ORIGINAL ARTICLE

Alcohol Abstinence in Drinkers with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Excessive alcohol consumption is associated with incident atrial fibrillation and adverse atrial remodeling; however, the effect of abstinence from alcohol on secondary prevention of atrial fibrillation is unclear.

METHODS

We conducted a multicenter, prospective, open-label, randomized, controlled trial at six hospitals in Australia. Adults who consumed 10 or more standard drinks (with 1 standard drink containing approximately 12 g of pure alcohol) per week and who had paroxysmal or persistent atrial fibrillation in sinus rhythm at baseline were randomly assigned in a 1:1 ratio to either abstain from alcohol or continue their usual alcohol consumption. The two primary end points were freedom from recurrence of atrial fibrillation (after a 2-week "blanking period") and total atrial fibrillation burden (proportion of time in atrial fibrillation) during 6 months of follow-up.

RESULTS

Of 140 patients who underwent randomization (85% men; mean [±SD] age, 62±9 years), 70 were assigned to the abstinence group and 70 to the control group. Patients in the abstinence group reduced their alcohol intake from 16.8±7.7 to 2.1±3.7 standard drinks per week (a reduction of 87.5%), and patients in the control group reduced their alcohol intake from 16.4±6.9 to 13.2±6.5 drinks per week (a reduction of 19.5%). After a 2-week blanking period, atrial fibrillation recurred in 37 of 70 patients (53%) in the abstinence group and in 51 of 70 patients (73%) in the control group. The abstinence group had a longer period before recurrence of atrial fibrillation than the control group (hazard ratio, 0.55; 95% confidence interval, 0.36 to 0.84; P=0.005). The atrial fibrillation burden over 6 months of follow-up was significantly lower in the abstinence group than in the control group (median percentage of time in atrial fibrillation, 0.5% [interquartile range, 0.0 to 3.0] vs. 1.2% [interquartile range, 0.0 to 10.3]; P=0.01).

CONCLUSIONS

Abstinence from alcohol reduced arrhythmia recurrences in regular drinkers with atrial fibrillation. (Funded by the Government of Victoria Operational Infrastructure Support Program and others; Australian New Zealand Clinical Trials Registry number, ACTRN12616000256471.)

Atrial fibrillation affects more than 33 million people worldwide and is a leading cause of stroke.[1] Alcohol consumption is ingrained in Western culture, with 57% of American adults drinking regularly.[2] Observational studies show a dose-dependent relationship between alcohol intake and incident atrial fibrillation, left atrial dilatation, atrial fibrosis, and recurrence of arrhythmia after ablation. Adverse effects have been reported even with consumption of 7 to 14 drinks per week. Moreover, alcohol is causally linked with other risk factors for atrial fibrillation, including hypertension, obesity, obstructive sleep apnea, and left ventricular dysfunction.[3]

Lifestyle modification has been shown to reduce arrhythmia burden and reverse atrial remodeling in studies focusing on weight loss that included recommended consumption of fewer than 3 drinks per week.[4-6] To date, despite the generally accepted association between alcohol and atrial fibrillation, there are limited prospective data on the role of reduction of alcohol intake in atrial fibrillation outcomes. We undertook a randomized, controlled trial to evaluate an intervention of abstinence from alcohol among regular drinkers with a history of atrial fibrillation.

Methods

Study Design

This was an investigator-initiated, prospective, open-label, multicenter, randomized clinical trial. Patients were recruited from six tertiary hospitals in Australia. Ethics committee approval was sought and obtained at each institution. The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry, and the study protocol is available online at the ANZCTR website (www.anzctr.org.au) and with the full text of this article at NEJM.org. None of the funders were involved in the design of the trial; the selection of participating centers; site supervision; participant enrollment or follow-up; the collection, storage, processing, or analysis of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol.

Study Population

Patients meeting inclusion criteria were invited to participate and provided written informed consent. The inclusion criteria were an age of 18 to 85 years, presence of symptomatic paroxysmal atrial fibrillation (two or more episodes in the 6 months before the start of the trial) or symptomatic persistent atrial fibrillation with a rhythm-control strategy, and regular alcohol consumption (10 or more standard drinks or approximately 120 g of pure alcohol per week). Key exclusion criteria were alcohol dependence or abuse, severe left ventricular systolic dysfunction (ejection fraction <35%), clinically significant noncardiac illness, and coexisting psychiatric disorder.

