

PRACTICAL POINTERS
FOR
PRIMARY CARE MEDICINE

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A Free Public-service Publication

APRIL 2012

KNOW THE PATIENT AS AN INDIVIDUAL, NOT JUST A DISEASE IN A PERSON [4-1]

**IS STATIN THERAPY INDICATED FOR PRIMARY PREVENTION? [4-2] **

RED MEAT IS BAD FOR YOU [4-3]

COFFEE IS GOOD FOR YOU [4-4]

SHOULD THE BAR FOR PRIMARY PREVENTION BE RAISED? [4-5]

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26th 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 reviews of the current literature and his 26-year publication of *Practical Pointers*.

2) The **FULL 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 APRIL 2012

Patients Have A Right To Understand The Options Available And To Be Supported To Make The Decision That Is Right For Them.

4-1 PUTTING PATIENTS FIRST

A guideline from NICE (the UK National Institute for Health and Clinical Excellence) aims to create sustainable changes that will result in a cultural shift toward a patient –centered service. It places the principle of a high quality patient experience at the heart of good clinical care. When implemented, the recommendations will lead to feasible and effective improvements in care.

However, much of the guideline states the obvious. Many challenges remain in providing a health service that systematically, reliably, and demonstrably puts patients first.

It is a sad indictment of modern health care that we need such guidance in the first place. Most people would expect that delivering good service would be secondary nature to the “caring profession”. Sadly, evidence suggests that this is not the case. The reality is that people who work in health care often seem to be immune to patient’s anxiety, excessive waiting, and unnecessarily distressing experiences. Almost every day they walk past, or participate in, care that is not delivering a good experience.

Improvements will not be seen until we understand and improve the attitudes and behaviors of health professionals as well as the systems and structures of care.

The definition of patient experience is limited by our inability to see into the lives of those we cared for.

The most important challenges are long-term conditions, aging, and multi-morbidity—the conditions patients live with. These consume about 70% of health and social care. A much broader definition of “patient experience” includes the experiences patients have every day, and not just the health care they receive. Self management is already default care for people living with long-term conditions. If the experience of patients who self-manage is to be improved, they must be recognized as active co-producers of their own health. They should be supported in developing the knowledge and skills to become confident self-managers of their own conditions.

All interventions to support self-management have a positive effect on clinical symptoms and outcomes, attitudes and behaviors, and quality of life. That such approaches are not the norm is one of the greatest failures of modern medicine.

Support for self management has a theoretical basis within health psychology, which profoundly distinguishes it from more didactic patient education and information provision.

NICE guidelines too often reinforce the myth of the “right way” to deliver care, at the risk of ignoring the principle of shared decision making. Patients have a right to understand the options available and to be supported to make the decision that is right for them.

BMJ April 7, 2012; 344:11 Editorial, first author Simon Eaton, Northumbrian Health Care, North Shields, UK . BMJ2012; 344:e2006

This editorial is linked to “Improving the Experience of Care for People using NHS Services: A summary of NICE guidelines”, first author Norman O’Flynn, Royal College of Physicians, London, UK BMH2012;344;D6422

The emphasis of health care has often been on clinical care and outcomes, which can come at the expense of patients’ experiences. Giving attention to the individual has become more difficult as healthcare has become more technical and specialized, involving more people and services. Patients have less opportunity to develop relationships with the professionals who treat them. They are more likely to be treated by a team.

The National Health Service recognized the experience of patients as one of 3 dimensions of quality. The other 2 are clinical effectiveness and safety.

The article summarizes the most recent recommendations on improving patients’ general experience of care. The recommendations cover mainly the interaction between healthcare staff and patients.

Recommendations for healthcare professionals:

- Know the patient as an individual
- Tailor healthcare services to the individual
- Ensure continuity of care and relationships
- Enable active participation of the patient in their care

There are 2 parts to every consultation: the disease, and the patient with the disease.

I have had my share of triumphs and tragedies over the years of active practice as a primary care internist. Looking back, I almost always focused on the disease. I would have been a better clinician if I had been more aware of the patient’s beliefs and feelings, and willingness and ability to participate in their own care.

I would be more willing to say at the end of the initial consultation—“Now tell me about yourself”. The goal is to try to know the patients as one would know a family member or a good friend. This takes time. We must save some time for it.

Getting to know the patient as a person is a remit of primary care. We have the privilege of following patients over years, and afterwards attending to their children. Specialists who consult with the patient for only one episode of medical illness or surgery lack this opportunity. It takes time

to establish an enduring relationship. Our early forebears in medicine relied mainly on kindness, presence, and attention for therapy. That was all they had to offer.

The article's focus on self-management is important. One of our greatest challenges is to convince patients to care for their own health. Success is infrequent. Keep trying. We must try to understand why a patient continues to smoke, abuse alcohol, lead a sedentary life, and will not follow a more healthy diet. Be aware, however, that some patients are economically unable to do all of this.

Caring for the patient is not a new imperative. What is new? More emphasis on involving the patient in decision making and encouraging them to take more responsibility for their health. If cure is not possible, provide comfort and encourage the patient to accept what cannot be changed.

Francis Peabody's famous aphorism bears repeating; "The secret of the care of the patient is the caring for the patient".

4-2 Should a 55-year old man who is otherwise well, with a systolic BP of 110, total cholesterol of 250, and no family history of CHD be treated with statins? (Primary prevention) Two groups of authorities debate. One says "yes". One says "no"

Statin Therapy Is A Critical Adjunct For Those Identified At Increased Risk Of CHD.

