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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

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HIGHLIGHTS AND *EDITORIAL COMMENTS* FEBRUARY 2011

"Important Implications For Diagnosis And Treatment Of Hypertension."

2-1 CONVENTIONAL VERSUS AUTOMATED MEASUREMENT OF BLOOD PRESSURES IN PRIMARY CARE PATIENTS WITH SYSTOLIC HYPERTENSION

There is concern about the accuracy of the measurement of BP in "real life" clinical settings. Imprecise and inconsistent measurements are often reported**.** Proposals for improved assessment include greater reliance on home and 24-hour monitoring. Out-of-office determinations lower risk of a spurious higher than usual BP due to the "white coat" effect (**WC**).

Use of automated office sphygmomanometers provides a third option for accurate assessment of BP. Measurement of BP with the patient sitting quietly alone eliminates patient-observer interactions such as conversation, an important cause of WC effect.

This trial was designed to evaluate the effect of automated office versus usual office BP on the management of hypertension (predominantly systolic) in routine practice.

Entered 555 primary care patients with systolic hypertension. All were over age 45. None had serious comorbidities None were using home BP measurements. All underwent ambulatory 24-hour BP measurement before randomization, with special attention to awake BP.

Randomized to: 1) Ongoing use of manual office BP measurement (controls) or 2) Automated office BP determination (interventions). Used an automated BP machine which determined 6 readings 2 minutes apart. The attendant left the room after the first reading, which was disregarded. The patient sat quietly alone while the 5 remaining readings were taken.

Main outcome = difference in systolic BP between groups.

Comparison of intervention group vs control group:

	Automatic office	Usual manual office
Last routine manual systolic	149.5	149.9
Office systolic after enrollment	135.6	141.4
Difference from last manual	-13.9	-8.5 (A 5.4 mm difference)

(Automated office readings resulted in about a 5 mmHg lower systolic compared with routine office measurement.)

Comparisons with pre-test 24-h ambulatory systolic (awake hours):

Post entry systolic	135.6	141.4
Pre-entry awake 24-h ambulatory	133.2	135.0
Difference between pre-entry 24-h awake systolic		

and test groups 2.4 6.54

(The office automated readings were closer to the ambulatory awake BP than the usual office readings.)

"This trial provides important and robust evidence supporting use of automated office BP measurements in routine practice."

Replacement to manual office BP determinations with automated office determinations virtually eliminated the WC effect. Automated determinations also showed a stronger correlation with awake ambulatory BP than did manual readings.

The net reduction in BP attributed to the automated group can be calculated at -5.4 mmHg. This is of considerable clinical importance.

Recently the American Heart Association recommended use of home BP monitoring. "Every hypertensive patient should purchase a home BP recording device. "

"This study has important implications for diagnosis and treatment of hypertension."

Conclusion: In compliant otherwise healthy primary care patients with systolic hypertension, introduction of automated office BP measurement significantly reduced the white coat response compared with ongoing use of manual office BP measurement.

Improvement of BP determinations are bound to improve over time

I believe most patients could learn to relax while taking a series of home BP measurements. Patients will likely note that BP declines with repeated determinations.

It would be interesting to ask patients to take 6 readings a few minutes apart and discard the first. However, these investigators mentioned that simply pushing a button on a home BP machine will raise BP.

Only24-hourambulatory measurement will determine "masked hypertension" an opposite of WC in which ambulatory BP is higher than office BP.

2-2 ASSOCIATION OF ALCOHOL CONSUMPTION WITH SELECTED CARDIOVASCULAR DISEASE OUTCOMES

Possible cardioprotective effects of alcohol seen in observational studies continue to be debated. In the absence of clinical trials, clinicians must interpret observational data to answer patients' questions about use of alcohol in relation to cardiovascular disease (**CVD**) and coronary heart disease (**CHD**).

This systemic review and meta-analysis analyzed 84 studies related to effects of alcohol on

cardiovascular outcomes and death. All were prospective cohort studies. All subjects were age 18 or over, without preexisting CVD.

At baseline, compared active alcohol consumption with a reference group of non-drinkers.

Relative risks (**RR**) of events in alcohol drinkers vs non-drinkers:

	RR	
CVD mortality	0.75	In only one of 23 studies RR was over 1.00
Incident CHD	0.75	In only 2 of 32 studies RR was over 1.00
CHD mortality	0.71	
Incident stroke	0.98	
Stroke mortality	1.06	Null effect
Hemorrhagic stroke mortality	1.14	Possible harm
All-cause mortality	0.87	

Dose response (relative risks):

Alcohol dose grams per day vs no-alcohol

	CVD	CHD	
		Incident	Mortality
<2.5 g/d (< 1 drink)	0.71`	0.96	0.91
2.5 to 14.9 g/d (1 drink)	0.75	0.75	0.79
15 to 29.9 g/d (1-2.5)	0.75	0.66	0.79
30 to 60 g/d (2.5 to 5)	85	0.67	0.77
> 60 g/d (>5)	0.99	0.76	0.75
Sex			
Male	0.80	0.71	0.77
Female	0.69	0.71	0.78

Pooled estimates showed lower risk for drinkers vs non-drinkers (RR = 0.87). However the association was "J shaped". Those with the lowest consumption (< 1 drink daily) had a higher risk than those drinking 1 to 2 drinks daily. Risks then rose as quantity increased.

The protective association of alcohol has been consistently observed in diverse populations and in both men and women.

The association is specific: moderate drinking (one drink daily for women and 2 drinks for men) is associated with lower risk of CVD, but is not uniformly protective for other conditions such as cancer.

The reduction in risk is notable, even when controlling for known confounders (smoking, diet,

and exercise). Any potential confounder would need to be very strong to explain away the apparently protective association.

