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HIGHLIGHTS AND *EDITORIAL COMMENTS* MAY 2004

5-1 A LOW-CARBOHYDRATE, KETOGENIC DIET VERSUS A LOW-FAT DIET TO TREAT OBESITY AND HYPERLIPIDEMIA: The Atkin's Diet

Recently, the low-carbohydrate ("low-carb"; **[LC];** Atkin's) diet has gained recognition despite modest supportive scientific evidence of efficacy. A popular version of this diet recommends extreme restriction of carbohydrate intake to less than 20 grams daily. This level can induce ketosis and weight loss.

This randomized trial compared the effects of the LC, ketogenic diet *vs* a low-fat, low-cholesterol reduced-calorie diet.

Over 24 weeks, otherwise healthy obese, hyperlipemic persons who followed a LC diet lost more body weight and fat than those on a low-fat diet. Triglyceride levels decreased; HDL-cholesterol levels increased. The LDL-c increased in some subjects. "Because the low-carbohydrate diet may adversely affect the LDL cholesterol level, it is prudent to monitor the serum lipid profiles. . . ."

The drop-out rate in persons on the LC diet was lower. This is important because the value of any diet depends on the degree to which patients adhere to it over time.

Weight loss in both groups resulted from reduced energy intake. The method of reducing energy intake differed greatly. The low fat diet group received counseling to restrict intake of fat, cholesterol, and energy. The LC diet group received counseling to restrict intake of only carbohydrates, not energy. "The voluntary reduction in energy intake among recipients of the LC diet merits future research."

Further observation is needed to determine the long-term (beyond 6 months) effects of the LC diet. Weight loss may be difficult to maintain. (*A companion study in the issue of the Annals (pp778-85) reported that the weight loss was similar between groups at one year, but benefits on dyslipidemia and glycemic control were maintained. RTJ)*

No matter what the diet, weight loss will vary considerably between individuals. An editorialist suggests that we can encourage overweight patients to experiment with various methods for weight control, including the LC diet, as long as they emphasize healthy sources of fat and protein and incorporate regular physical activity.

"We can no longer dismiss the very-low-carbohydrate diets. "

The determining factor in diet therapy is its effect on long-term (years) weight control. We wait results of these studies, Thus far, it seems doubtful that many persons on the LC diet will maintain their weight loss over time.

I believe studies of the LC diet will be forthcoming as related to diabetes, coronary disease, hypertension, and the metabolic syndrome, as well as obesity. RTJ

5-2 DIASTOLIC HEART FAILURE—Abnormalities Of Active Relaxation And Passive Stiffness Of The Left Ventricle.

This prospective clinical study analyzed measurement of diastolic function (pressures and volumes of the left ventricle) in patients with HF who had a normal ejection fraction.

Patients with HF and a normal ejection fraction (50%) had abnormalities in the diastolic properties of the left ventricle that were sufficient to explain the occurrence of HF. Pressure-volume relations were abnormal during

ventricular relaxation in earliest diastole, and during the entire time of passive ventricular filling the term "diastolic heart failure" can be appropriately used to describe the abnormalities in such patients.

Increased left ventricular stiffness in patients with diastolic heart failure makes them especially vulnerable to the development of pulmonary edema. Significant changes in pressure may be seen with little change in volume of the left ventricle. The ventricle is unable to accept venous return adequately without high diastolic pressures. Such high pressures result in decreased lung compliance, increased work of breathing, dyspnea, and exercise intolerance. Pulmonary edema is the direct consequence of increased passive chamber stiffness.

Patients with diastolic HF have a substantial increase in pulmonary venous pressures during exercise and a significant limitation in exercise tolerance. The non-compliant stiff ventricle has limited ability to use the Frank-Starling mechanism. During exercise, the left ventricle is unable to fill optimally, and despite the increased filling pressure, the cardiac output cannot increase. Exercise intolerance is the direct consequence of abnormal left ventricular diastolic function.

I freely interpreted the pathophysiology the authors described. I believe my interpretation to be accurate, although the article expresses it differently and gives more details. Simply put, in diastolic HF, for every volume of the left ventricle, pressures are higher than normal; and for every pressure, volumes are lower than normal.

I welcomed this article. It clarified my understanding. of diastolic HF It emphasized the importance of control of hypertension as a preventive measure. It did not lead to any suggestions for treatment. Pathological changes in the left ventricular myocardium are yet to be fully described. RTJ

5-3 MANAGEMENT OF DIASTOLIC HEART FAILURE IN OLDER ADULTS

The signs and symptoms of diastolic HF are similar to those of systolic HF. In diastolic HF, the ejection fraction remains normal (> 50%). Both experience volume overload. Distended neck veins are the most reliable sign of overload.

A more specific diagnosis would require documentation of an abnormal left ventricular relaxation pattern. This is often determined by a reduced ratio of early (E) to late (A) filling velocities by Doppler echocardiography The E:A ratio is reduced (<1) in advanced diastolic HF (eg E:A < 0.5). Normal is > 1. The ratio is difficult to assess in patients with atrial fibrillation. (*Ie, in diastolic HF, the early filling is less efficient than the late (atrial contraction) filling. The reverse is normal.)*

There is little evidence from large randomized trials to guide treatment. The author suggests some interventions.

5-4 CARDIORESPIRATORY FITNESS ATTENUATES THE EFFECTS OF THE METABOLIC SYNDROME ON ALL-CAUSE AND CARDIOVASCULAR DISEASE MORTALITY IN MEN

The estimated prevalence of the "metabolic" ("insulin-resistance") syndrome is over 20% among adults in the USA. Middle-aged men with the metabolic syndrome have significantly elevated risk of all-cause and cardiovascular disease **(CVD)** mortality.

It is defined by the *National Cholesterol Education Program* among persons with 3 or more of 5 risk factors:

1. BP at or over 130/85
2. Central obesity—waist circumference > 40 inches in men
3. High triglyceride levels—>150 mg/dL
4. Low HDL-cholesterol— < 40 mg/dL
5. High fasting plasma glucose—at or above 110 mg/dL

After adjustment for age, smoking status, alcohol consumption, and parental CVD, the relative risks **(RR)** of all-cause mortality and CVD mortality were higher in men with the metabolic syndrome who were unfit compared with the fit men. (RR = 2.0 and 2.3)

There was a graded increase in deaths according to fitness categories. Men in the middle tertile of fitness had 2.0 times the CVD death rate as those in the upper tertile of fitness. Those in the lower tertile of fitness had 3.5 times the risk.

The estimated population-attributable risk for CVD deaths in males with the metabolic syndrome is 11%. This suggests that about 1 in 10 CVD deaths are directly attributable to the metabolic syndrome. The public health burden is considerable.

Low cardio-respiratory fitness was an important risk factor for premature mortality in men with the metabolic syndrome. Being fit provides a strong protective effect.

As expected, physical fitness attenuated risk of death in men without the metabolic syndrome as well as those with. I omitted this data.

The study is a reminder of the definition of the metabolic syndrome and its importance as a health risk. I have to periodically jog my memory about the definition lest I forget the 5 requirements.

Fitness also attenuates risks of adverse outcomes in smokers; and in patients with obesity, coronary disease, hypertension, and diabetes. It is a basic health measure about which we continue to advise patients, but which they do not often follow. RTJ

5-5 LIPID-LOWERING THERAPY AND IN-HOSPITAL MORTALITY FOLLOWING MAJOR NON-CARDIAC SURGERY

Lipid-lowering therapy inhibits development of atherosclerotic plaques. It is anti-inflammatory and can improve endothelial function and produce a stabilizing effect on vulnerable plaques. These properties may be especially beneficial in the perioperative period because the disruption of unstable plaques is believed to be responsible for most cases of perioperative MI.

This retrospective cohort study was based on hospital and pharmacy records of over 790 000 patients who underwent major non-cardiac surgery at one of 329 hospitals in the USA.

Lipid-lowering therapy in the first 2 days was associated with a lower mortality: 2.18% of the lipid lowering group died compared with 3.15% of those who did not receive it, or for whom treatment was delayed beyond the first 2 days. The number needed to treat to prevent one death ranged from 30 in patients at high risk of cardiovascular disease to 186 for those at low risk.

What a remarkable effort! A noble attempt, subject to bias and confounding. A provocative study, not definitive—more hypothesis-generating than conclusive.

I suspect that most patients who used statins in the first 2 days were using statins before admission to the hospital for the surgery.

I do not fully understand "propensity matching" It is an attempt to subclassify participants into groups with common attributes. And to determine risk differences within the groups as one would do in a case-control study.

So. . . would you take a statin before undergoing an elective major surgery? Note that patients at the highest cardiovascular risk gained the most benefit. The majority of older persons in the USA have an indication for statin therapy. This being the case, should not many patients facing elective surgery take a statin beforehand? I believe I would. RTJ

5-6 PREVALENCE OF PROSTATE CANCER AMONG MEN WITH A PROSTATE-SPECIFIC ANTIGEN ≤ 4.0 NG PER MILLILITER

This study investigated the prevalence of prostate cancer **(PC)** among 3000 men whose PSA consistently remained at 4.0 or less over 7 years. A prostate biopsy was performed at year 7.

Overall prevalence of PC was a mean of 15%, increasing linearly from 6.6% to 26.9%

Overall prevalence of high-grade PC was a mean of 2.2%, increasing linearly from 1% to 6.7%

The positive predictive value of a PSA less than 4.0 has not been well defined. Previous large studies suggested for men over age 50, a value of 4.0 should be used as the upper limit of the normal range. Another study among men with a PSA 2.6 to 4.0 reported that detection of clinically important PC was the same as that among men with PSA over 4.0 It is not surprising that the predictive value of PSA levels is not known.

"There is no PSA value below which a man can be assured that he has no risk of prostate cancer." This is despite the impression of many clinicians that men with a level under 4.0 (92% of all men) have almost no risk of PC.

"Although the use of PSA testing in the United States has led to earlier diagnosis and a marked shift in the stage at which prostate cancer is identified, it is unclear whether PSA testing reduces the rate of death from prostate cancer."

The uncertain benefits of PSA screening have resulted in different recommendations from policymaking organizations. The large difference between a man's risk of death from PC (3% to 4%) and his lifetime risk of the diagnosis of PC (17%) suggests that many PCs detected in routine practice may be clinically unimportant. Lowering the PSA threshold for proceeding to biopsy would increase the risks of overdiagnosis and overtreating clinically unimportant disease.

