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SCREENING FOR PROSTATE CANCER A STRONG STATEMENT AGAINST ROUTINE SCREENING

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SCREENING MEN FOR PROSTATE AND COLORECTAL CANCER—WHICH IS MOST PRODUCTIVE?

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PREVENTION OF CHD AND STROKE WITH ATORVASTATIN IN PATIENTS WITH LOW CHOLESTEROL

EFFECT OF MULTIVITAMIN AND MINERAL SUPPLEMENTS ON INFECTION AND QUALITY OF LIFE

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HIGHLIGHTS APRIL 2003

4-1 SCREENING FOR PROSTATE CANCER

"Few issues are as controversial." Adequate evidence is absent.

An approach that recommends men should be fully informed of risks and benefits of screening and then asked to make up their own minds is disingenuous when it is clearly difficult for specialists advisors to know the best approach. At present patients are offered an "informed" choice. But, the most informed observer can point only to uncertainty.

"Tests have no meaning without clarity of purpose." The main aim of PC screening is not to detect cancerous tissue, but to identify men who are asymptomatic and would otherwise die or be disadvantaged by untreated PC in the future, perhaps in 10 to 15 years.

The weakness of the case for generalized screening rests on the poorly defined nature of the group identified for treatment. Current predictive values are poor. We still do not understand the natural history of PC well enough to distinguish those in whom disease is likely to progress from those whose pathology presents limited risk in terms of function and survival.

.There is . . . "no justification for screening programmes that expose men who might never be aware of the pathological changes within their prostates, to uncertainties about outcome and to certainties about the disagreeable nature of the treatment process." "Exposing healthy people to treatments with specific hazards and uncertain benefits is unacceptable"

"On the basis of the evidence, national programs of prostate screening are not justified." Screening is a striking instance of therapeutic optimism.

4-2 COLON CANCER SCREENING GUIDELINES

The rationale for offering several choices for screening, which vary widely in their efficacy and cost, is the hope of getting patients and physicians to consider an initial test. "We wanted to present options so physicians and patients can find something mutually agreeable, and increase the screening rate." "You get the biggest bang for the buck from that initial screen."

4-3 SCREENING MEN FOR PROSTATE AND COLORECTAL CANCER IN THE UNITED STATES.

Among men in the USA, PC screening is more common than CRC screening. Men who choose to be screened should be made aware of the known mortality benefit of CRC screening, and the uncertain benefits of screening for prostate cancer.

Men who insist on PSA screening should be informed of the greater benefit of colonoscopy.

4-4 MAMMOGRAPHIC SCREENING FOR BREAST CANCER.

Eight trials have been published. In patients between ages 50 and 69, all reports of studies comparing screening with no screening showed protective effects of screening—a statistically significant 20 to 35 percent reduction in mortality from BC.

The downside: False positive results necessitate further investigation. Nationally, an average of 11% of screening mammograms are read as abnormal. BC is subsequently found in about 3% of these women (0.3% of all mammograms). Thus, a woman has about a 10% chance of a false positive result with each mammogram. Because women are screened repeatedly, the risk of a false positive increases over time. One study estimated that, after 10 mammograms, about half of women age 40 to 64 will have had a false positive leading to needle biopsy or open biopsy in about 20%. The malpractice climate in the USA may work to increase the numbers of false positive reports.

4-5 PROSPECTIVE STUDY OF ALCOHOL CONSUMPTION AND RISK OF DEMENTIA IN OLDER ADULTS

Compared with abstinence, consumption of 1 to 6 drinks weekly was associated with a lower risk of dementia among older adults.

4-6 WEIGHT LOSS COUNSELING REVISITED.

If treatment success is defined exclusively as attaining ideal weight after losing a large amount of weight during a short term intervention, obesity treatment will almost certainly fail. "Obesity must be recognized as a chronic condition for which no cure can reasonably be expected." However, even small weight loss can reduce obesity-associated risk factors for chronic diseases such as diabetes and hypertension.

Physicians must remain non-judgmental and empathetic and distinguish between a “weight problem” and a “patient with a weight problem”. Recognize the challenges and frustrations the patient faces. Many obese patients, especially women, “have come to expect rejection and disparagement . . . and are favorably surprised when they receive the consideration that physicians usually accord patients”.

An initial goal of weight loss of 10% of initial weight during a 6-month period is achievable and can significantly reduce obesity-related conditions. Most patients do not reach their ideal weight. Acceptance of a modest weight-loss is critical to prevent future disappointment. Emphasize the important health benefits and achievability of smaller reductions and help the patient accept a modest weight loss goal at the start of treatment. .

Obesity is a chronic condition requiring long-term care. For those not willing or able to lose, clinicians can help the patient to avoid further weight gain.

Ultimately, prevention is the goal.

4-7 EFFICACY AND SAFETY OF LOW-CARBOHYDRATE DIETS

Despite the abundance of lay literature on the topic of low-carbohydrate (Atkins’) diets, marked discordance exists between the knowledge needed to guide dietary choices and the information that is available in the medical literature.

There is insufficient evidence to make recommendations for or against the use of low-carbohydrate diets. Among the published studies, participant weight loss while using low-carbohydrate diet was principally associated with decreased caloric intake and increased duration, but not with reduced carbohydrate content.

4-8 LOW-CARBOHYDRATE DIETS AND REALITIES OF WEIGHT LOSS

“Without carbohydrate-containing foods (eg, breads) less fat is ingested because few people eat much fat by itself.” Thus, low-carbohydrate diets reduce calorie intake.

A potential advantage of very low-carbohydrate diets is that removing sweets from the diet can reduce the gustatory stimulation that sweets produce. (This gustatory stimulation by sweets easily leads to over consumption.)

The low-carbohydrate diets do reduce consumption of high fructose soft drinks, but do not deal with the preference that many humans have for sweets. “The aspect of carbohydrates as a preference in the diet is one that still needs to be addressed.”

The broader issue of whether a unique diet exists that will produce long-term weight loss has yet to be evaluated. That “a calorie is a calorie” has been reaffirmed. The question of whether patients can adhere more easily to one type of diet or other remains to be answered.

4-9 ALDOSTERONE BLOCKADE AND HEART FAILURE

“The addition of aldosterone antagonists to the regimens of patients with left ventricular systolic dysfunction and ongoing symptoms of heart failure despite optimal treatment with ACE inhibitors and beta-blockers can substantially reduce overall mortality and the rate of sudden death.”

4-10 A CLINICAL PREDICTION RULE TO IDENTIFY PATIENTS WITH ATRIAL FIBRILLATION AND A LOW RISK FOR STROKE WHILE TAKING ASPIRIN

Stroke risk varies greatly in AF patients. This study sought to derive and validate a simple and easily applied clinical rule to identify individuals with non-valvular AF whose stroke risk while taking aspirin is low enough that oral anticoagulation is not necessary.

Irrespective of age, a patient with non-valvular AF without previous stroke or TIA, without hypertension, without symptomatic coronary heart disease or heart failure, and without diabetes can take aspirin for stroke prevention and would not likely benefit from anticoagulation.

Use of the rule would prevent almost one quarter of AF patients, regardless of age, to avoid anticoagulation. Sixteen percent of patients over age 75 were classified as low risk and thus would not be exposed to the risks of anticoagulation.

4- 11 PREVENTION OF CORONARY AND STROKE EVENTS WITH ATORVASTATIN IN HYPERTENSIVE PATIENTS WHO HAVE AVERAGE OR LOWER-THAN-AVERAGE CHOLESTEROL CONCENTRATIONS

In absolute terms, benefits were small, with absolute differences between groups of 0.6% to 2.1%. (NNT [to benefit one patient over 3 years] = 47 to 166.)

