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The Estimated Risk of Atrial Fibrillation Related to Alcohol Consumption

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Abstract

The risk of acute heavy alcohol intake on the development of atrial fibrillation (AF), aka 'holiday heart syndrome', has been well-described. However, whether chronic alcohol intake is also associated with increased risk of AF, or might even be protective as has been observed with other cardiac conditions, is more uncertain. A number of studies, from basic science to large cohort studies have been performed to analyze the association between alcohol and AF. Basic-level studies have found that alcohol causes changes in tissue electrophysiology, ion channels, and circulating hormones, which might promote development and maintenance of AF. Clinical studies have generally shown groups with the highest regular intake of alcohol to be at increased risk, with no association with more moderate use. However, these studies have not always accounted for other AF risk factors, been inconsistent in the assessment and validation of the quantity of alcohol consumed across populations, and been unable to completely separate drinking patterns from overall health of participants. As a result, solid conclusions about a threshold level for 'safe' chronic alcohol intake cannot be made with regard to AF risk, but it appears to be safe within currently recommended limits of 1 drink daily for women and 2 for men. In this review, we discuss these findings, limitations, and conclusions.

Introduction

In 1978, Philip Ettinger and colleagues described in the American Heart Journal a condition in which patients would present with cardiac arrhythmias after episodes of heavy alcohol consumption.[1] They called the condition 'holiday heart syndrome,' since it was noted that arrhythmia presentations seemed to occur on weekends or during the holidays, times when people tended to increase their alcohol consumption. Importantly, all of the cases in Ettinger's seminal paper occurred in people who had a long history of heavy alcohol intake: daily alcohol consumption in the patients varied from six ounces of martini daily to 12-15 beers daily to daily whiskey in "quart quantities."[1] In a paper in The Lancet in 1984, Thornton and colleagues pointed out this limitation of Ettinger's study, before going on to describe cases of four patients without a history of long-term heavy alcohol use who presented with atrial fibrillation (AF).[2] These four cases, noted to be 'light' drinkers as they consumed less than 30 grams of alcohol per day, presented in AF while still apparently intoxicated (the authors estimate consumption of about 138 grams of alcohol)[2], with reversion to sinus rhythm the following morning after presumed metabolic elimination of the ingest-

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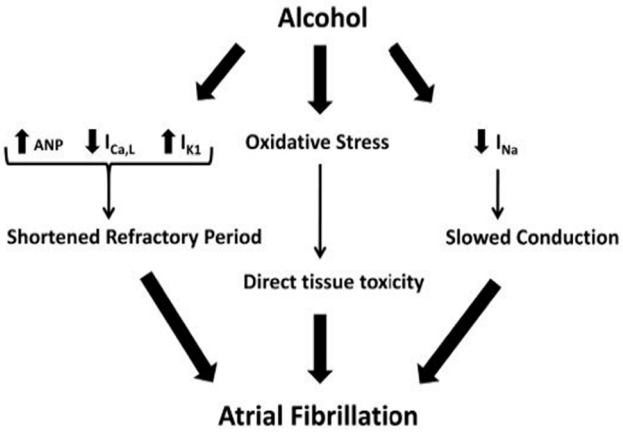
ed alcohol. Thornton's interpretation, supported by a variety of metabolic and electrocardiographic changes noted at the time,[1, 3, 4] was that it was the heavy acute intake of alcohol that was the precipitant for acute AF, and this hypothesis has since been supported by a number of studies that have described the risk of binge drinking on development of AF.[2, 5-8]

Other cardiac conditions have also been associated with binge drinking, including myocardial infarction,[9] stroke[10] and heart failure,[11] well-illustrating the potential of heavy alcohol intake to act as a direct cardiac toxin. However, more recently, observational studies have suggested alcohol might have a protective effect if taken in low to moderate amounts, with reduction in the risk of coronary heart disease, stroke, congestive heart failure,[12-16] as well as all-cause mortality.[17] For example, one six-month randomized trial examined regular wine intake among diabetic survivors of acute myocardial infarction and found a benefit of modest drinking on myocardial infarction.[18] These findings have raised the question

Figure 1: Possible mechanisms of alcohol-induced atrial fibrillation



of whether a similar paradoxical effect might be observed between alcohol and AF, with moderate alcohol intake having a protective effect and only binge drinking increasing risk. Since Ettinger, a number of studies have attempted to answer these questions. In this review, we will examine the evidence for an association between alcohol intake and AF, as well as the methodological limitations surrounding studies of the association.

Mechanistic Associations

Mechanistically, a number of hypotheses have been put forward with regard to how alcohol might increase the risk of AF (Figure 1). In their initial study, Ettinger and colleagues noted a modest increase in the PR, QRS, and QT intervals on the electrocardiograms of alcoholics presenting in AF[1], findings which have since been replicated in several other studies in humans.[19, 20] Specifically, abnormalities in the P wave, which represents atrial depolarization, have been noteworthy, including a study by Uyarel et al., who performed a randomized crossover study in otherwise healthy humans, and found that consumption of moderate-dose ethanol (0.97+/-0.12 g/kg body weight over 1 hour) was associated with a significant lengthening of both the P wave duration, as well as an increase in P wave dispersion.[21] Similarly, Steinbigler et al. found that P-wave signal average studies identified individuals who might be at risk for alcohol-induced AF,[22] indicating that the changes observed in the P wave with alcohol intake might be a precursor to the development of AF.

