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# Alcohol and arrhythmias: a comprehensive review.

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**Abstract**

The use of alcohol as a social lubricant is ubiquitous in human societies since ancient times. It has also long been recognized that alcohol produces undesirable cardiovascular effects, especially when imbibed in excess. Numerous investigators have noted a causal relationship between alcohol and arrhythmias, as well as sudden cardiac death. We have undertaken a comprehensive review of the literature on alcohol as a potential trigger for arrhythmias. We have reviewed the major epidemiological studies undertaken on this subject. We have also explored pathophysiological mechanisms that drive the arrhythmogenic effects of alcohol. In conclusion although there is definite proof in the literature to implicate alcohol as a culprit in arrhythmias, the relationship is complex.

## Introduction

Alcohol (French *alcool*; Arabic *al-kuhl*) refers to the intoxicating constituent of wine, beer, spirits or any of numerous beverages consumed in almost all societies for over 7000 years. The term is used interchangeably with *ethanol* or *ethyl alcohol* ( $C_2H_5OH$ ).

Recorded history has liberal references to alcohol use and some mention of the ill effects of it, especially in religious inscriptions. The earliest writings pertaining to the consumption of alcohol can be found in Mesopotamian clay tablets which date to 4000 BC(1). Societal and religious taboos prohibiting excess indulgence of alcohol can be found dating from the code of Hammurabi of Babylon (*circa*.1700 BC), ancient Egypt, imperial China, Persia and Buddhist India ( 5<sup>th</sup> century BC) (1).. Both the Old and New Testaments of the Bible and the Koran abound with references to the use of alcohol, as well as warnings against its abuse. As early as the nineteenth century, alcohol abuse was reported in the medical literature as detrimental to the heart. Examples included the Munich Beer Heart as reported by German pathologist Otto Bollinger, and the Tubingen Wine Heart, both popular references to deleterious consequences of alcohol excess identified during the early 20<sup>th</sup> century.

The latter half of the twentieth century witnessed considerable attention on the beneficial effects of alcohol, especially when consumed in moderation. Potential beneficial effects include reductions in total and cardiovascular mortality, coronary heart disease events, ischemic cerebrovascular events, and sudden cardiac death. Increased HDL, reduced plasma viscosity, decreased fibrinogen concentration, increased

fibrinolysis, decreased platelet aggregation and coagulation, and enhanced endothelial function are some of the mechanisms by which alcohol is thought to benefit the cardiovascular system (2). In the same vein we must mention that adverse cardiovascular effects from alcohol especially when imbibed in excess over long periods of time include alcoholic cardiomyopathy, hypertension and strokes.

Another important facet to the many effects of alcohol on the heart relates to its effects on heart rhythm and arrhythmias. In this review we will discuss the literature implicating alcohol as a culprit in the etiology of arrhythmias. We review basic science reports and animal models on this subject. We will discuss the types of arrhythmias seen, the levels of alcohol and or drinking patterns implicated, and potential pathophysiological mechanisms.

### **Alcohol and arrhythmias**

Numerous nineteenth century physicians noted an adverse relationship between chronic intake of excessive amounts of alcohol and heart disease. William MacKenzie is credited with having coined the term “*alcoholic heart disease*” in his text book from 1902 titled “*Study of the Pulse*” (3, 4). In 1929, reports on cardiac beriberi reported a “hyperkinetic circulatory state” but no arrhythmias, although the electrocardiogram was noted to show tachycardia and a shortened conduction time(5, 6). In 1959, William Evans reported on characteristic T wave changes (dimple, cloven, spinous, and blunt) in the electrocardiograms of alcoholic patients(7). He also noted the presence of atrial

fibrillation (AF), paroxysmal atrial tachycardia (PAT) and bundle branch blocks (7). In a study of 50 patients at London Hospital, Bridgen and Robinson reported that half of the patients had AF at some time; nodal rhythm, ventricular extra systoles, complete heart block, left and right bundle branch blocks were also noted(8). In 1978 Ettinger and colleagues, coined the term “*holiday heart*” defined as “*an acute cardiac rhythm and or conduction disturbance associated with heavy ethanol consumption in a person without other clinical evidence of heart disease and disappearing without evident residual, with abstinence.*” (9). The most common arrhythmia noted in this study was AF; others were atrial flutter (AFL), junctional tachycardia, isolated premature ventricular complexes (PVC), isolated premature atrial complexes (PAC), paroxysmal atrial tachycardia (PAT) and ventricular tachycardia (VT).

