PRACTICAL POINTERS

FOR

PRIMARY CARE MEDICINE

ABSTRACTED MONTHLY FROM THE JOURNALS

A Free Public-service Publication

NOVEMBER 2010

BINGE DRINKING, MODERATE DRINKING, AND WINE DRINKING RELATED TO ISCHEMIC HEART DISEASE [11-1]

EFFICACY AND SAFETY OF INTENSIVE LDL-CHOLESTEROL LOWERING [11-2]

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JAMA, NEJM, BMJ, LANCET
ARCHIVES INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE

PUBLISHED BY PRACTICAL POINTERS, INC.
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25TH YEAR OF PUBLICATION

This document is divided into two parts

1) The **HIGHLIGHTS AND *EDITORIAL COMMENTS* SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

EDITORIAL COMMENTS *are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 25-year publication of Practical Pointers.*

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 10 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.
Editor/Publisher.

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HIGHLIGHTS AND *EDITORIAL COMMENTS* NOVEMBER 2010

Binge Drinking Increases Risk. Wine And Regular Drinking Reduce Risk.

11-1 PATTERNS OF ALCOHOL CONSUMPTION AND ISCHEMIC HEART DISEASE IN CULTURALLY DIVERGENT COUNTRIES (PRIME study)

This prospective observational cohort study analyzed the patterns of alcohol consumption and their relation to myocardial infarction and coronary deaths **(MI and CD)** in men age 50-59 in Belfast, Northern Ireland (n = 2745) and in 3 cities in France (n = 7373).

Analyzed weekly alcohol consumption, volume of alcohol intake, frequency of consumption, and type of beverage consumed. One drink of alcohol was standardized as 10--12 g of ethanol.

Assessed the relation between baseline drinking characteristics and incidence of MI and CD and angina over 10 years. Defined groups: non-drinkers, daily drinkers, regular drinkers, and binge drinkers. Regular drinking was arbitrarily defined as intake of at least 3 consecutive drinks on at least one day a week, and if drinking on only one occasion, consuming less than 50 g of alcohol. Binge drinking was set at 50 g or more of alcohol on at least one day a week. It was not an occasional weekly behavior. It occurred regularly each week.

Patterns of drinking differed considerably between Belfast (B) and France (F).

	B (%)	F (%)		B (%)	F (%)
Non-drinkers	39	9	Wine	27	92
Regular drinkers	51	90	Beer	75	56
Daily drinkers	12	75	Spirits	61	73
Binge drinkers	9	0.5			

Men in F were much more likely to drink every day; men in B were much more likely to drink heavily on weekends. Among regular drinkers, the total amount of alcohol consumed was about equal in both B and F (282 g and 255 g weekly). However, the alcohol volume tended to be consumed on 1 or 2 days in B and through the week in F. Mean alcohol consumption in B was 2 to 3 times higher on weekends than in F.

In both countries the *highest* incidence of MI and CD was noted in the *non-drinking* group. Drinkers were *less* prone to MI and CD than non-drinkers. Incidence of angina did not vary in drinkers vs non-drinkers.

Regular drinkers, even those that drank heavily (> 75 g of alcohol daily) had a lower risk of CD and MI than non-drinkers.

Incidence of MI and CD in regular drinkers over 10 years: (%)

	Belfast	France
Non-drinkers	6.4	4.5
75 g daily	3.8	2.9

(Ie, whatever the quantity, regular drinking seemed to be protective.).

Whatever the category of alcohol consumption, the proportion of individuals who experienced MI or CD was always higher in B.

After 10 years of follow-up, a total of 5.3% in B and 2.6% in F had incident MI and CD.

(Ie, in B the rate of MI and CD was twice that of F. Absolute difference = ~ 3 per 100 men in 10 years.)

Conversely, consumption was not associated with angina. The risk of MI and CD in binge drinkers, and in never-drinkers, was similar--about two-fold higher than in regular drinkers.

Wine drinking, compared with no wine drinking was associated with a *lower* risk of MI and CD. Two by two comparisons showed significant differences in risk of MI and CD events between wine and beer drinking and between wine and other types of alcohol.

Hazard ratios for MI and CD in regular drinkers (adjusted): Beer 0.91 Wine 0.57 Other drinks 1.01.

"Our findings have important public health implications. The regions we studied are within countries for which alcohol consumption is the highest recorded worldwide and is of similar order of magnitude (11 to 14 liters of pure ethanol per capita in adults per annum.)"

"From our data alone however, it is difficult to conclude whether the pattern of alcohol intake has a major role in the incidence of ischemic heart disease **(IHD)** independent of other behaviors such as diet."

Conclusion: Regular and moderate alcohol intake throughout the week, the typical pattern in middle-aged men in France, is associated with a low risk of IHD, whereas the binge drinking pattern more prevalent in Belfast confers higher risk.

This is a long and complex article. I believe it carries an important message for primary care clinical practice.

The investigators carefully pointed out, however, that there may be confounding factors in the French population that contribute to the lower incidence of IHD in France.

The "French paradox" has been noted for years. Despite lifestyles, which are just as unhealthy as other countries, the incidence of IHD has consistently been lower in France. This has been attributed to regular wine-drinking. The present study seems to confirm this.

Heavy regular drinking (> 75 g daily; n = 1134 of 7373 in France mainly wine) seemed protective of IHD. However, it obviously is associated with other diseases and considerable social and family disasters. .

In High Risk Patients, More Intensive Therapy May Reduce Risk Of Mortality And Major Vascular Events.

11-2 EFFICACY AND SAFETY OF MORE INTENSIVE LOWERING OF LDL-CHOLESTEROL: ***A Meta-Analysis Of Data From 170 000 Participants In 26 Randomized Trials***

This meta-analysis of individual data assessed the benefits and safety of more intensive statin therapy. Trials were eligible if the main effect of the intervention was to lower LDL-c without any other modifications of risk factors.

