PRACTICAL POINTERS

FOR
PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

FEBRUARY 2002

JAMA, NEJM, BMJ, LANCET

ARCHIVES INTERNAL MEDICINE

ANNALS INTERNAL MEDICINE

www.practicalpointers.org

PUBLISHED BY PRACTICAL POINTERS, INC.

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HIGHLIGHTS FEBRUARY 2002

2-1 BETA-BLOCKERS IN HEART FAILURE: Clinical Applications

Beta-blockers should be initiated only in HF patients who are clinically euvolemic or receiving stable doses of diuretics without signs of fluid overload (pulmonary rales, jugular venous distention, or more than minimal peripheral edema).

Although there is currently insufficient evidence to recommend beta-blocker use in patients with asymptomatic LV dysfunction, guidelines suggest that they should be given because they reduce progression to HF.

Dosing should be guided by "start low" (about 1/10 the maximum dosage), "go slow" principle. This calls for doubling the dose every 2 to 4 weeks until the target is reached. When a dose is titrated upward, symptomatic hypotension can be expected to be greatest within 24 hours and improve within the next few doses.

There is some evidence for benefit from continuing very low doses of beta-blocker.

Practical point: "All heart failure (**HF**) patients with left ventricular (**LV**) systolic dysfunction should be considered for beta-blockers to reduce morbidity and prevent mortality."

2-2 BETA-BLOCKER THERAPY IN HEART FAILURE: Scientific Review

Acute treatment with beta-blockers decreases BP and cardiac index; long-term administration is associated with significant increases in ejection fraction and cardiac index, and a decrease in left ventricular diastolic pressure. A decrease in myocardial mass and LV volume improves hemodynamics. Beta-blockers have been evaluated in more than 10 000 patients with all grades of HF. Five meta-analyses have arrived at the same conclusion: beta-blockers are associated with a consistent 30% reduction in mortality and a 40% reduction in hospitalizations for HF. (NNT 1 year to prevent one death = 26.)

"The evidence suggests that virtually all patients with heart failure caused by LV systolic dysfunction benefit from beta-blockers."

2-3 GUIDELINES FOR MANAGING COMMUNITY ACQUIRED PNEUMONIA

Streptococcus pneumoniae remains the most common bacterial pathogen. Mycoplasma and chlamydia each cause about 10% of all pneumonias. Primary care clinicians make most of their management decisions without access to chest X-ray. Diagnosing pneumonia clinically is inaccurate and the etiological agent cannot be reliably predicted from clinical features.

The respiratory rate is a most important indicator of disease severity. In the elderly, assessment of the mental state is especially important. Guidelines identify four core adverse prognostic features: confusion; elevated blood urea; respiratory rate above 30; and BP less than 90 systolic or 60 diastolic. If available, pulse oximetry (saturation less than 92%) indicates severe disease.

Patients under age 50 years without comorbidity and lacking any of the core features, do not usually require hospitalization.

Practical point: See the abstract for suggested oral antibiotics for outpatients.

2-4 REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

Lifestyle changes (physical activity, diet, weight loss) and metformin (*Glucophage*) both reduced incidence of diabetes in persons at high risk. Lifestyle changes were more effective.

Practical point: This is one of several recent studies concluding that diabetes 2 can be prevented by improving lifestyle. Indeed, it might be possible to "cure" diabetes by lifestyle – ie, reduce glucose intolerance to a level below the WHO definition. Many people would rather take a pill to prevent diabetes than discipline themselves. I think this is misuse of an important drug.

2-5 DIETARY PATTERNS AND RISK OF TYPE 2 DIABETES MELLITUS IN MEN

Compared with the prudent diet (vegetables, fruit, fish, poultry, whole grains), the western type diet (red meat, processed meats, french fires, high-fat dairy, refined grains, sweets and deserts) was associated with an increased risk of DM-2. The more outrageous the intake of

western type foods, the higher the risk. Combining a long history of intake of western type foods with obesity and a sedentary lifestyle greatly increased risk. However, the diet was independently related to these factors, and the western diet alone increased risk.

Practical point: Another important benefit of a disciplined lifestyle.

2-6 QUALITY-OF-LIFE AND DEPRESSIVE SYMPTOMS IN POSTMENOPAUSAL WOMEN AFTER RECEIVING HORMONE THERAPY: Results from the Heart and Estrogen/Progestin Replacement Study (HERS) Trial

HRT may have either positive or negative effects on quality of life depending on the presence or absence of menopausal symptoms. Women with menopausal symptoms have improvement in emotional dimensions of quality of life when given HRT.

For women without menopausal symptoms, HRT was associated with net *negative* effects on physical dimensions of quality of life.

Practical point: Menopausal symptoms are the only reason to prescribe HRT. And the only effective treatment. Other drugs are more effective in preventing osteoporosis and cardiovascular disease.

2-7 POSTMENOPAUSAL HORMONE THERAPY AND QUALITY OF LIFE

All women in the study were well past the age of onset of menopausal symptoms. All had a history of cardiovascular events in the past which, along with their age, placed them at high risk for recurrence. The decline in quality of life in this cohort therefore may have been due to the increased rates of cardiovascular events associated with HRT in the first year of replacement therapy. (*Presumably due to a combination of high risk and a pro-thrombotic effect of HRT. RTJ*) Thus, in women with established cardiovascular disease, HRT may cause more harm than benefit.

The risk of cardiovascular events and other outcomes among younger women and for those without cardiovascular disease are less clear.

For prevention of osteoporosis and lipid disorders, more effective drugs are available.

Practical point: Menopausal symptoms make some women miserable. HRT is the most effective treatment. Despite the possible risk in women with many risk factors for heart disease, or with past history of cardiovascular disease, benefits may outweigh possible harms. Prophylactic aspirin and statin drugs may be given to lessen harms of HRT.

2-8 ASSOCIATION OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS WITH FIRST OCCURRENCE OF HEART FAILURE AND WITH RELAPSING HEART FAILURE

NSAID use was not associated with an increased risk of a first episode of HF.

In patients with past history of HF, current use of NSAIDs substantially increased risk of relapse.

Practical point: Use NSAIDs with caution in persons with heart failure history. And in those with hypertension.

2-9 RESIDUAL LIFETIME RISK OF DEVELOPING HYPERTENSION IN MIDDLE-AGE WOMEN AND MEN.

In persons with normal BP (<140/90) at ages 55 and 65, the likelihood of development of hypertension as they grow older approaches 90%. Efforts should be directed at primary prevention. Lifestyle management is essential. "The approach of waiting for hypertension to develop and only then treating the elevated blood pressure is injudicious."

Practical point: Drug therapy is not indicated in many older persons with BP > 140/90. Primary care clinicians use their clinical judgement. They resist rigid applications of “evidence-based medicine” because they know EBM inclusion and exclusion criteria simply do not apply to many of their individual patients.

2-10 AORTIC STENOSIS

When is the optimal time to intervene? What is the best intervention? In adults with calcified valves, balloon angioplasty may temporarily relieve symptoms but does not prolong survival. Replacement of the valve is required. Surgery is usually delayed until symptoms develop. Once angina, syncope, dyspnea or other symptoms of heart failure develop, the patient’s life span is drastically shortened unless the valve is replaced. The 10 year survival rates among those undergoing successful valve replacement approaches that of the normal population.

Practical point: “There is overwhelming evidence that once patients with severe aortic stenosis become symptomatic, prompt valve replacement is indicated." Sooner or later primary care clinicians will encounter a patient with AS at the most unexpected times.

2-11 PHYSICIAN-RELATED BARRIERS TO THE EFFECTIVE MANAGEMENT OF UNCONTROLLED HYPERTENSION

“Our findings suggest that an important reason why physicians do not treat hypertension more aggressively is that they are willing to accept an elevated systolic BP in their patients.”

Practical point: I believe primary care clinicians have good reason to accept a higher BP in some individual patients.

2-12 EFFECTS OF HYALURONATE SODIUM ON PAIN AND PHYSICAL FUNCTIONING IN OSTEOARTHRITIS OF THE KNEE

For resting pain relief, HS seems to be as effective as NSAIDs. HS may be superior to placebo or NSAIDs for improving functional performance and relieving pain with physical activity.

Practical point: Based on adequate informed consent, some patients will accept HS injections and will report benefit.