### **Clinical Features pertaining to Alcohol induced Arrhythmias**

#### **Alcohol and Supraventricular Arrhythmias**

Of all alcohol-induced supraventricular arrhythmias, the evidence is most compelling for AF. One of the earliest studies to address the relationship between alcohol and AF was a retrospective review in flying personnel by Lamb and Pollard in 1964(10). Of the 60 case histories reviewed, there were at least six instances of AF where excessive alcohol ingestion was noted. Furthermore, it was observed that bouts of AF occurred in the early hours of the morning or upon arising from an alcoholic binge. Ettinger et al., reported a seasonal peak in the incidence of arrhythmias at the end of the year and New Year’s Day; the “holiday heart”. AF was the most common arrhythmia, followed by AFL

and PVC's (9). Although this study was a retrospective review with a small sample size it succeeded in generating a lot of interest in the medical community.

Koskinen et al., queried the amount of alcohol consumed during the week preceding AF in 100 patients. They found that 15-30% of idiopathic AF may be alcohol related, and 5-10% of new episodes of AF can be explained by alcohol ( Figure 1)(11). In another study by the same group, self reported alcohol consumption was higher in young and middle aged patients with recurrent AF (especially males) compared to matched hospital control subjects(12).

Djoussé et al., using data from 10,333 subjects in the Framingham Study found that consumption of alcohol above 36 g/day increased the risk of AF by 34%, after adjusting for potential confounders(13). Of note, one alcoholic beverage equals 13.7g of ethanol. Frost et al., reported in a prospective cohort study of 47,949 Danes, the Danish Diet, Cancer and Health Study, an increasing risk of AF and AFL in men, but not in women, with an average intake of alcohol of 20g/day or more(14). In the prospective cohort study of 16,415 Danes, the Copenhagen City Heart Study, Mukamel et al., found that alcohol intake of 35 or more drinks per week was associated with higher AF risk in men(15). In the Women's Health Study, Conen et al., found that in healthy middle-aged women, alcohol consumption of up to 2 drinks per day was not associated with increased risk of AF (16).. However, in the subset of women consuming 2 or more drinks, the risk of AF was 1.6 times higher than women who did not consume alcohol.

Marcus et al., studied the association between AF/AFL and alcohol intake in 195 consecutive patients, specifically measuring the right Atrial Effective Refractory Period (AERP)(17). This study is also important because the authors found that daily alcohol intake was associated with a shorter right AERP ( $p=0.025$ ) and increased AFL in patients less than sixty years of age. The authors hypothesize that the shorter right AERP allows the right atrium to sustain a rapid rate in response to an initiating rhythm or to allow propagation of a critically timed PAC, thus suggesting a causal relationship for arrhythmias.

The evidence that alcohol predisposes to other types of supraventricular arrhythmias such as PAT is less impressive than with AF. A Kaiser Permanente study by Cohen et al., found an association between heavier drinking (6+ drinks vs. <1 drink) and all types of supraventricular arrhythmias(18). Koskinen and Kupari noted that coexistent electrolyte abnormalities and infections (or other acute illnesses) may act together with alcohol to produce supraventricular arrhythmias(19). Table I summarizes epidemiological studies pertaining to alcohol and its role in supraventricular arrhythmias.

Thus, data suggest a dose response relationship between alcohol and supraventricular arrhythmias. Larger studies such as the Kaiser Permanente Study, the Framingham Study, Danish Diet, Cancer and Health Study, the Copenhagen City Heart Study and the Women's Health Study involved over 10,000 subjects each and controlled



for confounders. However the sheer diversity in the design and scope of these studies makes further conclusions difficult.

### **Protective Effect of Alcohol against Supraventricular Arrhythmias**

While the above studies support the commonly observed association between alcohol and supraventricular arrhythmias, a few studies have noted a protective effect of alcohol against AF. Notably, Psaty et al., studied the incidence of AF among older adults during 3 years of follow-up in the Cardiovascular Health Study. Alcohol use was inversely associated with AF incidence(20). The low level of alcohol use (2-3 drinks/week), as well as the low incidence of binge drinking in this older cohort, may explain this finding. It thus appears that the relationship between alcohol and arrhythmias may be non-linear involving complex interactions among variables such as dose, drinking pattern, age and sex.

