

PRACTICAL POINTERS
FOR
PRIMARY CARE
ABSTRACTED MONTHLY FROM THE JOURNALS

2003

MEDICAL SUBJECT HEADINGS
HIGHLIGHTS-INDEX

JAMA, NEJM, LANCET
BRITISH MEDICAL JOURNAL
ARCHIVES OF INTERNAL MEDICINE
ANNALS OF INTERNAL MEDICINE

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STATEMENT BY THE EDITOR/PUBLISHER

This *Highlights-Index* begins with 162 medical subject headings (MESH). These act as a directory to the following 65 pages of highlights of articles abstracted from 6 flagship journals during 2003.

The highlights are designed for 2 purposes:

1. In one or two evenings, clinicians can rapidly scan, read, review, and recall to memory the studies and commentaries the editor considered to be new, clinically important, and interesting. Some highlights also contain the editor's comments on the clinical applicability of the article based on his years-long experience as a primary care internist.
2. The highlights can be used repeatedly for years as a reference.

I format the highlights so that the reader can easily refer to the full abstracts in each monthly issue of *Practical Pointers*. They are labeled according to the month and year (eg, 10-4 is the 4th article abstracted in October). The monthly issues can be accessed on the internet at www.practicalpointers.org in both HTML and pdf formatting.

The links in the HTML yearly index progress from the MESH to the highlights, and to the more detailed abstract. Each abstract ends with a citation of the journal date, volume, and page numbers as well as the name of the first author.

Original articles can be obtained by searching the web pages of the 6 journals. Unfortunately, only BMJ allows unlimited access. All others are limited, or require a subscription.

I hope you find the publication interesting and of value to your practice.

Richard T. James Jr. M.D. Editor/publisher

Practical Pointers is now in its 18th year of publication. It is being sent each month to 40 different countries.

I am always seeking new "subscribers". I will e-mail, by attachment, each monthly issue as it becomes available during the year to anyone supplying his or her e-mail address. Inquires to rjames6556@aol.com

There is never any charge for this public service. RTJ

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VITAMIN D

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XIMELAGATRAN

HIGHLIGHTS AND EDITORIAL COMMENTS 2003

ADDICTION

1-17 OPIOID ADDICTION

In early February 2003, the SAMHSA sent a “Dear Physician” letter outlining a new, office-based approach to opioid addiction. It represents a new era in addiction treatment.

The new treatment option is based on buprenorphine, a partial opiate agonist/antagonist recently approved by the FDA. Physicians can now provide opioid addiction treatment in their own offices. It also provides access to a supportive network of treatment specialists who can address the psychosocial needs of patients undergoing detoxification or maintenance.

Buprenorphine has a lower potential for abuse, a lower level of physical dependence, and weaker opioid effects than other drugs such as methadone.

1-8 ESCALATION OF DRUG USE IN EARLY-ONSET CANNABIS USERS VS CO-TWIN CONTROLS.

Associations between early cannabis use and later drug use and abuse/dependence cannot be explained solely by common predisposing genetic or environmental factors. Early initiation of cannabis (before age 17) was associated with significantly increased risk of other drug use and abuse/dependence later in life. This is consistent with early use of marijuana having a causal role as a risk factor.

Regardless of the mechanisms underlying the associations, it is apparent that young people who initiate cannabis at an early age are at heightened risk of progressing to other drug use and drug abuse/dependence.

ADVERTISING

1-7 DIRECT-TO-CONSUMER ADVERTISING AND SHARED LIABILITY FOR PHARMACEUTICAL MANUFACTURERS

Marketing of prescription drugs has undergone substantial change facilitated by the regulatory environment governing direct-to-consumer advertising. (DTCA). Physicians who write prescriptions on the request of patients who have been influenced by DTCA, do not relinquish any of their traditional control over prescribing

AGING

9-12 ASSESSING THE SUCCESS OF SUCCESSFUL AGING

Clinicians must learn what their patients expect and value, and develop treatment plans that balance longevity with other facets of life. We should determine what social roles patients most value, what features of functioning are most important, and which strategies of treatment and prevention will optimize the chances of success *as the patient defines it*.

Successful aging is possible *despite disease and disability*. If our concept of successful aging includes dignity, autonomy, social engagement, and the absence of suffering, we will be better positioned to configure our system of care to address the needs of the elderly. Pursuing the myth of the *Fountain of Youth* is not the answer.

Success in aging is “what I say it is” and what I make it. I will not depend on my clinician or on the public health service to define it.