Although there is great interest in differences between wine and spirits, alcohol drinking generally has similar effects on high density lipoprotein cholesterol. It is likely that any particular benefit of wine is confounded by diet and socio-economic status. This remains an important topic for further investigation.

Debate should center now on how to integrate this evidence into clinical practice.

Conclusion: Light to moderate alcohol consumption is associated with a reduction in multiple cardiovascular outcomes.

The consistency of the results is persuasive despite the risk of confounding.

Some authorities in the past have defined abstinence as a risk factor.

I believe this is the last work on this subject for a long time. A randomized controlled trial of alcohol ingestion would be impossible.

The studies must have average weekly consumption to calculate the daily consumption. I doubt all participants drank equal amounts every day. Consistently drinking small amounts of alcohol daily (a glass or 2 of wine with dinner) is the healthy way. Binge drinking (imbibing a week's ration of alcohol over the week-end) is related to increased risk of CHD.

Increases High Density **Lipoprotein Cholesterol; Decreases Fibrinogen**

2-3 EFFECTS OF ALCOHOL CONSUMPTION ON BIOLOGICAL MARKERS ASSOCIATED WITH RISK OF CORONARY HEART DISEASE.

This systematic review concerned interventional (experimental) studies (1950-2009) of the effects of alcohol on 21 biological markers associated with risk of coronary heart disease (**CHD**).

The relevant biomarker:

A. Lipids (47 studies): triglycerides, total cholesterol, high density lipoprotein cholesterol (**HDL-c**), low density lipoprotein cholesterol (**LDL-c**) and apolipoprotein A1, Lp(a) lipoprotein

B. Inflammatory markers (13 studies): C-reactive protein, leukocytosis, interleukins, tumor necrosis factor.

C. Adipocyite hormones (8 studies): adiponectin, leptin.

D. Hemostatic factors (14 studies) :plasminogen activator, von Will brand factor, tissue plasminogen activator, plasminogen, fibrinogen, thromboxane, e-secretin.

E. Endothelial factors (3 studies): intracellular adhesion molecule, vascular adhesion molecule.

All were experimental studies involving alcohol interventions vs no-alcohol controls.

Alcohol consumption produced favorable changes in 4 biomarkers..

Pooled mean differences --alcohol vs no alcohol:

1) HDL-c	+ 0.09 mmol/L (+3.4 mg/dL*?
2) Apolipoprotein A1	+0.103 g/L
3) Fibrinogen	-0.20 g/l
4) Adiponectin	+O.56 g/L

(* My calculation ED)

There was s dose-response of HDL- to alcohol:

1-2 drinks daily	+0.072 mmol/L (2.3 mg/dL)
2-4	+ 1.03 (3.9 mg/dL)
> 4	+0.140 (5.3 mg/dl)

Alcohol produced no significant effect on LDL-c, triglycerides, total cholesterol, C-reactive protein, or other biomarkers.

. "This meta-analysis showed that moderate consumption of alcohol up to one drink (15 g) alcohol per day for women, and up to 2 drinks (30 g) alcohol for men have beneficial effects on a variety of biomarkers linked to risk of coronary heart disease."

The study also determined effects of different types of alcohol (wine, spirits, beer). All had similar effects on the biomarkers. The preference for using wine, and in most cases red wine as the type of alcohol for intervention may be related to other clinical characteristics.

The significant changes in levels of HDL-c, fibrinogen, and .adiponectin are well within a pharmacologically relevant magnitude.

"Although we found that alcohol consumption has favorable effects on some of the biomarkers associated with coronary heart disease, this remains indirect evidence for the mechanism by which alcohol may cause cardiac protection"

"Both Can Be Prevented Through Lifestyle Modifications"

2-4 IMPACT OF OBESITY AND KNEE ARTHRITIS ON MORTALITY AND MORBIDITY IN OLDER AMERICANS

The obesity epidemic and longer life expectancy have contributed to the high incidence of knee osteoarthritis (**KA**) in older Americans. Obesity and KA are among the most common comorbid condition in this age group.

Both KA and obesity can be prevented through lifestyle modifications.

This study assessed the longitudinal effect of obesity and KA on the remaining duration and quality of life in a population with highest burden of both conditions--persons age 50 to 84. Used a model to estimate quality-adjusted life-years (**Q-A-L-Y**) lost in the U.S. populating age 50 to 84 with obesity, or symptomatic KA, or both, over the remaining life-span.

The model summarizes the 1 million unique person-histories to provide stable estimates of duration and quality of life.

Population description (estimated) ages 54-80

A. Total population	85 966 000:
B. Obese	31 615 000 (36%)
Obesity; no KA	28 742 000 (33%)
Obesity and KA	2 871 000 (3.3%)
C. KA	5 674 000 (6.6%)
KA; no obesity	2 802 000 (3.3%)
Ka and obesity	2 871 000 (3.3%)

(Thus, over 1/3 of the U.S. population age 54-80 is obese. One in 16 has KA. And half of all KA is associated with obesity.)

Per person Q-A--L-Y lost:		Total quality-years lost
Obesity alone	2.4	80 804 000
KA alone	1.8	15 259 000
KA and obesity	3.5	

(Thus, on average, every person with obesity and KA loses over 3 quality-adjusted years of life.)

Symptomatic KA and obesity affect Q-A-L-Y loss through different mechanisms.
Obesity is an independent risk factor for mortality, diabetes, coronary heart disease and other comorbid conditions that reduce survival. It reduces both the quality and quantity of life.

Symptomatic KA does not directly affect mortality, but considerably reduces Q-O-L, thereby diminishing quality-adjusted life expectancy.

With millions of Q-A- L-Y at stake, and the incidence of KA and obesity increasing, the potential public health effects of successful intervention to prevent these conditions is substantial.

These are estimates,, but, I think they have validity. The effect on public health is enormous. The costs to society, including cost of surgery, are huge.

I wish we had an answer.