### **Alcohol and Ventricular Arrhythmias and Sudden Cardiac Death**

The relationship between alcohol and VT as well as sudden cardiac death (SCD) is definite, albeit not straightforward. VT and SCD are discussed together here as the pathophysiological operators underlying both conditions are likely common. Epidemiological data from numerous studies suggests the risk of VT/SCD to be lower in individuals with low alcohol intake (2-6 drinks/week) compared to those who rarely or never consume alcohol or those with high intake (3-5 drinks/day) and binge drinkers (21).

This finding may be attributable to the protective effects of low to moderate alcohol consumption on the risk of CAD. Castelnovovo, et al studied 1 million subjects and almost 10,000 deaths in their meta-analysis of 34 prospective studies on alcohol and all cause mortality and observed a J-shaped relationship between alcohol and total mortality( Figure 2) (22).

In the prospective Physicians Health Study of 21,537 male physicians followed for over 12 years, Albert et al., observed that men who drank 2-6 drinks/week had a significantly reduced risk of SCD compared to those who rarely or never consumed alcohol(23). Unfortunately, this study lacks data on drink type or drinking pattern. In the British Regional Heart Study there was a two fold increase in SCD in individuals who consumed six or more drinks/day, a finding most evident in cases where there was no preexisting heart disease (Figure 3)(24). A study of middle aged Swedish men in Uppsala found that a larger proportion of SCD occurred in men known to have alcohol indulgence issues(25). In the Auckland Study, a higher proportion of heavy drinkers who sustained a myocardial infarction were likely to have that event manifest as SCD(26). In the Yugoslavia Cardiovascular Study, recent inebriation was positively correlated with SCD(27).

Greenspon et al., performed electrophysiologic studies on 14 patients with known heart disease and found that administration of alcohol precipitated sustained and non-sustained VT, as well as AFL and AF(28). This study albeit small was significant in that it touched on various mechanisms by which alcohol could potentially be an

arrhythmogenic stimulus. Table II summarizes studies implicating alcohol as an etiologic factor for VT and SCD.

The majority of large studies reviewed above are in agreement that alcohol has a definite relationship to SCD. It appears also that there is a dose response effect as in the case of supraventricular arrhythmias discussed previously. Notably the Auckland Study, Wannamethee et al., and the US Male Physician Study report an increased incidence of SCD at higher levels of alcohol consumption.

Arrhythmias in chronic alcohol abusers may represent clinical manifestations of dilated cardiomyopathy. Therefore, evaluation of cardiac function is mandatory. This issue is crucial, mostly in relation to SCD which can occur in alcoholic cardiomyopathy patients. Over time, alcohol abuse alters calcium homeostasis, mitochondrial function and the structure and function of contractile proteins, resulting in impaired myocardial function (29). These cellular and sub cellular effects eventually translate into increased left ventricular dilatation and mass, thinning and left ventricular dysfunction (systolic and diastolic). It has also been noted that abstinence from alcohol in patients with alcoholic cardiomyopathy improved the risk of SCD, thought to be related to improved left ventricular function (30).

### **Basic Investigations into Alcohol induced Arrhythmias**

In this section we will review the important aspects of the action of alcohol on the heart which are thought to be related to its arrhythmogenic effects.

### **Effect of Alcohol on the QT interval**

Prolongation of the QT interval is associated with ventricular arrhythmias and SCD. Studies in alcoholics have demonstrated QT interval prolongation(31). In alcoholics with liver disease, QT prolongation was an independent prognostic factor for SCD (Figure 4 )(32). Alcoholics also tend to have a higher incidence of polysubstance abuse and psychiatric morbidity, often requiring QT-prolonging medications such as tricyclic-antidepressants, SSRI's and lithium, potentially providing a veritable "*cocktail de la mort!*"

Berger et al, developed the QT variability index (QTvi), calculated by normalizing the QT to heart rate variability as a non-invasive marker of cardiac repolarization lability(33). In a study of patients experiencing acute alcohol withdrawal, Bär et al., found the QTvi was increased in alcohol withdrawers compared to controls(34). Possible mechanisms of increased QTvi include increased sympathetic activity in the setting of alcohol withdrawal, concurrent hypokalemia and hypomagnesaemia altering transmembrane potentials, and direct myocardial damage from alcohol(4). Alcohol withdrawal is also associated with rebound  $\beta$ -adrenergic hypersensitivity and elevated catecholamine levels, both of which in the milieu of electrolyte disarray, stages a dangerous setting for ventricular and other arrhythmias(35).