Run-in Phase and Randomization

After providing consent, patients entered a 4-week run-in period to confirm that inclusion criteria were met and that patients remained willing to participate. To assist them in reporting their alcohol consumption, patients were provided a visual guide depicting standard drinks (Fig. S1 in the Supplementary Appendix, available at NEJM.org), and they maintained a weekly alcohol diary (either written or electronic).

After completing the run-in phase, eligible participants were randomly assigned in a 1:1 ratio to either the abstinence group or the control group. A computerized central randomization scheme was generated with block randomization and sets of randomly selected blocks provided to investigating sites. At the time of randomization, all patients were required to be in sinus rhythm (with or without antiarrhythmic therapy), with no ablation planned; patients remained under the care of their treating physicians, who were discouraged from altering the patients' antiarrhythmic medications during the study period.

Patients in the abstinence group were encouraged to abstain completely from all forms of alcohol for 6 months. They were provided oral and written advice to assist them and received monthly oral and electronic communication from investigators who would assess adherence and provide positive reinforcement. Patients were advised that if no alcohol intake was logged, they could be subject to random urine testing for the alcohol metabolite ethyl glucuronide. (Information about urine testing and other testing and

monitoring procedures is available in the Supplementary Appendix.) Patients in the control group were advised to continue consuming their usual amounts of alcohol and were not required to increase consumption.

MONITORING

All patients underwent comprehensive rhythm monitoring after randomization. Time to recurrence and atrial fibrillation burden were determined either through cardiac rhythm management devices (pacemaker or implantable loop recorder) or through the AliveCor mobile phone application (app). Patients were asked to transmit twice-daily 30-second electrocardiogram (ECG) tracings regardless of their symptoms; if they did have symptoms, they were requested to transmit additional tracings at symptom onset and termination. Patients who did not adhere to ECG monitoring underwent adjunctive 7-day Holter monitoring. The follow-up schedule involved an in-person clinic visit with investigators at baseline and 6 months and monthly contact by either email or telephone to assess adherence to abstinence, collect the alcohol diary, or both. Patients who missed follow-up appointments were contacted by either telephone or email until contact was made. For patients who did not attend the 6-month visit, rhythm data were derived from remote monitoring (available for 82% of participants) or in-clinic interrogation of the device at a later date (Tables S2 and S3).

The investigators reviewed all ECGs, including all mobile app tracings, stored electrograms from implantable devices, and Holter recordings. All ECGs logged as "possible atrial fibrillation" by the computerized algorithm or those suspected to represent atrial fibrillation on initial review were then reviewed by two cardiologists who were unaware of the group assignments. The primary end point was met if both cardiologists concurred that the tracing represented atrial fibrillation.

PRIMARY AND SECONDARY END POINTS

The two prespecified primary end points in an intention-to-treat analysis were recurrence of atrial fibrillation, defined as any atrial tachyarrhythmia lasting 30 seconds or longer (after a 2-week "blanking period," a therapy stabilization period during which episodes of atrial fibrillation were not considered to be a failure of the treatment assignment or to have met the primary end point), assessed in a time-to-event analysis; and atrial fibrillation burden, defined as the percentage of time the patient was in atrial fibrillation during the entire 6-month follow-up period. Although the duration of the study was initially planned to be 12 months, it was modified to 6 months by the steering committee because of challenges in recruiting participants — in particular, unwillingness of many potential participants to adhere to abstinence for 12 months.