2-13 HYALURONATE SODIUM INJECTIONS FOR OSTEOARTHRITIS

Hope, Hype, And Hard Truths

This editorial presents a contrary view. It concludes that the present data fails to demonstrate and benefit beyond the placebo effect>

Practical point: Primary care clinicians frequently face divergent opinions such as this. They then depend on the individual patient’s acceptance and outcomes from the treatment

2-14 PLASMA HOMOCYSTEINE AS A RISK FACTOR FOR DEMENTIA AND ALZHEIMER’S DISEASE

An increased plasma homocysteine level was a strong, independent risk factor for the development of dementia and Alzheimer’s disease.

Practical point: The homocysteine connection lingers on in the literature. While not proven, the benefit/harm-cost of folate, B12, and B6 therapy may be high because harm and costs are low.

2-15 ROLAXIFENE AND CARDIOVASCULAR EVENTS IN OSTEOPOROTIC POSTMENOPAUSAL WOMEN

There was no evidence that raloxifene caused an early increase in risk of CV events in the group overall, or in the subset of women at high risk for CHD

Raloxifene for 4 years significantly reduced the risk of CV events among the subgroup at high risk and among those with established CHD.

Practical point: None at present. Wait for future developments.

2-16 OVERCOMING RESTENOSIS WITH SIROLIMUS

Preliminary studies using sirolimus coated stents have been quite promising and should reduce restenosis rate.

Practical point: This will probably be another advance tilting patients with coronary disease toward PTCA and away from CABG.

2-17 RECOMBINANT HUMAN PARATHYROID HORMONE

A recent FDA panel recommended approval of an N-terminal fragment of parathyroid hormone for treatment of osteoporosis (teriparatide; *Forsteo*). The application for approval was based on evidence from a randomized trial in women with osteoporosis demonstrating large increases in cancellous (trabecular) bone formation in the vertebral bodies and a greatly reduced risk of spine fracture.

PTH expands the bony envelope in the hip. Thus, its biggest impact may be in prevention of fractures of the hip. "From being one of medicine's most untreatable disorders, osteoporosis is following the footsteps of hypertension and proving amenable to treatment through several targets: estrogen receptors; osteoclasts (by targeting them with bisphosphonates) and now parathyroid hormone receptors."

Practical point: A potential advance in prevention and treatment of osteoporosis. Watch for developments.

2-18 INTRAVENOUS ZOLEDRONIC ACID IN POSTMENOPAUSAL WOMEN WITH LOW BONE MINERAL DENSITY

Zoledronic acid infusions given at intervals for up to 1 year produced effects on BMD and bone turnover as great as those achieved by oral bisphosphonates.

One annual infusion might be an effective treatment.

Practical point: A potential advance in prevention and treatment of osteoporosis. Watch for developments. See who wins.

For All Patients With Heart Failure

2-1 BETA-BLOCKERS IN HEART FAILURE: Clinical Applications

"All heart failure (**HF**) patients with left ventricular (**LV**) systolic dysfunction should be considered for beta-blockers to reduce morbidity and prevent mortality." The most recent ACC-AHA guidelines have introduced a broader disease-progression staging system. It ranges from patients without structural heart disease but at risk of HF (stage A), to severely ill patients with need for specialized interventions (stage D).

The guidelines endorse use of beta-blockers for all patients with HF except for those with a history of intolerance to beta-blockers or for those with a contradiction. For patients with refractory HF multiple hospitalizations, or need for specialized treatments (stage D), beta-blockers are not recommended unless a heart failure specialist is first consulted.

Beta-blockers should be initiated only in HF patients who are clinically euvolemic or receiving stable doses of diuretics without signs of fluid overload (pulmonary rales, jugular venous distention, or more than minimal peripheral edema). If fluid status worsens after beta-blocker is started, the dose of diuretic should be increased provided the patient has no hypotension, evidence of hypoperfusion, or requirement for intravenous positive inotropic support.

Use of a beta-blocker is most applicable for patients who are also receiving ACE inhibitors and digoxin.

Although there is currently insufficient evidence to recommend beta-blocker use in patients with asymptomatic LV dysfunction, guidelines suggest that they should be given because they reduce progression to HF.

Patients with symptomatic bradycardia should not receive beta-blockers until the cause of the bradycardia (< 60/min) is ascertained and treated. Patients with bronchospasm requiring inhaled beta-agonists should not receive beta-blockers. However, patients with mild chronic obstructive pulmonary disease may have greater absolute benefit than patients without.

Diabetes was once thought to be a contraindication, but beta-blockers have since been shown to be well tolerated, with little concern of masking hypoglycemia.

Patients should understand that beta-blockers will immediately reduce the chance of death from HF and other causes. They should know that 2 to 3 months may elapse before they notice a reduction in symptoms. They may experience a brief worsening of symptoms in the beginning. Patients should weigh themselves daily and report if weight increases or if they develop symptoms of hypotension or bradycardia. They must cooperate with the gradual

increase in dosage. Hypotension, bradycardia and worsened HF can occur in virtually any patient if the dosage is too high or escalated too rapidly. They should not stop beta-blockers abruptly without consulting their physician.

Which beta-blocker is the best choice? Opinions vary. Currently only carvedilol and long-acting metoprolol are approved by the FDA for use in HF. Metoprolol is highly selective for blocking cardiac (B1) receptors. Carvedilol is less cardio-selective but has ancillary vasodilating and antioxidant properties. "There is no evidence that differences between beta-blockers are associated with differences in patient outcomes."

Dosing should be guided by "start low" (about 1/10 the maximum dosage), "go slow" principle. This calls for doubling the dose every 2 to 4 weeks until the target is reached. When a dose is titrated upward, symptomatic hypotension can be expected to be greatest within 24 hours and improve within the next few doses.

There is some evidence for benefit from continuing very low doses of beta-blocker.

JAMA February 20, 2002; 287: 890-97 Review article, first author Michael F H Farrell, Yale University School of Medicine, New Haven Conn. **www.jama.com**

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A Sea Change In Therapy

2-2 BETA-BLOCKER THERAPY IN HEART FAILURE: Scientific Review

A medication once thought to be dangerous for patients with heart failure (**HF**) now is known to reduce morbidity and mortality.

Beta-blockers are important therapy for angina, hypertension, acute myocardial infarction, tachyarrhythmias — and now HF.

Conventional wisdom held that HF was solely due to a decline in systolic function, and that medications with a negative inotropic action were contraindicated. Studies evolved slowly demonstrating beneficial effects of beta-blockers. HF is a complex disorder characterized not only by declines in systolic function, but also by a maladaptive increase in adrenergic activity.

This article reviews the scientific rationale supporting the use of beta-blockers for patients with HF and presents current therapy recommendation. The author's goal is to accelerate the appropriate use of beta-blockers in clinical practice.

The pathophysiology of HF is related to activation of the adrenergic nervous system. Early in HF, drops in cardiac output lead to decreased organ perfusion. A compensatory increase in adrenergic drive occurs, with release of norepinephrine. Norepinephrine stimulates ventricular contraction, and increases cardiac output and BP. This compensatory mechanism occurs early, when patients are asymptomatic. Chronic activation of the adrenergic system leads to potentially deleterious effects on the heart. Myocardial oxygen demand and ischemia increase. At the same time, peripheral vasoconstriction increases both preload and afterload, causing additional stress on the failing ventricle. This long-term mechanical stress, in conjunction with cardiac fibrosis and necrosis promoted by

norepinephrine, contributes to a dilated, less contractile myocardium. "Thus prolonged activation of the adrenergic system may be maladaptive, causing progressive deterioration of myocardial function and portending a poor prognosis."

Acute treatment with beta-blockers decreases BP and cardiac index; long-term administration is associated with significant increases in ejection fraction and cardiac index, and a decrease in left ventricular diastolic pressure. A decrease in myocardial mass and LV volume improves hemodynamics.

Beta-blockers may also regulate heart rate and decrease arrhythmias.

Beta-blockers have been evaluated in more than 10 000 patients with all grades of HF. Five meta-analyses have arrived at the same conclusion: beta-blockers are associated with a consistent 30% reduction in mortality and a 40% reduction in hospitalizations for HF. (NNT 1 year to prevent one death = 26.) "The evidence suggests that virtually all patients with heart failure caused by LV systolic dysfunction benefit from beta-blockers."

Practice guidelines: Recommend beta-blockers in a wide range of HF patients, including those with asymptomatic LV systolic dysfunction, and those with severe symptomatic disease . However, those with severe HF who require intravenous inotropes or mechanical support should not receive them.

