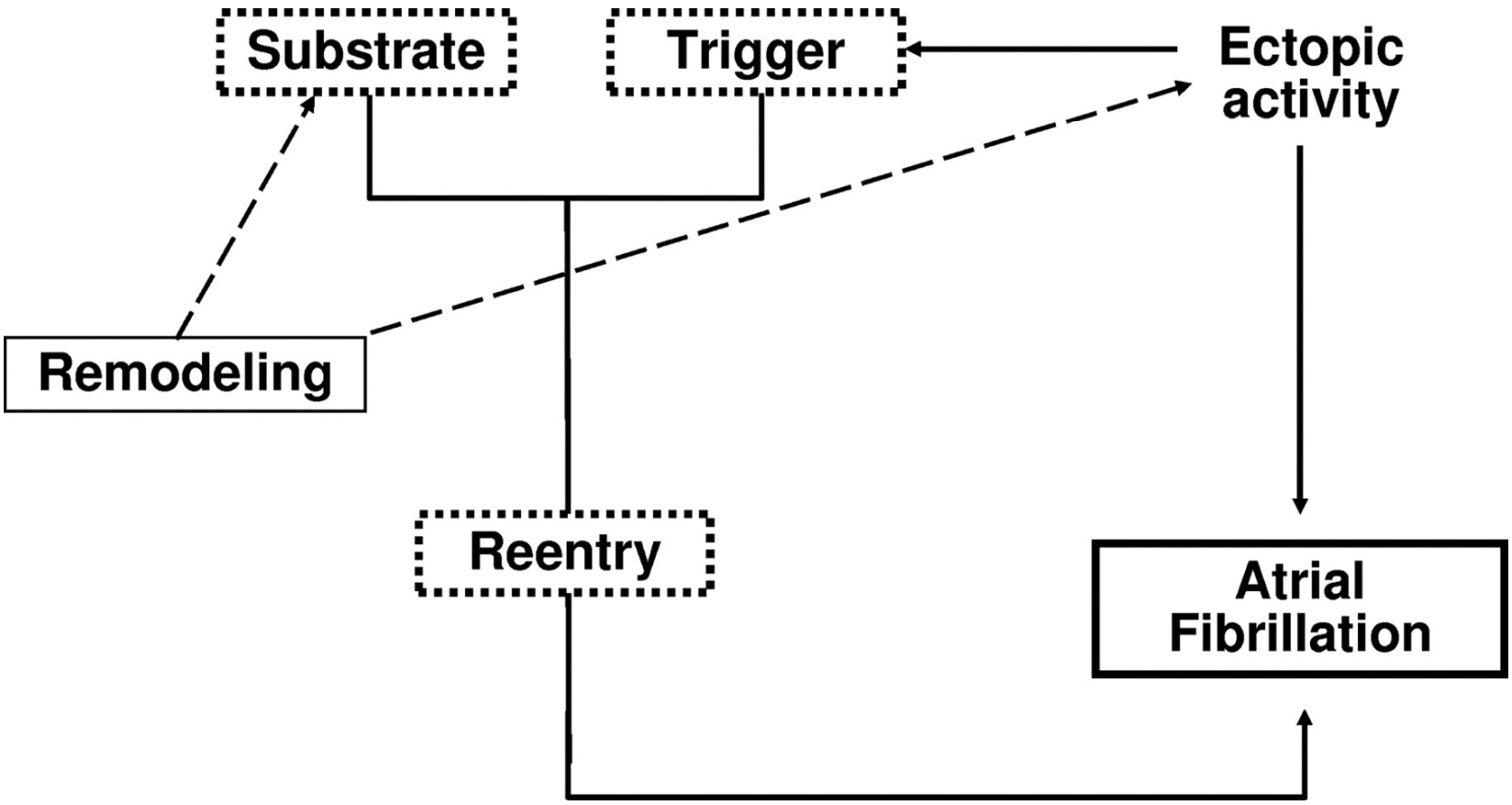


Treatment of AF



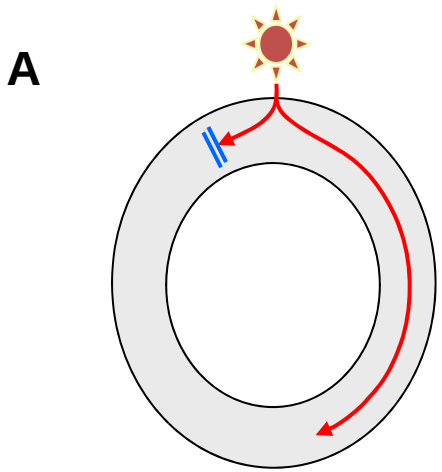
Verma et al CJC 2014

General schema representing AF mechanisms and the role of remodeling.

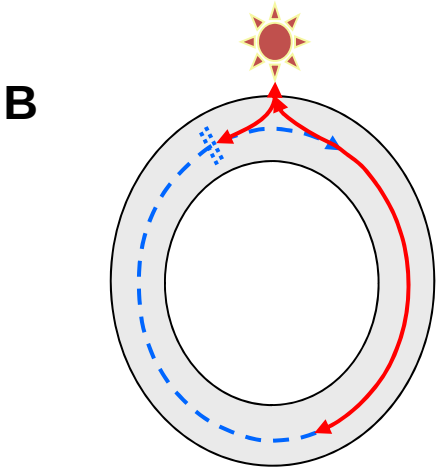


Stanley Nattel et al. Circ Arrhythm Electrophysiol. 2008;1:62-73

Substrate for Reentry in AF



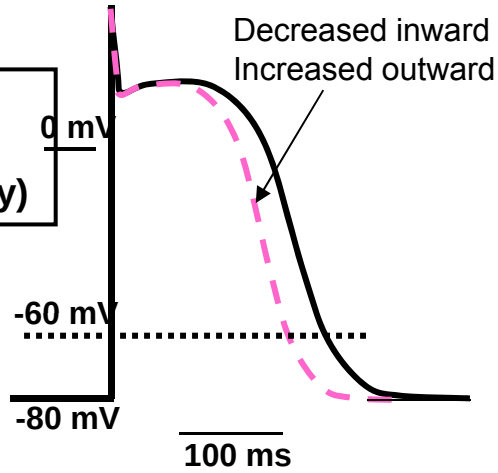
Fundamental determinants of reentry:
-ERP (short favors reentry)
-conduction velocity (slow favors reentry)



How remodeling promotes reentry

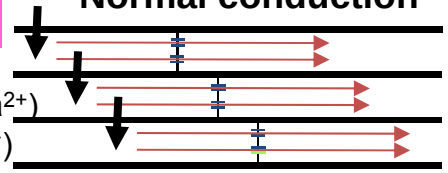
C

Shortened refractory periods

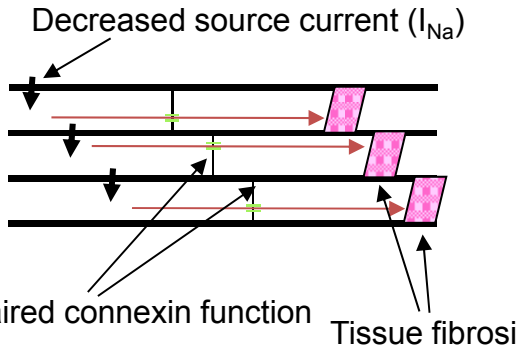


D

Normal conduction

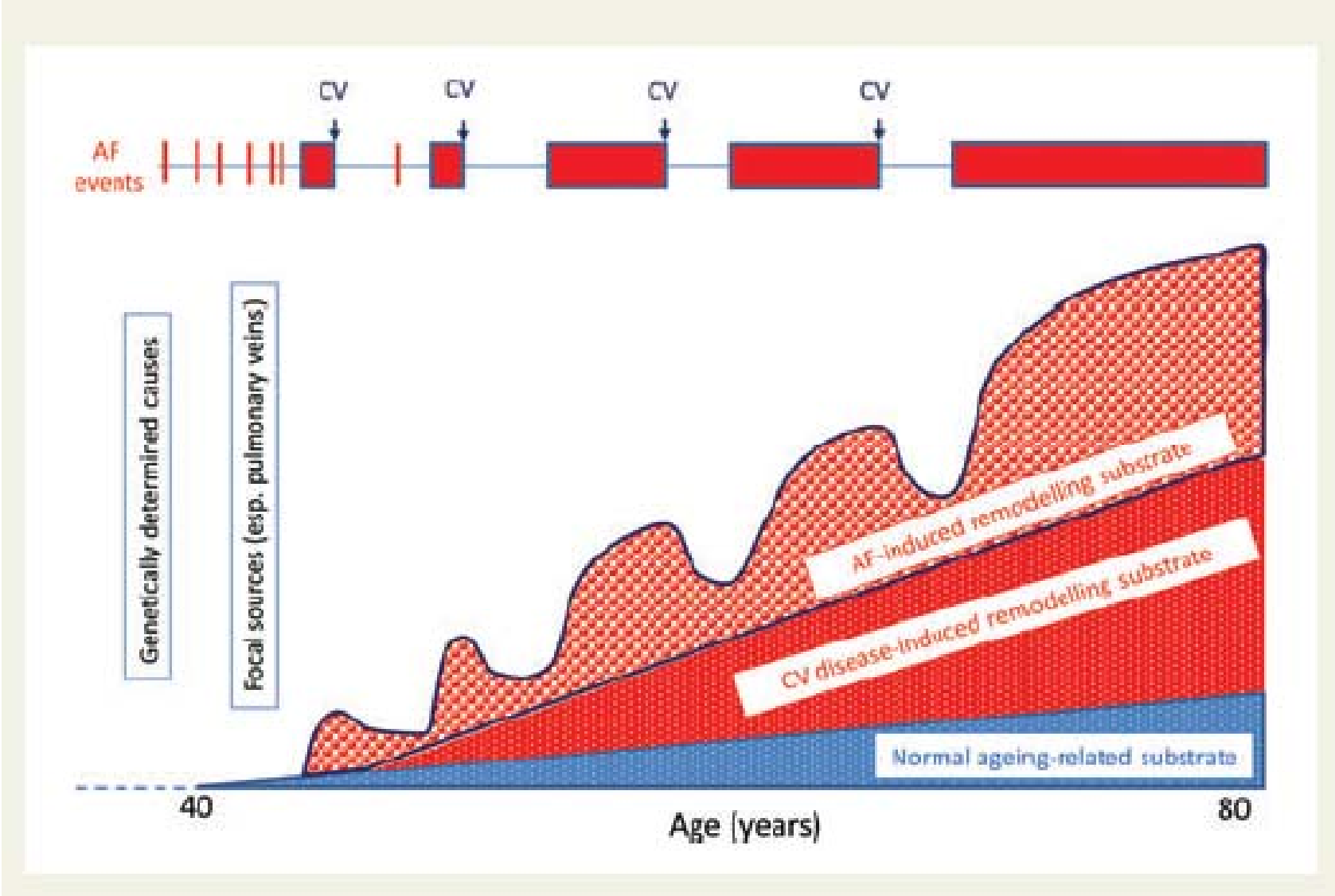


Slowed conduction



Adapted from Nattel S et al, Circ Arrhythm Electrophys 2008 Apr;1(1):62-73. .