Adverse Effects Are Rare

YES—STATIN THERAPY FOR HEALTHY MEN IDENTIFIED AT "INCREASED RISK"

Benefits (efficacy): Two large primary-prevention trials (WOSCOP and AFCAPS/TexCAP) included over 13 000 asymptomatic participants without a history of CHD, but with an elevated cholesterol—treated with statins vs placebo. The treated groups experienced a reduction in myocardial infarction, CHD-related deaths, and major coronary events by 31% to 40%.

Guidelines around the world support a combined lifestyle (always lifestyle changes) and pharmacologic approaches to cholesterol-lowering directed at patients with elevated CHD risk.

Harms (adverse effects): Are statins safe? Adverse effects are rare. About 5% of patients will develop muscle-related complaints. They are generally reversible after discontinuation. There is no good peer-reviewed evidence that statins lead to cognitive impairment or memory loss. The risk of development of diabetes associated with statins is mainly seen in those with preexisting glucose intolerance. Risk of diabetes is minimal in comparison with CHD event reduction.

Compliance: Do statins lead to lower adherence with a prudent lifestyle? There is evidence to the contrary. A physician's recommendation for statin therapy may motivate improvements in overall health behaviors.

Conclusion: Physicians must encourage lifestyle interventions along with medications. The cornerstone of therapy for patients with elevated cholesterol will always be dietary modifications and emphasis on physical activity. Statin therapy is a critical adjunct for those identified at increased risk of CHD.

Statins Are Not Effective In Improving Length Or Quality Of Life When Used For Primary Prevention.

No—HEALTHY MEN SHOULD NOT TAKE STATINS

Benefits (efficacy): A meta-analysis of 11 trials (65 229 healthy men and women with high cholesterol) with over 240 000 person-years of follow-up showed no reduction in mortality associated with statin treatment. A 2011 Cochrane review of statins among persons without documented CHD came to similar conclusions. A population-based cohort studying in the UK of more than 2 million statin users reported increased risk of liver dysfunction, acute renal failure, myopathy, and cataracts. Increased risk of diabetes has been seen in randomized clinical trials. Based on the current evidence, a healthy man with elevated cholesterol will not live any longer if he takes a statin.

Harms (adverse effects): Data from observational studies show much higher rates for statin-related myopathy than the 1% to 5% reported in clinical trials. The trials had excluded up to 30% of patients with many common co-morbidities, including those with muscle pain as well as those with renal and hepatic insufficiency. Many trials also excluded those who had adverse effects of treatment during an open-label run in period. The results of randomized trials of statins likely underestimate common symptoms such as myalgia, fatigue, and other minor muscle complaints because they often collect only data on more quantifiable adverse effects such as rhabdomyolysis. Numerous anecdotal reports and small studies have suggested cognitive impairment, which would not have been captured in randomized trials. The true extent of cognitive impairment associated with statins remains understudied.

Compliance: Prescribing a statin may undermine compliance with lifestyle changes by giving a sense of false security—ie, by taking a statin, patients may eat whatever they want and not exercise.

Conclusion:: Good data indicate that statins are not effective in improving length or quality of life when used for primary prevention.

(Please read the full abstract for details and the citations. Ed.)

I enjoyed this debate. National authorities, reviewing the same data, came to different conclusions. Both sides “cherry picked” data supporting their conclusions. (Sort of like quoting scripture.) How is the lonely primary care clinician to respond? What should the public believe?

I would give the debate prize to the “No” side. The side in favor of statin treatment weakened their argument by introducing another risk marker—the coronary artery calcium score—an expensive, invasive, and inconvenient application in primary care. This led to a change in the basic question, which was to consider a patient with only one risk factor (elevated total-cholesterol). They also quoted results in favor of statin therapy in large trials comprising over 12 000 subjects from the population. Certainly, many, if not most, of the subjects of these trials had more than one risk factor. And would be at greater risk than the subject in the scenario.

The debaters disagree on the adverse effects of statins. When a foreign substance is introduced into the body, some adverse effects are inevitable. The question for statins is how many and how severe. I believe harms of statins are underreported. Any drug taken by millions of patients must be associated with uncommon adverse effects, which evade notice in randomized trials. If a statin is prescribed, the patient should be carefully followed for any possible change in feelings. Statins may be the cause. If the drug is considered essential, a N of 1 trial may help.

In primary care practice, most patients considered for primary prevention will have more than one risk factor. All risk factors must be treated, including dyslipidemia. However, what reason to prescribe statin for a patient who continues to smoke?

I believe most patients would opt for statins. “Cholesterol” is a national obsession. “Know your cholesterol” is an imperative.

Note the important conclusion of both sides—lifestyle is the cornerstone of therapy for dyslipidemia. If a statin is prescribed, use a low-cost generic.

How should the primary care clinician respond to this dilemma?—by shared decision making. Describe the pros and cons of statin therapy and ask the patient to express his personal preference.

Secondary prevention is another matter.

Associated With A Significantly Elevated Risk Of Mortality

4-3 RED MEAT CONSUMPTION AND MORTALITY

This study investigated the association between red meat (**RM**) and cause-specific and total-mortality reported by 2 large cohorts.

Analyzed data from 2 prospective cohort studies: 1) the Health Professionals Follow-up

Study (**HPFS**; 1986-2008; n = 37 698 men) and 2) the Nurses Health Study (**NHS**; 1980-2008; n = 83 644 women). At baseline, none had a history of cancer or CVD.

Unprocessed RM included beef, pork, or lamb as a main dish. The standard serving size was 3 oz. Processed RM included bacon (2 slices) one hot dog, and sausage, salami, bologna, and other processed meat (1 piece-28 g).

