Moderate Alcohol Consumption and Coronary Heart Disease in the Middle Aged and Elderly

A. Study Purpose and Rationale

Rationale: For decades observational studies have shown a risk reduction in coronary heart disease (CHD) events in people who consume low to moderate doses of alcohol as compared to those who abstain. However, clinical trials have not been conducted to prove a causative benefit. If proven, moderate doses of alcohol in select populations could significantly reduce the burden of cardiovascular morbidity and mortality worldwide.

Background: Cardiovascular disease is the leading cause of death in the United States and the world. CHD accounts for approximately half of the deaths due to cardiovascular disease, and in 2007, 1 in 6 deaths in the US (406,351) were due to CHD. Annually 785,000 Americans had a new coronary attack and approximately 470,000 had a recurrent attack. While there are many effective means of prevention, the burden of disease remains high. In select populations, alcohol could be an effective method of decreasing both the primary and secondary risk of disease.

For decades the medical community has collected data from observational studies that demonstrate a decreased incidence of coronary heart disease and death in people who consume low to moderate doses of alcohol. The most recent and comprehensive meta-analysis included 84 studies conducted between 1980 and 2009, which showed a relative risk for alcohol drinkers relative to non-drinkers of 0.75(0.70-0.80; 95% CI) with regard to death from CVD, incident CHD, death from CHD, incident stroke and death from stroke. With regard to incident coronary disease, 29 studies were included which showed a relative risk of 0.71 (0.66-0.77; 95% CI). Of those 29 studies, only two had a relative risk greater than one. With regard to coronary heart disease mortality, 31 studies were included which showed a relative risk of 0.75 (0.68-0.81; 95% CI). Of those 31 studies, only two had a relative risk greater than one.

While the body of observational data is large and consistent with regards to the cardioprotective effect of alcohol, the potential for confounding is significant. Although there are many, we cite three pertinent examples. Since higher socioeconomic status likely correlates with better medical care, it is noteworthy that one meta-analysis of 10 populations found that life-long abstainers were of lower socioeconomic status than light drinkers. Secondly, there is also the potential for former drinkers to be included in the abstinence arm, as was found in the British Regional Heart study in which former drinkers diluted the abstinence arm with higher rates of blood pressure, bronchitis and coronary disease. Lastly, abstention could be an indicator of emotional or physical problems, as one cohort study of 400 men found that 33% of lifelong abstainers had poor physical health in childhood compared with 14% of moderate drinkers.

In spite of the potential for confounding, the observational data has led to many studies searching for indirect biological evidence of alcohol's protective effect on cardiovascular disease. In a companion study to the large meta-analysis of Ronksley et al, the same group of

investigators conducted a meta-analysis of 44 studies on 13 biomarkers associated with increased risk of coronary heart disease in patients without pre-existing disease. Alcohol was found to significantly increase levels of three protective biomarkers and decrease levels of one harmful biomarker: (1) high density lipoprotein lipase levels increased per person by 0.094 mmol/L (0.064 to 0.094; 95% CI), (2) apolipoprotein A1 levels increased per person by 0.101 g/L (0.073 to 0.129), (3) adiponectin levels increased per person by 0.56 mg/L (0.39 to 0.72) and (4) fibrinogen levels decreased per person by -0.20 g/L (-0.29 to -0.11).

Although we have a large, consistent body of data from observational studies, and biological plausibility demonstrated by the Brien et al meta-analysis, there have been no randomized clinical trials to prove or disprove causality. In considering the risk: benefit ratio and event rate, we decided the most appropriate initial randomized control trial would be a secondary prevention trial in patients with known coronary heart disease. If alcohol is shown to significantly reduce the risk of coronary heart disease, it could prove to be a cheap, effective method of secondary prevention in a certain patient population.

B. Study Design and Statistical Analysis

Goals: To determine if moderate alcohol consumption alters the risk of coronary heart disease events in people with established coronary disease.

Hypothesis: One drink of alcohol daily will reduce the incidence of nonfatal MI and CHD death by 20% as compared to no intervention.

Study Overview: This is a prospective randomized multicenter study that is blinded to the investigators but open label to the patients, which will investigate the effect of moderate alcohol consumption as a secondary prevention treatment of cardiovascular disease in subjects with established coronary heart disease. The primary objective is to compare the two groups for differences in rates of nonfatal MI or CHD death.

