Alcohol, Heart Disease, and Mortality: A Review

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Observational data suggest that moderate alcohol consumption is associated with reduced all-cause mortality compared with that associated with either abstinence or heavy drinking. Alcohol consumption reduces cardiovascular disease risk primarily by increasing production of high-density lipoprotein cholesterol, and possibly by increasing plasminogen, tissue plasminogen activator, and endothelial function, and decreasing platelet aggregability, fibrinogen, and lipoprotein(a). Red wine, containing antioxidants, has been purported to be especially cardioprotective. However, red wine consumption is not associated with reduced all-cause mortality in European countries, and American studies have found no relationship between the type of alcohol consumed and cardiovascular risk. Alcohol appears to be more cardioprotective if consumed with meals (possibly owing to protection against postprandial endothelial protection) and in moderation daily (as opposed to binge drinking). Despite the wealth of observational data, it is not absolutely clear that alcohol reduces cardiovascular risk, because no randomized controlled trials have been performed. Alcohol should never be recommended to patients to reduce cardiovascular risk as a substitute for the well-proven alternatives of appropriate diet, exercise, and drugs. Alcohol remains the number three cause of preventable premature death in this country, and the risk of alcohol habituation, abuse, and adverse effects must be considered in any patient counseling. [Rev Cardiovasc Med. *2002;3(1):7–13*]

Key words: Alcohol • Mortality • Cardioprotection • High-density lipoprotein cholesterol • Atherosclerosis

Alcoholic beverages have been consumed by many societies for thousands of years, their use often intertwined with culture and religion. The consumption of alcohol has both beneficial and adverse effects on morbidity and mortality. Most of the benefit of alcohol appears to be conferred by a reduction in atherosclerotic cardiovascular disease risk, but alcohol has adverse cardiac effects on blood pressure, ventricular function, and incidence of atrial fibrillation. Many noncardiac conditions and diseases, such as violence, accidents, liver and neurological disease, pancreatitis, and cancer are exacerbated by alcohol consumption.

