Alcohol and Heart Disease in Women

5th Annual Women’s Cardiac Health Conference
5 February 2010
Conflict of Interest Statement

• I have no financial conflicts of interest to disclose.
• Our research to date has been funded exclusively by the National Institute on Alcohol Abuse and Alcoholism and the American Heart Association.
Alcohol: A Brief Review

- CH$_3$CH$_2$OH
- 7 kcal / gram
- Produced from fermentation of sugars by yeast, concentrated by distillation
Alcohol Metabolism

- >90% of metabolism occurs in liver
- ADH is rate-limiting
- Acetaldehyde is aversive and mutagenic
## What Constitutes a Drink?

<table>
<thead>
<tr>
<th>Serving Size</th>
<th>Grams</th>
<th>Calories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td>12 oz</td>
<td>12.8</td>
</tr>
<tr>
<td>Wine</td>
<td>4-6 oz</td>
<td>13.8</td>
</tr>
<tr>
<td>Spirits</td>
<td>1-1.5 oz</td>
<td>14.0</td>
</tr>
<tr>
<td>Light Beer</td>
<td>12 oz</td>
<td>11.3</td>
</tr>
</tbody>
</table>

One ounce of alcohol is ~23.6 gm of alcohol
Alcohol Use in Women, 2007-8: National Survey on Drug Use and Health

![Bar chart showing alcohol use in women from 2007 to 2008. The chart indicates a comparison between any, any binge, and regular binge alcohol use in the past month.](chart.png)
“The Therapeutic Value of Alcohol”

“My personal experience...has indicated alcohol was not only not a cause of arteriosclerosis, but, so far as one could judge, was in many cases a preventative.”

Timothy Leary, NEJM 1931
A Very Messy Debate

“…post-menopausal women with no contraindications to alcohol use should be informed that they have, on average, net health benefits from the regular consumption of small-to-moderate amounts of alcohol.”

“… for this large group (of women less than 75 years of age), the only reasonable recommendation we can make is that there is no clear evidence that alcohol has medical benefits.”

Alcohol and Heart Disease in Women: Selected Themes

1. Cardiovascular disease
   1. CVD risk factors, drinking patterns, CHD/stroke

2. Other important diseases for women

3. Providing some context

4. Where to next?
Alcohol and Coronary Heart Disease: Potential Biological Mechanisms

Alcohol → Lipids (HDL-C and Triglycerides)

Alcohol → Hemostasis/Inflammation (Fibrinogen)

Alcohol → Insulin Sensitivity

Alcohol → Other

Coronary Heart Disease
Alcohol Intake and HDL-C: Meta-Analysis of 36 Randomized Trials

Effect 25% larger if baseline HDL-C <40 than if >48 mg/dl
P=0.04

Rimm et al, BMJ 1999
## Correlation of Lifestyle & HDL-C: NHLBI Family Heart Study

<table>
<thead>
<tr>
<th>Lifestyle</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol Use</td>
<td>0.27</td>
<td>0.21</td>
</tr>
<tr>
<td>Exercise</td>
<td>0.06</td>
<td>0.10</td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.09</td>
<td>-0.13</td>
</tr>
</tbody>
</table>

Ellison et al, Am J Epidemiol 1999
Alcohol Intake and HDL-C:
11,724 adults in Copenhagen City Heart Study

Johansen et al, ACER 1999
Alcohol Intake and Serum Triglycerides: 24-week crossover trial of 51 postmenopausal women

![Graph showing the relationship between alcohol consumption and serum triglycerides.](image)

*P trend = 0.001*

Davies et al, JAMA 2002
Alcohol Intake & Insulin Sensitivity:
24-week crossover trial of 51 postmenopausal women

P trend < 0.001

Davies et al, JAMA 2002
### Alcohol Intake and Adiponectin
Parallel crossover trials of 19 men, 36 women

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Alcohol</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin (mg/l)</td>
<td>7.9 ±0.2</td>
<td>9.0 ±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>4.9 ±0.02</td>
<td>4.8 ±0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Adiponectin (mg/l)</td>
<td>12.0 ±0.8</td>
<td>13.1 ±0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>6.0 ±0.04</td>
<td>5.9 ±0.04</td>
<td>0.09</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.64 ±0.13</td>
<td>1.42 ±0.13</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Beulens et al, Diabetologia 2007; Joosten et al, Diabetologia 2008
Alcohol and Serum Sex Steroids:
8-week crossover trial of 51 postmenopausal women