Inclusion/Exclusion Criteria: To be enrolled participants must be at least 50 years old and have evidence of established coronary artery disease. Established coronary artery disease is defined as evidence of one or more of the following criteria: myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary revascularization, or angiographic evidence of at least a 50% occlusion of 1 or more major coronary arteries.
Participants will be excluded for the following reasons: CHD event within 6 months of randomization; history of liver cancer, liver cirrhosis, hepatitis B or C; alcoholism or other drug abuse; unlikely to remain geographically accessible for study visits for at least 4 years; New York Heart Association class IV or severe class III congestive heart failure; uncontrolled hypertension (diastolic blood pressure ≥ 105 mm Hg or systolic blood pressure ≥ 200 mm Hg); uncontrolled diabetes (fasting blood glucose > 300 mg/dl); a history of dementia; participation in another investigational drug or device study.

Design: Multicenter randomized, single blinded (to investigator), open label (to subjects) study

Randomization: Eligible subjects will be randomized by computer algorithm at a central location with stratification according to clinical center. Each subject will have equal probability of being part of the alcohol arm or no alcohol arm. Subjects randomized to the alcohol arm will take by mouth 0.5 ounces of alcohol once daily (14 g daily) in the form of either12 oz of 4% beer, 5 oz of 10% wine, or 1.5 oz of 40% liquor.

Study Endpoints: The primary outcome is nonfatal MI or CHD death. Nonfatal MI will be diagnosed based on algorithm that accounts of ischemic symptoms, EKG abnormalities and elevated cardiac enzymes. CHD death could be a fatal documented MI, sudden death within 1 hour of onset of symptoms, unobserved death that occurred out of the hospital in the absence of other known cause, or death due to coronary revascularization procedure of congestive heart failure. Secondary outcomes include coronary artery bypass graft surgery, percutaneous coronary revascularization, hospitalization for unstable angina, resuscitated cardiac arrest, congestive heart failure, stroke or transient ischemic attack, peripheral artery disease, all cause mortality, cancer death, and noncancer or CHD death. All outcomes will be collected between randomization and the last day of the trial.

Follow Up: Following enrollment baseline characteristics will be assessed at the initial clinic visit, which will include demographics, risks for CHD, quality of life and medication usage. At the baseline visit subjects will be examined, a baseline EKG and lipid profiles will be obtained. Follow-up visits to the clinical center will occur every 3 months to provide refills of the study medication, assess compliance and collect outcome and adverse event data. Annual evaluations will include physical exam, EKG, and venipuncture (lipid profile).

Statistical Analysis: The occurrence of the primary outcome (nonfatal MI and CHD death) was estimated at 4% per year based on two sets of data. First the incidence of recurrent MI in the USA was calculated to be 4.9% in 2011 (AHA Statistics 2011). Secondly, we used the rate of primary outcome from the HERS trial to guide our estimate, which was 3.3% annually in women. The primary outcome rate of 4% annually was chosen given an anticipated increase in event rate from the HERS trial with the inclusion of men. However, we did not anticipate that event rate approaching 4.9%. We estimated an effect of 0.2 risk reduction with alcohol, making the proportions in each group 0.04 and 0.032. The effect was extrapolated from the most recent meta-analysis of observational studies (bmj foot note). (foot note ama and hers). Using the chi square test for 80% power and significant $p < 0.05$, we calculated the need for 1951 subjects in each treatment arm, with a total recruitment goal of 3,902 patients.

C. Study Procedure

Study duration will be six years with recruitment rolling over a four year period. Subjects anticipated duration of participation is anywhere between two years and eight years, with the goal being a mean of four years participation.

D. Study Drugs

see above

E. Medical Device
NA

F. Study Questionnaire
NA

G. Study Subjects
see above

H. Recruitment of Subjects
Recruitment will occur during hospital admissions for diagnoses of coronary heart disease and during clinic visits for both new and old patients at all sites that are participating in the study.

I. Confidentiality of Study Data
All study data will be kept in a secure computerized data base in a central location. Peripheral study cites will have

J. Potential Conflict of Interest
None

K. Location of the Study
The study center will be based in New York City and other medical centers will be recruited for participation as long as they are located in the United States. Different cultures consume different quantities of alcohol and often correlate with geographic location. To minimize these discrepancies all study locations will be located in the United States.

L. Potential Risks
Subjects who have never been exposed to alcohol previously may be at risk for alcohol dependence or abuse. Alcohol abuse has been shown to increase the risk of suicide. Alcohol is associated with increased risk of injury from accidents and trauma. At the mild dosages we use there is a potential risk of pancreatitis. At higher doses there is a risk of liver cirrhosis, hepatocellular carcinoma, breast cancer and gastrointestinal cancer. (#)However we do not use dosages that will expose patients to this level of risk

R. Radiation or Radioactive Substances
None

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