Progression of AF

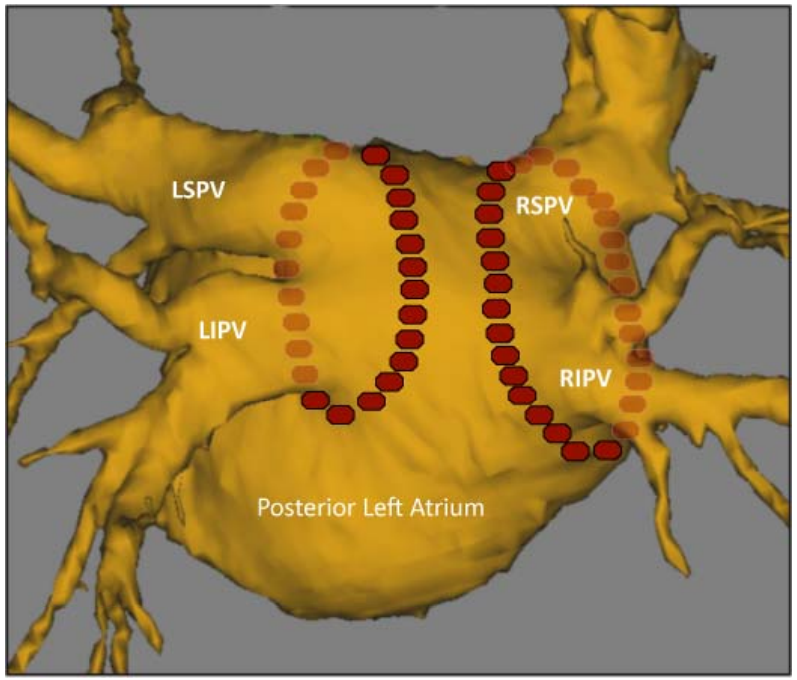


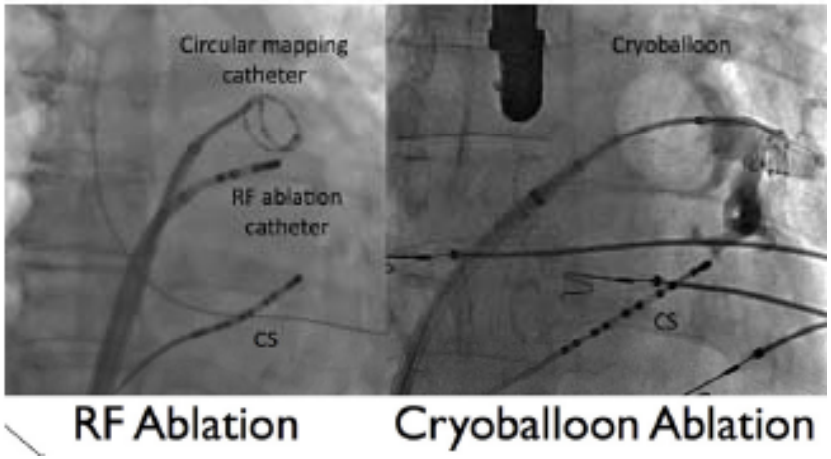
Established Risk Factors for AF

- Age and gender (>45 for men, >60 for women)
- PR interval (≥ 160 ms)
- Body Mass Index (≥ 30) Modifiable
- Valvular Heart Disease (higher risk if younger at onset)
- Heart Failure (higher risk if younger at onset)
- Systolic blood pressure (≥ 160 mm Hg) Modifiable
- Sleep Apnea Modifiable
- Alcohol intake Modifiable
- Exercise Modifiable

Schnabel et al. Lancet 2009;373:739-745

Current Status of Therapy in AF





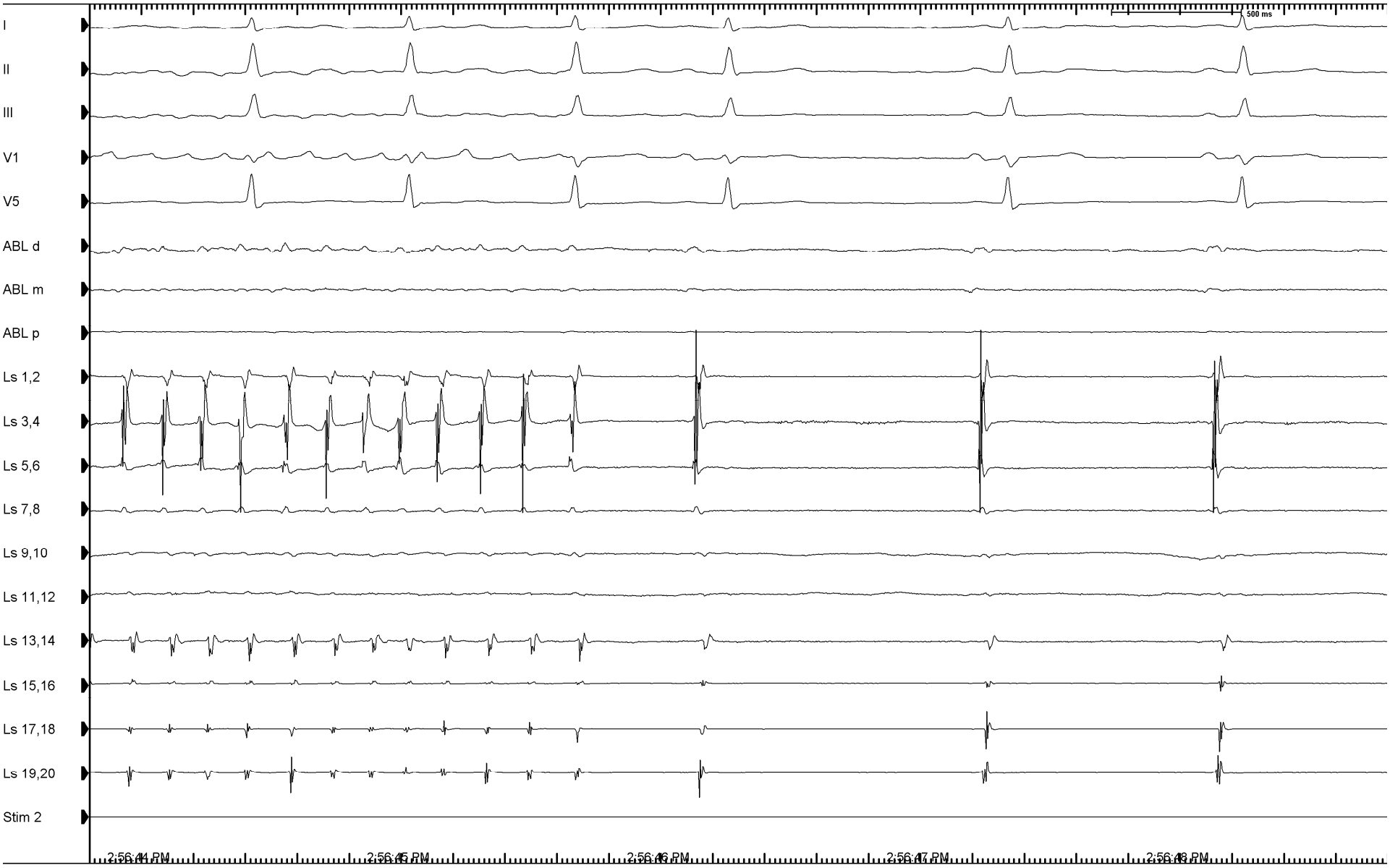
What are the incremental gains to be made in treatment of AF?

What are the incremental gains to be made in treatment of AF?

- Prevention of AF?
  - Target modifiable risk factors upstream including obesity, hypertension and its resultant effects including diabetes and sleep apnea
  - May be primary or secondary

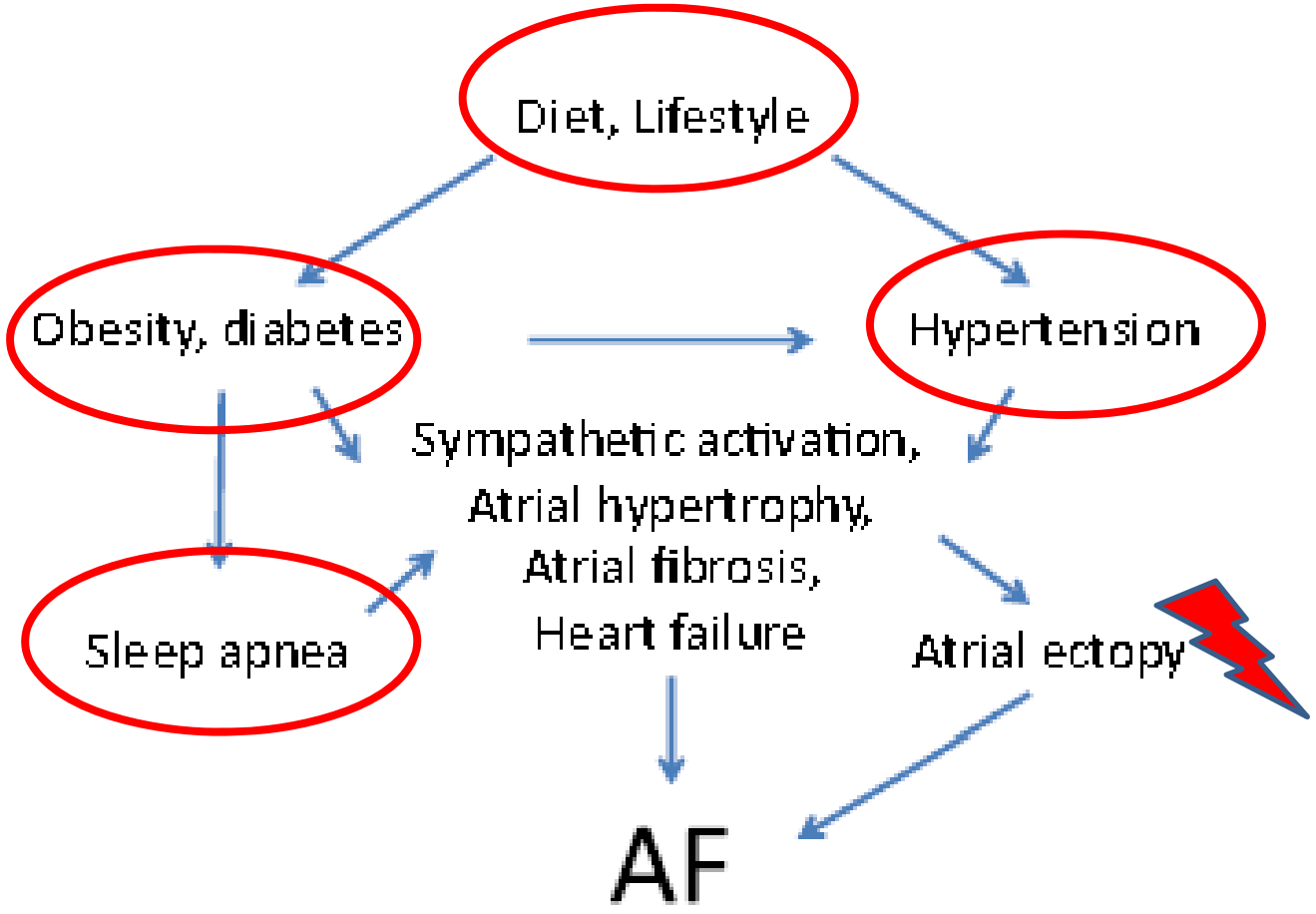
- Providing optimal care to those who have AF?
  - Specialized clinics: prevent ED visits, hospitalizations, address gaps in care
  - Access to catheter ablation

Is AF a disease?



AF is a symptom, not a disease

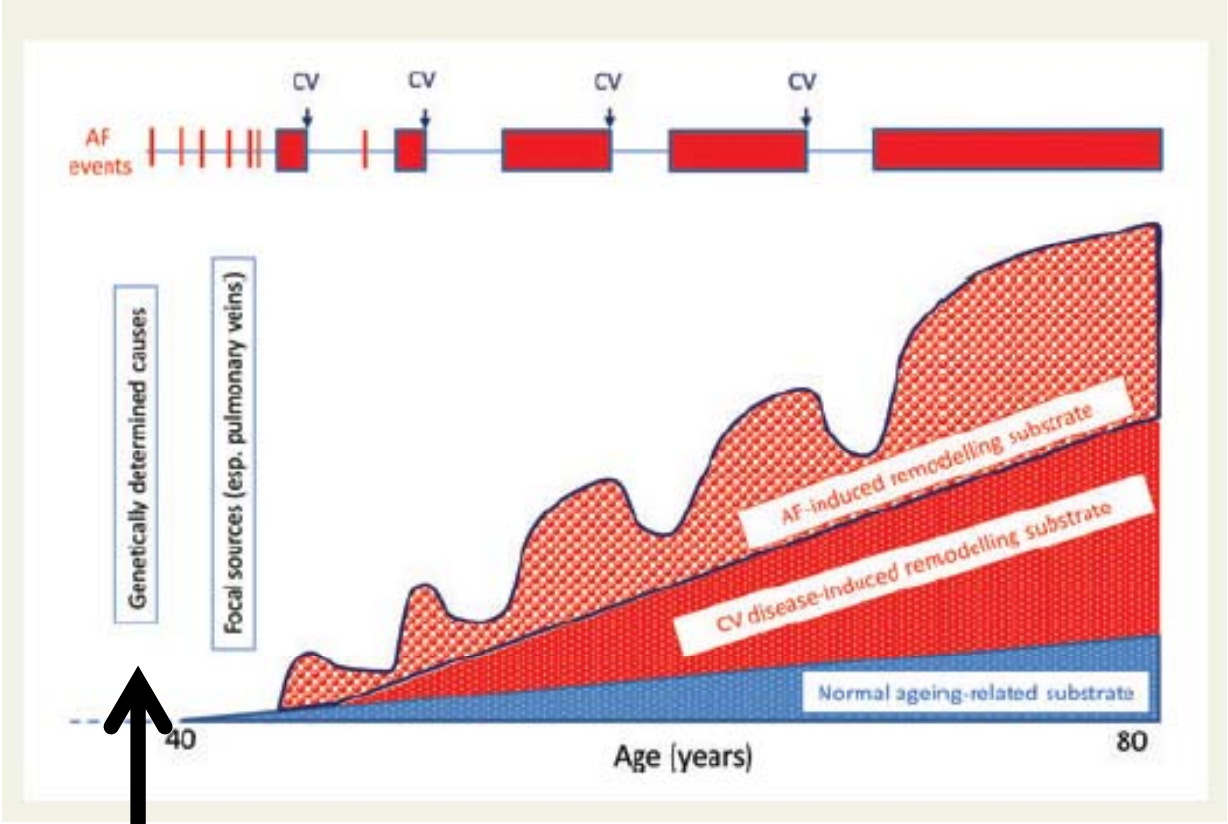
Substrate Modification to Prevent AF



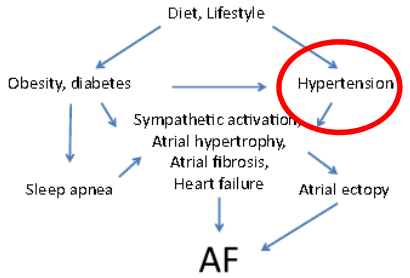
Van Wagoner et al. Heart Rhythm 2015; 12:e6-e22

Progression of AF – when is the right time to intervene?