"Their Efforts And Their Well Being Are Too Often Ignored."

2-5 FULFILLING OUR OBLIGATION TO THE CAREGIVER

Family caregivers are relied upon by our health care system. They provide the bulk of care given to more than a million Americans with Alzheimer disease. At the same time, they are neglected.

They are expected to shoulder increasing amounts of complex care in the home, at minimal cost to the public, a task that would require entire health-care teams in the institutional setting.

In return, their efforts and their well being are too often ignored.

Family caregivers are often thrust into this position with no training and little support. This results in increased prevalence of adverse physical, social and psychological outcomes. Caregivers are at great risk for depression and anxiety. They are less likely to engage in preventive health measures. There is some evidence that they are subject to increased risk of mortality.

Caregiving for those with dementia requires considerable out-pf-pocket expenses. Many caregivers stop working in order to give care.

In the real world setting, little has been done to decrease caregivers' burdens.

What can be done to foster healthy caregiving?

Providing information about the skills and support systems needed to help caregivers for patients with dementia may be beneficial. Several different caregiver interventions have shown improvements in caregivers' well-being. They have been integrated with primary care.

Resources for Enhancing Alzheimer's Caregiver Health (REACH; a randomized trial) is an individualized multicomponent home- and telephone-based intervention designed to enhance caregivers' coping skills and management of dementia behaviors. The intervention improved caregivers' quality of life in terms of burden, depression, emotional well-being, self-care and healthy behaviors, social support, and management of problem behaviors. It also resulted in one hour less per day caregivers were required to provide care, giving them some respite.

Can these caregiver interventions be applied in the real world?

An article in this issue of Annals [*See abstract*]]describes application of an intervention similar to REACH. This program within the Veteran's Administration resulted in improved caregiver outcomes including reductions in caregiver frustration, burden, and depression.

Does the heath care system have a duty to provide caregiver support? The contractual obligation is to the patient. However, if the system will increasingly rely on family members to deliver complex care, then we have the obligation to aid the caregivers in their tasks and reduce their personal costs.

Interventions focused on caregivers are beneficial and can be practically implemented.

"It is time that we fulfill our obligations to caregivers."

Annals Internal Medicine February 28 2011; 171: 359-60 "Commentary", first author Eric Widera, University of California, San Francisco

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Caregivers do suffer; sometimes more than the care receiver. Their suffering is often inured.

I believe the first step primary care clinicians can take is to have a discussion with the caregiver, ask about and validate their degree of suffering. Ask them what they think can be done in their unique situation.

I doubt the public treasury will be able to support an expensive intervention described by REACH. Small Medical Homes probably could not afford the time and expense.

Perhaps other members of the family can help, if only allowing the principal caregiver to take a few hours off each day and have an occasional vacation. Perhaps Hospice can help.

Would employment of home health-care be possible?

Benefits Of Statins Do Not Depend On CPR Levels

2-6 C-REACTIVE PROTEIN CONCENTRATION AND THE VASCULAR BENEFITS OF STATIN THERAPY The Health Protection Study [HPS]]

Inflammation is thought to contribute to the pathogenesis of coronary heart disease (**CHD**).

C-reactive protein (**CRP**) is an acute phase reactant synthesized by the liver. It is the most extensively studied marker of inflammation. A recent meta-analysis (2010) of 54 prospective observational trials reported that CRP concentrations were associated with risk of CHD. However, its associations with ischemic vascular disease were explained (confounded) largely by conventional risk factors. CRP is positively correlated with smoking, diabetes, BP, BMI, non-HDL cholesterol and triglycerides, and might not reflect causality.

The present randomized trial was undertaken in high risk patients in whom many vascular events took place during the study treatment period. This tested the hypothesis that the effect of statins differ according to the baseline concentrations of CRP and LDL-c.

Between 1994 and 1997, 20 536 persons age 40-80 (mean age 64) at high risk for vascular events

were recruited from 69 UK hospitals All had a previous diagnosis of CHD, occlusive disease of non-coronary vessels, diabetes, or hypertensive men over age 65. (A high-risk group.)

Randomized to: 1) 40 mg simvastatin daily, or 2) placebo. for 4 to 6 weeks.

The primary prespecified endpoint was major vascular events (coronary death, non-fatal myocardial infarction, fatal and non-fatal stroke, and coronary revascularization. (99% had complete follow-up for both mortality and morbidity.)

Duration of study = 5 years.

A total of 4518 (17%) major vascular events occurred over 5 years.

Overall, simvastatin resulted in a significant 22% reduction in the first major vascular events after randomization:

CRP level (mg/L)	Simvastatin (%)	Placebo (%)
<1.25	14.1	19.4
1.25-1.99	19.2	23.7
2.00-2.99	19.4	23.7
3.9904.99	23.0	29.5
5.00-7.99	25.6	30.6
>800	18.7	22.7
Total	19.8	25.2

There was no evidence that the proportional reduction in the endpoint or its components varied with baseline CRP concentrations.

Even in participants with baseline CRP less than 1.25 mg/L, major vascular events were reduced by 29%.

"In this study of more than 20 000 people at high risk of vascular events, 5 years of simvastatin therapy reduced the risk of a major vascular event by a quarter, but there was no indication that the proportional risk reduction was larger in those with higher baseline CRP concentrations."

In participants with CRP concentrations less than 1.25 mg/L, or with low concentrations of both LDL-c and CRP, there were significant reductions in the risks of major vascular events.

Hence, the present hypothesis-testing analysis, which is based on large numbers of major vascular events, does <u>not</u> lend support to the suggestion from hypothesis -generation studies, which included far fewer vascular events, that the beneficial effects of statin therapy are affected by baseline CRP concentrations.

The proportional reduction in the risk of major vascular events with statin therapy seem to be directly related to the absolute reduction in LDL-c that is achieved.