ALCOHOL

1-13 ROLE OF DRINKING PATTERN AND TYPE OF ALCOHOL CONSUMED IN CORONARY HEART DISEASE IN MEN

Among men, consumption of alcohol at least 3 to 4 times per week reduced risk of MI. Neither the type of beverage, nor the proportion consumed with meals substantially altered the association.

Men who increased their alcohol consumption by a moderate amount during the follow-up had a decreased risk of MI.

2-8 ALCOHOL CONSUMPTION AND RISK OF STROKE: A Meta-analysis

Heavy alcohol consumption increases risk of stroke. Light-to-moderate consumption protects against ischemic stroke, but not against hemorrhagic stroke.

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

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

9-9 ALCOHOL USE DISORDERS IN ELDERLY PEOPLE: Redefining An Age Old Problem In Old Age

Be vigilant for the role of alcohol when older people present with physical and psychiatric illness, cognitive impairment, and social problems. Use disorders may be more common in the elderly than you think .

Primary care clinicians should include sensitive questions about alcohol use in their systemic review of the patient history.

10-7 SHOULD DOCTORS PRESCRIBE ALCOHOL TO ADULTS ?

“There is no more emblematic standard of good health in the United States than the food guide pyramid. It is widely recognized if not well followed. The pyramid advises Americans to eat lots of grains and fruits and vegetables, some meat and dairy, and a small amount of fat and sugars.”

“One day soon, it (*the food pyramid*) may advise adult Americans to have a drink of beer, wine, or spirits every day as well. The idea is not as radical as it seems.”

Epidemiological evidence from more than 100 observational studies over the past 3 decades has shown that moderate alcohol consumption helps prevent heart disease. Other health benefits include reduced risk for ischemic stroke, peripheral vascular disease, and diabetes. Risk of heart disease among moderate drinkers is 35% or so lower than in non-drinkers. “Alcohol clearly has a sizable effect, and it’s not so easy to ignore that.”

The policy makers at the U.S. Department of Health and Human Services are reconsidering their stance on alcohol—which in the past has consisted of mentioning the health benefits of alcohol while emphasizing the adverse effects—as they update the U.S. dietary guidelines. With the policy experts talking ever more seriously about endorsing moderate drinking, is it time for physicians to consider selective prescription of alcohol for patients?

“For appropriate patients who do not drink, or do so only occasionally, and who wish to do so, encouraging a glass of wine or other alcoholic beverage with dinner every night may be the best advice you can give them.”

Some authorities urge caution. Most current guidelines recommend moderate drinking only for people who already drink, and urge abstainers *not* to start drinking for their health. Some physicians now believe clinicians should discuss alcohol consumption with all patients and inform those without contraindications of the benefit of regular moderate consumption.

ALDOSTERONE

4-9 ALDOSTERONE BLOCKADE AND HEART FAILURE

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

ALTERNATIVE/COMPLEMENTARY MEDICINE

12-9 EFFICACY AND SAFETY OF ECHINACEA IN TREATING UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN

Echinacea is a herbal remedy widely used for prevention and treatment of upper respiratory infections (**URIs**). It is one of the most commonly used herbal remedies in the USA . Three species of echinacea are used. Beneficial effects are thought to be due to its “immunomodulating” activity, most notably macrophage activation and enhanced neutrophil phagocytosis.

This study postulated that treatment with *E purpurea* would result in at least a 1.5- to 2-day reduction in duration of URIs in children, and that symptoms would be less severe than in patients receiving placebo.

The preparation used in this study was *not* effective in treating URIs in children. After the trial was completed, parents could *not* guess correctly whether their child had taken echinacea or placebo. “Our results do *not* support the use of echinacea for treatment of URIs in children.” Its use was associated with an increased risk of rash.

This study was supported by a grant from the National Center for Complementary and Alternative Medicine, Bastyr University (an alternative medicine institution) and National College of Naturopathic Medicine, Portland Oregon.

It continues to amaze me that so many persons take unstandardized and unproven nostrums and give them to their children. I am sure devotees will fault this study. They will remain convinced that echinacea is beneficial.

ALZHEIMER’S DISEASE

7-11 EFFECT OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ON RISK OF ALZHEIMER’S DISEASE

The study lends support to the hypothesis that NSAIDs may protect against the development of Alzheimer’s disease. They are too toxic to be used for this purpose in large numbers of patients.

This provocative study suggests that we may be on the way to developing safe preventive measures.

10-14 EXERCISE PLUS BEHAVIORAL MANAGEMENT IN PATIENTS WITH ALZHEIMER DISEASE.