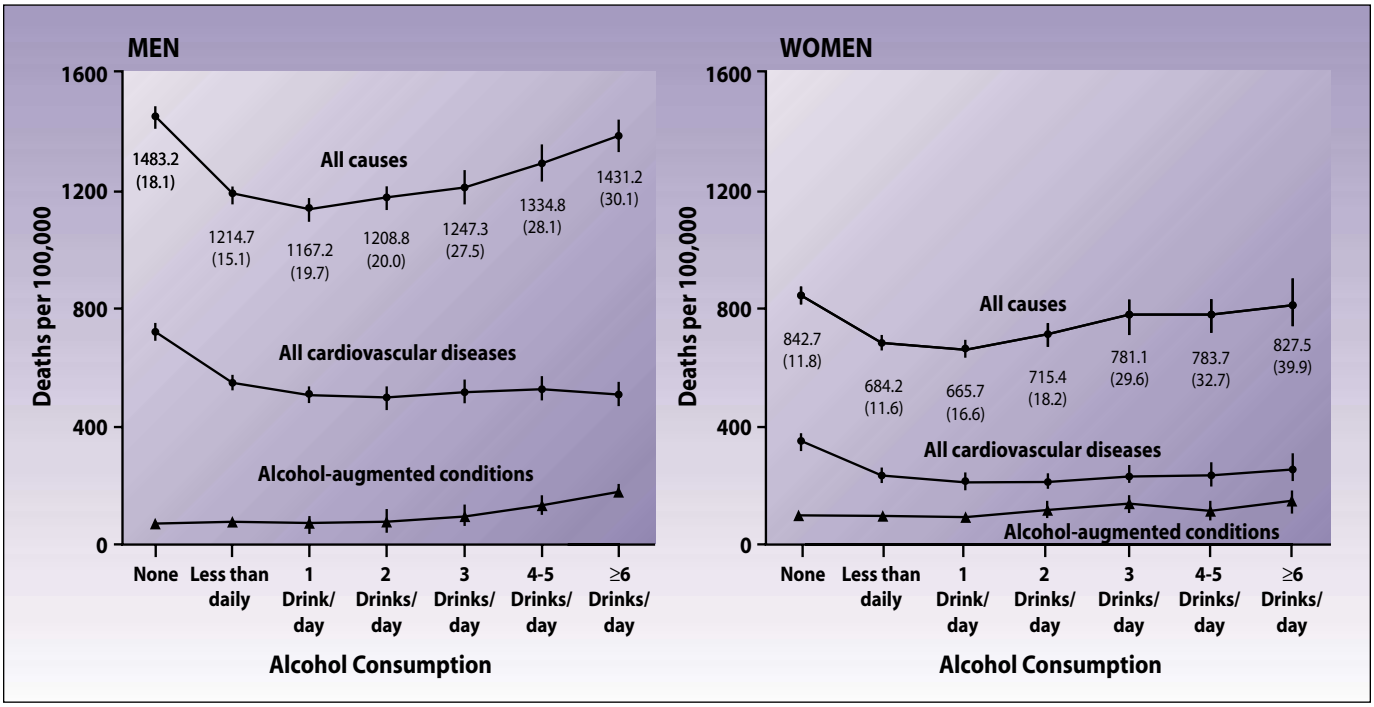

Figure 1. *The effect of alcohol consumption on total, cardiovascular, and non-cardiovascular mortality in middle-aged and older individuals. Reproduced with permission from Thun et al,*[7] N Engl J Med. *1997;337:1705–1714. © 1997 Massachusetts Medical Society. All rights reserved.*

A beneficial effect of alcohol on coronary heart disease was first reported in 1786 by Heberden, who noted relief of angina pectoris by "spirituous cordials."[1] Based on observational data, an inverse relationship between alcohol consumption and arteriosclerosis was first reported by Cabot in 1904.[2] Since that time, more than 60 geographic, case-control, cohort, and epidemiological studies have reported similar findings.[3–7] Moderate alcohol consumption, defined as 1 to 3 drinks daily, compared with abstinence is associated with a 30%–60% reduction in coronary heart disease risk in case-control and cohort studies. Similar observations have been found in comparisons of coronary arteriosclerosis demonstrated by angiography and autopsy with reported alcohol consumption. These observations appear to be independent of the confounders of diet and smoking. Despite adjustment for confounders in observational studies, no randomized controlled trials of alcohol have been performed with cardiovascular events as the endpoint. The reduction in cardiovascular risk is confined to middle-aged and older individuals, because coronary heart disease is a much larger factor in these groups (Figure 1). Somewhat less cardioprotection is apparent in women.[6]

The mortality rate from coronary heart disease in France, where red wine consumption is very high, is about 40% that of the United States at similar cholesterol levels and animal fat consumption, an observation termed the "French paradox."

In most analyses, 1 drink is defined as 1/2 ounce of alcohol, which is approximately equivalent to 12 ounces of beer; 4 ounces of wine (1/2 wine glass); or 1 ounce of spirits (2/3 jigger). Whereas these portions of beer and spirits are commonly understood to be "1-drink equivalents," most people are surprised to learn that a bottle of wine contains 7 drinks (ie, more than a six-pack of beer).

Beyond 2 drinks per day, no further reduction in cardiovascular mortality is observed.[7] This appears to be due to increases in non-coronary heart disease cardiovascular mortality, including hypertension, cardiomyopathy, atrial fibrillation, and possibly hemorrhagic stroke. In both men and women, non-cardiovascular disease mortality rises when drinking levels exceed about 2 drinks per day

Table 1
Ranked (Top to Bottom) Average Wine Consumption Versus Cardiovascular and Total Mortality in Developed Countries

Highest Wine Consumption	Lowest Cardiovascular Mortality	Lowest All-Cause Mortality
France	Japan	Japan
Italy	France	Belgium
Spain	Spain	Switzerland
Switzerland	Italy	Sweden
Belgium	Switzerland	Iceland
Germany	Belgium	Spain
Sweden	Germany	France
Japan	USA	Italy
USA	Iceland	USA
Iceland	Sweden	Germany

Data from Criqui and Ringel.[9]

(Figure 2). The opposite associations between alcohol consumption and cardiovascular and non-cardiovascular disease result in a U-shaped relationship between alcohol consumption and all-cause mortality for middle-aged and older individuals, with a minimum mortality at 1 drink per day.

Wine Consumption

Some studies have attributed the majority of the cardioprotective effect of alcohol to wine consumption, especially red wine.[8–13] Correcting for confounders is even more difficult in considerations of type of alcohol consumed, because wine drinkers tend to be less fat, to exercise more, and to drink with meals.[8] The mortality rate from coronary heart disease in France, where red wine consumption is very high, is about 40% that of the United States at similar cholesterol levels and animal fat consumption, an observation termed the "French paradox."[9] Part of the paradox appears to be due to differences in reporting causes of death.