Conclusion: This large randomized trial does not lend support to the hypothesis that baseline CRP concentrations modify the vascular benefits of statin therapy materially.

I expect a rebuttal from CRP advocates.

No mention of adverse effects of simvastatin.

This study addressed secondary prevention. Results in primary prevention will vary.

As reported before, the benefits of statin drugs extend to additional lowering of initially low levels of LDL-c.

If this correction is sustained, it would be an excellent example of how misleading medical research can be, even though it is done in good faith and with care. Fortunately, in medicine, the truth will eventually out.

ABSTRACTS FEBRUARY 2011

"Important Implications For Diagnosis And Treatment Of Hypertension."

2-1 CONVENTIONAL VERSUS AUTOMATED MEASUREMENT OF BLOOD PRESSURES IN PRIMARY CARE PATIENTS WITH SYSTOLIC HYPERTENSION

There is concern about the accuracy of the measurement of BP in "real life" clinical settings. Imprecise and inconsistent measurements are often reported. Failure to recognize and minimize patient anxiety is common. Studies suggest that accurate BP determination require at least 14 minutes, including an initial period of rest.

The likelihood of careful adherence to protocols for BP measurement is low in community-based office practice. Recently, there have been concerns about manual office measurements. A more limited role for them has been advocated.

Proposals for improved assessment include greater reliance on home and 24-hour monitoring. Out-of-office determinations lower risk of a spurious higher than usual BP due to the "white coat" effect (**WC**). They are also stronger predictors of future cardiovascular events. Detection and removal of the WC effect will lessen unnecessary drug treatment.

However, abandoning office measurements because of the deficiencies associated with conventional manual office readings is premature and unwise.

Use of automated office sphygmomanometers provides a third option for accurate assessment of BP. This reduces or eliminates many of the factors contributing to imprecise measurements in routine practice. Measurement of BP with the patient sitting quietly alone eliminates patient-observer interactions such as conversation, an important cause of WC effect. The absence of a health-professional during BP measurement may reduce patient-anxiety.

This trial was designed to evaluate the effect of automated office versus usual office BP on the management of hypertension (predominantly systolic) in routine practice. (WC is predominantly systolic)

STUDY

1. Entered 555 primary care patients with systolic hypertension. All were over age 45. None had serious comorbidities None were using home BP measurements. All underwent ambulatory 24-hour BP measurement before randomization, with special attention to awake BP.
2. Untreated patients had a systolic of at least 160 and a diastolic below 95 on their most recent office visit. Patients receiving treatment for hypertension were eligible if their systolic was 140 and above and diastolic below 90.

3. Randomized to: 1) Ongoing use of manual office BP measurement (controls) or 2) Automated office BP determination (interventions).
4. Used an automated BP machine which determined 6 readings 2 minutes apart. The attendant left the room after the first reading, which was disregarded. The patient sat quietly alone while the 5 remaining readings were taken.
5. Compared office BP in both groups before enrollment.
6. Obtained the last routine BP for each patient in both groups.
7. Main outcome = difference in systolic BP between groups.

RESULTS

1. No significant difference between groups at baseline:

(Means)	Automatic office (n = 299)	Usual manual office (n = 249)
Age	65	65
Duration of high BP	9 y	10 y
No. receiving BP treatment	9	12

2. Comparison of intervention group vs control group:

Last routine manual systolic	149.5	149.9
Office systolic after enrollment	135.6	141.4
Difference from last manual	-13.9	-8.5 (A 5.4 mm difference)

(Automated office readings resulted in about 5 mmHg lower systolic compared with routine office measurement.)

3. Comparisons with pre-test 24-h ambulatory systolic (awake hours):

Post entry systolic	135.6	141.4
Pre-entry awake 24-h ambulatory	133.2	135.0
Difference between pre-entry 24-h awake systolic and test groups	2.4	6.54

(The office automated readings were closer to the ambulatory awake BP than the usual office readings.)

4. Mean sequential systolic taken every 2 minutes:

1	147 (discarded)
2	140

3 136

4 134

5 132

6 133

Mean 2 - 6 = 136)

(Note the change between 1 and the mean 2-6)

DISCUSSION

1. "This trial provides important and robust evidence supporting use of automated office BP measurements in routine practice."
2. Awake ambulatory BP is considered to be the gold standard for defining BP status.
3. Routine manual office BP determinations correlate poorly with awake ambulatory BP determinations.
4. Replacing manual office BP determinations with automated office determinations virtually eliminated the WC effect. Automated determinations also showed a stronger correlation with awake ambulatory BP than did manual readings.
5. In this trial, the difference between routine office systolic BP and automated office determinations was 13.9 mmHg. However, the control groups' BP also fell by 8.5. By subtracting the decrease in BP of the control group from the decrease in the automated office group, the net reduction in BP attributed to the automated group can be calculated at -5.4 mmHg. This is still of considerable clinical importance.
7. Introduction of automated office determinations could be expected to decrease systolic BP by at least 5 mmHg, and probably by up to 9 to 13 mm.
8. Studies on WC have identified a subset of about 25% of the hypertensive population who have clinically important increases in BP when readings are taken in the treatment setting, especially by physicians. Even automated office readings can provoke a white coat response, especially if the observer remains in the room.
9. Recently the America Heart Association recommended use of home BP monitoring. "Every hypertensive patient should purchase a home BP recording device. "
10. "This study has important implications for diagnosis and treatment of hypertension."

CONCLUSION

In compliant otherwise healthy primary care patients with systolic hypertension, introduction of automated office BP measurement significantly reduced the white coat response compared with ongoing use of manual office BP measurement.