Before onset of clinical AF: Risk factors: Does intervention lead to prevention of AF?



Once AF develops, can we do better to prevent progression and quality of life?

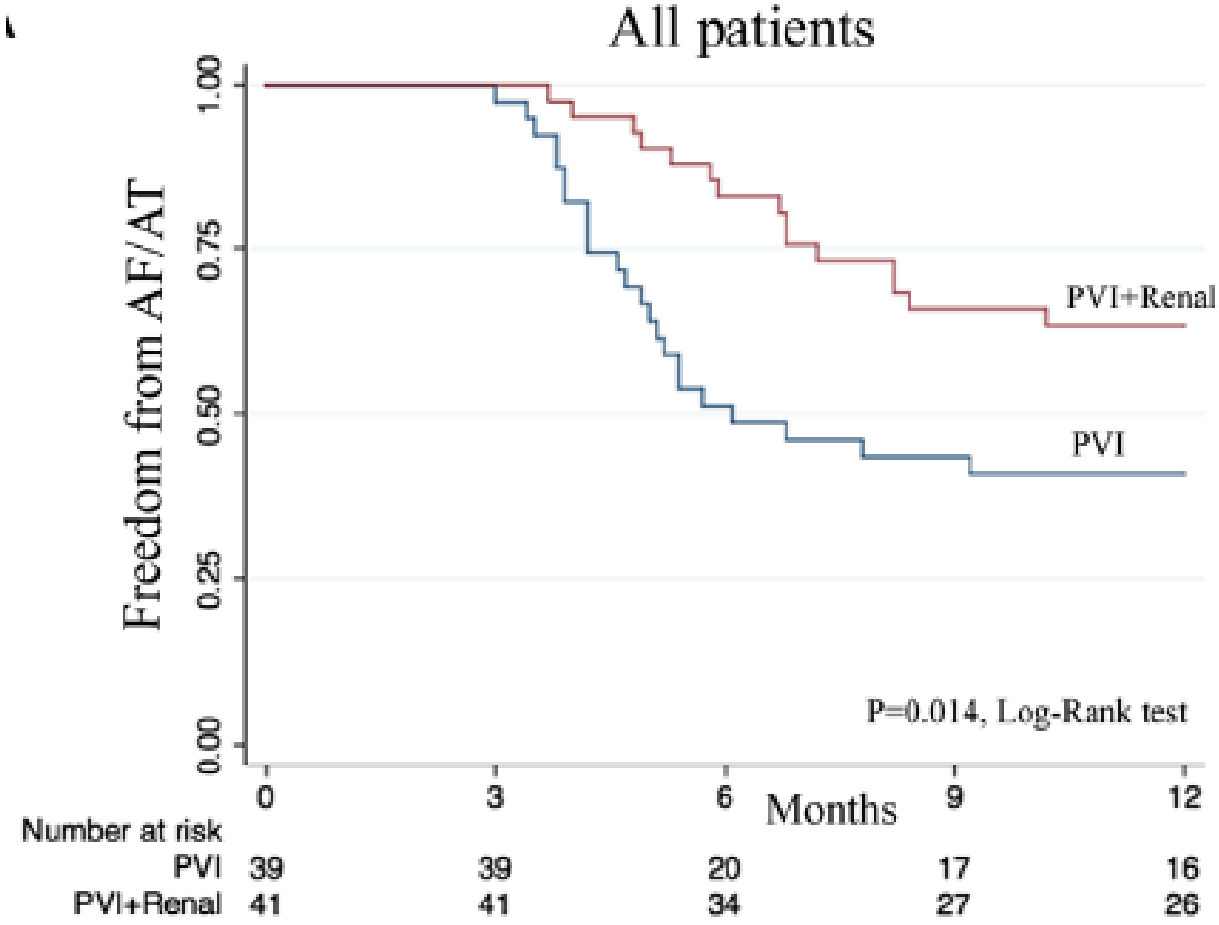


Blood pressure and AF

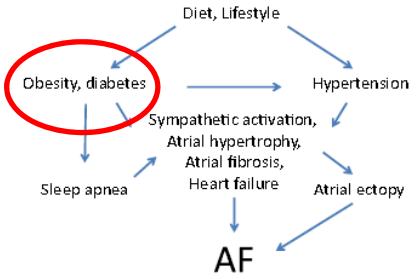
Systolic BP (mm Hg)	<120	120-129	130-139	140-159	≥160
Risk of AF	Ref	1.18 (0.9,1.52)	1.43 (1.09,1.87)	1.78 (1.34,2.38)	2.29 (1.45,3.63)

Conen et al. Circulation 2009;119:2146-52

Renal Denervation and AF

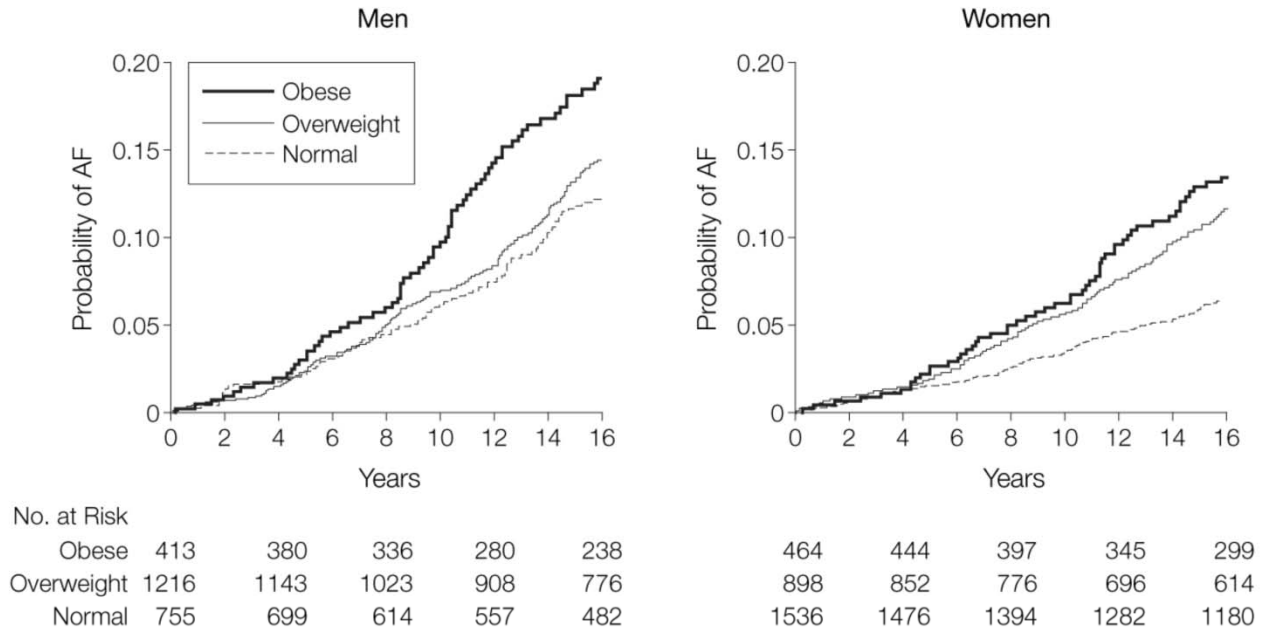


Pokushalov et al. Heart Rhythm 2014; 1131-38



From: **Obesity and the Risk of New-Onset Atrial Fibrillation**

JAMA. 2004;292(20):2471-2477. doi:10.1001/jama.292.20.2471

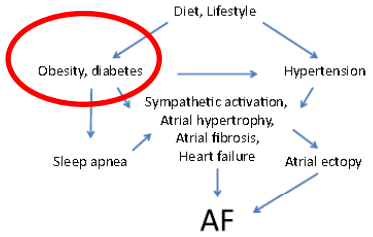


BMI >/= 30 in both men and women; BMI 25-30 in women also a risk

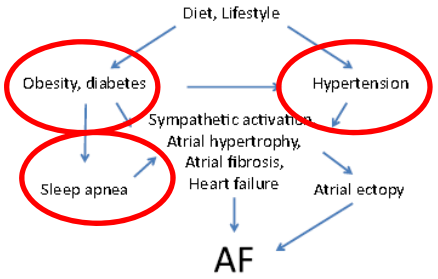
Figure Legend:

Horizontal axis represents time since the baseline examination. Bodymass index categories were as follows: normal, <25.0; overweight, 25.0to <30.0; and obese, ≥30.0.

Obesity – RCT data in AF

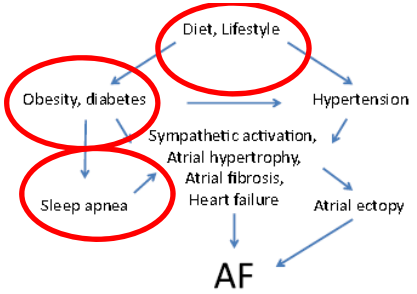


- Abed at al performed a single center RCT in patients with paroxysmal or persistent AF with one of the following: BMI > 27, waist circumference > 100 cm in men, >90 cm in women
- Patients underwent intensive management of obesity and cardiometabolic risk factors (hypertension, hyperlipidemia, glucose intolerance, sleep apnea and tobacco use)
- Patients were prescribed exercise, low-calorie diet



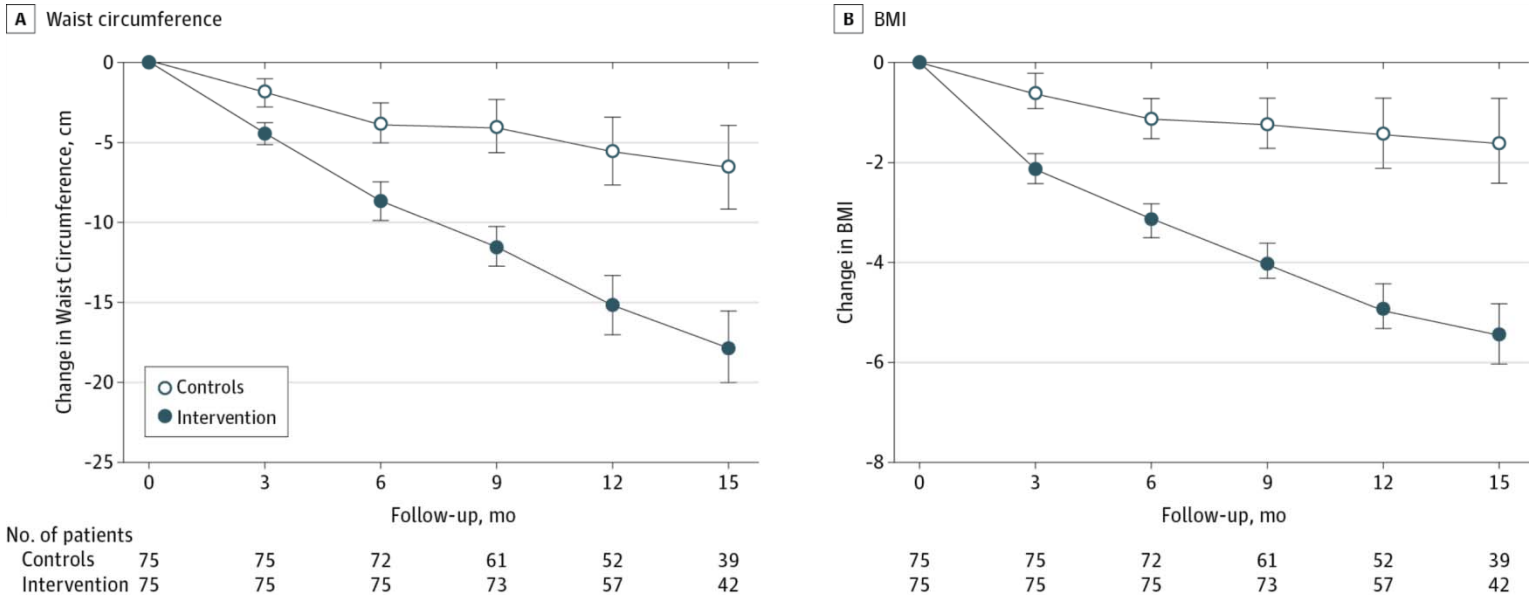
- Followed for 15 months
- Primary outcome AF symptom burden using AFSS
- Secondary outcome 7 day Holter derived AF episodes and duration, LA area, LV wall thickness

The JAMA Network



From: **Effect of Weight Reduction and Cardiometabolic Risk Factor Management on Symptom Burden and Severity in Patients With Atrial Fibrillation: A Randomized Clinical Trial**

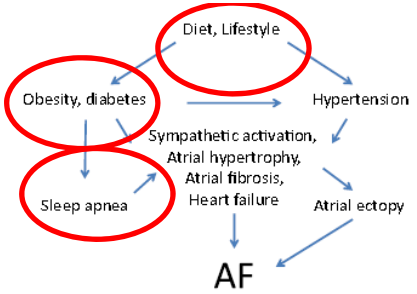
JAMA. 2013;310(19):2050-2060. doi:10.1001/jama.2013.280521



Significant reduction in BMI and Waist circumference

Figure Legend:

Changes in Waist Circumference and Body Mass Index From Baseline (Enrollment) to 15 Months' Follow-upError bars indicate 95% confidence intervals. BMI indicates body mass index, calculated as weight in kilograms divided by height in meters squared. A, Between-group level of significance: P = .21 at time 0, P = .01 at 3 months, P < .001 at 6, 9, 12, and 15 months. B, Between-group level of significance: P = .13 at time 0, P < .001 at 3, 6, 9, 12, and 15 months.