Improving physical conditioning in patients with AD may extend their independent mobility and enhance their quality of life despite progression of the disease. Even the oldest adults can improve cardiovascular function and increase flexibility, balance, and strength.

A number of studies link AD with physical deterioration. When compared with age-matched controls, AD patients show more signs of undernutrition, higher risk of falls and fractures, and a more rapid decline in mobility. Reduced muscle mass has been associated with loss of independence.

In this study exercise training improved physical health and lessened depression in patients with AD,

ANGINA

10-16 PROGNOSTIC VALUE OF MYELOPEROXIDASE IN PATIENTS WITH CHEST PAIN

Clinical criteria, ECG criteria, and conventional laboratory tests, including troponin T, often do not adequately predict the risk of cardiovascular events in patients presenting with acute coronary syndromes.

C-reactive protein and other markers have been advocated as a more accurate means of gauging risk, but additional tools are needed to predict vulnerability of coronary arteries to major events in the near term. Myeloperoxidase is an excellent candidate. It predicts cardiovascular risks independently of C-reactive protein and other markers of inflammation.

“Our findings suggest that myeloperoxidase serves as a marker of the vulnerable plaque and one that can be used to identify patients at *imminent* risk for major adverse cardiac events, independently of evidence of myocardial necrosis.”

A single measurement of myeloperoxidase independently predicted early risk of myocardial infarction, as well as the risk of major adverse cardiac events in the ensuing 30 days and 6 months.

ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

1-16 COMBINATION TREATMENT OF ANGIOTENSIN-II RECEPTOR BLOCKER AND ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR IN NON-DIABETIC RENAL DISEASE (COOPERATE)

Combined ACE-I and A II-I therapy safely retarded progression of non-diabetic renal disease more effectively than either drug alone.

2-2 A COMPARISON OF OUTCOMES WITH ANGIOTENSIN-CONVERTING-ENZYME INHIBITORS AND DIURETICS FOR HYPERTENSION IN THE ELDERLY. .

Initiation of antihypertension treatment with ACE inhibitor in older men appeared to lead to better outcomes than diuretics despite similar reductions of BP. Patients often required 2 or more drugs.

NNT to benefit one male patient over 1 year = 270. No benefit in females.

3-16 PROGNOSTIC IMPORTANCE OF WEIGHT LOSS IN CHRONIC HEART FAILURE AND THE EFFECT OF TREATMENT WITH ANGIOTENSIN-CONVERTING-ENZYME INHIBITORS

Cardiac cachexia is common in chronic HF. It independently predicts a poor outcome. This may assist decisions for Hospice care. Enalapril delays development of cardiac cachexia in some patients.

7-13 INTERACTION OF SPIRINOLACTONE WITH ACE INHIBITORS OR ANGIOTENSIN-RECEPTOR BLOCKERS

Spirinolactone and ACE inhibitors act synergistically or additively to increase plasma potassium levels. Toxic and even lethal concentrations may result. Spirinolactone is established as an important additive in therapy for patients with severe heart failure. The dose should not exceed 25 mg daily, and in some patients should be less.

9-3 EFFICACY OF PERINDOPRIL IN REDUCTION OF CARDIOVASCULAR EVENTS AMONG PATIENTS WITH STABLE CORONARY ARTERY DISEASE

Among patients with *stable* CAD without apparent heart failure, the angiotensin converting enzyme inhibitor, perindopril (*Aceon*) improved outcomes. This was in addition to use of other preventive drugs. [NNT(4 years to benefit one) = 50]

ACE inhibitors have been shown to have the broadest impact of any drugs in cardiovascular medicine, reducing the risk of death, myocardial infarction, stroke, diabetes, and renal impairment. They benefit patients with heart failure, post myocardial infarction left ventricular dysfunction, peripheral vascular disease, diabetes, stroke, and transient ischemic attacks.

As long-term therapy, perindopril is expensive. It has not been compared with less expensive ACE inhibitors (eg, enalapril) which may be just as effective.

ACE inhibition is underused in primary care practice.

11-12 VALSARTAN, CAPTOPRIL, OR BOTH IN MYOCARDIAL INFARCTION COMPLICATED BY HEART FAILURE, LEFT VENTRICULAR DYSFUNCTION, OR BOTH

Angiotensin-converting-enzyme inhibitors (**ACE-I**) do not completely block production and effects of angiotensin II. Likewise, angiotensin-receptor blockers (**ARB**) do not completely block angiotensin II. But, they do act differently. Investigators have speculated that adding the two would produce greater benefits than either one used alone.