"Reaction to the 36% relative reduction in the primary endpoint and the other benefits observed in ASCOT may need to be tempered by consideration of the absolute risk reduction of a coronary event of 3.4 per 1000 patients-years." "There are clearly financial implications." (*As well as adverse events from the drug. RTJ*)

4-12 EFFECT OF MULTIVITAMIN AND MINERAL SUPPLEMENT ON INFECTION AND QUALITY OF LIFE

A daily multivitamin-mineral supplement was associated with reduced incidence of patient-reported infection and related absenteeism in the subset of patients with type 2 diabetes who had a high prevalence of subclinical micronutrient deficiency.

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This month presents updates on three screening procedures widely used in primary care. Mammography and screening for colo-rectal cancer are reaffirmed as beneficial and cost-effective. Primary care clinicians should encourage them. Screening for prostate cancer by prostate specific antigen seems to be losing favor. Primary care clinicians should use utmost discretion when advising screening with PSA. RTJ

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"The Main Aim Of PC Screening Is Not To Detect Cancerous Tissue".

" Screening Is A Striking Instance Of Therapeutic Optimism."

4-1 SCREENING FOR PROSTATE CANCER

"Few issues are as controversial." Adequate evidence is absent. Energetic advocacy goes beyond specialist circles. A mild piece questioning the value of screening written by the editors of the *Western Journal of Medicine* was recently published in the *San Francisco Chronicle.* It provoked vitriolic e-mails because it "challenged the widespread belief in America that every man should know his PSA". Pressure, purportedly public, yet often stemming from special interest groups or enthusiastic journalists, is constantly applied to introduce screening, to reduce screening intervals, and extend age ranges.

Although the same evidence is available to all, differing approaches to the value of screening have appeared. The US Preventive Services Force and the American College of Physicians argue against *any* screening. The American Urological Association and the American Cancer Society recommend screening for *all* men age 50 and older who are expected to live for another 10 years.

An approach that recommends men should be fully informed of risks and benefits of screening and then asked to make up their own minds is disingenuous when it is clearly difficult for specialists advisors to know the best approach. At present patients are offered an "informed" choice. But, the most informed observer can point only to uncertainty. However, "If the criteria cannot support robust decision-making, the intuitive value of early detection and treatment is not readily countermanded."

Men are much more likely to die with, rather than from, PC. Tumor foci have been identified in 30%-40% of men age 60. The median age of onset of symptoms is 72. The life-time risk of dying from PC is about 3%. Only 16% of those with disease detected by screening benefit from radical treatments. In others, the disease would not have compromised their life expectancy or quality of life. "Thus, 84% of treatments for localized disease are done with no prospect of benefit."

Tumor progression is difficult to predict because of the wide variability found in progression with tumors of different grades.

"Tests have no meaning without clarity of purpose." The main aim of PC screening is not to detect cancerous tissue, but to identify men who are asymptomatic and would otherwise die or be disadvantaged by untreated PC in the future, perhaps in 10 to 15 years.

PSA is not diagnostic of PC. Such a diagnosis can be made only after biopsy (which itself brings risk of complications). The validity of PSA as a test for risk of death from PC is not knowable. "Whatever the cutpoint, 8 to 10% of men between ages 50 and 60 will have a raised PSA that would indicate a biopsy. The precise cut point for PSA is controversial. Indeed, at a commonly recommended cutpoint of 4 ug/L, up to 2/3 of PCs are missed. Conversely, many men with levels below 4.0 have PC. "Such concerns about an appropriate cut-off point have led to biopsies now being done in all men with PSA of 3 ug/L and higher."

The weakness of the case for generalized screening rests on the poorly defined nature of the group identified for treatment. Current predictive values are poor. We still do not understand the natural history of PC well enough to distinguish those in whom disease is likely to progress from those whose pathology presents limited risk in terms of function and survival.

The fundamental and unresolved issue is what proportion of cancers identified through screening would have progressed to become life threatening. Radical therapy causes severe urinary incontinence and impotence. There is . . . "no justification for screening programmes that expose men who might never be aware of the pathological changes within their prostates, to uncertainties about outcome and to certainties about the disagreeable nature of the treatment process." "Exposing healthy people to treatments with specific hazards and uncertain benefits is unacceptable"

Are screening programs effective in reducing death from PC? Studies reach different conclusions. One study compared uptake of PSA screening in Seattle-Puget Sound area vs Connecticut. Uptake was much higher in Seattle, but over the period of 1987-1997 there was no difference in mortality from PC between the two areas. However, "The difficulties with calculating causation and treatment benefits on the basis of observational data are well known."

The balance of proof must be high to justify exposing men older than age 50 to a process where, of 1 million men, about 110 000 with raised PSA will face anxiety over possible cancer, about 90 000 will undergo biopsy, and 20 000 will be diagnosed with cancer. If 10 000 of the 20 000 underwent surgery, about 10 would die of the procedure, 300 will develop severe urinary incontinence, and even in the best of hands 4000 will become impotent. The number of men whose prostate cancer would impinge on their lives is unknown.

Screening may benefit the group of men who are asymptomatic, whose screen-detected PC leads to beneficial treatment which otherwise would be denied, The difficulty of identifying men in this category renders the current case for screening very weak.

"On the basis of the evidence, national programs of prostate screening are not justified." Screening is a striking instance of therapeutic optimism.

"At the moment, there is no scientific case for doing routine prostate screening outside research programs designed to assess its effectiveness."

Lancet March 23, 2003; 361: 122-28 Commentary and opinion, first author Stephen Frankel, University of Bristol, UK www.thelancet.com

Comment:

If a man age 60 is screened with PSA and the report comes back "positive" (regardless of the cut-point used) there are several possibilities:

1. The test is a false positive. No cancer is present.
2. The patient has a PC which is so low grade, so slow growing and likely would never lead to death or decreased quality of life.(Ie, the patient dies with and not from the disease.) Nevertheless, he will likely undergo radical treatment with a high likelihood of harm.
3. The patient has an aggressive, high grade, fast growing PC which remains confined to the prostate. Radical treatment may indeed cure.
4. The patient has PC, but it has extended beyond the prostate and is not curable. Medical therapy may benefit.

I believe the patient can be told that possibility 1 is most likely. Possibility 2 leads to harms. Those in category 3 are the ones that keep enthusiasm for screening alive. There is a possibility of cure, although likelihood of an individual fitting this category is low. Those in category 4 have not benefited from screening. RTJ

New Guidelines Stress Importance Of An Initial Screening Test. "You Get The Biggest Bang For The Buck From That Initial Screen."

4-2 COLON CANCER SCREENING GUIDELINES

In February 2003, the US Multisociety Task Force on Colorectal Cancer published an update [1] This replaces the 1997 guidelines and summarizes new developments since 1997.

The initial screen is especially important because it detects the largest, most dangerous polyps which then can be removed. The initial screen helps patients get in the habit of screening, improves chances of early detection of colorectal cancer **(CRC),** and greatly increases the likelihood of survival. "Currently, only a minority of colorectal cancers are caught early."

Screening rates remain low. Although 93% of CRC occur in persons over age 50, in 1999 only about 20% of US men and women over age 50 reported a fecal occult blood **(FOBT)** screen in the past year; 33% reported a colonoscopy in the past 5 years.

A variety of screening methods is available: FOBT ; sigmoidoscopy; combined FOBT and sigmoidoscopy; double-contrast barium enema; and colonoscopy. FOBT slides should not be rehydrated.. Rehydration increases test sensitivity and increases false positives. Readability is unpredictable.

"The rationale for offering these choices, which vary widely in their efficacy and cost, is the hope of getting patients and physicians to consider an initial test." "We wanted to present options so physicians and patients can find something mutually agreeable, and increase the screening rate." "You get the biggest bang for the buck from that initial screen."