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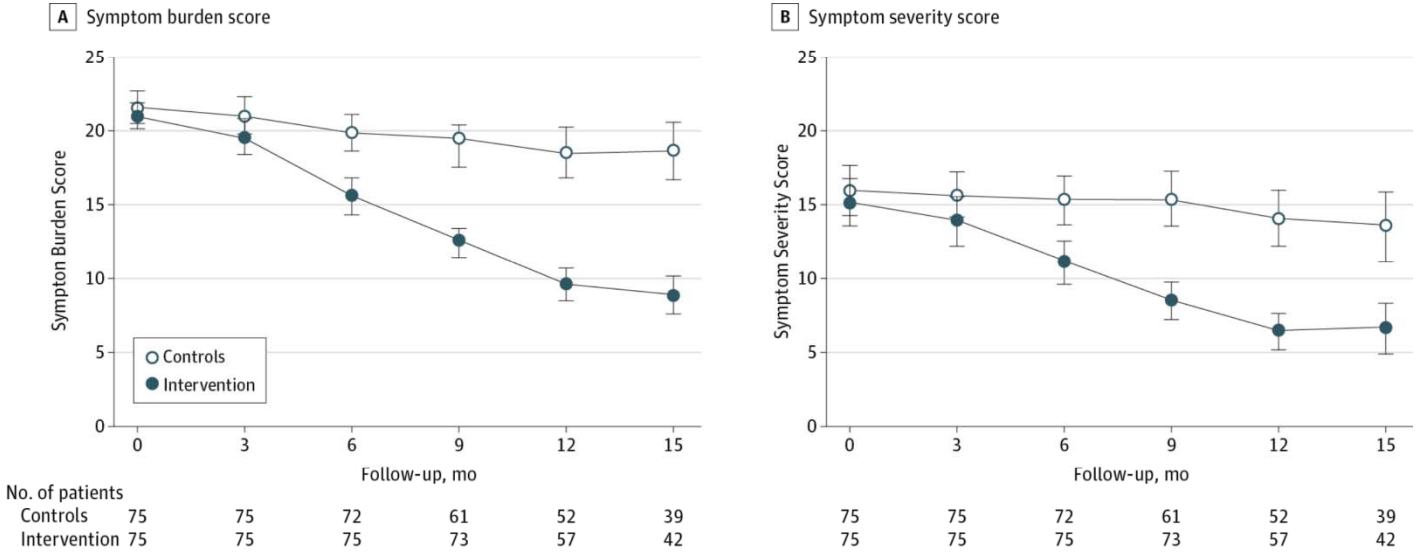
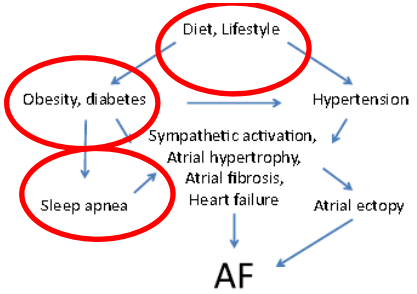


Significant reduction in AF symptom burden score and symptom severity score

Figure Legend:

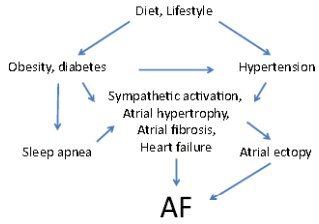
Changes in Atrial Fibrillation Symptom Scale (AFSS) Scores Over Study Follow-upError bars indicate 95% confidence intervals. A, Between-group level of significance: P = .41 at time 0, P = .12 at 3 months, P < .001 at 6, 9, 12, and 15 months. B, Between-group level of significance: P = .49 at time 0, P = .17 at 3 months, P < .001 at 6, 9, 12, and 15 months.

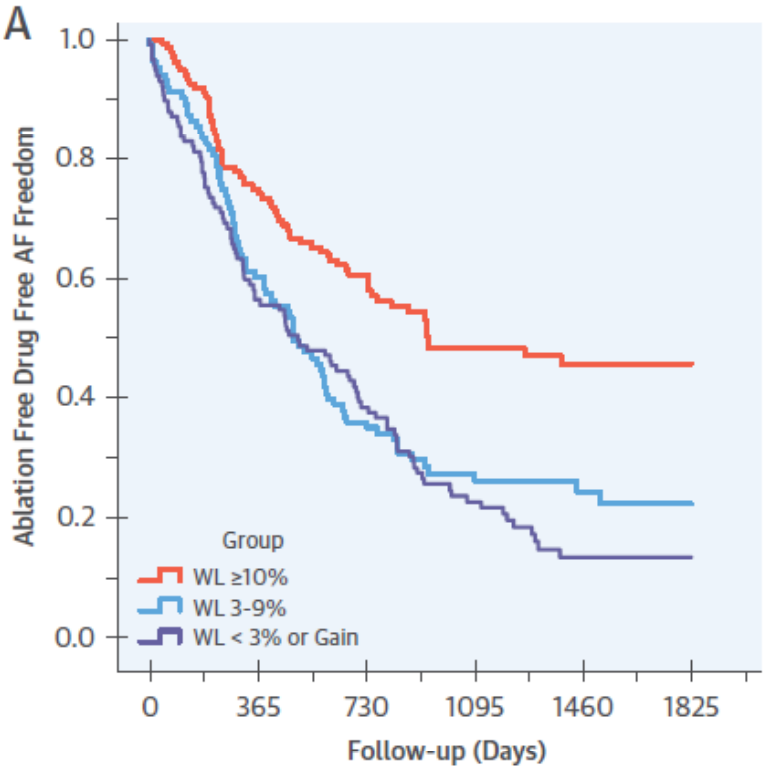
AF episodes and duration



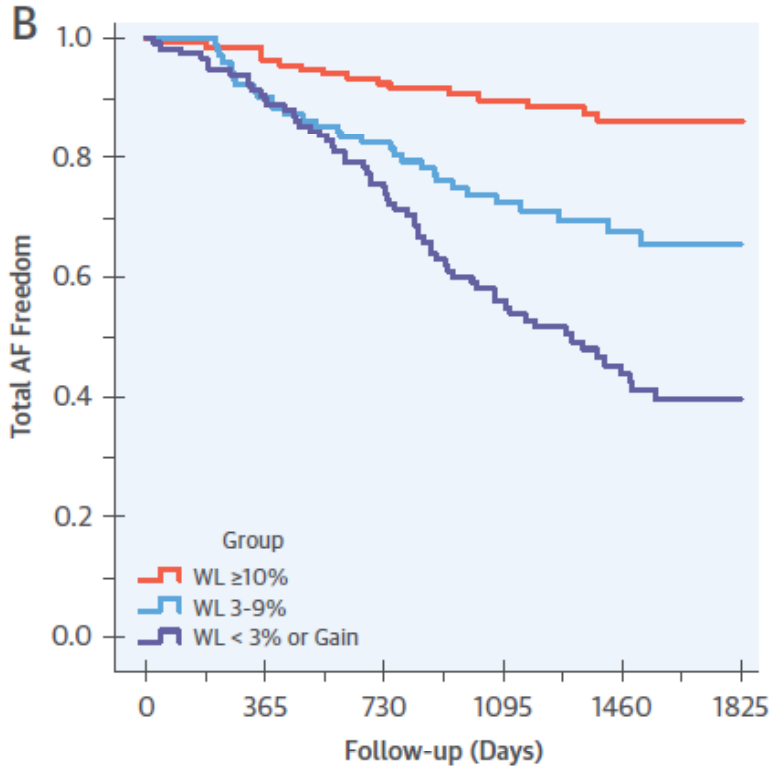
- Mean number of episodes decreased from 3.3 to 0.62 – on 7 day Holters done at baseline and 12 months
- Duration of AF decreased from 19.3 hours to 8.2 hours ($p<0.001$ for both)
- No change in the control group
- Also noted improvement in LA area and LV mass

LEGACY: cohort study





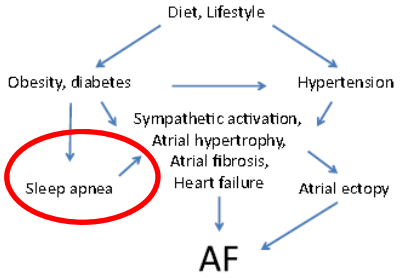
Time (Days)	0	365	730	1095	1460	1825
≥10 WL	135	101	72	42	31	18
3-9% WL	103	62	36	22	13	7
<3% WL or gain	117	66	44	22	11	9



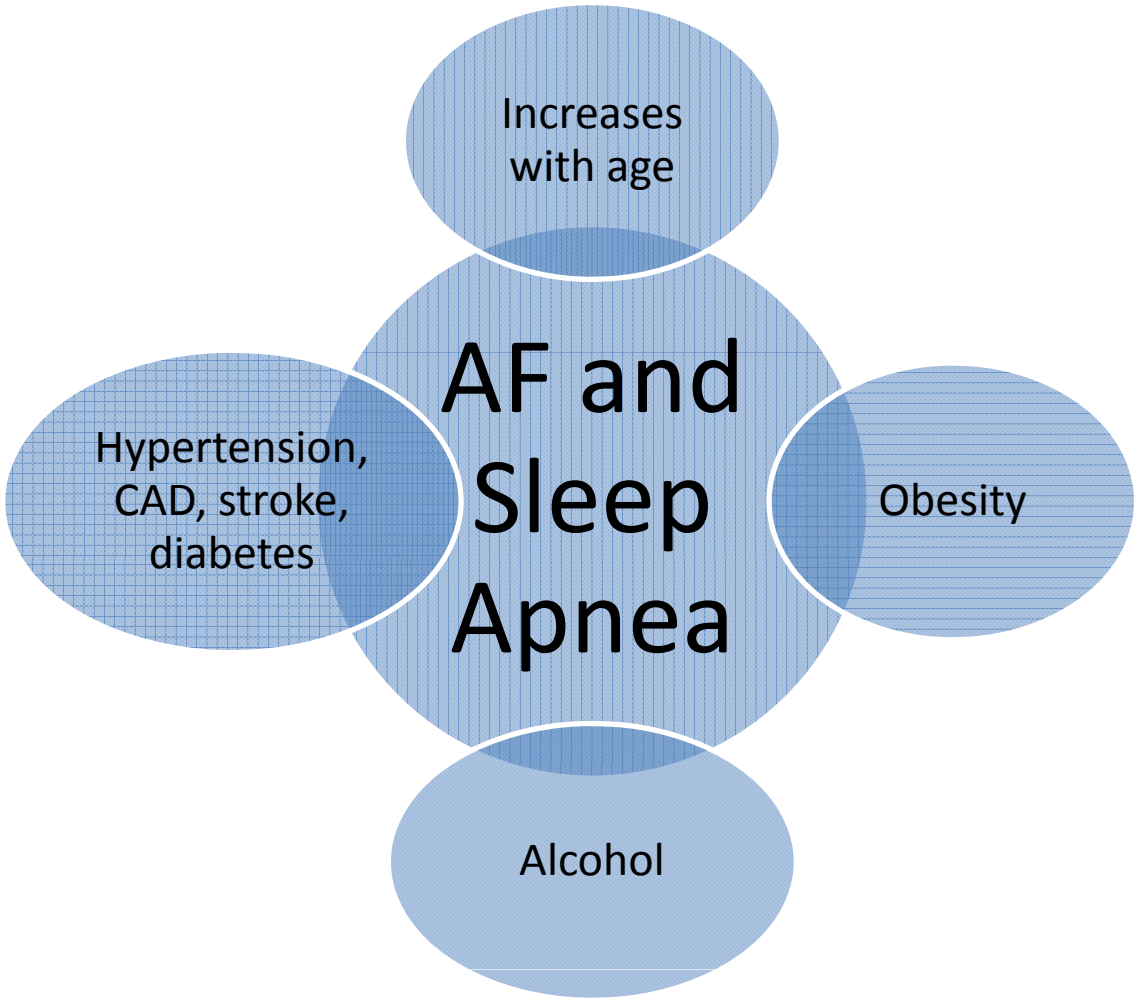
0	365	730	1095	1460	1825
135	130	114	86	67	36
103	93	83	57	35	22
117	105	85	53	32	22