Dorgan et al, JNCI 2001
Alcohol and FPG in Diabetes:
3-month parallel RCT in 91 diabetic patients
Red Wine in Patients with DM & MI: 1-year parallel RCT of advice to drink in 115 patients

Marfella et al, Diabet Med 2006
Red Wine & Glycemia: 1-year RCT in 115 post-MI patients with diabetes

<table>
<thead>
<tr>
<th></th>
<th>Red Wine</th>
<th>Usual Care</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Insulin</td>
<td>-3.8 ±1.5</td>
<td>-2.0 ±1.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>-1.2 ±0.9</td>
<td>-0.9 ±0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.8 ±0.7</td>
<td>0.9 ±0.2</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Marfella et al, Diabet Med 2006
Red Wine & LV Function:
1-year RCT in 115 post-MI patients with diabetes

Myocardial Performance Index
LV Ejection Fraction

Marfella et al, Diabet Med 2006
Alcohol Use and CHD: 6-yr Follow-up of the Diet, Cancer, & Health Study
Alcohol Use and Risk of CVD: 12-year Follow-up of the Women’s Health Study

Djoussé et al, Circulation 2009
Drinking Frequency and Risk of MI
Nurses Health Study

Mukamal et al, Circulation 2005
Alcohol Use and Mortality: Meta-analysis of 32 studies of men, 16 of women

Di Castelnuovo et al, Arch Intern Med 2006
Alcohol, Physical Activity, and CHD
Copenhagen City Heart Study

Level of physical activity:
- ● Inactive
- ○ Low
- ○ Moderate to high

Beverage Type and HDL-C:
12-week crossover trial of 11 men

Serum HDL-C (mmol/l) vs. Beverage Type

- Water vs. Alcohol: P<0.0001
- Water vs. Red wine: P=0.004
- Water vs. Beer: P=0.0002
- Water vs. Spirits: P=0.0009

van der Gaag et al, J Lipid Res 2001
Red vs. White Wine & CVD Risk Factors: Crossover Trial of 35 Women

Sacanella et al, Am J Clin Nutr 2007
Rimm et al., BMJ 1996
The Dominant Beverage Hypothesis

“In those studies that have found only one type of alcoholic beverage to be significantly inversely associated with coronary disease, that beverage is consumed by much of the population…”

Alcohol & Risk of MI/Ischemic Stroke: Kaiser Permanente cohort

Klatsky et al, Am J Cardiol 1986, 2001

N=85000 KP members
Alcohol Use and Stroke in Women: 
16 Case-Control and Cohort Studies

Reynolds et al, JAMA 2003
Meta-regression of Alcohol and Stroke: Meta-Analysis of 24 Studies

Reynolds et al, JAMA 2003
Alcohol and Heart Disease in Women: Selected Themes

- Cardiovascular disease
- Other important diseases for women
  - Diabetes, Cancer, Osteoporosis
- Providing some context
- Where to next?
Alcohol and Diabetes Risk in IFG: The Diabetes Prevention Program

Crandall et al, AJCN 2009
Alcohol Intake and Risk of Diabetes: Meta-analysis of 15 cohort studies

Koppes et al, Diabetes Care 2005
Alcohol Use and Risk of Breast Cancer: 7 Pooled Cohort Studies

N=322647 women

Smith-Warner et al, JAMA 1998
Alcohol Use and Upper GI Cancers: Meta-analysis of 28 studies

Bagnardi et al, Br J Cancer 2001
Alcohol and Lung Cancer in Women: 7 Pooled Cohort Studies

Hazard Ratio

Average Alcohol Use (gm/day)

None 0.1-4.9 5.0-14.9 15.0-29.9 30+

Freudenheim et al, AJCN 2005
Alcohol and Colon Cancer in Women: 8 Pooled Cohort Studies

Cho et al, Ann Intern Med 2004
Alcohol and Cancer in Women: 7-Year Follow-up of the Million Women Study

Hazard Ratio

- All Cancers
- Breast Cancer

Drinks per Week

Allen et al, JNCI 2009
Alcohol Use and Risk of Injury: National Alcohol Survey

N=1150 respondents

Cherpitel et al, Accid Anal Prev 1995
Alcohol and Femoral Neck BMD: Four Cohort Studies

Alcohol and Hip Fracture: Case-Control and Cohort Studies

Alcohol and Heart Disease in Women: Selected Themes

- Cardiovascular disease
- Other important diseases for women
- Providing some context
  - Potential sources of bias, how do these data compare?
- Where to next?
Observational Studies of Alcohol: Potential Sources of Bias