The article discusses 3 beta-blockers which produce significant mortality benefit:

	Cost	Starting dose
Bisoprolol (*Zebeta*; generic) beta 1 receptor blocker (heart)	10 mg $1.13 each	1.25 mg/d
Metoprolol succinate (*Toprol XL*) beta 1 receptor blocker (heart)	100 mg $1.02 each	12.5 mg/d
Carvedilol (*Coreg*) alpha 1, beta 1, and beta 2 blocker (peripheral vasculature, heart and lung)	25 mg $1.55 each	3.125 mg 2/d

Maximum dose; bisoprolol – 10 mg/d; *Toprol XL* - 200 mg/d; *Coreg* – 25 mg 2X/d

JAMA February 20,2002; 287: 883-89 Scientific review, first author JoAnne Micale Foody, Yale University School of Medicine, New Haven, Conn. **www.jama.com**

2-3 GUIDELINES FOR MANAGING COMMUNITY ACQUIRED PNEUMONIA

The British Thoracic Society has issued new guidelines for managing community acquired pneumonia (**CAP**). They are formulated using explicit search strategies and appraisal criteria. Recommendations are graded according to the strength of supporting evidence. However, many of the recommendations are based on the lowest grades of evidence.

Streptococcus pneumoniae remains the most common bacterial pathogen. Mycoplasma and chlamydia each cause about 10% of all pneumonias.

Primary care clinicians make most of their management decisions without access to chest X-ray. Diagnosing pneumonia clinically is inaccurate and the etiological agent cannot be reliably predicted from clinical features.

The respiratory rate is a most important indicator of disease severity. In the elderly, assessment of the mental state is especially important. Guidelines identify four core adverse prognostic features: confusion; elevated blood

urea; respiratory rate above 30; and BP less than 90 systolic or 60 diastolic. If available, pulse oximetry (saturation less than 92%) indicates severe disease.

Patients under age 50 years without comorbidity and lacking any of the core features, do not usually require hospitalization.

Chest X-rays are recommended for patients who fail to improve in 48 hours.

What about choice of initial antibiotic? First, use generous doses. Amoxicillin up to 1 gram three times a day is still the recommended antibiotic. First alternatives are erythromycin 500 mg four times a day, or clarithromycin (*Biaxin*) 500 mg twice daily. Clarithromycin causes less gastric upset, but is considerably more expensive. Ciprofloxacin (*Cipro*) is not a good choice because of unreliable activity against the pneumococcus. Treatment at home for 7 days is recommended for non-severe pneumonia; 14 to 21 days for more severely ill patients, or those caused by atypical pathogens (legionella, staphylococci, or gram negative bacilli).

Formerly, tetracycline was considered an agent of first choice. Resistance rates for pneumococci are lower than

for penicillin or erythromycin. It is active against atypical pathogens. However, it was not recommended because of issues related to safety in pregnancy and "would require a major change in current prescribing practice by general practitioners." (*In the UK*). This would limit compliance with the recommendations.

BMJ February 23, 2002; 324: 436-37 Editorial by Duncan Keely, The Health Center, Thame, UK

www.bmj.com/cgi/content/full/324/7336/436

Comment:

Immediacy of administration of the chosen antibiotic is an important therapeutic application. Do not wait for the prescription to be called to the pharmacy and delivered later. Immediate administration (first doses out of the doctor's bag or in the office will improve prognosis.

British recommendations for outpatient treatment:	Cost
Amoxicillin 1 gram orally three times daily for 10 days	$60
Erythromycin (generic) 500 mg orally four times daily	Inexpensive
Clarithromycin (Biaxin) 500 mg orally twice daily for 10 days	$80
US recommendations for outpatient treatment	
(Johns Hopkins guide (**www.hopkins-abxguide.org**)	
Doxycycline (*generic*)100 mg orally twice daily for 7-10 days	Inexpensive
Azithromycin (*Zithromax*) 500 mg orally once daily for 7 days	$104
Clarithromycin (*Biaxin*) 500 mg orally twice daily 7-10 days	$80
Erythromycin (*generic*) 500mg orally four times daily 7-10 days	Inexpensive

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Additional Evidence — DM2 Can Be Prevented

2-4 REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

Current methods of treating diabetes remain inadequate; prevention is preferable. The hypothesis that type 2 diabetes is preventable is supported by observational studies and two clinical trials of diet and exercise in persons at high risk.

Elevated plasma glucose in the fasting state, overweight, and a sedentary lifestyle are potentially reversible. This study hypothesized that modifying these factors with a lifestyle program or administration of metformin would prevent or delay development of diabetes.

Conclusion: Both lifestyle changes and metformin reduced incidence of diabetes in persons at high risk.

STUDY

1. Entered over 3000 non-diabetic persons who had elevated fasting and post-load plasma glucose concentrations. Mean age = 51; mean body mass index = 34. (Grossly obese.)
2. Baseline fasting plasma glucose concentrations were between 95 and 125 mg/dL (mean = 106);

   and between 140 to 199 mg/dL 2 hours post 75 g glucose load (mean = 164). Presence of both was required for entrance into the study. Participants were overweight and had elevated fasting and post-load glucose concentrations — 3 of the strongest risk factors.
3. Randomized to: 1) metformin (*Glucophage*) 850 mg twice daily. Dose was increased after one month to 1700 mg twice daily unless GI symptoms warranted a longer period (84% reached this goal); 2) lifestyle modification, or 3) placebo.
4. Lifestyle intervention was systematic and intensive and had the goal of at least a 7% weight loss, and at least 150 minutes of physical activity per week. Participants received individual counseling.
5. Primary outcome was diabetes — diagnosed by a fasting glucose of 126 mg/dL or higher, or a 2-h post glucose load concentration 200 or higher.
6. Follow-up = 3 years

RESULTS

1. Incidence of diabetes per 100 person-years: placebo – 11; metformin – 7.8; lifestyle – 4.8.
2. 55% of participants in lifestyle achieved the goal of weight loss of 7% or more; 74% met the goal of physical activity.
3. Daily energy intake decreased a mean of 249 kcal in the placebo group; 296 kcal in the metformin group; and 450 kcal in the lifestyle group. Average fat intake in the lifestyle group decreased by 7%, but only 1% in the other groups.
4. Over 4 years, mean fasting glucose rose from 106 to 114 in the placebo group; and to 108 in the other 2 groups.

5. Over 4 years the percentage of individuals maintaining normal fasting and post-load glucose levels was higher in the lifestyle group than in the other 2 groups. Metformin provided less effective maintenance of normal levels.
6. To prevent one case of diabetes during 3 years, 7 persons would have to participate in lifestyle changes, and 14 would have to take metformin.

DISCUSSION

1. "Our results support the hypothesis that type 2 diabetes can be prevented or delayed in persons at high risk."
2. Lifestyle intervention was significantly more effective than metformin.

CONCLUSION

Lifestyle changes and metformin both reduced incidence of diabetes in persons at high risk. Lifestyle changes were more effective.

NEJM February 7, 2002; 346: 393-403 Original investigation by the Diabetes Prevention Program Research Group **www.nejm.org**

Comment:

See also "Prevention Of Type 2 Diabetes Mellitus By Changes In Lifestyle Among Subjects With Impaired Glucose Tolerance" NEJM 2001; 344: 1343-50

Would taking a powerful and expensive drug with a potential for severe adverse effects for years be a reasonable preventive measure? I would hesitate prescribing it for this purpose. Lifestyle changes are much more reasonable, effective, and safe.

For another life-style related to DM2 see the following abstract. RTJ

Another Reason To Follow The Prudent Diet

2-5 DIETARY PATTERNS AND RISK OF TYPE 2 DIABETES MELLITUS IN MEN

Analysis of secular trends suggests that adoption of a western diet is associated with development of type 2 diabetes (**DM-2**). However it is difficult to separate the effects of diet from those of other risk factors such as obesity and physical activity.

The study assessed the association between 2 dietary patterns and risk of developing DM-2: 1) the "western diet", characterized by higher consumption of red meat, processed meats, french fries, high-fat dairy products, refined grains and sweets and deserts; and 2) the "prudent" diet, containing a high content of vegetables, fruit, fish, poultry, and whole grains.

Conclusion: The prudent diet was associated with a substantially reduced risk of developing DM-2

STUDY

1. The Health Professionals Follow-up Study followed over 42 000 male health professionals age 40 to 70. None had diagnosed diabetes, cardiovascular disease, or cancer at baseline.
2. Identified and validated two major dietary patterns using a frequency analysis based on data from a 131 item food frequency questionnaire.
3. Used dietary pattern scores to rank participants according to the degree to which they conformed to each dietary pattern. Divided dietary pattern scores into quintiles for both the prudent and the western diet.
4. Determined rate of development of DM-2 according to the quintiles of each diet.
5. Follow-up – 12 years.

