Impact of Alcohol Abstinence in Moderate Drinkers with Atrial Fibrillation: Results from the Alcohol-AF Randomized Controlled Trial

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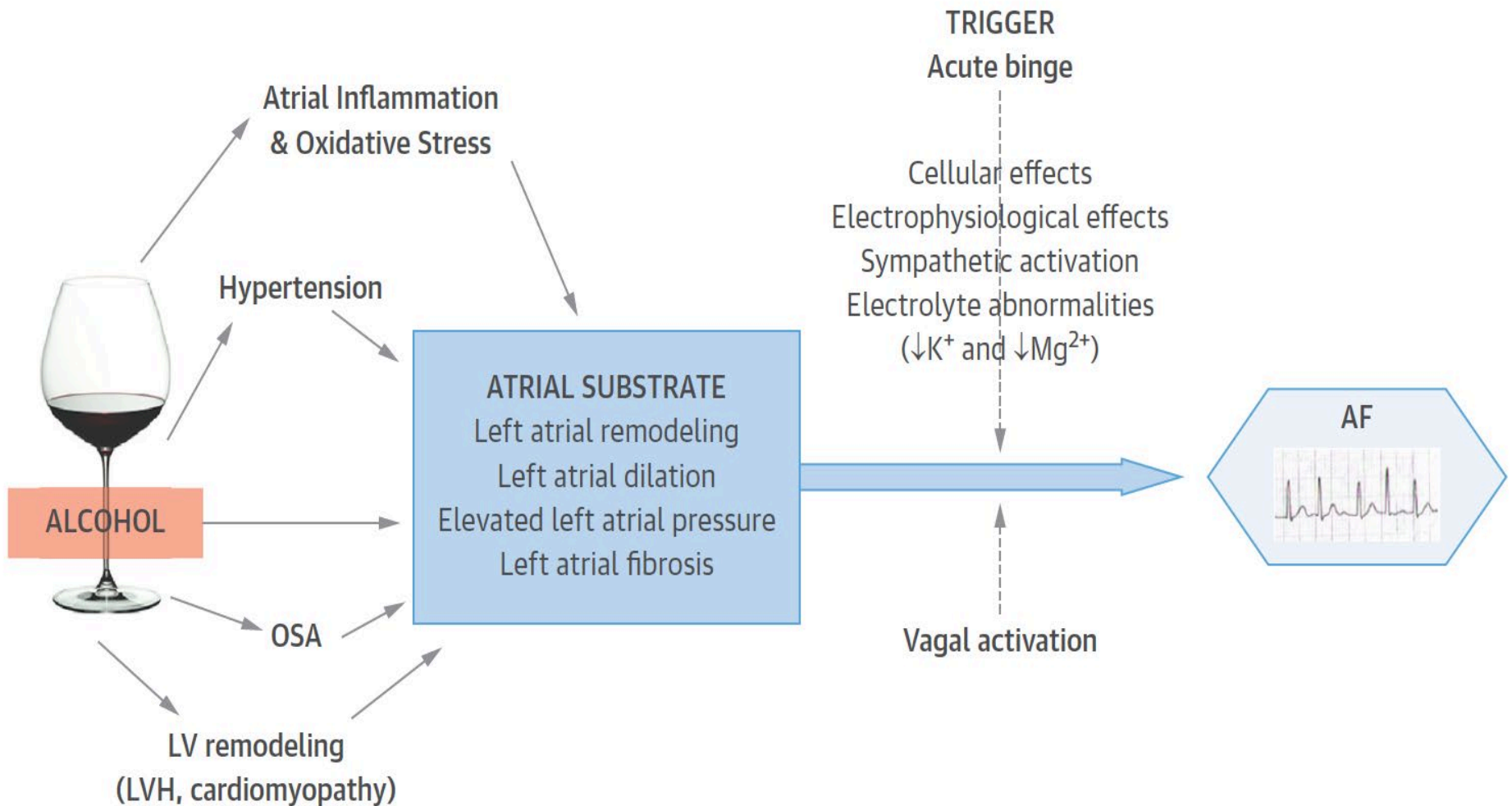
The Royal Melbourne Hospital

Australian New Zealand Clinical Trials Registry ACTRN 12616000256471

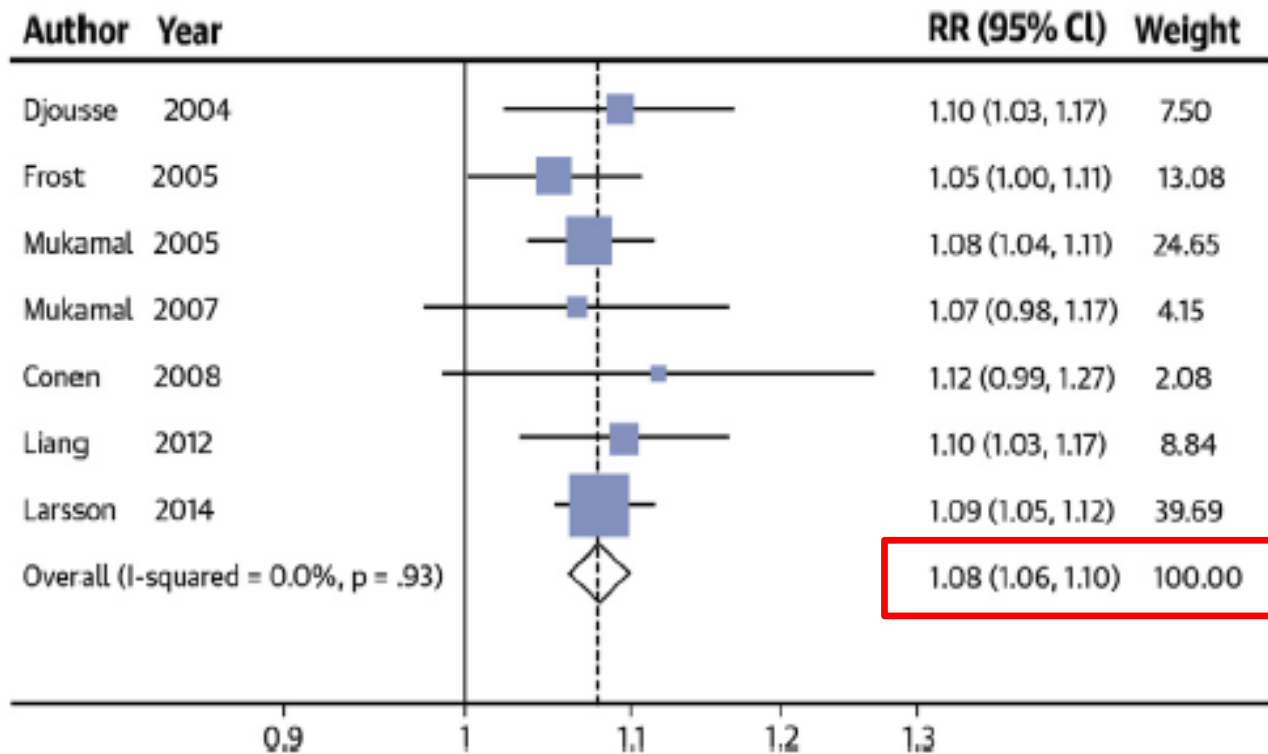American College of Cardiology – 67th Scientific Sessions, March 18, 2019