BMJ 2011;3342:286 doi:10.1136/bmjd286 Oregonian research, first author Marin G Myers, University of Toronto, Canada.
A short report appeared in the print version of BMJ February 12 2011; 372

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2-2 ASSOCIATION OF ALCOHOL CONSUMPTION WITH SELECTED CARDIOVASCULAR DISEASE OUTCOMES

Possible cardioprotective effects of alcohol seen in observational studies continue to be debated. In the absence of clinical trials, clinicians must interpret observational data to answer patients' questions about use of alcohol in relation to cardiovascular disease. (**CVD**)

This review included all relevant studies of effects of alcohol on CVD between 1950 and 2009.

STUDY

1. This systemic review and meta-analysis analyzed 84 studies related to effects of alcohol on cardiovascular outcomes and death. All were prospective cohort studies. All subjects were age 18 or over, without preexisting CVD.
2. At baseline, compared active alcohol consumption with a reference group of non-drinkers. Some non-drinkers had been life-time abstainers; some former drinkers.
3. When available, determined the amount of alcohol consumed (in grams of alcohol or standard drinks per day)
4. Studies included (n = 84)
   Cardiovascular disease mortality (n = 21)
   Coronary heart disease (**CHD**) mortality (n = 31)
   Incident coronary heart events (n = 21)
   Stroke mortality (n = 10)
   Incident stroke events (n = 17)
   (Some studies included more than one subject)
5. Secondary outcome = death from all causes.

6. When available, determined amount of daily alcohol consumed on average using 12.5 g alcohol per drink as the common unit of measure. Standardized portion size as 12 oz beer,; 5 oz wine; and 1.5 oz of spirits.
7. Volume of daily alcohol intake was categorized as:
   - < 2.5 g/d (<0.5 drinks daily)
   - 2.5 to 14/d (< 0.5 - 1 drinks daily))
   - 15 to 29 g/d (1 - 2.5)
   - 30 to 60 g /d (2.5 to 5.0)
   - > 60 g/f (>5)
8. Evaluated the number of years the subjects were followed.
9. Used relative risks as the common measure of association.

RESULTS

1. Relative risks (**RR**) of events in alcohol drinkers vs non-drinkers:

	RR	
CVD mortality	0.75	In only one of 23 studies RR was over 1.00
Incident CHD	0.75	In only 2 of 32 studies RR was over 1.00
CHD mortality	0.71	
Incident stroke	0.98	
Stroke mortality	1.06	Null effect
Hemorrhagic stroke mortality	1.14	Possible harm
All-cause mortality	0.87	

2. Dose response (relative risks):

   Alcohol dose grams per day vs no-alcohol

	CVD	CHD	
		Incident	Mortality
<2.5 g/d (< 1 drink)	0.71`	0.96	0.91
2.5 to 14.9 g/d (1 drink)	0.75	0.75	0.79
15 to 29.9 g/d (1-2.5)	0.75	0.66	0.79
30 to 60 g/d (2.5 to 5)	85	0.67	0.77
> 60 g/d (>5)	0.99	0.76	0.75
Sex			
Male	0.80	0.71	0.77

Female	0.69	0.71	0.78

Duration of alcohol use: no difference recorded.

3. Pooled estimates showed lower risk for drinkers vs non-drinkers (RR = 0.87). However the association was "J shaped". Those with the lowest consumption (< 1 drink daily) had a higher risk than those drinking 1 to 2 drinks daily. Risks then rose as quantity increased.

DISCUSSION

1. In this review, alcohol consumption of about 1 to 2 drink a day was consistently associated with a 14% to 25% reduction in risk of all-outcomes assessed compared with abstinence.
2. Consumption of large amounts of alcohol was associated with higher risk of stroke and mortality.

3 Consumption of higher doses seems to have an adverse association with BP. This is related to higher risk of hemorrhagic stroke.

4. Lower risk of CHD associated with alcohol consumption was at least as strong for women as for men.
5. Inclusion of former drinkers did not seem to bias the association between alcohol and CVD.
6. When studies were considered chronologically, the overall associations between drinking and CVD and CHD became apparent at least a decade ago. Ongoing studies will do little to revise the estimated associations.
7. The protective association of alcohol has been consistently observed in diverse populations and in both men and women.
8. The association is specific: moderate drinking (one drink daily for women and 2 drinks for men) is associated with lower risk of CVD, but is not uniformly protective for other conditions such as cancer.
9. The reduction in risk is notable, even when controlling for known confounders (smoking, diet, and exercise). Any potential confounder would need to be very strong to explain away the apparently protective association.
10. Only a limited subset of studies provides specific risk estimates for different beverages. Although there is great interest in differences between wine and spirits, alcohol drinking generally has similar effects on high density lipoprotein cholesterol. It is likely that any particular benefit of wine is confounded by diet and socio-economic status. This remains an important topic for further investigation.
11. Debate should center now on how to integrate this evidence into clinical practice.

CONCLUSION

Light to moderate alcohol consumption is associated with a reduction in multiple cardiovascular outcomes.

BMJ 2011;342:d671 doi:10,1136/bmjd671 Research article, first author Paul E Ronksley, Medical University of Calgary, Alberta, Canada

A brief abstract was published in the print issue BMJ February 26, 2011; 342: 479

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Increases High Density Lipoprotein Cholesterol; Decreases Fibrinogen

2-3. EFFECTS OF ALCOHOL CONSUMPTION ON BIOLOGICAL MARKERS ASSOCIATED WITH RISK OF CORONARY HEART DISEASE.

This systematic review concerned interventional (experimental) studies of the effects of alcohol on 21 biological markers associated with risk of coronary heart disease (**CHD**). A synthesis of research in this area may inform clinicians about the plausibility of the protective effects of alcohol on CHD reported by observational studies.

