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Drink to Your Health?

by Arthur L. Klatsky

Three decades of research shows that drinking small to moderate amounts of alcohol has cardiovascular benefits. (Per day that's about 1 shot = 1.5 oz = 3 Tbs of 40% whiskey, one 5 oz glass of 12% wine, one 12 oz can of 5% beer, or 0.6 oz = 1.2 Tbs of alcohol). A thorny issue for physicians is whether to recommend drinking to some patients.

Overview / Alcohol and Heart Health

- The large arteries of people who died of alcoholic live cirrhosis were remarkably free of atherosclerosis.
- An assortment of studies from around the world indicates that drinking in small to moderate amounts decreases the risk of dying from coronary heart disease by almost one third.
- Some research points to red wine as being particularly protective against coronary heart disease. Other healthful habits of red wine drinkers, however, may be partly responsible for the apparent effect.
- A select group of people—those with CHD or at risk for CHD and without risks associated with alcohol itself—may wish to consult their physicians about moderate drinking as part of a heart-healthy diet.

Addressing an Illinois temperance society in 1842, Abraham Lincoln said something about "intoxicating liquor" that probably got a frosty reception. "It is true that . . . many were greatly injured by it," the future president noted. "But none seemed to think the injury arose from the use of a bad thing but from the abuse of a very good thing."

America has always had trouble deciding whether alcohol is a bad thing or a good thing. Millions who remember Prohibition, when all alcoholic beverages were illegal, now witness a constant stream of advertisements from producers of alcoholic beverages encouraging people to drink. Despite alcohol's popularity today, however, many still consider abstinence a virtue. Certainly, heavy drinking and alcoholism deserve deep concern for the terrible toll they take on alcohol abusers and society in general. But worry about the dangers of abuse often leads to emotional denials that alcohol could have any medical benefits. Such denials ignore a growing body of evidence indicating that moderate alcohol intake wards off certain cardiovascular (circulatory system) conditions, most notably heart attacks and ischemic strokes (those caused by blocked blood vessels). A few studies even show protection against dementia, which can be related to cardiovascular problems.

The Alcohol Effect

A discussion of moderate drinking requires a working definition of "moderate." Simple definitions of light, moderate or heavy are somewhat arbitrary, but a consensus in the medical literature puts the upper limit for moderate drinking at two standard-size drinks a day [see illustration on opposite page]. Studies show that drinking above that level can be harmful to overall health, although sex, age and other factors lower and raise the boundary for individuals.

The main medical benefit of reasonable alcohol use seems to be a lowering of the risk for coronary heart disease (CHD), which results from the buildup of atherosclerosis (fatty plaque) in the arteries that feed blood to the heart. (The word "atherosclerosis" is in fact a descriptive union of two Greek words: athera, for "gruel" or "porridge," referring to the fatty deposits, and sclera, for "hard," pertaining to the loss of vessel flexibility.)

Atherosclerosis restricts blood flow to the heart and can promote the formation of vessel-blocking clots. It can thereby cause angina (chest discomfort resulting from low oxygen levels in the heart muscles), heart attack (the death of heart tissue that occurs when a blood clot or narrowing of the arteries prevents blood from reaching the heart) and death, often

without warning. The condition usually starts at a young age but takes decades to blossom into overt CHD. The most common form of heart disease in developed countries, CHD causes about 60 percent of deaths from cardiovascular ills and about 25 percent of all deaths in those nations.

Pathologists uncovered the first clues to the value of alcohol in the early 1900s, noting that the large arteries of people who died of alcoholic liver cirrhosis seemed remarkably "clean"—that is, free of atherosclerosis. One explanatory hypothesis assumed that alcohol was a nebulous solvent, essentially dissolving the buildup in the arteries; another explanation held that heavier drinkers died before their atherosclerosis had a chance to develop. Neither idea truly explained drinkers' unblocked arteries, however.

A more telling hint emerged in the late 1960s, when Gary D. Friedman of the Kaiser Permanente Medical Center in Oakland, Calif., came up with a novel idea: use computers to unearth unknown predictors of heart attacks. The power of computing could first identify healthy people who had risk factors similar to heart attack victims. Such factors include cigarette smoking, high blood pressure, diabetes, elevated levels of low-density-lipoprotein (LDL, or "bad") cholesterol, low levels of high-density-lipoprotein (HDL, or "good") cholesterol, male gender, and a family history of CHD. Friedman then searched for predictors of heart attacks by comparing the patients and the newly found controls in hundreds of ways—for example, their exercise and dietary habits and their respective levels of various blood compounds. The computers spit out a surprising discovery: abstinence from alcohol was associated with a higher risk of heart attack.