In this study, prevalence of PC in asymptomatic men with a PSA level consistently 4.0 and below, the risk of PC ranged from 66 per 1000 men to 269 per 1000 men, depending on level of PSA. And the risk of high-grade PC ranged from about 10 per 1000 men to 67 per 1000 men. Prevalence must be much greater still in men with PSA above 4. This must be the highest prevalence of any asymptomatic cancer, by far.

Progression to clinical disease must be low, since only up to 3% of men die of PC.

Obviously the disease is grossly overdiagnosed and overtreated.

Considering that 92% of men tested have a PSA of 4.0 or less, and that the prevalence of PC in this group varies up to 27%, does it not follow that the great majority of prostate cancers occur in men with a PSA 4.0 or less?

This study, I believe, will encourage primary care clinicians to be more circumspect in recommending routine PSA screening RTJ

5-7 PROSTATE CANCERS IN MEN WITH LOW PSA LEVELS—Must We Find Them?

There is disagreement as to what level of PSA should prompt a biopsy. Controversy stems from a dilemma: 1) Use of higher PSA thresholds risks missing an important cancer until it is too late. 2) Use of lower PSA thresholds increases the number of biopsies and the proportion of biopsies that identify clinically insignificant disease.

It should not be surprising that 10% to 27% of patients age 62 to 91with a PSA of 4.0 or less were found to have PC. Ninety percent of men age over 50 have PSA values 4.0 or less. Thus, quite a few of these men harbor PC. "Although it would be desirable to detect high-grade cancers that are likely to be life threatening in men with PSA below 4.0, the identification of such cancers will require the development of new biomarkers.

The commentator suggests that we should maintain a cutoff point of 4.0 and above for older men, and 2.5 be used for men age 40-50. Men with baseline PSA 1.0 to 4.0 are at significantly higher risk for a diagnosis of PC over the next 10 years than are men whose baseline PSA is below 1.0. Thus, in these men, it makes sense to track the rate of rise in PSA values. This has been shown to correlate directly with the risk of cancer. The cutoff value of PSA that results in 95% sensitivity (detection of 95 % of the cancers) is close to 4.0 for men between ages 50 to 70. The cutoff value of PSA that results in 95% sensitivity for men age 40 to 50 is close to 2.5 Because most of the variability in PSA levels is due to benign prostate enlargement that occurs with age, and men below age 50 are unlikely to have such enlargement, a threshold of 2.5 seems reasonable for men below age 50.

With a PSA in the range of 2.6 to 6.0, younger men are more likely to have curable PC—driven by the fact that younger men are more likely to have less aggressive cancers. The weight of the evidence suggests that the detection of PC at younger ages would have a greater effect on the likelihood of being free from disease after treatment than would the detection of PC in older men.

Men with baseline PSA 1.0 to 4.0 are at significantly higher risk for a diagnosis of PC over the next 10 years than are men whose baseline PSA is below 1.0. Thus, in these men, it makes sense to track the rate of rise in PSA values. This has been shown to correlate directly with the risk of cancer.

Considering the lifetime risk of death from PC is 3%, and the lifetime risk of a diagnosis of PC is 16%, it is apparent that any approach that finds more cancers without quantifying the clinical significance of the detected disease will increase overdiagnosis and overtreatment. This, together with the absence of proof that PSA screening saves lives, suggests that physicians should be circumspect about routinely recommending a prostate biopsy for men over age 50 who have a PSA level 4.0 or less.

Men who present for periodic health examinations should be made aware about the availability of the PSA test/ They should be informed (about risks as well as benefits) so they can make an informed decision about the

need for routine screening. The enthusiasm for screening in general in the USA suggests that most men will decide to be tested.

If up to one fourth of all men over age 62 with a PSA of 4.0 or less have PC, and about 90% of men have PSA below 4.0, it follows that the vast majority of PCs exists in men with a "low" PSA.

Few screening procedures have been more controversial. Undoubtedly screening with PSA has led to extension of life length in some men. I believe it has led to more unnecessary procedures and adverse complications, and has imposed great long-lasting anxiety.

The controversy continues. I believe it more prudent to screen men under age 60 than those above 60. As patients attain greater age, enthusiasm for screening should wane. RTJ

5-8 CARDIAC-RESYNCHRONIZATION THERAPY WITH OR WITHOUT AN IMPLANTABLE DEFIBRILLATOR IN ADVANCED CHRONIC HEART FAILURE

Intraventricular conduction delay is associated with dys-synchronous left ventricular contraction due to regional delays in the electrical activation of the chamber. It occurs in 15% to 30% of patients with heart failure **(HF)** due to dilated cardiomyopathy. It impairs systolic function.

Patients with HF and bundle-branch block have a mechanical disadvantage resulting from abnormal activation of the left ventricle. In these patients, the septum contracts before the lateral left ventricle wall. The lateral wall contracts during relaxation of the septum. This mechanical dysfunction increases left ventricular volume, reduces contractility, and worsens mitral regurgitation. Proper placement of the pacemaker leads permits pacing the right ventricle, the septum, and the lateral wall of the left ventricle simultaneously.

This study assessed the effectiveness of CRT in patients with advanced chronic HF who had intraventricular conduction delays. In the pacemaker group (compared with the drug-only group), CRT resulted in a reduction of death, hospitalization, a slightly higher systolic BP, a slight increase in distance walked in 6 minutes, and improvement in quality-of-life and in the NYHA class.

Note—this applies only to systolic HF.

The purpose of the normal Purkinje subendocardial conducting system is to rapidly conduct the electrical impulse to all parts of the ventricles so that all parts of the myocardium contract simultaneously. CRT is a feeble attempt to mimic this function.

In spite of some incremental improvements in therapy of HF over the past 10 years, prognosis remains miserable. Death and hospitalization for HF continued to increase in the subgroup of patients followed for 3 years. In the CRT group, only about 20% had event-free survival at 3 years, and the death rate increased from 12% at 1 year to about 30% at 3 years. Patients will welcome some improvement in quality-of-life. RTJ

5-9 DYING AND DECISION MAKING—Evolution Of End-Of-Life Options

The editorialist reviews decision-making options at the end of life:

Option	Legal Status	Ethical Consensus	Decision maker
1. Proportionately intensive symptom management	Legal	Consensus	Patient or surrogate.
2. Stopping (or not starting) potentially life saving therapy	Legal	Consensus	Patient or surrogate
3. Sedation to unconsciousness to relieve intractable symptoms	Legal	Uncertain	Patient or surrogate
4. Voluntarily stopping eating and drinking	Legal	Uncertain	Patient only
5. Physician-assisted suicide	Illegal (except in Oregon)	Uncertain	Patient only

5-10 HOMOCYSTEINE LEVELS AND THE RISK OF OSTEOPOROTIC FRACTURE

Homocystinuria is a rare autosomal recessive disease characterized by very high plasma homocystine levels. It is also characterized by early onset of generalized osteoporosis. The underlying pathophysiological mechanism is not completely understood. It may be related to a disturbance in collagen cross-linking in bone.

In the general population, a mildly elevated plasma homocysteine, termed hyper-homocysteinemia, is a common condition. Hyper-homocysteinemia is recognized as a major risk factor for atherosclerotic and thrombotic disease, as well as cognitive impairment, including Alzheimer's disease.

Are mildly elevated homocysteine levels related to age-related fractures?

This study followed over 2400 subjects, all over age 55 (a general, older population) who participated in two separate prospective studies:

When grouped with regard to sex and age-specific quartiles, those in the highest quartile had an increase in risk of fracture twice as high as the risk in the three lower quartiles.

The population-attributable risk of fracture related to a high homocysteine level was estimated at 19%

A companion study "Homocysteine as a Predictive Factor for Hip Fracture in Older Persons" comes to the same conclusion. Compared with the lowest quartile, those in the highest quartile had a greater risk of hip fracture (4 times higher in men and 2 times higher in women).

The authors comment that homocysteine levels are easily modifiable by dietary interventions. The FDA mandate in 1996 led to folic acid fortification of grain products. This has helped reduce the prevalence of low folate levels (< 7 mmol/L) from 22% to 2% and reduce the prevalence of homocysteine concentrations higher than 13 mmol/L from 19% to 10%. It remains to be seen if interventions by supplements will reduce rates of fracture.

Would this study lead primary care clinicians to more strongly advise a daily multivitamin supplement? (In addition to folic acid, supplements contain vitamin B12 and B6 which are also related to a lowering of homocysteine levels.)

Decisions regarding therapy in primary care often do not depend on conclusive evidence of efficacy. They are also based on reasonable assumptions (accepting that observational studies may be misleading), and a judgment of the benefit/harm-cost ratio of the therapy. For daily vitamin supplements, the harm is nil and the cost minimal. Even if the benefit is very modest, it might be reasonable to take them. I would advise older patients that a supplement might reduce risk of fracture and advise them to take a supplement. RTJ

5-11 PREVENTION OF DISABLING AND FATAL STROKES BY SUCCESSFUL CAROTID ENDARTERECTOMY IN PATIENTS WITHOUT RECENT NEUROLOGICAL SYMPTOMS.

Patients with substantial (60-99%) carotid narrowing are at increased risk of stroke. Risk is greater if they are already symptomatic (ie, have recently suffered some relevant neurological symptoms).

Carotid endarterectomy **(CEA)** can remove arterial narrowing. The surgical procedure involves risk of perioperative stroke and death. Moreover, even successful CEA might not permanently eliminate all thromboembolic risk. The balance of risk and long-term benefit is uncertain.

What is the benefit/risk ratio of CEA for *asymptomatic* patients?

Because of the immediate risk of stroke or perioperative death, benefits for CEA did not outweigh that of watchful waiting until after 2 years.

Among patients up to 75 years of age with severe carotid stenosis but no relevant neurological symptoms, CEA reduced incidence of stroke or death over 5 years by about 6%. (This takes into account the 3% perioperative hazard of death or stroke.)

Combining the perioperative events and the non-perioperative strokes, the net 5-year risks were 6.4% *vs* 11.8%. (Absolute difference = 5.4%; NNT = 18). For fatal strokes 2.1% *vs* 4.2% (NNT = 48).

Benefits will exceed risks only if perioperative hazards remain low. Surgical expertise may indeed be improving, but so is medical therapy (scrupulous and compliant regulation of lipids, glucose, BP, and cigarette smoking, as well as appropriate platelet inhibition).

What might the primary care clinician advise patients with asymptomatic carotid stenosis?

You have (at the minimum) one chance in 33 of dying or having a stroke as a result of surgery.

If you survive the operation and do not have a stroke due to the surgery, your prognosis will be more favorable in the next 5 years if you have successful surgery:

A. Chance of having a stroke without surgery is 11% over 5 years. (About one in ten)

B. Chance of having a stroke after successful surgery is 3.8% over 5 years. (About one in 25)

Chances of harm and benefit are equal for the first 2 years.