At a more basic level, acute ethanol infusion in animal models had been demonstrated as early as 1962 to shorten the atrial refractory period,[4] an effect that has since been observed in human atria[23] as well as in rabbit pulmonary vein isolates,[24] although it should be noted that no changes were observed in the rate of spontaneous firing or triggering in the pulmonary veins, as might have been expected in AF. Computer models have shown that

shortening of the atrial refractory period allows for multiple reentry wavelets, and thus alcohol-induced shortening of the atrial refractory period would create a pro-arrhythmic substrate accommodating the development and maintenance of AF.[25-27] Changes in several ion channels have been implicated in this process, including decreased activity of inward sodium (*I*Na) and calcium (*I*Ca,L) currents and increased activity of outward potassium currents (including *I*K1 and *I*Kur).[25] Several experiments have shown that treatment with ethanol causes depression of sodium[28,29] and calcium signaling,[28,30,31] as well as increased potassium channel function,[32] all of which would in theory shorten the atrial refractory period, although the reproducibility of some results has been variable.[33]

Cardiomyopathy as a result of excess alcohol intake is well-known, and many studies have identified depressed contractility with ethanol infusion in the ventricles[34] as well as the atria.[35] In rats consuming alcohol for 2 months,[36] atrial toxicity developed in the form of decreased response to inotropic agents and decreased calcium sensitivity,[36] supporting the notion that alcohol may cause direct effects on the health of atrial tissue leading to AF. However, despite these findings, replication of inducible AF in animal models has been variable. While Anadon and colleagues infused pigs with high doses of alcohol (up to 1,230 mg/kg of ethanol) and found that they could induce AF as well as atrial flutter more easily and for more sustained periods than at baseline,[37] Fenelon et al. were unable to detect any changes in atrial refractoriness, conduction velocity, or arrhythmia inducibility in dogs infused with moderate amounts of ethanol.[34] These results suggest that perhaps high doses of alcohol are needed to induce AF, although further studies are needed.

Other mechanisms by which heavy alcohol consumption has been noted to increase the risk of AF include the hyperadrenergic state of drinking and withdrawal,[38] impairment of vagal heart rate control and autonomic function,[38, 39] oxidative stress,[40] and an abnormal electrolyte profile.[38] As AF patients have also been noted to have increased oxidative stress,[41] this possible mechanism may have interesting treatment implications, as in one study investigators were able to reduce post-operative AF (another form of AF that has been linked to oxidative stress[41]) by treatment with the antioxidant ascorbate.[42] Another recent interesting mechanistic link was described by Djousse et al., who found a positive correlation between alcohol intake and plasma atrial natriuretic peptide (ANP)[43]. Others have also described an increase in plasma ANP after alcohol injection in rats,[44] and elevated ANP has been well-described in AF.[45, 46] As ANP has also been noted to shorten atrial refractoriness,[47] it may also be implicated directly in the arrhythmogenesis of alcohol-induced AF, although this specific mechanism, as well as the role of serum ANP levels in predicting development of alcohol-induced AF, has not been studied.

Clinical Studies

One of the earliest studies examining the relationship between alcohol intake and AF was performed in 1985 by Rich and colleagues.[8] This study was a case-control review of the medical records of 40 individuals presenting to the hospital with 'idiopathic' acute AF, with 64 age- and gender-matched controls. Among their findings, was the observation that not only did patients presenting with AF have nearly twice the likelihood of having a history of heavy alcohol use, but that they also were more likely than other patients without AF to have withdrawal symptoms. In addition to the likely sampling bias—62% of the AF cases had a history of heavy alcohol use—this study had a number of shortcomings, which will be reviewed in detail later.

Other observational studies, both case-control and cohort studies, on the association of alcohol and AF have been performed, and have revealed some informative, although mixed, results (Table 1). A number of case-control studies have been performed using cases of both chronic[73] and paroxysmal AF,[74, 75] as well as right atrial flutter.[23] In two studies of AF with significant findings,[73, 74] only the highest consumption groups—over 21 units per week[74] and over 42 units per week[73]—were associated with an increased risk of AF (OR 1.7 and 2.4 respectively). A third study, by Mattioli and colleagues did not find any significant association with alcohol and AF.[75] There was also no significant association in the AF arm of the study by Marcus and colleagues,[23] although this study did find an association of right atrial flutter and alcohol intake in a subgroup of participants under 60