Baseline characteristics of participants according to quintiles of total-RM consumption:

	Total RM intake by quintile				
	1	2	3	4	5
A. Men (Mean age 52)					
RM mean servings / day	0.22	0.62	1.01	1.47	2.36
B. Women (mean age 46)					
RM mean servings / day	0.53	1.04	1.52	2.07	3.10

Lowest intake was 1 to 2 servings per week; highest more than 21 servings per week.

Every 4 years, updated the association between RM consumption and cause-specific and all-cause mortality.

Higher intake of RM was associated with a higher intake of energy, but lower intake of whole grains, fruit, and vegetables, poultry and fish.

For both cohorts combined, there were 23 926 deaths including 5910 CVD and 9464 cancer deaths during 2.9 million person-years of follow-up

Hazard ratios (HR) for mortality after multivariate adjustment for major lifestyle and dietary risk factors according to RM intake (quintiles):

	1	2	3	4	5	
All-cause mortality	1.00 ^a	1.10	1.15	1.21	1.30	a Referent

HR for mortality for 1-serving per day increase of total RM.

Unprocessed RM	1.13
Processed RM	1.20

Unprocessed and processed RM intake were associated with an increased risk of total-, CVD-, and cancer-mortality. In the pooled analysis, for every one serving per day, mortality increased by 13% for un-processed RM, and 20% for processed RM.

Replacing 1 serving of RM with 1 serving of fish, poultry, nuts, legumes, low-fat dairy products, or whole grain was associated with a lower risk of total mortality: 7% for fish, 14% for poultry, 19% for nuts, 10% for legumes, 10% for low-fat dairy, and 14% for whole grains.

During follow-up an estimated 9.3% of total-deaths in men and 7.6% of deaths in women would have been prevented if participants consumed fewer than 0.5 servings per day of total RM.

Conclusion: Greater consumption of unprocessed and processed RM was associated with higher mortality risk. Compared with RM, other dietary components such as fish, poultry, nuts, legumes, low-fat dairy, and whole grains were associated with lower risk. Replacement of red meat with alternative healthy dietary components may lower the mortality risk.

(Please read the full abstract for details and the citations. Ed.)

Over the years, mortality was 23% higher in those who ate RM very frequently vs those who ate little.

I believe, this additional lifestyle intervention is an important public health application.

We are constantly reminded that, in observational studies, association does not prove causality. However, when the study is very large and long-term, it becomes more plausible..

High RM intake does not exist by itself. It is associated with lower intake of more healthy foods, which adds to risk.

A Dose-Dependent Inverse Association Providing Assurance That Coffee Does Not Adversely Affect Health.

4-4 ASSOCIATION OF COFFEE DRINKING AND TOTAL AND CAUSE-SPECIFIC MORTALITY

Results of previous studies relating coffee drinking (CD) to total mortality have been inconsistent. This is possibly due to inconsistent control for possible confounders and the small number of deaths.

This study used data from a very large cohort to determine whether CD is associated with total and cause-specific mortality. The study had ample power to detect even modest associations and allowed for subgroup analysis according to important baseline factors.

Between 1995-1996, over 617 000 persons returned a comprehensive questionnaire assessing diet and lifestyle. After exclusions, the study included 229 119 men and 173 141 women--age range 50-71 (median age 62) at baseline. None had cancer or cardiovascular disease.

The baseline questionnaire assessed demographic and lifestyle characteristics, including 124 dietary items. Coffee consumption was assessed only one time (at baseline).

Multivariate models were adjusted for multiple baseline factors, including smoking. BMI, age, alcohol consumption, consumption of fruit and vegetables, red meat, saturated fat, and other possible confounders.

During 14 years of follow-up (over 5 100 000 person-years) 33 731 men and 18 784 women died. After multivariate adjustments for potential confounders, a modest inverse association between CD and total mortality was observed for both men and women.

Hazard ratios (HR) for all-cause mortality among those who drank coffee, compared with those who did not drink coffee:

	None	< 1 cup/d	1 cup	2-3 cups	4-5 cups	6 or more
Men	1.00	0.99	0.94	0.90	0.88	0.90
Women	1.00	1.01	0.95	0.83	0.84	0.85

CD and cause-specific mortality: After multivariate adjustment, CD appeared to be inversely associated with most major causes of death in both men and women, including heart disease, respiratory disease, stroke, injuries and accidents, diabetes, and infections.

Smoking negates whatever benefit CD may have.

Associations between CD and death from cancer were not significant for any single category of coffee consumption.

In this large prospective cohort, there was a dose-dependent inverse association between CD and total mortality after adjusting for potential confounders.

As compared with men who did not drink coffee, men who drank 6 or more cups of coffee daily had a 10% lower risk of death. Women had a 15% lower risk.

There was no difference in outcomes between caffeinated and decaffeinated coffee.

Given the observational nature of this study, it is not possible to conclude that the inverse relationship reflects cause and effect.

Conclusion: There was a significant inverse association of CD with death from all-causes and specifically with deaths due to heart disease, stroke, respiratory disease, injuries and accidents, diabetes and infections. These results provide assurance that CD does not adversely affect health. *(Please read the full abstract for details and the citations. Ed.)*

This is a massive study. I congratulate the investigators on their deduction.

The difficulty observational studies have is in controlling for multiple possible confounding factors. The investigators did their best, but some doubt remains.

Concerning accidents and injuries, I believe caffeine may have some influence. It increases awareness and decreases drowsiness. This increases safety on the highway and in the home and shop.

The investigators mentioned the manner of preparation of coffee. Boiled coffee promoted dyslipidemia. Filtered coffee does not.

It is refreshing to learn that a pleasurable lifestyle intervention actually promotes health.

Medicine Must Negotiate A Precarious Bargain. Primary Prevention Of Disease Is A Philosophical Question, Just As It Is A Medical Question.