In this study, however, use of the two drugs together did not benefit any more than either used alone. Valsartan is as effective as captopril (but not more effective) as measured by risk of death in patients who are at high risk for cardiovascular events after a myocardial infarction. The combination increased adverse effects without improving survival.

I abstracted this study because it contrasts with other studies reported in *Practical Pointers*. Doubt remains about the efficacy of combined ACE inhibitors and ARBs. See “Effects of Candesartan on Mortality and Morbidity in Patients with Chronic Heart Failure” *Practical Pointers* September 2003. The study reported a slight benefit when candesartan was added to ACE inhibitors. (NNT = 25 to 50) Hyperkalemia, hypotension, and increased creatinine levels occurred more commonly in the combined group.

I believe primary care clinicians should avoid the combination until clarification is available. ARB may be used when ACE inhibitors are not tolerated. RTJ

ANGIOTENSIN RECEPTOR BLOCKERS

1-9 PROPHYLACTIC TREATMENT OF MIGRAINE WITH AN ANGIOTENSIN-II RECEPTOR BLOCKER

In this study, the angiotensin II blocker, candesartan, provided effective migraine prophylaxis with tolerability comparable to that of placebo.

1-16 COMBINATION TREATMENT OF ANGIOTENSIN-II RECEPTOR BLOCKER AND ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR IN NON-DIABETIC RENAL DISEASE (COOPERATE)

Combined ACE-I and A II-I therapy safely retarded progression of non-diabetic renal disease more effectively than either drug alone.

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9-6 EFFECTS OF CANDESARTAN ON MORTALITY AND MORBIDITY IN PATIENTS WITH CHRONIC HEART FAILURE

ACE inhibitors have been shown to have the broadest impact of any drug in cardiovascular medicine, reducing the risk of death, myocardial infarction, stroke, diabetes, and renal impairment. They benefit patients with heart failure, left ventricular dysfunction, peripheral vascular disease, diabetes, stroke, and transient ischemic attacks.

Candesartan, blocks angiotensin II at the cellular level. Given to patients with heart failure in *addition* to other drugs (including ACE inhibitors) it was associated with reduced cardiovascular deaths and hospital admissions for heart failure.

Reducing angiotensin II levels is a basic therapy in cardiovascular disease. ACE inhibitors have been the standard. Addition of an angiotensin II blocker may benefit slightly. They should be used when the patients cannot tolerate ACE inhibitor.

11-12 VALSARTAN, CAPTOPRIL, OR BOTH IN MYOCARDIAL INFARCTION COMPLICATED BY HEART FAILURE, LEFT VENTRICULAR DYSFUNCTION, OR BOTH

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ANTIBIOTICS

1-1 WHY DO GENERAL PRACTITIONERS PRESCRIBE ANTIBIOTICS FOR SORE THROAT?

Describing the difference between “Evidence Based Medicine” and the “Real World” of practice. Despite the power of EBM, there are many instances and reasons for deviation.

12-1 DELAYED PRESCRIPTIONS

Best evidence indicates that antibiotics are of minimal or no benefit for sore throat, acute bronchitis, the common cold, and otitis media. Antibiotics continue to be commonly used for these conditions. This is potentially inappropriate prescribing.

This has prompted the use of delayed (or “as needed”, or “if”) prescriptions. These prescriptions are written with the proviso that they are not to be used immediately—only later if symptoms do not improve in a few days. Use of a delayed prescription should be restricted to patients who request antibiotics or for whom the doctor thinks one is not immediately indicated.

A randomized trial in 1997 gave prescriptions for antibiotics for respiratory infections: 1) to be filled immediately, or 2) to be filled after 3 days, or 3) no antibiotic prescription.

The immediate group filled 99%.

The delayed group filled 31%.

In the no-prescription group, 13% filled an antibiotic prescription after a return visit to the physician.

The reduction in use of antibiotics for upper respiratory infections through using delayed prescriptions is as effective, and in many cases, more effective than educational projects.

ANTICOAGULANT THERAPY

9-1 EFFECT OF INTENSITY OF ORAL ANTICOAGULATION ON STROKE SEVERITY AND MORTALITY IN ATRIAL FIBRILLATION

Emboli of atrial origin are larger than average. The brain infarcts they produce are more disabling and lethal.

Among patients with non-valvular AF, the degree of anticoagulation at admission for stroke was associated with risk of disability and death. Anticoagulation that resulted in an INR of 2.0 or greater reduced frequency and severity of ischemic stroke and risk of death. This is evidence against INR targets below 2.0

Risk of hemorrhagic stroke did not increase until INR was 4.0 or above.