At your age, there is a much greater chance of your dying of a cause other than stroke. RTJ

5-12 INHALED INSULIN

Insulin can be effective given by inhalation. Two versions, a powder and an aerosol, may be nearing launch.

The bioavailability is 10-15%. The dose equivalent is about three times that of injected insulin. Advantages of inhaled insulin relate to patient preferences. It may improve compliance and result in more patients achieving glycemic control.

5-13 CYCLO-OXYGENASE-2 INHIBITORS VERSUS NON-SELECTIVE NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND CONGESTIVE HEART FAILURE OUTCOMES IN ELDERLY PATIENTS.

Non-selective NSAIDs are associated with an increased risk of heart failure **(HF).** In susceptible individuals, they raise systemic vascular resistance and reduce renal perfusion. BP may be elevated, and edema and HF may result.

The selective COX-2 inhibitors, celecoxib (*Celebrex*) and rofecoxib (*Vioxx*) are reported to be associated with a lower risk of gastrointestinal events than the non-selective NSAIDs. Might they also be associated with fewer cardiovascular and renal complications? Might celecoxib and rofecoxib differ in their risks?

Relative to non-NSAID users, the rate of admission for HF was significantly higher for users of rofecoxib (RR = 1.8) and non-selective NSAIDs (RR = 1.4) , but *not* celecoxib (RR = 1.0)

Patients with a history of HF were much more likely to be admitted for recurrent HF. Those taking celecoxib were more likely to be readmitted than controls (RR = 1.2), but much less likely than those taking non-selective NSAIDs (RR = 2.2) and rofecoxib (RR = 1.8)

The authors state that, in other studies, patients with long-standing hypertension showed greater increases in systolic BP among those receiving rofecoxib compared with those receiving celecoxib.

We too often concentrate on the adverse effects on the gastrointestinal tract, and forget those on the cardiovascular and renal systems.

Although celecoxib may have a slight edge as far as adverse effects are concerned, I would avoid its use (and that of any NSAID) in patients with a history of HF, or at risk of HF (including diastolic HF), as well as patients with hypertension. RTJ

"We can no longer dismiss the very-low-carbohydrate diets. "

5-1 A LOW-CARBOHYDRATE, KETOGENIC DIET VERSUS A LOW-FAT DIET TO TREAT OBESITY AND HYPERLIPIDEMIA: The Atkin's Diet

Fewer than 25% of Americans who attempt to lose weight actually reduce caloric intake and increase exercise as currently recommended. Persons who do lose weight have difficulty maintaining the loss.

Recently, the low-carbohydrate ("low-carb"; **[LC];** Atkin's) diet has gained recognition despite modest supportive scientific evidence of efficacy. Most evidence regarding the LC diet has come from small studies of short duration.

A popular version of this diet recommends extreme restriction of carbohydrate intake to less than 20 grams daily. This level can induce ketosis and weight loss.

This randomized trial compared the effects of the LC, ketogenic diet *vs* a low-fat, low-cholesterol reduced-calorie diet.

Conclusion: The LC diet resulted in better participant retention, greater weight loss, and some improvement in lipid profiles.

STUDY

1. Randomized, controlled trial entered 120 overweight, hyperlipemic volunteers from the community. (mean age 45; body mass index 30 to 60)
2. Randomized to: 1) a LC diet (< 20 grams of carbohydrate daily) + nutritional supplements, exercise recommendations, and group meetings (instructions to restricting carbohydrates, but not energy intake), or 2) a low-fat diet (less than 30% of energy from fat, < 300 mg cholesterol, and a caloric deficit of 500 to 1000, plus exercise recommendations and group meetings).
3. Participants in the LC diet were permitted unlimited amounts of meat, fowl, fish, and shellfish, unlimited eggs, 4 oz hard cheese, 2 cups of salad vegetables (eg, lettuce, spinach, celery), and 1 cup of low-carbohydrate vegetables (eg, broccoli, cauliflower, squash). [As published in a popular diet book.]
3. Measured body weight, body composition, fasting lipid levels, and tolerability.
4. Tested urine for ketones at each visit. Follow-up = 6 months.

RESULTS

1. At 6 months:	Atkin's LC	Low fat	
Completed the study	76 %	57%	
Weight loss	- 12.9%	- 6.7%	
Loss of fat mass	- 9.4 kg	- 4.8 kg	
Loss of fat-free mass	-3.3 kg	- 2.4 kg	
Serum triglycerides	- 74 mg/dL	- 28 mg/dL	
HDL lipoprotein	+ 5.5 mg/dL	- 1.6 mg/dL	
LDL lipoprotein	+ 0.4 mg/dL	- 0.19 mg/dL	(not statistically significant)
BP	-9.6/6.0	- 7.5/5.2	

2. Minor adverse effects were more frequent in the LC diet group (constipation, headache, halitosis, muscle cramps, diarrhea, general weakness) Only one person in the LC group dropped out because of adverse effects.
3. Ketonuria occurred in 86% at 2 weeks and declined to 42% at 24 weeks. (*Probably due to a reduction in compliance*.)

DISCUSSION

1. "Over 24 weeks, a low-carbohydrate diet program led to greater weight loss, reduction in serum triglyceride, and increase in HDL cholesterol compared with a low-fat diet." These effects are similar to those previously reported by 4 smaller randomized, controlled trials of the LC diet.
2. The magnitude of weight loss compares favorably with use of FDA approved medications such as orlistat, and sibutramine.
3. Weight loss in both groups resulted from reduced energy intake. The method of reducing energy intake differed greatly. The low fat diet group received counseling to restrict intake of fat, cholesterol, and energy. The LC diet group received counseling to restrict intake of only carbohydrates, not energy. "The voluntary reduction in energy intake among recipients of the LC diet merits future research."
4. The LC group lost a greater amount of water in the first 2 weeks. This confirms anecdotal reports of diuresis with the LC diet. After the 2 weeks, estimates of body water were similar in both groups.
5. The changes in fat-free mass in both groups were largely explained by changes in total body water, not lean tissue mass.
6. One concern about the LC diet is that the increase in fat intake will have detrimental effects on serum lipids. The LDL-c did increase in some subjects. "Because the low-carbohydrate diet may adversely affect the LDL cholesterol level, it is prudent to monitor the serum lipid profiles. . . ."
7. The changes in weight, BP, and lipid levels suggest that the LC diet may be an effective intervention in persons with the metabolic (insulin-resistance) syndrome. (Previous studies have reported the LC diet was associated with lowering serum glucose and insulin levels.)
8. Dissatisfaction with weight loss may have been the underlying reason for the greater dropout rate in the low-fat group.
9. Further observation is needed to determine the long-term (beyond 6 months) effects of the LC diet. Weight loss may be difficult to maintain. (*A companion study in the issue of the Annals (pp778-85) reported that the weight loss was similar between groups at one year, but benefits on dyslipidemia and glycemic control were maintained. RTJ)*

CONCLUSION

Over 24 weeks, otherwise healthy obese, hyperlipemic persons who followed a LC diet lost more body weight and fat than those on a low-fat diet. Triglyceride levels decreased; HDL-cholesterol levels increased.

Annals Int Med May 18, 2004; 140: 769-77 Original investigation, first author William S Yancy Jr., Duke University Medical Center, Durham, NC. www.annals.org

An editorial in this issue of the Annals (pp 836-37) by Walter C Willett, Harvard School of Pubic Health, comments:

> The lower drop-out rate in persons on the LC diet is important because the value of any diet depends on the degree to which patients adhere to it over time.
>
> What might be the physiological mechanisms of the effects of the LC diet? One hypothesis is that the glycemic load of the food intake is lowered. A high-glycemic load (low-fat) diet increases postprandial glucose levels. A higher insulin response occurs leading to hypoglycemia and hunger. In the LC diet postprandial glucose levels are lower, the insulin response is blunted; hunger is abated. *
>
> Even though the LC diet does not specifically restrict calorie intake, calorie intake must be lower. A lower calorie intake is essential for maintenance of weight loss.
>
> Dr. Atkins deserves credit for his observations. (*He started the revolution despite wide-spread doubt by other authorities RTJ*.) His LC diet has been modified considerably over time to include replacing saturated fat with mono- and poly-unsaturated fats (which reduce LDL-c, platelet aggregation, endothelial dysfunction, and insulin resistance). Evidence suggests that replacing meats with fish, nuts, legumes, and poultry will reduce incidence of diabetes and heart disease, even if the total fat intake remains high. Eating whole grains high in fiber, which is possible while maintaining a relatively low carbohydrate diet, may reduce risk of type 2 diabetes and coronary heart disease. Replacing refined carbohydrates with whole grains, vegetables, and some fruits (eg, apples) will also reduce spikes in glucose and insulin.
>
> No matter what the diet, weight loss will vary considerably between individuals. The editorialist suggests that we can encourage overweight patients to experiment with various methods for weight control, including the LC diet, as long as they emphasize healthy sources of fat and protein and incorporate regular physical activity.
>
> "We can no longer dismiss the very-low-carbohydrate diets. "

Comment:

* *Ketosis also blunts appetite.*

I would be concerned about possible long-term adverse effects of ketosis.

The determining factor in diet therapy is its effect on long-term (years) weight control. We wait results of these studies, Thus far, it seems doubtful that persons on the LC diet will maintain their weight loss over time.

I believe studies of the LC diet will be forthcoming as related to diabetes, coronary disease, hypertension, and the metabolic syndrome as well as obesity. RTJ

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For every volume of the left ventricle, pressures are higher than normal; for every pressure, volumes are lower.

5-2 DIASTOLIC HEART FAILURE—Abnormalities Of Active Relaxation And Passive Stiffness Of The Left Ventricle.

Heart failure **(HF)** can occur in the presence of either a normal or an abnormal left ventricular ejection fraction.

Patients with HF who have a normal ejection fraction differ substantially from those with HF who have a decreased ejection fraction. The pathophysiology of HF in patients with a decreased ejection fraction involves a

predominant (though not isolated) decrease in systolic function. This has justified the use of the term "systolic heart failure". In contrast, the pathophysiology in patients with HF and a normal ejection fraction involves a predominant (though not isolated) abnormality in diastolic function, termed "diastolic heart failure".

This prospective clinical study analyzed measurements of diastolic function (pressures and volumes of the left ventricle) during diastole in patients with HF who had a normal ejection fraction. The investigators hypothesized that these changes are sufficient to explain the signs and symptoms of diastolic HF.