### **Alcohol and Heart Rate Variability and Baroreceptor Sensitivity**

Electrophysiological findings associated with alcohol withdrawal syndrome include decreased heart rate variability (HRV) and reduced baroreflex sensitivity, both of which correlate with cardiac events(34). In healthy subjects, acute alcohol intake causes a significant decrease in HRV due to diminished vagal modulation(36, 37). A similar effect was noted in patients with CAD and acute alcohol exposure (38).

Carretta et al, found that alcohol reduces baroreflex sensitivity in healthy and hypertensive subjects, even before the onset of changes in heart rate or blood pressure (39). Animal and normal human volunteer studies have confirmed similar acute, as well as chronic, effects of alcohol on baroreceptor responsiveness (40, 41).. Gender-related differences in baroreceptor reflex control mechanisms have been demonstrated which might explain different dose response relationships between alcohol and arrhythmias in males and females (42).

### **Alcohol and Nutritional Abnormalities**

Electrolyte abnormalities frequently encountered in chronic alcoholics, acute alcohol intoxication and alcohol withdrawal include hypomagnesaemia and hypokalemia (43, 44). These electrolyte abnormalities may be due to a direct effect of alcohol, secondary to alcohol-induced diseases affecting other organs, malnutrition, vomiting or diarrhea, or as part of alcoholic ketoacidosis(45, 46). Hypokalemia, commonly seen in chronic alcoholics, can predispose to VT, torsades de pointes and SCD(47).

At a subcellular level, magnesium is intricately linked to calcium (channel activity) and potassium (transport) in the myocyte, affecting cell membrane stability and impulse generation(48). Alcohol exacerbates magnesium deficiency, mainly through excessive urinary loss(49, 50). Alcoholics can be malnourished. Additionally, alcoholics can have endocrine abnormalities such as secondary aldosteronism (especially in cirrhotics). Animal studies have shown that during acute alcohol withdrawal, catecholamine-induced lipolysis releases fatty acids that can bind intracellular magnesium (51). Magnesium deficiency is associated with QT interval prolongation instigating malignant ventricular arrhythmias such as torsades de pointes (52-54). Finally, magnesium deficiency is closely tied to potassium deficiency and can result in refractory hypokalemia(55, 56). Interestingly, dietary magnesium supplementation in a rat model attenuates alcohol-induced myocardial dysfunction(57).

### **Animal Models Relating to Alcohol Induced Arrhythmias**

Studies on isolated rat atria have demonstrated that alcohol causes shortening of the action potential and decreases contractility, which could predispose to ectopic complexes and arrhythmias (58). Rat cardiomyocytes exposed to alcohol have a dose dependant depression in contractility due, at least in part, to a depletion of sarcoplasmic calcium(59). Studies in mice and human tissue have shown that alcohol causes direct myocardial ultrastructural damage, including edema of sarcoplasmic reticulum, fragmentation of contractile elements, expansion of intercalated disc, and fatty deposits

(60, 61). Anadon et al., demonstrated in a porcine model that acute alcohol infusion resulted in dose dependant atrial arrhythmias, including AFL(62).

## **Conclusion**

We conclude there is credible evidence in the literature for a strong association between alcohol and arrhythmias. This is especially true for supraventricular arrhythmias; predominantly AF in younger men who tend to drink more. Alcohol is also positively correlated with VT and SCD in heavier drinkers. Chronic alcohol abuse produces multiple physiologic aberrancies in the heart, including ultrastructural changes, effects on the QT interval and HRV, and proarrhythmic electrolyte abnormalities. This creates a substrate for triggering nonfatal and fatal arrhythmias. (Figure 5) Indeed a significant number of alcoholics, especially those with coexistent ischemic heart disease, are victims of SCD (24, 63) .