Secondary end points, which were prespecified and compared between and within groups at baseline and at 6 months, included weight, blood pressure, symptoms of atrial fibrillation (assessed with the use of the modified European Heart Rhythm Association symptom classification; range, 1 to 4, with higher scores indicating greater severity of atrial fibrillation symptoms),[7] mood (assessed with the use of the Beck Depression Inventory; range, 0 to 63, with higher scores indicating more severe depression), quality of life (assessed with the use of the Medical Outcomes Study 36-Item Short-Form Health Survey [SF-36]; range, 0 to 100, with higher scores indicating better quality of life), and hospitalization for atrial fibrillation. Beck Depression Inventory and SF-36 questionnaires were mailed to participants at baseline and at 6 months. (Receiving and returning the questionnaires by mail, rather than in person at trial visits, allowed patients time and privacy to complete the lengthy surveys at home and ensured survey participation by patients who were too far from a participating hospital to attend follow-up visits at 6 months.) If weight and atrial fibrillation symptom scores were not obtained in person, they were ascertained during telephone or email contact (Table S4). Medical charts were also reviewed. In post hoc analyses, we also examined the change in the atrial fibrillation burden (comparing the burden during the 6-month period with the burden during the 4-week run-in, if available) and total number of atrial fibrillation episodes during the 6-month follow-up (Table S8). All secondary end points are reported here, with the exception of left atrial and ventricular remodeling assessed in a cardiac magnetic resonance imaging substudy.

STATISTICAL ANALYSIS

In the sample-size calculation for the primary end point of recurrence of atrial fibrillation, we assumed a 30% incidence of recurrence. To detect a minimum absolute difference in recurrence of 20 percentage points between groups, we enrolled 70 patients in each group to provide a power of 80% at an alpha level of 5%.

Continuous variables were summarized with means and standard deviations (if normally distributed) and medians and interquartile ranges (if positively skewed). Categorical variables were summarized as frequencies and percentages. Time-to-event analyses for recurrence of atrial fibrillation were performed with Kaplan–Meier plots and the log-rank test. Atrial fibrillation burden at follow-up had a skewed distribution (confirmed by the Shapiro–Wilk test) and was compared with the use of the Mann–Whitney U test. A univariate Cox proportional-hazards model was also used for the time-to-event analyses of atrial fibrillation recurrence and was extended to a multivariate model adjusted for patient characteristics (Table S10).

Continuous and categorical secondary end points measured at follow-up were compared with the use of linear and multinomial logistic-regression models, respectively, and adjusted for baseline measurements of the secondary end points to obtain estimated mean differences and geometric mean ratios or odds ratios with corresponding 95% confidence intervals. For all skewed secondary end points, log-transformed variables were used in the analysis models. We performed post hoc subgroup analyses of recurrence by fitting a Cox proportional-hazards model with a term for the interaction between the group and the variable (Table S11).

A substantial number of patients did not attend planned follow-up visits, did not return questionnaires, or had missing data for secondary outcome measures (see details below). In a sensitivity analysis, we used multivariate normal imputation to handle missing values for secondary end points with more than 5% missing data. (Additional information about data gathering and analysis is available in the Supplementary Appendix.) All patients had information available for the primary end point of recurrence of atrial fibrillation, although 3 patients were lost to follow-up before 6 months and their data were censored at the time they were lost to follow-up. For the other primary outcome, atrial fibrillation burden, 3 patients had missing data (1 of 70 [1%] in the abstinence group and 2 of 70 [3%] in the control group) and were omitted from the analysis. Hence, multiple imputation was not used for the primary end points owing to minimal missing data. Statistical analysis was performed by two independent statisticians with Stata software, version 15.0 (StataCorp).

The protocol did not prespecify a plan to adjust for the inclusion of two primary end points, so on the basis of a post hoc Bonferroni adjustment, the threshold for statistical significance for each outcome is $P<0.025$. Secondary outcome analyses are reported with 95% confidence intervals, without P values. All 95% confidence intervals presented in this report have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible.