The new guidelines for patients over age 50 who are at average risk differ from the 1997 guidelines:

1. Persons at average risk should be offered screening for CRC and adenomas beginning at age50.
2. They should be offered options for screening, with information about advantages and disadvantages associated with each approach. They should be given an opportunity to apply their own preferences.
3. If a screen is positive, a complete colonoscopy should be advised.
4. The screening interval for double-contrast barium enema has been shortened to 5 years (vs the old recommendation of 10 years).
5. Low risk patients with removal of 1 or 2 tubular adenomas less than 1 cm in diameter are now advised to have a follow-up colonoscopy *after 5 years* rather than 3 years. (Adenomas with important pathological characteristics are unlikely to develop in 3 years.)
6. Patients with advanced or multiple (3 or more) adenomas should have a follow-up colonoscopy at 3 years.

JAMA March 5, 2003; 289: 1089-90 "Medical News and Perspective" commentary by Mike Mitka, JAMA staff. www.jama.com

1 *Gastroenterology 2003; 124: 544-560*

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Among Men, PC Screening Is More Common Than CRC Screening Despite The Known Benefits Of The Latter.

4-3 SCREENING MEN FOR PROSTATE AND COLORECTAL CANCER IN THE UNITED STATES.

The prostate specific antigen **(PSA)** has been the subject of great hope and controversy. Some believe that screening with PSA carries the promise of reducing death from prostate cancer **(PC**). Others believe that the overall effect of screening will be more diagnoses of PC and will lead to potentially harmful therapy without any improvement in outcomes.

"There is no valid evidence from randomized trials to help settle this debate." Professional societies are widely divided in their recommendations.

Colorectal cancer **(CRC)** screening, on the other hand, is advocated by all major professional organizations. This unity is based on results of several trials, all of which have shown substantial reductions in CRC mortality in the screened population.

This study compared the prevalence of PSA and CRC screening among US men.

Conclusion: PSA screening is more common the CRC screening.

STUDY

1. In 2001 the Behavioral Risk Factor Surveillance System, an annual population-based telephone survey conducted by the CDC, gathered data on a representative sample of men above age 40.
2. Main outcome = proportion of men ever screened and up to date for both PC and CRC.

RESULTS

1. Men were more likely to report having ever been screened for PC than for CRC; 75% of those over age 50 had been screened with PSA vs 63% for any CRC screening test.
2. PSA screening was particularly common among elderly men; 69% of men age 70-79, and 56% of men age 80 and over[1] reported PSA screening in the past year.
3. Up-to-date PSA screening was also more common. For men age 50 to 69 (the group with the greatest acceptance of screening), 54% reported an up-to-date PSA, vs 45% with an up-to-date CRC screen.
4. Nationally, men in each age group were 15% to 20% more likely to be up-to-date on PSA than on CRC screening.

DISCUSSION

1. Although prostate and colorectal cancers are responsible for comparable numbers of deaths, CRC is responsible for a greater number of *premature* deaths. CRC accounts for 2 ½ times as many years of potential life lost before age 75 as PC.
2. Deaths from CRC were decreased by 14% to 33% in screened groups. “In contrast, no valid randomized trial evidence exists regarding the efficacy of prostate cancer screening.”
3. Why might men be more likely to have PSA screening? It is a simple blood test. Media messages have promoted PSA. Public personalities and even the US Postal Service (in the form of a stamp) have promoted PSA. Men may perceive themselves to be more vulnerable to PC. PC is more common (due in part to PSA testing). Men are more likely to know other men with PC than with CRC, and perceive themselves at higher risk.
4. It is likely that physician’s ordering practices are influenced by these factors, as well as perceived standards of care, meeting patient demand, and avoiding malpractice liability.
5. “Despite findings that most physicians are unsure about the benefits of PSA testing, the large majority routinely order the test.” “On the other hand, although most physicians are aware of strong evidence in favor of colorectal cancer screening, many refrain from recommending testing primarily because of anticipated patient resistance.”
6. “We recommend that physicians ensure that men who chose to be screened for cancer are aware of the known mortality benefit of colorectal cancer screening and the uncertainly about screening for prostate cancer.”
7. “Given the high rates of PSA screening among elderly men, physicians should ensure that elderly men (who are least likely to benefit and who may well be harmed by screening) make a well-informed decision about PSA screening.”

CONCLUSION

Among men in the USA, PC screening is more common than CRC screening. Men who choose to be screened should be made aware of the known mortality benefit of CRC screening, and the uncertain benefits of screening for prostate cancer.

JAMA March 19, 2003; 289: 1414-20 Original investigation, first author Brenda E Sirovich, Dartmouth Medical School, Hanover, New Hampshire. www.jama.com

Comment:

1 Gross overuse at this age. RTJ

Men who insist on PSA screening for PC should be informed of the much greater potential benefits of colonoscopy. RTJ

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Efficacy Of Mammography Is Reaffirmed

4-4 MAMMOGRAPHIC SCREENING FOR BREAST CANCER.

In 1990, for the first time in 25 years, mortality from breast cancer **(BC)** in the USA began dropping. By 1999, the age-adjusted mortality rate was at its lowest level since 1973 (27 per 100 000 population). In 1997, the great majority of women in the USA older than age 40 reported having undergone mammography during the previous year.

Ironically, just as screening (or better treatment or both) seemed to be lowering mortality, questions were raised about the validity of the studies that had led to widespread screening. Two Danish investigators concluded that only three of eight randomized trials were of significant quality to determine the effectiveness of mammography, and the combined results of these 3 trials showed no benefit.[1] This led to confusion about usefulness of mammography.

Women and their physicians need information about risk of the condition being screened for, the effectiveness of the procedure in preventing an untoward outcome such as death, and the potential ill effects of screening, such as false positive tests. (For policymakers, cost effectiveness is important.)

This review article presents clinical information about each of these issues with regard to BC and mammography.

Risk Of Development Of BC And Death From BC Per 1000 Women Over The Next 10 Years (1999):

Age	Cases of invasive BC	Death from BC	Death from any cause
40	15	2	21
50	28	5	55
60	37	7	126
70	43	9	309
80	35	11	670

(Access http://bcra.nci.nih.gov/brc/ for the BC Risk Assessment Tool which can be used to calculate the

5-year risk and life-time risk of individual women.)

Mammography And Mortality From BC:

Eight trials have been published. In patients age between ages 50 and 69, all reports of studies comparing screening with no screening showed protective effects of screening—a statistically significant 20 to 35 percent reductions in mortality from BC.

In-depth independent reviews of the criticisms by the Danish authors conclude that they do not negate the effectiveness of mammography, especially in women over age 50.

The latest analysis of four Swedish trials found that screening was most effective after age 55.

Mammography Of Women In Their 40s:

In general, the effect of screening younger women has been slower to appear and less dramatic than the effect on older women. The denser breast tissue of younger women may lead to reduced sensitivity of mammography. Their BC may spread faster. A meta-analysis of this age group reported that screening reduced 15-year mortality from BC by about 20%

Mammography In Women Older Than Age 70:

Too few older women have been randomized to permit conclusions. One case-control study reported that screening between 65-74 led to a 55% decrease in mortality from BC.

Risks Associated With Mammography:

False positive results necessitate further investigation. Nationally, an average of 11% of screening mammograms are read as abnormal. BC is subsequently found in about 3% of these women (0.3% of all mammograms). Thus, a woman has about a 10% chance of a false positive result with each mammogram. Because women are screened repeatedly, the risk of a false positive increases over time. One study estimated that, after 10 mammograms, about half of women age 40 to 64 will have had a false positive leading to needle biopsy or open biopsy in about 20%. The malpractice climate in the USA may work to increase the numbers of false positive reports.

False positives lead to anxiety and to greater health care visits for both BC and non-BC concerns.