STUDY

1. Prospectively identified 47 patients who met the diagnosis of diastolic HF. All had signs and symptoms of HF, a normal ejection fraction (over 50%), and an increase in left ventricular end diastolic pressure.
2. Ten patients who had no evidence of cardiovascular disease served as controls.
3. Assessed left ventricular diastolic function by cardiac catheterization and echocardiography.
4. Active relaxation of the left ventricle:

   During earliest phase of diastole (the milliseconds between closure of the aortic valve and opening of the mitral valve), no filling of the left ventricle occurs. (The period of isovolumetric relaxation.) It is an active process of the ventricular myocardium. As a consequence of myocardial relaxation, the pressure in the ventricle falls. Normally, pressure falls rapidly. If the myocardium is "stiff", pressure falls less rapidly and does not reach the normal (low) level by the time the mitral valve opens. In all 47 patients with diastolic HF, relaxation was incomplete. The minimal diastolic pressure was 12 mm Hg *vs* 4 mm Hg in controls.
5. Stiffness during passive filling of the left ventricle:

   In patients with diastolic HF, during diastole (after the above phase and during the entire filling phase of the left ventricle), at any given pressure in the left ventricle, the volume was less than normal. The end-diastolic pressure was higher and the end-diastolic volume was lower in patients than in controls.
6. Thus, in diastolic HF, there are abnormalities in volumes and pressures in the *left ventricle*:

	Diastolic HF (n =47)	Normal controls (n = 10)
Pulse rate (beats per min.)	72	72
Volume at minimal diastolic pressure (mL)	51*	55
Volume before atrial contraction (mL)	75**	88
End diastolic volume (mL)	103***	115
Pressure minimum (mm Hg)	12****	4
Pressure pre atrial contraction (mm Hg)	16****	6
End-diastolic pressure (mm Hg)	25****	8

* In most patients with systolic HF, the ventricular is dilated. Not so with diastolic HF. Patients with diastolic HF generally have normal or even small left ventricular volumes.

** Due to stiffness of the left ventricle there was less filling during the period of diastole after the mitral valve opened until the atrium contracted.

*** Even after atrial contraction, filling remained lower than in controls. (*Note the increase in ventricular volume in both groups due to atrial contraction. This augmentation is lost in atrial fibrillation.*

Note also that at the end of diastole, the volume of blood in the ventricle was lower by 12 mL in patients with diastolic HF. Thus if the ejection fraction were 50% in both groups, the absolute ejection volume would be 52 mL vs 58 mL, and the minute volume at a pulse rate of 72 would be 432 mL less in the diastolic HF group than in the control group. RTJ)

**** Pressure remained high throughout diastole.

7. During the entire period of diastole, from beginning isovolumetric relaxation to last millisecond of diastole after atrial contraction, left ventricular filling was impaired and pressures were elevated.

DISCUSSION

1. Patients with HF and a normal ejection fraction (50%) had abnormalities in the diastolic properties of the left ventricle that were sufficient to explain the occurrence of HF. Pressure-volume relations were abnormal during ventricular relaxation in earliest diastole, and during the entire time of passive ventricular filling The term "diastolic heart failure" can be appropriately used to describe the abnormalities in such patients.
2. Left ventricular stiffness in patients with diastolic heart failure makes them especially vulnerable to the development of pulmonary edema. Significant changes in pressure may be seen with little change in volume of the left ventricle. The ventricle is unable to accept venous return adequately without high diastolic pressures. Such high pressures result in decreased lung compliance, increased work of breathing, dyspnea, and exercise intolerance. Pulmonary edema is the direct consequence of increased chamber stiffness.
3. Patients with diastolic HF have a substantial increase in pulmonary venous pressures during exercise. The non-compliant ventricle has limited ability to use the Frank-Starling mechanism. During exercise, the small, stiff left ventricle is unable to fill optimally, and despite the increased filling pressure, the cardiac output cannot increase. Exercise intolerance is the direct consequence of abnormal left ventricular diastolic function.
4. Hypertensive heart disease is the disease process that most often leads to diastolic HF. More than 75% of subjects in studies of diastolic HF had hypertension.
7. Over 1/3 of patients in the current study had left ventricular hypertrophy. Its presence supports, but is not required for the diagnosis.

CONCLUSION

Patients who meet the criteria for diastolic HF have a normal ejection fraction. Abnormal active relaxation of the left ventricle very early in diastole, and decreased compliance during the entire filling phase result in increased ventricular pressures and lower ventricular volumes.

NEJM May6, 2004; 350: 1953-59 Original investigation, first author Michael R Zile, Medical University of South Carolina, Charleston www.nejm.org

Comment:

I freely interpreted the pathophysiology the authors described. I believe my interpretation to be accurate, although the article expresses it differently and gives more details. Simply put, in diastolic HF, for every volume of the left ventricle, pressures are higher than normal; and for every pressure, volumes are lower than normal.

I welcomed this article. It clarified my understanding. of diastolic HF It emphasized the importance of control of hypertension as a preventive measure. It did not lead to any suggestions for treatment. Pathological changes in the left ventricular myocardium are yet to be fully described. RTJ

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5-3 MANAGEMENT OF DIASTOLIC HEART FAILURE IN OLDER ADULTS

The signs and symptoms of diastolic HF are similar to those of systolic HF. In diastolic HF the ejection fraction remains normal, > 50%.

Both experience volume overload. Distended neck veins are the most reliable sign of overload.

A more specific diagnosis would require documentation of an abnormal left ventricular relaxation pattern. This is often determined by a reduced ratio of early (E) to late (A) filling velocities by Doppler echocardiography

The E:A ratio is reduced in advanced diastolic HF (eg E:A < 0.5). Normal is > 1. The ratio is difficult to assess in patients with atrial fibrillation. (*Ie, In diastolic HF, the early filling is less efficient than the late filling due to atrial contraction. The reverse is normal.)*

There is little evidence from large randomized trials to guide treatment. The author suggests some interventions:

Control BP. At least to < 145/85.

Begin with an angiotensin inhibitor.

Add a beta-blocker if the patient has coronary artery disease or atrial fibrillation.

Be cautious about diuretics. Excessive diuresis may reduce stroke volume.

Use digitalis only if symptoms persist in spite of other drugs.

Recheck weight daily. Gain of 1-2 kg over 2 to 3 days is an early sign of fluid overload. Extra doses of a diuretic may be taken to regain the baseline weight.

Counsel patient on salt and fluid restriction, smoking cessation, cutting down on alcohol, avoidance of NSAIDs. Physical activity should be as tolerated.

BMJ May 8, 2004; 328: 1114. "10 Minute Consultation", "Problems in Primary Care", commentary by Ali Ahmed, University of Alabama, Birmingham USA. www.bmj.org

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Low cardio-respiratory fitness—an important risk factor for premature mortality in men with the metabolic syndrome.

5-4 CARDIORESPIRATORY FITNESS ATTENUATES THE EFFECTS OF THE METABOLIC SYNDROME ON ALL-CAUSE AND CARDIOVASCULAR DISEASE MORTALITY IN MEN

The estimated prevalence of the "metabolic" ("insulin-resistance") syndrome is over 20% among adults in the USA. Middle-aged men with the metabolic syndrome have significantly elevated risk of all-cause and cardiovascular disease **(CVD)** mortality.

It is defined by the *National Cholesterol Education Program* among persons with 3 or more of 5 risk factors:

1. BP at or over 130/85
2. Central obesity—waist circumference > 40 inches in men
3. High triglyceride levels—>150 mg/dL
4. Low HDL-cholesterol— < 40 mg/dL
5. High fasting plasma glucose—at or above 110 mg/dL

Treatment guidelines include weight loss, and increased physical activity.

This study asks: In men with the metabolic syndrome, does cardiorespiratory fitness **(CRF)** attenuate risks?

Conclusion: A higher degree of CRF protected against mortality.

STUDY

1. Entered over 3500 otherwise healthy men mean age 45.
2. Determined CRF by time to exhaustion on a treadmill. (Maximum treadmill time is highly correlated with directly measured maximum oxygen uptake.)
3. Participants were assigned a fitness category according to time of the treadmill:
   1) Unfit—the lowest quintile
   2) Fit—the 2,3,4 , and 5^{th} quintiles.
4. Followed-up for mortality in the 5 groups.

RESULTS

1. A total of 480 deaths occurred over 196 000 man-years.
2. After adjustment for age, smoking status, alcohol consumption, and parental CVD, the relative risks **(RR)** of all-cause mortality and CVD mortality were higher in men with the metabolic syndrome who were unfit compared with the fit men. (RR = 2.0 and 2.3)
3. Relative risks:

	All-cause mortality	CVD mortality
Fit men (referent)	1.00	1.00
Unfit men	2.01	2.25

4. Deaths per 10 000 man-years (unfit vs fit):

	Unfit men	Fit men
All-cause deaths	65	28
CVD deaths	31	12

5. There was a graded increase in deaths according to fitness categories. Men in the middle tertile of fitness had 2.0 times the CVD death rate as those in the upper tertile of fitness Those in the lower tertile of fitness had 3.5 times the risk compared with those in the upper tertile.

DISCUSSION

1. Among men with the metabolic syndrome, the unfit were much more likely to die from all causes and from CVD than fit men. (CRF attenuates the risk.)

2. There was a dose response. Mortality among those in the highest tertile of fitness was much lower than those in the middle and lowest tertiles of fitness.
3. This supports the notion that fitness is an independent determinant of health status, regardless of body weight.
4. The estimated population-attributable risk of CVD deaths in men with the metabolic syndrome is 11%. This suggests that about one in 10 CVD deaths is directly attributable to the metabolic syndrome. The public health burden is considerable.

CONCLUSION

The metabolic syndrome was significantly associated with mortality. Low cardio-respiratory fitness was an important risk factor for premature mortality in men with the metabolic syndrome. Being fit provided a strong protective effect.

Archives Int Med May 24, 2004; 164: 1092-97 Original investigation, first author Peter T Katzmarzyk, Queen's University, Ontario, Canada. www.archinternmed.com

Comment:

As expected, physical fitness attenuated risk of death in men without the metabolic syndrome as well as those with. I omitted this data.

The study is a reminder of the definition of the metabolic syndrome and its importance as a health risk. I have to periodically jog my memory about the definition lest I forget the 5 requirements.

Fitness also attenuates risks of adverse outcomes in patients with obesity, coronary disease, hypertension, and diabetes, and in smokers.