RESULTS

1. During 12 years, 1321 cases of DM-2 were documented.
2. Western diet was associated with an increased risk of DM-2 (relative risk of 1.6). Those in the highest quintile of intake of the western type foods had over 2 times the incidence of DM-2 than those in the lowest quintile. (Ie, the more outrageous the intake of red meat, french fries, high fat dairy, and sweets, the higher the risk.) Foods with major contributions to the western pattern were all positively associated with risk of DM-2. Risks ratios for extreme quintiles of consumption of red meat = 1.3; processed meats = 1.5; high-fat dairy = 1.2.)

3. Conversely, in the prudent diet group, those in the highest quintile (ie, the best of the prudent diet) had a slightly reduced risk of developing DM-2 compared to those in least compliant group. Relative risk of 5^{th} quintile vs 1^{st} = 0.84. (By my calculation the absolute difference between the worst of the western diet and the best of the prudent diet would result in one less patient in every 1000 each year being spared development of diabetes. RTJ)
4. Risks were adjusted for potential confounders including body mass index, physical activity, and smoking. (Ie, the risk was dependent on the diet patterns alone.)
5. However, as expected, individuals within each quintile of the western diet who were obese had the highest risk, as were those with a positive family history and those who were sedentary.

DISCUSSION

1. The type of diet (prudent vs western) was associated with risk of developing DM-2 independent of other risk factors such as body mass index and lack of physical activity.
2. It seems unlikely that a single dietary factor was responsible for the observed association.

CONCLUSION

Compared with the prudent diet, the western type diet was associated with an increased risk of DM-2. The more outrageous the intake of western type foods, the higher the risk.

Combining a long history of intake of western type foods with obesity and a sedentary lifestyle greatly increased risk. However, the diet was independently related to these factors, and the type diet alone increased risk.

Annals Int Med February 5, 2002; 136: 201-209 Original investigation, first author Rob M van Dam, Harvard School of Public Health, Boston Mass. **www.annals.org**

Comment:

The "prudent" diet is similar to the "Mediterranean" diet which had been strongly linked to reduced risk of cardiovascular disease. Now there is the suggestion that it will reduce incidence of diabetes as well. RTJ

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Helpful if Menopausal Symptoms are Present

2-6 QUALITY-OF-LIFE AND DEPRESSIVE SYMPTOMS IN POSTMENOPAUSAL WOMEN AFTER RECEIVING HORMONE THERAPY: Results from the Heart and Estrogen/Progestin Replacement Study (HERS) Trial

There is widespread belief that post-menopausal hormones have generally positive effects on the health of older women. This is reflected in the common use of the term hormone replacement therapy (HRT) which suggests correction of an abnormal deficiency.

Does HRT produce any benefits in quality-of-life?

Conclusion Only in women with menopausal symptoms.

STUDY

1. Randomized, placebo-controlled, double-blind trial entered over 2700 postmenopausal women (mean age = 67); 434 (15%) had flushing at entry. (The investigators considered flushing a surrogate for menopausal symptoms in general.)
2. All had documented coronary artery disease. (Ie, at high risk of recurrence.)
3. Randomized to: 1) HRT -- 0.625 mg of conjugated equine estrogen (*Premarin*) plus 2.5 mg medroxyprogesterone, or 2) placebo
4. Outcome measures = Physical activity index, energy/fatigue scale, mental health scale, and depressive symptoms.
5. Follow-up = 3 years.

RESULTS

1. In all patients (including placebo) scores for physical function and energy/fatigue

declined significantly over 3 years (*Not unexpected since subjects were elderly and had documented coronary disease. RTJ*) However, those receiving HRT had slightly *greater* declines.

2. Depressive symptoms were not significantly changed.
3. In the group with flushing, those receiving HRT had improved mental health and fewer depressive symptoms compared with those receiving placebo. HRT was associated with significant improvements in flushing, vaginal dryness, and sleep.
4. Adverse effects during 3 years of follow-up:

	HRT	Placebo
Death	6.7%	5.5%
Non-fatal MI	7.0%	6.9%
Unstable angina or revascularization	16.2%	17.2%
Venous thromboembolism	2.0%	0.7%

5.. No difference in stroke or peripheral vascular disease. Increase in biliary tract surgery

DISCUSSION

1. In this large trial of clinically stable postmenopausal women (mean age 67.with documented coronary artery disease (a high risk group), HRT had overall significant *negative* effects on physical function.
2. The effect of HRT on quality-of-life was modified by the presence or absence of postmenopausal symptoms. Among women who continue to have symptoms, HRT significantly improved mental health and depressive symptoms.
3. "The results of this investigation do not necessarily apply to younger women and women without heart disease."

CONCLUSION

HRT may have either positive or negative effects on quality of life depending on the presence or absence of menopausal symptoms. Women with menopausal symptoms have improvement in emotional dimensions of quality of life when given HRT.

For women without menopausal symptoms, HRT was associated with net *negative* effects on physical dimensions of quality of life

JAMA February 6, 2002; 287: 591-97 Original investigation by the Heart and Estrogen/progestin Replacement Study (HERS) Trial, first author Mark A Hlatky Stanford University School of Medicine, Stanford CA
www.jama.com

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2-7 POSTMENOPAUSAL HORMONE THERAPY AND QUALITY OF LIFE

(*This editorial comments and expands on the preceding study*.)

Despite the common perception that postmenopausal hormone therapy improves quality of life, few randomized trials have addressed this issue. The high rates of discontinuation of HRT in the first few years of use cast doubt on this assumption.

A large majority of subjects in the trial were elderly women (mean age 67) — 85% did not have hot flashes. In this group, those who received HRT had greater declines in physical function and energy than those receiving placebo. No differences were noted in mental health or depressive symptoms.

Among the 15% who had hot flashes, HRT was associated with improvement in mental health and reduction in depressive symptoms without significant effects on physical function or energy level. Indeed, this is no surprise. Past studies have consistently reported that HRT benefits quality of life in women with menopausal symptoms.

All women in the study were well past the age of onset of menopausal symptoms. All had a history of cardiovascular events in the past which, along with their age, placed them at high risk for recurrence. The decline in quality of life in this cohort therefore may have been due to the increased rates of cardiovascular events associated with HRT in the first year of replacement therapy. (*Presumably due to a combination of high risk and a pro-thrombotic effect of HRT. RTJ*) Thus, in women with established cardiovascular disease, HRT may cause more harm than benefit.

The risk of cardiovascular events and other outcomes among younger women and for those without cardiovascular disease are less clear.

For prevention of osteoporosis and lipid disorders, more effective drugs are available.

JAMA February 6, 2002; 287: 641-42 Editorial, first author Kathryn M Rexrode, Brigham and Women's Hospital, Boston Mass. **www.jama.com**

Comment:

The subjects in the HERS trial were a very select group. They were at a mean age past the onset of the menopause by about 17 years, and were selected because of their history of cardiovascular disease. The women represented by this group are not the usual recipients of HRT. A study which at baseline includes only elderly women with established cardiovascular disease fails to answer the important question.

The question as to the benefit/harm-cost ratio of HRT in women at the start of menopause who are more likely to experience menopausal symptoms will hopefully be answered by forthcoming trials. HRT is the only consistently effective means of relieving menopausal symptoms. Menopausal women who experience symptoms can be miserable. The benefit/harm-cost of HRT in this group is high.

The two recent trials I know about both reported increased cardiovascular events in the first year or two of HRT. Thereafter there seemed to be a reduction in this risk. Long-term studies will be required to determine the true effects of primary prevention of cardiovascular disease in the group of women most likely to need HRT. It may still be possible that long-term HRT will provide protections against cardiovascular disease.

Menopausal symptoms are now the only indication for HRT. Prevention of osteoporosis and cardiovascular disease is best addressed by different drugs and lifestyles. HRT given in conjunction with bisphosphonates and statins may produce a small additive effect.

I believe primary care clinicians will continue to use HRT freely in symptomatic menopausal women. The recent trials should raise some cautions. For women at age 50 who suffer menopausal symptoms which would be relieved by HRT, but who have established cardiovascular disease or are at high risk, caution is warranted. I believe starting low-dose estrogen (eg, 0.3 mg *Premarin*) with low-dose aspirin and a statin in this group would reduce likelihood of a second cardiovascular event.