Various studies had missed the connection because they neglected to examine alcohol use as a behavior separate from smoking. We now know that because drinkers often also use cigarettes, the negative impact of smoking was masking the beneficial effect of alcohol. In 1974 my Kaiser Permanente colleagues Friedman and Abraham B. Siegelaub and I were the first, to our knowledge, to publish an examination of moderate drinking in the absence of smoking. We saw a clear connection between alcohol consumption and a decreased risk of heart attack.

Since then, dozens of investigations in men and women of several racial groups in various countries have correlated previous alcohol use with current health. These studies have firmly established that nondrinkers develop both fatal and non-fatal CHD more often than do light to moderate drinkers. In addition, in 2000 Giovanni Corrao of the University of Milan-Bicocca in Italy, Kari Poikolainen of the Järvenpää Addiction Hospital in Finland and their colleagues combined the results of 28 previously published investigations on the relation between alcohol intake and CHD. In this meta-analysis, they found that the risk of developing CHD went down as the amount of alcohol consumed daily went up from zero to 25 grams. At 25 grams—the amount of alcohol in about two standard drinks— an individual's risk of a major CHD event, either heart attack or death—was 20 percent lower than it was for someone who did not drink at all.

New data about alcohol protecting against death from CHD are even more impressive. At a meeting of the American Heart Association last November, my Kaiser Permanente colleagues Friedman, Mary Anne Armstrong and Harald Kipp and I discussed an updated analysis of 128,934 patients who had checkups between 1978 and 1985, with 16,539 of them dying between 1978 and 1998. CHD was responsible for 3,001 of those deaths. We discovered that those who had one or two alcoholic drinks a day had a 32 percent lower risk of dying from CHD than abstainers did.

The possible mechanisms by which alcohol has such an apparently profound effect on cardiovascular health primarily involve cholesterol levels and blood clotting. Blood lipids, or fats, play a central role in CHD. Numerous studies show that moderate drinkers have 10 to 20 percent higher levels of heart-protecting HDL cholesterol. And people with higher HDL levels, also known to be increased by exercise and some medications, have a lower risk of CHD.

That lower risk stems from HDL's ability to usher LDL cholesterol back to the liver for recycling or elimination, among other effects. Less cholesterol then builds up in the walls of blood vessels, and so less atherosclerotic plaque forms. Alcohol seems to have a greater influence on a different HDL subspecies (HDL3) than on the type increased by exercise (HDL2), although both types are protective. (The biochemical pathways in the liver that could account for alcohol's ability to raise HDL levels remain incompletely known; it is thought that alcohol probably affects liver enzymes involved in the production of HDL.) Three separate analyses aimed at determining specific contributions of alcohol all suggest that the higher HDL levels of drinkers are responsible for about half of the lowered CHD risk.

Alcohol may also disrupt the complex biochemical cascade behind blood clotting, which can cause heart attacks when it occurs inappropriately, such as over atherosclerotic regions in coronary arteries. Blood platelets, cellular components of clots, may become less "sticky" in the presence of alcohol and therefore less prone to clumping, although data on this question remain ambiguous. A 1984 study by Raffaele Landolfi and Manfred Steiner of Brown University's Memorial Hospital revealed that alcohol intake increases the level of prostacyclin, which interferes with clotting, relative to the level of thromboxane, which promotes clotting. Walter E. Laug of the University of Southern California Keck School of Medicine showed that alcohol raises levels of plasminogen activator, a clot-dissolving enzyme. Finally, several studies suggest that alcohol lowers levels of another promoter of blood clots, fibrinogen.

Overall, alcohol's anticlotting capacity is not as well established as its HDL effect, and some effects, such as platelet clumping, may be reversed by heavy or binge drinking. Nevertheless, anticlotting appears to have a role in the lower risk for heart attacks enjoyed by moderate drinkers. In addition, studies have shown a beneficial effect on CHD risk in people who have far fewer than two drinks a day—say, three or four drinks a week. Anticlotting could be a major factor in the protection accorded by alcohol in these small amounts, which seem insufficient to affect HDL levels greatly.