INR below 2.0 and aspirin protect against stroke less effectively than INR 2.0 to 3.0, but are superior to use of no anticoagulant. Aspirin is adequate prophylaxis in patients considered at low risk for thromboembolic stroke. Eventually almost all patients with AF will become high risk due to age and co-morbidity. As age progresses, risk of bleeding from warfarin increases. This dilemma must be solved on an individual basis. Patients accepting warfarin must be carefully controlled at a stable INR around 2.5.

“Our results provide further support for anticoagulation to achieve an INR of 2.0 or greater (eg, 2.5) in patients with non-valvular atrial fibrillation.”

9-2 ORAL XIMELAGATRAN FOR SECONDARY PROPHYLAXIS AFTER MYOCARDIAL INFARCTION

In patients with a recent MI, long term treatment with ximelagatran, combined with aspirin, was more effective than aspirin alone in reducing frequency of major cardiovascular events. [NNT (for 6 months to benefit one) = 33]

Ximelagatran is the first of a new class of *oral direct-thrombin inhibitors* under investigation. It is rapidly metabolized to its active form, melagatran. It is stable over time. Its metabolism is unaffected by age, sex, body weight, or ethnic origin. It is not affected by the hepatic cytochrome P450 enzyme system, thus providing a low potential for drug-drug interactions. There are no relevant food or alcohol interactions. “Melagatran’s pharmacokinetics are unchanged and the pharmacodynamic properties show only minor additive effects when oral ximelagatran and acetylsalicylic acid are given concomitantly.” Ximelagatran has undergone extensive assessment in patients with venous thromboembolism and atrial fibrillation. It has a rapid onset of action, achieves a peak level within 2 hours, and has a half-life of 4 hours. It is administered twice daily. There is no need of monitoring and dose adjustments. (*Monitoring of liver and kidney function is required. RTJ*) Ximelagatran is primarily excreted by the kidney. Data on patients with kidney dysfunction are limited.

With the 24 mg BID dose, the bleeding rate was low, and high concentrations of alanine amino transferase occurred less frequently (7%).

“It is good news that the more than half century wait of new and improved oral antithrombotics finally appears to be ending.”

10-2 TREATING THROMBOSIS IN THE 21ST CENTURY

Now, a minimal anti-thrombin-binding unit of heparin, a pentasaccharide called fondaparinux, has been synthesized and is undergoing clinical trials. Fondaparinux enhances anti-thrombin activity. It is a specific inhibitor of activated factor X (Xa). It requires subcutaneous administration. It can be given once a day on a weight basis. It does not require laboratory monitoring.

A second new anticoagulant (melagatran) took its cue from the leach which produces a direct thrombin inhibitor (hirudin). Hirudin acts independently of anti-thrombin and other plasma proteins. The discovery of hirudin led to other direct thrombin inhibitors, one of which is melagatran. Melagatran can also neutralize clot-bound thrombin. Chemical modification (to “ximelagatran”) allows better oral absorption. It is the first new oral anticoagulant since warfarin. Like fondaparinux, it does not require laboratory monitoring.

10-3 SUBCUTANEOUS FONDAPARINUX VERSUS INTRAVENOUS UNFRACTIONATED HEPARIN IN THE INITIAL TREATMENT OF PULMONARY EMBOLISM.

Once-daily fondaparinux without monitoring is at least as effective and safe as adjusted-dose IV unfractionated heparin in the initial treatment of hemodynamically stable patients with pulmonary embolism.

“Because of its simplicity, once-daily subcutaneous fondaparinux without anticoagulation monitoring could replace intravenous administration of unfractionated heparin in most patients.”

10-4 COMPARISON OF XIMELAGATRAN WITH WARFARIN FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM AFTER TOTAL KNEE REPLACEMENT

Fixed dose ximelagatran 36 mg bid, administered without coagulation monitoring, was significantly more effective than warfarin in prevention of thromboembolism after knee replacement. Safety was similar “It could therefore be considered an alternative to other thromboprophylactic agents.”

10-5 SECONDARY PREVENTION OF VENOUS THROMBOEMBOLISM WITH ORAL DIRECT THROMBIN INHIBITOR XIMELAGATRAN

Ximelagatran is a direct thrombin inhibitor undergoing active investigation as an anticoagulant. It is given in a fixed dose daily, and needs no monitoring.

Beginning and continuing extended secondary prevention of VTE with ximelagatran 24 mg bid for an additional 18 months after 6 months of standard anticoagulation effectively prevented recurrences. [NNT = 10]

The incidence of major hemorrhage was low and similar to placebo. Ximelagatran was equally effective in subgroups that had risk factors for recurrence—previous VTE, proximal deep VTE, and pulmonary embolism.