STUDY

1. Searched the literature (1950 - 2009) for articles about specific biomarkers for risk of CHD. Studies measured the effect on biomarkers after a specified amount of alcohol was consumed for a specific time frame compared with a like period of no alcohol consumption. No subject had prior CHD.
2. The relevant biomarker:
   - A. Lipids (47 studies): triglycerides, total cholesterol, high density lipoprotein cholesterol (**HDL-c**), low density lipoprotein cholesterol (**LDL-c**) and apolipoprotein A1, Lp(a) lipoprotein
   - B. Inflammatory markers (13 studies): C-reactive protein, leukocytosis, interleukins, tumor necrosis factor.
   - C. Adipocyite hormones (8 studies): adiponectin, leptin.
   - D. Hemostatic factors (14 studies):plasminogen activator, von Will brand factor, tissue plasminogen activator, plasminogen, fibrinogen, thromboxane, e-secretin.
   - E. Endothelial factors (3 studies): intracellular adhesion molecule, vascular adhesion molecule.

3. All were experimental studies involving alcohol interventions vs no-alcohol controls.
   Some were randomized, controlled trials; some before and after; some crossover design.
4. Determined sample size, age, number of men and women, exclusion criteria, characteristics of alcohol intervention (amount, frequency, duration) and information about specific biomarkers after the alcohol intervention.
5. Extracted information about the amount of alcohol consumed, using 12.5 g of alcohol to define one drink.
6. Categorized the portions of alcohol as in the preceding study.
7. The common unit of measurement across all studies was the mean change in the level of each biomarker compared with the no-alcohol control.
8. When appropriate, pooled data according to the dose of alcohol consumed. (From 1-2.5 drinks per day to > 5 drinks. Also pooled results for the biomarkers stratified by type of alcohol (wine, beer, spirits).
9. Studies lasted from 1-2 weeks to 6 weeks. Some studies used 1-2 drinks daily; some up to 6 drinks daily.

RESULTS

1. After the final review, 63 articles (1686 participants) were analyzed. Of these, 44 studies reported data adequate to permit pooled analysis.
2. Most studies used a wash-out period of no alcohol use usually similar in length of the study period.
3. Moderate alcohol consumption produced favorable changes in 4 biomarkers..
   Pooled mean differences --alcohol vs no alcohol.

1) HDL-c	+ 0.09 mmol/L (+3.4 mg/dL*?
2) Apolipoprotein A1	+0.103 g/L
3) Fibrinogen	-0.20 g/l
4) Adiponectin	+O.56 g/L

   (* My calculation ED)

4. There was s dose-response of HDL- to alcohol:

1-2 drinks daily	+0.072 mmol/L (2.3 mg/dL)
2-4	+ 1.03 (3.9 mg/dL)
> 4	+0.140 (5.3 mg/dl)

5. Alcohol produced no significant effect on LDL-c, triglycerides, total cholesterol, C-reactive protein,

or other biomarkers.

DISCUSSION

1. "This meta-analysis showed that moderate consumption of alcohol up to one drink (15 g) alcohol per day for women, and up to 2 drinks (30 g) alcohol for men) have beneficial effects on a variety of biomarkers linked to risk of coronary heart disease."
2. Evidence that alcohol decreases fibrinogen levels supports an important postulated mechanism by which alcohol consumption protects against coronary heart disease.
3. The study also determined effects of different types of alcohol (wine, spirits, beer). All had similar effects on the biomarkers. The preference for using wine, and in most cases red wine as the type of alcohol for intervention may be related to other clinical characteristics.
4. This review extended to adiponectin, which had not been previously evaluated.
5. The results implicate reverse cholesterol transport, hemostasis, and insulin sensitivity in the pathway by which alcohol consumption might prevent cardiovascular disease.
6. The significant changes in levels of HDL-c, fibrinogen, and adiponectin are well within a pharmacologically relevant magnitude.
7. The degree of increases in HDL-c is greater than any currently available single drug including fibrates.
8. An increase of 1 g/L of fibrinogen has been associated with nearly a 3-fold increase in risk of CHD. The magnitude of decrease in fibrinogen in this study could account for a substantial decrease in CHD.
9. "Although we found that alcohol consumption has favorable effects on some of the biomarkers associated with coronary heart disease, this remains indirect evidence for the mechanism by which alcohol may cause cardiac protection"
10. This thorough examination of the literature provides compelling indirect evidence in support of the causal protective effect of alcohol.

CONCLUSION

Favorable changes in several biomarkers provide indirect pathophysiological support for a protective effect of moderate alcohol use on CHD.

BMJ 2011;342:D636 First author Suns E Brien, Medical University of Calgary, Alberta, Canada

1 Adiponectin is an abundant polypeptide hormone produced by adipocytes. It has been associated with lower risk of both diabetes and CHD. It moderates glucose regulation, and fatty acid metabolism. Levels are inversely related to the amount of body fat. It plays a role in suppression of metabolic determinants of obesity, diabetes, atherosclerosis, and non-alcoholic fatty liver disease. It is an independent risk factor for the metabolic syndrome. (Source Wikipedia)

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"Both Can Be Prevented Through Lifestyle Modifications"

2-4 IMPACT OF OBESITY AND KNEE ARTHRITIS ON MORTALITY AND MORBIDITY IN OLDER AMERICANS

The obesity epidemic and longer life expectancy have contributed to the high incidence of knee osteoarthritis (**KA**) in older Americans. Obesity and KA are among the most common comorbid conditions in this age group.

Obesity leads to higher prevalence of major chronic conditions. It directly influences both the quantity and quality of life. Osteoarthritis is the 4th leading source of the non-fatal health burden, affecting 3% of total years lived with disability.

Both KA and obesity can be prevented through lifestyle modifications.

In order for health related messages to change behavior, persons must view the problem as relevant and serious, and must perceive that behavioral changes are beneficial.

Equipping physicians and public-health officials with estimates of quality-adjusted-life-years (**Q-A-L-Y**) lost owing to obesity and KA will enable them to convey the rational for behavior changes.

This study assessed the longitudinal effect of obesity and KA on the remaining duration and quality of life in a population with highest burden of both conditions--persons age 50 to 84.