Five-trials (n = 39 512) compared more intensive statin vs less intensive statin therapy. All had prior CHD. Baseline LDL--c was 96 mg/dL The mean further reduction in LDL-c at one year = 20 mg/dL . Compared with less intensive therapy, more intensive therapy produced a highly significant 15% reduction in major vascular events at 1 year.

There was no evidence, in the more vs less intensive therapy, that further lowering of LDL-c from 96 mg/dL to 76 mg/dL produced any adverse effects

Twenty-one trials (n = 129 526) compared statin vs placebo. 52% had prior CHD.
There was a highly significant reduction of 22% in major vascular events per 38 mg/dL reduction in LDL-c.

Across all 26 trials, all cause mortality was reduced by 10% per year per 38 mg/dL (1 mmol/.L) reduction in LDL-c. Absolute benefit = 8 per 1000 per year. This largely reflected significant reductions in death from coronary heart disease.

Overall, the risk reduction in major vascular events was 22% per 38 mg/dL reduction in LDL-c at 1 year, with a significant 12% reduction during the second year, and significant reductions in each year thereafter.

Ischemic stroke was reduced from 0.6% to 0.5% Absolute benefit = 1 per 1000 per year. Incidence of hemorrhagic stroke may be slightly increased.

In the more vs less statin trials, incidence of rhabdomyolysis was 4 per 10 000; in the statin vs placebo trials, the observed excess was 1 per 10 000.

There was no evidence of any hazard even when LDL-c concentrations lower than 76 mg/dL were reduced further.

The absolute reduction in cardiac mortality produced by lowering LDL-c with statins in a given population depends chiefly on the absolute risk of death due to coronary occlusion.

The size of the proportional reduction in major vascular events was in direct proportion to the absolute reduction in LDL-c. Each 38 mg/dL reduction in LDL-c reduced the risk of occlusive vascular events by about 20% irrespective of the baseline LDL-c concentration.

"These further reductions in vascular risk can be achieved safely."

"These findings suggest that the primary goal for patients at high risk of occlusive events should be to achieve the largest LDL cholesterol reduction possible."

Lowering LDL-c further in high-risk patients would produce additional benefits without any increase in non-vascular mortality.

The investigators were very enthusiastic about LDL-c reduction. They agree that a strong intervention is warranted only in those at high risk of CVD.

They tend to downplay risks of statins. (For a detailed account of adverse effects of statin see Practical Pointers June 2009 [6-2]). Adverse events may be anticipated by careful follow-up. This is costly and burdensome.

This presents a challenge for primary care. How should we judge when to augment statin therapy? There is clearly a group of patients for whom aggressive statin treatment is not indicated, and a group for whom aggressive treatment is indicated. The difficult decision lies for those in between. In this group many risk factors must be considered. This includes age of the patient. Young patients will face greater risk of adverse effects of statins because of longer usage. Old patients have less to gain. The patient must be given enough information to enable his informed consent--to balance his risk of IHD vs the possible harms and costs of statins

Investigators and editors stress benefits and risks in relative terms. This may be meaningful when comparing one treatment with another, but is meaningless when applied to the individual patient. Editors may present absolute numbers but leave it to the reader to calculate the absolute risk or benefit. Patients should be told, "If you take this medication or adopt this lifestyle, your chances of benefit are X in 100, and your chances of harm are Y in 100". The patient may then make a meaningful decisions to accept or reject based on informed consent.

Diagnosis And Treatment Of Disease Before It Is Clinically Manifest--A Clinical-Actuarial Correlation

[11-3] DESKTOP MEDICINE

Concepts of disease are essential for defining medicine. In the early 20th century, the dominant concept was pathology in an individual, the foundation for the bedside model of medicine. Bedside

medicine organizes the patient-physician relationship around the chief concern, which guides the focus of history-taking and physical examination. Medical training focused on history-taking and the physical examination, emphasizing laboratory-based science and physical diagnosis**.**

Today, a new model has emerged--desktop medicine. This describes how a desk with a network computer is transforming medical science and practice. The desktop is the space in which researchers discover risk factors and where patients, as well as physicians, go to gain information to diagnose, prevent, and treat disease. Desktop diseases such as dyslipidemia occupy a substantial portion of practice, and are leading causes of morbidity and mortality. Medicine may soon require an annual personalized health risk assessment.

Desktop diseases are discovered when studies show a factor (eg, blood pressure) is associated with a negative outcome (eg, stroke) and when a clinical trial shows that an intervention affecting the risk factor reduces the risk of the outcome event. The new technology enables physicians to discover the characteristics of persons at risk and to create models to assess whether a patient is at sufficient risk to warrant intervention.

The clinician gathers risk factors by taking the patient's history and physical examination and by reviewing published clinical studies; then determining whether the risk is sufficient to recommend treatment. The exercise of gathering risk factors and then assessing how well they predict health outcomes and the benefits of reducing these risks is a clinical-actuarial correlation.

Desktop medicine requires development of skills in probabilistic reasoning, epidemiology, and decision sciences as they apply to clinical practice. Physicians need skills in incorporating desktop and bedside models into the office visit and in shaping patient's expectation s for a visit to include both bedside and desktop diseases.

Bedside diseases are categorical. They are either present or absent. Desktop diseases are dimensional. Risk is continuous. Physicians should discuss disease as a probability. Rather than a disease label compelling treatment, a risk estimate allows patients and physicians to practice clinical-actuarial correlation (eg, Is my risk of cancer death too low to justify surgery?)

In applying desktop medicine, it is essential to improve skills in changing patients' behaviors.