The fixed-dose ximelagatran was well tolerated without monitoring measures of coagulation.

12-5 CLINICAL IMPACT OF BLEEDING IN PATIENTS TAKING ORAL ANTICOAGULANT THERAPY FOR VENOUS THROMBOEMBOLISM

In patients with venous thromboembolism (VTE), there is a perception that the clinical impact of preventing recurrent VTE and possible fatal pulmonary embolism outweighs the risk of bleeding associated with long-term anticoagulation..

The subgroup of patients with idiopathic (unprovoked) VTE, and VTE associated with factor V Leiden, prothrombin mutations, and deficiencies of protein C and protein S make up about half of the thousands of patients in whom symptomatic VTE is diagnosed each year in the USA.

The optimal duration of anticoagulation is still unclear.

This systematic review of randomized, controlled trials and prospective cohort studies (10 757 patients; 4373 patient-years) investigated patients with confirmed idiopathic VTE. All received oral anticoagulant therapy (target INR--2.0 to 3.0) for at least 3 months. Nine of 33 studies reported use for over 3 months (6 to 24 months).

The chances of a major bleed *per year of anticoagulation* were 7 in 100 patients with 1 in 1000 chance of fatality, and about 1 chance in 100 of an intracranial bleed.

The primary care clinician must make some attempt to balance the risk of bleeding vs the benefits of anticoagulation in each individual patient. (*I know of no means of doing this beyond “clinical judgment”.* RTJ)

AROMATASE INHIBITOR

11-5 A RANDOMIZED TRIAL OF LETROZOLE IN POSTMENOPAUSAL WOMEN AFTER FIVE YEARS OF TAMOXIFEN THERAPY FOR EARLY-STAGE BREAST CANCER

Letrozole, an aromatase inhibitor, begun after 5-years of tamoxifen had been completed, significantly improved disease-free survival. Aromatase is the enzyme which converts the androgenic substrates, androstenedione and testosterone, into estradiol. Letrozole (*Femara*) is one of several new aromatase inhibitors (a third generation). This drug binds to the aromatase and almost completely inactivates it, thus providing maximal endocrine control of breast cancer (BC).

The aromatase inhibitors are challenging tamoxifen, the previous gold standard for treatment of postmenopausal women with estrogen-receptor-positive BC. In advanced BC, letrozole is clearly superior to tamoxifen as first-line therapy. Aromatase inhibitors are also being considered in chemoprevention, a strategy in which tamoxifen has already been shown to reduce incidence of BC.

Tamoxifen blocks the binding of estradiol to the BC cells. It has dual effects which are complex, both antagonistic and agonistic. After 5 years of treatment its agonistic effects may predominate. Aromatase inhibitors do not have agonistic effects.

There was also a reduction in the frequency of new primary BC in the contralateral breast (relative reduction of 46%).

ARTHRITIS

12-6 INTRA-ARTICULAR HYALURONIC ACID IN TREATMENT OF KNEE ARTHRITIS

“Based on the findings of this meta-analysis, intra-articular hyaluronic acid has, at best, modest efficacy in the treatment of knee osteoarthritis. This effect . . . “is equivalent to the effect of NSAIDs over that of acetaminophen, an effect that itself remains controversial.” .” “Our findings suggest the controversy surrounding the efficacy of intra-articular hyaluronic acid is justified and the best evidence does not support its efficacy.”

At least 17 of the 22 trials were industry sponsored. Others have suggested that findings from industry-sponsored trials compared with those that were otherwise funded showed that research funded by pharmaceutical companies was more likely to have outcomes favoring the sponsor.

All 22 studies reported improvement of pain in the intra-articular placebo groups. Placebo injections may have efficacy for treating knee OA. The investigators calculated that intra-articular placebo accounted for 79% of the efficacy of intra-articular hyaluronic acid.

“This supports our hypothesis that the majority of the effect of intra-articular hyaluronic acid is an intra-articular placebo effect.”

Publication bias may overestimate the effect. Compared with lower-molecular-weight hyaluronic acid, the higher-molecular weight hyaluronic acid may be more efficacious, but heterogeneity of studies limits definitive conclusions.

I doubt this study will deter enthusiasts from using HA. Individual patients who have apparently obtained relief may insist on continuing.

The only way an individual’s response can be accurately determined is by an N-of-one trial. I doubt this would be feasible considering the ethical issues involved.

ASPIRIN

2-5 EFFECT OF IBUPROFEN ON CARDIOPROTECTIVE EFFECT OF ASPIRIN

Ibuprofen negates the protective effect of low dose aspirin. Use another NSAID.