STUDY

1. Used a model to estimate Q-A-L-Y lost in the U.S. population age 50 to 84 with obesity, or symptomatic KA, or both, over the remaining life-span.
2. The model was based on extensive data from NHANES 2005-06, National Center for Health Statistics, U.S. Census (2009), the Johnston County (NC) Osteoarthritis Project, and published literature.
3. The computer-based model estimated effects of:
   1) No obesity; no KA
   2) Obesity; no KA

3) KA; no obesity

4) Both obesity and KA.

4. Considered the effects of each on Q-O-L and death.

5. The model summarizes the 1 million unique person-histories to provide stable estimates of duration and quality of life.

6. Obesity: defined as a BMI 30 or greater. It directly affects survival and Q-O-L.

7. KA: Used radiographic progression to establish eligibility for knee replacement. which is generally done in patients with advanced disease.

RESULTS

1. Population description (estimated) ages 54-80

A. Total population	85 966 000:
B. Obesity total	31 615 000 (36%)
Obesity; no KA	28 742 000 (33%)
Obesity and KA	2 871 000 (3.3%)
C. KA	5 674 000 (6.6%)
KA; no obesity	2 802 000 (3.3%)
Ka and obesity	2 871 000 (3.3%)

(Thus, over 1/3 of the U.S. population age 54-80 is obese. One in 16 has KA. And half of all KA is associated with obesity.)

2. Per person Q-A--L-Y lost:

		Total quality-years lost
Obesity alone	2.4	80 804 000
KA alone	1.8	15 259 000
KA and obesity	3.5	

(Thus, on average, every person with obesity and KA loses over 3 quality-adjusted years of life.)

3. Health benefits of reversing trends in obesity:

The investigators estimate that weight control to reverse obesity to levels seen 10 years ago would greatly benefit society.

For example, reducing weight of an average person 5 feet 7 inches tall by 4 pounds would avert: 0.7% of cases of coronary heart disease; 2.5% of diabetes; and 1% of total knee replacements over the remaining lifetime of the population age 50-84. . And it would increase life expectancy by over 6 million years, and improve quality of life by over 7 million Q-A-L-Y.

DISCUSSION

1. In ages 54 to 80, an estimated 86 million Q-A-L-Y were lost owing to obesity, symptomatic knee arthritis, or both. This comprises 8.4% of remaining Q-A-L-Y .
2. These conditions affect 40% of the 85 000 000 US citizens in that age group Twelve % of the Q-A-L-Y lost were due to KA, and 88% due to obesity.
3. Symptomatic KA and obesity affect Q-A-L-Y loss through different mechanisms. Obesity is an independent risk factor for mortality, diabetes, coronary heart disease and other comorbid conditions that reduce survival. It reduces both the quality and quantity of life.
4. Symptomatic KA does not directly affect mortality, but considerably reduces Q-O-L, thereby diminishing quality-adjusted life expectancy.
5. The effect of symptomatic KA on Q-O-L is similar to that of metastatic breast cancer and other disabling conditions.
6. KA is more prevalent in women (especially Black and Hispanic women) than in men. Increasing weight in women elevates risk of KA even after adjustment for age.
7. Estimates show that mean reductions in BMI to levels expected a decade ago in adults age 50-84 would yield substantial health benefits.
8. In modeling studies, the value, precision, and completeness of input have important consequences for the findings. The model used in this study was derived from several sources. The authors believe, however, that their conclusions are conservative.
9. With millions of Q-A- L-Y at stake, and the incidence of KA and obesity increasing, the potential public health effects of successful intervention to prevent these conditions is substantial.

CONCLUSION

The number of quality-adjusted life-years lost by KA and obesity seems to be substantial. Reducing BMI to levels observed a decade ago in this population would yield significant health benefits.

Annals Internal Medicine February 15, 2011;154:217-225 Original investigation, first author Elena Losina, Brigham and Women's Hospital, Boston , Mass

Funded by The National Institute of Health and the Arthritis Foundation.

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"Their Efforts And Their Well Being Are Too Often Ignored."

2-5 TRANSLATION OF A DEMENTIA CAREGIVER SUPPORT PROGRAM IN A HEALTH CARE SYSTEM--REACH VA

"Resources for the Enhancement of Alzheimer's Caregiver Health" (REACH)was the first randomized trial concerning caregiver health. It proved that behavioral interventions for caregivers of demented patients could be beneficial.

The present study by the VA (REACH VA 2007-09)) is a clinical translational study based on REACH.

Clinical staff members from VA Primary Care programs in 15 states delivered the intervention to stressed caregivers of patients with dementia. The 6-month interventions was structured through a protocol and individualized through a risk assessment, targeted education, support, and skills-training to address caregiving risk areas of safety, social support, problem behaviors, depression, and health through 12 individual in-home and telephone sessions.

Collected data on burden, depression, health and health behaviors, care giving, frustrations, social support, dementia-related behaviors, and time spent providing care and on duty.

From baseline to 6 months, caregivers reported decreased burden, depression, impact of depression on daily life, caregiving frustrations, and a number of troubling dementia-related behaviors. A 2-hour decrease in hours per day of duty was helpful.

Almost all caregivers believed that the program should be provided by the VA.

The investigators concluded that this translational study provided clinically significant benefits for caregivers of veterans with progressive dementia. This mode of caregiver support can inform public policy in providing assistance to caregivers.

Archives Internal Medicine February 17, 2011; 171: 351-59 Original investigation, first author Linda Olivia Nichols, Memphis VA Medical Center, Memphis TN.

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Benefits Of Statins Do Not Depend On CPR Levels

2-6 C-REACTIVE PROTEIN CONCENTRATION AND THE VASCULAR BENEFITS OF STATIN THERAPY The Health Protection Study [HPS]]

Inflammation is thought to contribute to the pathogenesis of coronary heart disease (**CHD**).

