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HIGHLIGHTS OCTOBER 2002

10-1 BODY MASS INDEX, WAIST CIRCUMFERENCE, AND HEALTH RISK

Health risk is greater in individuals with high WC (> 40 inches in men and > 35 Inches in women) regardless of BMI category, including individuals with normal weight. A high WC independently predicts obesity-related disease.

10-2 THE NEW NATIONAL CHOLESTEROL EDUCATION PROGRAM GUIDELINES

The new NCEP-III guidelines present new clinical challenges to health care providers and their patients. They recommend stricter target lipid levels as well as a broader approach to risk assessment.

10-3 COMPLICATIONS OF DIABETES IN ELDERLY PEOPLE

As diabetes increasingly becomes a disease of elderly people, some of its unappreciated complication must be addressed. These include:

Cognitive disorders

Physical disability

Falls and fractures

Other geriatric syndromes

At least half of older diabetic adults will have a major physical or cognitive disability.

10-4 WHY MEN WITH PROSTATE CANCER WANT WIDER ACCESS TO PROSTATE SPECIFIC ANTIGEN TESTING: Qualitative Study

Most men with established or suspected PC received little information about risks and benefits of screening beforehand. Most thought that universal screening should be available.

Many men are ill prepared for test results, and for the possible iatrogenic effects of treatment.

10-5 NATURAL EXPERIMENT EXAMINING IMPACT OF AGGRESSIVE SCREENING AND TREATMENT ON PROSTATE CANCER MORTALITY IN TWO FIXED COHORTS FROM SEATTLE AREA AND CONNECTICUT

More intensive screening and treatment for PC was not associated with a lower PC-specific mortality over 11 years.

10-6 PROSTATE SPECIFIC ANTIGEN TESTING FOR PROSTATE CANCER

"If a patient asks a medical practitioner for help, the doctor does the best possible. The doctor is not responsible for defects in medical knowledge. If, however, the practitioner initiates screening procedures, the doctor is in a very different situation. The doctor should, in our view, have conclusive evidence that screening can alter the natural history of disease in a significant proportion of those screened."

The difficulty remains – who and when to screen, or not to screen at all. All men who choose screening should be adequately informed about risks and benefits beforehand.

10-7 HOME BASED EXERCISE PROGRAMME FOR KNEE PAIN AND KNEE OSTEOARTHRITIS

A simple home-based exercise program can produce significant reductions in knee pain and stiffness, and improvement in physical functioning over 2 years.

10-8 UNDERTREATMENT OF OSTEOPOROSIS IN MEN WITH HIP FRACTURE

The burden of hip fracture is high in old men as well as women. Few men receive antiresorptive therapy. Men should be tested for osteoporosis before fracture closes the door of effective therapy.

10-9 GLUCOSAMINE SULFATE USE AND DELAY OF PROGRESSION OF KNEE OSTEOARTHRITIS.

Long-term treatment with glucosamine sulfate retarded the progression of knee OA.

10-10 PRIMARY PREVENTION OF HYPERTENSION

Current recommendations for primary prevention involve a population-based approach and an intensive strategy targeted on individuals at high risk for hypertension. The 2 strategies are complementary. They emphasize 6 approaches with proven efficacy for prevention:

Engage in moderate physical activity

Maintain normal body weight

Limit alcohol consumption

Reduce sodium intake

Maintain adequate intake of potassium

Consume a diet rich in fruits, vegetables, and low-fat dairy products with reduced saturated and total fat.

10-11 THE SCOFF QUESTIONNAIRE AND CLINICAL INTERVIEW FOR EATING DISORDERS IN GENERAL PRACTICE.

Do you ever make yourself **S**ICK because you feel uncomfortably full?

Do you worry you have lost **C**ONTROL over how much you eat?

Have you recently lost more than **O**NE stone (14 pounds)?

Do you believe yourself to be **F**AT?

Would you say that **F**OOD dominates your life?

The predictive value of a positive test was low; predictive value of a negative test was high. (Ie, if the test is positive, a definite diagnosis cannot be made – further observation is needed. If the test is negative, it is highly likely that the patient does not have A-B.)

10-12 GLUCOCORTICOID AND BETA-RECEPTOR AGONIST INTERACTIONS IN ASTHMA

The preferred approach in asthma management combines a low-dose corticosteroid with an LABA. "It is notable that current management is based on pharmacological modification of two molecules that the adrenal glands produce in response to stress, namely adrenaline and hydrocortisone. It would make biological sense for these agents to potentiate each other's effects, therefore maximizing the benefits that can be obtained from smaller quantities of either agent alone."

10-13 ELECTRODE POSITIONING FOR CARDIOVERSION OF ATRIAL FIBRILLATION

If control by cardioversion to sinus rhythm is chosen, positioning the electrodes anterior-posterior is more effective.

For management of AF, two alternative strategies have emerged: 1) attempts to cardiovert and maintain sinus rhythm, or 2) attempts to maintain ventricular rate control while AF continues and is treated with long-term anticoagulation.

Cumulatively, the data suggest that, compared with heart-rate control, maintaining sinus rhythm does *not* confer risk-benefits for mortality or thromboembolic events, or for major quality-of-life improvements.

10-14 HEPARIN PLUS ALTEPLASE COMPARED WITH HEPARIN ALONE IN PATIENTS WITH SUBMASSIVE PULMONARY EMBOLISM

Treatment with alteplase + heparin improved the clinical course of stable patients with acute submassive PE. It prevented further clinical and hemodynamic deterioration which would have required escalation of treatment.

10-15 DIGOXIN – NEW PERSPECTIVE ON AN OLD DRUG.

Digoxin has a narrow therapeutic window. In patients with normal cardiac rhythm, the beneficial hemodynamic, neuro-hormonal, and clinical effects are found with a low concentration of approximately 0.7 ng/mL. Additional benefits are not seen with higher doses traditionally considered therapeutic (with serum concentrations of 1.0 to 1.5 ng/mL). These higher concentrations may predispose to arrhythmias.

Since digoxin may result in adrenergic stimulation at higher concentrations, or in patients with ischemia, the combination of digoxin with beta-blockade may have theoretical advantages

We should not abandon a therapy that may help patients with heart failure. Rather we should use a dose that will result in a serum concentration lower than 1.0 ng per milliliter.

10-16 SCREENING AND BRIEF INTERVENTION OF EXCESSIVE ALCOHOL USE: Qualitative Interview Study Of Experiences Of General Practitioners.

Screening and brief intervention programs may fail to detect harmful drinkers, while requiring considerable resources for primary prevention in groups of hazardous drinkers. Screening-based brief interventions left the practitioners with a sense of failure in achieving rapport and compliance, and was not congruent with contemporary approaches to dealing with lifestyle issues.

Screening for excessive alcohol use created more problems than it solved.

10-17 PREVENTION OF DEMENTIA WITH ANTIHYPERTENSIVE TREATMENT

New Evidence from the Systolic Hypertension in Europe (Syst-Eur) Trial

A 4-year follow-up study extending antihypertension therapy reinforced the evidence that BP-lowering therapy initiated with a long-acting dihydropyridine calcium blocker (nitrendipine) protects against dementia in older patients with systolic hypertension.

10-18 FISH, MEAT, AND RISK OF DEMENTIA: A Cohort Study

Regular consumption of fish was associated with a lower risk of future development of dementia.

10-19 STATIN-ASSOCIATED MYOPATHY WITH NORMAL CREATININE LEVELS

"Some patients who develop muscle symptoms while receiving statin therapy have demonstrable weakness and histopathologic findings of myopathy despite normal serum creatinine kinase levels." Symptoms and histologic features reverted to normal on withdrawal of the drug.

10-20 XIMELAGATRAN VERSUS WARFARIN FOR PREVENTION OF VENOUS THROMBOEMBOLISM AFTER TOTAL KNEE ARTHROPLASTY

Introducing a new anticoagulant. More confirmatory studies will be required before it can be entered into primary care practice. If it pans out, its fixed dose, oral administration, absence of interactions with food and drugs, and the fact that it requires no anticoagulation monitoring will be great advantages. RTJ

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A High Waist Circumference Increases Risk Even If Weight Is Within Normal Range.

10-1 BODY MASS INDEX, WAIST CIRCUMFERENCE, AND HEALTH RISK

Body mass index (**BMI**) is defined as weight in kilograms divided by the square of height in meters. The NIH has arbitrarily divided persons into categories according to their BMI:

Underweight	< 18.5
Normal	8.5 to 24.9
Overweight	25.0 to 29.9
Class I obesity	30.0 to 34.9
Class II and III	35 and over.

The NIH has also categorized waist circumference (**WC**) as a dichotomy:

Men: Normal < 102 cm (< 40 inches) ; high > 102 cm (> 40 inches)

Women: Normal < 88 cm (35 inches); high > 88 cm (> 35 inches).

Abdominal obesity (as measured by WC) is an index of abdominal fat content and is considered a greater health hazard than lower-body obesity (hip and buttocks).

The NIH grades health risks on the basis of combined BMI and WC. Health risks increase in a graded fashion when moving from normal weight through class II obese BMI categories. Individuals with high WC values have a greater health risk than those with normal WC.

This study examined whether the prevalence of cardiovascular risk factors is greater in individuals with high vs normal WC within the same BMI categories. It asked the question – Do WC cutoff points predict health risks beyond that already predicted by BMI?

Conclusion: Even if your weight is "normal", a high WC increases risk.

