

# What do you recommend for individual patients and the general public about consumption of alcohol? Do the benefits outweigh the risks?

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*Extensive research suggests that moderate alcohol consumption lowers the risk of atherosclerotic cardiovascular disease (CVD) by 20%. However, this benefit requires serious qualification: it does not cover nonatherosclerotic CVD; it applies to no more than two drinks daily in men and one in women; it is confined to those aged 60 and over with, or at increased risk of, atherosclerotic CVD; and even in this category, it is not so clear-cut as to warrant recommending therapeutic use of alcohol in abstainers. Elsewhere, in the population at large, the benefit-risk ratio even in strictly medical terms is resoundingly negative, notably in women, due to greater bioavailability and the dose-response association with breast cancer, and in younger adults in whom any level of alcohol consumption may increase coronary calcification.*

**Keywords:** alcohol; abuse; epidemiology; guideline; cardiovascular disease; atherosclerosis; observational study; cardioprotection

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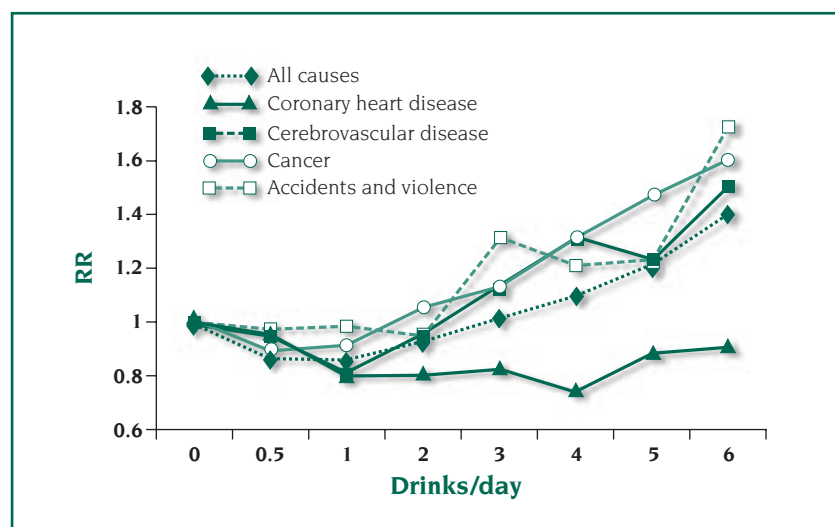
The title of this paper poses three separate questions: recommendations to the individual patient, recommendations to the general public, and the risk-benefit ratio. Answering these questions first requires a focused view of the research in this area. We will review observational studies, experimental studies, and address the implications for the individual patient and the general public separately.

## OBSERVATIONAL STUDIES

The large body of research on the relation of alcohol consumption to cardiovascular disease (CVD) has produced reasonably consistent results. First, moderate consumption of alcohol, defined as 1 to 2 drinks per day, is associated with a reduced risk of CVD from atherosclerotic causes, in particular coronary heart disease, stroke, and peripheral arterial disease.<sup>1-3</sup> Although individual studies show considerable variation, this risk reduction averages around 20%. Despite widespread opinion to the contrary, studies within defined populations show that the effect size does not differ for red wine, white wine, beer, or spirits.<sup>4</sup> However, the apparently greater benefit for wine in ecologic studies across populations<sup>5</sup> suggests that the differential manner in which

wine is consumed compared with other alcoholic beverages (sipped, with meals) may be a healthier way to consume alcohol.<sup>6</sup> It is important to note that consumption of alcohol is not protective for nonatherosclerotic cardiovascular diseases, such as arrhythmias, cardiomyopathy, and hemorrhagic stroke. In fact, alcohol, especially at higher doses, but even in moderate doses, may lead to or exacerbate the latter conditions.<sup>7</sup>