2-8 ASSOCIATION OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS WITH FIRST OCCURRENCE OF HEART FAILURE AND WITH RELAPSING HEART FAILURE

The Rotterdam Study

Nonsteroidal anti-inflammatory drugs (**NSAIDs**) have been associated with hospitalization for congestive heart failure (**HF**). NSAID-inhibition of cyclo-oxygenase results in a decrease in prostaglandin synthesis. Prostaglandins play an important role in renal physiology. Their inhibition may give rise to fluid retention and adverse effects on cardiovascular homeostasis. Patients with a propensity for HF seem to be particularly susceptible to cardiovascular effects of NSAIDs. Moreover, NSAIDs may interfere with the cardiovascular effects of ACE inhibitors and diuretics.

Can NSAIDs cause a *first* occurrence of (incident) HF? Ie, in patients without a history of HF.

Do they increase *recurrence* of HF in patients with a past history of HF?

Conclusion: NSAIDs were not associated with an increased risk of incident (a first occurrence) HF. They were associated with increased risk of recurrent HF in patients with past HF.

STUDY

1. Followed over 7000 patients from an interview date until: 1) diagnosis of a first episode of HF, or 2) diagnosis of recurrent HF
2. Excluded all patients with signs and symptoms of HF at baseline and all with left ventricular fractional shortening less than 30%.
3. Determined 1) a first occurrence of HF, and 2) a recurrence of HF in patients with past history of HF.
4. Determined use of NSAIDs by computerized pharmacy records.
5. Follow-up = 8 years.

RESULTS

1. A first episode of HF developed in 345 participants (5%) during follow-up. Current use of NSAIDs was not related — relative risk of incident HF = 1.1 in patients taking NSAIDs vs non-takers.

2. In the group with past history of HF, those who filled at least one prescription for NSAIDs had an increased risk of recurrence — adjusted relative risk of a relapse = 10.

DISCUSSION

1. Current use of NSAIDs was *not* associated with increased risk of a *first* occurrence of HF.
2. Use of NSAIDs in patients with a past history of HF was associated with a substantially increased risk of recurrence of HF.
3. Adverse effects of NSAIDs on cardiovascular homeostasis are well known, In the clinical setting of reduced renal perfusion as seen in patients with dehydration, cardiovascular disease, and renal dysfunction, NSAIDs may impair the adequacy of renal prostaglandin production. Impaired renal function, defined as a creatinine level of 1.1 mg/dL or more seems to be associated with an increased risk of NSAID-associated HF.
4. Patients who developed HF during the study and continued to take NSAIDs were at substantially increased risk of relapse. Cardiovascular homeostasis is much more likely to be prostaglandin dependent in patients with prevalent HF than in patients with unimpaired left ventricular function.

CONCLUSION

NSAID use was not associated with an increased risk of incident HF.

In patients with prevalent HF, current use of NSAIDs substantially increased risk of relapse.

Archives Int Med February 11, 2002; 162: 265-70 Original investigation, first author Johan Feenstra, Erasmus Medical Center, Rotterdam, Netherlands. **www.archintmed.com**

Comment:

This is an important clinical point. Use NSAIDs with caution in patients with current or past HF. Also in patients with hypertension. RTJ

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2-9 RESIDUAL LIFETIME RISK OF DEVELOPING HYPERTENSION IN MIDDLE-AGE WOMEN AND MEN.

The long-term risk of developing hypertension is best described by the lifetime risk -- the probability that an individual will develop hypertension over the course of his or her remaining lifetime. It is possible that the lifetime risk may have increased in recent years because of the increased longevity of the population and the national increase in obesity.

This study estimated the residual lifetime risk of developing hypertension among the Framingham Heart Study participants.

Conclusion: Development of hypertension (>140/90) is almost universal.

STUDY

1. Community-based prospective cohort study estimated the residual lifetime risk of hypertension in older US adults (normotensive at baseline ages 55 and 65), and evaluated temporal trends in risk.
2. Followed 1300 participants for development of hypertension (> 140.90) or use of antihypertension medications. (Risk increases markedly during and after the sixth decade of life.)

RESULTS

1. The residual lifetime risk of developing hypertension (>140/90 regardless of treatment) for subjects normotensive at ages 55 and 65 rose incrementally from about 55% in 10 years to over 90% in 20 to 25 years.
2. The lifetime probability of receiving antihypertension treatment was 60%

DISCUSSION

1. In individuals who had normal BP at ages 55 and 65, the residual lifetime risk for developing hypertension (BP > 140/90, or taking antihypertension medication) was about 90%.
2. These data indicate the residual risk of persons who have normal BP at ages 55 and 65. It is important to note that a considerable proportion of individuals with hypertension have the onset at an earlier age. Therefore, the actual lifetime risk for hypertension for younger individuals may be different.
3. On an individual basis, risk will vary according to factors such as obesity, family history, dietary sodium and potassium intake, and alcohol consumption.
4. Control of stage 1 hypertension (140/90 -159/99) is important. A substantial proportion of cardiovascular diseases is attributable to stage 1.
5. Lifestyle management is essential. "The approach of waiting for hypertension to develop and only then treating the elevated blood pressure is injudicious."

CONCLUSION

In persons with normal BP (<140/90) at ages 55 and 65, the likelihood of development of hypertension as they grow older approaches 90%. Efforts should be directed at primary prevention.

JAMA February 27, 2002; 287: 1003- 10 Original investigation from the Framingham Heart Study, first author

Ramachandran S Vasan, Framingham Mass. **www.jama.com**

Comment:

The question then is – is drug treatment of stage 1 hypertension (140/90 to 159/99) in elderly persons always indicated? I believe many will do well without drug therapy. Primary care clinicians treat the patient, not the BP.
RTJ

Review Article

2-10 AORTIC STENOSIS

Aortic stenosis (**AS**) is the most common cardiac valve lesion. Two factors contribute: 1) bicuspid aortic valve is a relatively common anomaly. It is prone to stenosis; 2) the population is aging. AS increases with age. (Primary care clinicians will encounter AS if they practice long enough in the most unexpected patients and times. RTJ)

Physical findings include a systolic ejection murmur at the right upper sternal border with radiation into the neck; peaking of the murmur late in systole; palpable delay of the carotid upstroke; and a soft single 2nd sound. The aortic component of S2 disappears when the valve no longer opens and closes well. This leaves the pulmonic component of S2 alone to compose the second sound.

Calcific aortic stenosis has many features in common with coronary disease: both are more common in the elderly and in patients with hypertension. Both derive in part from an active inflammatory process.

AS is distinguished from aortic sclerosis by the degree of valve impairment. In sclerosis, the valves are abnormally thickened, but obstruction to outflow is minimal. Measurable obstruction occurs in stenosis. However, little hemodynamic disturbance occurs until the valve area is reduced from the normal of 3 to 4 cm^2 to 1.5 to 2 cm^2. Severe obstruction then leads to progressive overload of the left ventricle. The resultant myocardial hypertrophy results in decreased coronary blood flow reserve, even if the coronary arteries are normal. Congestive failure ensues. A gradient of 50 mm Hg and a valve area no larger than 1 cm^2 indicates severe disease.

When is the optimal time to intervene? What is the best intervention? In adults with calcified valves, balloon angioplasty may temporarily relieve symptoms but does not prolong survival. Replacement of the valve is required. Surgery is usually delayed until symptoms develop. Once angina, syncope, dyspnea or other symptoms of heart failure develop, the patient's life span is drastically shortened unless the valve is replaced. The 10 year survival rates among those undergoing successful valve replacement approaches that of the normal population. "There is overwhelming evidence that once patients with severe aortic stenosis become symptomatic, prompt valve replacement is indicated."

Conversely, patients who remain asymptomatic generally have an excellent prognosis. However, an occasional asymptomatic patient will die suddenly, or have a very rapid progression of symptoms. Decisions about surgery may be aided by exercise testing. (Exercise testing is unwarranted and dangerous in symptomatic patients.) Latent symptoms may be uncovered. Exercise-induced hemodynamic instability may lead to timely valve replacement.

Outlook in patients with left ventricular dysfunction who have a substantial gradient (> 40 mm Hg) is excellent with surgery despite a reduced ejection fraction. Once the obstruction is relieved, left ventricular function returns to, or approaches, normal. Conversely, those with a small gradient (< 30) and a reduced ejection fraction have a high operative risk. The poor outcome is related to presence of both severely depressed myocardial contractility and the excessive afterload.