Disclosures

- Investigator-initiated and funded study.

- No commercial sponsor

- Dr Voskoboinik is supported by an Australian National Health and Medical Research Council and National Heart Foundation scholarship, Baker Research Institute Bright Sparks scholarship & CSANZ Travelling Fellowship.

Multiple mechanisms linking alcohol to AF

Voskoboinik A et al. JACC 2016;68:2567-76

Relative risk (RR) of incident AF
per 1 drink/day increment in alcohol consumption

Author	Year	RR (95% CI)	Weight
Djousse	2004	1.10 (1.03, 1.17)	7.50
Frost	2005	1.05 (1.00, 1.11)	13.08
Mukamal	2005	1.08 (1.04, 1.11)	24.65
Mukamal	2007	1.07 (0.98, 1.17)	4.15
Conen	2008	1.12 (0.99, 1.27)	2.08
Liang	2012	1.10 (1.03, 1.17)	8.84
Larsson	2014	1.09 (1.05, 1.12)	39.69
Overall (I-squared = 0.0%, p = .93)		1.08 (1.06, 1.10)	100.00

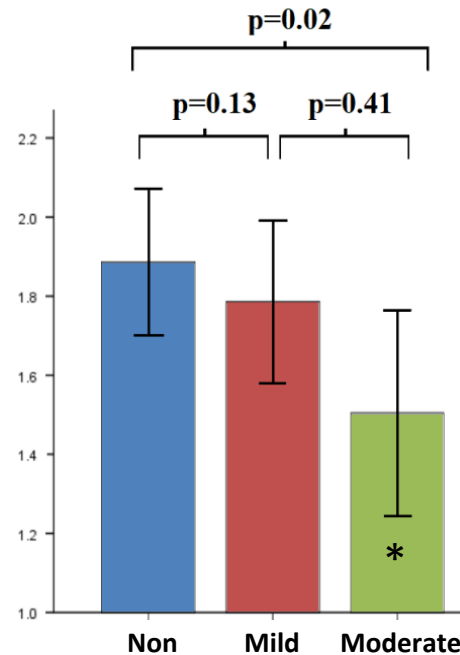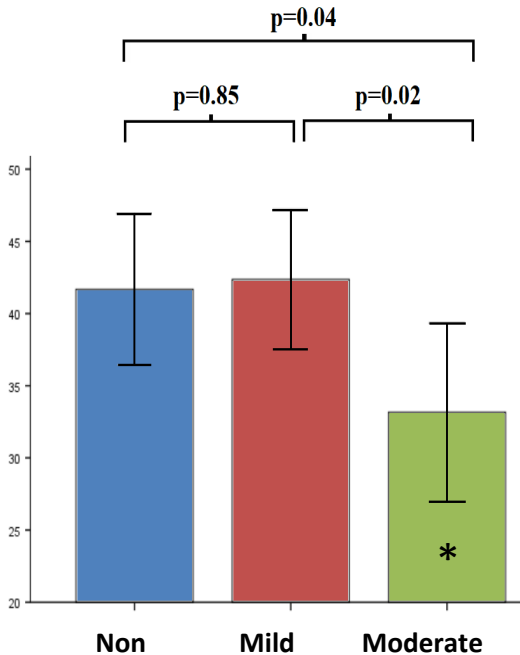**CENTRAL ILLUSTRATION** Forest Plot of Relative Risks of Atrial Fibrillation
Per 1 Drink/Day Increment in Alcohol Consumption

Larsson SC et al. JACC 2014;64(3):281-9

Adverse atrial remodelling and higher AF recurrence rates with increasing alcohol consumption

Atrial substrate

AF Recurrence rates following ablation

LA CONDUCTION VELOCITY

LA MEAN VOLTAGE

Voskoboinik A, et al. Heart Rhythm 2019;16(2):251-259.
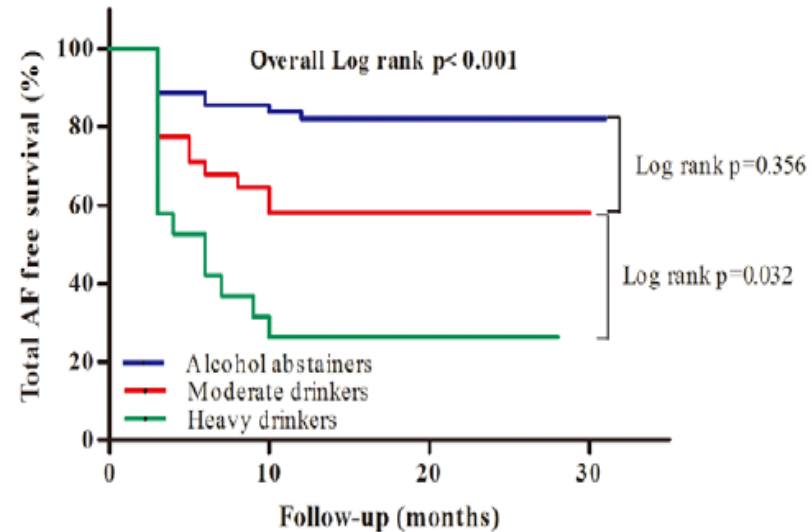
Qiao Y, et al. J Am Heart Assoc 2015

*   moderate: 7 - 28 standard drinks per week

Alcohol-AF trial

No randomized controlled trial to date looking at the impact of alcohol abstinence in moderate drinkers with atrial fibrillation.