Fitness is a basic health measure about which we continue to advise patients, but which they do not often follow. RTJ

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Statins may reduce risk of perioperative death

5-5 LIPID-LOWERING THERAPY AND IN-HOSPITAL MORTALITY FOLLOWING MAJOR NON-CARDIAC SURGERY

Among patients undergoing major non-cardiac surgery the overall incidence of perioperative myocardial infarction **(MI)** is 2% to 3%. It may be up to 34% in high risk populations such as those undergoing vascular surgery.

Although perioperative beta-blockade is a major therapeutic advance, prevention strategies remain limited. The risk of MI remains even in those taking beta-blockers, especially in high-risk patients.

Lipid-lowering therapy inhibits development of atherosclerotic plaques. It is anti-inflammatory and can improve endothelial function and produce a stabilizing effect on vulnerable plaques. These properties may be especially beneficial in the perioperative period because the disruption of unstable plaques is believed to be responsible for most cases of perioperative MI.

This study examined the association between perioperative treatment with lipid-lowering drugs and in-hospital mortality following major non-cardiac surgery.

Conclusion: Immediate treatment with lipid-lowering agents in the first 2 days after surgery may reduce risk of death following major non-cardiac surgery.

STUDY

1. Retrospective cohort study was based on hospital and pharmacy records of over 790 000 patients (median age 64) who underwent major non-cardiac surgery at one of 329 hospitals in the USA. This included orthopedic, abdominal, gynecologic, urologic, neurosurgical, otolaryngologic, plastic, and transplant surgery.
2. Only patients who survived to at least the second hospital day after surgery were included.
3. Patients were "propensity matched" to adjust for numerous baseline differences.
4. Determined treatment with lipid-lowering agents at anytime during the hospitalization. Patients were divided into 2 groups: 1) Treated group—those receiving lipid-lowering therapy on the first or second postoperative day (n = 77 000), and 2) Non-treated group—those not receiving any lipid-lowering therapy and those who received it after the 2nd day. (n = 703 000). About ¼ of patients with ischemic heart disease received treatment in the early postoperative period.
5. The lipid-lowering drug used was overwhelmingly a statin (91%) either alone or in combination with another drug.
7. Patients treated on the first or second day were categorized as having received either statin-based or non-statin based therapy. Those who received combination therapy were analyzed in the statin group.
8. Major outcome measure = in-hospital mortality.

RESULTS

1. Over 20 000 patients (3%) died during the hospitalization.
2. Lipid-lowering therapy in the first 2 days was associated with a lower mortality: 2.18% of the lipid lowering group died compared with 3.15% of those who did not receive it, or for whom treatment was delayed beyond the first 2 days.
3. After adjustment, the odds ratio of mortality was 0.62 in the treated group *vs* the non-treated group.
4. The number needed to treat to prevent one death ranged from 30 in patients at high risk of cardiovascular disease to 186 for those at low risk.
5. About 10% of the patients were taking a non-statin lipid-lowering drug in the first two postoperative days. Compared with those taking a statin, outcomes were less favorable (mortality was 2.5% vs 2.2%).

DISCUSSION

1. In this large observational study, administration of lipid-lowering therapy during the first 2 days after major surgery was associated with a 1% absolute reduction in hospital mortality in patients undergoing major non-cardiac surgery.

2. “Our findings suggest that lipid-lowering therapy may represent an important addition to the limited armamentarium of the perioperative consultant. “
3. What might be the mechanism? In time frames of 4 to 8 weeks, statins have been shown to reduce platelet aggregation, improve endothelial-dependent vasodilation, and lower levels of C-reactive protein. Statins may reduce coronary artery plaque formation and stabilize existing plaques during periods of stress.
4. The authors were not able to determine how far in advance of surgery drugs might be needed to bring about the favorable effect. Many of the patients receiving lipid-lowering drugs in the immediate postoperative period were likely receiving them beforehand as outpatients. The authors do not state how many.
5. The authors do not claim that the association is causal. Clinical trials are necessary to determine any relationship.

CONCLUSION

Treatment with lipid-lowering agents may reduce risk of death following major non-cardiac surgery.

JAMA May 5, 2004; 291: 2092-99 Original investigation, first author Peter K Lindenauer, Baystate Medical Center, Springfield, Mass. www.jama.com

Comment:

What a remarkable effort! A noble attempt, subject to bias and confounding. A provocative study, not definitive—more hypothesis-generating than conclusive.

I suspect that most patients who used statins in the first 2 days were using statins before admission to the hospital for the surgery

I do not fully understand “propensity matching” It is an attempt to subclassify participants into groups with common attributes. And to determine risk differences within the groups as one would do in a case-control study.

So. . . would you take a statin before undergoing elective major surgery and in the postoperative period? Note that patients at the highest cardiovascular risk gained the most benefit. The majority of older persons in the USA have an indication for statin therapy. This being the case, should not many patients facing elective surgery take a statin beforehand? I believe I would. RTJ

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“There is no PSA value below which a man can be assured that he has no risk of prostate cancer.”

5-6 PREVALENCE OF PROSTATE CANCER AMONG MEN WITH A PROSTATE-SPECIFIC ANTIGEN ≤ 4/0 NG PER MILLILITER

The potential of PSA as a screening test was recognized after the test was introduced in 1979. Disease detection subsequently increased dramatically. Experience led to the consensus that a PSA level of more than 4.0 ng/mL had predictive value for the diagnosis of PC. More recently, data suggest that a level of 2.5 ng/mL has a predictive value similar to that of 4.0 ng/mL. The optimal upper limit of the normal range of prostate-specific antigen **(PSA)** is unknown.

This study investigated the prevalence of prostate cancer **(PC)** among men whose PSA consistently remained at 4.0 or less over 7 years.

Conclusion: PC, including high-grade PC, is not rare among men with a PSA below 4.0

STUDY

1. Enrolled over 18 500 men in a prevention trial. Half (9500—the placebo control group of the study) were randomly assigned to an annual measurement of PSA and a digital rectal examination. During follow-up, an abnormal digital rectal exam or a PSA over 4.0 led to recommendation for a biopsy.
2. Among these 9500, 2950 never had a PSA over 4.0 or an abnormal rectal examination. None had undergone a prostate biopsy or a transurethral resection.
3. All 2950 men (age 62 to 91) had a final PSA determination (which remained under 4.0) and underwent prostate biopsy after being in the study for 7 years.

RESULTS

1. Of the 2950 men, PC was diagnosed in 449 (15.2%) The majority of PCs detected in this group had a Gleason score of 6.0, a value associated with an increased risk of disease progression
2. 67 (15%) of the 449 had high grade cancer (Gleason score of 7 or higher). (*2.2% of the 2950.)*
3. Risk of PC *per 1000* men with varying PSA values:*

Under 0.5	0.6 to 1.0	1.1 to 2.0	2.1 to 3.0	3.1 to 4.0
66	101	170	238	269

(Overall prevalence was a mean of 15%, increasing linearly from 6.6% to 26.9%)

4. Risk of high-grade PC (Gleason grade 7 or higher) *per 1000* men according to varying PSA values:*

Under 0.5	0.6 to 1.0	1.1 to 2.0	2.1 to 3.0	3.1 to 4.0
8	10	20	45	67

(Overall prevalence was a mean of 2.2% increasing linearly to 6.7%)

5. Risk of PC *per 1000* men according to age at time of biopsy:**

62-65	66-70	71-75	Over 75
147	138	172	153

(*Overall prevalence did not appear to appreciably increase with age. This is surprising. RTJ*)

(My calculations from table 2 p 2243. ** My calculations from table 1 p 2241)*

DISCUSSION

1. In one of the first reported series of PSA screening, PC was detected in 22% of men with a PSA 4.0 to 9.9; and in 67% of men with a PSA 10 or more. In a subsequent study, PC was detected in 26% and 50% respectively. After these reports there was a dramatic increase in the detection of prostate cancer.
2. The positive predictive value of a PSA less than 4.0 has not been well defined. Previous large studies suggested for men over age 50, a value of 4.0 should be used as the upper limit of the normal range. Another study among men with a PSA 2.6 to 4.0 reported that detection of clinically important PC was the same as

that among men with a PSA over 4.0. The appropriate upper limit has been confounded by changes in the biopsy procedures. It is not surprising that the predictive value of PSA levels is not known.

3. "There is no PSA value below which a man can be assured that he has no risk of prostate cancer." This is despite the impression of many clinicians that men with a level under 4.0 (92% of all men[1]) have almost no risk of PC.
4. "Although the use of PSA testing in the United States has led to earlier diagnosis and a marked shift in the stage at which prostate cancer is identified, it is unclear whether PSA testing reduces the rate of death from prostate cancer."
5. The uncertain benefits of PSA screening have resulted in different recommendations from policymaking organizations. The large difference between a man's risk of death from PC (3% to 4%) and his lifetime risk of the diagnosis of PC (17%) suggests that many PCs detected in routine practice may be clinically unimportant Lowering the PSA threshold for proceeding to biopsy would increase the risks of overdiagnosis and overtreating clinically unimportant disease.

Conclusion

Biopsy-detected PC, including high-grade cancers, is not rare among men with a PSA level of 4.0 ng/mL or less—levels generally thought to be in the normal range.

NEJM May 27, 2004; 350: 2239-46 Original investigation from The Prostate Cancer Prevention Trial, first author Ian M Thompson, University of Texas Health Sciences Center at San Antonio www.nejm.org

Comment:

1 *Considering that 92% of men tested have a PSA of 4.0 or less, and that the prevalence of PC in this group varies from 6% to 27%, does it not follow that the great majority of prostate cancers occur in men with a PSA 4.0 or less?*

In this study, prevalence of PC in asymptomatic men age 62-91 with a PSA level consistently 4.0 and below, the risk of PC ranged from 66 per 1000 men to 269 per 1000 men, depending on level of PSA. And the risk of high-grade PC ranged from about 10 per 1000 men to 67 per 1000 men. This must be the highest prevalence of any asymptomatic cancer, by far. Prevalence must be much greater in men with PSA above 4.

Progression to clinical disease must be low, since only up to 3% of men die of PC.

Obviously the disease is grossly overdiagnosed and overtreated.

This study, I believe, will discourage more primary care clinicians from routinely recommending PSA screening. RTJ

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Cutoff Point of 4.0 for men over 50; 2.5 for men under 50

5-7 PROSTATE CANCERS IN MEN WITH LOW PSA LEVELS—Must We Find Them?

Today, with the widespread use of PSA screening, most prostate cancers are identified at an earlier stage, and can be treated effectively. Once PSA screening became widespread, the rate of death from PC declined. "It is

difficult to believe that earlier detection has no effect on the continued decline in mortality, given the 50% to 70% decline in incidence of distant disease between 1986 and 1999 among men 50 years of age or older." There is disagreement as to what level of PSA should prompt a biopsy.