Second, alcohol consumption at levels beyond 2 drinks per day does not produce additional benefit. In fact, consumption at higher levels in several studies is typically associated with increased cardiovascular risk and virtually always associated with increased risk of several non-CVD end points, including liver disease, cancer, accidents, and violence.<sup>8</sup> In addition, total mortality begins to increase sharply at more than 2 drinks per day. Thus, there is a U-shaped relationship between alcohol consumption and both total cardiovascular and noncardiovascular outcomes. This is illustrated by *Figure 1*, from a prospective study of 276 802 men followed for 12 years.<sup>8</sup> Although there is some benefit for coronary mortality even at higher levels of drinking, it is clear that the full benefit is achieved at a single drink per day. Above two drinks per day, mortality from other causes, including cerebrovascular disease,



**Figure 1.** Alcohol drinks per day and relative risks (RR) of all-cause and cause-specific mortality over 12 years in American Cancer Society prospective study of 276 802 men aged 40 to 59 years. RRs adjusted for age and smoking habits.

Modified from reference 8: Boffetta P, Garfinkel L. Alcohol drinking and mortality among men enrolled in an American Cancer Society prospective study. *Epidemiology*. 1990;1:342-348. Copyright © 1990, Lippincott Williams & Wilkins.

cancer, and accidents and violence, steadily increases, leading to an increase in total mortality, which is after all the bottom line. The large number of subjects and extended length of follow-up make these data particularly useful. Similar findings are found in cross-cultural ecologic studies, where the "French paradox" for wine consumption holds for coronary mortality, but not for total mortality.<sup>5</sup>

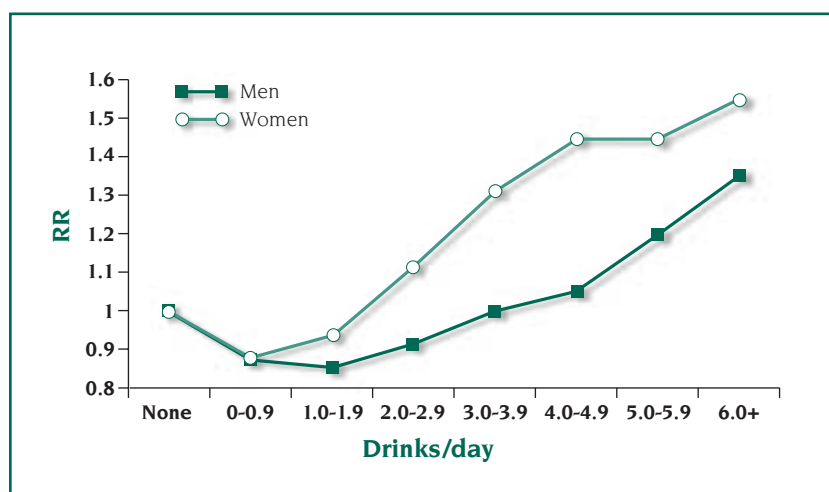
Third, the benefit is limited to individuals at increased risk of atherosclerotic cardiovascular disease. By definition, a cardioprotective factor cannot produce a significant benefit unless there is a significant underlying risk. Thus, we would expect little benefit in younger and lower-risk individuals, and in fact the data support no benefit in anyone below the age of 60.<sup>9,10</sup> In addition, in some studies, benefit is limited to, or particularly noticeable in, subjects with known high baseline risk such as more than one CVD risk factor,<sup>10</sup> diabetes,<sup>11</sup> the metabolic syndrome,<sup>12</sup> or elevated LDL chole-

sterol.<sup>13</sup> While men and women at low risk of atherosclerotic CVD cannot benefit from alcohol consumption, they are nonetheless subject to harm from it. The difference in outcomes between men and women is particularly noteworthy. *Figure 2* shows the results of a pooled analysis of the sex-specific association

between alcohol consumption and total mortality in 14 cohort studies.<sup>14</sup> Note again that a benefit for total mortality is limited to 2 drinks or less per day in men, but that in women the benefit is limited to 1 drink per day or less. This reflects on average greater bioavailability in women for the same dose of ethanol,<sup>15</sup> as well as the known dose-response association between alcohol and breast cancer in women.<sup>16</sup>