Educating physicians to practice desktop medicine is especially important for the care of elderly patients who have competing risks.

Comparing desktop medicine and bedside models of medicine

	Bedside	**Desktop**
Concept	**Disease as pathology**	**Disease as a risk of future impairment**
Examples	**Alzheimer disease, congestive heart failure, colitis, influenza**	**Diabetes, dyslipidemia, hypertension, osteoporosis.**

Core sciences	**Anatomy, biology, histology, chemistry Pathology, physiology**	**Economics, epidemiology, laboratory science, genetics, psychology, statistics.**
Patient-physician Interaction	**Emphasizes patient's chief concern and guides a workup and intervention to address it**	**Emphasizes fostering patient's appreciation of risks and then adopting and adhering to strategies for risk reduction**
Approach to diagnosis and treatment	**Clinical-pathological correlation using results of the history, physical examination and studies to select the disease that best explain the chief concern. Uses judgment to select the best treatment**	**Clinical-actuarial correlation using the results of the patient's risk factor assessment to correlate with models that estimate whether risk is sufficient to warrant treatment**

JAMA November 10. 2010; 304: 2061-62 "Commentary" "by Jaason Karlawish, University of Pennsylvania, Philadelphia, PA

I enjoyed this commentary. I have been privileged to experience 7 decades of medical practice As the editorialist comments, I was taught to elicit the "chief complaint" and then go on to conduct a review of systems in order not to miss any detail of the patient's history. The physical examination was then paramount.

Over the years, the introduction of determination of risk factors occurred so gradually, we scarcely realized this remarkable change in practice.

Desktop medicine is an addition, not a replacement to bedside medicine. Note the Case Records of the Massachusetts General Hospital published frequently in NEJM. These are examples of pure bedside medicine, beginning with chief concern, history, lab work, imaging, pathology and differential diagnosis.

Now that desktop medicine gives us the ability to predict the likelihood of an adverse event, we face the challenge of persuading the patient to reduce his risk. If risk reduction is in the form of medication, the challenge is relatively easy. If it is in the form of lifestyle change (as it often is) the challenge is difficult.

Combined Aerobic And Resistance Training Was More Effective In Reducing Hba1c

11-4 EFFECTS OF AEROBIC AND RESISTANCE TRAINING ON HEMOGLOBIN A1C LEVELS IN PATIENTS WITH TYPE-2 DIABETES

Regular exercise provides substantial benefits in patients with type-2 diabetes. (DM-2). The benefit related to the exact exercise prescription (aerobic vs resistance) is less clear. For a given amount of time, is the combination of aerobic + resistance better than either alone?

This study was designed to compare the effects of aerobic training, resistance training and the combination on HbA1c levels in previously sedentary persons with DM-2.

Recruited participants (age 30-75; n = 2421 screened for eligibility) from 2007 to 2009 in a community in Louisiana for a 9-month exercise interventions study. After exclusions randomized 262 participants into 4 groups:

1) Control (n = 41) were offered weekly stretching and relaxation classes

2) Aerobic exercise (n =72) 140 minutes per week on the treadmill.

3) Resistance exercise (n = 73) exercised 3 times a week. Each session consisted of: two sets of 4 upper body exercises; 3 sets of 3 leg exercises; and 2 sets each of abdominal crunches and back exercises.

. 4) Combined aerobic-resistance (n = 76) had 2 resistance periods per week of one set of exercises and the remainder of the time on the treadmill.

Exercise interventions were designed to be of approximately equal time. The exercises were standardized to body weight, Estimated that 150 minutes per week of moderate intensity exercise (50% to 80% of maximum O2 consumption) would burn 10 to 12 kcal/kg of body weight per week.

Primary outcome = change in HbA1c over 9 months.

Baseline characteristics (means and %): Age 56; female 63%; 47% non-white; HbA1c 7,7%; duration of DM -2 7 years; BMI 35; waist circumference 112 cm; BP 126/76.

Baseline and 9-month changes in HbA1c: HbA1c %

A. Intentions -to-treat (n = 262)	Baseline	9-month	Mean change
Control	7.62	7.74	+0.12
Resistance	7.58	7.53	--0. 05
Aerobic	7.56	7.43	--0.13
Combined exercise	7.59	7.36	--0.23

When intention -to treat group was limited to those with baseline HbA1c 7.0% and over, the difference in HbA1c levels between controls and combined exercise group grew to -0.35%. And when limited to those with a baseline HbA1c 7% or more who actually completed the trial the difference grew to -0.45

The combination group had fewer increases and more reductions in antidiabetes medications.

Cumulative benefit across all outcomes was greater in the combination group compared with either the aerobic or the resistance groups.

The differences in HvbA1c between the combination group and the control group occurred even

though the control group had increases in use of diabetes medications while the combination group had decreases.

Conclusion: Among patients with DM-2, a combination of aerobic and resistance training, improved HbA1c levels more than aerobic exercise alone and resistance exercise alone.

How generalisable is this trial? One way of judging generalizability is to follow the participant flow chart.

The study began with 2421 individuals screened for eligibility.

After all exclusions, only 262 individuals remained for randomization and the intention-to-treat analysis.

The benefits were indeed modest,

Nevertheless, I believe the trial has some applicability to primary care practice. Some patients may find it more convenient to perform resistance exercises periodically and combine them with brisk walking. A combined program will lead to improved fitness and well-being, and likely lower risks of cardiovascular disease.

There were no dietary restrictions in the trial. If they were applied, benefits would be greater.

Primordial Prevention--The Next Step?

11-5 OPTIMAL CARDIOVASCULAR PREVENTION STRATEGIES FOR THE 21ST CENTURY

Death rates from cardiovascular disease **(CVD)** remains by far the leading cause of morbidity and mortality in the US. CVD chronically affects over 80 million US adults.