Moderate regular alcohol consumption produces desirable health benefits which are lost as the dose escalates or a binge pattern is assumed. The relation of alcohol to arrhythmias has strong evidence in the literature based on epidemiological studies, basic science investigations and animal models, as we have outlined. However, the exact relationship between alcohol and arrhythmias continues to be controversial and potentially can never be answered as there is little likelihood of a randomized controlled trial addressing these issues. Nevertheless, the ACC/AHA guidelines do suggest complete

abstinence from alcohol when a correlation is suspected between alcohol use and ventricular arrhythmias.



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## Figures

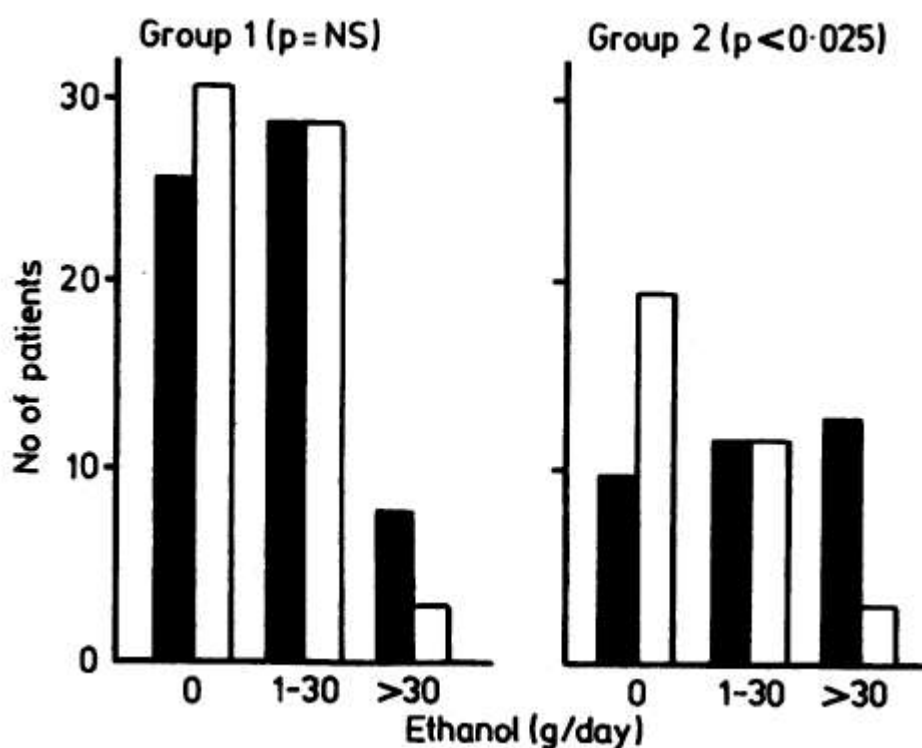


Figure 1. Average daily alcohol consumption of the patients (black columns) and their controls (white columns) during the week preceding atrial fibrillation Group 1, atrial fibrillation with an associated disease. Group 2, idiopathic atrial fibrillation. Reprinted with permission from Koskinen P, Kupari M, Leinonen H, LuomanmuÅ'aki K. Alcohol and new onset atrial fibrillation: a case-control study of a current series. *British Heart Journal* 1987;57(5):468-73.