Table 1 **Clinical studies of alcohol and atrial fibrillation**

STUDIES	Number of AF cases	Alcohol consumption of highest risk group	Adjusted Risk (CI) versus nondrinkers	Adjusted covariates
Case-control studies				
UK General Practice Research Database[73], 2002	1,035	> 42 units/week	OR 2.4 (CI 1.4 – 4.1)	Age, sex, cardiovascular morbidity
Mattioli et al.[75], 2005	116	>50 mL/day	Non-significant	Age, sex, life stress, espresso coffee consumption, body mass index, income and smoking
UK General Practice Research Database[74], 2005	525	>21 units/week	OR 1.7 (CI 1.1 – 2.6)	Age, sex, BMI, cardiovascular morbidity, smoking
Marcus et al.[23], 2008	195	> 2 drinks/day	*Non-significant	Age, sex, race, hypertension, congestive heart failure, coronary artery disease, BMI
Cohort studies				
Framingham Heart Study[77], 2004	1,055	> 36 g/day	RR 1.34 (CI 1.01 – 1.78)	Sex-stratified, adjusted for systolic blood pressure, age at baseline examination, education, and cumulative history of myocardial infarction, congestive heart failure, diabetes mellitus, left ventricular hypertrophy, and valvular heart disease
Danish Diet, Cancer, and HealthStudy[78], 2004	556	Mean 68.7 ± 22.8 g/week in highest quintile	HR 1.46 (CI 1.05 – 2.04)	Sex-stratified, adjusted for age, body height, body mass index, smoking, systolic blood pressure, treatment for hypertension, total serum cholesterol, and level of education
Copenhagen City Heart Study[61], 2005	1071	>35 drinks/week	HR 1.45 (CI 1.02 – 2.04)	Sex-stratified; adjusted for age, smoking, education, cohabitation, family history of cardiovascular disease, diabetes, income, physical activity, BMI, FEV1, and height
Cardiovascular Health study[72], 2007	1232	>14 drinks/week	†Non-significant	Age, sex, race, income, height, waist circumference, physical activity, use of psychoactive medication, diabetes, hypertension, coronary heart disease, congestive heart failure, and total cholesterol level
Women's Health Study[62], 2008	653	> 2 drinks/day	HR 1.60 (CI 1.13 – 2.25)	(Women only) Age, systolic blood pressure, history of hypertension, body mass index, smoking, history of diabetes, history of hypercholesterolemia, and randomized treatment assignment

* Significant effect in subgroup of AFL under 60 years of age (see text)
† Non-drinkers limited to lifelong abstainers, former drinkers excluded (see text)

years of age who consumed over 1 drink per day.

In addition to the common limitations of case-control studies, these were primarily registry or medical record reviews, with the largest having 1,035 cases.[73] In few of the studies was the focus of the analysis specifically on alcohol and AF, and thus there was limited validation of alcohol consump-

tion. All of these studies were limited by a small number of participants in the highest consuming group (range from 5.9% of 525 cases[74] to 11% of 116 cases[75]), and as a result even those with significant results had wide confidence intervals. For example, in the largest case-control study, the General Practice Research Database study, the 95% confidence interval was 1.4 – 4.1 (ARR 2.4) for the group with the highest alcohol intake (over 42 units/week).[73] A key limitation of these case-control studies was that there was no information about whether the significance of the groups with the highest alcohol intake was driven by individuals with extremely high levels of chronic intake or whether there was a threshold effect at the chosen cut-point.

The role of alcohol on incident AF has been examined in several large cohort studies, including the Cardiovascular Health Study,[72, 76] the Framingham Heart Study,[77] the Copenhagen City Heart Study,[61] the Women's Health Study,[62] and the Danish Diet, Cancer, and Health Study.[78] Similar to the case-control studies, the general trend among cohort studies was that only the group or quintile with the highest consumption had a significant association with AF.

An important recognition among investigators of cohort studies was the need to stratify by gender, as women in general tended to consume less alcohol than men. This issue is exemplified in the Women's Health Study, which analyzed data from a cohort of women health professionals in the United States and found that women who consumed more than 2 drinks per day were at an increased risk of AF compared with nondrinking women.[62] Other studies that stratified by gender, including the Framingham Study,[77] the Danish study,[78] and the Copenhagen City Heart Study[61], all failed to find a significant association between alcohol and AF in women, despite non-significant trends toward higher risk in the group with the highest intake. One explanation for this phenomenon has been that fewer women were available in each study that drank in the highest consumption group;[62] however, other studies with non-significant results have had large numbers of women in the highest consumption group. For example, in the Danish study, which divided participants into quintiles, the highest quintile with 5,084 participants consumed 38.8 g per day of alcohol, yet lacked even a trend toward increased risk of AF with an unadjusted HR of 1.01 (CI 0.63 – 1.61), while in men a significantly increased risk of 45% was observed with consumption in the highest quintile (68.7 g/day).

Despite the general trend of increased risk in the highest consuming group, extrapolation of results across studies is difficult. For one, the actual amount consumed varies substantially across studies. The highest group in the Framingham study consumed greater than 36.0 g/day and had an increased relative risk of 1.34 (CI 1.01 – 1.78),[77] while in the Danish study the highest quintile consumed 68.7 g/day on average, with an increased risk of 1.45 (CI 1.05 – 2.01). Interestingly, quintile 4 of the Danish study, which consumed 38.1 – 68.7 g/day did not have a significantly increased risk of AF (RR 1.24, CI 0.88 – 1.73), highlighting this important limitation in comparisons across studies. In studies that examined consumption in drinks per week, there was also a large variation present in terms of actual amounts of alcohol between studies. In the Copenhagen City Heart Study, the highest group of men consumed over 35 drinks per week, and had an increased risk of AF of 1.62 (CI 1.16 – 2.27) in the age-adjusted model.[61] On the other hand, in the Cardiovascular Health Study, there was no increased risk seen in the highest consumption group; however, the highest consumption group only consumed greater than 14 drinks per week,[72] well below that of the Copenhagen City Heart Study. One likely reason for this discrepancy was the substantial difference in age between the cohorts; nonetheless, such a wide range of cut-points for the highest level of alcohol consumption across studies makes generalization difficult in terms of finding a threshold risk level.