Primary prevention reduces the chances of a first event. It is more difficult to implement than secondary prevention. All manifestations of CVD have common predisposing factors, especially smoking, adverse lipids, blood glucose, and high BP. However, most first CVD events occur in individuals with only mildly elevated levels of risk factors who would not typically qualify for preventive efforts. Extensive CVD prevention can be achieved only through lifestyle and environmental modifications

Primordial Prevention goes beyond secondary and primary prevention. It is a more radical concept. It ensures that the levels of CVD risk factors observed in healthy children are preserved into adulthood. Individuals who maintain a profile of ideal CVD risk factors from young adulthood into middle age essentially escape remaining lifetime risk of major CVD events. Both CVD and non- CVD mortality

rates are reduced. This results in the addition of 10 years longevity, better health-related quality of life, and lower annual Medicare costs.

The American Heart Association recently endorsed primordial prevention for improving cardiovascular health in all Americans. Barely 5% of the US population now maintain this ideal profile into middle age.

One recent study published in the Bulletin of the World Health Association demonstrated that, if the majority of the US population reached middle-age with an ideal phenotype, more than 90% of coronary heart disease deaths might be prevented.

Population-based strategies aim to improve health of the entire population by favorably shifting the distribution of risk factors.

Vascular surgery, hospitalizations, and expensive drugs for lipid reduction, hypertension and diabetes drive the economic burden of CVD. Medication-based primary prevention is relatively costly. Primordial prevention will generate savings.

Reducing mean population levels of cholesterol or BP by 5%, or legislation to eliminate trans fat, or reducing dietary salt intake by 3 grams per day would generate over a billion dollars of savings per year.

Delays in identifying more effective strategies for CVD prevention will be very costly.

"The status quo is not acceptable politically, ethically, or economically."

One of the greatest failures of the medical profession has been our inability to convince individual patients to maintain healthy living habits. The failure is not the profession's alone. It is a societal problem requiring continuing educating, reduction in poverty, general awareness of risk and a change in national living habits. This may take decades.

Prevention must begin in early life. Our present risk assessment and reduction models now extend for only 10 years.

Governments may play a role over the objections of the Libertarians.

ABSTRACTS NOVEMBER 2010

Binge Drinking Doubled The Risk Of IHD. Wine Drinking Is Associated With Lower Risk Of IHD

11-1 PATTERNS OF ALCOHOL CONSUMPTION AND ISCHEMIC HEART DISEASE IN CULTURALLY DIVERGENT COUNTRIES (PRIME study)

The WHO estimated that 17 million people died from cardiovascular disease **(CVD)** in 2004 (20% of all deaths). In 2004, cardiovascular disease accounted for 10% of all diseases attributable to alcohol. The CDC reported that excessive alcohol was responsible for about 70 000 deaths in the US each year.

In Europe, in 2006. 20% of persons over age 15 reported they consumed 5 or more alcoholic drinks (over 50 grams of alcohol) on one occasion (binge drinking) at least once a week. The prevalence of binge drinking varied considerably among countries.

Conversely, many observational studies have reported that some behaviors related to alcohol are related to a *decrease* in ischemic heart disease. (Inverse relationship)

The role of specific alcoholic beverages (wine, spirits, beer) in ischemic heart disease **(IHD)** is still debated. The type of beverage is often considered a proxy for more complex inter-relationships between lifestyle, diet, and socioeconomic factors.

The incidence of IHD is higher in Northern Ireland than in France. According to the WHO MONICA project (1999) the ratio of incident myocardial infarction and coronary deaths **(MI and CD)** in Belfast compared with 3 cities in France is 2:1 to 3:1 Is it possible that the disparity could be, at least in part, due to alcohol behaviors specific to each country?

This prospective observational cohort study analyzed the patterns of alcohol consumption and their relation to MI and CD in men age 50-59 in Belfast, Northern Ireland and in 3 cities in France.

STUDY

1. Analyzed weekly alcohol consumption, volume of alcohol intake, frequency of consumption, and type of beverage consumed. One drink of alcohol was standardized as 10--12 g of ethanol.
2. Determined all coronary events during a 10-year follow-up period.
3. Assessed the relation between baseline drinking characteristics and incidence of MI and CD and angina.
4. Defined four groups: non-drinkers, daily drinkers, regular drinkers, and binge

drinkers. Regular drinking was arbitrarily defined as intake of at least 3 consecutive drinks on at least one day a week, and, consuming less than 50 g of alcohol on any one occasion..

Binge drinking was set at 50 g of alcohol on at least one day a week. It was not an occasional weekly behavior. It occurred regularly each week.

RESULTS

1. Between 1991 and 1994, 10 600 men age 50-59 were examined; 2745 in Belfast **(B),** and 7855 in France **(F).** Of these, 849 were excluded because of a past diagnosis of myocardial infarction or angina. Others were lost to follow-up or died, leaving a total of 9778 for follow-up: 2498 in B and 7373 in F. All were free of ischemic heart disease **(IHD)** at baseline

2. Pattern of alcohol consumption:

	B	F
Non-drinkers (%)	39	9
Binge drinkers	9	0.5
Regular drinkers	51	90

Almost all men in F consumed alcohol vs about 60% in B. Men in F were more likely to be regular drinkers (75% drank daily vs 12% in B).

Binge drinking was 20 times more prevalent in B.

Men in B were much more likely to drink heavily on weekends.

Men in F were much more likely to drink every day.

Drinkers in B mainly drank beer (75%) followed by spirits (61%)) and wine (27%). In F 92% drank wine, 73% spirits and 56% beer.

3. Amount of alcohol consumed:

Among regular drinkers, the total amount of alcohol consumed was about equal in both B and F (282 g and 255 g weekly).