RESULTS

PATIENT POPULATION

Of 697 patients who were screened for participation and met inclusion criteria (Fig. 1), 140 were randomly assigned between March 2016 and February 2018 to the abstinence group (70 patients) or the control group (70 patients); the last patient completed follow-up in August 2018. A large percentage of patients at screening (491 patients, 70.4%) were not willing to consider abstinence, and 17 patients were excluded after the run-in period for the same reason. Baseline clinical characteristics (Table 1), including atrial fibrillation phenotype and method of rhythm monitoring, were fairly well-balanced between the groups. Most patients (104 of 140, 74.3%) were not regular binge drinkers, and wine and beer were the predominant beverages consumed (Table 2). A total of 53 patients (37.9%) had continuous rhythm monitoring (loop recorder or pacemaker). Adherence to mobile app recordings in the rest of the patients was satisfactory (median, 257 tracings per patient during follow-up; interquartile range, 124 to 382), with 7-day Holter monitoring reserved for 4 patients who did not adhere to digital monitoring. Of the total 140 participants, 137 (97.9%) completed the 6-month follow-up with complete rhythm data and alco-

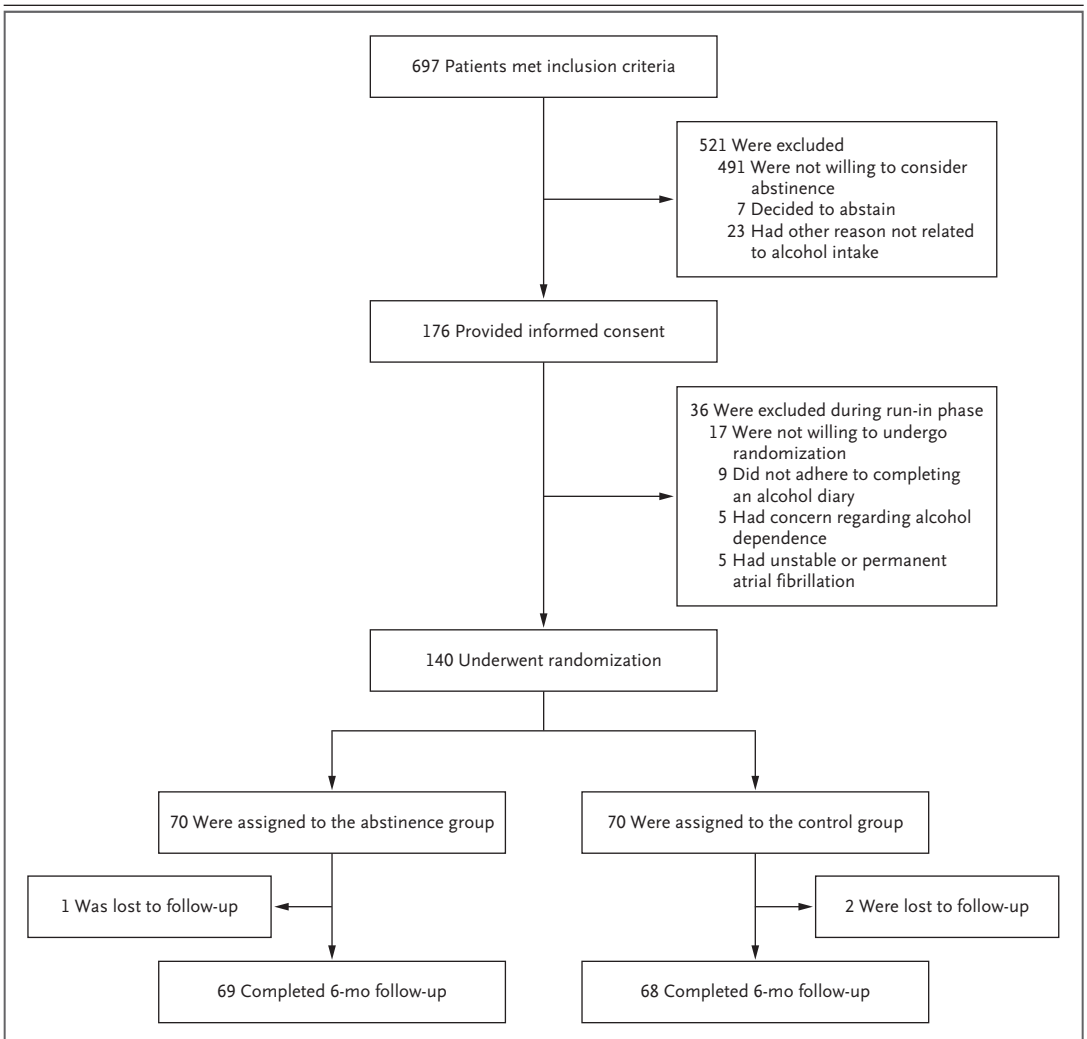

Figure 1. Screening, Randomization, and Follow-up.

hol history available. In 4 of 140 patients (2.9%), changes in antiarrhythmic medications, atrial fibrillation-related procedures, or both occurred before their first documented arrhythmia recurrence (Table S5).