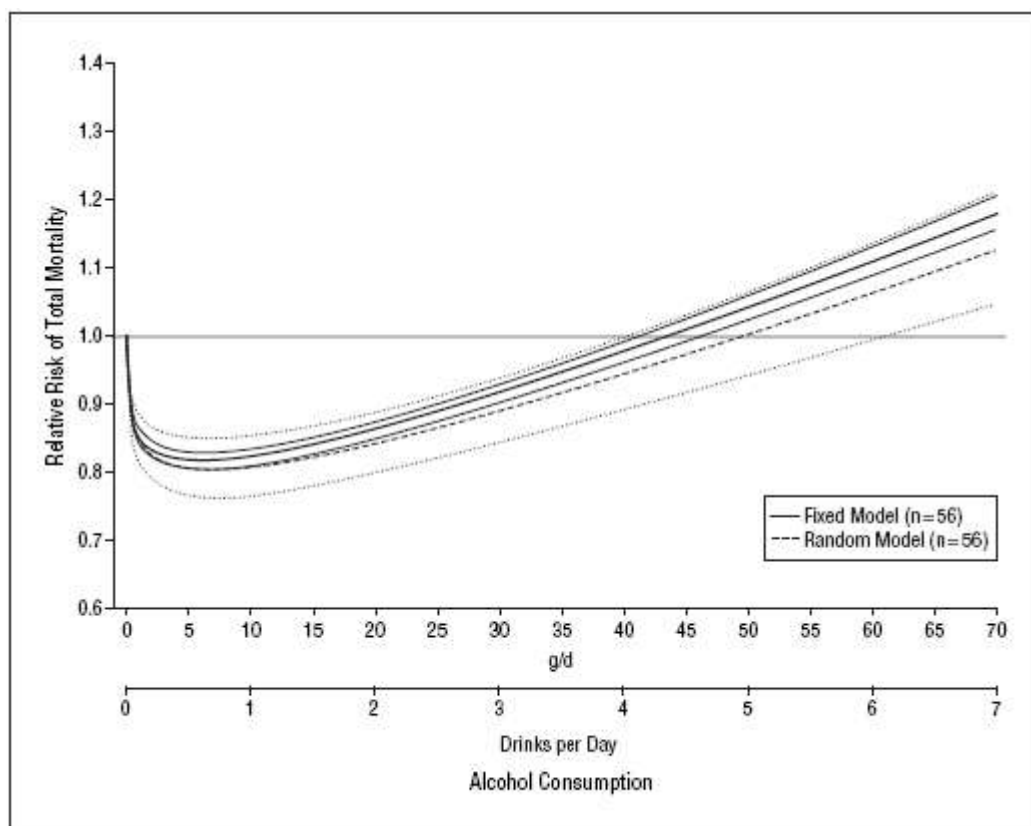


Figure 2: Relative risk of total mortality (95% confidence interval) and alcohol intake extracted from 56 curves using fixed- and random-effects models. (Reprinted with permission. Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. Alcohol Dosing and Total Mortality in Men and Women: An Updated Meta-analysis of 34 Prospective Studies. *Arch Intern Med* 2006;166(22):2437-2445.

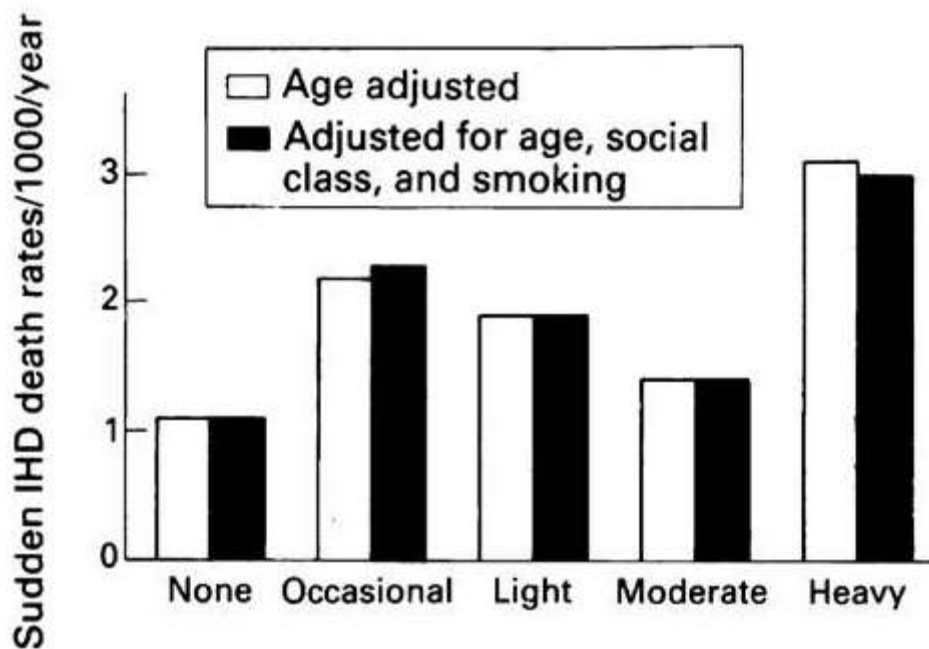


Figure 3: Abscissa refers to alcohol intake (adjusted for age and age, social class and smoking—none, occasional, light, moderate and heavy). Ordinate refers to sudden death rates/1000/year. IHD = ischemic heart disease. Reprinted with permission from Wannamethee G, Shaper AG. Alcohol and sudden cardiac death. *British Heart Journal*. 1992;68(5):443-8.