However, the alcohol volume tended to be consumed on 1 or 2 days in B and through the week in F. Mean alcohol consumption in B was 2 to 3 times higher on weekends than in F. On Fridays drinkers in B consumed about 61 g vs 34 g in F. On Saturdays 91 g vs 41 g.

4, Incidence of myocardial infarction **(MI)** and coronary death (**CD)**)in men who drank every day vs non-drinkers.:

	Non-drinkers	1-24 g /d	25-49 g/d	50-74 g /d	75 g and over
Belfast					
MI and CD (%)	6.4	3.8	6.2	4.1	3.8
Angina	4.5	4.9	5.7	6.3	4.6
France					

MI and CD	4.6	2.5	2.4	2.1	2.9
Angina	3.5	3.1	3.9	2.6	3.1

In both countries, the *highest* incidence of MI and CD was noted in the *non-drinking* group. In F the proportion of individuals who experienced MI or CD differed significantly between drinkers and non-drinkers. Drinkers seemed to be less prone to MI and CD than non-drinkers. Incidence of angina did not vary in drinkers vs non-drinkers.

Whatever the category of alcohol consumption, the proportion of individuals who experienced MI or CD or angina was always higher in B.

6. After 10 years of follow-up, a total of 5.3% in B and 2.6% in F had incident MI and CD.
7. After multivariate adjustments for eleven classical IHD risk factors, alcohol consumption remained associated with the occurrence of MI and CD in both B and F. Conversely, consumption was not associated with angina.
8. The risk of MI and CD in binge drinkers, and in never-drinkers, was similar--about two-fold higher than in regular drinkers.
9 Hazard ratios for MI and CD in regular drinkers (adjusted): Beer 0.91 Wine 0.57 Other drinks 1.01.
10. Wine drinking, compared with no wine drinking was associated with a lower risk of MI and CD in regular alcohol drinkers. Two by two comparisons showed significant differences in risk of MI and CD events between wine and beer drinking and between wine and other types of alcohol. There was no significant association for beer compared with no-beer or other alcoholic beverages.

DISCUSSION

1. Alcohol consumption patterns in men differed radically between B and F. In B most consumption was concentrated on one day of the weekend. In F consumption was spread evenly throughout the entire week. The volumes consumed each week were similar Different drinking habits could play a substantial role in the disparity between B and F.
2. The prevalence of binge drinking, which doubled the risk of IHD compared with regular drinking, was almost 20 times higher in B. The residual differential risk for MI and CD between B and F persisted after multivariate adjustments.
3. The consumption of wine seems to be associated with lower risk of IHD in both B and F. But the study's low power to detect subgroup differences does not allow for firm conclusions.
4. Conversely, no associating was observed for incident angina pectoris. This suggests that the pathophysiological mechanism of the effect of alcohol on IHD and its clinical expression are more likely to be related to thrombosis than to atherosclerosis.

5. When the entire cohort (including binge drinkers and non-drinkers) was considered, as the number of drinking days increased, the risk of incident MI and CD decreased confirming the *inverse* association previously reported in both men and women.
6. One study reported that mortality after an acute MI was twofold higher in binge drinkers than in drinkers who do not binge. This suggests that a risk exists for episodic alcohol intake, even when the amount consumed is moderate.
7. Episodic consumption seems at least as crucial as the volume of alcohol consumed in determining the positive association between binge drinking and incidence of MI and CD.
8. The role of the type of alcohol in relation to IHD has been debated. A favorable effect of wine on the incidence of IHD and on mortality rates is often reported in populations in which wine is the predominant alcoholic drink. In this study, wine drinking was associated with a lower risk of IHD in both B and F. "Thus we suggest that wine consumption in itself is of greater importance than the volume of wine consumed, and that wine-associated behavior is at least as significant as wine consumption." It has been reported that people in F who drink wine and drink moderately have healthier lifestyles and reduced frequency of cardiovascular risk factors than abstainers and those who drink other beverages.Wine drinking in B tended to be associated with people of higher socioeconomic status in whom health expectations are better.
9. The biological effects of alcohol depend on how much and how often alcohol is consumed. This association has been attributed to the relation between alcohol and higher HDL-cholesterol and temporary changes in fibrinolytic activity. The higher BP levels observed in B on Mondays and Tuesdays are associated with binge drinking patterns.

POLICY IMPLICATIONS:

"Our findings have important public health implications. The regions we studied are within countries for which alcohol consumption is the highest recorded worldwide and is of similar order of magnitude (11 to 14 liters of pure ethanol per capita in adults per annum.)"

The prevalence of binge drinking, which was formerly a marginal drinking behavior in the majority of Mediterranean countries has tended to increase in the younger generation. Education has a pivotal role in the campaign to reduce harmful drinking habits.

The alcohol industry takes every opportunity to imbue alcohol with a positive image, emphasizing its beneficial effects on risk of IHD, but people also need to be informed about the health consequences of heavy drinking. In both B and F, the same behaviors were associated with IHD. Binge and irregular heavy drinking doubled the risk of developing an MI in comparison with regular and moderate drinking.

Consuming a high quantity of alcohol on each drinking occasion, which characterizes binge drinking, was particularly prevalent in B, could contribute to the higher risk of IHD observed there.

"From our data alone however, it is difficult to conclude whether the pattern of alcohol intake has a major role in the incidence of IHD independent of other behaviors such as diet."

CONCLUSION:

Regular and moderate alcohol intake throughout the week, the typical pattern in middle-aged men in France, is associated with a low risk of IHD, whereas the binge drinking pattern more prevalent tin Belfast confers higher risk.

