Cardiovascular and Overall Mortality Risk in Relation to Alcohol Consumption in Patients With Cardiovascular Disease

Simona Costanzo, ScD; Augusto Di Castelnuovo, ScD; Maria Benedetta Donati, MD, PhD; Licia Iacoviello, MD, PhD; Giovanni de Gaetano, MD, PhD

Alcohol, in striking contrast to tobacco and illicit drugs, is linked to an extensively documented J-shaped dose-effect curve, with regular moderate consumption reducing cardiovascular and overall mortality, whereas excessive or binge drinking has the opposite effect. Data indicative of a lower risk of cardiovascular events among moderate drinkers in apparently healthy people are extensive and consistent, whereas the role of alcohol intake among patients with cardiovascular disease (CVD) is less clear.

Among the factors that contribute to prevention in survivors of primary cardiovascular events, lifestyle and dietary habits play a major role. However, guidelines in this area are based either on studies of apparently healthy subjects or on a few studies of cardiovascular patients. In particular, recommendations about alcohol consumption in patients with previous CVD reflect experts’ consensus rather than circumstantial evidence. The US Food and Drug Administration warns that heart disease patients should stop drinking, and people who take aspirin regularly should not drink alcohol. However, in the American Heart Association/American College of Cardiology guidelines for secondary prevention, CVD patients are encouraged to maintain a lifestyle that includes drinking alcohol in moderation. The “Diet and Lifestyle Recommendations” scientific statement from the American Heart Association Nutrition Committee advises, “If you consume alcohol, do so in moderation (equivalent of no more than 1 drink in women or 2 drinks in men per day).” The latter statement is largely accepted within the scientific community, definitely when referring to healthy people, although some would advise people to abstain completely rather than encouraging them to drink small amounts regularly. It has in fact been suggested that the consumption of alcohol for certain health benefits should not be encouraged, because the harm would far outweigh the gain, especially among poor populations and in low-income countries, where the disease burden per unit of alcohol consumption is greater.

The consistent J-shaped dose-response curves observed for alcohol consumption and cardiovascular events or all-cause mortality confirm the hazards of excessive drinking but also indicate potential windows of alcohol intake that may confer a net beneficial effect. Moderate ethanol consumption has lately emerged as a dominant component of a Mediterranean diet score, used as a predictor of lower mortality. The message for a general population might be summarized as follows: “Heavy drinkers should be urged to cut their consumption, but people who already regularly consume small to moderate amounts of alcohol should be encouraged to continue.” The question here is, should one recommend moderate alcohol consumption to patients who have had an ischemic cardiovascular event? randomized controlled trials to assess either the effectiveness or the harm of alcohol consumption in these patients are not feasible for several reasons, including ethical considerations, so we have to rely on data from observational studies. Here, we review the evidence on the beneficial or harmful effects of alcohol in patients who have experienced a first cardiovascular event and briefly discuss the major mechanisms underlying the relationship.

Alcohol and Secondary Events in CVD Patients

The reviewed studies are listed in Table 1. In a pioneering study started in 1978, Doll et al analyzed the association of alcohol with total mortality according to whether or not the patient had had any previous CVD or type 2 diabetes mellitus at the time of recruitment of 12,321 British doctors; for those who had already had some vascular disease, there was a clear U-shaped relation between alcohol intake and total mortality. In another, larger study (152,240 CVD, hypertensive, or diabetic patients), alcohol drinking reduced the risk of coronary heart disease (CHD) mortality for both sexes and in each category of intake (up to 40 g/d). When these 2 studies were analyzed together with 3 other cohort studies, a 20% reduction in all-cause mortality risk was found in moderate drinkers.
The main characteristics and results of studies conducted in CVD patients are summarized in Tables 1 and 2. In all of these studies, the relative risks reported were adjusted at least by age. Findings from these studies indicate that light-to-moderate alcohol consumption is associated with a decrease in the risk of cardiovascular and all-cause mortality (Figures 1 and 2; Table 2).

The inclusion in the reference groups of former drinkers who may have stopped drinking because of health problems is questionable. For the majority of studies, the reference group only included either “abstainers” or “nondrinkers” (Table 2). Former drinkers were reportedly excluded in several but not all studies. Janszky et al considered both “sick quitters” (drinkers who had stopped after acute myocardial infarction [AMI]) and “long-time” former drinkers (who stopped drinking before AMI). Moderate current drinkers (up to 20 g/d) had lower cardiovascular and all-cause mortality than abstainers, with or without the exclusion of the “long-time” former drinkers from the reference group (Table 2). Moreover, “sick quitters” had higher mortality than long-term abstainers. These findings support previous conclusions in healthy people.