4-5 CARDIOVASCULAR PRIMARY PREVENTION

These editorialists argue that the bar for treatments for primary prevention must be raised. Long-established preventive practices (based on biomarkers and surrogate endpoints) may be erroneous. Large randomized, controlled trials must show that the primary prevention treatments improve mortality and morbidity before implementation.

Surrogate endpoints disagree with hard (clinical) outcomes, and with each other.

These contradictions further undermine our ability to trust surrogate endpoints (improvement in biomarkers). They force us to confront a very difficult question—should we demand that cardiovascular agents improve morbidity and mortality before being used in primary prevention?

Primary prevention is unlike so much of medicine because it is performed in asymptomatic patients in their efforts to live longer and better and to delay onset of symptoms. When primary prevention is prescribed, a question remains—is it introduced in error? Empirical evidence suggests that nearly half of trials testing standards of care ultimately do not support the practice and constitute medical reversals.

Medicine must negotiate a precarious bargain—accepting promising, but unproven, therapies for primary prevention, sorting them out in the decades that follow, or, alternatively, setting a high barrier for primary prevention and implementing only preventions that have met the requirement to reduce morbidity and mortality.

Primary prevention makes sense when a disease is prevalent, when there is an effective therapy, and when there is evidence that early action leads to improved clinical outcomes beyond what might be achieved with later treatment. What counts as effective therapy? There should be evidence from randomized, controlled trials showing that the screening program and preventive treatment improves morbidity and mortality.

(Please read the full abstract for details and the citations. Ed.)

Much of primary care medicine is based on identifying and treating risk factors (biomarkers; surrogates for clinical events). Then, if they are elevated, applying some preventive treatment. If we treat the biomarker and reduced risk, we assume we have benefited the patient.

For example, if the patient's BP (a biomarker; a risk factor) is high, we treat to lower it into "normal" range. But there is no way we can determine if the preventive treatment actually prevents a stroke in an individual patient. The best we can do is to inform him that the chances are that treatment will, over the observation time, reduce the incidence of stroke by 1 in XXX, based on the number needed to treat (NNT) demonstrated in long-term randomized trials. If the patient develops a stroke, he bore the expense and harms of the drug without benefit.

Off hand I can think of at least 10 commonly applied risk factors (biomarkers). Often a patient will have several risk markers. Treatment with drugs inevitably places the patient at harm from long-term adverse drug effects and costs.

Millions and millions of patients in the US are taking preventive drugs at a cost of billions and billions. (Do not underestimate the power of marketing departments of drug companies.) But, we cannot determine benefits in an individual patient.

Nevertheless, we continue to rely on treatment of biomarkers. I believe they have brought benefits to patients. As the editorialists suggest, we cannot reasonably wait for proof of clinical benefits for drugs. We are stuck with treatment of biomarkers.

Not all patients considered for primary prevention and treatment are equal. Some can be classified at low risk; some at high risk. We should concentrate on the latter. Primary care clinicians must make a judgment call. How aggressive should we be?

Secondary prevention is more straightforward.

Lifestyle interventions are associated with the highest benefit / harm-cost ratio, far exceeding drug therapy. I keep coming back to a healthy lifestyle as the basic preventive therapy.

FULL ABSTRACTS APRIL 2012

4-2 Should a 55-year old man who is otherwise well, with a systolic BP of 110, total cholesterol of 250, and no family history of CHD be treated with statins? Two groups of authorities debate. One says “yes”. One says “no”

YES—STATIN THERAPY FOR HEALTHY MEN IDENTIFIED AT “INCREASED RISK”

The “lipid” hypothesis of coronary heart disease (**CHD**) is clearly established: 1) Circulating cholesterol plays a central role in atherogenesis and is an integral component of the requisite lesion—the coronary plaque; 2) Cholesterol levels, beginning in childhood, predict lifetime risk of atherosclerotic CHD events in a dose-response relationship; 3) Statins lower cholesterol levels and reduce CHD events directly proportional to the degree of low-density cholesterol (**LDL-c**) lowering. As a result, guidelines around the world support a combined lifestyle (always lifestyle changes) and pharmacologic approaches to cholesterol-lowering directed at patients with elevated CHD risk.

Assuming a HDL-c level of 40, the patient would have an “intermediate” 10-year risk of developing CHD (approximately 10%) based on the Framingham Risk Score.

If the patient’s total-c remains elevated despite lifestyle attempts, statin therapy should be considered with the goal of reducing CHD risk. In a shared decision-making process, the clinician should explicitly inform the patient that a statin is likely to reduce the chance of a first CHD event, reduce the chance of a stroke, and may offer a survival benefit that is likely to become more evident over a lifetime.

Evidence Supporting Primary Prevention:

The WOSCOP study (1995) enrolled 6595 men age 46-65 with a mean total cholesterol of 272. None had a history of CHD, (A primary prevention trial.) Compared with placebo, pravastatin 40 mg/d reduced myocardial infarctions and CHD-related deaths by 31%. [174 vs 248 events and 106 vs 135 deaths.]

The AFCAPS/TexCAP randomized 6605 asymptomatic adults with mean LDL-c 221 and low HDL-c (36) to lovastatin 20 to 40 mg vs placebo. Treatment reduced the first major coronary event by 37% and myocardial infarction by 40%. [116 vs 183 and 57 vs 95]

Risk-based Individualized Treatment Decisions:

Nearly all US adults have elevated cholesterol levels compared to their evolutionary ancestors. (*And compared with their levels during infancy. Ed.*) The debate over cholesterol therapy needs to be rephrased. Clinicians should never treat elevated cholesterol levels in isolation.