- Former drinkers may have quit for health-related reasons
- Uncontrolled confounding
- Imperfect animal models (e.g., HDL metabolism)
- No long-term RCT data
The Bias of Former Drinkers:
Meta-Analysis of 48 Prospective Studies

Di Castelnuovo et al, Arch Intern Med 2006
Comorbidity Among Abstainers:
2003 Behavioral Risk Factor Surveillance System

Prevalence Ratio of Abstention

Low Income
Low Activity
BMI 30-35
BMI 35-40
Fair Health
Poor Health
Smoker

Mukamal et al, BMC Public Health 2006
The alcohol treatments also decreased the plasma levels of...HDL cholesterol at almost all time intervals.
Integrating Trials & Observational Data: The HRT example

Barrett-Connor et al, Maturitas 1997
Integrating Trials & Observational Data: The HRT example

A Comparable Dietary Example: Trans Fatty Acids

Alcohol and Heart Disease in Women: Selected Themes

• Cardiovascular disease
• Other important diseases for women
• Providing some context
• Where to next?
  – Personalizing risk, pushing the evidence
## Effects of 1 Drink Every 1-2 Days:
Survey of Beliefs of 878 HCA Patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Causes</th>
<th>Prevents</th>
<th>Neither</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial Infarction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstainers</td>
<td>19</td>
<td>27</td>
<td>54</td>
</tr>
<tr>
<td>Drinkers</td>
<td>10</td>
<td>32</td>
<td>58</td>
</tr>
<tr>
<td><strong>Breast Cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstainers</td>
<td>11</td>
<td>2</td>
<td>87</td>
</tr>
<tr>
<td>Drinkers</td>
<td>8</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td><strong>Cirrhosis or Liver Damage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstainers</td>
<td>57</td>
<td>2</td>
<td>41</td>
</tr>
<tr>
<td>Drinkers</td>
<td>52</td>
<td>1</td>
<td>47</td>
</tr>
</tbody>
</table>

Mukamal et al., Fam Med 2008
## Kinetic Activity of ADH Alleles

<table>
<thead>
<tr>
<th></th>
<th>ADH1B</th>
<th>ADH1C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta_1\beta_1$</td>
<td>$\gamma_1\gamma_1$</td>
</tr>
<tr>
<td></td>
<td>$\beta_2\beta_2$</td>
<td>$\gamma_2\gamma_2$</td>
</tr>
<tr>
<td></td>
<td>$\beta_3\beta_3$</td>
<td></td>
</tr>
<tr>
<td>$V_{max}$, min $^{-1}$</td>
<td>9.2</td>
<td>400</td>
</tr>
</tbody>
</table>

Bosron et al, Mol Aspects Med 1988
ADH1C, Alcohol, and HDL-C: The Nurses’ Health Study

Frequency of alcohol consumption among 325 women in the Nurses’ Health Study

Hines et al, NEJM 2001
ADH1C, Alcohol, and Risk of Diabetes:
The Nurses’ Health and Health Professionals Follow-up Studies

Beulens et al, Diabetes 2007
Interaction of Alcohol and CETP Taq1B Genotype on HDL and MI

N=246 cases, 486 controls

Jensen et al, Eur Heart J 2008
AAA Pilot Study

- Funded by NIAAA
- 40 subjects 55+
- Aortic MRI & CVD risk factors
- Randomized to 15 gm (10%) alcohol for 6 months
Help us learn whether alcohol affects your arteries and risk factors for heart disease in a study sponsored by the National Institutes of Health!

Are you 55 or older?

Do you drink alcohol at least once a month?

If you would like to learn more about this study, contact Brian at:

(617) 754-1436  or aaapilot@bidmc.harvard.edu

Reimbursement for your time and travel will be provided.

Confidentiality Statement: Participation in this study will remain completely anonymous. Your medical records will remain protected under the law.
Alcohol & Heart Disease in Women: Summary

- Alcohol use is common among women – ask!
- Consistent association of moderate alcohol intake with lower risk of coronary heart disease
- No clear relationship with beverage type
- Weaker relationship with ischemic stroke
- Appears to be mediated by higher HDL-C, lower fibrinogen, better insulin sensitivity
Alcohol & Heart Disease in Women: Summary

• Moderate intake also associated with lower risk of diabetes but higher risk of breast cancer
• Complex relationship with injury, BMD, fractures
• Imperfect evidence on both benefits and risks, trials of uncertain feasibility (but starting!)
• Balance of risks and benefits likely to shift toward benefit with age and CVD risk factors