In addition to the variability in quantities, there are also differences in the type of alcohol consumed, i.e. beer, wine, or spirits, across populations, and some have speculated that substances in certain alcoholic beverages, such as resveratrol in red wine, might have anti-oxidant properties that prevent AF.[79] Mukamal and colleagues looked at this issues specifically in the Copenhagen City Heart Study, and did not detect a difference based on the type of alcoholic beverage consumed,[61] although other studies that have looked at this issue have noted a difference in the drink preferences of consumption groups within the same study, such as in the study by Frost and colleagues, who found

that while heavy drinking men (who were also the only group at higher risk for AF) drank mostly beer, lighter drinking men and all women tended to drink mostly wine[78], and had no increased risk.

In addition to the above studies, meta-analyses have also been performed[80, 81] exploring, among other issues, the question of what is the safe limit of alcohol consumption with regard to AF risk. The most recent, by Kodama and colleagues, examined pooled estimates from fourteen eligible studies that included both case-control studies and cohort studies. The overall conclusion from their analysis was that consumption of over 4 drinks per day was significantly associated with a 74% increased risk of AF.[81] Further analysis using linear and spline regression models found that there was a very modest dose-response relationship between alcohol intake and AF with an increase in relative risk of 1.08 (CI 1.05 – 1.10) for every increase of 10 grams of alcohol consumed per day. Although the graph of the cubic spline suggested a possible threshold of 33.1 g/day, which is similar to that seen in individual cohort studies,[61] there was no significant difference between the spline model and the linear one (p = 0.77). The authors' interpretation of their analysis was that the risk of AF is increased at any level of alcohol consumption.[81] However, a more interesting finding from the meta-analysis was the stronger effect in case-control than cohort studies, which was nearly statistically significant (p=0.06). As case control studies tend to assess recent consumption better than cohort studies because the reporting in cohort studies may occur years or even decades before AF develops, this finding suggests that the effect might be due to acute, rather than chronic, alcohol consumption, and thus supports the hypothesis that the highest drinking groups were merely identifying individuals more likely to binge drink.

The large variation in the design and results of the individual studies of alcohol consumption and AF suggests that combining studies in a meta-analysis, while useful in principle, may not be entirely feasible. The authors of this most recent meta-analysis acknowledged these limitations and others in their discussion, in addition to finding statistical evidence of publication bias (via an Egger's test p = 0.03).[81]

Limitations of Clinical Studies

In addition to the specific limitations mentioned above, some general limitations exist in studies attempting to estimate the risk of AF related to alcohol consumption. The first limitation applies to any epidemiological analysis of AF, which is the effect of confounding by the multiple risk factors that have been associated with increased risk. Such factors as advanced age, hypertension,[48-50] gender,[51-53] diabetes,[54] myocardial infarction,[54] congestive heart failure,[54] body mass index,[55] kidney function,[56] bradycardia,[57] forced-expiratory volume at 1 second (FEV-1),[58] C-reactive protein[59] and N-terminal-pro-Brain Natriuretic Peptide (NT-proBNP) level,[60] all increase the risk of AF, and as a result, any non-randomized control study with a goal of examining a potential new mediator of AF may be limited by potential confounding unless it is large enough to adjust for these multiple factors. The study by Rich et al. only included 104 total participants, which allowed adjustment for only age, gender, and cardiac function.[8] In contrast, the recent analyses from the Copenhagen City Heart Study[61] and the Women's Health Study[62] examined data from 16,415 and 34,715 participants, respectively, and thus were able to adjust for significantly more covariates, as well as exclude participants with risk factors, such as self-reported coronary heart disease, stroke, use of cardiac medication or antihypertensives.[61] The importance of having a sufficient sample size also concerns the limitation of having enough members of the 'high risk' group, as in the Women's Health Study only 3.9% of participants consumed alcohol in the highest amount (> 2 drinks/day),[62] a finding that the investigators suggested may have accounted for the prior negative findings of smaller prior studies in women.

Because of confounding, it is ultimately impossible to ascribe causation in observational studies. Moderate alcohol intake as a marker for healthy lifestyle has been described in other studies,[67, 68] and abstinence has been shown to reflect underlying illness,[69] prior alcoholism,[70] or lower socioeconomic class.[71] To this point, Mukamal and colleagues found that former drinkers had a 25% increased risk of AF compared with lifelong abstainers, in addition to a 27% increase in mortality.[72] In that same study, the investiga-

tors noted from the Kaplan-Meier curves that heavy drinkers had an initial benefit that attenuated over time, postulated to reflect a 'healthy user' phenomenon in which only healthy older adults are able and willing to consume alcohol[72]. In some occasions, multivariate analysis can be performed to adjust for some of these factors, although in many cases it is difficult as these characteristics are often not known or easily quantified.