Inclusion criteria:

- **Paroxysmal AF** (atrial fibrillation and/or flutter), with minimum 2 episodes in the last 6 months **or persistent AF** requiring cardioversion (all patients in sinus rhythm and on stable medical therapy at randomization)

- Average alcohol intake **≥ 10 standard drinks per week** (1 SD ~ 12g ETOH)

Key exclusion criteria:

- Permanent AF
- Severe left ventricular systolic dysfunction (LVEF < 35%)
- Alcohol dependence or significant psychiatric comorbidity
- Liver cirrhosis

Study design

- Multicenter, prospective, open-label, randomized controlled trial at six Australian hospitals.

- Randomization 1:1 to undertake abstinence or continue usual consumption.

- Four week run-in phase

- Comprehensive rhythm monitoring

  - Implantable loop recorder or existing pacemaker

  - Twice daily AliveCor® mobile phone app in conjunction with Holter monitoring

- Follow-up 6 months

Group allocation

Abstinence arm:

- All patients counselled to abstain completely.
- Provided verbal and written advice to assist with compliance
- Urine testing for alcohol metabolite (urine ETG)
- Positive reinforcement through monthly contact with study investigators

Control arm:

- Allowed to continue usual alcohol consumption.
- Not required to increase their usual drinking as part of the trial.

Co-primary endpoints – at 6 months

(1) Freedom from AF recurrence, defined as any atrial tachyarrhythmia lasting ≥ 30 seconds (after a 2-week blanking period)

(2) AF burden, defined as percentage of time in AF during the 6-month follow-up period.

- calculated based on the time-weighted average of the proportion of EKGs during the six months which indicated the presence of AF.

- Blinded adjudication by two cardiologists
- Primary endpoints shortened from 12 months to 6 months in June 2017 by the steering committee due to challenges with recruitment, in particular unwillingness to be randomized to abstinence for 12 months.
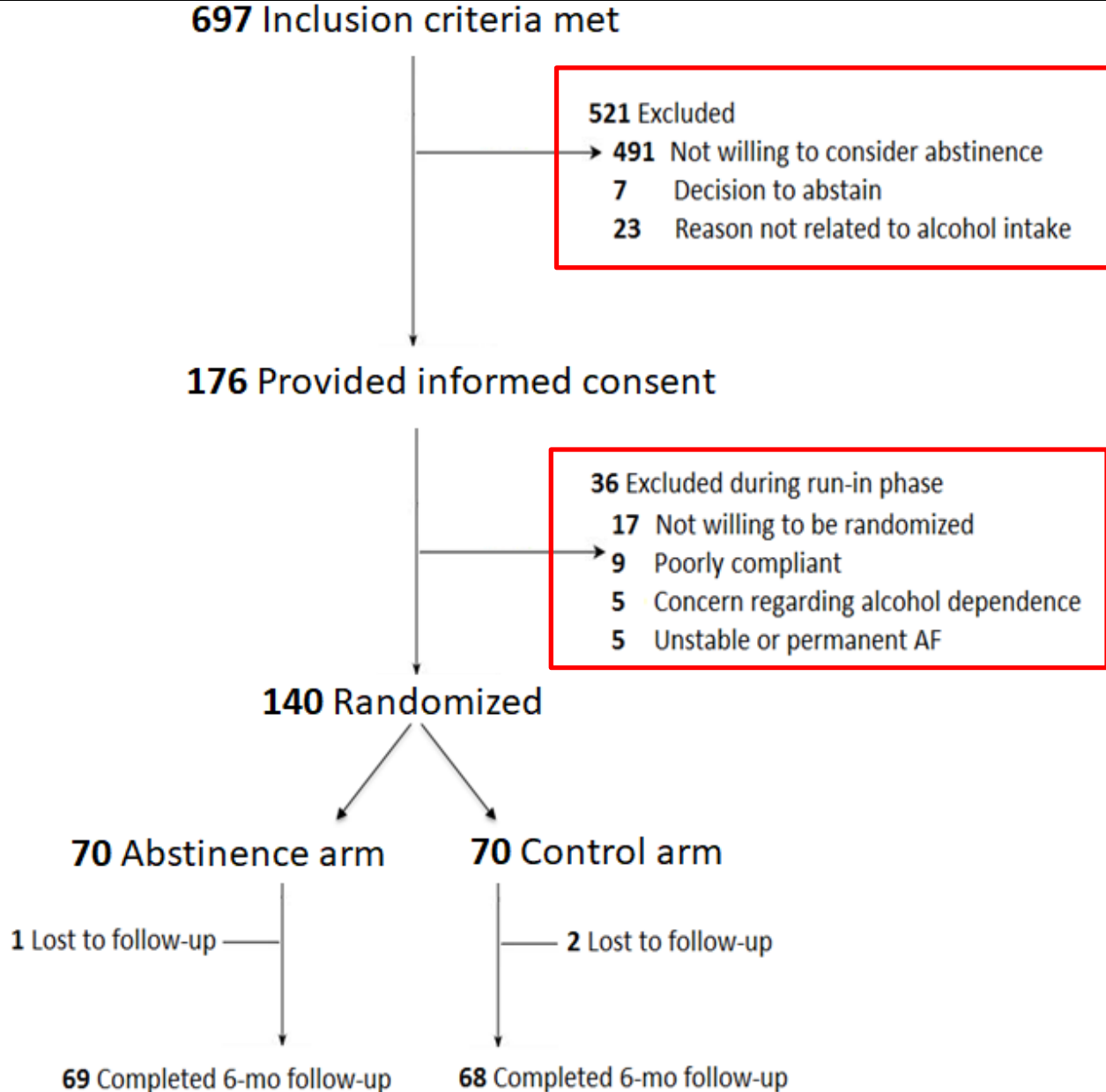
Secondary endpoints – at 6 months

- Change in weight
- Change in systolic and diastolic blood pressure
- Change in AF symptom severity
- AF-related hospitalizations
- Structural remodelling (cardiac MRI)

Pre-specified statistical analysis

- **Power calculation: 70 patients in each group** to provide a power of 0.8 at an alpha value of 0.05 to detect a minimum absolute difference in recurrence of 20% between groups (assuming a 30% recurrence rate).