What if the patient in the scenario is uncertain about the absolute benefit of treatment? The best predictor of risk in intermediate-risk patients is the coronary artery calcium (CAC) score. CAC score is a direct measure of the burden of coronary artery disease. It enables the clinician to integrate risk exposure over a lifetime and to use the information to guide decisions. High CAC scores (> 100) signify higher CHD risk. A score of 0 equates to a very low near-term (5-year) CHD risk. “The CAC scan is the single best test for reclassifying intermediate risk patients into their most appropriate treatment groups.” A 55-year old patient with a total-c of about 250 and a normal BP would have a 50% chance of having a CAC score of 0. This translates into an estimated 10-year risk of CHD to less than 2% after an estimated 35% event reduction in cholesterol by treatment with statins. Simple presence of CAC would increase the risk nearly 4-fold.

The CAC score is a helpful tool enabling clinicians to direct statin treatment at disease (coronary atherosclerosis) and illustrates the concept of risk-based individualized decision-making.

Argument Against Selective Use of Statins

What are the main points of contention?

1) Are statins safe? Adverse effects are rare. About 5% of patients will develop muscle-related complaints. They are generally reversible after discontinuation. There is no good peer-reviewed evidence that statins lead to cognitive impairment or memory loss. The risk of development of diabetes associated with statins is mainly seen in those with preexisting glucose intolerance. Risk of diabetes is minimal in comparison with CHD event reduction.

2) Do statins lead to lower adherence with a prudent lifestyle? There is evidence to the contrary. A physician’s recommendation for statin therapy may motivate improvements in overall health behaviors. Physicians must encourage lifestyle interventions along with medications.

3) Should statins be prescribed only after a myocardial infarction? There is no apparent logic in waiting for a MI or stroke to occur before starting risk-reducing therapy.

4) Is statin therapy cost-effective? With the emergence of generics such as simvastatin and atorvastatin (some at \$4 a month) therapy is increasingly cost-effective.

Conclusion; The cornerstone of therapy for patients with elevated cholesterol will always be dietary modifications and emphasis on physical activity.

Statin therapy is a critical adjunct for those identified at increased risk of CHD.

JAMA April 11, 2012; 307: 1489-90 “Viewpoint”, first author Michael J Blaha, Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD.

NO—HEALTHY MEN SHOULD NOT TAKE STATINS

Higher cholesterol levels are associated with a greater risk of heart disease. At the population level, elevated cholesterol is associated with a diet higher in fatty foods, particularly saturated fat, trans fats, and meats, and low intake of fruits and vegetables.

The important questions:

1) Does treatment of elevated cholesterol in otherwise healthy persons decrease mortality or prevent other serious health problems?

2) What are the adverse effects associated with statins in healthy persons?

3) Do the potential benefits outweigh the potential risks?

The answers to these questions suggest that statin therapy should not be recommended in men with elevated cholesterol who are otherwise healthy.

1) What is the benefit in healthy men? A meta-analysis of 11 trials (65 229 healthy men and women with high cholesterol) with over 240 000 person-years of follow-up showed no reduction in mortality associated with statin treatment. A 2011 Cochrane review of statins among persons without documented CHD came to similar conclusions.

2) What about adverse effects? Data from observational studies show much higher rates for statin-related myopathy than the 1% to 5% reported in clinical trials. The trials had excluded up to 30% of patients with many common co-morbidities, including those with muscle pain as well as those with renal and hepatic insufficiency. Many trials also excluded those who had adverse effects of treatment during an open-label run in period. The results of randomized trials of statins likely underestimate common symptoms such as myalgia, fatigue, and other minor muscle complaints because they often collect only data on more quantifiable adverse effects such as rhabdomyolysis.

Numerous anecdotal reports and small studies have suggested cognitive impairment, which would not have been captured in randomized trials. “The true extent of cognitive impairment associated with statins remains understudied.”

A population-based cohort studying the UK of more than 2 million statin users reported increased risk of liver dysfunction, acute renal failure, myopathy, and cataracts. Increased risk of diabetes has been seen in randomized clinical trials.

3) Potential benefits vs potential risks: Based on the current evidence, a healthy man with elevated cholesterol will not live any longer if he takes a statin. For every 100 patients with elevated

cholesterol who take statins for 5 years, a myocardial infarction will be prevented in 1 or 2 patients. However, by taking statins, 1 or more patients will develop diabetes and 20% or more will experience disabling symptoms, including muscle weakness, fatigue, and memory loss.

Non-drug Approaches to Reducing Cholesterol:

There are effective methods to reduce CV risk in otherwise healthy men: dietary modification, weight loss, and increased exercise. These strategies increase longevity, and improve mood and sexual function. But prescribing a statin may undermine compliance with lifestyle changes by giving a sense of false security—ie, by taking a statin, patients may eat whatever they want and not exercise.

For the 55 year-old man in the scenario, the risk of MI in the next 10 years (according to the Framingham Score) varies from 10% to 20%. The risk is driven mainly by his age rather than his cholesterol. Age has a much greater influence on risk than high levels of cholesterol. The recent data on increased risk of diabetes, cognitive dysfunction, and muscle pain associated with statins suggest that there is risk with no evidence of benefit.

There are significant opportunities for improvement in lifestyle. Lifestyle counseling should be the focus of primary prevention.

Conclusion: “Good data indicate that statins are not effective in improving length or quality of life when used for primary prevention”.

JAMA April 11, 2012; 307: 1491-92 “Viewpoint”, first author Rita E Redberg, University of California, San Francisco.