BMJ 2010.341:c6077 Original investigation, by the Prospective Epidemiological Study of Myocardial Infarction (PRIME), first author Jean-Bernard Ruidavets, Toulouse University Toulouse, France Doi.10.1135/bmj.c6077 A brief summary appeared in BMJ November 37, 2010

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In High Risk Patients, More Intensive Therapy May Reduce Risk Of Mortality And Major Vascular Events.

11-2 EFFICACY AND SAFETY OF MORE INTENSIVE LOWERING OF LDL-CHOLESTEROL: ***A Meta-Analysis Of Data From 170 000 Participants In 26 Randomized Trials***

Observational studies show that there is a continuous positive relation between coronary disease risks and blood cholesterol concentrations. Larger reductions in LDL-cholesterol (**LDL-c**) might well produce larger reductions in risk.

Standard statin regimens (eg, 20-40 mg simvastatin) typically reduce LDL-c by about a third. Regimens involving higher doses of simvastatin (40 - 80 mg), or more powerful statins such as atorvastatin or rosuvastatin, can halve LDL-c.

This meta-analysis of individual data assessed the benefits and safety of more intensive statin therapy.

STUDY

1. Included all eligible trials up through 2009. Trials were eligible if the main effect of the intervention was to lower LDL-c without any other modifications of risk factors. All trials included at least 1000 participants and were at least 2 years in duration.
2. Prospective outcomes were coronary death, non-fatal myocardial infarction; coronary revascularization; stroke; and new cancers.

3. Analyses were to include all randomized patients, regardless of whether they received the allocated treatment (intention-to-treat).
4. The primary meta-analyses were the effects on disease events in each trial weighted by the absolute LDL-c differences at 1 year, and reported as effects per 1.0 mmol/L (about 38 mg/dL) reduction in LDL-c.

RESULTS

(Note: The article cites LDL-c levels as mmol/L I have transposed mmol/L to mg,/dL, which is more familiar in the US. One mmol LDL-c = ~ 38 mg.)

1. Five-trials (n = 39 512) compared more intensive statin vs less intensive statin therapy: All had prior CHD.
   A. Baseline LDL--c was 96 mg/dL.
   B. The mean further reduction in LDL-c at one year = 20 mg/dL.
   C. Compared with less intensive therapy, more intensive therapy produced a highly significant 15% reduction in major vascular events at 1 year.
   D. There were significant reductions in coronary death or non-fatal myocardial infarction of 15%; in coronary revascularization of 19%; and in stroke of 16% per 38 mg/dL reduction in LDL-c.
   E. Events (% per year): more statin = 4.5%; less statin (control) = 5.3%.
   (Absolute benefit = 8 per 1000 per year)
2. Twenty one trials (n = 129 526) compared statin vs placebo. 52% had prior CHD.
   A. Baseline LDL-c was 140 mg/dL.
   B. LDL-c reduction = 74 mg/dL.
   C. Events (% per year): statin = 2.8%; no statin (control) = 3.6%.
   (*Absolute benefit = 8 per 1000 per year)*
3. Overall (n = 169 138)
   A. Difference in LDL-c at 1 year = 41 mg/dL/
   B. Events (% per year) 3.2% vs 4.0%.
   (Absolute benefit = 8 per 1000 per year)
   C. Overall, the risk reduction in major vascular events was 22% per 38 mg/dL reduction in LDL-c at 1 year, with a significant 12% reduction during the second year, and significant reductions in each year thereafter.
   D. Risk reduction per 38 mg/dL reduction in LDL-c:

Non-fatal MI = 27%, coronary death = 20%, any revascularization procedure. = 27%.

E Across all 26 trials, all cause mortality was reduced by 10% per 38 mg/dL reduction in LDL-c. This largely reflected significant reductions in death from coronary heart disease.

4. Effect on stroke

A. Five trials (more vs less statin) per 19 mg/dL difference per year.

Ischemic stroke 0.5% vs 0.6%

(Absolute benefit = 1 per 1000 per year)

Hemorrhagic stroke 0.1%vs 0.1%

B. 21 trials statin vs placebo

Ischemic stroke 0.4% vs 0.5% per year per 38 mg/dL difference in LDL-c

(Absolute benefit = 1 per 1000 per year)

Hemorrhagic stroke 0.1% vs 0.1% per year per 38 mg/dL differences in LDL-c

(No statistical difference)

5. Adverse effects:

Only cases of myopathy that progressed to rhabdomyolysis were sought in this meta-analysis. In the more vs less statin trials, incidence was 4 per 10 000; in the statin vs placebo trials, the observed excess of rhabdomyolysis was 1 per 10 000.

All of the excess of rhabdomyolysis with more intensive therapy occurred in two trials comparing 80 mg simvastatin vs 20 mg. These 2 trials also reported definite excess of myopathy.

No excess of any cancer or any non-vascular cause.

DISCUSSION

1. This meta-analysis has shown that additional reductions in LDL-c by more intensive therapy further reduced the incidence of major vascular events.
2. The relation between absolute LDL-c reductions and the proportional risk reductions is consistent between the trials of more vs less intensive statin therapy and the trials of statin vs placebo.
3. “These further reductions in vascular risk can be achieved safely.”
4. Overall, a reduction in LDL-c of about 19 mg/dL was achieved. This reduced the risk of major vascular events by about a sixth, with separate significant reductions in coronary death and non-fatal myocardial infarction, coronary artery revascularization, and ischemic stroke.
5. The proportional reduction in major vascular events per 38 mg/dL reduction in LDL-c was similar to that observed in trials of statin vs placebo.
6. The statin vs placebo trials in patients with low LDL-c before treatment provided good evidence of

benefit, with no evidence of any hazard even when LDL-c concentrations lower than 76 mg/dL are reduced further.