- **Intention-to-treat analysis.**

- Performed by independent statisticians masked to group allocation.

- Time-to-event analyses for AF recurrence performed with Kaplan-Meier plots and the log-rank test. Univariate and multivariate analyses were performed using Cox's proportional hazards accounting for co-variates.

- AF burden: Shapiro-Wilk test performed to determine if the data was normally distributed. A student t-test was performed if data were normally distributed; otherwise a Mann-Whitney test was utilized.

CONSORT diagram

697 Inclusion criteria met

521 Excluded
- **491** Not willing to consider abstinence
- **7** Decision to abstain
- **23** Reason not related to alcohol intake

176 Provided informed consent

36 Excluded during run-in phase
- **17** Not willing to be randomized
- **9** Poorly compliant
- **5** Concern regarding alcohol dependence
- **5** Unstable or permanent AF

140 Randomized

70 Abstinence arm   **70** Control arm

1 Lost to follow-up   2 Lost to follow-up

69 Completed 6-mo follow-up   **68** Completed 6-mo follow-up

Baseline demographics

Parameter	Abstinence group (n=70)	Control group (n=70)
Age (years)	61.6±9.4	62.8±8.6
Gender (% male)	61 (87.1%)	58 (82.9%)
Weight (kg)	89.9±16.0	89.3±13.3
Body mass index (BMI)	28.4±4.4	28.5±4.5
Hypertension (%)	31 (44.3%)	26 (37.1%)
Diabetes mellitus (%)	5 (7.1%)	6 (8.6%)
TIA / stroke	7 (10.0%)	5 (7.1%)
Previous / current smoker	13 (18.6%)	11 (15.7%)
Obstructive sleep apnea	12 (17.1%)	16 (22.9%)
Coronary artery disease	10 (14.3%)	5 (7.1%)
Prior heart failure	6 (8.6%)	6 (8.6%)

# Baseline AF & clinical characteristics

Parameter	Abstinence group (n=70)	Control group (n=70)
CHA_2DS_2-VASc score	1.5±1.2	1.3±1.1
Time from first AF diagnosis (yrs)	6.9±7.2	5.0±5.3
AF type (paroxysmal / persistent)	45/25 (64.3% / 35.7%)	43 / 27 (61.4% / 38.6%)
Previous AF ablation	20 (28.6%)	25 (35.7%)
Pacemaker or loop recorder	23 (32.9%)	27 (38.6%)
Antiarrhythmic therapy	44 (62.9%)	49 (70.0%)
Amiodarone	6 (8.6%)	4 (5.7%)
Sotalol	20 (28.6%)	23 (32.9%)
Flecainide	18 (25.7%)	22 (31.4%)
Echocardiographic variables		
LA area (cm^2)	27.3±8.3	26.8±6.8
LVEF (%)	57±8	57±11
LV mass index (g/m^2)	100.0±23.2	94.9±23.4

Baseline drinking status

Parameter	Abstinence group (n=70)	Control group (n=70)
Alcohol intake (drinks/week)	16.8±7.7	16.4±6.9
Beverages consumed		
Wine	48 (68.6%)	47 (67.1%)
Beer	34 (48.6%)	34 (48.6%)
Spirits	13 (18.6%)	9 (12.9%)
Binge drinking	20 (28.6%)	16 (22.9%)
MCV (fL)	91±3	93±5
GGT (U/L)	41±29	47±26