For patients with AS undergoing non-cardiac surgery, intraoperative hemodynamics must be closely monitored. In patients with asymptomatic AS, there is no need for concomitant valve replacement.

Doppler echocardiography should be done initially to assess severity of the stenosis as well as left ventricular dysfunction. Those whose symptoms and signs are changing should be reevaluated.

Replacement is recommended in patients with moderate or severe stenosis who are undergoing coronary bypass surgery or other valve surgery.

Standard antibiotic prophylaxis against infectious endocarditis is recommended.

NEJM February 28, 2002; 346: “Clinical Practice” review article by Blasé A Carabello, Baylor College of Medicine, Houston TX **www.nejm.org**

Comment:

One challenge for the primary care clinician is to decide when symptoms are due to the stenosis.

Statin drugs have been reported to benefit patients with calcific AS. RTJ

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2-11 PHYSICIAN-RELATED BARRIERS TO THE EFFECTIVE MANAGEMENT OF UNCONTROLLED HYPERTENSION

Physicians may not be aggressive enough with the management of hypertension. This study identified barriers primary care clinicians may have in their willingness to increase intensity of treatment among patients with uncontrolled hypertension.

Improving quality of care for hypertensive patients is a priority. Efforts to understand poor BP control have usually focused on patient adherence. These include lack of adherence to therapy, limited access to care, financial barriers, and lack of knowledge about the seriousness of uncontrolled hypertension.

Clinician practices play an important role in effective management of "uncontrolled hypertension". These include patient-management time constraints, physician-practice patterns, drug adverse effects, and complexity of treatment and difficulty in monitoring drug regimens.

This study identified barriers to physician's willingness to increase the intensity of treatment among patients with uncontrolled hypertension as suggested by consensus guidelines. These include the importance of systolic hypertension.

Conclusion: The most important reason physicians do not treat hypertension more aggressively is that they are willing to accept an elevated systolic BP in their patients.

STUDY

1. Descriptive survey study sampled 270 patient visits (median age = 69) to primary care physicians

to identify patients with uncontrolled hypertension. Determined practice patterns. Lifestyle recommendations were not considered.

2. The average BP was 152/84 during the prior 6 months. Almost all were taking antihypertension drugs.

RESULTS

1. Pharmacological treatment was initiated or changed at only 38% of visits despite documented hypertension (their definition >140/90) for at least 6 months before the most recent visit.
2. At 93% of the visits, systolic BP was 140 mm systolic or higher; 35% were 150 or higher.
2. Reason given most frequently for not changing the regimen was the physician was satisfied with the BP response. On average, physicians reported that 150 was the lowest systolic BP at which they would recommend pharmacological treatment; and a diastolic of 91.
3. Other reasons for not recommending change were: the focus of the visit was not on BP; competing medical problems; need to continue monitoring the patient before change in drug.
4. Patients were very satisfied with their care even though their BP was not controlled.

DISCUSSION

1. Uncontrolled hypertension is a significant public health problem. Only about 25% of patients are adequately controlled.
2. The study suggested that physicians placed more importance to the diastolic BP than to the systolic.
3.Adverse drug effects have been identified as a factor related to physician prescribing patterns. Quality-of-life is reduced as intensity of treatment is increased. Other studies have reported that many switched because of adverse drug effects. About 10% stopped the drugs completely.

CONCLUSION

"Our findings suggest that an important reason why physicians do not treat hypertension more aggressively is that they are willing to accept an elevated systolic BP in their patients."

Archives Int Med February 25, 2002; 162: 413-20 Original investigation, first author Susan A Oliveria, Weill Medical College of Cornell University, New York **www.archintmed.com**

Comment:

I believe many primary care physicians will resist defining uncontrolled hypertension as any value above 140/90. This is an arbitrary cut point defined by expert guidelines. It does not apply to the many varied patients primary care clinicians encounter. Indeed, it may apply to relatively few, especially the elderly.

This illustrates a dichotomy between the best of "evidence-based medicine" and clinical practice. Evidence based studies select patients with defined entrance and exclusion criteria. Clinical practice encounters many exceptions; individual patients will simply not fit the criteria. Primary care clinicians then use their best clinical judgement to guide therapy.

Certainly systolic pressure should be the main target. But 140 is not the "holy grail" of therapy. Many clinicians, for many patients will accept 150 or anything up to 160 as satisfactory control. Aggressively increasing dosage and adding a second or third drug may decrease systolic to the 140 goal. But this is done at a cost of added adverse effects, complexity, and cost.

I believe "Treat the patient, not the blood pressure" is still a good maxim. Some patients will indeed benefit from aggressive lowering (diabetics, smokers, those with lipid abnormalities, obesity, and sedentary lifestyles.) In some patients these risk factors should be treated perhaps more aggressively than the BP. There is no good reason to aggressively lower systolic in frail 80 year-old women.

Trying to achieve a standard universal goal for treatment of BP is bad medicine.

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2-12 EFFECTS OF HYALURONATE SODIUM ON PAIN AND PHYSICAL FUNCTIONING IN OSTEOARTHRITIS OF THE KNEE

Hyaluronic acid (**HA**) is a major component of the articular matrix. It assumes an important role in viscoelastic structure and function. Osteoarthritis (**OA**) is characterized by a decrease in the concentration and molecular weight of hyaluronic acid. This may lead to pain and loss of function. HA is a large molecular component of the articular matrix. It acts as a "lubricant" when movements are slow (viscous properties), and as a "shock absorber" when movements are fast (elastic). Intra-articular visco-supplementation with hyaluronate sodium (HS) may restore the concentration and molecular weight of HA in the articular matrix, resulting in improvement of pain and function.

This study assessed the effect of treatment of knee OA with HS.

Conclusion: HS was superior to standard treatment in improving pain and functioning.

STUDY

1. Randomized, double-blind placebo controlled trial entered 120 patients (mean age 67) with unilateral medial compartment knee OA.
2. Randomized to 4 treatment groups:
   1) 2 mL HS injected at a concentration of 10 mg/mL + placebo. [HS alone]
   2) NSAID (75 mg diclofenac and 200 mg misoprostol) + HS injection. [NSAID + HS]
   3) NSAID + placebo. [NSAID alone]
   4) Placebo [Placebo]
3. HS was injected once weekly over 3 weeks. NSAIDs and placebo given orally twice daily over 12 weeks.
4. Main outcomes: 1) Global measure of pain, stiffness, and disability, 2) Visual analogue scores for pain at rest and following functional walking and stepping, and 3) Functional performance (exercise time, heart rate, and predicted maximum oxygen uptake).
5. Outcomes were measured at baseline, and weeks 4 and 12.

RESULTS

1. At week 12: Compared with baseline, HS alone, HS + NSAID, and NSAID alone were associated with significantly greater improvement in pain scale and score for resting pain, and improved self-paced walking and stepping
2. HS alone, and HS + NSAID were associated with significantly less pain during walking and stepping.
3. HS alone was associated with significantly faster self paced walking and stepping.
4. Predicted maximum oxygen uptake was significantly higher with HS alone and HS + NSAID.

DISCUSSION

1. This study supports the use of visco-supplementation with HS for treatment of OA of the knee.
2. The effect of HS on activity-related pain and functional performance seems to improve with time from intervention. This contrasts with the effect of NSAIDs which did not show continued improvement after 4 weeks.
3. Exercise is also recommended as standard treatment. However, adoption rates are low. Better adoption of simple resistive exercise therapy is needed to complement HS therapy.
4. HS can be re-administered over time with no apparent adverse effects.

CONCLUSION

For resting pain relief, HS seems to be as effective as NSAIDs. HS may be superior to placebo or NSAIDs for improving functional performance and relieving pain with physical activity.

Archives Int Med February 11, 2002; 162: 292-98 Original investigation, first author Robert John Petrella, University of Western Ontario, London, Canada. **www.archintmed.com**

Comment:

Study supported by Bioniche Life Sciences. (Canada)

In the US, *Synvisc* is widely advertised and used. It is approved by Medicare and by the FDA

See the following editorial. RTJ

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2-13 HYALURONATE SODIUM INJECTIONS FOR OSTEOARTHRITIS

Hope, Hype, And Hard Truths

Investigators interested in developing new therapies for OA were mindful of the diminution of HA levels in osteoarthritic joints. They developed forms of HA as potential treatments.