STUDY

1. The Third National Health and Nutrition Examination consisted of over 14 500 adult participants considered to be a cross-sectional survey of the population.
2. Calculated BMI. Measured WC at a point half way between lower ribs and iliac crest with the patient

at minimal inspiration. (*I presume this was standing and not supine, although the study did not state. RTJ*)

3. Compared risk factors in individuals within each of 3 BMI categories:

Normal weight with normal WC vs normal weight with high WC

Overweight with normal WC vs overweight with high WC

Class I obese with normal WC vs class I obese with high WC.

RESULTS

1. Considering only the normal weight subjects and comparing those with normal vs those with high WC for both men and women:

Age and BMI were higher in the high WC group. BP, fasting glucose, total cholesterol, LDL-cholesterol, and triglycerides were also higher

Prevalence of hypertension, type 2 diabetes, high LDL-c, low HDL-c, hypertriglyceridemia and the metabolic syndrome was higher in the high WC group.

2. In the overweight and class I obese, these factors varied in the same way.

DISCUSSION

1. Health risks were greater in individuals with a high WC regardless of their BMI category.
2. "These observations underscore the importance of incorporating BMI and WC evaluation into routine clinical practice and provide substantive evidence that the sex-specific NIH cutoff points for the WC help to identify those at increased health risk within various BMI categories."
3. The additional health risk explained by the WC likely reflects its ability to act as a surrogate for abdominal and, in particular, visceral fat.
4. Those with high WC were older than those with normal WC independent of sex and BMI. A high WC remained a significant predictor of obesity-related comorbidity after adjusting for age and other confounding variables.
5. This does not imply the dichotomous approach to WC values (40 inches in men and 35 inches in women) is the ideal threshold to denote increased health risk. The relation between WC and visceral fat is influenced by race and age. The ideal threshold values are not known.

CONCLUSION

Health risk is greater in individuals with high WC (> 40 inches in men and > 35 I nches in women) regardless of BMI category, including those with normal weight. A high WC independently predicts obesity-related disease.

Archives Int Med October 14, 2002; 162: 2074-79 Original investigation, fist author Ian Janssen, School of Physical and Health Education, Queen's University, Kingston, Ontario, Canada www.archinternmed.com

Comment:

Just as there are no ideal dichotomous cut points for BP, lipids, plasma glucose and other risk factors, there are no ideal dichotomous cut points to assess the risk of weight and waist circumference. The risks rise linearly.

As age increases BMI and WC increase. Older persons should be made aware of the importance of maintaining a trim figure as they age. RTJ

Drug therapy now recommended for 36 million persons in the USA. We are becoming a nation of statin-takers.

10-2 THE NEW NATIONAL CHOLESTEROL EDUCATION PROGRAM GUIDELINES

The new NCEP-III guidelines present new clinical challenges to health care providers and their patients. They recommend stricter target lipid levels as well as a broader approach to risk assessment. This is an effort to reduce premature death and disability from coronary heart disease (**CHD**) and stroke.

Following the guidelines, the number of US adults eligible for lipid modification (compared with NCEP II) has increased from 52 million to 65 million for therapeutic lifestyle changes, and from about 13 million to 36 million for drug therapy.

The new guidelines include consideration of a history of all occlusive vascular diseases (any CHD event: ischemic stroke; TIA; symptomatic carotid artery stenosis; peripheral atherosclerosis). Diabetes is elevated to a CHD risk equivalent. All patients with diabetes should be treated as aggressively as patients who have survived a prior occlusive event of heart, brain, or peripheral arteries.

The guideline focuses on global risk assessment rather than lipid parameters. Health-care workers are asked to calculate the 10-year risk of developing CHD for all primary care patients who have 2 or more risk factors using the Framingham Risk Assessment System.[1] This includes age, sex, total-c level, smoking status, HDL-c level, and systolic BP. If the absolute risk is 20% or greater, a primary prevention patient should be treated as aggressively as patients who have experienced a previous CVD event.

The guidelines also target primary prevention patients at high risk due to the metabolic syndrome. Over 25 % of US adults have the metabolic syndrome defined as: a constellation of 3 or more of 5 risk factors: abdominal obesity (waist > 40 inches men and > 35 inches women), low HDL-cholesterol (< 40 mg/dL in men and < 50 in women), high triglyceride levels (> 150 mg/dL), increased BP (> 130/85) and high fasting blood glucose (> 110 mg/dL). The new guidelines redefine low HDL-c and high triglycerides .

In patients with prior CVD, or with a 10 year risk of CHD over 20%, the goal is to reduce LDL-c to under 100 mg/dL.

Therapeutic lifestyle changes do confer large benefits in terms of risk reduction. But, unfortunately, most individuals prefer pills to proscription of harmful lifestyles. Lifestyle changes + statins have additive benefits.

The guidelines recommend statin drugs as the first line drug of choice for virtually all patients eligible for lipid modification. The overwhelming majority of patients will reach the LDL-c level of a reduction of about 35% with use of statins. All statins have favorable safety profiles.

Fluvastatin (*Lescol*) and pravastatin (*Pravachol*) have the advantage of a reduced potential for interactions with other drugs because of their different metabolic effects on liver enzymes. (The cytochrome P450 system is not influenced by these drugs. Thus, interactions with other drugs metabolized by this system do not occur.)

Cost is a consideration. (*See below.)*

Clinical judgment

Use of the guidelines requires clinical judgment. African-Americans, patients with a family history of premature CVD, obese and sedentary patients, (*and those with high abdominal girth*), are not included in the risk assessment of the guidelines, but should be included by the clinician when judging need for lipid control. The new guidelines recognize that probably no level of HDL-c (even below 60 mg/dL) protects against high LDL-c levels. And there is likely to be *no* low level of LDL-c that protects against low HDL-c levels. There needs to be wider use of statins in patients with high LDL-c levels despite the presence of normal or high HDL-c. Lipid modification may also be warranted in patients with "normal" LDL-c levels and low HDL-c.

Concerning triglycerides, there is emerging data to support their role as an independent risk factor. Gemfibrozil (*Lopid*) increases HDL-c by 6% and decreases triglyceride levels by 31%, leading to a decrease in risk of CHD.

A number of non-invasive assessments are available: ankle-brachial index, ultrasound of carotid intima, electron beam tomography of the coronary arteries, exercise ECG. These help to further assess risk and may be used for therapeutic decisions.

"The clinician should not let the perfect be the enemy of the possible. While there are clear research challenges, the clinical challenges are equally clear."

Archives Int Med October 14, 2002; 162: 2033-36 Commentary, first author Rachael S Eidelman, Mount Siani Medical Center, Miami Beach, FL **www.archinternmed.com**

1 www.nhlbi.nih.gov/guidelines/choesterol/profmats.htm

Comment:

Cost of lipid-altering drugs is an important consideration since they are to be taken for years. Most statins are in tablet form and can be cut. A $3 pill cutter may save hundreds of dollars annually. Unfortunately, fluvastatin comes in capsule form and would not be readily cut.

Cost of each dose quoted by my pharmacy in $: I have found the easiest method of getting price quotes is to access **www.eckerds.com** go to pharmacy; then to pricing; then print the name of the drug (usually the trade name) and enter. The $ costs per each tablet accessed November 2002:

Fluvastatin (*Lescol*)	20 mg – 1.54	40 mg – 1.45	80 mg – 2.10	
Mevacor (*generic*)	10 mg – 1.31	20 mg – 2.26	40 mg – 2.58	
Pravastatin (*Pravachol*)	10 mg – 2.67	20 mg – 2.57	40 mg – 3.72	80 mg -- 3.89
Simvastatin (*Zocor*)	10 mg – 2.24	20 mg – 3.77	40 mg – 4.00	80 mg – 3.93

Gemfibrozil

Generic	600 mg – 0.19
Lopid	600 mg – 1.46

The variation in cost is amazing. Look at the difference between *Lopid* and its generic.

If the quotations are correct, Some higher doses cost less than lower doses. For long-term use, the starting dose should be low (eg, 10 mg), unless there is some clinical urgency. Dose can be adjusted upward every month if necessary. RTJ

I believe a clever person could cut an 80 mg tablet into 8 approximately equal pieces, giving a starting dose of 10 mg daily of simvastatin and pravastatin (cost less than 50 cents daily). It would not be essential to have all doses exactly equivalent to 10mg. The daily dose would average 10 mg. RTJ

Based on a combination of price and safety, I believe pravastatin would be a good first choice. RTJ

At Least Half Of Older Diabetic Adults Will Have A Major Physical Or Cognitive Disability.

10-3 COMPLICATIONS OF DIABETES IN ELDERLY PEOPLE

People over age 65 will make up most of the diabetic population in the USA over the next 25 years. The proportion of the diabetic population 74 years or older is projected to exceed 30% in the next 50 years.

Progress has been made in reducing risk for the traditionally recognized microvascular complications (retinopathy, nephropathy, neuropathy), and the macrovascular complications (coronary heart disease, stroke, peripheral arterial disease). But, as diabetes increasingly becomes a disease of elderly people, some of its unappreciated complication must be addressed. These include:

Cognitive disorders

Physical disability

Falls and fractures

Other geriatric syndromes

Such outcomes have a direct impact on quality of life, loss of independence, and demands on caregivers. These increasing causes of disability may ultimately be as great a concern to older people with diabetes as the more traditionally recognized vascular complication.

The potential for diabetes to cause cognitive impairment among the aged is well documented. There is approximately a doubling of the overall risk of dementia. The association with Alzheimer's disease may be weaker, and the association with stroke-mediated dementia considerably stronger.