Compliance
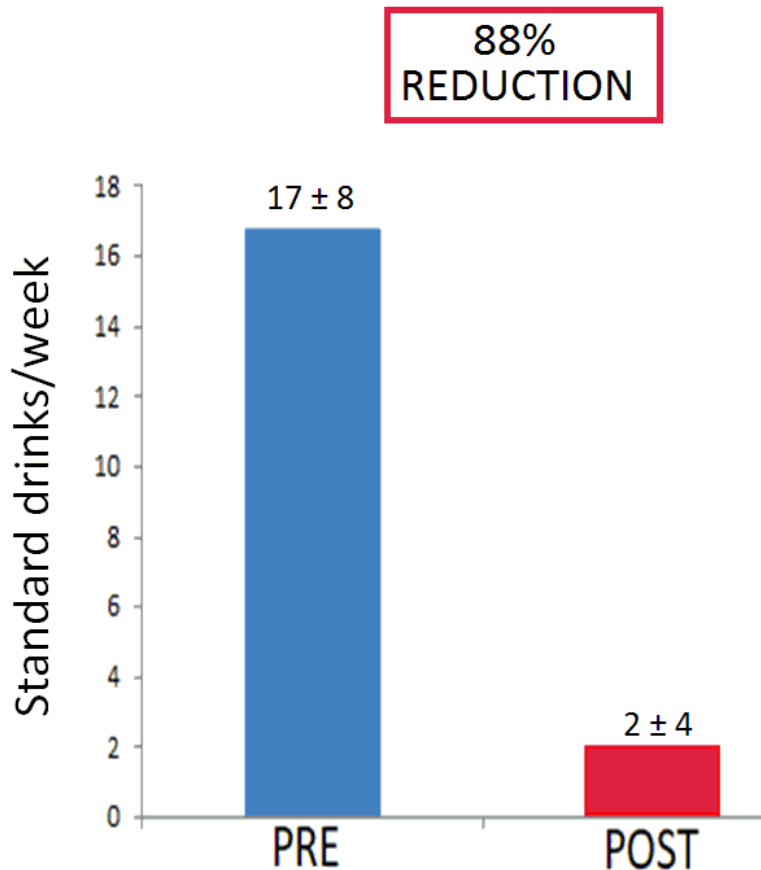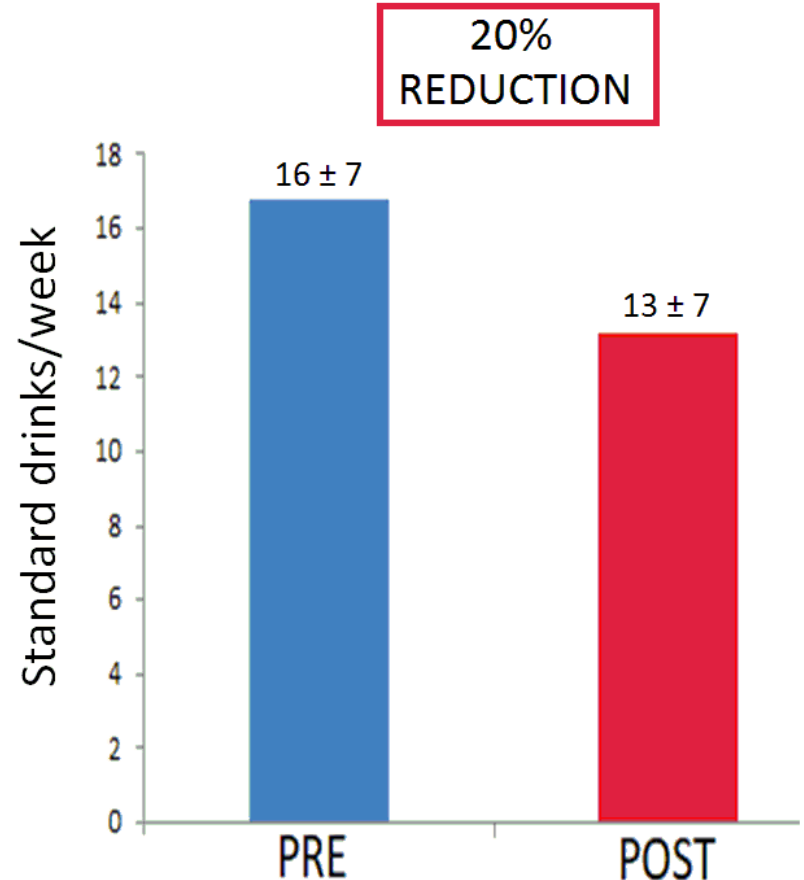
Time to AF recurrence
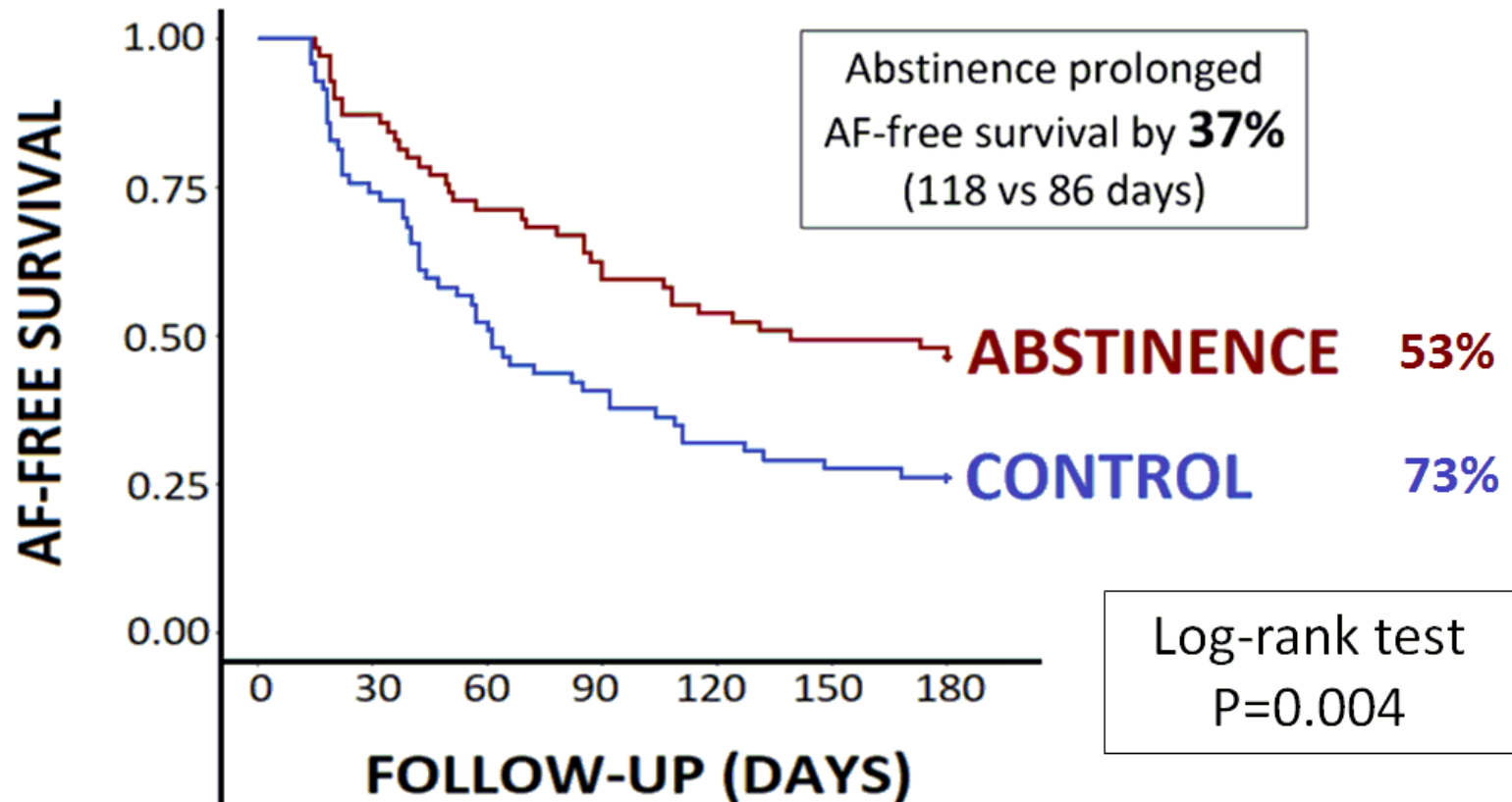
AF burden