Another potential limitation in establishing the effects of alcohol in patients who have experienced a cardiovascular event is that patients may modify their drinking habits shortly after diagnosis of a CVD, usually reducing their alcohol intake. However, when those studies recorded drinking habits more than 2 months after diagnosis of the second event (which more likely reflects the real intake of alcohol before the event) were examined, the protective effect of moderate alcohol consumption on cardiovascular and all-cause mortality could be confirmed. In the only study in men with a history of stroke, mortality was lower among patients with light-to-moderate alcohol consumption (1 to 6 drinks/wk) than among those who never or only rarely drank (Table 2).

**Major Mechanisms Underlying the Association**

Alcohol influences a wide range of vascular and biochemical functions that have potential cardioprotective benefits. These include an increase in HDL cholesterol, a decrease in platelet aggregation/function, reduced myocardial ischemia-reperfusion injury, increased endothelial cell–dependent vasorelaxation, simultaneous activation of endothelial cell antiapoptotic and proapoptotic pathways, lower plasma levels of coagulation factor VII and fibrinogen, increased fibrinolysis, and higher levels of atrial natriuretic peptide.

Besides ethanol, other components of alcoholic beverages (polyphenols in particular) may contribute to the protective role. The effects include increased vasorelaxation of aortic rings, downregulation of tissue factor gene transcription in cultured human endothelial cells and monocytes, reduced thrombosis or inflammation, inhibition of platelet aggregation/function, inhibition of smooth muscle cell proliferation, increased fibrinolysis, and up-regulation of fibrinolytic protein gene transcription in cultured human endothelial cells.

A recent study determined the proportion of CVD risk reduction explained by potential intermediate factors in a cohort of 26,399 women. A large proportion of the lower CVD risk associated with moderate alcohol drinking appeared to be explained by factors related to glucose metabolism, lipids, and inflammation/hemostasis factors.

Mechanisms that support the beneficial role of drinking in moderation in experimental animals or apparently healthy people could be similarly effective in patients with a history of CVD. An increase in HDL cholesterol blood levels is considered one of the most plausible mechanisms. Nevertheless, because raising HDL cholesterol pharmacologically reportedly had no effect on vascular risk in patients at high risk for coronary events, the association of alcohol with elevated HDL cholesterol per se, without considering the effects on its function, might have less value.

Wine might exert additional antiatherogenic effects mainly attributable to the biological activities of polyphenols. In a German study, nondrinkers and heavy drinkers had higher C-reactive protein concentrations than moderate drinkers. In a trial on the effects of wine and gin on inflammatory biomarkers, plasma fibrinogen and cytokine interleukin-1α decreased significantly after either beverage.
## Table 2. Relative Risks (95% Confidence Intervals) for Cardiovascular and Total Mortality at Different Levels of Alcohol Intake in Studies of CVD Patients