7. Overall, there was a 22% proportional reduction in major vascular events for each 38 mg/dL reduction in LDL-c. This implies that, at least within the range of LDL-c studied to date, a 76 mg/dL reduction would reduce the risk by about 40% and 114 mg/dL reduction would reduce risk by about 50%.
8. Overall, in both more vs less statin and statin vs placebo trials, mortality was reduced by about a fifth per 38 mg/dL reduction in LDL-c, but the reduction in cardiac deaths that were not attributed to coronary disease was only half as large. This may reflect relative lack of benefit from lowering LDL-c on causes of death that are mediated by non-occlusive mechanisms (eg, heart failure).
9. The findings of this meta--analysis suggest that the absolute reduction in cardiac mortality produced by lowering LDL-c with statins in a given population depends chiefly on the absolute risk of death due to coronary occlusion.
10. There was no evidence, in the more vs less intensive therapy, that further lowering of LDL-c from 95 mg/dL to 76 mg/dL produced any adverse effects.
11. There was no evidence of any increase in any type of cancer at any site.
12. Previous observational studies have generated the hypothesis that lower cholesterol concentrations might be associated with increased risk of intracranial hemorrhage. This meta-analysis, which included nearly 500 confirmed hemorrhagic strokes, showed the lowering of LDL-c with statin therapy was associated with a non-significant excess (257 vs 220) of hemorrhagic strokes. In a trial of atorvastatin vs placebo in patients with previous cerebrovascular disease there was a significant proportional reduction in ischemic stroke (218 vs 275), and a significant excess of hemorrhagic stroke (55 vs 33) This would indicate, in absolute terms, a few extra hemorrhagic strokes per 10 000 participants -- an incidence about 50 times smaller than incidence of ischemic stroke.
13. In this meta-analysis, the size of the proportional reduction in major vascular events was in direct proportion to the absolute reduction in LDL-c by more aggressive statin therapy, even if baseline LDL-c was lower than 78 mg/dL. Each 38 mg/dL reduction in LDL-c reduced the risk of occlusive vascular events by about 20% irrespective of the baseline LDL-c concentration. This implies that a 76 to 114 mg/dL reduction would reduce risk by about 40% to 50%.
14. “These findings suggest that the primary goal for patients at high risk of occlusive events should be to achieve the largest LDL cholesterol reduction possible without materially increasing myopathy risk.”

15. Current guidelines suggest that the objective in high -risk patients should generally be to reduce LDL-c to below 100 mg/dL . By contrast the results of this meta-analysis suggest that lowering LDL-c further in high-risk patients would produce additional benefits without any increase in non-vascular mortality.

CONCLUSION

Further reductions in LDL-c safely produced definite further reductions in the incidence of myocardial infarction, of revascularization, and of ischemic stroke. Each 38 mg/dL reduction resulted in an annual rate of major vascular events by just over one fifth.

Lancet November 11, 2010; 376: 1670-81 Original investigation by the Cholesterol Treatment Trialists (CTT) collaboration. Doi.10.1016/S0140-6736(10)61350-5
Funded in part by the UK Medical Research Council

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Combined Aerobic And Resistance Training Was More Effective In Reducing Hba1c

11-4 EFFECTS OF AEROBIC AND RESISTANCE TRAINING ON HEMOGLOBIN A1C LEVELS IN PATIENTS WITH TYPE-2 DIABETES

Regular exercise provides substantial benefits in patients with type-2 diabetes. (DM-2). The benefit related to the exact exercise prescription (aerobic vs resistance) is less clear. For a given amount of time, is the combination of aerobic + resistance better than either alone?

This study was designed to compare the effects of aerobic training, resistance training and the combination on HbA1c levels in previously sedentary persons with DM-2.

STUDY

1, Recruited participants (age 30-75; n = 2421 screened for eligibility) from 2007 to 2009 in community in Louisiana for a 9-month exercise interventions study. All had DM-2.

2. After exclusions randomized 262 participants into 4 groups:

1) Control (n = 41) were offered weekly stretching and relaxation classes.

2) Aerobic exercise (n =72) 140 minutes per week on the treadmill.

3) Resistance exercise (n = 73) exercised 3 times a week. Each session consisted of: two sets of 4 upper body exercises; 3 sets of 3 leg exercises; and 2 sets each of abdominal crunches and back exercises.

4) Combined aerobic-resistance (n = 76) had 2 resistance periods per week of one set of exercises and the remainder of the time on the treadmill.

3. Exercise sessions had a 5-minute warm-up period and a 5-minute cool-down period.

4. Exercise interventions were designed to be of approximately equal time. An estimated 150 minutes per week of moderate intensity exercise (50% to 80% of maximum O2 consumption) would burn 10 to 12 kcal/kg of body weight per week.

5. Primary outcome = change in HbA1c over 9 months.

RESULTS

1. Baseline characteristics: (means and %)

Age 56; female 63%; 47% non-white; HbA1c 7,7%; duration of DM -2 7 years; BMI 35; waist circumference 112 cm; BP 126/76. Participants were taking a variety of medications.