Associated With A Significantly Elevated Risk Of Mortality

4-3 RED MEAT CONSUMPTION AND MORTALITY

Evidence from epidemiological studies shows that consumption of meat, especially red meat (RM), is associated with increased risk of diabetes, cardiovascular disease, and certain cancers.

This study investigated the association between RM and cause-specific and total-mortality reported by 2 large cohorts.

STUDY

1. Analyzed data from 2 prospective cohort studies: 1) the Health Professionals Follow-up

Study (**HPFS**; 1986-2008; n = 37 698 men) and 2) the Nurses Health Study (**NHS**; 1980-2008; n = 83 644 women). At baseline, none had a history of cancer or CVD.

2. Assessment of meat consumption: A food frequency questionnaire (FFQ) asked how often, on average, participants consumed each food of a standard portion size. There were 9 possible responses—never or less than once a month to 6 or more times a day. Unprocessed RM included beef, pork, or lamb as a main dish. The standard serving size was 3 oz of unprocessed RM. Processed RM included bacon (2 slices) one hot dog, and sausage, salami, bologna, and other processed meat (1 piece-28 g).

3. Baseline characteristics of participants according to quintiles of total-RM consumption:

	Total RM intake by quintile				
	1	2	3	4	5
A. Men (Mean age 52)					
RM mean servings / day	0.22	0.62	1.01	1.47	2.36
B. Women (mean age 46)					
RM mean servings / day	0.53	1.04	1.52	2.07	3.10

Lowest intake was 1 to 2 servings per week; highest more than 21 servings per week.

4. Deaths were identified from reports of next-of-kin, the postal authorities, and the National Death Index. The causes of death were determined from medical records and death certificates.

5. Every 4 years, updated the association between RM consumption and cause-specific and all-cause mortality.

6. Created cumulative averages of food intakes from baseline to death from repeated FFQs.

7. Estimated the effect on mortality by substituting 1 serving of an alternative food for 1 serving of RM.

RESULTS

1. For both cohorts combined, there were 23 926 deaths including 5910 CVD and 9464 cancer deaths during 2.9 million person-years of follow-up

2. Higher intake of RM was associated with a higher intake of energy, but lower intake of whole grains, fruit, and vegetables, poultry and fish.

3. Mortality after adjustment for major lifestyle and dietary risk factors:

	HR for mortality according to RM intake (quintiles)				
	1	2	3	4	5
A. All-cause mortality					
Total RM	1.00 ^a	1.10	1.15	1.21	1.30
Unprocessed RM	1.00	1.08	1.10	1.15	1.23

^a Referent

Processed RM	1.00	1.05	1.11	1.15	1.23
B. Cardiovascular mortality					
Total RM	1.00	1.12	1.13	1.23	1.40
Unprocessed RM	1.00	1.16	1.09	1.17	1.30
Processed RM	1.00	1.01	1.12	1.13	1.27
C. Cancer mortality					
Total RM	1.00	1.05	1.09	1.16	1.19
Unprocessed RM	1.00	1.03	1.03	1.09	1.17
Processed RM	1.00	1.03	1.08	1.08	1.14

Risk of death rose linearly as intake of RM increased. Over the years, mortality was 23% higher in those who ate RM very frequently vs those who ate little.

4. HR for mortality for 1-serving per day increase of total RM.

Unprocessed RM	1.13
Processed RM	1.20

Unprocessed and processed RM intake were associated with an increased risk of total-, CVD-, and cancer-mortality. In the pooled analysis, for every one serving per day, mortality increased by 13% for un- processed RM, and 20% for processed RM.

5. There were no statistically significant differences among specific unprocessed RM or specific processed RM for association with total mortality. However, bacon and hot dogs tended to be associated with higher risk than other items.

6. Replacing 1 serving of RM with 1 serving of fish, poultry, nuts, legumes, low-fat dairy products, or whole grain was associated with a lower risk of total mortality: 7% for fish, 14% for poultry, 19% for nuts, 10% for legumes, 10% for low-fat dairy, and 14% for whole grains. Similar reductions occurred for replacements of unprocessed RM and processed RM.

7. During follow-up an estimated 9.3% of total-deaths in men and 7.6% of deaths in women would have been prevented if participants consumed fewer than 0.5 servings per day of total RM. For CVD- deaths, the estimates were 8.6% for men and 12.2% for women. However, only 22.8% of men and 9.6% of women were in the low-risk category for total RM intake.

DISCUSSION

1. In these large cohorts of US men and women, a higher intake of RM was associated with a significant elevation risk of total-, CVD-, and cancer-mortality.
2. Risk was relatively greater for processed RM.

3. Substitution of fish, poultry, nuts, legumes, low fat dairy, and whole grains for RM was associated with a significant lower risk of mortality.
4. Several studies have suggested that vegetarians have greater longevity than non-vegetarians, but this may not be ascribed to the absence of RM only.
5. The FFQs used in this study were validated against multiple diet records. However, measurement errors are inherent in dietary assessments.
6. Several mechanisms may explain the adverse effects of RM:

Saturated fat and cholesterol from RM may partially explain the association. The investigators could not, however, assess whether lean RM has the same health risks as meat with higher fat content. Dietary iron, particularly heme iron from RM, has been positively associated with myocardial infarction and fatal CHD. Unprocessed and processed RM contain similar amounts of saturated fat and heme. Other constituents in processed RM, particularly sodium (affecting BP) and nitrates (endothelial dysfunction and impaired insulin response) might explain the additional risk of processed RM.
7. Regarding cancer mortality, RM intake has been associated with increased risk of colon and other cancer. Several components in RM, or created by high-temperature cooking, are potential carcinogens. Heme iron and iron overload might be associated with increased risk.