<table>
<thead>
<tr>
<th>Study and Alcohol Intake</th>
<th>Cardiovascular Mortality</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Janszky, 2008</strong>&lt;sup&gt;20&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total n = 1346</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term abstainers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent quitters</td>
<td>4.47</td>
<td>1.60–12.5</td>
</tr>
<tr>
<td>0–5 g/d</td>
<td>0.61</td>
<td>0.36–1.02</td>
</tr>
<tr>
<td>5–20 g/d</td>
<td>0.62</td>
<td>0.36–1.07</td>
</tr>
<tr>
<td>&gt;20 g/d</td>
<td>0.69</td>
<td>0.38–1.25</td>
</tr>
<tr>
<td><strong>Total n = 1284</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstainers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-drinkers</td>
<td>0.86</td>
<td>0.38–1.90</td>
</tr>
<tr>
<td>0–5 g/d</td>
<td>0.48</td>
<td>0.27–0.86</td>
</tr>
<tr>
<td>5–20 g/d</td>
<td>0.48</td>
<td>0.26–0.89</td>
</tr>
<tr>
<td>&gt;20 g/d</td>
<td>0.53</td>
<td>0.27–1.02</td>
</tr>
<tr>
<td><strong>Masunaga, 2006</strong>&lt;sup&gt;21&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;65 years, n = 3003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstainers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>0.60</td>
<td>0.29–1.24</td>
</tr>
<tr>
<td>Heavy</td>
<td>0.84</td>
<td>0.44–1.62</td>
</tr>
<tr>
<td>Age ≥65 y, n = 842</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstainers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1.00</td>
<td>0.64–1.55</td>
</tr>
<tr>
<td>Heavy</td>
<td>5.16</td>
<td>3.64–7.31</td>
</tr>
<tr>
<td><strong>Aguilar, 2006</strong>&lt;sup&gt;22&lt;/sup&gt; n = 2036</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrinkers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light to moderate</td>
<td>1.00</td>
<td>0.75–1.34</td>
</tr>
<tr>
<td>Heavy</td>
<td>0.87</td>
<td>0.40–1.87</td>
</tr>
<tr>
<td><strong>Jackson, 2003</strong>&lt;sup&gt;23&lt;/sup&gt; n = 1320</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rarely/never</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 drink/wk</td>
<td>0.89</td>
<td>0.58–1.36</td>
</tr>
<tr>
<td>1–6 drinks/wk</td>
<td>0.56</td>
<td>0.40–0.79</td>
</tr>
<tr>
<td>≥1 drink/d</td>
<td>0.64</td>
<td>0.46–0.88</td>
</tr>
<tr>
<td><strong>Mukamal, 2001</strong>&lt;sup&gt;24&lt;/sup&gt; n = 1913</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstainers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7 drinks/wk</td>
<td>0.75</td>
<td>0.55–1.02</td>
</tr>
<tr>
<td>≥7 drinks/wk</td>
<td>0.67</td>
<td>0.41–1.17</td>
</tr>
<tr>
<td><strong>Shaper, 2000</strong>&lt;sup&gt;25&lt;/sup&gt; n = 596</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teetotalers</td>
<td>0.98</td>
<td>0.53–1.82</td>
</tr>
<tr>
<td>Ex-drinkers</td>
<td>1.39</td>
<td>0.86–2.26</td>
</tr>
<tr>
<td>Occasional</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Light</td>
<td>0.94</td>
<td>0.65–1.35</td>
</tr>
<tr>
<td>Moderate/heavy</td>
<td>1.34</td>
<td>0.91–1.98</td>
</tr>
<tr>
<td><strong>Valmadrid, 1999</strong>&lt;sup&gt;26&lt;/sup&gt; n = 262</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-drinkers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-drinkers</td>
<td>0.71</td>
<td>0.34–1.49</td>
</tr>
<tr>
<td>&lt;2 g/d</td>
<td>0.51</td>
<td>0.24–1.12</td>
</tr>
<tr>
<td>2–13 g/d</td>
<td>0.43</td>
<td>0.15–1.22</td>
</tr>
<tr>
<td>≥14 g/d</td>
<td>0.26</td>
<td>0.08–0.81</td>
</tr>
</tbody>
</table>

(Continued)
Alcohol affects several factors that maintain the equilibrium between clot formation and dissolution. It has been associated with increased levels of tissue plasminogen activator, lower levels of fibrinogen and antithrombin III, and reduced susceptibility of platelets to aggregate. Several polyphenols interfere with arachidonic acid metabolism in both platelets and leukocytes, which results in inhibition of platelet aggregation and reduced synthesis of prothrombotic and proinflammatory mediators. Polyphenols can also downregulate the expression of adhesive molecules and tissue factor activity, which results in functional effects on cell-cell interactions and procoagulant activities.

The Lyon Diet Heart Study showed that moderate wine consumption in CHD patients was associated with higher...
levels of “marine” ω3 fatty acids in plasma. More recently, ω3 fatty acids in red blood cells were positively associated with alcohol (especially wine) intake in apparently healthy subjects of the IMMIDIET study (Dietary Habit Profile in European Communities With Different Risk of Myocardial Infarction: the Impact of Migration as a Model of Gene-Environment Interaction). The possibility that moderate consumption of alcohol raises ω3 polyunsaturated fatty acid levels is of interest in the setting of secondary prevention, in which protection against CVD after AMI was found after supplementation with ω3 polyunsaturated fatty acids.