Ductal carcinoma in situ **(DCIS)** was a relatively rare diagnosis before introduction of mammography. In 1998 30 per 100 000 women were so diagnosed. Prognosis is excellent. It may be an example of overdiagnosis—finding early neoplasms which will never become invasive BC. However, DCIS can progress to invasive cancer

Guidelines, Conclusions, And Recommendations:

The US Preventive Services Task Force recommends mammography for women age 40 to 70.

When the benefits of medical interventions are controversial, and when hazards exist, shared decision making is necessary. The clinician provides the facts and the patient assesses the situation according to her personal values.

For women with a family history of BC or ovarian cancer, indications for mammography are stronger.

Discussion about mammography should begin at about age 40 and continue until life expectancy is less than 10 years. Usefulness is strongest for women age 50-69. Screening should be routinely recommended for this age group. For women age 40-49, shared decision making is important. The table cited above may be used to inform

the patient about risk. There is a one-in eight lifetime risk for a new born who lives to age 90. The risk increases with age.

To decrease the risk of false positives, patients should be referred to experienced mammographers whose recall rate is less than 10%. Previous mammograms should be available for comparison. Screening at intervals of 18 months or less also decreases the false positive rate. Indeed, women "should be encouraged to undergo screening more frequently than every 18 months".[2]

NEJM April 24, 2003; 348: 1672-80 "Clinical Practice", review article, first author Suzanne W. Fletcher, Harvard Medical School, Boston, Mass www.nejm.org

1 Lancet 2001; 358: 1340-42

2 This is the first recommendation I have encountered suggesting this frequency of screening.

Comment:

NEJM presents "Clinical Practice" periodically. They highlight a common problem, present evidence supporting various strategies, a review of formal guidelines when they exist, and ends with the author's clinical recommendations.

Two other studies appeared this month in Lancet. Both report benefits.

1. "Mammography Service Screening And Mortality In Breast Cancer Patients: 20-Year Follow-Up Before And After Introduction Of Screening" Lancet April 26, 2003; 361: 1405-10 The 20-year study followed over 210 000 women. Conclusion—"Mammography screening is contributing to substantial reductions in breast cancer mortality in two Swedish counties."

2. "Initiation Of Population-Based Mammography Screening In Dutch Municipalities And Effect On Breast-Cancer Mortality: A Systematic Review" Lancet April 26, 2003; 361: 1411-17 Conclusion—Breast cancer mortality rates in women age 55-74 fell by 20% in 2001 compared with baseline 1986. "Routine mammography screening can reduce breast-cancer mortality rates in women age 55-74 years."

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Another Putative Benefit Of Moderate Alcohol Consumption

4-5 PROSPECTIVE STUDY OF ALCOHOL CONSUMPTION AND RISK OF DEMENTIA IN OLDER ADULTS

Atherosclerotic vascular disease is a risk factor for non-vascular as well as vascular dementia. Because moderate alcohol consumption is associated with a lower risk of cardiovascular disease in the elderly, such consumption might be expected to lower risk of dementia. However, even moderate consumption may have effects that increase dementia risk. Blood alcohol levels as low as 0.02% impair driving ability, and moderate use is associated with a greater risk of cerebral hemorrhage. Based on MRI data, moderate alcohol consumption has been associated with greater brain atrophy, but fewer silent infarcts and less white matter disease.

This study addressed the risk of dementia in a large cohort of adults in whom alcohol consumption was repeatedly reported.

Conclusion: Compared with abstinence, consumption of 1 to 6 drinks weekly was associated with lower risk of incident dementia.

STUDY

1. Cardiovascular Health Cognition Study entered over 3500 community-dwelling subjects in 1991-94. All were over age 65 and without cognitive impairment.
2. All received extensive cognitive testing at baseline. (Mean Mini-mental State Examination score = 28 of possible 30.)
3. Determined self-reported consumption of beer, wine, and liquor.
4. Followed to 1999 for incident dementia. (Mean follow-up = 6 years.)
5. Over the follow-up, 373 subjects developed incident dementia. (Mean age = 77)
6. The present study then compared alcohol consumption in these 373 cases with consumption by 373 matched controls who did not develop dementia.
7. Compared amount of alcohol consumption in the 2 groups.

RESULTS

1. Compared with abstinence, the adjusted odds for dementia in those consuming alcohol weekly:

Alcohol intake less than one drink weekly	0.65	
1 to 6 drinks	0.46	(Lowest odds)
7 to 13 drinks	0.69	
14 or more drinks	1.22	

2. Of 373 subjects who developed dementia, 33 (8.8%) drank 1 to 6 drinks weekly. Of 373 subjects who did not develop dementia, 72 (19.0%) drank 1 to 6 drinks weekly.
   (By my calculation the absolute benefit in reducing risk of dementia associated with 1 to 6 drinks was 10 in 100 over 6 years. [NNT(to benefit one person over 6 years) = 10])
2. There were generally similar relationships of alcohol use in Alzheimer disease and vascular dementia.
3. As expected, lower baseline MMSE scores, previous stroke, diabetes, and APOE e4 allele were more common in the dementia group.
4. The type of alcoholic beverage did not differ significantly.

DISCUSSION

1. "In this case-control study, moderate alcohol consumption had an inverse relationship with risk of dementia, even after multivariate adjustments and exclusion of former drinkers. Abstainers had odds of dementia that were about twice as high as the odds among consumers of between 1 and 6 drinks per week."
2. Previous studies have reported moderate alcohol use is associated with lower prevalence of white matter lesions and subclinical infarcts (thought to be of vascular origin).

CONCLUSION

Compared with abstinence, consumption of 1 to 6 drinks weekly was associated with a lower risk of dementia among older adults.

JAMA March 19, 2003; 289: 1405-13 Original investigation, first author Kenneth J Miasmal, Beth Israel Deaconess Medical Center, Boston, Mass. www.jama.com

Comment:

Many studies have reported a variety of benefits associated with moderate alcohol consumption. All have been observational studies. A prospective randomized, double-blind, placebo control study would be difficult or impossible to attempt. We have all experienced the problems with observational studies – how they may mislead.

Still, I believe moderate drinkers may be told there is likely to be a benefit. RTJ

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Distinguish Between A "Weight Problem" And A "Patient With A Weight Problem" Set Modest Weight-Reduction Goals

4-6 WEIGHT LOSS COUNSELING REVISITED.

Fewer than half of obese patients report being advised to lose weight by their health care professional. Physicians often perceive that obesity treatment is labor intensive and unsuccessful.

Patients who do attempt to lose weight often arrange to do so through commercial or self-help programs, independent of their physician.

If treatment success is defined exclusively as attaining ideal weight after losing a large amount of weight during a short term intervention, obesity treatment will almost certainly fail. "Obesity must be recognized as a chronic condition for which no cure can reasonably be expected." However, even small weight loss can reduce obesity-associated risk factors for chronic diseases such as diabetes and hypertension.The National Institutes of Health's practical tool for organizing weight-loss counseling uses 5 A's:

1) Assess obesity risk; 2) Ask about readiness to lose; 3) Advise in designing a weight-control program; 4) Assist in establishing the appropriate intervention; 5) Arrange follow-up.

Assess Obesity Risk:

1) Anthropometric measurements:

A. Body Mass Index (BMI) weight in kg/ height in meters^2

Overweight --- 25 to 29

Obese – 30 and above.

B. Waist circumference

Men > 102 cm (40")

Women > 88 cm (35")

(Abdominal fat accumulation is a marker for increased cardiovascular disease risk.)

2) Check for obesity related risk factors:

Dyslipidemia, hypertension, smoking, impaired fasting glucose, physical inactivity,

3) Overweight patients and those with a large waist circumference who have 2 or more risk factors are candidates for weight loss.

Ask About Readiness To Lose Weight

Is the patient motivated to lose? Is he willing to invest the considerable time, effort and expense required?

Patients experiencing major life stressors, depression, or eating disorders usually need to address these issues first.