Four observations reduce the argument for an apparent selective benefit of red wine. Whereas cardiovascular risk is lower in the predominately red wine producing and consuming countries of France, Italy, Spain, and Switzerland, the all-cause mortality in these countries is not reduced (Table 1). This is surprising, because cardiovascular mortality makes up about one third of total mortality in developed countries. By contrast, Japan, with the lowest cardiovascular (one half that of France) and all-cause mortality of any westernized country, has a per capita wine consumption one sixth that of France and an alcohol consumption less than one half that of France.[9] A better explanation

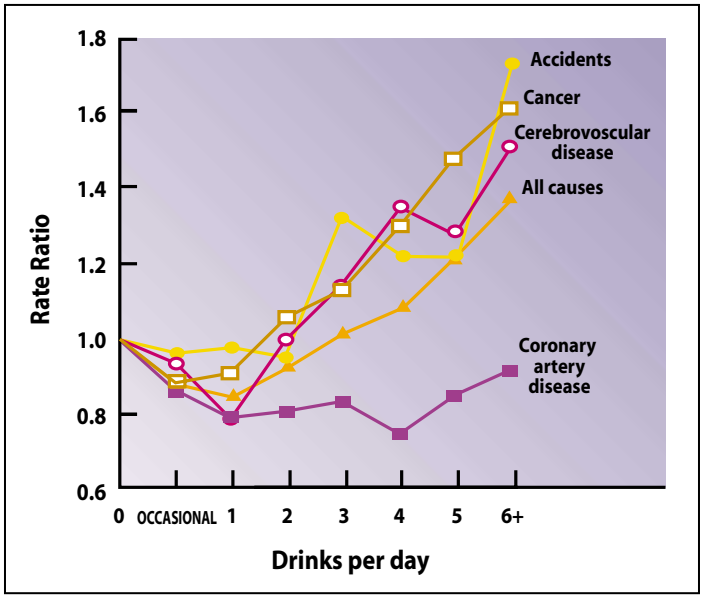

Figure 2. *Rates of death from accidents, cancer, cerebrovascular disease, coronary artery disease, and all causes as a function of the daily amount of alcohol consumed. Adapted from Folts et al.*[5]

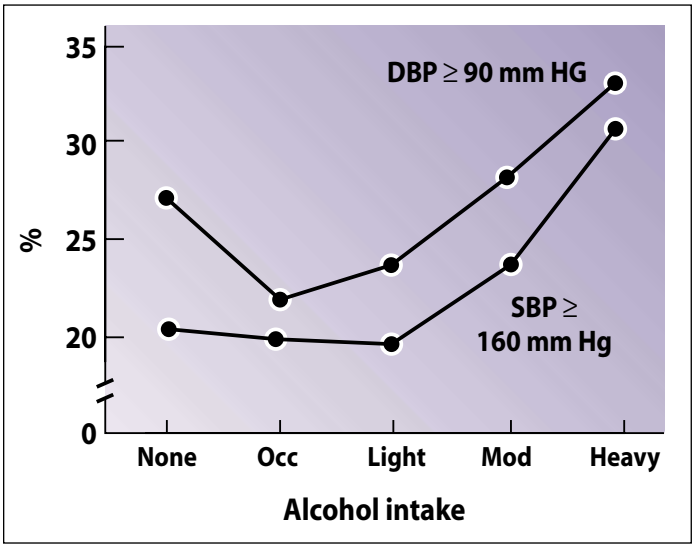

Figure 3. *The incidence of systolic blood pressure (SBP) > 160 mm Hg and diastolic blood pressure (DBP) > 90 mm Hg as a function of the amount of alcohol consumed. Mod, moderate; Occ, occasional; %, % of subjects. Adapted from Shaper, AG, Ashby D, Pocock SJ. Blood pressure and hypertension in middle-aged British men.* J Hypertens. *1988;367–374, with permission from the publisher.*

for the low mortality in Japan is the per capita consumption of animal fat and fruit, which are one half and twice, respectively, that of France.