Pathak et al JACC 2015; 2159-69

Sleep Apnea and AF



Associated Factors with OSA



Franklin KA and Lindberg E, J Thorac Dis 2015;7(8):1311-1322

Arrhythmogenic Mechanisms: Sleep apnea in AF Increase in LVEDP

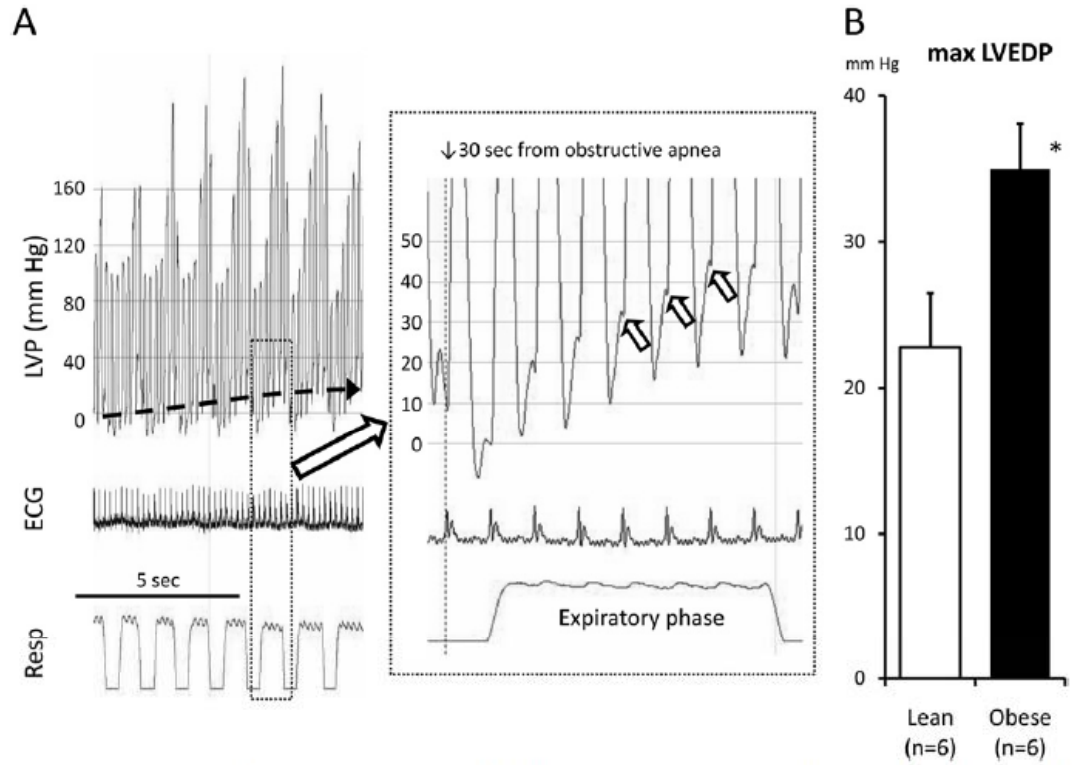


Figure 3 Left ventricular pressure changes during obstructive apnea. **A:** Obstructive apnea progressively increased left ventricular end-diastolic pressure (LVEDP), with a gradual increase *(dashed arrow)* superimposed on periodic changes associated with respiration *(open arrows)*. **B:** Maximum LVEDP during obstructive apnea was higher in obese vs lean rats.

Iwasaki et al. Heart Rhythm 2012;9:1409-1416

Arrhythmogenic Mechanisms: Sleep apnea in AF Left atrial distension

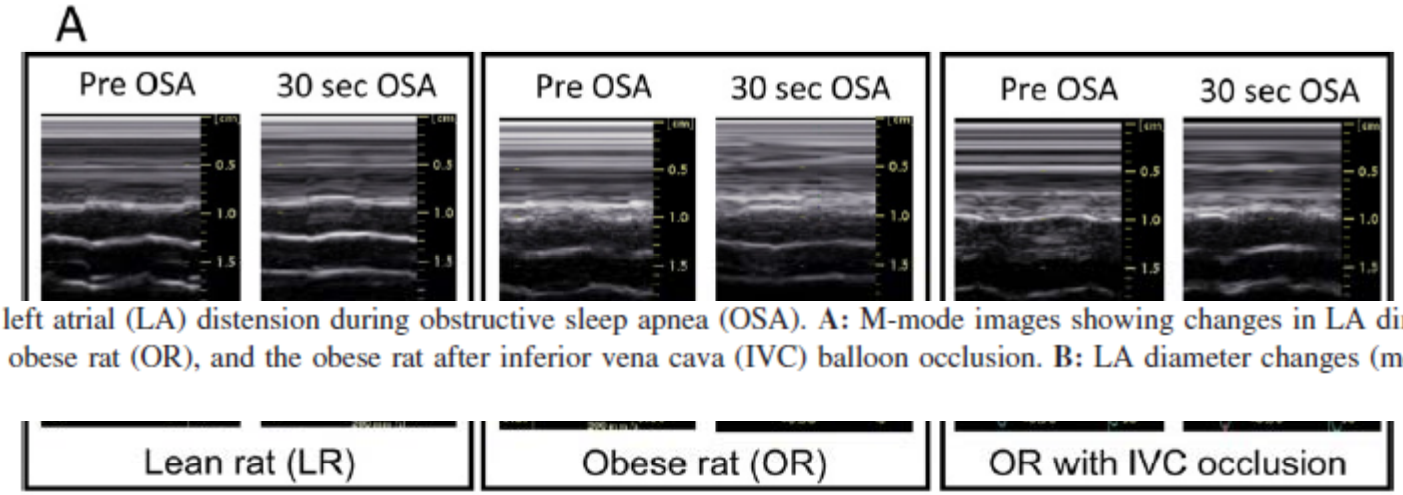
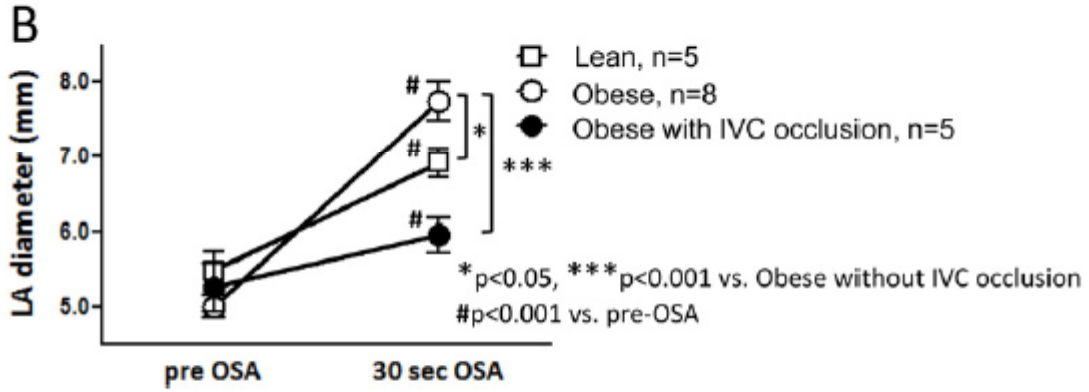
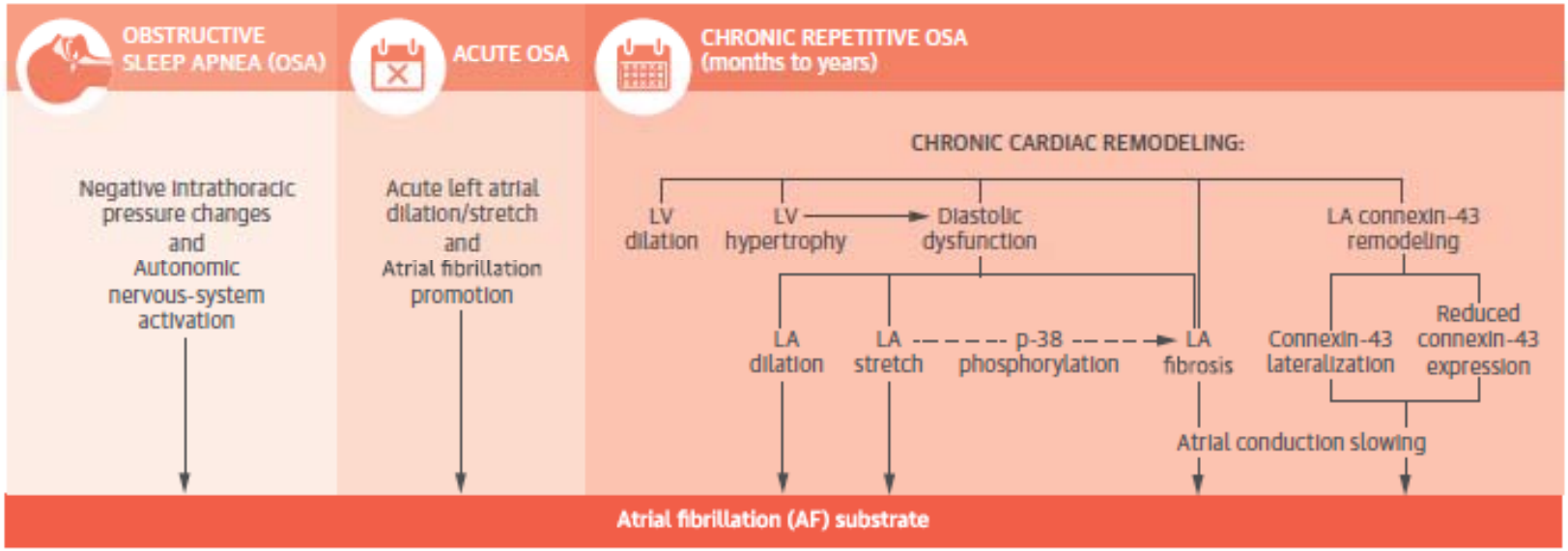
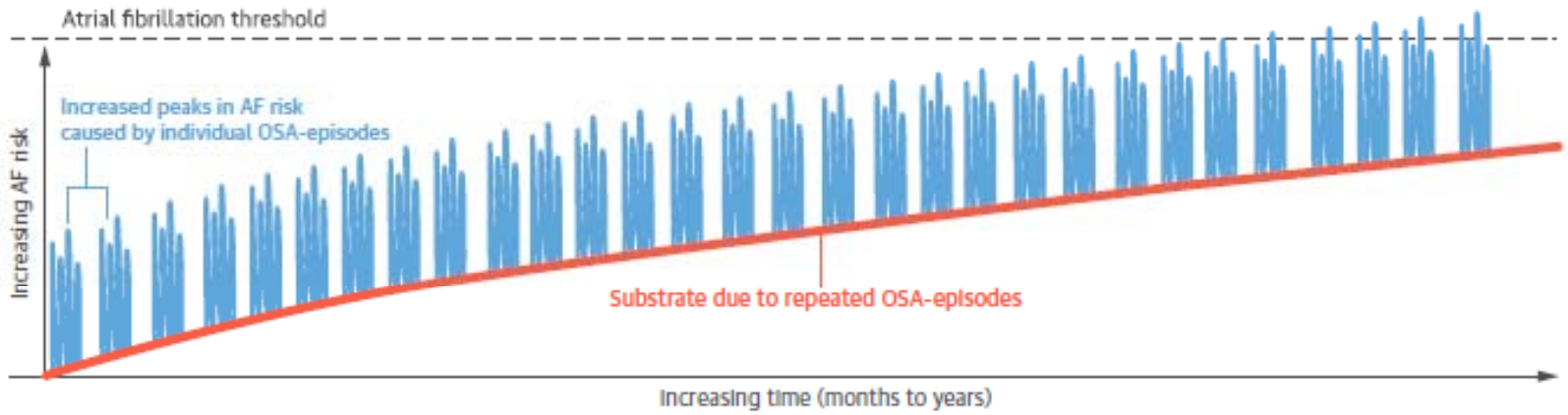


Figure 4 Acute left atrial (LA) distension during obstructive sleep apnea (OSA). **A:** M-mode images showing changes in LA dimensions with OSA in a lean rat (LR), an obese rat (OR), and the obese rat after inferior vena cava (IVC) balloon occlusion. **B:** LA diameter changes (mean ± SEM).