Genetic regulation of individual response to alcohol was proposed on the basis of the relations between alcohol dehydrogenase type 3 polymorphisms, the level of alcohol consumption, and the risk of AMI. Moderate drinkers who were homozygous for the slow-oxidizing ADH1C allele had higher HDL levels and substantially less AMI. Additional studies are needed to elucidate the role of genetic factors in the association of alcohol with CVD risk.

**Detrimental Effects of Alcohol Consumption**

Abuse of alcohol, binge drinking, and drinking outside meals have all been associated with detrimental effects, such as fetal alcohol syndrome, liver cirrhosis, pancreatitis, certain cancers, cardiomyopathy, hypertriglyceridemia, hypertension, hemorrhagic stroke, overweight, alcohol intoxication, and addiction. Excess and irregular alcohol intake must be avoided by patients with CVD, because it can have serious unhealthy consequences, including exacerbation of existing pathological conditions. Alcohol abuse or binge drinking is a major cause of hyperlipidemia, vasoconstriction, increased clotting activity, and a lower threshold for ventricular fibrillation.

A meta-analysis found that binge and heavy drinking are associated with excess CHD risk. Among CVD patients, binge drinkers, defined as those who consumed 3 or more drinks within 1 to 2 hours, had double the total and cardiovascular mortality risk of regular drinkers. Episodic heavy alcohol drinking is reportedly associated with risk of atrial fibrillation; however, recent studies obtained no evidence that long-term alcohol intake (especially moderate consumption) was an important factor in the development of atrial fibrillation, and moreover, no association of alcohol consumption with risk of death was found among subjects with atrial fibrillation.

In patients with alcoholic cardiomyopathy, both abstinence and alcohol consumption (up to 60 g/d) improved cardiac function. However, abstinence continues to be recommended because of the lack of large studies on this topic. Few studies have investigated whether drinking with or without meals modifies the negative association between moderate alcohol consumption and CVD or total mortality. Drinking outside mealtimes is related to increases in CHD and hypertension risk, independent of the amounts drunk. In a large cohort, drinking wine outside meals increased mortality rates compared with drinking wine at meals.

**Alcohol and Cardiovascular Medications**

Drugs and alcohol may be co-metabolized, potentially altering the absorption, distribution, or metabolism of the alcohol, medications, or both, and affecting the therapeutic and adverse effects of the latter. Alcohol and medications interact in a variety of situations that differ depending on the timing...
of alcohol and medication consumption and the drinking pattern. The majority of these interactions occur among individuals who drink heavily.58,59

In patients with CVD, the potential interactions with alcohol have mainly been investigated for antiplatelet or oral anticoagulant drugs.58 Aspirin and other nonsteroidal antiinflammatory drugs, when combined with alcohol, can raise the risk of gastrointestinal bleeding by injuring the gastric mucosa and increasing the bleeding tendency58; however, aspirin and alcohol appeared to act as independent risk factors, with additive effects on gastrointestinal bleeding but no interaction.60 Experimental data61 suggest that wine polyphenols might interact with aspirin, because they form stable complexes in the platelet cyclooxygenase-1 enzyme channel. Mixtures of resveratrol, quercetin, and gallic acid did potentiate the platelet inhibitory effect of subinhibitory concentrations of aspirin. The activity of the cytochrome P-450 enzyme system in the liver can increase 10-fold among those who drink alcohol regularly and heavily.58,59 This speeds up the breakdown of many medications, including warfarin and clopidogrel.62 However, in a trial in men who had undergone coronary bypass surgery, moderate drinking did not adversely influence the safety of warfarin or lovastatin.63

Because most CVD patients are taking lipid-lowering drugs, a question of whether alcohol drinking can be combined with hypolipidemic treatment arises. Insufficient research has been conducted until recently to determine whether the consumption of alcohol in combination with hypolipidemic therapy should be recommended and whether it is safe.64 Thus, there is a need to define the possible benefit and establish which lipid-lowering drug behaves better in such a setting.

Alcohol in Hypertensive and Diabetic Patients

In the general population,10,65 the prevalence of hypertension rises linearly with alcohol consumption. Guidelines for the management of hypertension66 recommend avoiding binge drinking and suggest regular alcohol consumption, limited to no more than 2 to 3 drinks per day for men and 1 to 2 drinks per day for women, if not total abstinence.