A second issue is the predominant consumption of red wine with meals.[8] By contrast, alcohol consumption at other times appears to be less cardioprotective. This finding suggests that wine consumption may be a marker for other lifestyle confounders. It may also represent a specific mechanism of the cardioprotection afforded by alcohol. Wine consumption has been shown to reduce the postprandial endothelial dysfunction induced by a high fat meal (see below).

In an 11-year study, Gronbaek and colleagues followed 24,523 men and women 20–98 years of age according to their total and type of alcohol consumption.[10] Although moderate wine drinkers had about 20% less all-cause mortality than did non–wine drinkers, there was no effect according to the amount of wine consumed. Subjects whose wine intake made up 1%–30% of their total alcohol intake had lower mortality than did those who drank wine predominantly (>30% of total alcohol intake). Again, this observation suggests a lifestyle confounding factor identified by any amount of wine consumption, as opposed to wine consumption, itself.

The most relevant argument against a selective benefit from red wine is based on data originating in the United States. Klatsky and colleagues followed mortality in 128,934 Californians enrolled in a health maintenance organization for 13 years, according to their total and type of alcohol consumption.[11,12] At 8 years of follow-up, a 30% reduction in all-cause mortality, due to a reduction in coronary heart disease, was observed in moderate drinkers, with the greatest reduction in risk in older individuals. No difference was observed according to the type of alcohol consumed. Women who drank heavily had an especially high mortality. At 13 years of follow-up, the same U-shaped relationship was found. Controlling for the total amount of alcohol consumed, beer drinking appeared to be slightly more protective in men and red and white wine more protective in women. There was no evidence for any selective effect of red wine. In a Boston area, case-control study of 340 subjects, Gaziano and colleagues followed the incidence of myocardial infarction according to the type of alcohol consumed.[13] Again, no significant differences were observed by type of alcohol. These data strongly exclude a selective benefit from red wine in the American population.

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Adverse Effects of Alcohol

The proposed cardiovascular benefits of alcohol must be evaluated against numerous adverse effects. Alcohol is the third leading cause of preventable premature death in the United States, causing approximately 100,000 deaths annually (Table 2).[14] It trails only cigarette smoking and the combined effects of inappropriate diet and inactivity. It should be remembered that alcohol is habituating in about 10% of drinkers and has potentially lethal consequences upon withdrawal. Adverse non-cardiac effects predominant in younger individuals include accidents, violence, suicide, and fetal alcohol syndrome. These consequences in younger individuals are especially tragic given that no data support a benefit of alcohol in this age group. In older individuals, liver and neurological diseases, pancreatitis, and cancer emerge as the major adverse effects. Most of these adverse effects are associated with chronic intake of more than 3 drinks daily. Acute alcohol ingestion is associated with decreased left ventricular function and proarrhythmic effects, most notably paroxysmal atrial fibrillation, which is termed the "holiday heart" syndrome.

Table 2
Preventable Causes of Death in the United States in 1990

Cause	Number	% of Total
Tobacco	400,000	19
Diet and activity	300,000	14
Alcohol	100,000	5
Microbial agents	90,000	4
Toxic agents	60,000	3
Firearms	35,000	2
High-risk sexual behavior	30,000	1
Motor vehicle injuries	25,000	1
Illicit drugs	20,000	<1
Total	1,060,000	49

Reproduced with permission from Bartecchi et al,[14] *N Engl J Med*. 1994;330:907–912.

More than 50 cross-sectional and 10 prospective epidemiologic studies have demonstrated an association between alcohol consumption and systolic and diastolic hypertension (Figure 3).[8] The frequency of hypertension rises steeply beyond moderate drinking in most studies,[15] but the Nurses' Health Study found a linear rise in blood pressure in women 30–50 years old whose alcohol consumption was more than 2 drinks daily.[16] A protective effect of alcohol on the incidence of stroke has been found with moderate consumption. Stroke incidence increases with consumption above 4 drinks daily, predominantly because of increased intracerebral and subarachnoid hemorrhage.[8]