Diabetes is also associated with greater risks of disability related to mobility and tasks of daily living among the elderly. People with diabetes have 2 to 3 times the prevalence of inability to walk 400 meters, do house work, prepare meals, and manage money. Risk of falls and hip fractures is higher. The association of diabetes with physical disability is explained in part by classic complications (coronary heart disease, peripheral arterial disease, and visual impairment). However, a 60% excess prevalence of disability remains after controlling for these factors.

Management of elderly patients with diabetes will be complex. They may have several other diseases and require numerous medications. At least half of older diabetic adults will have a major physical or cognitive disability.

BMJ October 26, 2002; 325: 916-17 Editorial, first author Edward W Gregg, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta GA

www.bmj.com/cgi/content/full/325/7390/916

Comment:

We usually think of the complications of diabetes as micro- or macrovascular. As the article points out, other complications of old age are likely to be greater in patients with diabetes.

I am not as pessimistic as the authors. Many elders with diabetes control their risk factors by drug and lifestyle measures as well or better than some without diabetes. Indeed, I believe a patient with diabetes who controls his lifestyle, BP, lipids, and glucose as closely as he can, is likely to have a better prognosis than a non-diabetic who neglects his health risks. RTJ

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"Many men are ill prepared for test results, and for the possible iatrogenic effects of treatment."

10-4 WHY MEN WITH PROSTATE CANCER WANT WIDER ACCESS TO PROSTATE SPECIFIC ANTIGEN TESTING: Qualitative Study

"Screening for prostate cancer (**PC**) cannot be justified while uncertainty remains about whether early detection and treatment saves lives." However, support groups and much of the media do not question the benefit of screening and rarely mention the lack of evidence supporting open access to PSA testing. Although men who have received reliable information on screening are less inclined to request the test, many men continue to request it.

This study explored the attitudes of men with confirmed or suspected PC toward testing. Clearly, men with PC do not represent all men who might seek a PSA test, but as "cancer survivors" their views command attention and have influenced the media.

Conclusion: Most men did *not* subscribe to the argument that evidence of the benefits of treatment is a prerequisite for a screening program.

STUDY

1. Recruited 52 men with suspected or confirmed PC. All had received a PSA test.
2. Interviewers asked the men to tell their story, from when they first noted their symptoms and had the test.

RESULTS

1. Almost all remembered their PSA, but recalled being given little information beforehand.
2. Arguments in favor of increased access to testing included the belief that early diagnosis would

reduce mortality, improve quality of life, and save the health care system money.

3. The men also thought that a national screening program should be available because symptoms can be ambiguous. A national program would encourage men to be screened. They felt screening would be responsible health behavior.
4. The majority of men were keen about others having a PSA tests for various reasons:

    Belief that early diagnosis is important to cure PC or to prevent it from spreading.

    Regarding screening as a responsible behavior similar to women's cancer screening.

    Saving the health services money.

    A right to information and improved access.

    Equitability (ie, rights and parity with other health care spending).
5. Concerns about the accuracy of the PSA were mentioned, but not considered a convincing deterrent.
6. Only 4 men opposed screening. They had gathered information alerting them to uncertainty about the benefits of treatment. Two regretted that they had been tested. They emphasized that those who seek a PSA test should have pretest counseling. One man who was not in favor believed that total screening would terrify so many people that it would do more harm than good. One regretted having received the screen. If he had not known the results he would have happily lived on in ignorance. Another became intensely anxious and expected to die.

DISCUSSION

1. The study looked at PSA testing from the unique view point of men with suspected or confirmed PC. Many followed a different set of principles from those intended to guide screening programs. They did not dwell on the lack of a clear treatment choice.
2. The fact that PSA screening is offered routinely to men with private health insurance in the UK may promote the notion that it is valuable.
3. Practitioners in the UK are been advised to ensure that men who have PSA testing are making an informed choice. A key component in this information should be the uncertainty about benefits and risks of treatments. "However, arguments based on principles such as the 'right to information' about one's health, equality, and the 'imperative to avoid regret' will persuade some men to have the test, even if they understand that no treatment in known to prolong life."
4. Doctors and policy makers need to understand why people want wider access to PSA testing, so they can find better ways of communicating information about risk.

CONCLUSION

Most men with established or suspected PC received little information about risks and benefits of screening beforehand. Most thought that universal screening should be available.

Many men are ill prepared for test results, and for the possible iatrogenic effects of treatment.

BMJ October 5, 2002; 325; 735-79 Original investigation, first author Alison Chapple, University of Oxford, Oxford, UK. **www.bmj.com/cgi/content/full/325/7367/735**

Comment:

This is the UK view. I suspect the USA view will be similar.

I believe many men in the USA are given PSA tests as part of a general physical examination without any prior discussion. This is wrong. Adequate information should be given beforehand to give men an informed choice about screening. RTJ

More intensive screening and treatment for PC was not associated with a lower PC-specific mortality

10-5 NATURAL EXPERIMENT EXAMINING IMPACT OF AGGRESSIVE SCREENING AND TREATMENT ON PROSTATE CANCER MORTALITY IN TWO FIXED COHORTS FROM SEATTLE AREA AND CONNECTICUT

During the early 1990s, the incidence of prostate cancer (**PC**) in the USA rose after the introduction of prostate specific antigen (**PSA**) testing. In the mid-1990s, population-based PC mortality peaked and then decreased by about 15%. The subsequent decline in incidence was probably due to depletion of prevalent cases from the pool of men undergoing screening.

This article presents an 11-year longitudinal study of two cohorts of male Medicare beneficiaries, one from the Seattle area (high incidence of screening) and one from Connecticut (lower incidence of screening). It asked whether more intensive screening and treatment for PC would lead to lower mortality.

Conclusion: More intensive screening and treatment for PC was *not* associated with a lower PC-specific mortality over 11 years.

STUDY

1. Population-based, natural experiment compared two fixed cohorts of men from 1987 to 1997.
2. Subjects were male Medicare beneficiaries age 65-79 drawn from Seattle (n > 94 000) and Connecticut (n > 120 000). All were without PC as of January 1987.
3. Determined rates of screening and treatment with radical prostatectomy with surgery and radiation.
4. Determined PC-specific mortality 1987 to 1999.

RESULTS

1. PSA testing rates in Seattle was over 5 times that of Connecticut. Biopsy rate was over twice that of Connecticut.
2. Ten year cumulative incidence of radical prostatectomy and external beam radiotherapy was higher in Seattle. (2.7% and 3.9% of the cohort compared with 0.5% and 3.1%)
3. No significant difference in PC-specific mortality existed between the cohorts over the entire 11 years of follow-up. Adjusted rate ratio of PC mortality was 1.03 in Seattle compared with Connecticut. (Confidence interval = 0.95 to 1.11)

DISCUSSION

1. The authors stress that the study included only men over age 65. Screening younger men may have resulted in different conclusions.
2. The follow-up of 11 years may not have been long enough to see a difference in mortality.

CONCLUSION

More intensive screening and treatment for PC was not associated with a lower PC-specific mortality over 11 years.

BMJ October 5, 2002; 325: 740-43 Original investigation, first author Grace Lu-Yao, HealthStat, Princeton, New Jersey. **www.bmj.com/cgi/content/full/325/7367/740**

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"Becoming a patient with an elevated PSA is not a trivial matter."

10-6 PROSTATE SPECIFIC ANTIGEN TESTING FOR PROSTATE CANCER

(This editorial comments and expands on the previous articles.)

"Medical screening is an example of 'institutionalization of risk'. In practice, this often entails imperfect tests, sometimes inappropriately presented to the public, that discover diseases we do not fully understand and cannot adequately treat."

Pressures for the establishment of national screening programs are widespread. But attempts to resist public pressures for new screening programs may be mistrusted as attempts to save money, betray the science, to fool the public, or as sex discrimination.

Traditionally, the response to such apparent public ignorance or irrationality has been to argue that the public needs to be educated, and people's views corrected to align more correctly with what policy makers and scientists want them to believe. Perhaps what is needed now is not so much public understanding of science as understanding of the public by scientists.

Trial, epidemiological, and clinical evidence may play a small part in the public's demand for screening for PC. Instead, the irresistible logic of finding the cancer early, the drive to avoid regretting later the decision not to have the test, the right to obtain more information about oneself by testing, and a perceived right to parity with women's access to screening may all be more important lay arguments. What they mostly do not recognize are the costs of screening. Becoming a patient with an elevated PSA is not a trivial matter. It has profound health, social, psychological, and economic consequences.

"If a patient asks a medical practitioner for help, the doctor does the best possible. The doctor is not responsible for defects in medical knowledge. If, however, the practitioner initiates screening procedures, the doctor is in a very different situation. The doctor should, in our view, have conclusive evidence that screening can alter the natural history of disease in a significant proportion of those screened." (*Cochrane and Holland – 3 decades ago*)

By engaging with people and exploring their beliefs and priorities, much can be done to address public concerns and produce workable solutions to complex issues around the interface between individual risk and wider costs.

BMJ October 5, 2002; 325: 725-26 Editorial by Hazel Thornton and Mary Dixon-Woods, University of Leicester, UK **www.bmj.com/cgi/content/full/325/7367/725**

Comment:

The debate continues – to screen or not to screen.

I believe screening and treatment will indeed prolong the lives of a few select men. See "A Randomized Trial Comparing Radical Prostatectomy with Watchful Waiting in Early Prostate Cancer" NEJM September 12, 2002; 347: 781-89 (*Practical Pointers* September 2002) This study selected men mean age 65 with newly diagnosed PC. All were in generally good physical and mental condition and expected to live at least another 10 years. All cancers were in an early stage, localized, and mildly- to moderately-well differentiated. PC-specific death was 4% lower in the surgery group at 6 years. (NNT = 25) All-cause death did not differ between groups.