### EXPERIMENTAL STUDIES

In observational studies, alcohol consumption is associated with mostly favorable differences in CVD risk factors.<sup>17</sup> Clinical trials looking at the short-term changes with alcohol on these potential mediators of the alcohol effect by and large confirm these associations to be causal.<sup>18</sup> While most of these changes are favorable (eg, increased high-density lipoprotein [HDL] cholesterol, decreased thrombotic factors), some reverse with alcohol withdrawal,<sup>19</sup> and blood pressure is in fact increased by alcohol consumption.<sup>20</sup>



**Figure 2.** Relationship of usual alcohol intake to all-cause mortality, derived from a pooled analysis of 14 cohort studies. RR, relative risk.

Modified from reference 14: Holman CD, English DR, Milne E, Winter MG. Meta-analysis of alcohol and all-cause mortality: a validation of NHMRC recommendations. *Med J Aust*. 1996;164:141-145. Copyright © 1996, The Medical Journal of Australia.

**What are the recommendations about alcohol consumption? - Criqui**

Although observational data on CVD events and clinical trial data on alcohol's effect on CVD risk factors are informative, particularly when carefully analyzed, we should rely to the extent possible on data from randomized controlled trials on CVD events in making policy recommendations for preventive or therapeutic strategies. In the area of alcohol, this presents a conundrum. There are no randomized trials of alcohol consumption with an end point of CVD events, nor are there likely to be any. Such trials would be difficult to conduct, and of limited value when completed. A true placebo control is not possible, and maintenance of consumption in the experimental (say 2 drinks per day) and in the control (abstinence) groups would be difficult in a randomized study over even a short follow-up, let alone a long one as required in CVD event trials. Thus, in terms of data on CVD events we are limited to inferences from observational data in formulating recommendations. Multivariate analyses of observational data evaluating potential biologic pathways have shown that a beneficial effect of alcohol on CVD events is likely mediated at least in part by increased HDL cholesterol,<sup>1</sup> and a hazardous effect of higher levels of alcohol is mediated by increased blood pressure.<sup>21</sup> Such observations strengthen the likelihood, but do not guarantee, that alcohol in light-to-moderate amounts is causally protective for atherosclerotic CVD.

However, we should remain cautious since we lack truly definitive evidence. The lesson of hormone replacement therapy in women comes to mind. Just a few short years ago there was general consensus that restoring estrogen in women after the menopause reduced CVD risk, and there was evidence this effect was mediated by the known causal

effect of estrogen in raising HDL cholesterol and lowering low-density lipoprotein (LDL) cholesterol.<sup>22,23</sup> Despite sophisticated statistical control for potential confounding variables in observational studies, recent clinical trials have proved the consensus was wrong. Not only is there no protection, but estrogen therapy actually increases the risk of atherosclerotic CVD, including coronary disease and ischemic stroke.<sup>24,25</sup> In addition, recent evidence in younger adults indicates that any level of alcohol consumption is associated with an increase in coronary calcification,<sup>26</sup> a potent risk factor for CVD events. The observational findings for light-to-moderate alcohol use seem less likely to be spurious than those for estrogen replacement, primarily because favorable changes in risk factors, such as inflammatory factors, are present more often with light-to-moderate alcohol consumption than with estrogen therapy.<sup>27,28</sup> although again the beneficial associations for alcohol are limited to light-to-moderate consumption.<sup>27</sup> Nonetheless, any recommendations about alcohol consumption should consider the (unlikely) possibility that the observational associations are artifactual.