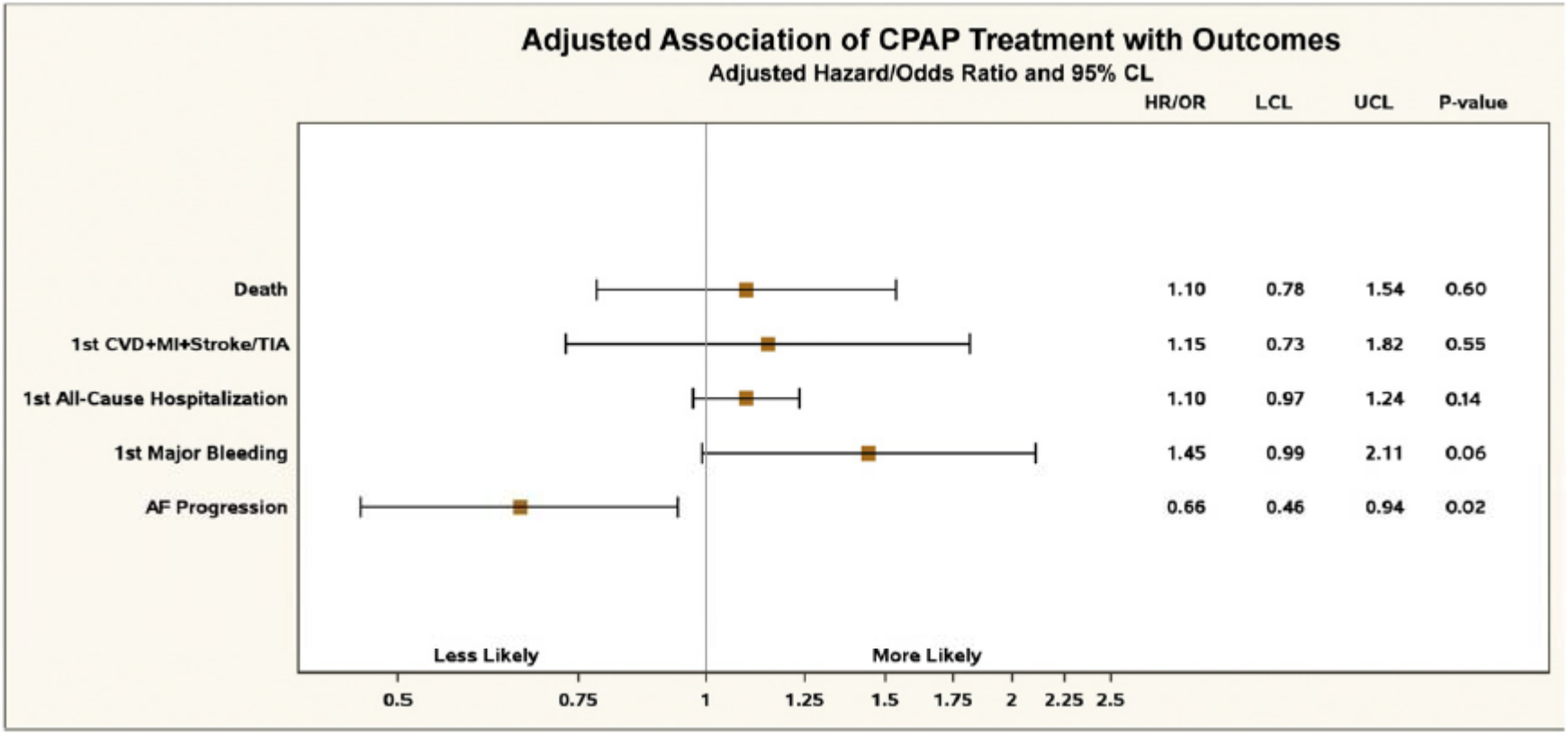
Iwasaki et al. Heart Rhythm 2012;9:1409-1416





Iwasaki, Y., et al., J Am Coll Cardiol. 2014; 64(19):2013-23.

ORBIT AF – 1 in 5 patients had OSA



Holmqvist et al Am Heart J 2015;169:647-654.e2

Effect of CPAP on Cardiovascular Outcomes

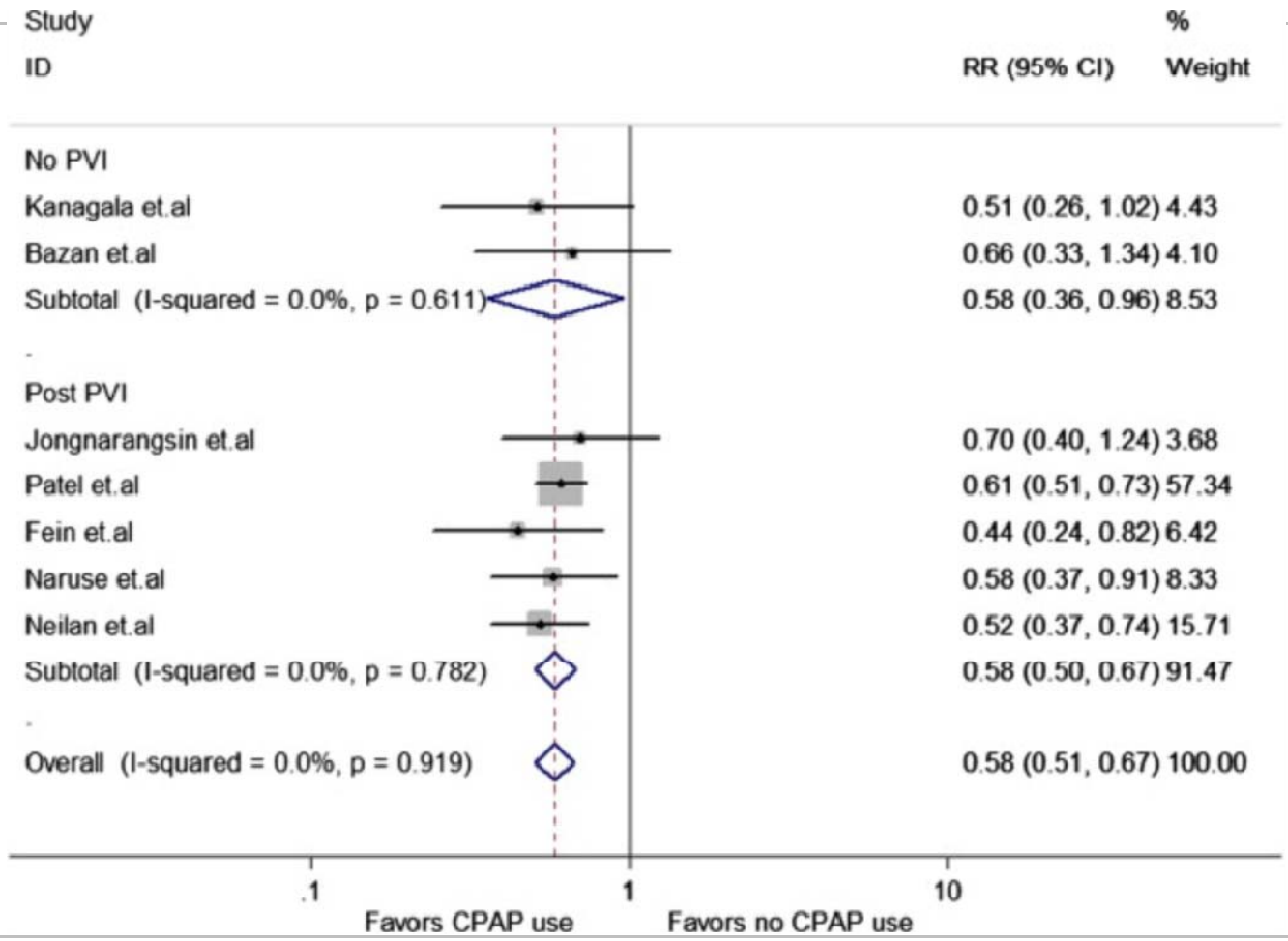
Outcome	CPAP (n = 937) No. of events (events/100 patient-years)	No CPAP (n = 687) No. of events (events/100 patient-years)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
All-cause death	68 (4.44)	54 (4.86)	0.92 (0.67-1.25)	.58	1.10 (0.78-1.54)	.60
First hospitalization (all-cause)	471 (43.9)	329 (41.9)	1.05 (0.93-1.18)	.42	1.10 (0.97-1.24)	.14
CV death, MI, stroke/TIA	57 (3.78)	41 (3.73)	1.02 (0.68-1.52)	.94	1.15 (0.73-1.82)	.55
Major bleeding	71 (4.81)	43 (3.99)	1.20 (0.85-1.71)	.29	1.45 (0.99-2.11)	.06

Outcome	CPAP (n = 602) No. of events (percent)	No CPAP (n = 411) No. of events (percent)	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Progression of AF type	94 (16)	75 (18)	0.74 (0.55-0.99)	.04	0.66 (0.46-0.94)	.02

Holmqvist et al. AHJ 2015; 169:647-654.e.2

JACC Journals

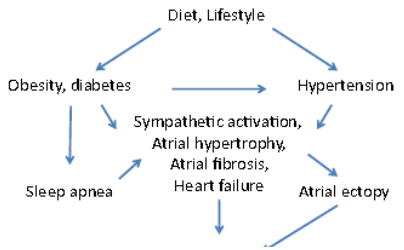
Effect of Obstructive Sleep Apnea Treatment on Atrial Fibrillation Recurrence

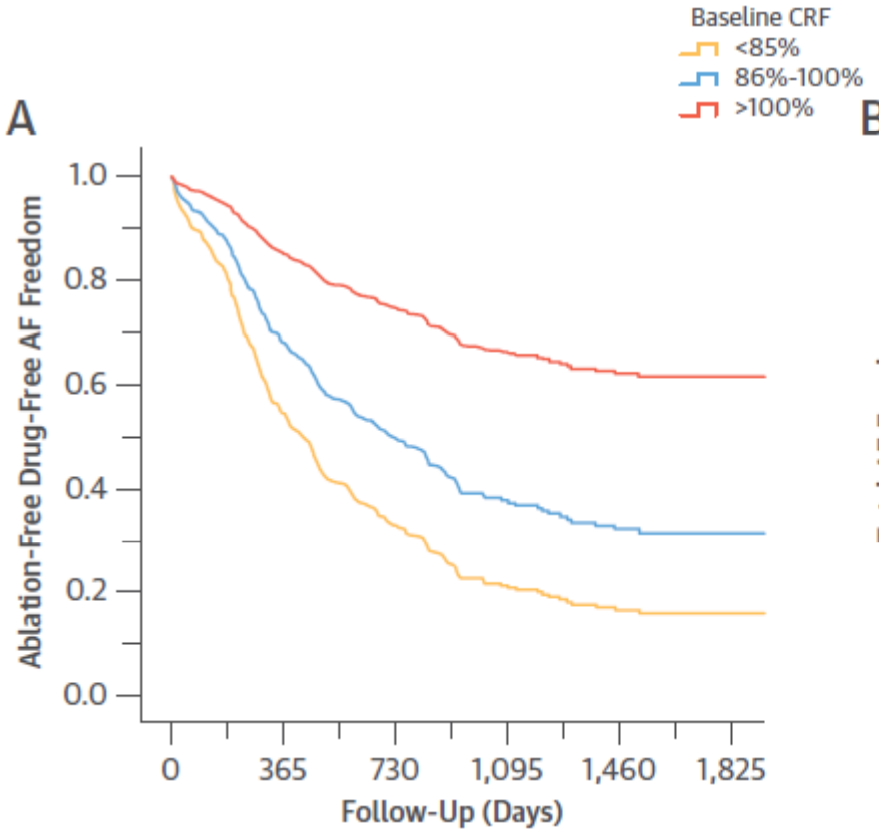


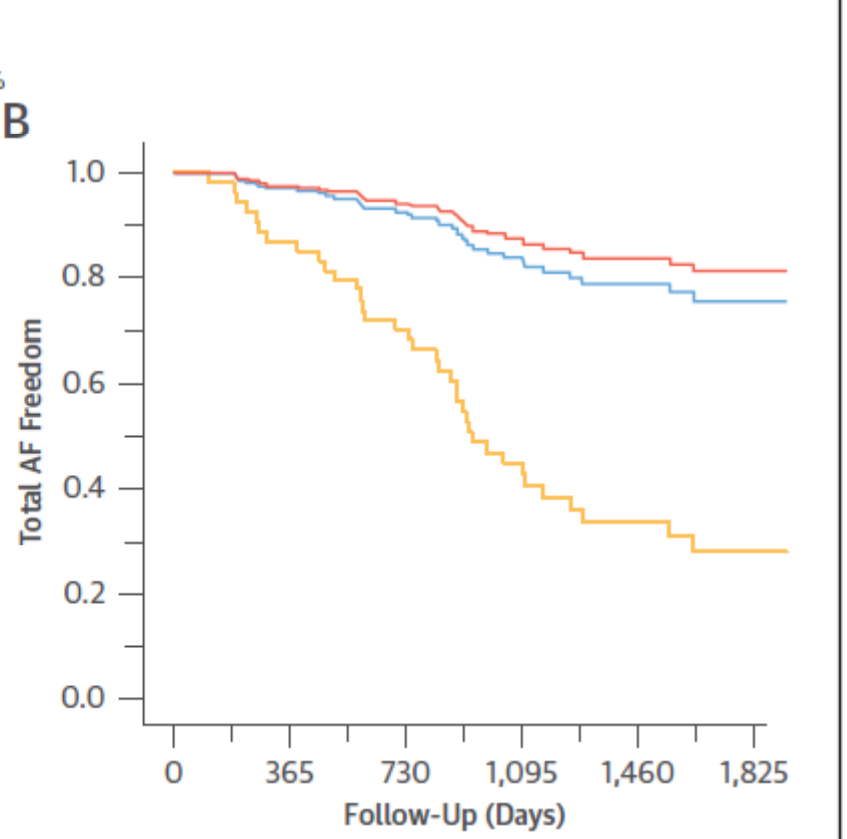
JACCCEP. 2015;1(1):41-51.
doi:10.1016/j.jacep.2015.02.014

I am unable to sleep during meetings.