So, the difficulty remains – who and when to screen, or not to screen at all. All men who choose screening should be adequately informed about risks and benefits beforehand.

I believe the excellent point that patient-initiated requests for screening differ greatly from doctor-initiated screening should be considered by all primary care clinicians. RTJ

Simple Home-Based Exercises Reduced Pain And Stiffness.

10-7 HOME BASED EXERCISE PROGRAMME FOR KNEE PAIN AND KNEE OSTEOARTHRITIS

Physiotherapy is often recommended for osteoarthritis, but many programs use intensive supervision and expensive equipment. A less expensive, community-based approach would be desirable.

This study assessed whether a home-based exercise program can improve outcomes in patients with knee pain.

Conclusion: A simple home-based program can significantly reduce knee pain.

STUDY

1. Pragmatic, randomized, controlled trial in two general practices followed over 750 patients (age > 45) with self-reported knee pain for most days for at least a month.
2. Randomized to: 1) exercise therapy; 2) monthly telephone contact; 3) exercise therapy + telephone contact; and 4) no intervention.
3. The exercise program was simple and applicable for all age groups. It was designed to maintain and improve the strength of muscles around the knee, the range of motion at the knee, and locomotive function. The program was self-paced and became progressively more challenging. Graded exercise bands were used to increase the resistance against which the muscles worked. The initial training period, taught in

the patients' homes by a trained researcher, consisted of 4 visits lasting about 30 minutes in the first 2 months, with follow-up at intervals of 6 months. Participants were encouraged to perform the program for 20-30 minutes a day, increasing the number of repetitions up to a maximum of 20 per leg.

4. The primary outcome was self-reported knee pain at 2 years on a knee-specific osteoarthritis index. The score could range for 0 to 20, with higher scores indicating more pain. Baseline score in exercise group = 6.9
5. Other outcomes were self-reported knee-specific physical function and stiffness, psychological outlook and depression, and isometric muscle strength.
6. Follow-up = 2 years.

RESULTS

1. Forty eight % of the exercise group completed the study.
2. At 24 months highly significant reductions in knee pain were apparent in the pooled exercise groups, compared with the non-exercise groups. Mean difference in pain score was -1.12 favoring the exercise group. (Number needed to treat to achieve > 50% improvement in knee pain = 13.)
3. Similar improvements were evident at 6, 12, and 18 months. The reduction in pain was greater the closer patients adhered to the exercise plan.
4. Regular telephone contacts alone did not reduce pain.
5. Scores of stiffness and physical function also showed significant improvement in the exercise groups.
6. General physical function, anxiety and depression were not improved.

DISCUSSION

1. A simple home-based exercise program produced small but significant reductions in knee pain. The program was generally well tolerated. Adherence was moderate.
2. Social support alone produced no benefit. The beneficial effects could reasonably be attributed to exercise alone.

CONCLUSION

A simple home-based exercise program can produce significant reductions in knee pain and stiffness, and improvement in physical functioning over 2 years.

BMJ October 5, 2002; 752-55 Original investigation, first author K S Thomas, City Hospital, Nottingham, UK.
www.bmj.com/cgi/content/full/325/7367/752

Comment:

It would be reasonable to suggest that the knee pain was primarily due to osteoarthritis.

I congratulate the authors and patients for attaining a 50% compliance with exercise over 2 years.

Compliance in unselected primary care patients in the USA would, I believe, be lower -- nevertheless, worth a try.

Physiotherapy and muscle strengthening around the knee joint have a place in treatment of osteoarthritis.

Both are neglected therapies. See "Effectiveness of Manual Physical Therapy and Exercise in Osteoarthritis of the Knee" (*Annals Int Med* February 1, 2000; 132: 173-81; *Practical Pointers* February 2000) A combination of physical therapy and exercise improved function and delayed or prevented knee surgery and corticosteroid injection. RTJ

Old men should be evaluated for osteoporosis long before the first fracture event. Few now receive antiresorptive therapy

10-8 UNDERTREATMENT OF OSTEOPOROSIS IN MEN WITH HIP FRACTURE

In the USA, the lifetime risk of hip fracture in women is about 17%, and about 6% in men. Men account for about 25% of all hip fractures. There is high awareness of the problem of osteoporosis in women, less so in men. Men older than age 55 become susceptible to age-related bone mineral loss which continues for the rest of their lives.

Overall, in the USA, women are not aggressively treated for osteoporosis; men even less so. Practitioners may not generally be aware that use of antiresorptives in men can increase bone density, and perhaps reduce fracture, even in the oldest patients.

This study hypothesized that, after hip fracture, men receive less treatment for osteoporosis than women. It determined the frequency of prescriptions for antiresorptive therapy given to men with hip fracture at the time of discharge from the hospital.

Conclusion: Few men received antiresorptive treatment.

STUDY

1. Reviewed data from medical records of 363 patients (110 men, 253 women; mean age = 80) age 50 and over who sustained a low-energy hip fracture.
2. Main outcome = osteoporosis treatments prescribed at discharge and current treatments over a 5-year follow-up.

RESULTS

1. Most fractures resulted from falls from a standing height.
2. At hospital discharge, 5% of men received treatment of any kind for osteoporosis, compared with 27% of women.
3. At 1 to 5 year follow-up, 27% of men were taking any kind of osteoporosis treatment vs 71% of women. Treatment for men consisted of calcium-vitamin D only in 18% vs 23% of women. Only 3 men received bisphosphonates vs 35 women; 17% of women received estrogen.
4. Twelve month mortality for men was 32% for men vs 17% for women.

DISCUSSSION

1. Attention to treatment of men with osteoporosis has been minimal.

2. In this study, over a 5-year period after hip fracture only about ¼ of men were taking any treatment for osteoporosis. Of these, most were taking non-aggressive therapy with only calcium-vitamin D.
3. "We suggest that the problem is not the lack of available treatment, but rather a lack of physician awareness of the lifetime risk of osteoporosis and fracture in men."
4. Few old men receive bone-density measurements.
5. The urgency of the situation is illustrated by the high mortality and disability (especially for men) after hip fracture.
6. Older men (as well as women) should be evaluated for osteoporosis long before the first fracture event.
7. Responsibility for long-term therapy with bisphosphonates and calcium/vitamin D in both men and women , with and without fracture, rests primarily on the primary care clinician. Identification of risk and prophylactic therapy should begin early, before a fracture begins to close the door of effective therapy.

CONCLUSION

The burden of hip fracture is high in old men as well as women. Few men receive antiresorptive therapy.

Archives Int Med October 28, 2002; 162: 2217-22 Original investigation, first author Gary M Keibzak, Baylor College of Medicine, Houston TX. **www.archinternmed.com**

Comment:

Anyone living in a retirement complex will recognize how common osteoporosis and fractures are in old men. Men continue to lose height. Kyphosis is common. Old men proceed to the dining hall slowly with their backs bent, following their wheeled walkers. Hip fractures occur following simple falls. Disability results from combined osteoarthritis-osteoporosis.

I believe all men over age 50 should receive supplementary vitamin D/calcium. Height should be checked periodically. As soon as loss of height begins, antiresorptive treatment may be indicated. . RTJ

Cost: Alendronate (*Fosamax*) -- 35 mg = $16 each tablet; 70 mg = $15.50

(If my pharmacy quote is correct, this is another example of the higher dose tablet costing less than the lower dose. There is evidence that 35 mg once weekly provides as much benefit in raising BMI as 70 mg once weekly. A pill cutter will reduce cost in half to $7.75 RTJ

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The first agent that meets the current requirements to be classified as a symptom and structure-modifying drug

10-9 GLUCOSAMINE SULFATE USE AND DELAY OF PROGRESSION OF KNEE OSTEOARTHRITIS.

Current therapeutic modalities for osteoarthritis (**OA**) are aimed primarily at reducing pain and improving joint function by use of non-specific symptomatic agents. NSAIDs do not favorably modify long-term progression of the disease. Attention is now being given to more specific compounds that may affect some of the underlying disease, thus delaying progression.

Glucosamine sulfate is a pharmaceutical derivative of the naturally occurring amino-mono-saccharide, glucosamine, a constituent of glycol-amino-glycans in cartilage matrix and synovial fluid.

Other studies have reported benefit from glucosamine. This trial was designed to possibly confirm previous results and to extend results to long-term use.

Conclusion: Glucosamine sulfate retarded progression of knee OA.

STUDY

1. Randomized and followed to completion 121 patients with knee OA (mean age = 62) to:
   1) glucosamine sulfate 1500 mg once daily, or 2) placebo. OA had been present a mean of 10 years.
2. Crystalline glucosamine was used. It is available by prescription in Europe, and as a nutritional supplement in the USA. (Rotta Pharmaceuticals, Wall, NJ.)
3. Determined changes in the radiographic joint space width in the medial compartment of the tibio-femoral joint
   Also assessed symptom change by indices – pain, maximum distance walked, stiffness, and limitation of physical function.
4. Follow-up = 3 years.