AF burden significantly lower in the Abstinence group (p=0.016):

	Mean	Median
Abstinence group	5.6 ± 12.4%	0.5% (IQR 0–3.7%)
Control group	8.2 ± 14.5%	1.2% (IQR 0.0–10.5%)
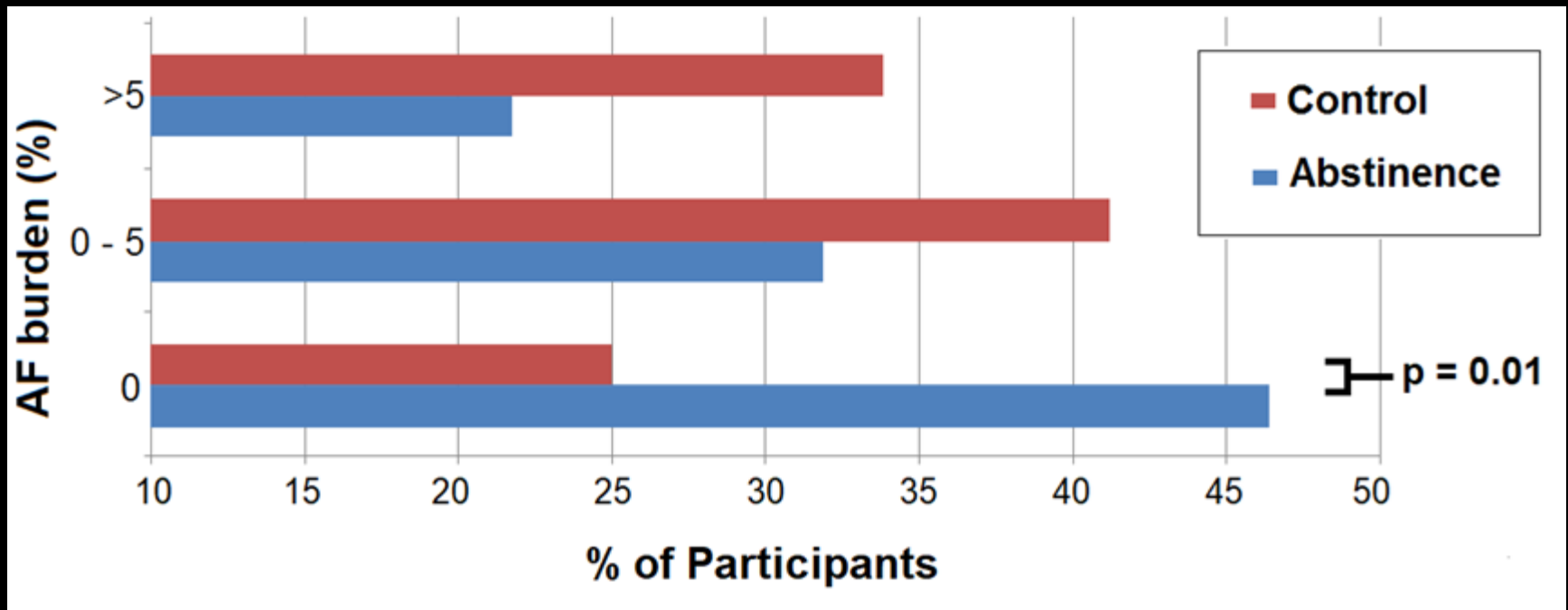
AF symptom severity (EHRA score)
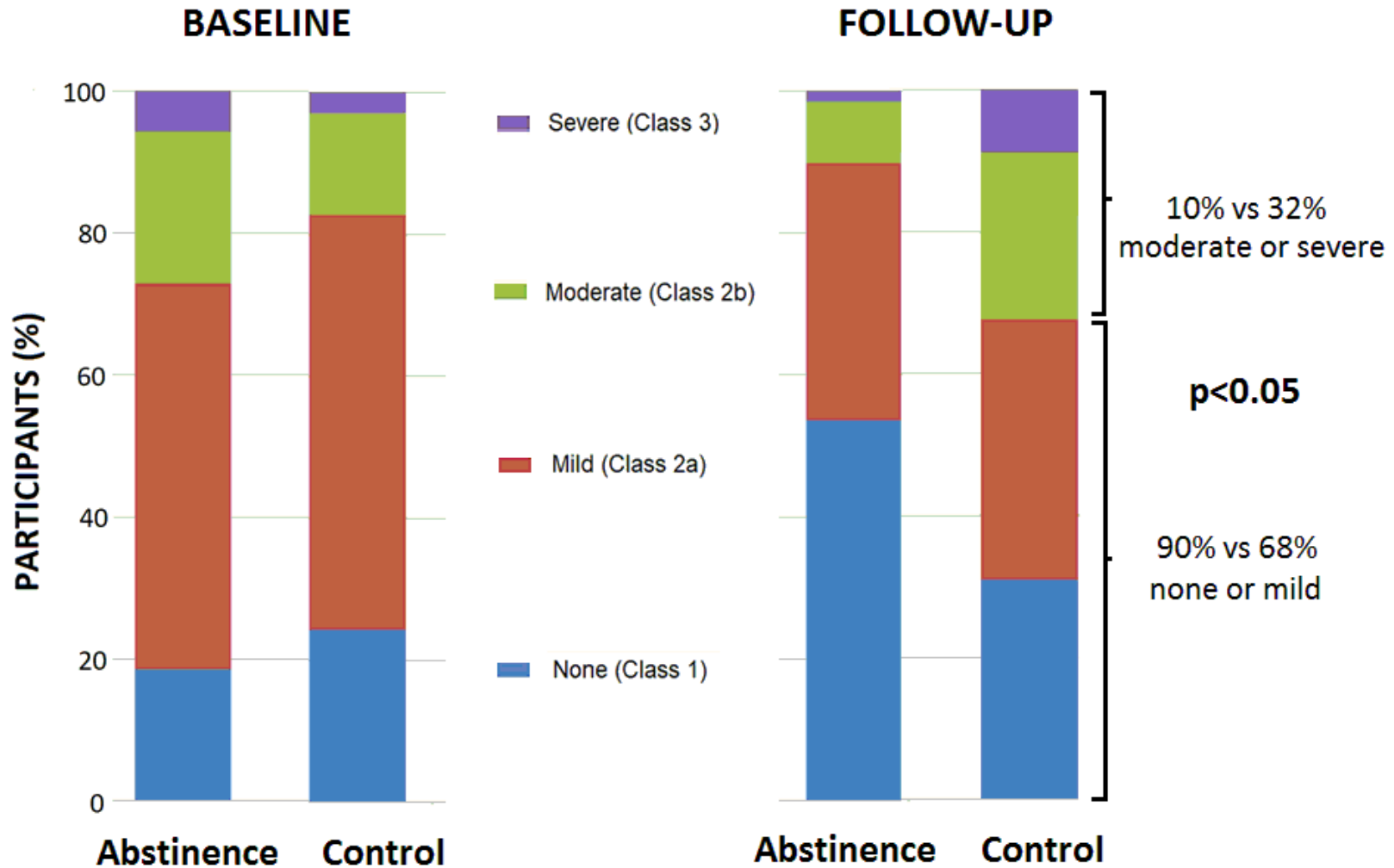
AF-related hospitalizations occurred in 6 (9%) of
Abstinence patients and 14 (20%) Controls (p=0.053).