C-reactive protein (**CRP**) is an acute phase reactant synthesized by the liver. It is the most extensively studied marker of inflammation. A recent meta-analysis (2010) of 54 prospective

observational trials reported ` that CRP concentrations were associated with risk of CHD. However, its associations with ischemic vascular disease were explained largely (confounded)) by conventional risk factors. CRP is positively correlated with smoking, diabetes, BP, BMI, non-HDL cholesterol and triglycerides, and might not reflect causality.

Nevertheless, the ability of CRP to predict vascular risk suggests that it might be useful as a biomarker to identify individuals who would benefit from therapy to reduce risk.

Some, but not all, subgroup analyses undertaken in previous randomized trials of statin therapy have suggested that the vascular benefits might be greater in the presence of inflammation than in its absence. It has even been suggested that people with low concentrations of both LDL-cholesterol (**LDL-c**) and CRP might not benefit much from statin therapy.

The large JUPITER trial[1] randomized healthy persons with LDL-c less than130 mg/dL and CRP on 2 mg/L or more to rosuvastatin or placebo. Allocation to rosuvastatin reduced both LDL-c and CRP, and was associated with a reduction in the primary composite outcome of myocardial infarction, stroke, revascularization, unstable angina for death from cardiovascular causes. This raised the possibility that benefits of statins might be proportionally greater in persons with high CRP.

The present randomized trial was undertaken in high risk patients in whom many vascular events took place during the study treatment period. This tested the hypothesis that the effect of statins differs according to the baseline concentrations of CRP and LDL-c.

STUDY

1. Between 1994 and 1997, 20 536 persons age 40-80 (mean age 64) at high risk for vascular events were recruited from 69 UK hospitals.
2. All had a previous diagnosis of CHD, occlusive disease of non-coronary vessels, diabetes, or hypertensive men over age 65. (A high-risk group.)
3. Took a baseline blood sample. Categorized CRP into 6 basic groups, each containing about 3000 individuals.
4. Randomized to: 1) 40 mg simvastatin daily, or 2) placebo. for 4 to 6 weeks.
5. At the final visit, blood was withdrawn to recheck LDL-c and CRP.
6. Determined information about any myocardial infarction, stroke, vascular procedure, and hospitalizations.
7. The primary prespecified endpoint was major vascular events (coronary death, non-fatal myocardial infarction, fatal and non-fatal stroke, and coronary revascularization. (99% had complete follow-up for both mortality and morbidity.)

8. Duration of study = 5 years.

RESULTS

1. A total of 4518 (17%) major vascular events occurred over 5 years.

2.Overall, simvastatin resulted in a significant 22% reduction in the first major vascular events after randomization:

CRP level (mg/L)	Simvastatin (%)	Placebo (%)
<1.25	14.1	19.4
1.25-1.99	19.2	23.7
2.00-2.99	19.4	23.7
3.9904.99	23.0	29.5
5.00-7.99	25.6	30.6
>800	18.7	22.7
Total	19.8	25.2

3. Effects on major coronary events, stroke, and revascularization effects were similar.

4. There was no evidence that the proportional reduction in the endpoint or its components varied with baseline CRP concentrations.

5. Even in participants with baseline CRP less the 1.25 mg/L, major vascular events were reduced by 29%.

6. To test the hypothesis that the proportional effect of simvastatin vs placebo on vascular events might differ according to whether individuals have greater than mean baseline concentrations of LDL-c, CRP, both, or neither, participants were categorized into 4 groups based on the median concentrations of LDL-c (127 mg/dL() and CRP (1.56 mg./dL)

High -high High - low Low- high Low-low

There was no significant heterogeneity in the proportional events between the 4 groups. In particular, the proportional risk reduction in participants with low LDL- and low CRP (27%) was statistically similar to participants with high LDL-c and high CRP (23%).

7. Even when the threshold used to define low LDL-c was reduced to 92 mg/dL (the median baseline concentration in the JUPITER trial) the proportional reduction in major vascular events in participants with low LDL-c and low CRP was still similar to the reduction overall (13.6% vs 18.9%; risk reduction 0.73)

DISCUSSION

1. "In this study of more than 20 000 people at high risk of vascular events, 5 years of simvastatin therapy reduced the risk of a major vascular event by a quarter, but there was no indication that the proportional risk reduction was larger in those with higher baseline CRP concentrations."
2. In participants with CRP concentrations less than 1.25 mg/L, or with low concentrations of both LDL-c and CRP, there were significant reductions in the risks of major vascular events.
3. Hence, the present hypothesis-testing analysis, which is based on large numbers of major vascular events, does not lend support to the suggestion from hypothesis -generation studies, which included far fewer vascular events, that the beneficial effects of statin therapy are affected by baseline CRP concentrations.
4. The proportional reduction in the risk of major vascular events with statin therapy seem to be directly related to the absolute reduction in LDL-c that is achieved.
5. These results are applicable, not only to the wide range of people with preexisting vascular disease, but also to people without known vascular disease, since the proportional benefits of statins are as large in primary prevention.
6. The different effects of statins on the risk of major vascular events can be largely, if not wholly explained by differences in reduction of LDL-c
7. The findings of this study that reducing LDL-c with simvastatin reduces risk of major vascular events to a similar extent irrespective of presenting CRP concentrations (including among individuals with low concentrations of both CRP and LDL-c) are probably broadly generalisable to other statins.

CONCLUSION

This large randomized trial does not lend support to the hypothesis that baseline CRP concentrations modify the vascular benefits of statin therapy materially.

Lancet February 5, 2011; 377:469-76 Original investigation. Correspondences to: The Heart Protection Study Collaboration Group. University of Oxford, Oxford UK

1. NEJM November 2008; 359 Abstracted in Practical Pointers November 2008 [11-2]