A second general limitation of studies assessing the association of alcohol and AF is difficulty in the quantification of alcohol intake by participants. Investigators have been left to questionnaires, interviews, and medical record review to assess the quantity of alcohol intake, with variable degrees of validity. Initial efforts, such as those of Rich et al.[8] as well as several other early studies[53, 63, 64], used a dichotomous approach based on intake of alcohol above or below a certain amount,[8, 63] or the presence or absence of alcohol abuse,[53, 64] to analyze the effect of alcohol. As a result, these early studies were limited by the inability to analyze or describe a dose-response effect of alcohol, or to explore potential thresholds for increased risk, as later studies that included multiple incremental categories were able to do.[61, 62]

However, even with the use of more sophisticated and thorough validation methods, investigators using current methods are still limited in their ability to assess the day-to-day alcohol intake and blood alcohol levels in participants. This leaves open the important question of whether the risk of alcohol is due to chronic intake at a constant level, or fluctuating above a given threshold on a given number of occasions—a critical issue if one is to make assessments about a 'safety threshold' for alcohol consumption. As mentioned, binge drinkers are well-known to have an increased risk for AF,[2, 65] but many studies did not obtain enough information to determine if the highest consuming individuals were also more likely to have periods of excess consumption or binging, and whether it was this behavior rather than the chronic consumption that increased risk.

Conclusions

Atrial fibrillation is the most common sustained cardiac arrhythmia, and its prevalence in the population is increasing.[82] Treatment of AF, regardless of the etiology, is a heavy burden on the healthcare system, with annual U.S. costs for AF management $6.65 billion total, with $2.93 billion for hospitalizations alone.[83] Moderate alcohol intake has been associated with a lower risk of cardiovascular disease, as well as overall mortality, and in terms of AF, most studies to date suggest that alcohol intake at moderate levels (2 drinks/day for men and 1 drink/day for women) is not associated with an increased risk. As far as the threshold level of alcohol consumption at which risk for AF increases, the data are less clear. Several barriers exist in the study of the effects of alcohol and AF, including study size limitations to adjust for the multiple other risk factors for AF, limitations in methods for accurate determination of alcohol consumption patterns across differing populations and demographics, and ultimately limitations in our understanding of the specific arrhythmogenic mechanisms for alcohol-induced AF. Despite these limitations, clinical and basic science studies seem to suggest that individuals who consume large amounts of alcohol are at increased risk of AF. The key question is whether these are individuals who are more likely to have 'binge' drinking episodes, which have been well-described to increase the risk of AF, or whether there is a risk from chronic alcohol use, whose safety threshold remains to be determined.

Atrioventricular nodal ablation and pacemaker implantation is another strategy that may be safe in select patients. However, close attention to the type of pacemaker (biventricular versus single versus dual chamber), the programming, and the patient's functional status is likely needed to select those who will benefit most. Furthermore, there is limited data comparing the relative efficacy of this approach, in which patients may remain in atrial fibrillation but with better controlled ventricular rates, with that of pulmonary vein isolation / trigger-guided ablation, in which maintenance of sinus rhythm is the principal goal.

To date, published data support that ablative strategies are relatively safe and efficacious in elderly patients. Future randomized prospective trials are needed to further assess the safety and efficacy of pulmonary vein isolation in elderly patients. Elderly subsets of the CABANA

trial may offer some insights into the relative efficacy of pulmonary vein isolation when compared with antiarrhythmic drugs in managing patients with atrial fibrillation. Further studies are needed to better evaluate the relative benefits and risks of different approaches aimed at rate versus rhythm control in the elderly population and specifically, the role and timing of ablation strategies.