Controversy stems from a dilemma:

1) Use of higher PSA thresholds risks missing an important cancer until it is too late.
2) Use of lower PSA thresholds increases the number of biopsies and the proportion of biopsies that identify clinically insignificant disease

Should we now recommend lowering the threshold for biopsy? (under 4.0) The editorialist believes not:

1) It should not be surprising that 10% to 27% of patients age 62 to 91with a PSA of 4.0 or less were found to have PC. Ninety percent of men age over 50 have PSA values 4.0 or less. Thus, quite a few of these men harbor PC.[1] "Although it would be desirable to detect high-grade cancers that are likely to be life threatening in men with PSA below 4.0, the identification of such cancers will require the development of new biomarkers.
2) PCs detected at a lower PSA are more likely to have a small volume (less than 0.5 mL) and to be low grade. They are more likely to be clinically insignificant. Only cancers that are much larger than 1 mL in volume and are poorly differentiated are associated with metastatic disease. Unexpected detection of cancer at lower PSA levels is more likely to identify disease for which treatment may be unnecessary.
3) There is no convincing evidence that, with contemporary therapy, men who are treated when their cancers are detected at PSA levels at or below 4.0 have better outcomes than men who are treated when the PSA is slightly higher than 4.0. "In short, detection of prostate cancer at a PSA threshold lower than 4.0 has not been shown to improve the disease-free outcome." With a PSA in the range of 2.6 to 6.0, younger men are more likely to have curable PC—driven by the fact that younger men are more likely to have less aggressive cancers. The weight of the evidence suggests that the detection of PC at younger ages would have a greater effect on the likelihood of being free from disease after treatment than would the detection of PC in older men.
4) Men with baseline PSA 1.0 to 4.0 are at significantly higher risk for a diagnosis of PC over the next 10 years than are men whose baseline PSA is below 1.0. Thus, in these men, it makes sense to track the rate of rise in PSA values. This has been shown to correlate directly with the risk of cancer. The cutoff value of PSA that results in 95% sensitivity (detection of 95 % of the cancers) is close to 4.0 for men between ages 50 to 70. The cutoff value of PSA that results in 95% sensitivity for men age 40 to 50 is close to 2.5 Because most of the variability in PSA levels is due to benign prostate enlargement that occurs with age, and men below age 50 are unlikely to have such enlargement, a threshold of 2.5 seems reasonable for men below age 50.
5) Considering the lifetime risk of death from PC is 3%, and the lifetime risk of a diagnosis of PC is 16%, it is apparent that any approach that finds more cancers without quantifying the clinical significance of the detected disease will increase overdiagnosis and overtreatment. This, together with the absence

of proof that PSA screening saves lives, suggests that physicians should be circumspect about routinely recommending a prostate biopsy for men over age 50 who have a PSA level 4.0 or less.

Men who present for periodic health examinations should be made aware about the availability of the PSA test. They should be informed (about risks as well as benefits) so they can make an informed decision about the need for routine screening. The enthusiasm for screening in general in the USA suggests that most men will decide to be tested.

NEJM May 27, 2004; 350: 2292-94 Editorial by H Ballentine Carter, Johns Hopkins School of Medicine, Baltimore MD. www.nejam.org

Comment:

1 If u*p to one fourth of all men over age 62 with a PSA of 4.0 or less have PC, and about 90% of men have PSA below 4.0, it follows that the vast majority of PCs exists in men with a "low" PSA.*

Few screening procedures have been more controversial. Undoubtedly screening with PSA has led to extension of life length in some men. I believe it has led to comparatively more unnecessary procedures and adverse complications, and has imposed great long-lasting anxiety.

The controversy continues. I believe it more prudent to screen men under age 60 than those above 60. As patients attain greater age, enthusiasm for screening should wane. RTJ

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Attempting to repair a damaged Purkinje conducting system electrically

5-8 CARDIAC-RESYNCHRONIZATION THERAPY WITH OR WITHOUT AN IMPLANTABLE DEFIBRILLATOR IN ADVANCED CHRONIC HEART FAILURE

Intraventricular conduction delay is associated with dys-synchronous left ventricular contraction due to regional delays in the electrical activation of the chamber. It occurs in 15% to 30% of patients with heart failure **(HF)** due to dilated cardiomyopathy. It impairs systolic function.

Biventricular stimulation (cardiac-resynchronization therapy; **CRT**) synchronizes the activation of the intraventricular septum and the left ventricular wall. It improves left ventricular systolic function.

This study assessed the effectiveness of CRT in patients with advanced chronic HF who had left intraventricular conduction delays.

Conclusion: In patients with advanced HF and a prolonged QRS interval, CRT decreased the combined risk of death and hospitalization.

STUDY

1. Enrolled over 1500 patients with advanced HF (NYHA class III or IV) due to ischemic heart disease or non-ischemic cardiomyopathy. All had a QRS interval of at least 120 msec (mean = 160 msec; left bundle branch block), an ejection fraction of 0.35 or less (mean = 0.20), sinus rhythm, and a hospitalization for HF in the preceding 12 months. Mean age was 67 years. Mean duration of HF = 3.5 years.

2. Randomized to: 1) optimal drug therapy (diuretics, ACE-inhibitors, beta-blockers, and spirinolactone as tolerated), or 2) CRT with a pacemaker combined with optimal drug therapy.
3. The pacemaker leads were placed in the right ventricular apex and in a lateral branch of the coronary sinus vein. Proper setting and timing of the leads permitted simultaneous contraction of the septum and the lateral left ventricular wall.
4. Primary composite endpoint = time to death or hospitalization from any cause.

(I omitted the details on the combined CRT-defibrillator outcomes to concentrate on the CRT application. RTJ)

RESULTS

1. Compared with optimal pharmacologic therapy, CRT reduced the risk of the primary end point (hazard ratio = 0.8). Risk of death or hospitalization from HF was reduced by 34%. And risk of death from any cause by 24%.

2. Outcomes at 12 months:	Drug only (%)	Pacemaker (%)	Absolute difference (%)	NNT*
Death or hospitalization from any cause	68	56	12	8
Death from any cause	19	15	4	25

(* Number needed to treat to benefit one patient over 1 year.)

3. In the pacemaker group (compared with the drug-only group), CRT resulted in a slightly higher systolic BP, a slight increase in distance walked in 6 minutes, and improvement in quality-of-life and in the NYHA class.
4. About 2/3 of patients in each group had a moderate-to-severe adverse event. Implantation was successful in 87%. Events related to the pacemaker-implantation procedure occurred in 10%, including coronary venous dissection, coronary venous perforation, and coronary venous tamponade. Five deaths occurred.

DISCUSSION

1. "Our results indicate that the use of biventricular stimulation to resynchronize left ventricular contraction can improve major clinical outcomes in patients with a prolonged QRS interval and advanced symptomatic heart failure as a result of moderate-to-severe left ventricular systolic dysfunction."
2. Much of the benefit was related to the favorable effects on systolic function. (*I could not find any reference to improvement in ejection fraction. RTJ*)

CONCLUSION

In select patients with advanced HF and a prolonged QRS interval, CRT with a pacemaker improved the clinical course of chronic HF due to dilated cardiomyopathy.

NEJM May 20, 2004; 350: 2140-50 Original investigation by the "Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators, first author Michael R Bristow, University of Colorado Health Sciences Center, Denver. www.nejm.org

A companion editorial in this issue of NEJM "Electromechanical Associations" first author Joseph G Rogers, Washington University School of Medicine, St. Louis comments and clarifies:

Further benefit from drugs that antagonize neruo-humoral pathways is unlikely to be achieved.

At least half of patients with HF die suddenly.

Patients with HF and left bundle-branch block have a mechanical disadvantage resulting from abnormal activation of the left ventricle. In these patients, the septum contracts before the lateral left ventricle wall. The lateral wall contacts during relaxation of the septum. This mechanical dysfunction increases left ventricular volume, reduces contractility, and worsens mitral regurgitation. Proper placement of the pacemaker leads permits pacing the right ventricle, the septum, and the lateral wall of the left ventricle simultaneously.

Comment:

Study supported by Guidant.

Note—this applies only to systolic HF.

The purpose of the normal Purkinje subendocardial conducting system is to rapidly conduct the electrical impulse to all parts of the ventricles so that all parts of the myocardium contract simultaneously. CRT is a feeble attempt to mimic this function.

In spite of some incremental improvements in therapy of HF over the past 10 years, prognosis remains dismal. Death and hospitalization for HF continued to increase in the subgroup of patients followed for 3 years. In the CRT group, only about 20% had event-free survival at 3 years, and death rate increased from 12% at 1 year to about 30% at 3 years. Patients will welcome some improvement in quality-of-life. RTJ

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Five options for responding to intolerable suffering

5-9 DYING AND DECISION MAKING—Evolution Of End-Of-Life Options

The author cites an example of an elderly man (his father) who developed dementia. While mentally competent, he had made his wishes clear about any prolongation of his dying,. But then he lost the capacity to make decisions for himself. He was miserable. No one knew how long he would continue to live.

Over the past decade there have been substantial improvements in palliative care for severely ill patients. Unlike Hospice care, palliative care is offered alongside the active treatment of the underlying disease, regardless of the prognosis. The author's father was a candidate for palliative care, given his progressive loss of memory and poor prognosis. He consented to "do-not-resuscitate" status, but wanted to receive all other potentially effective treatments. Every effort had been made to treat his agitation and insomnia as well as his dementia, but he continued to worsen. Would he be a candidate for Hospice care?

Hospice continues to be the premier home care program. In order to qualify, patients must meet Medicare's requirements: a life expectancy of less than 6 months and willingness to forego all treatment directed at the underlying disease. Relatively few diseases fit neatly into this prognostic model, and many patients would like to continue to receive some potentially effective treatments even though the likelihood of success is low. Therefore, a minority of dying patients receive Hospice care. Those that do are often referred only when death is imminent. Efforts are being made to provide "Hospice-like" services to patients who are continuing to receive some active treatment. Access to these programs is limited.

The father was admitted to Hospice on the condition that, if his condition stabilized, he would have to be discharged. He continued to deteriorate.

The Supreme Court has decided unanimously that there is *no constitutionally-protected right* to physician-assisted suicide, but made it clear that they would not interfere with state-based efforts at legalization. The decision was not based on moral or ethical grounds, but on concerns about the inadequacies of access to, and delivery of, palliative care. The Oregon state *Death with Dignity Act* was allowed to stand.