CARDIO FIT





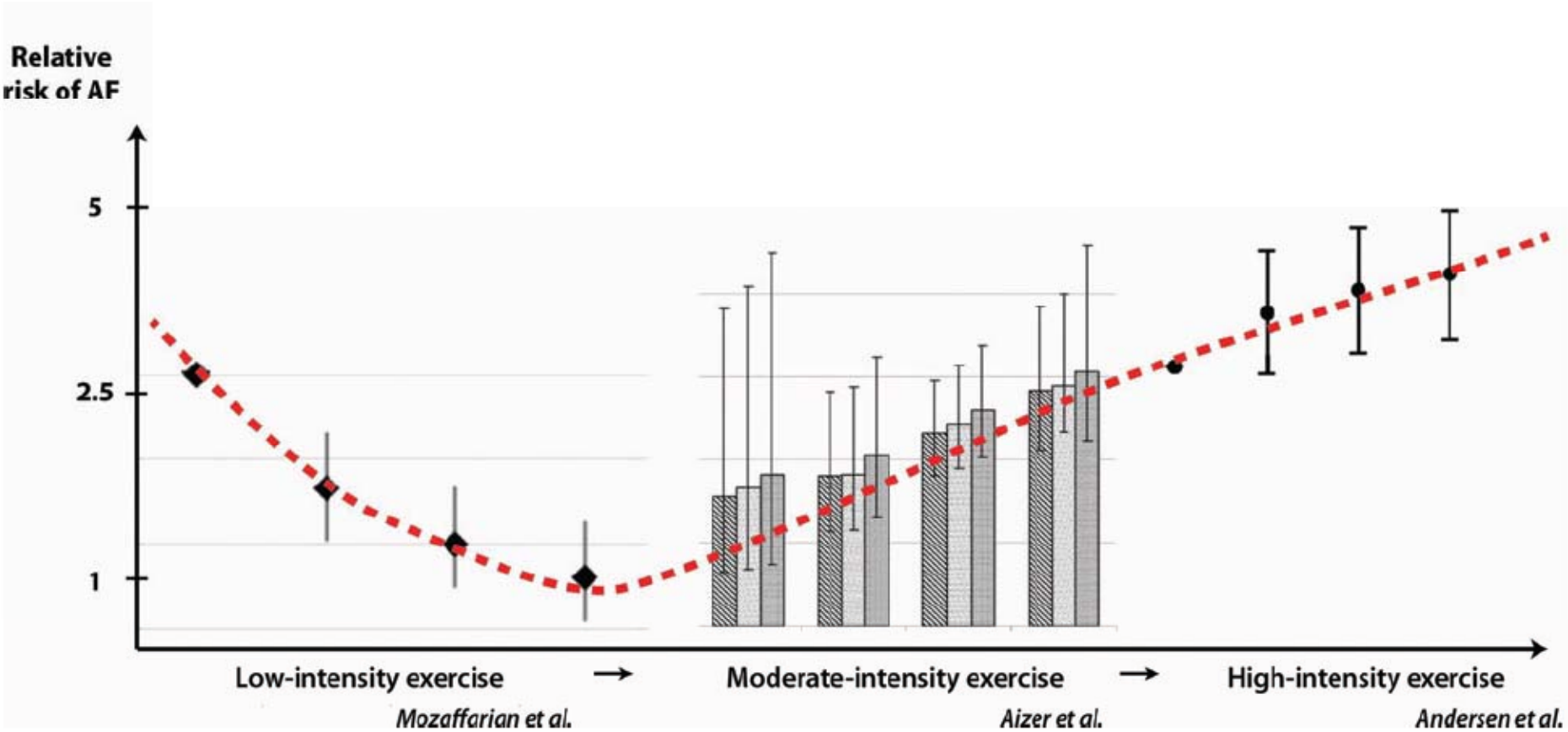


Time (Days)	0	365	730	1,095	1,460	1,825
<85% Predicted	95	54	36	16	12	6
86%-100% Predicted	134	93	56	34	19	11
>100% Predicted	79	63	50	36	26	18

0	365	730	1,095	1,460	1,825
95	78	58	33	20	11
134	133	119	86	56	33
79	78	63	51	36	21

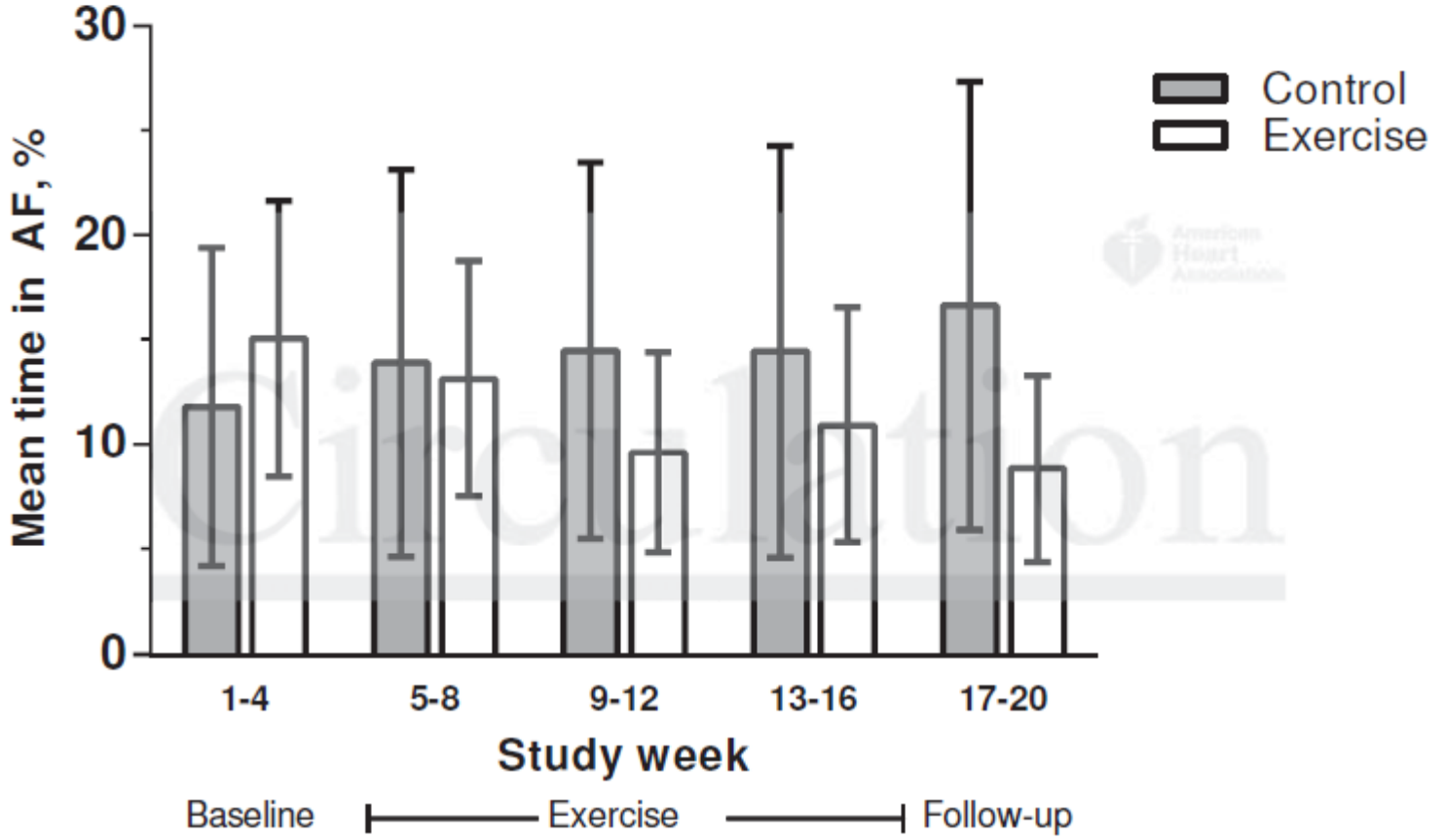
Pathak et al JACC 2015;985-96

J shaped curve for AF?



La Gerche et al EHJ 2013;3599-3602

High Intensity Interval Training found to be superior to reduce AF

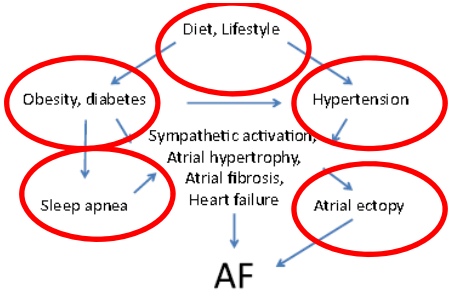


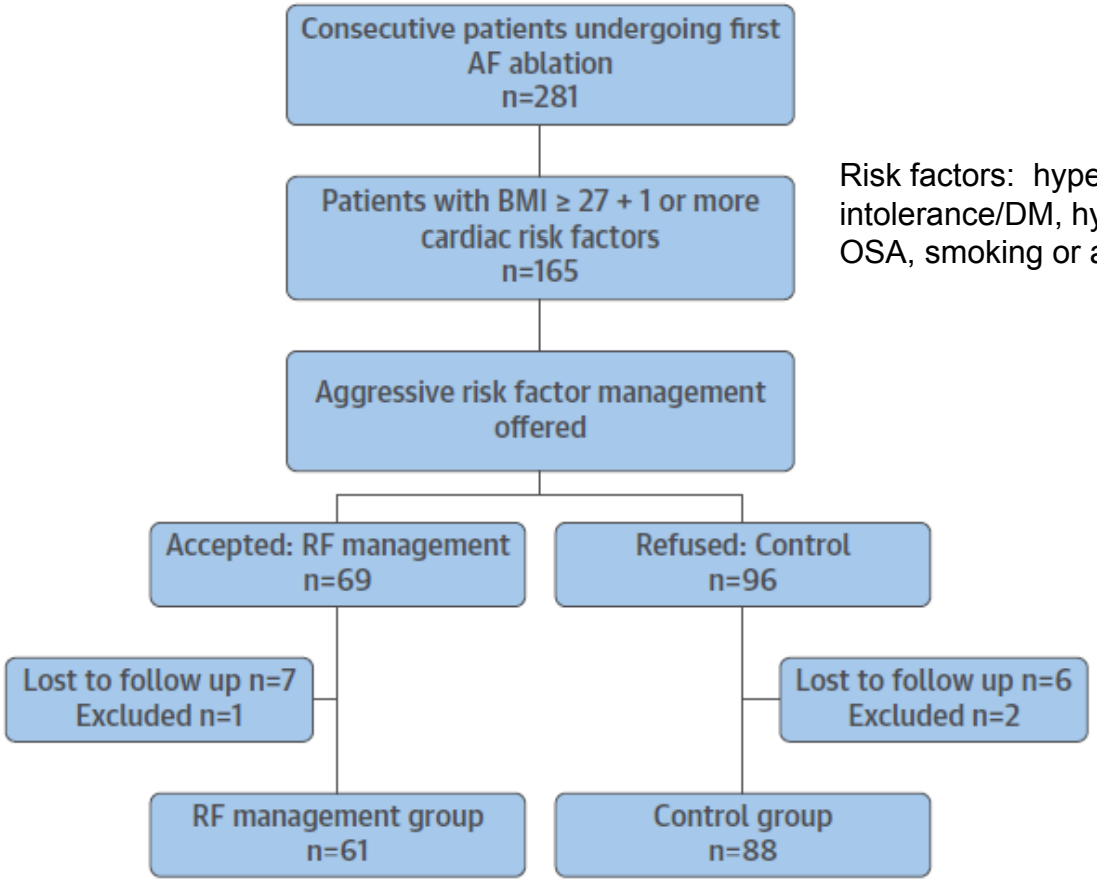
Malmo et al Circulation 2016

Characteristic	Control (N=25)	Exercise (N=26)
Male sex – no. (%)	22 (88)	20 (77)
Age – yr	62±9	56±8*
Paroxysmal atrial fibrillation– no. (%)	14 (56)	15 (58)
Height – cm	182±8	180±8
Weight –kg	93.7±16.9	91.4±15.5
Medical history – no. (%)		
Stroke	2 (8)	1 (4)
Diabetes mellitus	1 (4)	2 (8)
Hypertension	8 (32)	10 (38)
Coronary artery disease	2 (8)	0 (0)
Medication at baseline – no. (%)		
Antiplatelet therapy	7 (28)	6 (23)
Anticoagulation	11 (44)	14 (54)
Antiarrhythmic agents	15 (60)	16 (62)
Flecainide	9 (36)	7 (27)
Amiodarone	2 (8)	7 (27)
Sotalol	4 (16)	2 (8)
Beta-blockers	7 (28)	8 (31)
Digoxin	0	1 (4)
Calcium blockers	5 (20)	4 (15)
ACE- inhibitors/Angiotensin II-antagonists	10 (40)	8 (31)
Aldosterone antagonists	1 (4)	0
Thiazides	4 (16)	4 (15)
Alpha–blocking agents	1 (4)	0
Statins	6 (24)	4 (15)