HA is cleared from the synovial fluid compartment after a few hours, perhaps a day. Macromolecular forms of HA (eg, hyaluronate sodium; HS) were developed to try to lengthen stay in the joint. These macromolecular preparations have half-lives of up to 1.5 days. Evidence supporting long-term increases in viscosity in knees is meager. A modest increase of 10% has been reported, But post-treatment levels are well below the normal range for the human joint.

These editorialists carried out a systematic search of the literature of placebo-controlled studies of intra-articular HS. They found 3 large trials. Two of the trials were null, showing no significant efficacy of HS vs placebo on an intention to treat analysis. The 3rd trial reported that the HS group did significantly worse than the controls.

"We conclude that hyaluronate sodium is no more effective than placebo injections in the treatment of OA of the knee."

Despite the suggestion in the preceding study that HA is efficacious, "We believe that data they present fail to demonstrate this, providing further evidence that hyaluronate sodium is not efficacious in the treatment of OA."

Archives Int Med February 11, 2002; 162: 245-46 Editorial, first author David T Felson, Boston Medical Center, Mass. **www.archinternmed.com**

Comment:

So . . . what are primary care clinicians to do with these diverse opinions? I expect they will act as always when faced with uncertainty — depend on the individual patient's response. I am sure some patients will report considerable improvement, be it placebo effect or not. These will continue to receive HS. RTJ

==========

Can Dietary Fortification Reduce Incidence Of Dementia?

2-14 PLASMA HOMOCYSTEINE AS A RISK FACTOR FOR DEMENTIA AND ALZHEIMER'S DISEASE

Persons with cardiovascular risk factors and a history of stroke are at increased risk of both vascular dementia and Alzheimer's disease. Plasma total homocysteine has recently emerged as a major vascular risk factor. This has led to the hypothesis that elevated homocysteine may be a risk factor for dementia and Alzheimer's. If this is valid, it points to a modifiable risk factor since plasma homocysteine can be lowered by supplementation with folic acid.

This study examined plasma homocysteine in relation to newly diagnosed dementia and Alzheimer's. Do elevated levels precede onset of dementia?

Conclusion: An increased plasma homocysteine was a strong, independent risk factor for later development of dementia and Alzheimer's.

STUDY

1. Entered over 1000 subjects (mean age = 76) from the Framingham study. None had dementia.

2. Examined the relation between plasma total homocysteine, measured at baseline, and risk of newly diagnosed dementia on follow-up.
3. Also had determined homocysteine levels 8 years previously.
4. Determined plasma concentrations of folate, vitamins B6, and B12.

RESULTS

1. Over a follow-up period of 8 years, dementia developed in 111 subjects (10%) – 83 with a diagnosis of Alzheimer's.
2. Adjusted relative risk of dementia was 1.4 for each increase of one standard deviation in homocysteine level at baseline and 8 years earlier. Elevation of homocysteine occurred well before the onset of clinical manifestations.
3. An increment of 5 umol/L increased risk by 40%. With a level greater than 14 umol/L (defined as hyper-homocysteinemia) risk of dementia and Alzheimer's nearly doubled.
4. Low serum levels of folate and vitamins B12 and B6 have been associated with elevated homocysteine levels. In this study, the observed association between homocysteine and risk of dementia was not significantly altered by adjustment for the plasma levels of these vitamins.

DISCUSSION

1. This prospective observational study indicated a strong, graded association between plasma homocysteine and risk of dementia and Alzheimer's. Individuals with sustained elevations over 8 years had the greatest risk of dementia.
2. The magnitude of increases in risk of dementia were similar in magnitude to the increases of the risks of death from cardiovascular causes and stroke associated with similar increments of homocysteine.
3. The association was independent of multiple other risk factors.
4. Elevated homocysteine is associated with carotid atherosclerosis and an increased risk of stroke. Atherosclerosis and stroke in turn increase risk of clinical Alzheimer's disease.
5. Hyperhomocysteinemia has been related to cerebral microangiopathy, endothelial dysfunction, and impaired nitric acid activity – all factors associated with aging of the brain.
6. Folic acid therapy, alone or in combination with B6 and B12 can reduce plasma homocysteine, but there are no prospective studies of their effect on the incidence of dementia.

CONCLUSION

An increased plasma homocysteine level was a strong, independent risk factor for the development of dementia and Alzheimer's disease.

NEJM February 14, 2002; 346:476-83 Original investigation, first author Sudha Seshadri, Boston University School of Medicine, Mass. **www.nejm.org**

A commentary in this issue (pp 466-68): The simple addition to a normal diet of large doses of folate, vitamins B6 and B12 will substantially reduce homocysteine levels in most people. Does lowering homocysteine with vitamin therapy reduce risk of dementia? This question is unanswered. The study found no relation between blood levels of these vitamins and risk of dementia.

Comment:

The hyper-homocysteinemia-vascular disease association is a frequent topic in the current literature. If vitamin supplementation were truly related to a decrease in risk, this would be a great therapeutic advance. We do not know yet if this association is valid. Meanwhile, I believe many individuals will take supplements on the chance that the association is valid — especially since the harm-cost of the benefit/harm-cost ratio is so low.

Reduces Risk In Women At Increased Risk Without Increasing Risk Initially

2-15 ROLAXIFENE AND CARDIOVASCULAR EVENTS IN OSTEOPOROTIC POSTMENOPAUSAL WOMEN

Previous observational studies reported hormone replacement therapy (**HRT**) provides a protective effect against cardiovascular events in postmenopausal women. Recent trials have not confirmed these benefits. Indeed, women assigned to HRT experienced an early increase in acute coronary events.

This study was designed to determine the effect of raloxifene (*Evista*, a selective, estrogen receptor modulator; SERM) on bone mineral density and vertebral fractures in postmenopausal women. Conclusion: Raloxifene therapy for 4 years did not significantly affect risk of cardiovascular events in women overall, but reduced the risk in the subset of women with increased risk.

STUDY

1. Multicenter randomized, double-blind, placebo-controlled trial entered over 7700 osteoporotic postmenopausal women (mean age = 67). Determined cardiovascular risk factors at study entry (prior coronary events or multiple cardiovascular risk factors – history of hypertension, hypercholesterolemia, type 2 diabetes).
2. Randomized to: 1) raloxifene 60 mg/d, 2) 120 mg/d, or 3) placebo.
3. Main outcome measures — cardiovascular events (myocardial infraction, unstable angina, coronary ischemia), and cerebrovascular events (stroke and TIA).
4. Follow-up = 4 years.

RESULTS

1. In the overall cohort there were no significant differences between the 3 groups in the number of combined coronary and cerebrovascular events (placebo -3.7%; 60 mg - 3.2%; and 120 mg - 3.7%).
2. Similar results were obtained when coronary and cerebrovascular events were analyzed separately.
3. Among the 1035 women who at baseline had increased cardiovascular risks, those assigned to raloxifene had a significant benefit over 4 years— a lower risk of cardiovascular events compared with placebo.

In absolute terms:	Placebo %	Raloxifene %	Absolute difference %	NNT (4y)
Any cardiovascular event	12.9	7.8	5.1	20
Any coronary event	7.6	5.0	2.6	38
Any cerebrovascular event	5.4	2.8	2.6	41

4. During the first year there was no significant difference overall between groups in cardiovascular events. Benefits occurred later among women with established CHD or at increased cardiovascular risk,

DISCUSSION

1. In this secondary analysis of data from a large study of osteoporotic postmenopausal women, raloxifene did not significantly affect the risk of cardiovascular events in the overall study population (they were at relatively low risk). But it did significantly lower risk of cardiovascular events in a subset of women at high risk.
2. There was *no* evidence that raloxifene was associated with an early increase in cardiovascular morbidity or mortality overall, even in women at high risk. (*Contrast this to the early adverse effect of hormone replacement in women at increased risk. RTJ*)
3. 13% of the total population were at high risk of CV events. In this group raloxifene was associated with a 40% reduction in risk of CV events. **1**
4. Raloxifene improved total cholesterol and LDL-c levels with no effect on HDL-c. **2**

CONCLUSION

There was no evidence that raloxifene caused an early increase in risk of CV events in the group overall, or in the subset of women at high risk for CHD.

Raloxifene for 4 years significantly reduced the risk of CV events among the subgroup at high risk and among those with established CHD.

JAMA February 20, 2002; 287: 847-57 Original investigation by the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, First author Elizabeth Barrett-Conner, University of California, San Diego. **www.jama.com**

Comment:

1 Note, as usual, the investigators report a relative risk reduction (in this case, 40%). This appears more

favorable than the clinically applicable absolute risk reduction (5%). [NNT over 4 years to benefit one = 20]

2 Could the delay in benefit (over one year) in high risk women have been due to the effect of raloxifene on lipids?

Raloxifene has favorable effects on LDL-cholesterol, and improves vascular endothelial function in postmenopausal women.