Mechanisms of Action

Most of the beneficial effects of alcohol are due to increases in high-density lipoprotein (HDL) cholesterol.[17,18] Two drinks daily increases HDL cholesterol 10% to 15%, although there is a considerable individual variation in response. Alcohol increases both the smaller HDL_3 fraction and the larger, probably more protective HDL_2 fraction (Figure 4).[17] The increases in HDL cholesterol result from an increased production of apo A-I and apo A-II, the precursors of HDL, without a change in HDL catabolism.[18] Alcohol also increases triglycerides, as do other sugars. In some individuals, this is a marked effect, and the possibility of excess alcohol consumption must be considered in any patient with elevated triglycerides, especially if HDL cholesterol is also elevated. Exogenous estrogen also produces elevations in both of these lipid fractions. Alcohol can increase endogenous estradiol substantially, which in part may explain its lipid effects. Less substantial reductions in low-density lipoprotein (LDL) cholesterol also result from alcohol consumption, even in the presence of normal hepatic function. With alcoholic hepatic decompensation, more marked reductions in LDL cholesterol occur.

A second protective effect of alcohol consumption is a reduction in hemostatic parameters.[19] Alcohol inhibits platelet aggregation to specific agonists in platelet-rich plasma in vitro and in vivo.[20] The acute consumption of 2 drink equivalents reduces platelet deposition in an exteriorized venovenous shunt by 60% to 70% for about 6 hours, persisting even after blood alcohol levels return to baseline.[20] One to two days of platelet disaggregation is especially evident following a drinking binge, which then is followed by reactive hyperaggregability. This phenomenon may, in part, explain the increased incidence in myocardial infarction on Monday, because most heavy drinking occurs on Friday and Saturday, followed by abstinence on

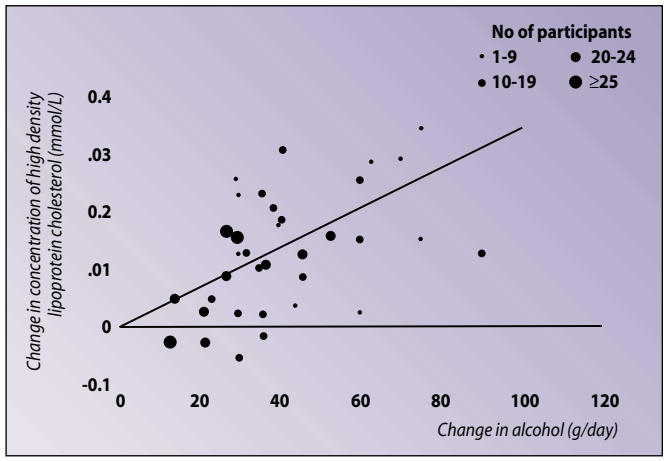

Figure 4. *Increase in HDL cholesterol according to the amount of alcohol consumed in 42 prospective studies. Adapted from Rimm et al,[19] with permission from the BMJ Publishing Group.[19]*

Sunday. The clinical message is that alcohol consumption is probably more beneficial in a pattern of daily moderation rather than periodic excess. Alcohol consumption also reduces hemostasis by increasing plasminogen and tissue plasminogen activator (tPA), both responsible for thrombolysis.[19] At the same time, fibrinogen and lipoprotein(a), a prothrombotic form of LDL cholesterol, are reduced.

Recent studies have shown that alcohol, especially in the form of red wine, protects endothelial function and reduces inflammation, factors thought to be important in the genesis of atherosclerosis.[21–23] Alcohol reduces the postprandial endothelial dysfunction caused by a high-fat meal.[21] Eight ounces daily of red wine for 30 days was found to normalize brachial artery flow-mediated vasodilation, an index of endothelial function, in healthy subjects given a high-fat diet, but had no effect on subjects given a low-fat diet. In a parallel observation, a high-fat meal given to healthy subjects increased nuclear factor-κB, a nuclear transcription factor, which induces several genes for inflammatory proteins, including C-reactive protein.[22] The acute administration of red wine along with the high-fat meal reduced the increase in nuclear factor-κB, an effect not seen with vodka. A recent observational study, however, found that C-reactive protein has a U-shaped relationship to alcohol consumption, independent of type of beverage.[23] In 1801 men and women 18–88 years of age, minimum C-reactive protein was associated with an alcohol intake of 2–4 drinks daily. The findings that alcohol protects against postprandial endothelial dysfunction and inflammation induction probably explain why alcohol appears to be more protective if taken with meals. Perhaps the concept of "wine and cheese" makes good biological sense.