References

1. Ettinger PO, Wu CF, De La Cruz C, Jr., Weisse AB, Ahmed SS, Regan TJ. Arrhythmias and the "Holiday Heart": alcohol-associated cardiac rhythm disorders. Am Heart J. 1978;95(5):555-562.
2. Thornton JR. Atrial fibrillation in healthy non-alcoholic people after an alcoholic binge. Lancet. 1984;2(8410):1013-1015.
3. James TN, Bear ES. Effects of ethanol and acetaldehyde on the heart. Am Heart J. 1967;74(2):243-255.
4. Gimeno AL, Gimeno MF, Webb JL. Effects of ethanol on cellular membrane potentials and contractility of isolated rat atrium. Am J Physiol. 1962;203:194-196.
5. Koskinen P, Kupari M, Leinonen H, Luomanmaki K. Alcohol and new onset atrial fibrillation: a case-control study of a current series. Br Heart J. 1987;57(5):468-473.
6. Koskinen P, Kupari M, Leinonen H. Role of alcohol in recurrences of atrial fibrillation in persons less than 65 years of age. Am J Cardiol. 1990;66(12):954-958.
7. Peter RH, Gracey JG, Beach TB. A clinical profile of idiopathic atrial fibrillation. A functional disorder of atrial rhythm. Ann Intern Med. 1968;68(6):1288-1295.
8. Rich EC, Siebold C, Campion B. Alcohol-related acute atrial fibrillation. A case-control study and review of 40 patients. Arch Intern Med. 1985;145(5):830-833.
9. McElduff P, Dobson AJ. How much alcohol and how often? Population based case-control study of alcohol consumption and risk of a major coronary event. BMJ. 1997;314(7088):1159-1164.
10. Hansagi H, Romelsjo A, Gerhardsson de Verdier M, Andreasson S, Leifman A. Alcohol consumption and stroke mortality. 20-year follow-up of 15,077 men and women. Stroke. 1995;26(10):1768-1773.
11. Wu CF, Sudhaker M, Ghazanfar J, Ahmed SS, Regan TJ. Preclinical cardiomyopathy in chronic alcoholics: a sex difference. Am Heart J. 1976;91(3):281-286.
12. Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. N Engl J Med. 1988;319(5):267-273.
13.Tolstrup J, Jensen MK, Tjonneland A, Overvad K, Mukamal KJ, Gronbaek M. Prospective study of alcohol drinking patterns and coronary heart disease in women and men. BMJ. 2006;332(7552):1244-1248.
14. Reynolds K, Lewis B, Nolen JD, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: a meta-analysis. JAMA. 2003;289(5):579-588.
15. Walsh CR, Larson MG, Evans JC, Djousse L, Ellison RC, Vasan RS, Levy D. Alcohol consumption and risk for congestive heart failure in the Framingham Heart Study. Ann Intern Med. 2002;136(3):181-191.
16. Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. Alcohol consumption and mortality in patients with cardiovascular disease: a meta-analysis. J Am Coll Cardiol. 2010;55(13):1339-1347.
17. Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. Arch Intern Med. 2006;166(22):2437-2445.
18. Marfella R, Cacciapuoti F, Siniscalchi M, Sasso FC, Marchese F, Cinone F, Musacchio E, Marfella MA, Ruggiero L, Chiorazzo G, Liberti D, Nicoletti GF, Saron C, D'Andrea F, Ammendola C, Verza M, Coppola L. Effect of moderate red wine intake on cardiac prognosis after recent acute myocardial infarction of subjects with Type 2 diabetes mellitus. Diabet Med. 2006;23(9):974-981.
19. Kupari M, Koskinen P. Alcohol, cardiac arrhythmias and sudden death. Novartis Found Symp. 1998;216:68-79; discussion 79-85.
20. Lorsheyd A, de Lange DW, Hijmering ML, Cramer MJ, van de Wiel A. PR and OTc interval prolongation on the electrocardiogram after binge drinking in healthy individuals. Neth J Med. 2005;63(2):59-63.
21. Uyarel H, Ozdol C, Karabulut A, Okmen E, Cam N. Acute alcohol intake and P-wave dispersion in healthy men. Anadolu Kardiyol Derg. 2005;5(4):289-293.
22. Steinbigler P, Haberl R, Konig B, Steinbeck G. P-wave signal averaging identifies patients prone to alcohol-induced paroxysmal atrial fibrillation. Am J Cardiol. 2003;91(4):491-494.
23. Marcus GM, Smith LM, Whiteman D, Tseng ZH, Badhwar N, Lee BK, Lee RJ, Scheinman MM, Olgin JE. Alcohol intake is significantly associated with atrial flutter in patients under 60 years of age and a shorter right atrial effective refractory period. Pacing Clin Electrophysiol. 2008;31(3):266-272.
24. Chen YC, Chen SA, Chen YJ, Tai CT, Chan P, Lin CI. Effect of ethanol on the electrophysiological characteristics of pulmonary vein cardiomyocytes. Eur J Pharmacol. 2004;483(2-3):215-222.
25. Nattel S, Maguy A, Le Bouter S, Yeh YH. Arrhythmogenic ion-channel remodeling in the heart: heart failure, myocardial infarction, and atrial fibrillation. Physiol Rev. 2007;87(2):425-456.
26. Nattel S, Shiroshita-Takeshita A, Brundel BJ, Rivard L. Mechanisms of atrial fibrillation: lessons from animal models. Prog Cardiovasc Dis. 2005;48(1):9-28.
27. Nattel S. New ideas about atrial fibrillation 50 years on. Nature. 2002;415(6868):219-226.
28. Laszlo R, Eick C, Schwiebert M, Schreiner B, Weig HJ, Weretka S, Bosch RF, Schreieck J. Alcohol-induced electrical remodeling: effects of sustained short-term ethanol infusion on ion currents in rabbit atrium. Alcohol Clin Exp Res. 2009;33(10):1697-1703.
29. Klein G, Gardiwal A, Schaefer A, Panning B, Breitmeier D. Effect of ethanol on cardiac single sodium channel gating. Forensic