CONCLUSION

Greater consumption of unprocessed and processed RM was associated with higher mortality risk. Compared with RM, other dietary components such as fish, poultry, nuts, legumes, low-fat dairy, and whole grains were associated with lower risk. “Replacement of red meat with alternative healthy dietary components may lower the mortality risk”.

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Original investigation, first author Am Pan, Harvard School of Public Health, Boston. Mass

A Dose-Dependent Inverse Association Providing Assurance That Coffee Does Not Adversely Affect Health.

4-4 ASSOCIATION OF COFFEE DRINKING AND TOTAL AND CAUSE-SPECIFIC MORTALITY

Results of previous studies relating coffee drinking (**CD**) to total mortality have been inconsistent. This is possibly due to inconsistent control for possible confounders and the small number of deaths.

Data are lacking to clarify the association between CD and mortality, to determine whether there is a dose-response relationship, and to assess whether associations are consistent across various subgroups.

This study used data from a very large cohort to determine whether CD is associated with total and cause-specific mortality. The study had ample power to detect even modest associations and allowed for subgroup analysis according to important baseline factors.

STUDY

1. Between 1995-1996, over 617 000 persons returned a comprehensive questionnaire assessing diet and lifestyle. After exclusions, the study included 229 119 men and 173 141 women--age range 50-71 (median age 62) at baseline. None had cancer or cardiovascular disease.
2. The baseline questionnaire assessed demographic and lifestyle characteristics, including 124 dietary items.
3. Coffee consumption was assessed according to 10 frequency categories ranging from 0 to 6 or more cups per day.
4. Participants were followed from 1995-96 to the end of 2008.
5. Determined deaths and specific causes of death from National Registries and data from various state records.
6. Multivariate models were adjusted for multiple baseline factors, including smoking, BMI, age, alcohol consumption, consumption of fruit and vegetables, red meat, saturated fat, and other possible confounders.
7. Determined consumption of caffeinated and decaffeinated coffee.

RESULTS

1. CD at baseline was associated with several other dietary and lifestyle factors: smoking, alcohol and red meat consumption, lower consumption of fruit and vegetables. CDs were less likely to engage in physical activity.
2. About 2/3 of CDs reported drinking predominantly caffeinated coffee; 1/3 decaf.
3. CD and total mortality:

During 14 years of follow-up (over 5 100 000 person-years) 33 731 men and 18 784 women died. After multivariate adjustments for potential confounders, especially smoking, a modest inverse association between CD and total mortality was observed for both men and women.

Hazard ratios (**HR**) for all-cause mortality among those who drank coffee, compared with those who did not drink coffee:

	None	< 1 cup/d	1 cup	2-3 cups	4-5 cups	6 or more
Men	1.00	0.99	0.94	0.90	0.88	0.90
Women	1.00	1.01	0.95	0.83	0.84	0.85

4. Most drank 2-3 cups. Relatively few drank 1 or 6 cups.

5. CD and cause-specific mortality: After multivariate adjustment, CD appeared to be inversely associated with most major causes of death in both men and women, including heart disease, respiratory disease, stroke, injuries and accidents, diabetes, and infections. There was a borderline positive association between cancers and CD in men. (HR for 6 or more cups daily = 1.08)

6. The multivariate HRs for deaths in men:

	None	6 or more cups /d
Heart disease	1.00	0.88
Respiratory disease	1.00	0.81
Stroke	1.00	0.83
Injuries	1.00	0.72
Diabetes	1.00	0.60
Infection	1.00	0.59

7. Trends for women were similar.

8. Associations between CD and mortality were generally similar across subgroups stratified according to duration of follow-up and baseline factors such as age, BM, alcohol consumption, red meat, fruit and vegetables. The largest differences across strata were observed for cigarette smoking, with stronger inverse associations between CD and mortality among those who never smoked than among those who were current smokers. Smoking negates whatever benefit CD may have.

9. Associations between CD and death from cancer were not significant for any single category of coffee consumption.

DISCUSSION

1. In this large prospective cohort, there was a dose-dependent inverse association between CD and total mortality after adjusting for potential confounders.
2. As compared with men who did not drink coffee, men who drank 6 or more cups of coffee daily had a 10% lower risk of death. Women had a 15% lower risk.
3. There was no difference in outcomes between caffeinated and decaffeinated coffee.
4. This study is larger than previous studies and includes over 52 000 deaths, more than similar prior studies. The Health Professionals Follow-up Study reported a HR for death among men who drank 6 or more cups per day vs those who drank rarely of 0.80. HR for women in the Nurse's Health Study was 0.83.
5. The association between CD and death from heart disease has been controversial. Several studies have suggested an increased risk. But, the inverse relationship in this study is consistent with a recent meta-analysis, which reported a comparable HR of 0.89.
6. This study lacked data on how the coffee was prepared (boiled or filtered). The constituents of coffee may vary according to the method of preparation.
7. Given the observational nature of this study, it is not possible to conclude that the inverse relationship reflects cause and effect.
8. What might be a plausible mechanism of the health benefits? Coffee contains more than 1000 compounds that might affect the risk of death. The most studied compound is caffeine. This study does not support caffeine as the cause because there was no difference in the effects of decaffeinated and caffeinated coffee. Other compounds may be causal (antioxidants; polyphenols).

CONCLUSION

There was a significant inverse association of CD with death from all-causes and specifically with deaths due to heart disease, stroke, respiratory disease, injuries and accidents, diabetes and infections.

These results provide assurance that CD does not adversely affect health.

NEJM May 17, 2012; 366: 1891-1904 Original investigation, first author Neal D Freedman, National Institutes of Health Rockville MD The National institutes of Health-AARP Dietary Health Study

Medicine Must Negotiate A Precarious Bargain. Primary Prevention Of Disease Is A Philosophical Question, Just As It Is A Medical Question.