Special Populations

Persons with diabetes mellitus, especially type 2, are at very high risk for cardiovascular disease, partly secondary to the frequently associated risk factors of obesity, dyslipidemia, and hypertension. Diabetic patients have impaired endothelial function and hypercoagulability. In the most recent National Cholesterol Education Program guidelines, the presence of diabetes is no longer listed a risk factor but is considered a coronary heart disease equivalent for cholesterol management purposes.[24] Moderate alcohol consumption, except for its effects on triglycerides, would be thought to be beneficial in middle-aged and older diabetic patients. Three recent studies have found this to be true.[25–27] In a 12-year study of 983 older (mean age 69 years) type 2 diabetic subjects, 1 drink or more daily reduced coronary heart disease risk 79% compared to abstinence.[25] In the Physicians Health Study of 87,938 men, similar reductions in cardiovascular risk with moderate alcohol consumption were found in the 2790 diabetic subjects (39% reduction) compared with the nondiabetic subjects (58% reduction) over 5 years of follow-up.[26] Peripheral artery disease and sudden death were also reduced by moderate alcohol consumption in this study.[28,29] Lastly, the 5103 female diabetic subjects in the Nurse's Health Study were found to have a 55% cardiovascular risk reduction with moderate alcohol intake compared to abstinence over 14 years of follow-up.[27]

The clinical message is that alcohol consumption is probably more beneficial in a pattern of daily moderation rather than periodic excess.

Alcohol also appears to have a beneficial effect in those with established heart disease. In a study of 1913 subjects experiencing a myocardial infarction, those reporting consumption of up to 1 drink daily experienced an adjusted decrease in mortality of 21% compared to nondrinkers over 4 years of follow-up, and those consuming 1 or more drinks daily experienced a 32% decrease in mortality.[30] Although acute and chronic alcohol consumption impair left ventricular function, mild to moderate alcohol ingestion neither increases the incidence of congestive heart failure nor worsens its prognosis once established. In a study of 2235 elderly (mean age 74 years) subjects without heart failure at baseline, moderate alcohol consumption was associated with a 47% reduction in the new appearance of heart failure compared to abstinence in 14 years of follow-up.[31] More importantly, in the Studies of Left Ventricular Function (SOLVD), light-to-moderate drinkers with ischemia-associated left ventricular ejection fractions less than 35% experienced a 45% all-cause mortality risk reduction compared to nondrinkers.[32] Subjects with nonischemic cardiomyopathy experienced an insignificant decrease in mortality (7%).

Clinical Message

- The adverse medical and psychological effects of alcohol must be considered before advising patients about drinking. Do not advise teetotalers to drink. Most importantly, advise drinking patients to drink moderately and responsibly.
- The ideal amount of alcohol is

about 1 drink daily, which is associated with the lowest all-cause mortality in observational studies, primarily owing to a decrease in cardiovascular risk. This effect is only evident in middle-aged and older individuals.

- ♦ There appears to be no real advantage of one type of alcoholic beverage over another. The predominant beneficial effect is an increase in HDL cholesterol. Drink what you like.
- ♦ Alcohol appears to be most protective if consumed modestly and regularly, rather than episodically in large quantities.
- ♦ Drinking with meals makes good epidemiological and physiological sense. ■

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Main Points

- Most of the benefit of alcohol appears to be conferred by a reduction in atherosclerotic cardiovascular disease risk, but alcohol has adverse cardiac effects on blood pressure, ventricular function, and incidence of atrial fibrillation.
- Alcohol is the third leading cause of preventable premature death in the United States, causing approximately 100,000 deaths annually, trailing only cigarette smoking and the combined effects of inappropriate diet and inactivity. Alcohol is habituating in about 10% of drinkers and has potentially lethal consequences upon withdrawal.
- Most of the beneficial effects of alcohol are due to increases in high-density lipoprotein (HDL) cholesterol. Two drinks daily increases HDL cholesterol 10%–15%, although there is a considerable individual variation in response.
- Some studies have attributed the majority of the cardioprotective effect of alcohol to wine consumption, especially red wine. It may be, however, that confounding factors associated with wine consumption account for this effect; and U.S.-based studies have shown no difference in mortality according to the type of alcohol consumed.
- The findings that alcohol protects against postprandial endothelial dysfunction and inflammation induction probably explain why alcohol appears to be more protective if taken with meals.
- Three recent studies have found that moderate alcohol consumption, except for its effects on triglycerides, is beneficial in middle-aged and older diabetic patients. Alcohol also appears to have a beneficial effect in those with established heart disease.