Although alcohol reduces heart disease risk mainly by raising HDL levels and reducing clotting, it acts in other ways that could lower the risk more subtly. Moderate drinking may lessen CHD risk indirectly by decreasing the risk of type 2 (adult-onset) diabetes, which is a powerful predictor of CHD. This benefit appears to be related to enhanced insulin sensitivity, which promotes proper glucose usage. (Heavy drinking, however, has been connected to higher blood glucose levels, a marker for future diabetes.) Evidence is also growing that inflammation contributes to CHD, and alcohol's anti-CHD power may be related to an anti-inflammatory action on the endothelial tissue that lines blood vessels.

Before accepting alcohol's benefits, an epidemiologist attempts to locate hidden factors possibly at work. For instance, could lifelong abstainers differ from drinkers in psychological traits, dietary habits, physical exercise habits or other ways that might account for their higher CHD risk without the need to invoke the absence of alcohol? Were such traits to explain away alcohol's apparent protection, they would need to be present in both sexes, various countries and several racial groups. Considering that no such traits have been identified, the simpler and more plausible explanation is that light to moderate alcohol drinking does indeed enhance cardiovascular health.

In fact, the available evidence satisfies most standard epidemiological criteria for establishing a causal relation. The numerous studies examining light and moderate alcohol intake and health reach consistent conclusions. The prospective studies that exist have the correct temporal sequence—that is, individuals' habits of interest are identified, after which their health is monitored over the long term, and alcohol users have different health profiles than nondrinkers do. The positives associated with alcohol can be attributed to biologically plausible mechanisms. Alcohol offers specific enhancement of cardiovascular health, not general protection against all illness. And alcohol's effect can be identified independent of

known “confounders,” other alcohol-related factors that could be responsible for a subject’s cardiovascular condition.

The 30 percent reduction in risk is, perhaps surprisingly to some, less convincing evidence than the arguments above, because a strong unknown con-founder could still account for the connection. To take an extreme example, consider a hypothetical set of genes that confers on the possessor 60 percent less CHD risk and causes a strong predisposition toward liking moderate amounts of alcohol. The independent consequences of the genes could appear causally linked. (In fact, however, no such confounder is known or likely, and the 30 percent risk reduction appears to be a probable measure of alcohol’s beneficial effect.)

Because heavy drinking is not more protective than lighter drinking, this absence of a clear dose-response relation is also a weakness. Nevertheless, the collected data make a strong case for the cardiac benefits of controlled drinking. I should note, however, that the kind of study considered to be the gold standard in human research—a prospective randomized blinded clinical trial—has not yet been done. Such a study might, for example, engage a large pool of nondrinkers, half of whom, chosen at random and without the knowledge of the researchers, would commence a moderate drinking regimen, while the other half remained abstainers. The two groups would be followed for years in a search for eventual differences in cardiovascular disease and heart-related deaths.

Wine, Beer or Spirits?

Beer, wine and liquor all seem to be related to a lower risk of coronary heart disease (CHD). A tantalizing question, however, is whether one kind of drink—wine, for example—is better than the others. The short answer: the jury is still out.

The death rate from CHD in France, where red wine consumption is common, is only about half that in the U.S., despite similar fat intake and sedentary lifestyles. That observation led to the catchphrase “the French paradox” and the idea that red wine is the beneficial alcoholic beverage. This belief has a hypothetical basis—red wine especially contains a number of ingredients with potential antioxidant and other atherosclerosis-fighting benefits.

An excellent 1995 Danish study, in which almost 13,000 people were followed during a 12-year period, suggested that wine drinkers have lower death rates from CHD than do other alcohol imbibers. My Kaiser Permanente colleagues Mary Anne Armstrong and Gary D. Friedman and I published on the risk of CHD death (in 1990) and the risk of CHD hospitalization (in 1997); in these investigations, which included almost 130,000 Californians, wine and beer drinkers had a lower CHD risk than did hard-liquor drinkers. At a meeting of the American Heart Association in November 2002, I presented new data that updated the 1990 study. We were surprised to find that those drinking wine daily had about a 25 percent lower risk of CHD death than did those who drank beer and wound up taking in the same amount of alcohol. And the wine drinkers had about a 35 percent lessened CHD death risk compared with the light to moderate hard-liquor drinkers. Significantly, there was no difference in apparent benefit between red wine and white wine.