Sci Int. 2007;171(2-3):131-135.
30. Cofan M, Nicolas JM, Fernandez-Sola J, Robert J, Tobias E, Sacanella E, Estruch R, Urbano-Marquez A. Acute ethanol treatment decreases intracellular calcium-ion transients in mouse single skeletal muscle fibres in vitro. Alcohol Alcohol. 2000;35(2):134-138.
31. Nicolas JM, Antunez E, Thomas AP, Fernandez-Sola J, Tobias E, Estruch R, Urbano-Marquez A. Ethanol acutely decreases calcium transients in cultured human myotubes. Alcohol Clin Exp Res. 1998;22(5):1086-1092.
32. Kobayashi T, Ikeda K, Kojima H, Niki H, Yano R, Yoshioka T, Kumanishi T. Ethanol opens G-protein-activated inwardly rectifying K+ channels. Nat Neurosci. 1999;2(12):1091-1097.
33. Kennedy RH, Liu SJ. Sex differences in L-type calcium current after chronic ethanol consumption in rats. Toxicol Appl Pharmacol. 2003;189(3):196-203.
34. Fenelon G, Balbao CE, Fernandes R, Arfelli E, Landim P, Ayres O, Paola AA. Characterization of the acute cardiac electrophysiologic effects of ethanol in dogs. Alcohol Clin Exp Res. 2007;31(9):1574-1580.
35. Tsai CS, Loh SH, Jin JS, Hong GJ, Lin HT, Chiung CS, Chang CY. Effects of alcohol on intracellular pH regulators and electromechanical parameters in human myocardium. Alcohol Clin Exp Res. 2005;29(10):1787-1795.
36. Piano MR, Rosenblum C, Solaro RJ, Schwertz D. Calcium sensitivity and the effect of the calcium sensitizing drug pimobendan in the alcoholic isolated rat atrium. J Cardiovasc Pharmacol. 1999;33(2):237-242.
37. Anadon MJ, Almendral J, Gonzalez P, Zaballos M, Delcan JL, De Guevara JL. Alcohol concentration determines the type of atrial arrhythmia induced in a porcine model of acute alcoholic intoxication. Pacing Clin Electrophysiol. 1996;19(11 Pt 2):1962-1967.
38. Denison H, Jern S, Jagenburg R, Wendestam C, Wallerstedt S. Influence of increased adrenergic activity and magnesium depletion on cardiac rhythm in alcohol withdrawal. Br Heart J. 1994;72(6):554-560.
39. Maki T, Toivonen L, Koskinen P, Naveri H, Harkonen M, Leinonen H. Effect of ethanol drinking, hangover, and exercise on adrenergic activity and heart rate variability in patients with a history of alcohol-induced atrial fibrillation. Am J Cardiol. 1998;82(3):317-322.
40. Meagher EA, Barry OP, Burke A, Lucey MR, Lawson JA, Rokach J, FitzGerald GA. Alcohol-induced generation of lipid peroxidation products in humans. J Clin Invest. 1999;104(6):805-813.
41. Mihm MJ, Yu F, Carnes CA, Reiser PJ, McCarthy PM, Van Wagoner DR, Bauer JA. Impaired myofibrillar energetics and oxidative injury during human atrial fibrillation. Circulation. 2001;104(2):174-180.
42. Carnes CA, Chung MK, Nakayama T, Nakayama H, Baliga RS, Piao S, Kanderian A, Pavia S, Hamlin RL, McCarthy PM, Bauer JA, Van Wagoner DR. Ascorbate attenuates atrial pacing-induced peroxynitrite formation and electrical remodeling and decreases the incidence of postoperative atrial fibrillation. Circ Res. 2001;89(6):E32-38.
43. Djousse L, Hunt SC, Eckfeldt JH, Arnett DK, Province MA, Ellison RC. Alcohol consumption and plasma atrial natriuretic peptide (from the HyperGEN study). Am J Cardiol. 2006;98(5):628-632.
44. Guillaume P, Gutkowska J, Gianoulakis C. Increased plasma atrial natriuretic peptide after acute injection of alcohol in rats. J Pharmacol Exp Ther. 1994;271(3):1656-1665.
45. Wozakowska-Kaplon B, Opolski G, Herman Z, Kosior D. Natriuretic peptides in patients with atrial fibrillation. Cardiol J. 2008;15(6):525-529.
46. Hodgson-Zingman DM, Karst ML, Zingman LV, Heublein DM, Darbar D, Herron KJ, Ballew JD, de Andrade M, Burnett JC, Jr., Olson TM. Atrial natriuretic peptide frameshift mutation in familial atrial fibrillation. N Engl J Med. 2008;359(2):158-165.
47. Crozier I, Richards AM, Foy SG, Ikram H. Electrophysiological effects of atrial natriuretic peptide on the cardiac conduction system in man. Pacing Clin Electrophysiol. 1993;16(4 Pt 1):738-742.
48. Tokushima T, Reid CL, Gardin JM. Left ventricular diastolic function in the elderly. Am J Geriatr Cardiol. 2001;10(1):20-29.
49. Lewis JF, Maron BJ. Cardiovascular consequences of the aging process. Cardiovasc Clin. 1992;22(2):25-34.
50. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, Tu JV, Levy D. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. Circulation. 2009;119(24):3070-3077.
51. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol. 1998;82(8A):2N-9N.
52. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med. 1982;306(17):1018-1022.
53. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med. 1995;98(5):476-484.
54. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994;271(11):840-844.
55. Tedrow UB, Conen D, Ridker PM, Cook NR, Koplan BA, Manson JE, Buring JE, Albert CM. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (women's health study). J Am Coll Cardiol. 2010;55(21):2319-2327.
56. McManus DD, Corteville DC, Shlipak MG, Whooley MA, Ix JH. Relation of kidney function and albuminuria with atrial fibrillation (from the Heart and Soul Study). Am J Cardiol. 2009;104(11):1551-1555.
57. Grimsmo J, Grundvold I, Maehlum S, Arnesen H. High prevalence of atrial fibrillation in long-term endurance cross-country skiers: echocardiographic findings and possible predictors--a 28-30 years follow-up study. Eur J Cardiovasc Prev Rehabil.