Secondary endpoints

- Abstinence associated with significant reductions in:
   - **Blood pressure**
    - **Weight**
    - **Body mass index**

	Abstinence			Control		
	Baseline	Follow-up	P	Baseline	Follow-up	P
Blood pressure						
Systolic BP (mmHg)	138±16	126±17	<0.001	133±17	131±15	0.40
Diastolic BP (mmHg)	78±10	75±12	0.03	77±10	76±11	0.62
Mean BP (mmHg)	98±10	92±12	<0.001	96±11	95±10	0.48
Weight (kg)	90±16	87±14	<0.001	89±13	91±14	0.04
BMI	28.4±4.4	27.7±3.8	<0.001	28.5±4.5	28.9±4.9	0.03

Secondary endpoints

Cardiac MRI	Abstinence			Control		
	Baseline	Follow-up	p value	Baseline	Follow-up	p value
LA area (cm^2)	29.5±4.9	27.1±4.5	<0.01	31.7±6.0	31.9±7.2	0.84
LAVI (mL/m^2)	56.7±11.9	53.7±6.4	0.09	56.0±16.7	50.0±4.4	0.40
LA emptying fraction (%)	42±14	50±8	0.02	38±11	41±5	0.27
Epicardial fat area (cm^2)	4.3±2.4	3.9±1.8	0.19	4.3±3.7	5.5±3.0	0.07
LVEF (%)	58.3±10.5	58.8±9.8	0.30	60.0±6.0	56.6±9.8	0.39