**WHAT IS THE BEST METRIC FOR THE RISK-BENEFIT RATIO?**

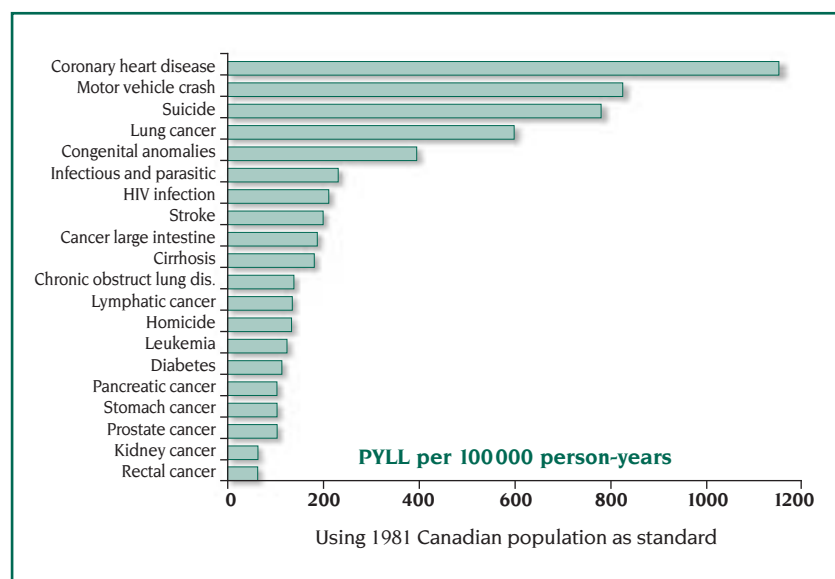
All of the above studies of CVD events base their conclusions on morbidity and mortality rates in populations. In order to have adequate power, studies typically have an older minimum age requirement. Thus, study participation is predicated on survival to the minimum age for inclusion. CVD events occur disproportionately in older (and higher-risk) adults, and the observed benefit from moderate alcohol consumption is largely at older ages. Let us consider a different metric,

and focus instead on the age range from birth up to the average life expectancy, 75 years. Rather than simply mortality rates, let us use a measure that takes into account the potential years of life lost (PYLL) from a given fatal disease event. In PYLL analyses, a death at age 40 results in 35 PYLL, while a death at age 70 only results in 5 PYLL. Thus, an earlier demise is weighted more heavily than a later one.

*Figure 3* shows the data for men for PYLL in 1990 in Canada, and *Figure 4* shows similar data for women.<sup>29</sup> Note that in men, while coronary disease is the leading cause of PYLL, motor vehicle crashes and suicide are close behind. Both of the latter outcomes are positively linked to alcohol consumption, and together are associated with about 50% more PYLL than coronary disease. Other alcohol-linked outcomes also make significant contributions to PYLL in men, including HIV infection, stroke, cancer of the large intestine, cirrhosis, and homicide. In women, both breast cancer and motor vehicle crashes contribute more PYLL than coronary disease. Suicide, stroke, cancer of the large intestine, homicide, and cirrhosis also contribute substantially to PYLL in women. Using the PYLL metric as opposed to event rates gives us a better understanding of the overall contribution of alcohol to unfavorable outcomes in populations.

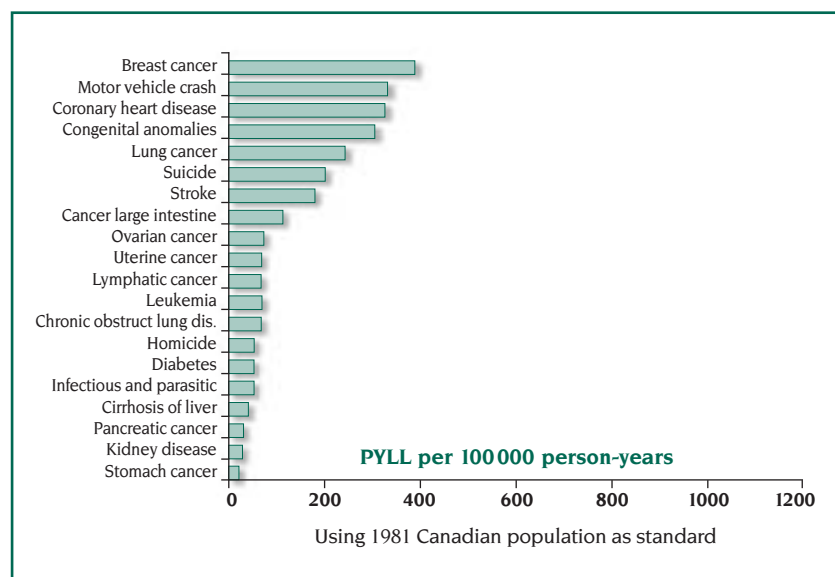
**WHAT DO WE RECOMMEND TO INDIVIDUAL PATIENTS?**