RESULTS

1. OA was of mild or moderate severity at enrollment. Average joint space widths were slightly less than 4 mm, and an index score less than 9 points. All patients were able to extend the knee.
2. Over 3 years, joint narrowing progressed in the placebo group (-0.19 mm). There was no average change with glucosamine (+0.4 mm) -- a significant difference between groups.
3. Fewer patients in the glucosamine group experienced predefined severe narrowing (> 0.5mm -- 5% vs 14%).
4. Symptoms improved modestly with placebo, but as much as 25% with glucosamine. Final differences in the symptom-indexes were significant. Benefit was evident at one year.
5. The drug was safe – no difference in adverse effects between groups.

DISCUSSION

1. Long-term oral glucosamine sulfate for 3 years can delay progression of knee OA. Symptoms and limitation of motion were improved compared with the placebo group.
2. On average, glucosamine patients did not undergo progressive joint structure changes.
3. The authors calculate that 11 patients needed to be treated to prevent one from experiencing clinically substantial joint space loss.
4. After oral administration, glucosamine is bioavailable, and reaches the articular cartilage. It is preferentially incorporated by the chondrocytes into the components of the glycol-amino-glycan chains in the intact cartilage. It stimulates the synthesis of proteoglycans, and decreases the activity of catabolic enzymes.
5. “Glucosamine sulfate is the first agent that meets the current requirements to be classified as a symptom and structure-modifying drug in osteoarthritis.”

CONCLUSION

Long-term treatment with glucosamine sulfate retarded the progression of knee OA.

Archives Int Med October 14, 2002: 2113-23 Original investigation, first author Karel Pavelka, Charles University, Prague, Czech Republic. **www.archinternmed.com**

Comment:

Note that the trial included only those with mild-to moderate OA.

Rotta Pharmaceuticals, Neptune, NJ is promoting glucosamine by direct mail to physicians. (Trade name "DONA") It is sold over-the-counter without prescription as a dietary supplement. The company states it is manufactured and standardized according to strict pharmaceutical standards. Apparently, it is a safe drug.

The company brochure states there is no evidence of benefit in combining chondroitin with glucosamine.

Cost – 1500 mg (the daily dose) = $1.50.

Could this "dietary supplement" enter the established body of therapeutics? Should primary care clinicians "prescribe" it? Certainly, there should be no objection to use by interested patients. Are there toxic effects when added to other drugs? RTJ

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One of the most important functions of primary care medicine.

10-10 PRIMARY PREVENTION OF HYPERTENSION

This article updates the National High Blood Pressure Education Program Committee's statement on primary prevention using new evidence since 1993.

Current recommendations for primary prevention involve a population-based approach and an intensive strategy targeted on individuals at high risk for hypertension. The 2 strategies are complementary. They emphasize 6 approaches with proven efficacy for prevention:

Engage in moderate physical activity

Maintain normal body weight

Limit alcohol consumption

Reduce sodium intake

Maintain adequate intake of potassium

Consume a diet rich in fruits, vegetables, and low-fat dairy products with reduced saturated and total fat.

JAMA October 16, 2002; 288: 1882-88 "Special Communication" for the National High Blood Pressure Education Program Coordinating Committee, first author Paul K Whelton, Tulane University Health Sciences Center, New Orleans, LA **www.jama.com**

Comment:

We are constantly reminded of these basic preventive measures. I believe repetition is warranted from time to time. Prevention is much more rewarding than treatment.

The main responsibility for primary prevention rests on the primary care clinician. This includes primary prevention for themselves as role models. RTJ

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"A Brief And Memorable Questionnaire"

10-11 THE SCOFF QUESTIONNAIRE AND CLINICAL INTERVIEW FOR EATING DISORDERS IN GENERAL PRACTICE.

The questionnaire (one point for every positive answer):

Do you ever make yourself **S**ICK because you feel uncomfortably full?

Do you worry you have lost **C**ONTROL over how much you eat?

Have you recently lost more than **O**NE stone (14 pounds)?

Do you believe yourself to be **F**AT?

Would you say that **F**OOD dominates your life?

Healthcare for patients with anorexia and bulimia nervosa (**A-B**) needs improvement. Primary care is at the forefront of screening and managing these patients.

This study presents a brief and memorable questionnaire tool to detect eating disorders and aid treatment. In a past study it showed excellent validity and reliability. This study assessed use of the questionnaire in primary care.

Two general practices invited sequential women attendees (age 18 to 50) to participate (341 consented)/ They were asked the SCOFF questionnaire. This took about 2 minutes.

Then a researcher, blinded to the SCOFF scores conducted a clinical diagnostic interview lasting 10 to 15 minutes, based on *DSM IV*. Women identified as having an eating disorder were invited to discuss this and were offered the contact number for the Eating Disorder Association.

Of the women screened, one had anorexia (body mass index = 17); three had bulimia; nine had an "eating disorder not otherwise specified". [Total prevalence = 4%; 13/341]

A cut point of two or more positive answers in the SCOFF identified all 4 cases of anorexia and bulimia and 7 of 9 cases of eating disorder not otherwise specified.

However, there were 34 false positives (10%).

Sensitivity of a test = the percentage of patients *with* the target disorder who have a *positive* test. (The true positive test %) (The number of true positive tests / total number of subjects with the target disorder.) Of all patients in this study who actually had A-B (n = 13), 11 had a positive test (11/13 = 85%)

Sensitivity of this test = 85% (85% were true positives; 15% false negatives).

Specificity of a test = the percentage of subjects who do *not* have the target disorder who have a

negative test. (The number of true negative tests / total number of negative tests.) Of all patients in this study who did *not* have A-B (n = 328), 294 had a negative test (294/328 = 90%) Specificity of this test = 90%. (90% true negatives; 10% false positives)

Predictive value of positive tests = ratio of true *positive* tests to all *positive* tests. Of all patients in this study who had positive tests (n = 45), 11 were true positives, 34 false positives). *Positive* predictive value = 11/45 = 24% Thus, in this study, even if 2 or more questions are answered positively, there is still considerable doubt that anorexia-bulimia is present. (Too many false positives.)

Predictive value of negative tests = ratio of true *negative* tests to total of all *negative* tests. Of all patients in this study who had negative tests (n = 296), 294 were true negatives; 2 were false negative. 294/294 = 99%. Thus, in this study, if 4 or 5 questions were answered negatively, the probability of A-B was very low.

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The authors considered the SCOFF an efficient screening tool for detecting eating disorders. Two missed cases reflect the reality of clinical situations, in which denial and non-disclosure may occur. It may be more difficult to detect patients who do not meet the full criteria for anorexia and bulimia.

The predictive value of positive tests is low because of the low prevalence of eating disorders in this sample which is consistent with the Western population as a whole. Over inclusion is acceptable for screening instruments designed for disorders with high mortality rates, particularly as the questionnaire is short and easy to administer. Positive results should be followed by further questioning rather than by automatic referral.

BMJ October 5, 2002; 325: 755-56 Original investigation, first author Amy J Luck, St George's Hospital Medical School, university of London, UK **www.bmj.com/cgi/content/full/325/7367/755**

Comment:

This article presents an excellent opportunity to review some of the applications of evidence-based medicine. I have to review the calculations periodically, or I lose them. Even then, I have to think hard and recalculate several times to get it right. The easiest is to make the classical 2 X 2 chart. Remember to place the target disorder on top and the test results at the left side: The denominator of the calculations is always the total

In this example:

	A-B present	A-B not present	Total
SCOFF positive (2,3,4,or 5 questions "yes")	11 (True positive)	34 (False positive)	45
SCOFF negative (4 or 5 "no")	2 (False negative)	294 (True negative)	296
Total	13	328	

Sensitivity of the test is calculated from the left column. (11/13 = 85%)

Specificity is calculated from the right column/ (294/328 = 90%)

Predictive value of positive tests is calculated from the top row. (11/45 = 24%) In this study, even if the test was positive, the likelihood that the respondent actually has A-B is only one in 4.

Predictive value of negative tests is calculated from the bottom row. 294/296 = 99%) In this study, if test was negative, the likelihood that the respondent actually had A-B is only one in 100.

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Long-acting beta-agonists potentiate the anti-inflammatory actions of corticosteroids

10-12 GLUCOCORTICOID AND BETA-RECEPTOR AGONIST INTERACTIONS IN ASTHMA

Long-acting beta-agonists (**LABA**) were introduced for treatment of asthma 10 years ago. Concerns were then raised that use might mask airway inflammation and lead to an insidious worsening of the asthma. Recommended management at that time was mainly based on titration of the inhaled steroid dose according to clinical response.

Subsequent studies found that adding an LABA was more effective than increasing the dose of inhaled steroid in improving symptoms, increasing peak expiratory flow rates, reducing reliever inhaler usage, and reducing asthma exacerbations.

Conventional wisdom has been that steroids and LABAs act through separate and distinct pathways -- steroids act as anti-inflammatory agents, and LABAs as bronchodilators. An alternative possibility is that LABAs potentiate the anti-inflammatory effect of steroids by acting on similar pathways, or by independent effects on steroid-insensitive pathways. The converse is certainly true -- steroids can potentiate beta-agonists by up-regulating beta-receptor numbers, or by preventing receptor uncoupling in response to inflammatory stimuli.

Several studies have now shown that LABAs potentiate the anti-inflammatory actions of corticosteroids in either an additive or synergistic manner. Beta-agonist monotherapy does not have anti-inflammatory properties.

Clinically, short-acting beta-agonists are much less effective than LABAs in long-term asthma control. This is possibly because their tissue clearance is rapid.

The preferred approach in asthma management combines a low-dose corticosteroid with an LABA. “It is notable that current management is based on pharmacological modification of two molecules that the adrenal glands produce in response to stress, namely adrenaline and hydrocortisone. It would make biological sense for these agents to potentiate each other’s effects, therefore maximizing the benefits that can be obtained from smaller quantities of either agent alone.”