Physicians must remain non-judgmental and empathetic and distinguish between a "weight problem" and a "patient with a weight problem". Recognize the challenges and frustrations the patient faces. Many obese patients, especially women, "have come to expect rejection and disparagement . . . and are favorably surprised when they receive the consideration that physicians usually accord patients".

Most obese patients are well aware of their obesity. They will usually raise their obesity as an issue when they are confident and comfortable with their physician.

Advise In Designing A Program

For patients who are not ready or motivated to lose, clinicians should provide counseling to *maintain* weight. Weight maintenance alone can be considered a partial therapeutic success. Without active intervention, weight gain can be expected.

Ask open-ended questions about the level of interest in losing weight. What behaviors are perceived as contributing to the weight problem, and what confidence the patient has in ability to change these behaviors.

An initial goal of weight loss of 10% of initial weight during a 6-month period is achievable and can significantly reduce obesity-related conditions. Most patients do not reach their ideal weight. Acceptance of a modest weight-loss is critical to prevent future disappointment. Emphasize the important health benefits and achievability of smaller reductions and help the patient accept a modest weight loss goal at the start of treatment. .

Assist In Establishing Appropriate Interventions

The National Institute of Health concluded there is strong evidence that a comprehensive lifestyle program provides the most successful therapy.

Caloric reduction is the cornerstone. A 500 to 1000 daily calorie deficit produces a loss of one to two pounds per week. Very low calorie diets (< 800 kcal/d), compared with 800-1500 kcal/d, show no difference in weight loss at one year because of weight regain. Train the patient to choose low-calorie foods in the grocery store and restaurants, modify cooking methods, and eat smaller portions. Encourage the patient to record food intake. Identify eating habits and foods that contribute to the problem (snacking, overeating at social events, soda consumption), and help patients develop concrete plans for change.

Physical activity is essential for long-term success. Begin walking at a slow pace for 10 minutes 3 times a week and gradually increase to 30-45 minutes 5 times a week , and up to 30-60 minutes daily if feasible.

Professional expertise can be obtained from dieticians, nurse educators, psychologists, and exercise physiologists. Weight-loss programs vary widely in quality and costs. The Partnership for Health Weight Management has developed a model to evaluate programs and compare popular programs.

A web site (www.consumer.gov/weightloss) contains ideas on setting goals, a BMI chart, weight loss brochures, and information on weight loss advertising.

Arrange Follow-Up

Maximum weight loss usually occurs around 6 months after beginning the program. After plateauing,, weight begins to increase. The patient should begin an active weight *maintenance* program about 6 months after initiation of treatment. If weight increases a specific amount, begin a plan for reinstitution of weight loss.

After initial weight loss, clinicians should continue to reinforce patient efforts and treat weight-related behaviors. This requires long-term support and frequent communication. Long-term maintenance of weight loss is often more difficult than initial weight loss. It requires continuous effort.

Pharmacotherapy may provide an adjunct strategy for weight maintenance, but data on safety and effectiveness for more than 2 years are not available.

CONCLUSION

Obesity treatment can be successful if clinicians set modest weight-reduction goals (10% of initial weight), and recognize that obesity is a chronic condition requiring long-term care. For those not willing or able to lose, clinicians can help the patient to avoid further weight gain.

Ultimately, prevention is the goal.

JAMA April 9, 2003; 289: 1747-50 "Contempo Updates" commentary, first author Mary K Serdula, Centers for Disease Control and Prevention, Atlanta, GA. www.jama.com

Comment:

This detailed account may not be an appropriate "practical point for primary care". Since primary care clinicians encounter this problem daily, I believe they should develop some therapeutic approach. This may not be more than gently asking the patient if she believes there is a problem and if she is ready to start doing anything about it.

What about the Adkins's diet (very low carbohydrate)? See the following

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"Insufficient Evidence To Make Recommendations For Or Against"

4-7 EFFICACY AND SAFETY OF LOW-CARBOHYDRATE DIETS

In the 1860s William Banting claimed that, when consuming a low carbohydrate diet, he was never hungry. At age 66, in a period of one year, he lost 46 pounds of his initial 202. He wrote, "The great charms and comfort of the system are that its effects are palpable within a week of trial and create a natural stimulus to persevere for a few weeks more".

Low-carbohydrate diets (**LCD**; as promoted by Dr. Robert Atkins[1]) have now become popular in the USA as a means of rapid weight loss. Millions of copies of Dr. Adkins' books have been sold. Long-term efficacy and safety remain poorly understood. Numerous professional organizations (eg, The American Dietetic Association)

have cautioned against LCD. There are concerns that LCD lead to abnormal metabolic functioning that may have serious medical consequences, particularly for patients with cardiovascular disease, type 2 diabetes, dyslipidemia, and hypertension. The diet causes accumulation of ketones and may result in abnormal metabolism of insulin and impair liver and kidney function.

Advocates claim that diets higher in protein and lower in carbohydrate promote metabolism of adipose tissue in the absence of available dietary carbohydrate. They claim that this results in rapid weight loss without significant long-term adverse effects.

Numerous heterogeneous studies of relatively few subjects have been published without detailed evidence of efficacy or safety. There is no clear consensus as to what amount of carbohydrate per day constitutes a LCD.

This systematic review evaluated changes in weight, lipids, fasting glucose, and serum insulin levels in adults using a LCD in the outpatient setting. Of over 2600 potentially relevant articles, 107 articles describing 94 dietary interventions in over 3200 patients were chosen for this analysis. Of the 3200, 660 subjects received 60 g/day or less of carbohydrates; 71 received 20 g/day or less.

Studies were highly heterogeneous with respect to design, total caloric content, diet duration, and participant characteristics. Only 5 studies evaluated the diets for more than 90 days.

RESULTS

1. Given the heterogeneity of all trials, little can be concluded about the summary mean change in weight when all studies are combined.
2. When only randomized, controlled trials and the randomized cross-over trials are included, statistical analysis suggests that the studies are homogeneous. At the end of both lower- and higher-carbohydrate diets, participants' weight, body mass index, and percentage of body fat decreased.
3. Summary of mean changes in these randomized trials:

	Carbohydrates in diet g/day	
	Less than 60 (7 trials)	Over 60 (75 trials)
Weight changes over all	8 pounds	5 pounds
Weight change		
Intake less than 1500 kcal/d	38	7
Over 1500 kcal/d	11	3
Diet duration		
15 days	13	3
16- 60 days	12	8
Over 60 days	5	2

3. Based on the data, it can be concluded that lowest-carbohydrate diets did *not* result in significantly greater weight loss than lower-carbohydrate diets.
4. When the 22 diets with the greatest mean weight loss (mean > 22 pounds) were considered, they varied widely with respect to carbohydrate content (range 10 to 271 g/day). However these diets 1) restricted caloric intake (mean = 1077 kcal/day), were of 2) longer duration, and included 3) participants who were

significantly overweight at start (mean 222 pounds). "This suggests that these three variables may be more important predictors of weight loss than carbohydrate content."

5. Overall, no change was found in any serum lipid levels. In the more homogeneous group of higher carbohydrate diets, there was a significant *decline* in total cholesterol levels, but not in other lipids.
6. No change was found in either fasting glucose or insulin levels among participants of either lower- or higher-carbohydrate diets—even among those with the greatest weight loss.
7. There was no change in systolic BP.