ALCOHOL INTAKE

Patients in the abstinence group reduced their alcohol intake from 16.8±7.7 to 2.1±3.7 drinks per week (87.5% reduction; mean difference, 14.7; 95% confidence interval [CI], 12.7 to 16.7). Complete abstinence was achieved by 43 of the 70 patients (61%) in the abstinence group, with intake of 2 or fewer drinks per week achieved by 53 of the 70 patients (76%); 60 patients (86%) in the abstinence group reduced their alcohol intake by more than 70% of baseline (Table S6). A small reduction in alcohol intake was observed in the control group; alcohol intake was reduced from 16.4±6.9 to 13.2±6.5 drinks per week (19.5% reduction; mean difference, 3.2; 95% CI, 1.9 to 4.4).

PRIMARY END POINTS

At 6 months, recurrences of atrial fibrillation of more than 30 seconds' duration (after a 2-week blanking period) were documented in 37 patients (53%) in the abstinence group and in 51 patients

(73%) in the control group. The time to recurrence (Fig. 2) was longer in the abstinence group than in the control group (hazard ratio, 0.55; 95% CI, 0.36 to 0.84; P=0.005 by the log-rank test). Overall atrial fibrillation burden was significantly lower in the abstinence group, with a median percentage of time in atrial fibrillation of 0.5% (interquartile range, 0.0 to 3.0) in the abstinence group and 1.2% (interquartile range, 0.0 to 10.3) in the control group (P=0.01) (Fig. 3).

SECONDARY END POINTS

Atrial fibrillation–related hospital admissions occurred in 6 patients (9%) in the abstinence group and in 14 patients (20%) in the control group (Table S4). Data on weight were available at 6 months for 84% of the patients in the abstinence group and 80% of the patients in the control group. After adjustment for baseline weight, the mean difference in weight at 6 months between the abstinence group and the control group was −3.7 kg (95% CI, −4.8 to −2.5). Scores on the modified European Heart Rhythm Association classification of atrial fibrillation symptoms at the 6-month follow-up were available for 99% of patients in the abstinence group and for 97% of patients in the control group; symptom scores were better in the abstinence group than in the control group, with fewer patients in the abstinence group reporting moderate or severe symptoms (10% vs. 32%) at 6 months (Fig. S2).

Data on blood pressure, quality-of-life scores, and depression scores were missing for more than 35% of patients at 6 months (Table S14). Results of analyses based on both complete data and multiple imputation are shown in Table S7 and should be interpreted with caution given the missing data.

In a post hoc analysis that included patients in both groups, the risk of recurrent atrial fibrillation was higher among the patients who consumed 1 to 9 drinks per week (40 patients) and among the those who consumed 10 or more drinks per week (57 patients) than among those who achieved complete abstinence over 6 months (43 patients) (hazard ratio with 1 to 9 drinks per week vs. complete abstinence, 2.1; 95% CI, 1.2 to 3.7; and hazard ratio with ≥10 drinks per week vs. complete abstinence, 2.3; 95% CI, 1.3 to 4.0).