3-11 A RANDOMIZED TRIAL OF ASPIRIN TO PREVENT COLORECTAL ADENOMAS IN PATIENTS WITH PREVIOUS COLORECTAL CANCER

Compared with placebo, a daily dose of 325 mg aspirin reduced risk of adenoma development in patients with a history of surgery for CRC. (High risk patients.)

3-12 A RANDOMIZED TRIAL OF ASPIRIN TO PREVENT COLORECTAL ADENOMAS

Low-dose aspirin had a moderate chemoprotective effect on adenoma formation.

3-13 ASPIRIN AND PREVENTION OF COLORECTAL CANCER

Among persons with a history of adenomas or CRC the number of recurrences of adenomas prevented by aspirin (*secondary prevention*) would be higher than the number of episodes of bleeding. However, the cumulative clinical importance of bleeding probably exceeds that of surrogate neoplasm-related outcomes, especially when the effect of colonoscopic surveillance is taken into account.

If aspirin is used for *primary* prevention of CRC, it would have to be given for 10 to 20 years, the time it takes for CRC to develop. The cumulative adverse effects of aspirin over this time outweigh any benefit in prevention of CRC, particularly when prevention by screening for CRC is considered. Long-term use of aspirin for primary prevention of CRC is not cost-effective. It does not obviate the need for screening and surveillance.

Aspirin does reduce risk of recurrent colorectal neoplasia. Whether aspirin has a role in preventing colorectal cancer and whether it can be used to decrease the required frequency of screening or surveillance must await results of clinical trials.

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

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

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

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

ASTHMA

3-8 EARLY INTERVENTION WITH BUDESONIDE IN MILD PERSISTENT ASTHMA

Long-term, once-daily low-dose inhaled budesonide decreased the risk of severe exacerbations and the need for systemic corticosteroids and improved asthma control in patients with mild, persistent asthma of recent onset.

3-9 INHALED GLUCOCORTICOID VERSUS LEUKOTRIENE RECEPTOR ANTAGONIST AS SINGLE AGENT ASTHMA TREATMENT

Anti-leukotrienes as single agents were *less* effective than inhaled corticosteroids in the treatment of adults with mild to moderate asthma.

3-10 ACCESSIBILITY, ACCEPTABILITY, AND EFFECTIVENESS OF ROUTINE TELEPHONE REVIEW OF ASTHMA: Pragmatic, Randomized, Trial

Telephone consultations enabled more patients with asthma to be reviewed. There was no apparent clinical disadvantage or loss of satisfaction. They may be an efficient option for primary care practice.

ATHEROSCLEROTIC DISEASE

1-15 DRUG ELUTING STENTS IN VASCULAR INTERVENTION

Immunosuppressive agents (which inhibit tumor-cell growth) may also inhibit the benign tissue proliferation characterizing intimal hyperplasia. Several immunosuppressants have been tested for potential to inhibit restenosis. Stents coated with the agents are becoming available. Local drug delivery achieves higher tissue concentrations of drugs, while producing no systemic effects. This is associated with a marked reduction in the risk of re-stenosis.

“The clinical impact of the elimination of restenosis may influence the approach to coronary artery disease, the future of cardiac surgery, and health-care economics.”

8-8 EMERGING RISK FACTORS FOR ATHEROSCLEROTIC VASCULAR DISEASE.

This critical review highlights 4 emerging risk predictors: C-reactive protein, Lipoprotein (a), Fibrinogen, and Homocysteine.

“Their optimal use in routine screening and risk stratification remains to be determined.”

“The explanatory power of the *major established* cardiovascular risk factors has been systematically underestimated.”

(See previous abstract.)

Primary care clinicians and their patients have not even begun to assess, prevent, and treat the established major, modifiable risk factors. Until we do, I believe we need no more risk factors.

We will, with interest, however, follow the basic science investigations aimed at determining the best mix of risk factors on which to base clinical interventions.

11-4 STARTING EARLIER TO PREVENT HEART DISEASE.

Two studies reported in the November 5 issue of JAMA measured carotid artery intima/media thickness (IMT) in young adults (age 24 to 37). LDL-cholesterol and BMI had been measured in childhood, up to 22 years earlier. Higher childhood levels of both predicted increased adult carotid IMT. In one study, systolic BP and smoking in adolescence also predicted increased IMT. (The higher the carotid IMT, the greater the extent of coronary atherosclerosis.)