Lancet October 26, 2002; 360: 1265 Editorial by Alan J Knox and Linhua Pang, Nottingham City Hospital, Nottingham, UK

Rhythm Control vs Rate Control – Which is Preferable?

10-13 ELECTRODE POSITIONING FOR CARDIOVERSION OF ATRIAL FIBRILLATION

There are two components in the management of patients with atrial fibrillation (**AF**): 1) stroke prevention due to embolization from the heart, and 2) rhythm management. Clear guidelines for use of anticoagulation to prevent stroke are well established.

For management of AF, two alternative strategies have emerged: 1) attempts to cardiovert and maintain sinus rhythm, or 2) attempts to maintain ventricular rate control while AF continues and is treated with long-term anticoagulation. This editorial comments on a study in this issue of Lancet "Electrode Positioning For Cardioversion Of Atrial Fibrillation" (pp 1275-79).

The editorial goes on to comment on rhythm vs rate control for patients with AF:

Guidelines for rhythm management are more complex and less clearly defined, in part because the likelihood of maintaining sinus rhythm is variable. Although it has been assumed that restoration of sinus rhythm is beneficial, the question has only recently been studied.

Three recent trials compared the benefit of rate control vs rhythm control. Only one has been published to date.[1] The information available injects new imponderables into the decision-making process. Cumulatively, the data suggest that, compared with heart-rate control, maintaining sinus rhythm does *not* confer risk-benefits for mortality or thromboembolic events, or for major quality-of-life improvements.

Drug therapy will convert some patients with AF to sinus rhythm. Long-term drug therapy is needed in an attempt to maintain sinus rhythm.

Thus, issues related to rate vs rhythm control strategies remain relevant. [2]

Lancet October 26, 2002; 360: 1263-64 Editorial, first author Robert J Myerburg, University of Miami School of Medicine, Miami, FL **www.thelancet.com**

Comment:

1 "Rhythm Or Rate Control In Atrial Fibrillation—Pharmacological Intervention In Atrial Fibrillation (PIAF): A Randomized Trial" Lancet November 25, 2000; 356: 1789-94. See abstract in *Practical Pointers* November 2000.

The study contrasts the two approaches. Both have adverse effects as well as benefits:

Rhythm control:

Upside: If successful, no need for warfarin prophylaxis; exercise tolerance better.

Downside: Requires drug or electrical conversion. Both may fail. Adverse effects of drugs to maintain sinus rhythm (eg, amiodarone). (High rate of withdrawal due to adverse effects.) Reversion to AF common (about 50% revert to AF within one year). Hospitalizations more frequent. Higher costs.

Rate control:

Upside: Simpler -- avoidance of cardioversion. Fewer adverse drug reactions. Fewer hospitalizations. Exercise tolerance lower. Lower costs.

Downside: Continued drug therapy (calcium blocker; digoxin; warfarin)

Individualization according to clinical status and the informed preference of the patient obviously required.

2 This editorial responds to the study "Anterior-Posterior Versus Anterior-Lateral Positions Of External Cardioversion Of Atrial Fibrillation: A Randomized Trial" Lancet October 26, 2002; 360: 1275-79 The study reported that the anterior-posterior positioning was more effective than the usually recommended anterior-lateral placement.

I believe that the A-P position may also be more effective in converting ventricular fibrillation. RTJ

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Combined therapy prevented further clinical and hemodynamic deterioration

10-14 HEPARIN PLUS ALTEPLASE COMPARED WITH HEPARIN ALONE IN PATIENTS WITH SUBMASSIVE PULMONARY EMBOLISM

Thrombolysis is established treatment for acute massive pulmonary embolism (**PE** with hemodynamic instability or cardiogenic shock). Treatment of hemodynamically stable patients with submassive PE remains controversial.

Thrombolysis may reduce risk of death in patients with right ventricular dysfunction due to PE, even in the absence of arterial hypotension or shock.

This study compared heparin + alteplace (*Activase*; tPA) with heparin alone in treatment of submassive PE.

The study focused on patients with pulmonary hypertension, right ventricular dysfunction, or both. Excluded those with hemodynamic instability.

Conclusion: Alteplase + heparin was more beneficial than heparin alone.

STUDY

1. Followed patients with acute PE who had pulmonary hypertension or right ventricular dysfunction, or both. None had arterial hypotension or shock.
2. Randomized 256 patients (mean age = 61). All patients received an intravenous bolus of 5000 U unfractionated heparin before undergoing further work up. They were then randomized to: 1) 100 mg alteplace as a 10 mg bolus followed by 90 mg over two hours, + heparin 1000 U per hour adjusted to activated partial thromboplastin time of 2.0 to 2.5 times upper limits of normal, or 2) heparin only. Heparin was continued for at least 4 days. Overlapping warfarin started on day 3.
3. Patients had at least one of the following: echocardographically detected right ventricular dysfunction defined as: 1) right ventricular enlargement combined with loss of inspiratory collapse of the inferior vena cava and without left ventricular or mitral valve disease); 2) echocardographically detected pulmonary artery hypertension (defined as tricuspid regurgitant jet velocity greater than 2.8 m per second), followed by confirmation by ventilation-perfusion lung scan, spiral computed CT, or pulmonary arteriography; 4) a mean pulmonary artery pressure > 20 mm Hg combined with a pulmonary wedge pressure below 18mm Hg followed by confirmation of a PE; or 5) new ECG signs of right ventricular strain (complete

or incomplete right bundle branch block, S waves in lead 1 combined with Q waves in lead III or inverted T waves in precordial leads, followed by confirmation of PE. (Ie, diagnostic criteria were strict.)

4. Primary outcome = in-hospital death or clinical deterioration requiring an escalation of treatment (catecholamine injection, "rescue" thrombolysis due to worsening symptoms, cardiopulmonary resuscitation, or emergency embolectomy or thrombus fragmentation by catheter).

RESULTS

1. A higher incidence of escalation of therapy occurred in the heparin-alone group (25% vs 10%).
2. Mortality was low in both groups (3.4% in the heparin-alteplase group vs 2.2% in the heparin alone group). Heparin alone was associated with almost three times the risk of treatment escalation as was combined therapy. (Ie, event-free survival was much higher in the combined group.)
3. No fatal bleeding occurred in the combined group.

DISCUSSION

1. In treatment of *massive* PE, thrombolytic agents dissolve PE and improve pulmonary perfusion and right ventricular function. The present study assessed whether *submassive* PE would respond favorably to thrombolysis.
2. Results indicate that alteplase, given with heparin, improves the clinical course of hemodynamically stable patients with acute submassive PE with a low risk of hemorrhagic complications.
3. The clinical course and prognosis of acute PE vary widely, depending on the clinical and hemodynamic status at the time of diagnosis . Right ventricular dysfunction is a predictor of adverse outcomes.
4. The current trial focused on patients with evidence of pulmonary hypertension and right ventricular dysfunction. Patients with persistent arterial hypotension or shock resulting from overt right ventricular failure were excluded. (*In this subset, immediate thrombolysis is indicated*.)
5. Although in-hospital mortality was similar (and low) in the two randomized groups, the incidence of clinical deterioration requiring escalation of treatment was much higher in the heparin-alone group.
6. "It seems reasonable to assume that delayed resolution (or lack of resolution), or recurrence of pulmonary embolism with heparin alone, resulted in persistence or deterioration of pulmonary hypertension and right-sided heart failure."

CONCLUSION

Treatment with alteplase + heparin improved the clinical course of stable patients with acute submassive PE. It prevented further clinical and hemodynamic deterioration which would have required escalation of treatment.

NEJM October 10, 2002; 37: 1143-50 Original investigation, first author Starvos Konstantinides, Georg-August-Universistat, Gottingen, Germany. **www.nejm.org**

Comment:

Since these patients are likely to experience repeat PE during the acute episode, I believe thrombolysis is strongly indicated, not only to dissolve the PE, but to lyse the distal venous clots which are likely at any time to break off, embolize, and cause sudden death.

In addition, lysis of clots in peripheral veins may prevent chronic obstruction and lessen the likelihood of chronic venous obstructive disease and leg-ulcer formation. RTJ

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Digoxin Remains A Useful Drug At Lower Doses Than Usually Recommended

10-15 DIGOXIN – NEW PERSPECTIVE ON AN OLD DRUG.

"Since 1785, when Sir William Withering published his treatise on the use of foxglove, our perspective on the use of digitalis has continued to change." Withering believed that digitalis had a diuretic effect in edematous patients with a weak and irregular pulse. Only in the early 20th century did digitalis begin to be considered useful in patients with heart failure and normal cardiac rhythm.

In the 1970s, challenges to digoxin therapy were due to a high incidence of digitoxin intoxication, a perceived increase in mortality associated with use of the drug in patients with myocardial infarction, and introduction of newer promising therapies.

In the 1980s, there was renewed interest in digoxin because it was understood that interaction with other dugs (eg, quinidine) could increase serum digoxin levels and thus lead clinicians to lower doses of digoxin. Several trials demonstrated benefit from digoxin in patients with heart failure and normal cardiac rhythm.