DISCUSSION

1. The data suggest that there is insufficient evidence to make recommendations for or against the use of these diets. Despite the large numbers of Americans who have apparently adopted this approach to weight loss, we know little of its effects or consequences. In particular, the diets have not been evaluated for use longer than 90 days, for individuals age 53 and over, or for patients with hyperlipidemia, hypertension, or diabetes.
2. The lowest carbohydrate diets (< 20 g/day; the recommended threshold for some of the most popular diets) have been studied in only 71 participants for whom no data on lipids, fasting glucose, and insulin levels, and BP were reported.
3. "We found insufficient evidence to conclude that lower-carbohydrate content is independently associated with greater weight loss compared with higher-carbohydrate content."
4. Diets with restricted calorie intake and longer duration were associated with weight loss. "When lower-carbohydrate diet results in weight loss, it also is likely due to the restriction on calorie intake rather than carbohydrate intake.
5. Significant gaps in the published literature of low-carbohydrate diets exist: long term follow-up is inadequate; no data on effect of the diet among different races and ethnic groups; no data on degree of associated physical activity; no data on how adherence was measured and if counseling or other supportive measures were provided; no data presenting intention-to-treat (ie, many reported only those who completed the studies).

CONCLUSION

Despite the abundance of lay literature on the topic of low-carbohydrate diets, marked discordance exists between the knowledge needed to guide dietary choices and the information that is available in the medical literature.

There is insufficient evidence to make recommendations for or against the use of low-carbohydrate diets. Among the published studies, participant weight loss while using low-carbohydrate dies was principally associated with decreased caloric intake and increased duration, but not with reduced carbohydrate content.

JAMA April 9, 2003; 289: 1837-50 Original investigation, first author Dena M Bravata, Center for Primary Care and Outcome Research, Stanford, Conn. www.jama.com

1 Dr. Atkins tragically died a few months ago as a result of a fall on the ice.

Comment:

Several other articles of interest appear in the current journals:

"A Low Carbohydrate As Compared With A Low-Fat Diet In Severe Obesity" NEJM May 22, 2003; 348: 2074-81 "A Randomized Trial Of A Low-Carbohydrate Diet For Obesity" NEJM May 22, 2003; 348: 2082-90 "Diet, Obesity, And Cardiovascular Risk" NEJM May 22, 2003; 348: 2057-58 (Editorial) "Interpreting Incomplete Data In Studies Of Diet And Weight Loss" (Editorial) NEJM May 22, 2003; 348: 2136-37

These articles express common points when comparing the low CBH diet with the traditional low fat diet:

1) The low CBH diet does indeed lead to more weight loss during the first 6 months. Thereafter weight loss tapers off so the difference in weight loss is no longer significant at 12 months compared with the low fat diet.
2) There is a very high drop-out rate (~ 40%) even in subjects entering an enthusiastic trials. Attrition is high; adherence low. Intention-to-treat analysis is not possible. Bias is likely.
3) The weight loss may be modest compared with the degree of obesity in individual patients.
4) The effect on weight was due to a concomitant reduction in calorie intake. ("Calories still count") This could be due to a) satiety, b) monotony of the diet, c) ketosis. (One study reported that ketosis was prevalent during the first 6 months, but the authors did not consider it a significant factor in weight loss. (However, ketosis does blunt appetite. RTJ)
5) The low CBH diet was *not* associated with any deleterious effects on lipids, at least during the period of the studies. Insulin sensitivity improved.
6) Long-term safety and benefits are unknown.
7) "Any approach to caloric restriction that is not compatible with the daily lifestyle pattern is difficult to maintain long-term."

Would I recommend the LCD to my patients? No. If they wish try it, I would tell them they are strictly on their own. The appeal is in the rapid weight loss. It may be possible after several months for patients to switch to a more sensible diet balancing caloric intake with expenditure in order to try to maintain the loss. RTJ

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Lead To Rapid Weight Loss, But It Is Not Sustained

4-8 LOW-CARBOHYDRATE DIETS AND REALITIES OF WEIGHT LOSS

(This editorial comments and expands on the preceding article.)

"Without carbohydrate-containing foods (eg, breads) less fat is ingested because few people eat much fat by itself." Thus, low-carbohydrate diets automatically reduce calorie intake.

Given the lack of evidence supporting the use of low-carbohydrate diets, why have these diets been such a persistent theme for authors of diet books and such "cash cows" of publishers? One reason is that some of these diets produce quick weight loss, something prized by dieters. Removing carbohydrates from the diet, and thus lowering caloric intake, requires the body to mobilize endogenous glycogen stores from the liver and muscle in order to provide glucose while gluconeogenesis is being activated. Since glycogen stores can account for 5 % of liver weight and 1% of muscle weight, their loss produces solute free intracellular fluid that needs to be excreted.

Thus, the rapid weight loss from low-carbohydrate diets is largely by diuresis. After 7 to 14 days, diuresis ends and the phase of rapid weight loss slows.

The ketosis produced by diets that contain less than 50 g/day of carbohydrate is an index of fatty acid utilization. It can be used to monitor adherence to the diet. One concern about ketosis is that excretion of ketonic anions requires cations that must come from either food or body stores, of which the largest stores are found in bones. Prolonged ketosis may leach cationic minerals from bone.

A potential advantage of very low-carbohydrate diets is that removing sweets from the diet can reduce the gustatory stimulation that sweets produce. (This gustatory stimulation by sweets easily leads to over consumption.) High fructose corn sweeteners were introduced into the food industry at exactly the same time as the prevalence of obesity began to rapidly rise--about 1970. The increase in soft drink consumption parallels the decrease in milk and calcium consumption. The low-carbohydrate diets do reduce consumption of high fructose soft drinks, but do not deal with the preference of many humans have for sweets. “The aspect of carbohydrates as a preference in the diet is one that still needs to be addressed.”

When weight loss reaches a plateau, as it must when neurochemical compensatory mechanisms come into play, many patients become frustrated and conclude that their diet is not working. They have not reached their weight goal. Relapse may follow. But, maintaining weight at a lower plateau over time means that the diet is working.

The broader issue of whether a unique diet exists that will produce long-term weight loss has yet to be evaluated. That “a calorie is a calorie” has been reaffirmed. The question of whether patients can adhere more easily to one type of diet or other remains to be answered.

JAMA April 9, 2003; 289: 1853-55 Editorial by George A Bray, Louisiana State University, Baton Rouge.

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Aldosterone Blockers Benefit When Added To Optimum Drug Therapy In Severe Heart Failure.

4-9 ALDOSTERONE BLOCKADE AND HEART FAILURE

Aldosterone is the sodium retaining-potassium excreting hormone produced by the adrenal.

A study published in 1999[1] proved that antagonism of aldosterone with spirinolactone had an important role in the management of heart failure **(HF**). Spirinolactone is an old inexpensive drug. It reduced mortality, improved ventricular function, and enhanced exercise tolerance.

This issue of NEJM introduces a new aldosterone blocker, eplerenone.[2]

Why is aldosterone blockade effective and in what patients should it be used?

In patients with HF, aldosterone levels may reach 20 times normal due to increased production and reduced hepatic clearance. In addition to being produced by the adrenal glands, aldosterone is synthesized by vascular cells. It induces abnormal vasomotor reactivity. In addition, aldosterone may promote organ fibrosis.

Aldosterone was originally thought to be important in the pathophysiology of HF only insofar as it increased retention of sodium and loss of potassium. It was also believed that optimum doses of ACE inhibitors would

suppress the production of aldosterone since angiotensin II (the product of ACE) is a potent stimulator of aldosterone secretion. In fact, both angiotensin II and aldosterone ultimately escape the effects of long-term ACE inhibititors.

Which patients should receive an aldosterone antagonist?

Guidelines recommend low-dose spirinolactone in patients with symptoms of HF *at rest* despite use of digoxin, diuretics, ACE inhibitor, and a beta-blocker. They caution that use for patients with mild-to-moderate HF has not been tested. Caution is urged in those with base-line elevations of potassium or creatinine. Despite these cautions, anecdotes suggest that spirinolactone has been widely used in patients with HF without consideration of their functional class. The effects on these patients are not known.

"The addition of aldosterone antagonists to the regimens of patients with left ventricular systolic dysfunction and ongoing symptoms of heart failure despite optimal treatment with ACE inhibitors and beta-blockers can substantially reduce overall mortality and the rate of sudden death."