The authors point out that the trial was not originally designed to test the effect of raloxifene on cardiovascular outcomes. This is a secondary analysis. Larger trials are required to confirm the results.

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Another Advance – Coated Stents

2-16 OVERCOMING RESTENOSIS WITH SIROLIMUS

Percutaneous coronary interventions (**PCIs**) have surpassed coronary artery bypass grafting as the most common means for treating symptomatic coronary artery disease (**CAD**).

Restenosis remains the Achilles' heel. Restenosis is a reduction in luminal size after an intra-arterial procedure. It is defined as a reduction greater than 30% of the initial post-procedure lumen size. It is a maladaptive response of the vasculature to injury. Studies have reported a restenosis rate up to 40% post-PCI at 6 months.

Stenting has significantly reduced the rate of restenosis. However, the rate still remains at about 20% despite aggressive anticoagulation and antiplatelet therapy.

Several interventions have been used to lower restenosis rates.

Sirolimus is a natural immunosuppressant recently approved by the FDA for prophylactic treatment of renal transplant rejection. Cyclosporine (*Sandimmune*) and tacrolimus (*Prograf*) are other members of this class of compound.

Growth and migration of vascular smooth muscle are major features of neointimal proliferation after vascular injury. Sirolimus inhibits proliferation and migration of vascular smooth muscle cells.

The potential for short and long-term complications when immunosuppressive agents are given systemically has led to a reluctance to use them. Another way to abate migration and proliferation of smooth muscle cells without producing systemic toxicity is to deliver the inhibitor locally through a coated stent. A pioneer study used stents coated with sirolimus in 30 patients with angina. There was little neointimal hyperplasia and no in-stent or edge restenosis, and no major complications at 8 months.

Preliminary studies using sirolimus coated stents have been quite promising and should reduce restenosis rate.

Lancet February 16. 2002; 359: 619-22 "Viewpoint" commentary, first author Michael Poon, Mount Sinai School of Medicine, New York. **www.thelancet.com**

Comment:

It was not clear to me why sirolimus instead of tacrolimus or cyclosporine.

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Another Promising Treatment for Osteoporosis

2-17 RECOMBINANT HUMAN PARATHYROID HORMONE

A recent FDA panel recommended approval of an N-terminal fragment of parathyroid hormone for treatment of osteoporosis (teriparatide; *Forsteo*). The application for approval was based on evidence from a randomized trial in women with osteoporosis demonstrating large increases in cancellous (trabecular) bone formation in the vertebral bodies and a greatly reduced risk of spine fracture.

Currently, PTH seems to be the most effective treatment for postmenopausal osteoporosis. (Although this apparent advantage will be contested by promoters of bisphosphonates.) Side effects have been few and mild. The need to inject with a penlike device, as used for insulin, is a nuisance, although preferable to the dyspepsia caused by some bisphosphonates.

Data now also indicate efficacy in osteoporosis in men and in patients receiving corticosteroids.

PTH expands the bony envelope in the hip. Thus, its biggest impact may be in prevention of fractures of the hip.

"From being one of medicine's most untreatable disorders, osteoporosis is following the footsteps of hypertension and proving amenable to treatment through several targets: estrogen receptors; osteoclasts (by targeting them with bisphosphonates) and now parathyroid hormone receptors."

BMJ February 23, 2002; 324: 435-36 Editorial by Jonathan Reeve, Addenbrooke's Hospital , Cambridge, UK
www.bmj.com/cgi/content/full/324/7336/435

Comment:

The ability to prevent and treat postmenopausal osteoporosis is a therapeutic triumph. We should no longer see obvious "dowager's humps" in our older female patients (as well in elderly males). Newer therapies (including more powerful bisphosphonates) are being introduced. (See following abstract on zoledronic acid.) More convenient dosing is available with weekly oral alendronate (*Fosamax*)

There is no doubt that hormone replacement therapy will delay development of postmenopausal osteoporosis. However, in view of the recent data indicating increased risk of cardiovascular events in high risk patients, HRT has lost some of its appeal. It is being displaced by other drugs for prevention and treatment of osteoporosis. Since HRT is the only adequate treatment for menopausal symptoms, would it be advisable to routinely add another agent to prevent or treat osteoporosis in women taking HRT? RTJ

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Can BMD Be Increased By One Injection A Year?

2-18 INTRAVENOUS ZOLEDRONIC ACID IN POSTMENOPAUSAL WOMEN WITH LOW BONE MINERAL DENSITY

Zoledronic acid is the most potent bisphosphonate studied thus far in clinical trials. Because it has high potency, small doses are required for the inhibition of bone resorption. Long dosing intervals may be used.

Oral bisphosphonates increase bone mineral density (BMD) and decrease the rate of fracture in patients with osteoporosis. However, they do have limitations related to long-term compliance because of gastrointestinal intolerance. Absorption can be poor and variable. Intermittent intravenous administration might address some of these problems. Intravenous bisphosphonates have been effective in treatment of malignant hypercalcemia and Paget's disease, and reduce the rate of bone complications in patients with breast carcinoma and multiple myeloma.

This study assessed the effects of different doses of zoledronic acid in post menopausal women with low BMD.

Conclusion: Small doses of zoledronic acid given at long intervals were as effective as oral bisphosphonates.

STUDY

1. Randomized, double-blind, placebo-controlled trial entered over 350 women — all at least 5 years post-menopause. (mean age = 64)
2. All had osteoporosis with BMD at the lumbar spine at least 2 standard deviations below that of young female adults. (T score lower than -2). None had more than one vertebral fracture at baseline.
3. All received a calcium supplement of 1 g/d. (No mention of vitamin D.)

4. Randomized to 1) one of 5 zoledronic acid regimens, or 2) placebo injections.
5. Zoledronic acid regimens:
   Intravenous zoledronic acid 0.25 mg, 0.5 mg , and 1 mg at three month intervals for 1 year. Or 2 doses of 2 mg twice a year, or a total dose of 4 mg once at the beginning of the trial. (Total doses of 1 mg, 2 mg, and 4 mg per year). All infusions were given in 20 mL volume over 5 minutes.
6. Primary end point – change in lumbar spine BMD.

RESULTS

1. There were similar increases in BMD in all zoledronic acid groups. About 5% absolute increase in BMD of lumbar spine and 2.5% in the femoral neck. Placebo BMD declined slightly.
2. Biochemical markers of bone resorption were significantly suppressed during the year in the zoledronic acid groups.
3. Adverse effects: Myalgia, nausea, and fever occurred more often in the zoledronic acid groups – all considered mild. Dropout rates were similar between the zoledronic acid and placebo groups. No new vertebral fractures occurred during the study. The drug was "generally well tolerated".

DISCUSSION

1. Intermittent intravenous zoledronic acid administration resulted in changes in biochemical markers of bone turnover and in bone mineral density similar to those observed with daily oral bisphosphonates.
2. The study did not define the optimum dose or interval of dosing.
3. How a single dose of zoledronic acid suppresses bone turnover for so long remains to be determined. Prolonged suppression is not due to persistence of the drug in the circulation. (At 24 hours, blood levels are less than 1% of peaks and 40% of the drug has been excreted in the urine.)
4. The balance of the dose is presumably bound to bone and is slowly released back into the circulation. The terminal half life in plasma is 167 hours. It is thought that bisphosphonates are located exclusively on osteoclastic surfaces although other sites and actions are postulated.

CONCLUSION

Small doses (1 to 4 mg total) of zoledronic acid infusions given at intervals for up to 1 year produced effects on BMD and bone turnover as great as those achieved by oral bisphosphonates.

One annual infusion might be an effective treatment.

NEJM February 28, 2002; 346: 653-61 Original investigation, first author Ian R Reid, University of Auckland, New Zealand. **www.nejm.org**

"Perspective" in this issue (p 642) comments:

Compliance is a problem with oral bisphosphonates. Dosing is inconvenient, gastrointestinal adverse effects common. But they are the only medications thus far proved to reduce risk of hip fracture. At present, weekly oral

dosing is being studied.

Studies with zoledronic acid are needed to determine if the fracture rate is reduced, and to determine long-term safety.

Comment:

Remarkable — a low dose of 1 mg a year resulted in increased BMD. Does zoledronic acid represent a sea-change in osteoporosis treatment and prevention? RTJ

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