The myth that excellent palliative care is incompatible with the provision of legal access to physician-assisted death as a last resort has largely been debunked by five years of data from Oregon. Physician-assisted suicide has accounted for very few deaths. Most of these patients died while enrolled in Hospice. Patients who have chosen this option have been motivated mainly by loss of autonomy, loss of control of bodily functions, decreased ability to enjoy life, and tiredness of dying. Unrelieved pain has *never* been the main reason. Clinical depression has not seemed to confound the decision.

Currently, Oregon has become a leader in terms of excellence of palliative care. Markers of this success include: high levels of referral to Hospice; prescribing of morphine; death at home; and public awareness of end-of-life options. Of course, physician-assisted-suicide is useful only to mentally competent, terminally ill patients who are physically capable of *independently* ingesting medication.

What other last-resort options might be available to patients like the author's father? The article cites 5 options for responding to intolerable suffering:

Option	Legal Status	Ethical Consensus	Decision maker
1. Proportionately intensive symptom management	Legal	Consensus	Patient or surrogate.
2. Stopping (or not starting) potentially life-saving therapy	Legal	Consensus	Patient or surrogate
3. Sedation to unconsciousness to relieve intractable symptoms	Legal	Uncertain	Patient or surrogate
4. Voluntarily stopping eating and drinking	Legal	Uncertain	Patient only
5. Physician-assisted suicide	Illegal (except in Oregon)	Uncertain	Patient only

Option 1: Accepting a proportional risk of sedation or respiratory depression if it is deemed necessary in order to provide management of intractable symptoms is a permissible option

Option 2: As in option 1.

Option 3: Sedation to the point of unconsciousness to relieve otherwise unbearable symptoms in those for whom death is imminent (terminal sedation) has had legal protection since the 1997 Supreme Court decision. Consensus in society is still evolving.

Option 4: Allowing patients who are still physically capable of eating and drinking to voluntarily stop doing so appears to be legal, but remains morally controversial. (*Continue to offer food and drink, but no tubes. RTJ*)

Option 5: Physician-assisted suicide remains highly contentious. It is generally illegal outside of Oregon. It is a secret practice, however, in many parts of the country, quietly tolerated according to a "don't ask, don't tell" policy. As noted above, this is a decision of a patient who remains mentally competent.

Knowledge about these last-resort options is important to those who fear being trapped in a life filled with unacceptable suffering without the prospect of a timely escape. Most, however, will not need that escape if they receive adequate palliative care.

What course did the author take in regard to his father? Since the father had lost his capacity to decide for himself, the surrogates (the family), in collaboration with Hospice and his primary physician elected to try low-dose phenobarbital.[1] He was kept mildly sedated. He subsequently appeared more peaceful than he had in months. He awakened periodically to exchange a few words. He almost completely stopped eating and drinking. He died peacefully 5 days later.

Because, while mentally competent, the father had been very clear about his wishes, and because the family understood how the system works and had relevant knowledge and resources, they were able to use the fragmented heath-care system to provide him with humane end-of-life care. Most families are not so fortunate.

NEJM May 13, 2004; 350: 2029-32 "Perspective", by Timothy E Quill, University of Rochester School of Medicine, Rochester, NY. www.nejm.org

1 A variation of option 3.

Comment

I would stress several critical points:

1. *While mentally competent we all should express clearly and repeatedly, to our family and physicians, our wishes about terminal care. (Preferably in writing.) The patient should designate which of the 5 options are acceptable to him. If, when terminally ill, cognitive function is still preserved, the patient should be allowed to chose, and his choice should be honored. .*
2. *We should endeavor to help family members to arrive at a consensus, avoiding an almost inevitable conflict if all surrogates are not in agreement.*
3. *If and when we become mentally incompetent, a specific surrogate should be designated to make the final decision.*

Was the time I spent in abstracting this article in detail worth the effort? I believe so. The principles apply to all of us—physician, family, and patient. It is well to dwell on these matters while we can. RTJ

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Increased homocysteine levels appeared to be a strong independent risk factor for fractures.

5-10 HOMOCYSTEINE LEVELS AND THE RISK OF OSTEOPOROTIC FRACTURE

Homocystinuria is a rare autosomal recessive disease characterized by very high plasma homocystine[1] levels. It is also characterized by early onset of generalized osteoporosis. The underlying pathophysiological mechanism is not completely understood. It may be related to a disturbance in collagen cross-linking in bone.

In the general population, a mildly elevated plasma homocysteine,[1] termed hyper-homocysteinemia, is a common condition. Hyper-homocysteinemia is recognized as a major risk factor for atherosclerotic and thrombotic disease, as well as cognitive impairment, including Alzheimer's disease.

This study asked—Are mildly elevated homocysteine levels related to age-related fractures?

Conclusion: Increased homocysteine levels appeared to be a strong independent risk factor for fractures.

STUDY

1. Followed over 2400 subjects, all over age 55 (a general, older population) who participated in two separate prospective studies:
    A. The Rotterdam study:
        1) A cohort of over 550 subjects with a mean follow-up of 8 years, and
        2) A cohort of over 550 subjects followed for 6 years.
    B. The Longitudinal Aging Study Amsterdam:
        1) A single cohort of over 1250 subjects followed for almost 3 years.
2. Analyzed risk of fracture associated with increased levels of homocysteine adjusted for age, sex, body-mass index, and other characteristics.

RESULTS

1. In all 3 cohorts, mean homocysteine levels increased with age, higher in men than in women.
2. During over 11 000 person-years of follow-up, 191 subjects sustained an osteoporotic fracture (135 women and 56 men). The majority were hip and wrist fractures.
3. High homocysteine levels were associated with an increased risk of fracture. Risk was similar in all 3 groups. Risk was similar in men and women.
4. When grouped with regard to sex and age-specific quartiles, those in the highest quartile had an increase in risk of fracture twice as high as the risk in the three lower quartiles.
5. In the first Rotterdam cohort, over an accumulated 11 years, those in the highest quartile of homocysteine levels, had twice as many fractures as those in the lower quartiles (30% vs 15%). (*My estimations from figure 1 p 2038. RTJ*)
6. The population-attributable risk of fracture related to a high homocysteine level was estimated at 19%.
7. There was no difference in bone mineral density between quartiles. [2]

DISCUSSION

1. "Our analyses . . . show a strong association between increased homocysteine and the risk of osteoporotic fractures."[2] "The calculated population attributable risk of the effects of increased homocysteine levels is considerable." It is comparable to the population-attributable risk of myocardial infarction
2. Risk was independent of age, sex, and other risk factors for fracture.
3. Homocysteine has been shown to interfere with the formation of collagen cross-links and fibrils. Fewer

cross-links have been found in patients who have homocystinuria. Collagen cross-links are important for the stability and strength of the collagen network. Impaired cross-linkage results in fragile bone. This interference with the development of the microarchitecture of bone is independent of the amount of mineral in the bone.

5. Randomized, controlled studies have shown that folic acid-based vitamin supplements can effectively reduce homocysteine levels and reduce rate of coronary restenosis. Additional studies are needed to assess whether such therapy will reduce the risk of fracture.

CONCLUSION

An increased homocysteine level appears to be a strong and independent factor for fractures in older men and women.

NEJM May 13, 2004; 350: 2033-41 Original investigation, first author Joyce B J vanMeurs, Erasmus Medical Center, Rotterdam, the Netherlands. www.nejm.org

1 To clarify terminology:

Cysteine is a simple sulfur containing amino acid (a mono-sulfide),

Cystine (no "e") is a combination of 2 cysteine molecules (a disulfide).

For practical purposes, the terms are often used interchangeably.

"Homo" simply signifies the addition of one carbon atom to the chain.

2 Since the defect in bone is not related to the mineral content, should this be termed "osteoporosis"?

Alternatively, should the definition of osteoporosis be expanded?

A companion study in this issue of NEJM (pp 2033-41) "Homocysteine as a Predictive Factor for Hip Fracture in Older Persons" (first author Robert P McLean, the Framingham Study, Boston) comes to the same conclusion. Compared with the lowest quartile, the highest quartile had a greater risk of hip fracture (4 times higher in men, and 2 times higher in women).

The authors comment that homocysteine levels are easily modifiable by dietary interventions. The FDA mandate in 1996 led to folic acid fortification of grain products. This has helped reduce the prevalence of low folate levels (< 7 mmol/L) from 22% to 2% and reduce the prevalence of homocysteine concentrations higher than 13 mmol/L from 19% to 10%. It remains to be seen if interventions by supplements will reduce rates of fracture.

Comment:

Would this study lead primary care clinicians to more strongly advise a daily multivitamin supplement? (In addition to folic acid, supplements contain vitamin B12 and B6 which are also related to a lowering of homocysteine levels.)

Decisions regarding therapy in primary care often do not depend on conclusive evidence of effectiveness. They are also based on reasonable assumptions (accepting that observational studies may be misleading), and a judgment of the benefit/harm-cost ratio of the therapy. For daily vitamin supplements, the harm is nil and the cost minimal. Even if the benefit is very modest, it might be reasonable to take them.

I would advise older patient that a supplement might reduce risk of fracture.

I would advise them to take a supplement. RTJ

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Is the benefit worth the risk?

5-11 PREVENTION OF DISABLING AND FATAL STROKES BY SUCCESSFUL CAROTID ENDARTERECTOMY IN PATIENTS WITHOUT RECENT NEUROLOGICAL SYMPTOMS.

Patients with substantial (60-99%) carotid narrowing are at increased risk of stroke. Risk is greater if they are already symptomatic (ie, have recently suffered some relevant neurological symptoms).

Carotid endarterectomy **(CEA)** can remove arterial narrowing. The surgical procedure involves risk of perioperative stroke and death. Moreover, even successful CEA might not permanently eliminate all thromboembolic risk. The balance of risk and long-term benefit is uncertain.

This study asks: What is the benefit/risk ratio of CEA for *asymptomatic* patients?

Conclusion: Among patients up to 75 years of age with severe carotid stenosis on ultrasound but no relevant neurological symptoms, CEA reduced incidence of stroke or death over 5 years by about 6%. (This took into account a 3% perioperative hazard of death or stroke.)

STUDY

1. Starting in 1993, a multicenter study entered over 3000 *asymptomatic* patients (mean age 68) with substantial carotid narrowing. Randomized to: 1) Immediate CEA (within 1 month to 1 year); or 2) control group of patients—indefinite deferral of CEA.
2. All patients had unilateral or bilateral stenosis on ultrasound of 60% or more. No patient had any stroke or TIA within the past 6 months. Both doctors and patients were substantially uncertain whether to choose immediate CEA or deferral until a more definite need was evident. None had an indication for joint CEA + coronary artery by-pass.
3. All other treatments were at the discretion of the clinicians (antiplatelet, antihypertensive, lipid-lowering therapy).
4. Centers were chosen if the surgeons involved demonstrated experience in CEA, with outcomes indicating no more than a 6% perioperative risk of stroke or death.
5. Follow-up for up to 5 years (mean = 3.4 years).