NEJM April 3, 2003; 3348: 1380-82 Editorial by Mariell Jessup, University of Pennsylvania, Philadelphia.

www.nejm.org

1 "The Effect Of Spirinolactone On Morbidity And Mortality In Patients With Severe Heart Failure" NEJM 199;341: 709-17 first author B Pitt. .

2 "Eplerenone, A Selective Aldosterone Blocker, In Patients With Left Ventricular Dysfunction After Myocardial Infarction" NEJM April 3, 2002; 348: 1309-21 first author Bertram Pitt, University of Michigan, Ann Arbor The study concluded that eplerenone (vs placebo), added to optimal medical therapy including ACE inhibitors, reduced morbidity and mortality after MI.

Eplerenone is approved in the US for use in hypertension. It may be associated with fewer adverse effects than spirinolactone. Serious hyperkalemia occurred in 6% of patients. RTJ

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No Previous Stroke, No Hypertension, No Coronary Heart Disease, No Diabetes = Can Use Aspirin

4-10 A CLINICAL PREDICTION RULE TO IDENTIFY PATIENTS WITH ATRIAL FIBRILLATION AND A LOW RISK FOR STROKE WHILE TAKING ASPIRIN

Atrial fibrillation **(AF)** more than quadruples the risk for stroke. Oral anticoagulation is considerably more efficacious than aspirin for preventing stroke in these patients. But, oral anticoagulation is troublesome and has a greater likelihood of complications.

Stroke risk varies greatly in AF patients. This study sought to derive and validate a simple and easily applied clinical rule to identify individuals with non-valvular AF whose stroke risk while taking aspirin is low enough that oral anticoagulation is not necessary. Acceptably low stroke risk was defined as that which did not exceed the observed stroke rate in age-and sex-matched patients in the community as defined by the Framingham Heart Study (previously stroke-free people age 55-84). (*Presumably most of these patients did not have AF. RTJ)*

Risk-stratifications for stroke in AF patients usually consider age since stroke risk rises sharply with age. Risks of anticoagulation also rise with age.

This study presents a clinical prediction rule for use of aspirin which is *independent of age*.

Conclusion: Irrespective of age AF patients with none of the 4 clinical features described who take aspirin had stroke rates comparable to age-matched community-dwelling individuals.

STUDY

1. Included over 2500 adult patients (mean age 70), all with non-valvular AF during 6 clinical trials.
2. All were free of stroke or TIA for at least 6 to 24 months.
3. All received aspirin (75 to 325 mg daily).
4. Primary outcome = stroke or TIA.

RESULTS

1. Overall, 166 patients (6.6%) had an event during over 4600 person-years of observation—equivalent to 3.5 events per 100 person-years. All were taking aspirin.
2. Determined characteristics of patients among the group associated with a low risk of stroke or TIA.
   Patients classified as low risk had *all* of 4 criteria:
   1) No previous stroke or TIA
   2) No treated hypertension or systolic BP > 139 mmHg.
   3) No symptomatic coronary heart disease
   4) No diabetes.

   (Other studies have found an increase in stroke for each of these risk factors in patients with AF.)
3. The prediction rule classified 24% of patients as low-risk.
4. Patients with low risk experienced 1 event per 100 person-years while taking aspirin. This compared with a rate of 1.2 events per100 person-years in the age and sex matched Framingham community cohort.
5. All other patients had an event rate of 4.2 per 100 person-year.

DISCUSSION

1. Using patient characteristics that are readily available at the bedside, the prediction rule identified AF patients whose annual rate of risk of stroke or TIA while receiving aspirin was comparable to that expected in the community. (Ie, a cohort presumably free of AF.)
2. Irrespective of age, a patient with non-valvular AF without previous stroke or TIA, without hypertension, without symptomatic coronary heart disease, and without diabetes can take aspirin for stroke prevention and would not likely benefit from anticoagulation.
3. Use of the rule would prevent almost one quarter of AF patients, regardless of age, to avoid anticoagulation. Sixteen percent of patients over age 75 were classified as low risk and thus would not be exposed to the risks of anticoagulation.
4. Since strokes are more common in patients with AF, and the benefits from aspirin in preventing stroke outweigh risk of gastrointestinal bleeding, it seems prudent to recommend aspirin for these low risk patients.

CONCLUSION

A simple and accurate prediction rule identified patients with AF receiving aspirin who, irrespective of age, had an annual risk of stroke comparable to that expected in the community. This group would not benefit substantially from anticoagulation.

Annals Int Med April 28, 2003; 163: 936=43 Original investigation, first author Carl van Walraven, Ottawa Health Research Institute, Ottawa, Ontario, Canada. www.annals.org

See also "Lessons From The Stroke Prevention In Atrial Fibrillation Trials" Annals Int Med, May 20, 2003; 138: 831-38 Antithrombotic prophylaxis should be individualized on the basis of estimated risk of stroke during aspirin therapy, and the risk for bleeding during anticoagulation. Overall, nearly one third of patients with AF are low risk and should be treated with aspirin; about one third are high risk and should receive warfarin if it can be given safely. For patients at moderate risk, patient preferences and access to reliable anticoagulation monitoring are relevant.

The clinical features that identify high- vs low-risk are similar to those in the preceding article. They add left ventricular dysfunction and heart failure as high-risk markers.

Comment:

I believe this prediction rule may be of clinical importance to patients in primary care. Patients, especially older patients, may be given this information to help their individual preference—aspirin or warfarin? Warfarin therapy imposes burdens. It must be carefully monitored (INR 2 to 3). The risk of intracranial hemorrhage, especially in the elderly, must be carefully considered. I believe many elderly would opt for aspirin. RTJ

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Slight Benefit In High Risk Patients Who Have Only Modest Elevations Of Cholesterol

4- **11 PREVENTION OF CORONARY AND STROKE EVENTS WITH ATORVASTATIN IN HYPERTENSIVE PATIENTS WHO HAVE AVERAGE OR LOWER-THAN-AVERAGE CHOLESTEROL CONCENTRATIONS**

Dyslipidemia is a major independent risk factor for coronary heart disease **(CHD).** Statins lower risk of major coronary events. Evidence for reduction of risk of stroke is less clear, although some trials report a benefit. Benefits from statins have also been reported in patients with total cholesterol levels much lower than average.

"Most cardiovascular events and deaths attributable to raised blood pressure and dyslipidemia occur among patients with blood pressure and lipid concentrations deemed normal"

Lowering cholesterol by about 1.0 mmol/L (~ 40 mg/dL) over 5 years corresponds to about a 25-35% less risk of CHD irrespective of the original cholesterol concentrations. The benefit in reducing risk of cerebrovascular disease is less clear.

When risk factors co-exist, (eg, dyslipidemia and hypertension) the risk is multiplicative. However, relative benefits of lipid lowering are similar among hypertensive and normotensive patients.

This study assessed benefits of the statin drug atorvastatin (*Lipitor*) in *primary* prevention of cardiovascular disease in hypertensive patients who were not considered dyslipidemic by conventional standards.

Conclusion: "The reductions in major cardiovascular events with atorvastatin are large." [1]

STUDY

1. Multicountry, randomized study entered over 10 000 *high risk* patients (age 40 to 79; mean = 63)
   All had hypertension (defined as 160 systolic or more and diastolic as 100 or more; or both if untreated; or 140/90 or more if treated) *and* at least 3 other cardiovascular risk factors: left ventricular hypertrophy, ECG abnormalities, type 2 diabetes, peripheral arterial disease, previous stroke or TIA, male sex, age 55 or over, microalbuminuria, smoking, total cholesterol/HDL-c over 6. (*This is a high risk group, except for only modestly increased cholesterols. RTJ*)
2. All had a total cholesterol levels under 250 mg/dL. (Mean total-c = 210; mean LDL-c = 132)
3. Randomized to:
   1) Atorvastatin 10 mg daily (dose not titrated) + antihypertension treatment, or
   2) Placebo + antihypertension treatment.
4, Primary end-point = non-fatal myocardial infarction + fatal CHD
5. Follow-up was planned for 5 years, but the study was stopped after a median of 3.3 years because of perceived benefit.