Table 1. Characteristics of the Patients at Baseline.*

Variable	Abstinence Group (N=70)	Control Group (N=70)
Age — yr	61.6±9.4	62.9±8.6
Male sex — no. (%)	61 (87)	58 (83)
Weight — kg†	89.7±16.0	89.3±13.2
Body-mass index‡	28.4±4.4	28.5±4.5
Hypertension — no. (%)	31 (44)	26 (37)
Diabetes mellitus — no. (%)	5 (7)	6 (9)
TIA or stroke — no. (%)	7 (10)	5 (7)
Dyslipidemia — no. (%)	11 (16)	18 (26)
Previous or current smoker — no. (%)	13 (19)	11 (16)
Obstructive sleep apnea — no. (%)	12 (17)	16 (23)
Coronary artery disease — no. (%)	10 (14)	5 (7)
Previous heart failure — no. (%)	6 (9)	6 (9)
CHA_2DS_2-VASc score§	1.5±1.2	1.3±1.0
Time since first diagnosis of atrial fibrillation — yr¶	6.9±7.2	4.9±5.2
Paroxysmal atrial fibrillation — no. (%)	45 (64)	43 (61)
Persistent atrial fibrillation — no. (%)	25 (36)	27 (39)
Previous atrial fibrillation ablation — no. (%)	20 (29)	25 (36)
Pacemaker or loop recorder — no. (%)	25 (36)	28 (40)
Antiarrhythmic therapy — no. (%)	44 (63)	48 (69)
Amiodarone — no. (%)	6 (9)	4 (6)
Sotalol — no. (%)	20 (29)	23 (33)
Flecainide — no. (%)	18 (26)	22 (31)

* Plus–minus values are means ±SD. There were no significant differences between the groups in patients' baseline characteristics. TIA denotes transient ischemic attack.
† Data on weight were missing for 3 patients in the control group (4%) and 1 in the abstinence group (1%).
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 5 patients in the control group (7%) and 3 in the abstinence group (4%).
§ The CHA_2DS_2-VASc score is a measure of the risk of stroke among persons with atrial fibrillation; scores range from 0 to 9, with higher scores indicating a greater risk.
¶ Data for time since the first diagnosis of atrial fibrillation were missing for 2 patients in the control group (3%).

DISCUSSION

Atrial fibrillation is the most common sustained arrhythmia,[1] and alcohol is consumed by a majority of U.S. adults.[2] The current study showed that among regular drinkers, a substantial reduction in alcohol consumption by patients with symptomatic atrial fibrillation was associated

Table 2. Alcohol Intake at Baseline.

Variable	Abstinence Group (N=70)	Control Group (N=70)
Alcohol intake — no. of standard drinks/wk	16.8±7.7	16.4±6.9
Beverages consumed — no. (%)		
Wine	48 (69)	47 (67)
Beer	34 (49)	34 (49)
Spirits	13 (19)	9 (13)
Binge drinking — no. (%)*	20 (29)	16 (23)

* Binge drinking was defined as consumption of 5 or more drinks on a single occasion at least once a month.

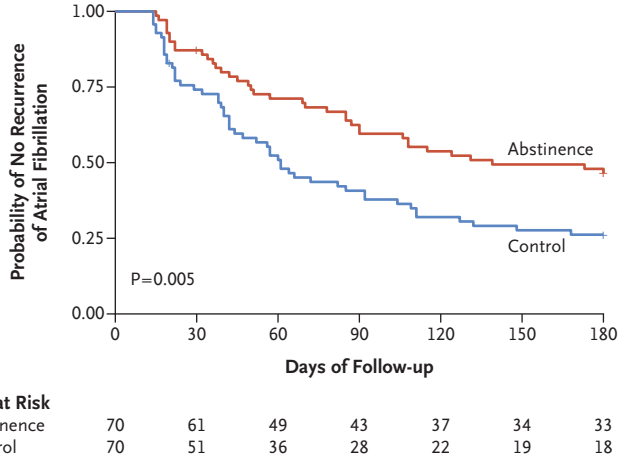

Figure 2. Time to Recurrence of Atrial Fibrillation.

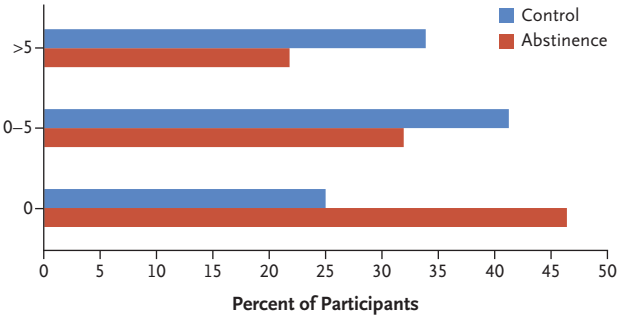

Figure 3. Atrial Fibrillation Burden in the Abstinence and Control Groups.
Atrial fibrillation burden is the percentage of time the patient was in atrial fibrillation during the entire 6-month follow-up period.