RESULTS

1. Outcomes *(From figure 3 p 1495)*	CEA (%)	Controls (%)
Death or stroke		
Within 30 days	3.1	Nil
30 days to 5 years	3.8	11.8
Totals	6.9	11.8
Difference	5.9	

NNT (for CEA to benefit one over 5 years)	18	
Fatal or disabling strokes over 5 years		
or perioperative death	4.2	2.1
NNT (for CEA to benefit one over 5 years)	48	

(Note: these outcomes were for patients age 75 and younger. There was no net benefit for those over age 75.)

2. Benefits were evident in both sexes, for those with 70%, 80%, and 90% narrowing, and for those younger than age 65, and those between ages 65-74. But *not* for older patients, half of whom died within 5 years from unrelated causes.

DISCUSSION

1. Because of the immediate risk of stroke or perioperative death, benefits for CEA did not outweigh that of watchful waiting until after 2 years. [1]
2. Among patients up to 75 years of age with severe carotid stenosis but no relevant neurological symptoms, CEA reduced incidence of stroke or death over 5 years by about 6%. (This takes into account the 3% perioperative hazard of death or stroke.)
3. "Although the main reduction was in the risk of ipsilateral stroke, contralateral carotid stroke was also significantly reduced, presumably through mechanisms involving collateral arterial flow through the circle of Willis." "Because the reduction in contralateral stroke was so definite (11 vs 35 events) exclusion of such strokes from the main analysis of carotid stroke would have underestimated the net benefit of successful CEA. (*In the CEA group, there were almost as many contralateral strokes as ipsilateral*.)
4. There were about ten times as many deaths from other causes as from stroke in this study. The effects of CEA on overall mortality could not be reliably estimated.
5. "The reduction . . . in carotid ischemic stroke is so extreme that it can reasonably be generalized to patients with severe carotid artery stenosis in a whole range of . . . circumstances." [2]
6. Although many patients in the study were receiving good medical therapy, it is possible that more effective therapy might improve non-surgical outcomes.

CONCLUSION

In asymptomatic patients younger than age 75 with carotid diameter reduction of about 70% or more, CEA reduced the net 5-year stroke risk.

Risk of stroke or death within 1 month of CEA was 3%. Combining the perioperative events and the non-perioperative strokes, the net 5-year risks were 6.4% *vs* 11.8%. (Absolute difference = 5.4%; NNT = 18). For fatal strokes 2.1% *vs* 4.2% (NNT = 48).

Lancet May 8, 2004; 363: 1491-502 Original investigation by The Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group, correspondence to Allison Halliday, St George's Hospital Medical School, London. www.thelancet.com

1 The authors comment that CEA in asymptomatic patients should be considered a long-term investment. When the short-term risk of surgery is considered, benefits of CEA did not accumulate until after 2 years.

2 *I believe this is an overstatement. I believe the investigator's inclusion of contralateral coronary strokes in their final analysis is misleading. RTJ*

An editorial in this issue of Lancet (pp 1486-87) by H J M Barnett, King City, Ontario, Canada comments:

In asymptomatic patients with 60-99% stenosis the Asymptomatic Carotid Atherosclerosis Study (1995), detected only modest benefit favoring CEA. The 30-day combined risk of stroke and death from angiography and surgery was 2.3%. The absolute risk-reduction projected to 5 years was 5.9%. The NNT to prevent one stroke in 2 years was at least 67.

Before concluding that the route has been cleared to the operating room for asymptomatic patients consider:

With good medical care, these patients face only a 2% annual risk of stroke.

Benefits will exceed risks only if perioperative hazards remain low. Surgical expertise may indeed be improving, but so is medical therapy (scrupulous and compliant regulation of lipids, glucose, BP, and cigarette smoking, as well as appropriate platelet inhibition).

In the trial, the main analysis of the effects of surgery involved not only ipsilateral, but contralateral strokes.

No comparative curves were presented for just ipsilateral strokes (which is the type most expected to be reduced by operating on one artery). "The striking statistical observation that contralateral strokes were significantly reduced by ipsilateral carotid endarterectomy cannot yet be promised to patients as a bonus effect."

Comment:

How did these carotid lesions come to be diagnosed? I could find no reference to this point.

I can think of no other circumstances wherein primary care clinicians must be more carefully selective in choosing the referral surgeon. And in informing an asymptomatic patient of the immediate risks (at least a 3% chance of immediate disability or death) vs long-term benefits of surgery—one chance in 18 of avoiding a stroke over the next 5 years.

From personal experience, I know how devastating it is to refer a patient for CEA and have him experience immediate conversion from his asymptomatic state to severe disability.

What might the primary care clinician advise patients with asymptomatic carotid stenosis?

If your are 75 years old or older, do not even consider CEA.

You have (at the minimum) one chance in 33 of dying or having a stroke as a result of surgery.

If you survive the operation and do not have a stroke due to the surgery, your prognosis will be more favorable in the next 5 years if you have successful surgery:

A. Chance of having a stroke without surgery is 11% over 5 years. (About one in ten)

B. Chance of having a stroke after successful surgery is 3.8% over 5 years. (About one in 25)

Chances of harm and benefit are equal for the first 2 years.

There is a much greater chance of your dying of a cause other than stroke. RTJ

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May lead patients to use insulin much earlier and more aggressively, affecting the progression of diabetes complications

5-12 INHALED INSULIN

"A recent attempt to circumvent the need for injections that may soon hit a clinic near you."

Insulin can be effective given by inhalation. Two versions, a powder and an aerosol, may be nearing launch. The bioavailability is 10-15%. The dose equivalent is about three times that of injected insulin.

Onset of action is rapid. Duration of action is slightly longer than that of fast-acting insulin given subcutaneously. A Cochrane review concluded that inhaled insulin provided equivalent control to fully injected regimens. Data would imply bioequivalence. Adding inhaled insulin to oral hypoglycemic regimens improves control .

Advantages of inhaled insulin relate to patient preferences. It may improve compliance and result in more patients achieving glycemic control.

What are potential problems?

Inhaled insulin bioavailability is affected by asthma (decreased), and by smoking (increased).

Formation of antibodies is higher. This is dismissed as not affecting insulin requirements.

There are concerns abut possible long term effects on lung structure and function. (No short term adverse effects have been reported.)

Few people like injections. Some are so terrified they refuse appropriate treatment.

Where inhaled insulins could really have an impact will be if professionals and patients begin to use insulin much earlier and more aggressively, affecting the progression of diabetes complications.

We await further studies to see if inhaled insulin is safe, and how much it will cost.

BMJ May 22, 2004; 328: 1215-16 Editorial, first author Stephanie A Amiel, King's College School of Medicine, London. www.bmj.org

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Is Celebrex safer than Vioxx?

5-13 CYCLO-OXYGENASE-2 INHIBITORS VERSUS NON-SELECTIVE NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND CONGESTIVE HEART FAILURE OUTCOMES IN ELDERLY PATIENTS.

Non-selective NSAIDs are associated with an increased risk of heart failure **(HF).** In susceptible individuals, they raise systemic vascular resistance and reduce renal perfusion. BP may be elevated, and edema and HF may result.

The selective COX-2 inhibitors, celecoxib (*Celebrex*) and rofecoxib (*Vioxx*) are reported to be associated with a lower risk of gastrointestinal events than the non-selective NSAIDs. Might they also be associated with fewer cardiovascular and renal complications? Might celecoxib and rofecoxib differ in their risks?

This study assessed rates of admission for HF in elderly patients for whom COX-2 inhibitors were newly dispensed.

Conclusion: Rofecoxib and non-selective NSAID were associated with increased risk of HF. Celecoxib was not.

STUDY

1. A population-based, retrospective study identified NSAID-naïve patients, all over age 66 (mean age = 76), who were:
   - Started on rofecoxib (n = over 14 500).
   - Started on celecoxib (n = over 18 500).
   - Started on non-selective NSAIDs (n = over 5000).
2. Randomly selected as controls 100 000 subjects who were not using NSAIDs.

RESULTS

1. During over 55 000 person-years, recorded 654 admissions for HF. Relative to non-NSAID users, the rate of admission for HF was significantly higher for users of rofecoxib (RR = 1.8) and non-selective NSAIDs (RR = 1.4) , but *not* celecoxib (RR = 1.0)
2. Patients with a history of HF were much more likely to be admitted for recurrent HF. Those taking celecoxib were more likely to be readmitted than controls (RR = 1.2), but much less likely than those taking non-selective NSAIDs (RR = 2.2) and rofecoxib (RR = 1.8)
4. Crude HF admission rate per 1000 person-years:

	Patients *without* a history of HF	Patients *with* a recent history of HF*
Non- NSAID users	6.6	169
Celecoxib	9.7	202
Rofecoxib	19.3	330
Non-selective NSAIDs	10.2	350

*(*Note the remarkable difference in risk. RTJ*)

DISCUSSION

1. "Compared with non-NSAID-users, we have recorded higher rates of admission for congestive heart failure in elderly patients who were initiated on treatment with rofecoxib and non-selective NSAIDs, but not celecoxib." "These differences are clinically important in view of the large numbers of patients given NSAIDs any type."
2. In individuals who had been previously admitted for HF, rofecoxib and non-selective NSAIDs were related to

a greater risk of readmission for HF (compared to celecoxib) 3. One possible mechanism: rofecoxib has substantially longer elimination half-life than celecoxib. Celecoxib does not accumulate in the blood; rofecoxib does.

CONCLUSION

Relative to non-users of NSAIDs, there was a higher risk of a first admission for HF in users of rofecoxib and non-selective NSAIDs, but not for celecoxib. Risk was magnified in patients with a history of HF.

Lancet May 29, 2004: 1715-56 Original investigation, first author Muhammad Mamdani, Institute for Clinical Evaluative Sciences, Toronto, Canada. www.thelancet.com

Comment:

The authors state that, in other studies, patients with long-standing hypertension showed greater increases in systolic BP among those receiving rofecoxib compared with those receiving celecoxib.

We too often concentrate on the adverse effects of NSAIDs on the gastrointestinal tract, and forget those on the cardiovascular and renal systems.

Although celecoxib may have a slight edge as far as adverse effects are concerned, I would avoid its use (and that of any NSAID) in patients with a history of HF, or at risk of HF (including diastolic HF), as well as patients with hypertension. RTJ

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