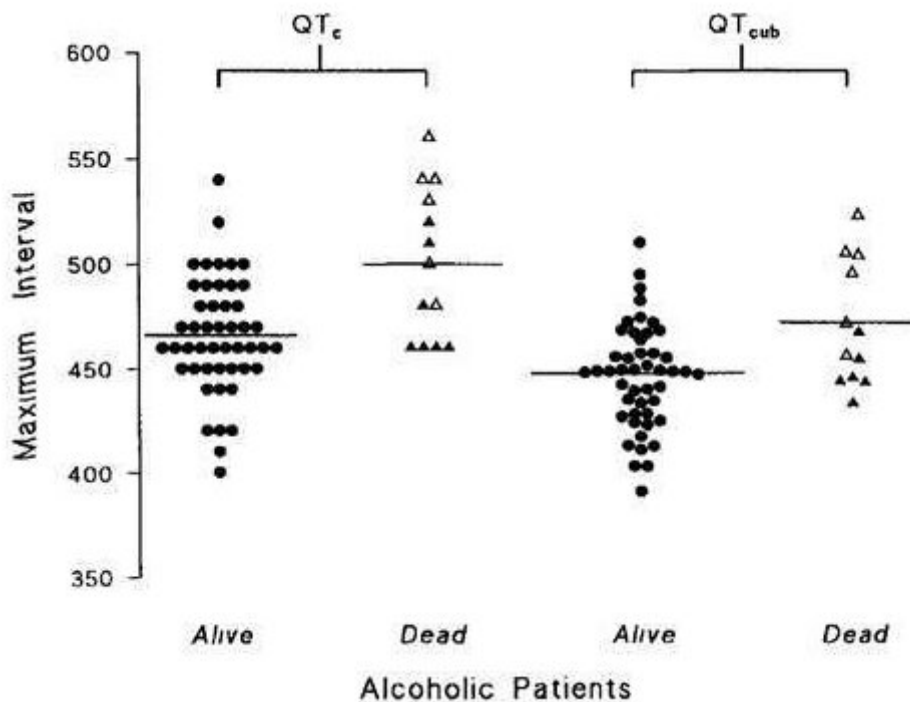


Figure 4: Corrected QT intervals in alcoholic patients and survival.  $\Delta$  = cardiac sudden death,  $\blacktriangle$  = non-cardiac cause of death. Horizontal lines represent means.  $QT_c$  = QT interval corrected for rate (Bazett's formula);  $QT_{cub}$  = QT interval corrected for rate (cube root formulae). Reprinted with permission from Day CP, James OF, Butler TJ, Campbell RW. QT prolongation and sudden cardiac death in patients with alcoholic liver disease. *Lancet*. 1993;341(8858):1423-8.



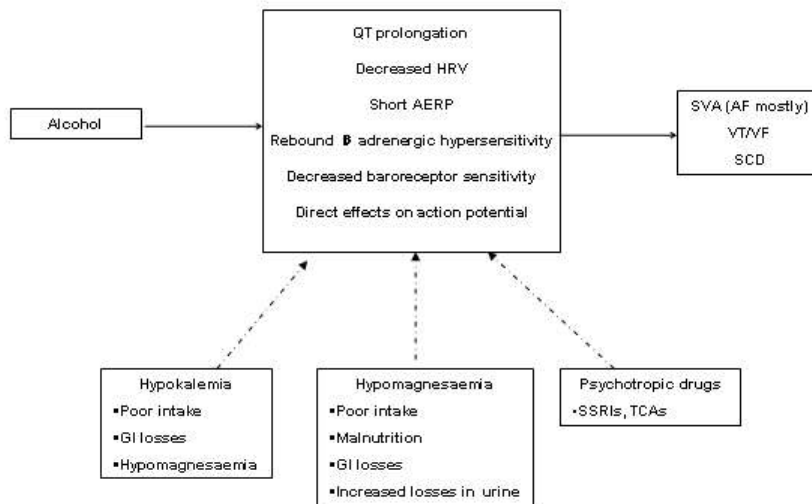


Figure 5: Potential mediators of alcohol-induced cardiac arrhythmias. TCA = tricyclic antidepressants, SSRI = selective serotonin reuptake inhibitors.