2. Baseline and 9-month changes in HbA1c:

	HbA1c %		
A. Intentions -to-treat (n = 262)	Baseline	9-month	Mean change
Control	7.62	7.74	+0.12
Resistance	7.58	7.53	--0. 05
Aerobic	7.56	7.43	--0.13
Combined	7.59	7.36	--0.23
B. Per protocol (n = 215; ie, those who actually completed 9 months:			
Control	7.61	7.72	+0/11
Resistance	7.55	7.46	-0.09
Aerobic	7.50	7.42	-0.08
Combined	7.54	7.27	-0.27
C. Intention-to-treat (n =119) limited to those with baseline HbA1c 7.0% and above:			
Control	8.00	8.18	+0.18
Resistance	7.97	7.83	-0.14
Aerobic	7.97	7.64	-0.33
Combined	7.99	7.64	-0.35
D. Per protocol (n = 94) limited to those with baseliner HbA1c 7.0% and above:			
Control	7.99	8.17	+0.18
Resistance	7.95	7.78	-0.17
Aerobic	7.89	7.64	-0.25
Combined	7.97	7.52	-0.45

4. All 3 intervention groups improved fitness. The combination group improved peak oxygen consumption more than the other groups, and also had greater decreases in weight, waist circumference and fat mass.
5. The combination group had fewer increases and more reductions in antidiabetes medications.
6. The composite outcome of either decreasing hypoglycemic medications or a reduction in HbA1c of 5% without increasing medications was 22% in the controls, 26% in the resistance, 28% in the aerobic, and 41% in the combination groups.

DISCUSSION

1. Only those in the combination group who actually completed the trial (the per protocol group) achieved statistically significant reductions in HbA1c.
2. Cumulative benefit across all outcomes was greater in the combination group compared with either the aerobic or the resistance groups.
3. These exercise prescriptions are consistent with the 2008 Physical Activity Guidelines of 500 to 1000 METS per week of aerobic exercise combined with 2 days of resistance training.
4. The time spent exercising across all 3 groups was approximately 140 minutes per week.
5. An absolute decrease of 1% in HbA1c is related to decrease in both micro-vascular and macro-vascular complications of DM-2. The improvements in cardiovascular fitness and strength obtained from exercise likely add to the benefits.
6. The differences in HvbA1c between the combination group and the control group occurred even though the control group had increases in use of diabetes medications while the combination group had decreases.

CONCLUSION

Among patients with DM-2, a combination of aerobic and resistance training, compared with a non-exercise group improved HbA1c levels more than aerobic exercise alone and resistance exercise alone

JAMA November 24, 2010; 394: 2253-62 Original investigation by the Health Benefits of Aerobic and Resistance Training in type-2 Diabetes (HART-d) trial, first author Timothy S Church, Louisiana State University, Baton Rouge**.**

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Primordial Prevention--The Next Step?

11-5 OPTIMAL CARDIOVASCULAR PREVENTION STRATEGIES FOR THE 21ST CENTURY

Death rates from cardiovascular disease **(CVD)** remains by far the leading cause of morbidity and mortality in the US. CVD chronically affects over 80 million US adults. Even though CVD death rates have recently leveled off among young adults (age 35-54), the overall CVD burden is predicted to increase as the population ages, and prevalence of obesity and diabetes increases.

Current Status of CVD Prevention:

A. Secondary prevention: After CVD events occur, we have an array of evidence-based therapies to decrease recurrence.

B. Primary prevention: Reducing the chances of a first event is more difficult to implement. All manifestations of CVD have common predisposing factors, especially smoking, adverse lipids, blood glucose, and high BP. However, most first CVD events occur in individuals with only mildly elevated levels of risk factors who would not typically qualify for preventions efforts. Extensive CVD prevention can be achieved only through lifestyle and environmental modifications. Because population-wide medications (eg, the polypill) are considered inappropriate, other population-wide strategies are needed.

C. Primordial Prevention--Beyond Secondary and Primary Prevention

Is a more radical concept. It ensures that the levels of CVD risk factors observed in healthy children are preserved into adulthood. Individuals who maintain a profile of ideal CVD risk factors from young adulthood into middle age essentially escape remaining lifetime risk of major CVD events. Both CVD and non- CVD mortality rates are reduced. This results in the addition of 10 years longevity, better health-related quality of life, and lower annual Medicare costs.

The American Heart Association recently endorsed primordial prevention for improving cardiovascular health in all Americans. Barely 5% of the US population now maintains this ideal profile into middle age.

One recent study published in the Bulletin of the World Health Association demonstrated that, if the majority of the US population reached middle-age with an ideal phenotype, more than 90% of coronary heart disease deaths might be prevented.

Choosing the Best CVD Prevention Strategies

Preventive strategies fall into 2 complementary categories:

1) High-risk strategies focus on the detection and treatment of individuals identified as

being at unacceptably high short term risk for CVD.

2) Population-based strategies aim to improve the health of entire population by favorably shifting the distribution of risk factors. There is evidence of effectiveness and surprisingly rapid benefits. Indoor smoking bans have been followed within months by substantial reductions in hospitalizations for CVD events. CVD rates in Poland decreased within 3 years after the repeal of subsidies of meat and animal fat. In Finland, comprehensive community-based and national policy interventions focused on favorably influencing dietary habits and reducing smoking, were followed by a decline of over 80% in CVD mortality over 25 years.

CVD Prevention: Possible Options:

US governments now address CVD prevention by 1) encouraging clinicians to identify and treat individuals at high risk and 2) policy initiatives (eg, promoting smoke-free legislation and salt restriction). However, the current policies still focus on subsidies for certain crops (tobacco, corn) that can promote disease rather than health. Favorable subsidies or policies in the US could promote polyunsaturated vegetable oils, skim milk, whole grains, and fresh fruits and vegetables.

Economic Issues

The economic burden of CVD is driven by vascular surgery, hospitalizations, and expensive drugs for lipid reduction, hypertension and diabetes. Medication-based primary prevention appears relatively costly. Primordial prevention will generate savings.

Reducing mean population levels of cholesterol or BP by 5%, or legislation to eliminate trans fat, or reducing dietary salt intake by 3 grams per day would generate over a billion dollars of savings per year.

Delays in identifying more effective strategies for CVD prevention will be very costly.

"The status quo is not acceptable politically, ethically, or economically."

JAMA November 10, 2010; 304: 2057-58 "Commentary" first author Simon Capewell, University of Liverpool, UK

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