A recent analysis investigated whether reducing alcohol consumption lowered blood pressure without losing the cardiovascular benefits of drinking in moderation.67 Moderate drinking was associated with a lower risk of heart failure, AMI, and cardiovascular and all-cause mortality in hypertensive subjects.68,69 In addition, the risk related to hypertension appears to be similar regardless of the level of alcohol consumption.70 The Physicians’ Health Study reported a protective effect of moderate alcohol consumption on secondary CHD outcomes in men who had hypertension at baseline.71

Diabetic patients have a CHD risk 2 to 4 times that of nondiabetic individuals.72 A meta-analysis of 15 prospective cohort studies showed a J-shaped relation between alcohol consumption and risk of developing diabetes, with a 30% lower risk in moderate alcohol consumers (1 to 2 drinks per day).12 Two quantitative reviews73,74 concluded that moderate alcohol consumption was associated with a lower incidence of heart disease or total mortality in patients with type 2 diabetes mellitus. Obviously, the decrease in CVD risk associated with moderate alcohol consumption in hypertensive or diabetic subjects does not reduce the importance of controlling blood pressure or blood glucose, regardless of drinking habits.

Limitations of Observational Studies on Alcohol and Health or Disease

A weakness of studies on alcohol consumption is the heterogeneity of the reference groups, which sometimes include lifelong teetotalers, ex-drinkers, and/or occasional drinkers. However, as discussed above, the lower risk associated with moderate alcohol consumption does not appear to be substantially related to the inclusion of former drinkers in the reference groups.

Those who drink in moderation may have a different lifestyle from people who do not drink,2 and the apparent healthy effects associated with moderate drinking may be mostly due to favorable risk profiles in moderate drinkers.1,75–77 In a meta-analysis on alcohol and total mortality in apparently healthy people,1 we found, however, that when adjusted and unadjusted data from the same studies were compared, the maximal protection afforded by light-to-moderate drinking only dropped from 19% to 16%. In a study77 in apparently healthy US adults, moderate drinkers did indeed have better risk factor profiles than nondrinkers. Although these would explain part of the survival advantage associated with alcohol use, moderate drinkers maintained a significant survival advantage even after adjustment for all risk factors. As discussed for studies of apparently healthy people,1 it is hard to assume a stronger role of confounding or the existence of additional nontraditional confounders in CVD patients.

The association of moderate alcohol consumption with prevention of secondary events appeared to be comparable in studies that included only men and in those that enrolled both men and women. Considering the not unexpected relative paucity of data on women, it is prudent to suggest that women with CVD, similarly to healthy women,1 can safely drink less alcohol than men.

Implications for Practice and Policy

The present review provides reasonable evidence that regular and moderate alcohol intake is significantly associated with a reduction in the incidence of secondary cardiovascular and all-cause mortality in patients with a history of CVD. This conclusion extends to patients with ischemic cardiovascular disease, a finding reported repeatedly in apparently healthy people.1,9 However, the fact that regular (nonbinge) moderate alcohol consumption is not easily attainable or maintainable in all parts of the world must be taken into serious consideration. Although the encouragement of “sensible” drinking might actually make heavy drinking more acceptable, we disagree with the proposal not to give alcohol any positive connotations because people might misinterpret them. There are certainly appreciable differences between Mediterranean and Northern European or Russian habits of alcohol consump-
tion. Therefore, in some low-income populations and poor countries, even if the net effect on CVD might be beneficial, the effect of alcohol on the overall burden of disease might be detrimental because of more frequent uncontrolled alcohol-use disorders, cancer, liver cirrhosis, and injury.2

Conclusions
Cardiovascular patients who do not consume alcohol should not be encouraged to start regular drinking. If not contraindicated, patients who drink alcohol should not exceed 1 to 2 drinks per day for women or up to 2 to 3 drinks per day for men as a component of a balanced cardioprotective dietary pattern with appropriate energy-intake levels. Alcohol is not recommended for young people (who are generally at very low risk of CVD), pregnant women, those at risk of alcoholism, or anyone whose activity calls for concentration, skill, or coordination. Alcohol is best avoided by people with cardiomyopathy or cardiac arrhythmias.2,56

There is no question that heavy or binge drinking is associated with adverse health outcomes.2 If cardiovascular patients are heavy drinkers, they must be strongly advised to abstain or at least substantially reduce drinking; regular moderate drinkers need not be told to modify their drinking habits but should avoid heavy or binge drinking.

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References


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