## Tables

**Table 1: Studies of Alcohol and Supraventricular Arrhythmias**

Study	Study type	N	Mean age (years)	Alcohol amount/pattern	Arrhythmia	Results	Comments
Lamb & Pollard 1964 <sup>12</sup>	Case series	60	36.6	Excessive	AF	AF occurred when arising from excess use.	Flying personnel, no control group, small sample size.
Ettinger et al 1978 <sup>11</sup>	Case series	24	43	6-10 drinks/day	AF, AFL, PAT, VT	Episodes followed heavy weekend or holiday sprints.	“Holiday Heart”, no control group, small sample size
Koskinen & Kupari 1987 <sup>13</sup>	Case-control	100	48	1-30/>30 g/day	AF	15-30% of AF may be alcohol related.	Small sample size, short follow up.
Kaiser Permanente study Cohen et al 1988 <sup>20</sup>	Prospective cohort	10,7139	--	6+drinks/day	AF,AFL,APC,SVT	Relative risk=2.3 for 6+vs<1 drink	Large cohort, role of bingeing not studied
Framingham Study Djoussé et al 2004 <sup>15</sup>	Case-control	10,333	44.6♂ 47♀	>36 g/day	AF	34% increase in AF	Large sample size, long follow up, adjusted for confounders.
Danish Diet, Cancer & Health Study Frost et al 2004 <sup>16</sup>	Prospective cohort	47,949	56	>20g/day in ♂ not ♀	AF, AFL	25-46% increase in ♂	Large cohort study, adjusted for confounders. limited power in ♀
Copenhagen City Heart Study Mukamel et	Prospective cohort	16,415	50	>35 drinks/wk in ♂	AF	Relative risk=1.45	Large observational study, Native born Danes

al 2005 <sup>17</sup>							
Women's Health Study Conen et al 2008 <sup>18</sup>	Prospective cohort	34,715	53	> 2 drinks/day in ♀	AF	1.6 fold risk compared to non-drinkers	Large cohort study, long follow up

(AF-Atrial Fibrillation; AFL-Atrial Flutter; APC-Atrial Premature Contraction; PAT-Paroxysmal Atrial Tachycardia; SVT-Supra Ventricular Tachycardia; VT-Ventricular Tachycardia)

**Table II: Studies of Alcohol and VT/SCD**

Study	Study type	N	Mean age (years)	Alcohol/Habits	Arrhythmia	Results	Comments
Auckland study Fraser et al, 1981 <sup>27</sup>	Registry based cohort	326	58.6	167g/week, ♂ 194g/week, ♀ 75g/week,)	SCD	High alcohol intake is seen frequently in acute coronary syndromes manifest as SCD	Did not prove alcohol is associated with VF.
Yugoslavia Cardiovascular Study Kozarevic et al 1982 <sup>28</sup>	Cohort study	11,121	46	Alcohol summary codes (0-16)	SCD	Recent drunkenness associated with sudden death.	Only Yugoslav males studied
Holiday Heart Greenspon et al 1983 <sup>29</sup>	Case series	14	57	EP study	VT, NSVT, VPC	Increased risk in patients with heart disease	Induction of tachyarrhythmia with small doses of alcohol in EP lab
Lithell et al 1987 <sup>26</sup>	Case-control	2700	50	Registration at Temperance Board	SCD	Large proportion of SCD in individuals with known alcohol intemperance	SCD more common in alcoholics who have MI
Wannamethee et al 1992 <sup>25</sup>	Prospective cohort	7,735	50	>6 drinks/day	SCD	Two fold increase in SCD risk	Study accounts for pre-existing heart disease
US Male Physicians & SCD Albert et al 1999 <sup>24</sup>	Prospective cohort	21,537	53	2-6 drinks/week	SCD	Decreased SCD risk	No information on drink type or drinking pattern

(MI-Myocardial Infarction; NSVT-Non-Sustained Ventricular Tachycardia; SCD-Sudden Cardiac Death; VF-Ventricular Fibrillation; VPC-Ventricular Premature Complex)