Recurrence by AF type
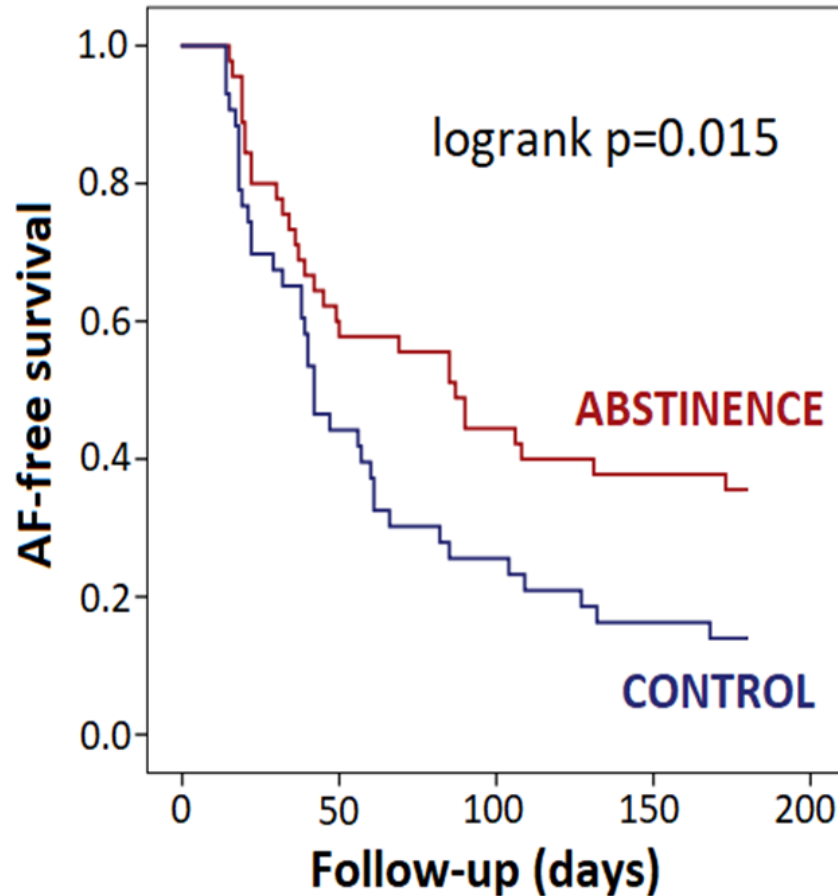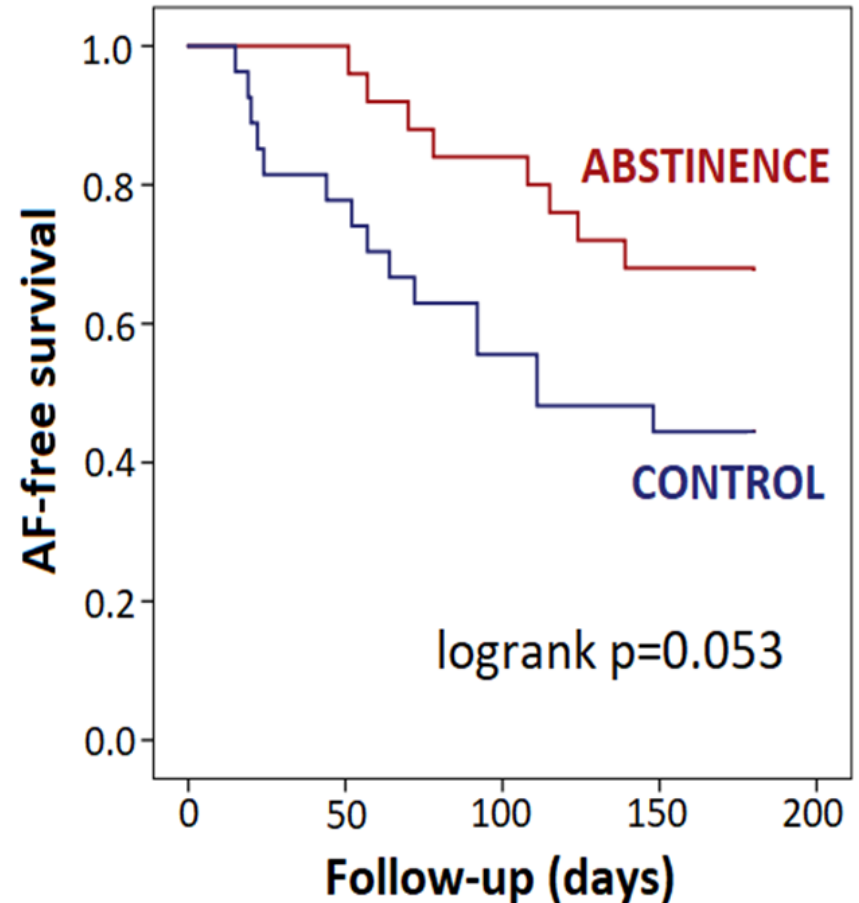
Multivariate predictors of AF recurrence
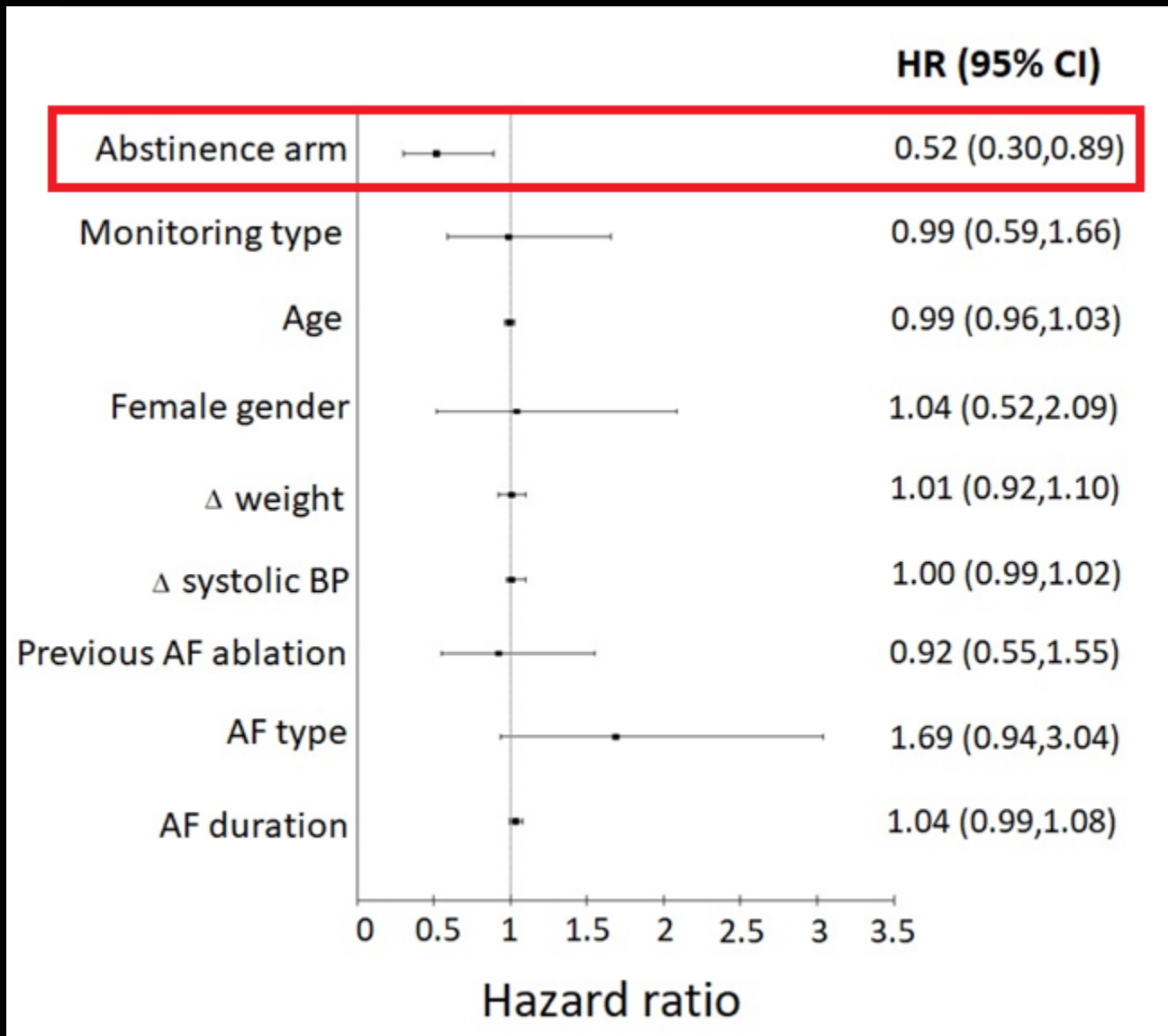
ABSTINENCE ARM: Hazard ratio 0.52, 95% CI 0.30 – 0.89

Conclusion

- In AF patients with moderate alcohol consumption, alcohol abstinence was independently associated with:
  - Reduction in AF burden
  - Reduction in AF recurrence rates
  - Improvement in symptom severity.
  - Weight loss and improved blood pressure control

Significant reduction in alcohol intake should be part of the lifestyle intervention in moderate drinkers with AF.