In the late 1980s, there was a paradigm shift emphasizing the importance of neuro-hormonal abnormalities in the progression of heart failure. During this time, it was discovered that digoxin, in addition to improving hemodynamics, has important neuro-hormonal modulating effects (eg, reducing renin and norepinephrine levels). In spite of these findings, the importance of digoxin was again questioned with the advent of more specific neuro-hormonal modulators (eg, ACE inhibitors and beta-blockers)

In the mid 1990s, the results of the "Randomized Assessment of Digoxin on Inhibitors of the Angiotensin-converting Enzyme" (RADIENCE) trial and the Digitalis Investigation (DIG) trial prompted the FDA to approve digoxin under current regulations for treatment of heart failure. The RADIENCE trial reported that discontinuation of digoxin in patients who were continuing to receive ACE inhibitors and diuretics was associated with worsening heart failure and a decrease in exercise tolerance. The DIG trail enrolled over 6500 patients with systolic dysfunction while taking ACE inhibitors and diuretics. Patients were randomized to digoxin (0.25 mg daily) or placebo. There was no difference in mortality after 3 years. There was a 12% reduction in death due to pump failure offset by an increase in death presumed to be due to arrhythmia. The DIG study led to the hypothesis that digoxin may have bidirectional effects on mortality – beneficial effect at serum concentrations lower than 1.0 ng/mL and a detrimental effect at concentrations of 1.0 ng/mL or higher.

Digoxin has a narrow therapeutic window. In patients with normal cardiac rhythm, the beneficial hemodynamic, neuro-hormonal, and clinical effects are found with a low concentration of approximately 0.7

ng/mL. Additional benefits are not seen with higher doses traditionally considered therapeutic (with serum concentrations of 1.0 to 1.5 ng/mL). These higher concentrations may predispose to arrhythmias.
Since digoxin may result in adrenergic stimulation at higher concentrations, or in patients with ischemia, the combination of digoxin with beta-blockade may have theoretical advantages. Beta-blockers produce an anti-ischemic, anti-adrenergic effect leading to improved function while digoxin maintains hemodynamic compensation.

The dose of digoxin should be carefully considered, especially in women. "We should not abandon a therapy that may help women with heart failure. Rather we should use a dose that will result in a serum concentration lower than 1.0 ng per milliliter."

NEJM October 31, 2002; 347: 1394-95 "Perspective", editorial, first author Eric J Eichhorn, Medical City Dallas Hospital, Dallas TX. **www.nejm.org**

Comment:

I once heard an authority state – "Digitalis has been used for over 200 years. We still don't know how to use it properly."

I believe digoxin remains a useful drug. Low doses and careful monitoring are essential. RTJ

Screening For Excessive Alcohol Use Created More Problems Than It Solved

10-16 SCREENING AND BRIEF INTERVENTION OF EXCESSIVE ALCOHOL USE: Qualitative Interview Study Of Experiences Of General Practitioners.

Primary care practice is emphasized as a suitable place for screening programs. A consensus is emerging that screening for excessive alcohol use followed by a brief intervention to modify drinking behavior should be implemented in primary care practice. However, implementation of such programs is far from straight forward. The bulk of evidence consists of efficacy studies rather than pragmatic studies.

This study explored the suitability of screening patients for excessive alcohol use by describing the experiences of primary care clinicians who tried screening in their everyday practice.

Conclusion: Screening for excessive alcohol use created more problems than it solved for the participating MDs.

STUDY

1. Conducted qualitative interviews with primary care clinicians who had participated in a pragmatic study of a combined program of screening and a brief intervention for excessive alcohol use. Over 6500 patients age 18-64 had been screened.
2. . Screening was done using the AUDIT alcohol use disorders identification test. About 15% of patients drank excessively (over 12 units per week.). Alcohol dependence was suspected in 3%.
3. The study then interviewed the general practitioners who had conducted the screen and attempted intervention. Doctors in 24 practices volunteered for the study. They were interviewed in focus groups and individually

to investigate the suitability, validity, and effectiveness of such a program.

RESULTS

1. Doctors were surprised at how difficult it was to establish rapport with the patients who had a positive result on screening and to ensure compliance with the intervention.
2. Doctors often failed to follow-up on initial interventions. Some expressed a lack of confidence in their ability to counsel patients effectively on lifestyle issues.
3. Doctors questioned the rationale of screening in young drinkers who may grow out of excessive drinking behaviors. A large number of young hazardous drinkers was identified. Many doctors felt that the prevention of alcohol problems in young people should chiefly take place earlier and elsewhere in the community and in their families. They felt that systematic interventions for young drinkers were not a natural part of their job, and questioned the rationale of screening in young drinkers.
4. The program needed considerable resources. It interrupted the natural course of consultations and was inflexible.
5. The doctors could not recommend the screening and intervention program, although they thought it important to counsel their patients on drinking.
6. Most doctors were convinced that some patients did not respond honestly to the questionnaire. Many drinkers declined screening or gave poor excuses for not being able to participate.
7. Almost all doctors experienced negative reactions from some patients, ranging from uneasiness or embarrassment, lying about their drinking behaviors, or to finding another doctor. However, most doctors felt their relationships with patients were robust enough for them to give advice on sensible drinking.
8. Most patients in the intervention group who revisited their primary care clinician had not been followed up on their drinking,
9. Some doctors said that a few patients may have been encouraged to take steps to modify their drinking behavior, but in general they were deeply skeptical about the effects of the intervention on behavior.
10. Lack of time and lack of training were considered by doctors to be important barriers to the effectiveness of the program. Ten minutes of intervention several times a day was experienced as stressful. Some believed that 10 to 15 minutes was too little time anyway, as alcohol problems were often part of a much more complex problems.
11. Both focus groups and 4 of the 5 doctors who were interviewed individually concluded that they could not recommend screening, nor would they screen their patients in the future.

DISCUSSION

1. Brief interventions on lifestyle matters are efficacious. They can work in ideal conditions and for selected patients. However, how doctors actually feel, think, and perform with respect to such programs may diverge from the official rhetoric on health promotion programs in primary care practice.
2. Clinical health promotion programs should take account of the professional, practical, technical,

and ethical factors.

3. These results underline the value of pragmatic studies of the suitability of apparently efficacious programs before they are implemented on a wider scale.

CONCLUSION

Screening and brief intervention programs may fail to detect harmful drinkers, while requiring considerable resources for primary prevention in groups of hazardous drinkers. Screening-based brief interventions left the practitioners with a sense of failure in achieving rapport and compliance, and was not congruent with contemporary approaches to dealing with lifestyle issues.

Screening for excessive alcohol use created more problems than it solved.

BMJ October 19, 2002; 325: 870-72 Original investigation, first author Anders Beich, University of Copenhagen, Denmark. **www.bmj.com/cgi/content/full/325/xxxx/870**

Comment:

I believe the authors advice to test a screening intervention pragmatically is good advice.

Primary care clinicians are encouraged to screen and intervene for alcohol problems. They are said to be effective in reducing alcohol abuse. These recommendations are based on experimental data, not tested in the real world. The real world may differ.

This reminds me of advice given for screening for depression. Simple questions may be as revealing as a more detailed screen. Do you drink excessively – ie, more than one drink a day? Do you think you may have a drinking problem? Would you like to do something about it?

The difficulty is choosing who to ask. RTJ

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BP-lowering therapy may protect against dementia in older patients with systolic hypertension

10-17 PREVENTION OF DEMENTIA WITH ANTIHYPERTENSIVE TREATMENT

New Evidence from the Systolic Hypertension in Europe (Syst-Eur) Trial

"Hypertension is associated with increased risk of both vascular dementia and Alzheimer disease."

The Syst-Eur randomized, double-blind study[1] observed that, compared with placebo, antihypertension therapy, reduced the incidence of dementia by 50% -- from 7.7 to 3.8 cases per 1000 patient-years. [NNT(benefit one patient per year = 256)]. The study was criticized because of the small number of cases.

This study extended the trial into an open-label, active treatment follow-up study in the same population, based on the original active study medication.

Conclusion: The extended study reinforced the evidence that BP-lowering therapy protected against dementia in older patients with systolic hypertension.

STUDY

1. Over 2000 patients entered in the original study. All were at least 60 years old at baseline. Systolic BP was between 160 and 219, with diastolic below 95. None had dementia..
2. Drug treatment was continued in the active group and started in the previous control group.
3. Treatment was based on the dihydropyridine calcium-blocker nitrendipine (10-40 mg/d) with possible addition of the ACE inhibitor enalapril (*Vasotec*; 5- 20 mg), hydrochlorothiazide 12.5 -25 mg, or both add-on drugs.
4. The original study covered 2 years. The add-on study continued treatment for an additional 2 years (4 years overall).

RESULTS

1. Incidence of dementia doubled in the 3rd and 4th years from 32 to 64 cases, 41 of whom had Alzheimer disease.
2. During the 3rd and 4th years, BP in the previous control group (n = 1400) was 7/3.2 mm Hg higher than in the subjects first randomized to active treatment.
3. At last examination, fewer patients in the previous control group were taking the active drugs than in the previous active treatment group.
4. Compared with previous controls, long-term antihypertension treatment was associated with a reduction in incidence of dementia from 7.4 to 3.3 cases per 1000 patient-years; (43 vs 21 total cases of dementia; 29 vs 12 cases of Alzheimer disease).
5. After adjustment for sex, age, education, and entry BP, the relative hazard rate of dementia associated with the use of nitrendipine was 0.38.
6. Treatment of 100 patients for 5 years was calculated to prevent 2 cases of dementia.