2010;17(1):100-105.
58. Kang H, Bae BS, Kim JH, Jang HS, Lee BR, Jung BC. The relationship between chronic atrial fibrillation and reduced pulmonary function in cases of preserved left ventricular systolic function. Korean Circ J. 2009;39(9):372-377.
59. Pellegrino PL, Brunetti ND, De Gennaro L, Ziccardi L, Grimaldi M, Biase MD. Inflammatory activation in an unselected population of subjects with atrial fibrillation: links with structural heart disease, atrial remodeling and recent onset. Intern Emerg Med. 2011.
60. Patton KK, Ellinor PT, Heckbert SR, Christenson RH, DeFilippi C, Gottdiener JS, Kronmal RA. N-terminal pro-B-type natriuretic peptide is a major predictor of the development of atrial fibrillation: the Cardiovascular Health Study. Circulation. 2009;120(18):1768-1774.
61. Mukamal KJ, Tolstrup JS, Friberg J, Jensen G, Gronbaek M. Alcohol consumption and risk of atrial fibrillation in men and women: the Copenhagen City Heart Study. Circulation. 2005;112(12):1736-1742.
62. Conen D, Tedrow UB, Cook NR, Moorthy MV, Buring JE, Albert CM. Alcohol consumption and risk of incident atrial fibrillation in women. JAMA. 2008;300(21):2489-2496.
63. Cohen EJ, Klatsky AL, Armstrong MA. Alcohol use and supraventricular arrhythmia. Am J Cardiol. 1988;62(13):971-973.
64. Wilhelmsen L, Rosengren A, Lappas G. Hospitalizations for atrial fibrillation in the general male population: morbidity and risk factors. J Intern Med. 2001;250(5):382-389.
65. Puddey IB, Rakic V, Dimmitt SB, Beilin LJ. Influence of pattern of drinking on cardiovascular disease and cardiovascular risk factors--a review. Addiction. 1999;94(5):649-663.
66. Shaper AG, Wannamethee G, Walker M. Alcohol and mortality in British men: explaining the U-shaped curve. Lancet. 1988;2(8623):1267-1273.
67. Mackenbach JP, van den Bos J, Joung IM, van de Mheen H, Stronks K. The determinants of excellent health: different from the determinants of ill-health? Int J Epidemiol. 1994;23(6):1273-1281.
68. Poikolainen K, Vartiainen E, Korhonen HJ. Alcohol intake and subjective health. Am J Epidemiol. 1996;144(4):346-350.
69. Wannamethee G, Shaper AG. Men who do not drink: a report from the British Regional Heart Study. Int J Epidemiol. 1988;17(2):307-316.
70. Vaillant GE. A long-term follow-up of male alcohol abuse. Arch Gen Psychiatry. 1996;53(3):243-249.
71. Fillmore KM, Golding JM, Graves KL, Kniep S, Leino EV, Romelsjo A, Shoemaker C, Ager CR, Allebeck P, Ferrer HP. Alcohol consumption and mortality. I. Characteristics of drinking groups. Addiction. 1998;93(2):183-203.
72. Mukamal KJ, Psaty BM, Rautaharju PM, Furberg CD, Kuller LH, Mittleman MA, Gottdiener JS, Siscovick DS. Alcohol consumption and risk and prognosis of atrial fibrillation among older adults: the Cardiovascular Health Study. Am Heart J. 2007;153(2):260-266.
73. Ruigomez A, Johansson S, Wallander MA, Rodriguez LA. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. J Clin Epidemiol. 2002;55(4):358-363.
74. Ruigomez A, Johansson S, Wallander MA, Garcia Rodriguez LA. Predictors and prognosis of paroxysmal atrial fibrillation in general practice in the UK. BMC Cardiovasc Disord. 2005;5:20.
75. Mattioli AV, Bonatti S, Zennaro M, Mattioli G. The relationship between personality, socio-economic factors, acute life stress and the development, spontaneous conversion and recurrences of acute lone atrial fibrillation. Europace. 2005;7(3):211-220.
76. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. Circulation. 1997;96(7):2455-2461.
77. Djousse L, Levy D, Benjamin EJ, Blease SJ, Russ A, Larson MG, Massaro JM, D'Agostino RB, Wolf PA, Ellison RC. Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham Study. Am J Cardiol. 2004;93(6):710-713.
78. Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. Arch Intern Med. 2004;164(18):1993-1998.
79. Chen WP, Su MJ, Hung LM. In vitro electrophysiological mechanisms for antiarrhythmic efficacy of resveratrol, a red wine antioxidant. Eur J Pharmacol. 2007;554(2-3):196-204.
80. Samokhvalov AV, Irving HM, Rehm J. Alcohol consumption as a risk factor for atrial fibrillation: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2010;17(6):706-712.
81. Kodama S, Saito K, Tanaka S, Horikawa C, Saito A, Heianza Y, Anasako Y, Nishigaki Y, Yachi Y, Iida KT, Ohashi Y, Yamada N, Sone H. Alcohol consumption and risk of atrial fibrillation: a meta-analysis. J Am Coll Cardiol. 2011;57(4):427-436.
82. Majeed A, Moser K, Carroll K. Trends in the prevalence and management of atrial fibrillation in general practice in England and Wales, 1994-1998: analysis of data from the general practice research database. Heart. 2001;86(3):284-288.
83. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. Value Health. 2006;9(5):348-356.