A vexing complication of all these studies, however, is that the overall habits of wine drinkers, beer drinkers and hard-liquor drinkers tend to differ greatly. In Denmark, for example, wine drinking goes hand in hand with a healthful diet (high in fruits, vegetables, fish, salads and olive oil) and two other markers for better health in general: higher socioeconomic status and higher IQ. In our California studies, those who preferred wine also smoked less, had more education and had more temperate drinking habits than those who preferred beer or hard liquor.

Lifestyle differences among those who prefer one type of alcoholic beverage over another thus make it exceedingly difficult to determine whether the differences in apparent health effects are actually related to the beverage type itself (and therefore to wine constituents besides alcohol), to drinking pattern (imbibed slowly and with food, for wine) or to other factors.

To Drink or Not to Drink

Most people drink for reasons other than alcohol's health benefits, and many of them are already using alcohol in amounts that appear to promote cardiovascular health. But the accumulated research on alcohol's positive effects presents a challenge to physicians. On one hand, mild to moderate drinking seems better for heart health than abstinence for select people. On the other hand, heavy drinking is clearly dangerous. It can contribute to noncardiovascular conditions such as liver cirrhosis, pancreatitis, certain cancers and degenerative neurological disorders, and it plays a part in great numbers of accidents, homicides and suicides, as well as in fetal alcohol syndrome. (No conclusive evidence links light to moderate drinking to any of these problems.)

Heavy drinking also contributes to cardiovascular disorders. Too much alcohol raises the risk of alcoholic cardiomyopathy, in which the heart muscle becomes too weak to pump efficiently; high blood pressure (itself a risk factor for CHD, stroke, heart failure and kidney failure); and hemorrhagic stroke, in which blood vessels rupture in or on the surface of the brain. Alcohol overindulgence is also related to "holiday heart syndrome," an electrical signal disturbance that disrupts the heart rhythm. The name refers to its increased frequency around particular holidays during which people engage in binge drinking.

Given the potential dangers of alcohol, how can individuals and their physicians make the decision as to whether to include alcoholic beverages in their lives and, if so, in what amounts? The ability to predict accurately an individual's risk of a drinking problem would be a great boon; the least disputed possible consequence of moderate drinking is problem drinking. Individual risk can be approximated using family and personal histories of alcohol-related problems or conditions, such as liver disease or, of course, alcoholism. Even when known factors are taken into account, however, unpredictable events late in life may result in deleterious drinking changes.

Exactly because of these dangers, public health concerns about alcohol until recently have been appropriately focused solely on the reduction of the terrible social and medical consequences of heavy drinking. And the correlation between total alcohol consumption in society and alcohol-related problems has been used to justify pushes for abstinence. Ultimately, however, a more complex message is necessary. Merely recommending abstinence is inappropriate health advice to people such as established light drinkers at high risk of CHD and at low risk of alcohol-related problems—which describes a large proportion of the population. Of course, the most important steps for this group are proper diet and exercise; effective treatment of obesity, diabetes, high blood pressure and high cholesterol; and avoidance of tobacco. But there is a place on that list of beneficial activities for light drinking. Most light to moderate drinkers are already imbibing the optimal amount of alcohol for cardiovascular benefit, and they should continue doing what they are doing.

Abstainers should never be indiscriminately advised to drink for health; most have excellent reasons for not drinking. Yet there are exceptions. One case is the person with CHD who "goes clean"— quits smoking, switches to a spartan diet, starts exercising and, with good intentions, gives up the habit of a nightly bottle of beer or glass of wine. This self-imposed prohibition should be repealed. In addition, a number of infrequent drinkers might think about increasing their alcohol intake to one standard drink daily, especially men older than 40 and women older than 50 at high risk of CHD and low risk of alcohol-related problems. But women also have to consider one possible drawback of alcohol: several studies link heavy drinking—and a few even link light drinking—to an increased risk of breast cancer, a less common condition than heart disease in postmenopausal women but certainly quite a serious one. For young women, who are generally at low short-term risk of CHD and therefore may not benefit greatly from alcohol's positive cardiovascular effects, this possible breast cancer link looms larger in estimating the overall risks and benefits of alcohol. And for all women, the upper

limit on moderate drinking should be considered one drink a day.