RESULTS

1. Atorvastatin lowered total cholesterol from a mean of 210 mg/dL to 161; and LDL-c from a mean of 132 to 89.
2. Changes in HDL-c were minimal.
3. BP was 138/80 in both groups at the end of the trial.
4. Outcomes over 3.3 years

(My calculations RTJ)	Atorvastatin (n = 5168)	Placebo (n = 5137)	Absolute difference	NNT 3 years
Primary endpoint (Non-fatal MI + fatal CHD)	100 (1.9%)	154 (3.0%)	1.1%	91
Total coronary events	178 (3.4%)	247 (4.8%)	1.2%	83
Stroke	89 (1.7%)	121 (2.3%)	0.6%	166
Total cardiovascular events (All statistically significant.)	389 (7.5%)	486 (9.6%)	2.1%	47
Deaths	185 (3.5%)	212 (4.1%)	0.6%	166 ns

5. The benefit emerged in the first year. But *no benefit was apparent among women* (19% of cohort).
6. No significant adverse effects noted.

DISCUSSION

1. "In hypertensive patients who on average were at moderate risk of developing cardiovascular events, cholesterol lowering with atorvastatin 10 mg conferred a 36% reduction in fatal CHD and non fatal myocardial infarction compared with placebo." [1]
2. In absolute terms, benefits were small with absolute differences between groups of 0.6% to 2.1%.

NNT [to benefit one patient over 3 years] = 47 to 166.

2. The apparent lack of benefit in women may have been due to chance. (The number of women entered was relatively small.)
3. "Current guidelines for the use of lipid-lowering agents vary strikingly around the world. Recommendations relating to treatment thresholds have been driven more by cost considerations than by evidence of treatment benefits."
4. "Reaction to the 36% relative reduction in the primary endpoint and the other benefits observed in ASCOT may need to be tempered by consideration of the absolute risk reduction of a coronary event of 3.4 per 1000 patients-years." "There are clearly financial implications."

CONCLUSION

"The reductions in major cardiovascular events with atorvastatin are large,[1] given the short follow-up time. These findings may have implications for future lipid-lowering guidelines "

Lancet April 5, 2003l 361: 1149-58 Original investigation by the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT –LLA) www.thelancet.com

Comment:

1 Investigators and editors of major journals (and I believe, to the delight of marketing departments of drug companies) persist in reporting relative risk reductions (which are misleading) instead of absolute risk reductions and the numbers needed to treat. In this study a 36% reduction = only about 1 out of every 100 patients treated for 3 years. The authors do modify their results in the last paragraph of the discussion.

Lipitor 10 mg daily according to a website pharmacy costs about $2500.00 for 3 years. Patients should be informed that unless they are compliant in taking the drug regularly, they will not benefit. RTJ

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Supplements Were Associated With A Reduced Incidence Of Infection And Related Absenteeism In Participants With Type 2 Diabetes.

4-12 EFFECT OF MULTIVITAMIN AND MINERAL SUPPLEMENT ON INFECTION AND QUALITY OF LIFE

About 40% of adults in the USA use supplements regularly. About half of these take a combination vitamin and mineral product. Little evidence supports the purported health benefits. The extent to which subtle deficiencies of various micronutrients contribute to clinically significant infections is not clear. Some studies indicate that vitamin supplementation may improve various immunologic factors.

This study assessed the effect of a typical once-a-day multivitamin and mineral supplement on risk of acquiring infections and perceived quality-of-life. It was based on prior research reports that indicate that even modest vitamin-mineral deficiencies can impair immune function.

Conclusion: The supplement reduced incidence of patient-reported infection and related absenteeism only in participants with type 2 diabetes.

STUDY

1. Randomized, double-blind, placebo-controlled trial, conducted in primary care clinics, followed 158 community-dwelling adults. All were considered to be relatively healthy.
2. Subjects were stratified by age 45 to 64 (n = 33) and 65 and over (n = 125); and by the presence of type 2 diabetes (n = 51)
3. Assessed nutritional status by a 3-day food diary. Defined nutrient deficiency as intake below the 33rd percentile of the recommended daily allowance for zinc, selenium, iron, folic acid, and vitamins A, C. E, or B6. (Choice of the 33rd percentile was arbitrary.) Thirty three subjects were considered deficient in one or more nutrients.
4. Randomized to: 1) multivitamin vitamin/mineral supplement; or 2) placebo taken once daily. The supplement was similar to that available over-the-counter (without a prescription) at drug stores.
5. Follow-up = 1 year.

RESULTS

1. More patients in the placebo group reported an infectious illness and absenteeism:

2. Overall	Placebo	Supplement
Infectious illness reported	73%	43%
Infection-related absenteeism	57%	21%
3. Subgroups		
Type 2 Diabetes patients (n = 51)		
Infection reported	93%	17%
Infection-related absenteeism	89%	0
No diabetes (n = 79)		
Infection reported	60%	59%
Infection-related absenteeism	35%	33%
Age		
Under 65 (n = 33)		
Infection reported	78%	43%
Infection-related absenteeism	58%	21%
65 and over		
Infection reported	59%	44%
Infection-related absenteeism	53%	19%

3. The infections reported were upper respiratory, influenza-like, gastrointestinal, lower respiratory, and a few urinary tract. Twenty percent experienced more than one infection during the year. None required hospitalization.

4. Quality-of-life scores did not differ between groups. Vitamin supplementation had no effect on physical or mental health scores.

DISCUSSION

1. Supplements had no effect in physical or mental health measures of quality-of-life. “Thus, it seems that multivitamin and mineral supplements do not enhance health or energy level anymore than does placebo.”
2. Benefit was observed almost entirely in participants with type 2 diabetes for whom the magnitude of benefit was dramatic.”
3. Diabetic subjects were more likely than non-diabetic subjects to be deficient in one or more micronutrients. However, the issue of how to define micronutrient deficiency remains unresolved. “We believe, however, that diabetic persons we studied had substantial preexisting micronutrient deficiencies.”
4. The lack of statistically significant benefit in those older than age 65 may have been because the number of subjects was small.
5. “Most participants correctly guessed what they were taking.” However, the investigators believed that this defect in blinding did not influence the results.
6. In certain diabetic samples, perhaps those with a high prevalence of micronutrient deficiency, daily use of a supplement can decrease infection frequency. “These dramatic results warrant testing in a larger clinical trial.

CONCLUSION

A daily multivitamin-mineral supplement was associated with reduced incidence of patient-reported infection and related absenteeism in the subset of patients with type 2 diabetes who had a high prevalence of subclinical micronutrient deficiency.

Annals Int Med March 4, 2003; 138: 365-71 Original investigation, first author Thomas A Barringer, University of North Carolina School of Medicine at Carolinas Medical Center, Charlotte, NC www.annals.org

Comment:

I believe the investigators will agree--this is a provocative, not a definitive study. The possibility of bias is ever present. And note that 28 of the originally randomized 158 subjects did not complete the trial. Compliance will be less in clinical practice.

How should primary care clinicians apply these results? We have no simple, reliable way to determine which of our patients are deficient in vitamins-minerals. I believe most clinicians advise daily supplements to their patients regardless. The benefit/harm-cost of a daily supplement may be very high. (Especially from their vitamin D and folate content.)

It is interesting to speculate which of the vitamin-mineral components of the daily supplement might offer the greatest benefit. I would place folic acid high on the list. RTJ