with a reduction in recurrence of atrial fibrillation and a reduced proportion of time spent in atrial fibrillation. Earlier meta-analyses showed that alcohol was associated with a dose-related increased risk of incident atrial fibrillation, with increased risk observed even among drinkers who consumed as few as 7 drinks per week.[8] Current trends show a rise in alcohol consumption among adults older than 60 years of age,[2] coupled with greater prevalence of atrial fibrillation in this age group. The present study, with participants having an average intake of approximately 17 drinks per week at baseline, suggests that consumption at these levels may contribute to atrial fibrillation.

The mechanisms by which abstinence reduces arrhythmia burden are probably multifactorial. Alcohol is the most common trigger of atrial fibrillation reported by 35% of patients[9] and is associated with autonomic modulation with reduced heart rate variability,[10,11] sympathetic effects,[12] and vagal stimulation.[13] Binge drinking has also been associated with acute cardiac inflammation.[14] Observational studies link regular alcohol consumption (as compared with no alcohol consumption) with dose-related increases in left atrial size,[15] impairments in atrial mechanical and reservoir function,[16] and adverse electrical remodeling.[17] Numerous studies have also reported higher rates of recurrence of atrial fibrillation after catheter ablation among regular drinkers than among nondrinkers.[18-20]

Given an energy content of 7 kcal per gram, excessive alcohol consumption can contribute to weight gain.[21] In the present study, abstinence was associated with modest weight loss without specific additional measures employed. Since epicardial fat has proarrhythmic properties that are mediated by inflammation and profibrotic paracrine effects, reduction in epicardial fat through weight loss may mitigate these proarrhythmic effects.[22,23] Alcohol has been causally linked to systolic hypertension. Proposed mechanisms include activation of the renin–angiotensin system, increased vascular reactivity, and inhibition of endothelial nitric oxide production.[24] A recent meta-analysis showed a dose-dependent risk of hypertension among men, even with consumption of 1 to 2 drinks per day.[25] Although our analyses of blood pressure should be interpreted with caution owing to missing data for many

patients, our findings are consistent with a systematic review of 36 trials that showed a reduction in blood pressure with decrease in alcohol intake, particularly among drinkers who had been consuming more than 14 drinks per week.[26]

Our trial had several limitations. The study included a heterogeneous population with different mechanisms of arrhythmia detection, although these were well-balanced between groups. The clinical applicability of abstinence requires separate attention, since only a minority of patients who were screened agreed to abstain completely, and patients with previous alcohol-triggered arrhythmias may have been overrepresented.

Despite rigorous selection of motivated patients, close follow-up, urine testing, and access to a visual guide to maximize the accuracy of alcohol consumed, reporting of alcohol quantities by the patients themselves remains a considerable study limitation owing to recall and misclassification bias. Conclusions pertaining to secondary outcomes are limited by a lack of a prespecified plan to adjust for multiple comparisons as well as missing data and patient-reported data for some outcomes. Sleep-disordered breathing, which was not assessed, may be a confounding factor. Differences in rhythm-control therapy after the first recurrence of atrial fibrillation may have underestimated differences in arrhythmia burden between groups.

Epidemiologic studies suggest that light-to-moderate alcohol consumption is associated with a lower incidence, in a U-shaped pattern, of coronary artery disease and cardiovascular events.[27,28] Complete abstinence may increase the risk of these events, and this study was underpowered to determine the effect on cardiovascular disease, heart failure, stroke, or mortality. Thus, potential cardiovascular benefits of modest alcohol consumption must be reconciled with the potential for atrial proarrhythmia.

Regular alcohol consumption is a potentially modifiable risk factor for atrial fibrillation. In this trial involving regular alcohol drinkers with atrial fibrillation, patients randomly assigned to the abstinence group decreased their drinking from about 17 drinks per week to 2 drinks per week and had a reduction in both atrial fibrillation burden and risk of recurrence of atrial fibrillation.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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