4-5 CARDIOVASCULAR PRIMARY PREVENTION

Some recent trials in cardiovascular (CV) medicine have contradicted current medical practice.

Extended-release niacin and fenofibrate, widely prescribed to improve lipid profiles, have failed to provide benefit when added to statin therapy. Ezetimibe, approved on the basis of improvement of one surrogate marker (low-density lipoprotein cholesterol [LDL-c]) has yielded conflicting results on another surrogate marker—carotid intimal arterial thickness (CIMT). Its effect on mortality remains unknown.

What are the implications of these reversals on primary prevention?

These editorialists argue that the bar for treatments for primary prevention must be raised. Large randomized, controlled trials should show that primary prevention measures improve mortality and morbidity before implementation.

Reversals in cardiovascular prevention:

1) Niacin has been used for decades to treat dyslipidemia. In 2009, a study showed promising results regarding another surrogate endpoint. The addition of niacin to statin resulted in a significant reduction in carotid intimal-medial thickness (CIMT). The AIM-HIGH study (2011) investigated whether extended-release niacin added to statin therapy would improve CV outcomes. The trial was terminated early when niacin failed to offer any additional benefit.

2) Fenofibrate: The ACCORD study (2010) determined whether the addition of fenofibrate to simvastatin would reduce the risk of CV events. At a mean follow-up of 4.7 years, the addition of fenofibrate did not diminish the primary outcome of myocardial infarction, stroke, or cardiovascular events.

3) Ezetimibe (*Zetua*; *Ezetrol*; blocks cholesterol absorption from the gi tract, lowering LDL-c). Ezetimibe improves lipid profiles. However, the addition of ezetimibe to statin did not improve CIMT and carried the suggestion of increased CV events. Its effect on outcomes remains unknown.

4) Torcetrapib reliably increases HDL-c and lowers LDL-c. “It was touted to be one of the most important compounds of our generation.”¹ However, it was withdrawn because of a 60% increase in all-cause mortality. If the drug had not been tested for hard (clinical) endpoints, countless patients would have been harmed.

How do we make sense of this data? The first theme to emerge is that long-established preventive practices may be erroneous. Fenofibrate was first approved in 1993 for treatment of severe hyper-triglyceridemia. Indications were broadened to cholesterol-lowering in 1999 based on 3 studies of its effect on lipid endpoints. The drug (*Tricor*) quickly became a blockbuster. Sales topped a billion dollars. However, a meta-analysis published in 2005 cast doubt on fibrates, showing no improvement in overall survival. This finding was confirmed in ACCORD. Although it was prescribed for over a decade to further improve lipid profiles for patients already prescribed statins, we now know the error of this practice.

The second theme to emerge is that surrogate endpoints disagree with hard (clinical) outcomes, and with each other. Niacin improves lipid profiles and decreases CIMT, yet, when added to statin therapy it did not improve clinical outcomes. The addition of ezetimibe to statin did not improve CIMT and carried the suggestion of increased CV events. Its effect on outcomes remains unknown.

These contradictions further undermine our ability to trust surrogate endpoints and forces us to confront a very difficult question—Should we demand that cardiovascular agents improve morbidity and mortality before being used in primary prevention?

The hardest question:

Primary prevention is unlike so much of medicine because it is performed in asymptomatic patients in their efforts to live longer and better and to delay onset of symptoms. When primary prevention is prescribed, a question remains—Is it introduced in error? Empirical evidence suggests that nearly half of trials testing standards of care ultimately do not support the practice and constitute medical reversals.

Meanwhile, billions of dollars may be spent.

However, there is a trade-off. Up-front testing for hard clinical outcomes may delay introduction of potentially beneficial drugs. It is impossible to determine ultimate harms at an early stage. Indeed, it may take decades. Medicine must negotiate a precarious bargain—accepting promising, but unproven, therapies for primary prevention, sorting them out in the decades that follow, or, alternatively, setting a high barrier for primary prevention and implementing only preventions that have met the requirement to reduce morbidity and mortality.

The principle of prevention and how we have strayed:

Screening may guide preventive therapy. Primary prevention makes sense when a disease is prevalent, when there is an effective therapy, and when there is evidence that early action leads to

improved clinical outcomes beyond what might be achieved with later treatment. What counts as effective therapy? The examples given above constitute notable failures. There should be evidence from randomized, controlled trials showing that the screening program improves morbidity and mortality. Even for statin drugs, the question remains whether treatment based on screening really reduces morbidity and mortality.

If so, is the cost justified?

Exuberance for cardiovascular prevention has led to recommendations to screen adolescents for hypercholesterolemia. Proponents of this approach must show there is a benefit from this screening. Opponents must not be burdened with demonstrating that harms and costs outweigh benefits.

Beyond cardiovascular screening:

Screening for breast, prostate, and colon cancer decreases cancer-specific mortality. But no prospective trial has shown an overall mortality benefit.

Likely, the relative infrequency of these deaths (compared with CV deaths) would require a very large screening program for a given cancer to show benefit.

Primary prevention of disease is a philosophical question, just as it is a medical question. At what point is it reasonable to screen and institute a novel therapy? This has been a moving target over the past half-century, shifting with advances in treatment as well as social priorities and budgets. In our current climate, based on the lessons of recent pivotal trials, it is time to raise the bar.

Archives Internal Medicine April 23, 2012; 172: 656-59 “Special Article” first author Vinay Prasad, Northwestern University, Chicago, IL

1 Quoted from an editorial comment by Rita F Redberg in this issue of Archives page 659.