The only clear-cut message regarding alcohol and health, then, is that all heavy drinkers should reduce or abstain, as should anyone with a special risk related to alcohol, such as a family or personal history of alcoholism or preexisting liver disease. Beyond that, however, the potential risks and benefits of alcohol are best evaluated on a case-by-case basis. Cardiovascular surgeon Roger R. Ecker and I constructed an algorithm that can help health practitioners and their patients decide how much—if any—alcohol is right for a given individual [see box on page 78].

In short, health professionals should provide balanced, objective guidelines regarding their patients' use of alcohol, and such advice needs to be tailored to each person. I believe that it is possible to define a clear, safe limit for alcohol consumption that would offer a probable benefit to a select segment of the population. The ancient Greeks urged "moderation in all things." Three decades of research shows that this adage is particularly appropriate when it comes to alcohol.

"Standard" servings of alcoholic beverages:

Although there is no formal definition of a standard-size drink, something of a consensus does exist. Beer is often sold in a 12-ounce bottle or can, which is a useful reference point as one standard drink. The amount of alcohol, about 0.6 ounce, in 12 ounces of beer is virtually the same as is found in a 5-ounce glass of wine or a 1.5-ounce = 1 shot glass of distilled spirits, such as vodka, gin, bourbon or scotch. Wine and distilled spirits in these amounts are thus also considered standard drinks.

HOW ALCOHOL MIGHT PROTECT AGAINST CHD

Alcohol Effect	*Probable Action*	*Evidence*
Raises blood HDL cholesterol	Removes and transports LDL cholesterol from vessel wall	Solid supporting evidence; effect explains at least half of alcohol's benefit
Lowers blood LDL cholesterol	Reduces level of one major CHD risk factor	Evidence weak; effect probably not independent of diet
Lowers the oxidation of LDL	Prevents the plaque formation associated with LDL oxidation	Largely hypothetical, although antioxidants are plentiful in red wine
Lowers levels of fibrinogen in blood	Lessens the risk of clot formation on atherosclerotic plaques	Moderate supporting data
Exerts other anticlotting actions: lessens platelet stickiness; raises levels of prostacylin; lowers levels of thromboxane	Lessens the risk of clot formation on atherosclerotic plaques	Inconsistent data; possible reversal of effect with heavy or binge drinking
Lessens insulin resistance	Lessens key risk factor for adult-onset diabetes and atherosclerosis	Evidence comes from a small number of studies
Lessens psychosocial stress	Unclear	No supporting data or likely mechanism
Improves conditioning of heart muscle	Imparts better resistance to damage from oxygen deprivation	Preliminary supporting evidence

DRINKING: RISKS AND BENEFITS

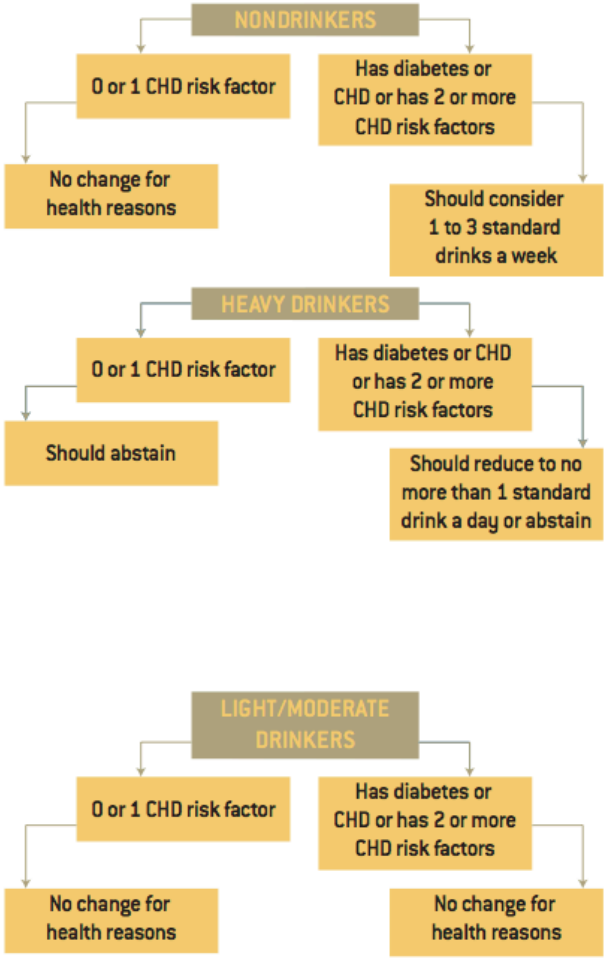
Light/Moderate Drinking		Heavy Drinking	
RISKS	BENEFITS	RISKS	BENEFITS
Established Heavy drinking ***Unresolved*** Breast cancer Fetal damage ***Unlikely*** Bowel cancer Hemorrhagic stroke High blood pressure	***Probable*** Decreased risk of CHD Decreased risk of ischemic stroke Decreased risk of gallstones ***Possible*** Decreased risk of diabetes Decreased risk of peripheral vascular disease (narrowing or clogging of the arteries carrying blood to the arms and legs)	***Noncardiovascular*** Liver cirrhosis Pancreatitis Certain cancers Accidents Homicides Suicides Fetal damage Degenerative disorders of the central nervous system ***Cardiovascular*** High blood pressure Arrhythmia Hemorrhagic stroke Cardiomyopathy (damaged heart muscle)	None