Malmo et al Circulation 2016

ARREST-AF Cohort Study





Risk factors: hypertension, glucose intolerance/DM, hyperlipidemia, OSA, smoking or alcohol excess

Pathak et al. JACC 2014; 64: 2222-31

Intervention

- Risk factor management in a physician-directed clinic at the time of initial assessment
- Attended RFM clinic every 3 months
- BP measured 3x/day with home BP monitor
- EST done to optimize BP therapy
- Lifestyle advice regarding salt restriction
- BP< 130/80
- Structured motivational, goal-directed program with face-to-face counseling for weight reduction – meal plan and behaviour modification
- Lipid management with medications or lifestyle
- Glycemic control – lifestyle, medications, specialized diabetes clinic if $HbA_{1c} > 7\%$
- Sleep testing in hospital
- Smoking cessation
- Alcohol reduction

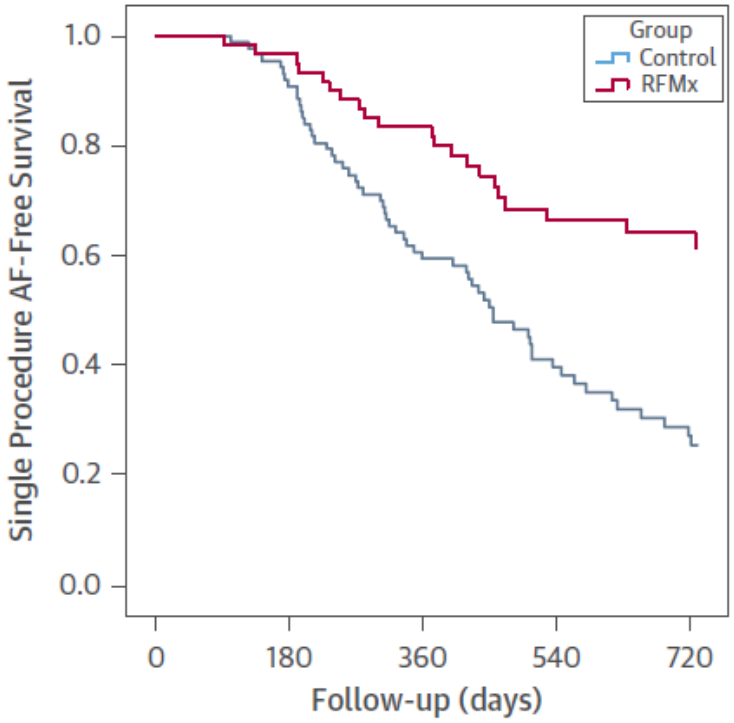
Pathak et al. JACC 2014; 64: 2222-31

Effect of RFM intervention

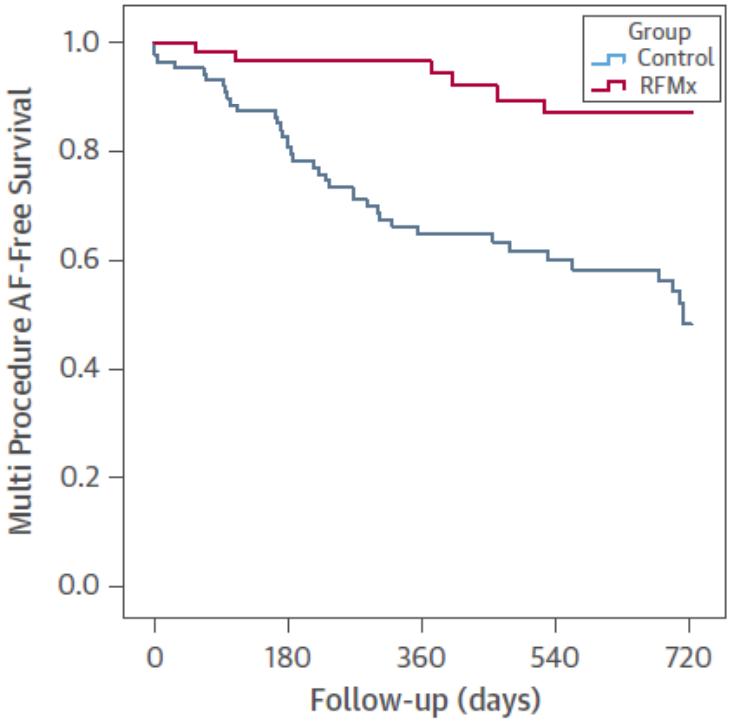
- Significant decrease in weight 100 to 87.5
- Drop in SBP from 161 to 127
- No patients with HbA1c >/= 7% at follow up
- Sleep apnea improved dramatically
- LA size decreased
- AF severity improved dramatically
- Median follow up 42 months

Pathak et al. JACC 2014; 64: 2222-31

Recurrence of AF



Time (days)	0	180	360	540	730
RFM	61	59	48	33	27
Control	88	79	51	28	16



0	180	360	540	730
61	55	46	32	25
88	72	51	36	23

Pathak et al. JACC 2014; 64: 2222-31

Integrated Management Approach to AF

Baseline Characteristics	AF Clinic (n = 168)	Usual Care (n = 168)	P value
Age (mean ± SD)	62.8 ± 14.5	61.9 ± 15.4	0.56
Female	58 (39.5%)	64 (38.1%)	0.82
Hypertension	64 (38.1%)	62 (36.9%)	0.91
Diabetes	20 (11.9%)	18 (10.7%)	0.86
Congestive heart failure	17 (10.1%)	15 (8.9%)	0.85
Stroke	9 (5.4%)	11 (6.5%)	0.82
Prior myocardial infarction	10 (6%)	11 (6.5%)	1
Peripheral vascular disease	6 (3.6%)	3 (1.8%)	0.5
Cerebrovascular disease	2 (1.2%)	5 (3%)	0.45
Chronic pulmonary disease	22 (13.1%)	16 (9.5%)	0.39
Sleep apnea	16 (9.5%)	11 (6.5%)	0.42
LVEF (mean ± SD)	57.3 ± 8.2	56 ± 9.3	0.17
$CHADS_2$ (mean ± SD)	1.0 ± 1.2	1.1 ± 1.2	0.4
CHADS-VASC (mean ± SD)	2.0 ± 1.7	2.0 ± 1.7	0.85
BMI>27	117 (58.0%)	-	

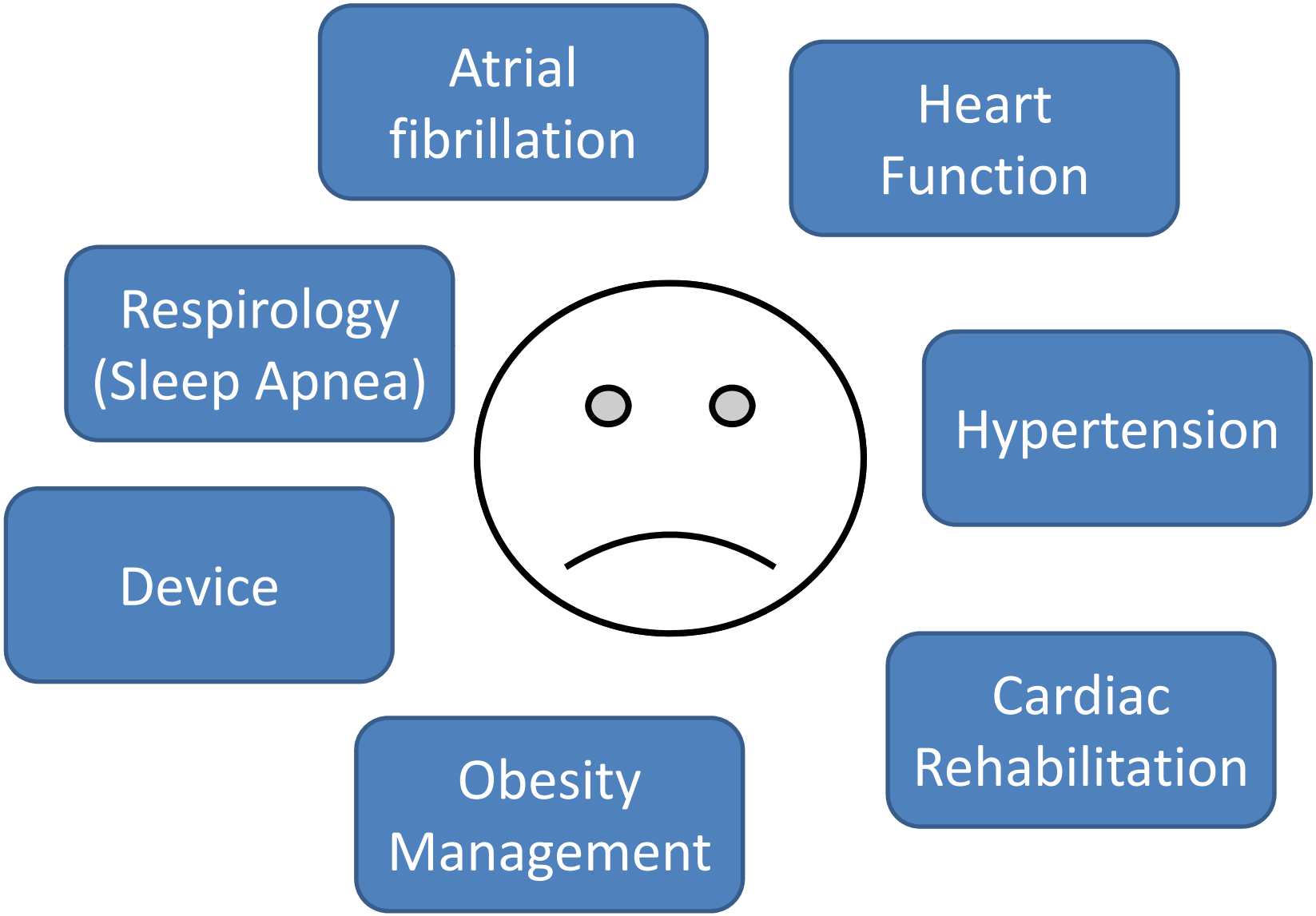
Present at baseline, not when screening performed

Carter et al. JAHA 2016; 25;5(1)

What are the clinical questions that remain unanswered in risk factor management in AF?

Risk Factor	Current Evidence	Research needed
Obesity	2 RCTs at same center, both single center; QOL, recurrence of AF; used 7 day Holters to quantify AF	How best to promote and maintain weight loss over long term
Alcohol Intake	-	Effect of alcohol reduction on recurrence of AF is required
Physical Activity/Exercise	Recent RCT suggests aerobic interval training	Exact exercise prescription - ?dose response relationship
Sleep apnea	SR suggests reduction in AF	RCT with other lifestyle interventions is required to show benefit of screening and treatment ?mild sleep apnea
Hypertension	SMAC AF – results in one year; SPRINT	In combination with other risk factors
Diabetes	Abed et al; ARREST AF	Effect of glycemic control on recurrence of AF is unknown

Other Considerations:
Dietary consumption – fish oil???
Air pollutions
Early intervention with catheter ablation


Atrial fibrillation
Heart Function
Respirology (Sleep Apnea)
Hypertension
Device
Cardiac Rehabilitation
Obesity Management

Conclusions

- Good evidence that risk factors lead to AF and are associated with progression
- Some low quality evidence that modification of these improve AF episodes
- Currently, insufficient evidence to result in a systematic change in AF management

Thank you!