DISCUSSION

1. The present study demonstrated a high degree of consistency with the original study in the reduction of risk of dementia associated with antihypertension therapy based on nitrendipine.
2. The original hypothesis was that treatment of hypertension would protect mainly against vascular dementia. Recent studies suggest that hypertension, and more generally, all risk factors involved in arteriosclerosis, may contribute to the incidence of degenerative dementias.
3. “There is a growing awareness that the distinction between Alzheimer disease and vascular dementia is less clear than initially envisaged, both conditions sharing similar mechanisms and lesions albeit to different degrees.”
4. In this study, benefit was predominantly attributable to the prevention of degenerative dementia rather than dementia occurring in association with cardiovascular events such as stroke.
5. Some reports suggest that calcium channel blockers may confer specific neuroprotection. The

aging brain loses its ability to regulate intracellular calcium, leading to a cascade of cellular impairments and ultimately to cell death. Calcium channel blockers might provide better protection against stroke than treatment based on diuretics and beta-blockers. [2]

CONCLUSION

A 4-year follow-up study extending antihypertension therapy reinforced the evidence that BP-lowering therapy initiated with a long-acting dihydropyridine calcium blocker (nitrendipine) protects against dementia in older patients with systolic hypertension.

Archives Int Med October 14, 2002; 162: 2046-52 Original investigation, first author Francoise Forette, Hopital Broca, University of Paris V, Paris France. **www.archinternmed.com**

1 "Prevention of Dementia in Randomized, Double-blind placebo-controlled Systolic Hypertension in Europe Trial" Lancet 1998;352: 1347-51 **www.thelancet.com**

Comment:

2 Do calcium blockers have a special role in prevention of dementia? These conclusions require confirmation by other randomized trials. The point that long-acting calcium blockers have a special effect on prevention of dementia is intriguing but tentative. Primary care clinicians should treat systolic hypertension for its established benefits, hoping that prevention of dementia will be added to them.

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Regular Consumption Of Fish Was Associated With A Lower Risk Of Future Development Of Dementia?

10-18 FISH, MEAT, AND RISK OF DEMENTIA: A Cohort Study

Is there a role of fat in the risk of dementia? Fatty acids could be involved through several pathways: atherosclerosis, thrombosis, and inflammation.

This study evaluated whether there is a relation between consumption of fish (rich in polyunsaturated fatty acids) or meat (rich in saturated fatty acids) and risks of dementia.

Conclusion: Individuals consuming fish regularly had less risk of dementia and Alzheimer's disease.

STUDY

1. Obtained data from the PAUID (Personnes Agees QUID) epidemiological study of cognitive and functional ageing.
2. In 1991-92 visited over 1600 persons, all aged over 68. All were without dementia and living at home in southwestern France.
3. Determined frequency of consumption of fish or seafood: daily, at least once a week (but not every day), from time to time (but not every week), and never.
4. Followed participants for up to 7 years for onset of dementia.
5. Incidence of dementia was confirmed by a visited by a neurologist to confirm the diagnosis. (*DSM-III-R*)

6. Calculated incidence of dementia per 100 person-years.

RESULTS

1. During 7 years, 170 new cases of dementia occurred, including 135 cases of Alzheimer's disease.
2. Risk of dementia decreased as consumption of fish or seafood increased:

	Incidence per 100 patient-years	
Fish or seafood consumption	Dementia	Alzheimer's
Once a day	1.00	1.00
At least once a week	2.05	1.64
From time to time	2.90	2.24
Never	6.61	5.29

3. Participants who ate fish or seafood at least once a week had a significantly lower risk of being diagnosed as having dementia in the 7 subsequent years. (Hazard ratio = 0.66) The hazard ratio for Alzheimer's was 0.69)

DISCUSSSION

1. Elderly persons who ate fish or seafood at least once a week were at lower risk of developing dementia, including Alzheimer's disease over a period of 7 years.
2. The Rotterdam study reported similar results over a period of 2 years.
3. In addition to providing vascular protection,, the n-3 fatty acids contained in fish oils could reduce inflammation in the brain and may have a specific role in brain development and regeneration of nerve cells.

CONCLUSION

Regular consumption of fish was associated with a lower risk of future development of dementia.

BMJ October 26, 2002; 325: 932-33 Original investigation, first author Pascale Barberger-Gateau, INSERM U330, Universite Victor Segalen, Bordeaux, France

www.bmj.com/cgi/content/full/325/7390/932

Comment:

Not a conclusive study, but the concept is interesting enough to watch for follow-up studies. RTJ

Don't automatically dismiss patients' complaints of muscle weakness as being unrelated to statin therapy

10-19 STATIN-ASSOCIATED MYOPATHY WITH NORMAL CREATININE LEVELS

Statin drugs have been exceptionally beneficial and safe. Randomized trials and community surveillance have demonstrated an extremely low incidence of serious muscle toxicity from statins (about 1 case per 10 000). Some patients develop muscle symptoms. Some have severe muscle toxicity.

There have been credible reports of patients who have muscle symptoms and normal creatine kinase levels while receiving statins. Others have described muscle pain. “Thus it appears that muscle symptoms of some patients receiving statin therapy might represent muscle toxicity below the threshold needed to increase creatine kinase (**CK**) levels.”

This paper is an anecdotal report of 4 patients who developed myopathy during statin therapy despite normal CK levels. All had statin blood levels within the normal therapeutic range.

Symptoms reversed on discontinuation of the drug. On rechallenge, muscle symptoms recurred, and all 4 were able to accurately distinguish blinded statin therapy from placebo. Strength testing confirmed weakness during therapy. (Eg, difficulty ascending stairs.) This also reversed on discontinuation.

All had muscle biopsies which revealed extensive lipid-filled vacuoles distributed within the myocytes, ragged red fibers, and cytochrome oxidase-negative muscle fibers consistent with myopathy. Histology reverted to normal after the drug was discontinued. (*Illustrations page 583*.)

“Some patients who develop muscle symptoms while receiving statin therapy have demonstrable weakness and histopathologic findings of myopathy despite normal serum creatinine kinase levels.”

Annals Int Med October 1, 2002; 137: 581-85 Original investigation, first author Paul S Phillips, Scripps Mercy Hospital and University of California, San Diego. **www.annals.org**

Comment:

Although this is an anecdotal report, I found it convincing. It would not be unusual for rare and undescribed toxicities to appear in a few patients when drugs are used in millions of persons. This would include myopathy and neuropathy associated with statins.

The clinical message is – don’t automatically dismiss patients’ complaints of muscle soreness and weakness as being unrelated to statin therapy. A one-of-one trial may distinguish the few patients with statin-related symptoms from the many patients with other more common causes.

An accompanying editorial in this issue of Annals by Scott M Grundy, University of Texas Southwestern Medical Center, Dallas -- pp 617-18) comments:

To date, no evidence indicates that prolonged statin therapy leads to permanent muscle damage or progressive myopathy in patients with normal CK levels. For high-risk persons, the proven benefits of statins outweighs the unlikely possibility of permanent muscle damage. Prescription of statins for eligible patients should continue despite the results of this study. In most patients with muscle symptoms, the symptoms will be found not related to the statin.

As usual, physician judgment of the individual patient, balancing risks and benefits along with the patient’s own assessment, will help to distinguish those for whom the drug should be discontinued from those who should continue. Fortunately, the need for this decision will be infrequent. RTJ

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Introducing A Novel Oral Direct Thrombin Inhibitor

10-20 XIMELAGATRAN VERSUS WARFARIN FOR PREVENTION OF VENOUS THROMBOEMBOLISM AFTER TOTAL KNEE ARTHROPLASTY

Ximelagatran is a novel oral direct thrombin inhibitor. It is rapidly absorbed and transformed into its active form, melagatran. Melagatran provides competitive inhibition of both free and clot-bound thrombin.

Ximelagatran results in predictable plasma concentrations of melagatran which increase linearly in relation to dose. Fixed doses without coagulation monitoring have been studied in phase II trials. They have shown promising results in prophylaxis of venous thromboembolism after hip and knee surgery. A fixed dose of ximelagatran produces predictable plasma melagatran concentrations and has no known food or drug interactions. Animal studies indicate it has a wide therapeutic window and increases bleeding only slightly at therapeutic doses. Plasma concentrations are influenced by renal function and weight.

This phase III randomized trial compared efficacy and safety of ximelagatran with warfarin in over 650 patients who underwent total knee arthroplasty.

Seven to 12 days of ximelagatran therapy (24 mg twice daily), starting the day after surgery was as safe and effective in prophylaxis of venous thromboembolism as warfarin. (19% of oral ximelagatran patients vs 25% in the warfarin group developed deep vein thrombosis (DVT); 1.7% vs 1.8% developed symptomatic DVT; 0.6% vs 1.8% developed symptomatic pulmonary embolism.

Major bleeding occurred in 1.7% vs 0.9% and minor bleeding in 7.8% vs 6.4%.

The investigators concluded that ximelagatran was well tolerated and at least as effective as adjusted-dose warfarin for prophylaxis of venous thromboembolism. Its advantage is a fixed dose without need of coagulation monitoring.

Annals Int Med October 15, 2002; 137: 648-55 Original investigation, first author Charles W Francis, University of Rochester Medical Center, Rochester, NY. www.annals.org

Comment:

I abstracted this study in order to acquaint myself with this new anticoagulant. More confirmatory studies will be required before it can be entered into primary care practice. If it pans out, its fixed dose, oral administration, absence of interactions with food and drugs, and the fact that it requires no anticoagulation monitoring will be great advantages.

See also: “Ximelagatran And Melagatran Compared With Dalteparin For Prevention Of Venous Thromboembolism After Total Hip Or Knee Replacement” Lancet November 9, 2002; 360: 1441. Therapy was effective and safe.

Ximelagatran is manufactured by AstraZeneca.

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