MAKING THE DRINKING DECISION

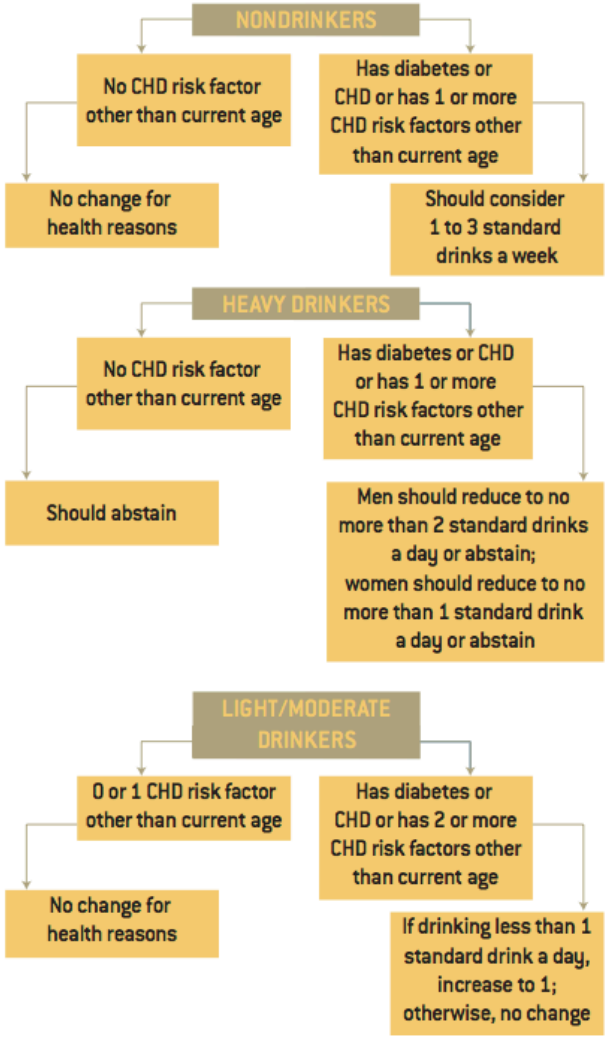
Roger R. Ecker, a cardiovascular surgeon at Summit Medical Center in Oakland, Calif., and I developed these charts to help individuals determine whether to include alcoholic beverages, and in what amounts, in their diets. The charts are designed to be used by physicians in consultation with patients. Coronary heart disease (CHD) risk factors are listed at the bottom. "Light/Moderate" is defined as up to one standard drink a day for women and up to two standard drinks a day for men. "Heavy" is three or more drinks a day for men and two or more drinks a day for women.