We can see from the above review that whether the benefits outweigh the risks depends on the patient. Whether the practitioner is a cardiologist, other specialist, or generalist, there is only one group of patients that could potentially benefit from light-to-moderate alcohol con-



**Figure 3.** Rates of potential years of life lost (PYLL) before age 75, by cause of death, males, Canada, 1990.

Modified from reference 29: Wilkins K, Mark E. Potential years of life lost, Canada 1990. *Chron Dis Can.* 1992;13:111-115. Copyright © 1992, Minister of Public Works and Government Services Canada.



**Figure 4.** Rates of potential years of life lost (PYLL) before age 75, by cause of death, females, Canada, 1990.

Modified from reference 29: See Figure 3 caption.

sumption, ie, patients at high risk of, or with known, atherosclerotic CVD. But even in this group, recommendations need to be carefully considered. If the patient already consumes alcohol, there is rarely an occasion to suggest increased consumption, since the maximum ben-

efit is obtained at a single drink per day. Should a nondrinker in this high-risk group ever be told to start drinking? Consider the reasons why patients are nondrinkers. Reasons include a personal history of alcoholism; a family history of alcoholism (the risk of alcoholism is four-

fold, and primarily genetic, since concordance in monozygotic twins is twice that of dizygotic); experience with alcohol abuse in relatives or friends; a medical contraindication; a religious, ethical, or moral objection; and dislike of the taste of alcohol or the feeling of intoxication. In which of these abstainer groups would you feel comfortable recommending beginning to drink? Abstaining patients with a history of abuse have been documented to use such a recommendation as an excuse to return to drinking and then alcoholism. Thus, in the clinical setting, the practitioner is ethically essentially limited to discussions encouraging alcohol consumption with nondrinking patients or patients considering quitting drinking who are at high risk of atherosclerotic CVD and known to have neither a personal nor family history of abuse. This is a small target group indeed.

### WHAT DO WE RECOMMEND TO THE GENERAL PUBLIC?

In theory, the question here is not really so different from that for the individual patient, ie, there may be benefit for persons at high risk of atherosclerotic CVD and low risk of abuse. However, such messages translate poorly at the population level. The heaviest drinking is done by younger persons,<sup>30</sup> who may be susceptible to the suggestion that alcohol is "good for your heart." The alcohol industry advertises extensively in the media, and the ads typically feature young persons partying. The young have nothing to gain and everything to lose by beginning or increasing drinking. Although the alcohol industry has strongly supported "responsible drinking," they also know that since about 8% of the United States adult population are alcoholics, it is mathematically

**What are the recommendations about alcohol consumption? - Criqui**

inevitable that about half the alcohol production is consumed by alcoholics.<sup>31</sup> They thus have an economic conflict of interest.

Thus, the most appropriate recommendation to the general public is rather simple—alcohol is a dangerous drug. If this conclusion seems oversimplified, consider what the situation would be if alcohol were a newly discovered pharmacologic agent showing favorable effects on HDL cholesterol and selected other CVD risk factors, and clinical trials were conducted with the aim of a new drug indication for cardioprotection. Clinical trials would report favorable effects on risk factors, but in addition a uniform dose-dependent suppression of coordination and cognitive function, with severe psychosocial dysfunction in some subjects. Given availability, about 8% of subjects in these trials would develop profound addiction with devastating consequences for themselves, their families, and occasionally innocent strangers. Despite the fact that most subjects in these trials would have no problems and would probably receive some cardioprotection, there is no chance a regulatory body such as the United States Food and Drug Administration (FDA) would ever grant approval to a drug with this profile. The risk-benefit ratio would surely disqualify it for licensure. This simple fact should be kept in mind when making any recommendations concerning alcohol consumption.

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