These charts do *not* apply to the following people, who should abstain from alcoholic beverages: anyone under the age of 21; pregnant women; nondrinkers with a family history of alcoholism, with moral or religious beliefs that preclude alcohol, with a personal history of alcohol abuse, with known organ damage from alcohol, with any chronic liver disease, or with a genetic risk of breast or ovarian cancer. —*A.L.K.*

MEN AGE 21 to 39 / WOMEN AGE 21 to 49



MEN AGE 40 AND OLDER / WOMEN AGE 50 AND OLDER



Coronary heart disease (CHD) risk factors, according to National Cholesterol Education Program guidelines:

1. Family history of CHD (father or brother younger than 55 with CHD, mother or sister younger than 65 with CHD)
2. Smoking
3. High blood pressure
4. Total cholesterol higher than 200
5. HDL cholesterol lower than 35 (if HDL is higher than 60, subtract one risk factor)
6. Age 40 and older for men, 50 and older for women

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MORE TO EXPLORE

Alcohol Consumption before Myocardial Infarction: Results from the Kaiser-Permanente Epidemiologic Study of Myocardial Infarction. Arthur L. Klatsky, Gary D. Friedman and Abraham B. Seigelaub in Annals of Internal Medicine, Vol. 81, No. 3, pages 294–301; September 1974.

Epidemiology of Coronary Heart Disease—Influence of Alcohol. Arthur L. Klatsky in Alcoholism: Clinical and Experimental Research, Vol. 18, No. 1, pages 88–96; January 1994.

Alcohol in the Western World. Bert L. Vallee in Scientific American, Vol. 278, No. 6, pages 80–85; June 1998.

Alcohol and Coronary Heart Disease. Giovanni Corrao, Luca Rubbiati, Vincenzo Bagnardi, Antonella Zambon and Kari Poikolainen in Addiction, Vol. 95, No. 10, pages 1505–1523; October 2000.

Alcohol in Health and Disease. Edited by Dharam P. Agarwal and Helmut K. Seitz. Marcel Dekker, 2001.

SCIENTIFIC AMERICAN June 2003 pp. 13,14: Letters, DRINK UP?

I enjoyed “Drink to Your Health?” by Arthur L. Klatsky, but I believe some important caveats are in order. First, observational studies, such as those quoted in support of the benefits to cardiovascular health of moderate alcohol drinking, are fraught with difficulties. Until recently, physicians advised postmenopausal women—based on observational studies—that hormone replacement therapy with estrogen would reduce their risks of cardiovascular disease. Now randomized, controlled trials demonstrate that such therapy actually increases the risk of coronary heart disease and stroke. As Klatsky notes, the question of alcohol and coronary health could be answered only by a randomized, controlled trial, a lengthy and probably impractical undertaking.

Second, observational studies are hampered by the low proportion of North American and European adults who do not drink—a proportion of these people have quit drinking because of previous alcohol-related problems, and their health outcomes cannot be extrapolated to the wider population. The reliability of observational studies can thus be questioned. In Scandinavia (with its higher proportion of alcohol abstainers), health outcome comparisons are less pronounced.

Third, as Klatsky points out, alcohol wreaks serious damage on individuals, communities and society. As a primary care physician, I regularly see patients whose lives have been ruined by excess alcohol. It behooves us to be extremely cautious about alcohol consumption for perceived cardiovascular benefits.

Steve Cottam
Great Eccleston Health Center
Lancashire, England

KLATSKY REPLIES:

Cottam is right that observational data cannot completely rule out confounders for associations. Undoubtedly, a confounder of the observational association between hormone replacement therapy and cardiovascular disease was that women who chose such therapy because they believed it to be beneficial also had a generally healthy lifestyle. This situation was long suspected, and that fact influenced the decision to perform clinical trials. It is unlikely, though, that moderate drinkers were similarly motivated, because most reports of the inverse alcohol-coronary relationship predated any wide-spread knowledge of benefit, and drinking is not typically a prescribed treatment.

I cannot agree, however, with the implication that the alcohol-coronary data are inconsistent or unreliable. I’m not sure which Scandinavian studies are exceptions, but the Copenhagen Heart Study, for one, has shown strong evidence for protection conferred by moderate drinking. As Eric B. Rimm of the Harvard School of Public Health recently wrote: “Few other associations are so uniformly reported in the literature despite diverse population samples, varying exposure, and inconsistent control for confounding.”

Finally, I emphatically agree that all considerations of benefit by moderate drinking need to be considered in light of the terrible toll of heavy uncontrolled intake.