It is clear that risk factors begin to matter during adolescence, the age range during which fatty streaks in the coronary arteries begin to be converted to raised lesions, and when high-risk populations begin to diverge from low-risk populations. "It may be possible that risk factors in the early teen-age years are associated with permanent damage to the arterial wall."

Assessing risk factors in youth is easy and inexpensive. Cholesterol and other risk factors do matter during adolescence. It may now be time to reconsider the age at which measurement of cholesterol and life-style changes should begin. The difficulty of changing life styles in teenagers, however, should not be underestimated. Physicians caring for children and adolescents should be sure their patients and their parents know it is beneficial and safe to promote and maintain a healthy life style.

Changing ingrained life-style habits in teen-agers is almost impossible. Parents must set the example and begin lifetime habits of their children at a pre-teen age.

ATRIAL FIBRILLATION

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

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

8-4 A RISK SCORE FOR PREDICTION OF STROKE OR DEATH IN INDIVIDUALS WITH NEW-ONSET ATRIAL FIBRILLATION IN THE COMMUNITY: *The Framingham Heart Study*

This risk score for embolic stroke was derived from 5 risk predictors: advancing age, female sex, increasing systolic BP, prior stroke or TIA, and diabetes. The score can be used to estimate *absolute* risk of stroke (5% to 75% over 5 years) and help to negotiate treatment decisions with patients with AF at the time they are first diagnosed. . Risk may be stratified into mild, moderate or severe.

Although some physicians and patients may more readily accept and act on a numerical risk prediction, I believe primary care clinicians can just as accurately judge risk without creating a numerical 5-year "risk". Most patients will eventually end up receiving anticoagulation. It is nevertheless important to spare those at low risk from the potential adverse effects of warfarin therapy and use aspirin instead. Patients with AF, but without structural heart disease, (including no hypertension) are at relatively low risk, especially if they are under age 65.

To anticoagulate or not anticoagulate is a difficult and important decision. It remains a clinical-judgment call. For each patient, clinicians must strike an acceptable balance between risk of ischemic stroke and bleeding. In the absence of an absolute or important relative contraindication, the data seem compelling that warfarin therapy should be offered to most patients with AF. The difficulty is to know what threshold of stroke risk is low enough so that the potential risk of warfarin therapy outweighs its potential benefits. For most patients the potential benefits of stroke prevention will outweigh the potential risks of bleeding secondary to warfarin.

An article (*Annals Internal Medicine* April 28, 2003; 139: 936-43; *Practical Pointers* April 2003) differs somewhat in suggesting that up to 1/3 of patients with AF can be classified as low-risk and treated with aspirin.

9-1 EFFECT OF INTENSITY OF ORAL ANTICOAGULATION ON STROKE SEVERITY AND MORTALITY IN ATRIAL FIBRILLATION

Emboli of atrial origin are larger than average. The brain infarcts they produce are more disabling and lethal.

Among patients with non-valvular AF, the degree of anticoagulation at admission for stroke was associated with risk of disability and death. Anticoagulation that resulted in an INR of 2.0 or greater reduced frequency and severity of ischemic stroke and risk of death. This is evidence against INR targets below 2.0

Risk of hemorrhagic stroke did not increase until INR was 4.0 or above.

INR below 2.0 and aspirin protect against stroke less effectively than INR 2.0 to 3.0, but are superior to use of no anticoagulant. Aspirin is adequate prophylaxis in patients considered at low risk for thromboembolic stroke. Eventually almost all patients with AF will become high risk due to age and co-morbidity. As age progresses, risk of bleeding from warfarin increases. This dilemma must be solved on an individual basis. Patients accepting warfarin must be carefully controlled at a stable INR around 2.5.

“Our results provide further support for anticoagulation to achieve an INR of 2.0 or greater (eg, 2.5) in patients with non-valvular atrial fibrillation.”

11-7 STROKE PREVENTION WITH ORAL DIRECT THROMBIN INHIBITOR XIMELAGATRAN COMPARED WITH WARFARIN IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION.

Ximelagatran is a direct thrombin inhibitor which is given orally. Its pharmacokinetic profile is predictable and stable overtime. It has low potential for drug-drug interactions and does not require monitoring or dose adjustment.

Fixed dose ximelagatran was at least as effective as well-controlled warfarin for prevention of stroke and systemic embolism. It is much easier to use.

Practical Pointers has abstracted several articles on the new oral anticoagulant ximelagatran. (See October 2003 issue.)

Ximelagatran looks very promising.

BARRETT'S ESOPHAGUS

9-11 RISK OF ADENOCARCINOMA IN BARRETT'S ESOPHAGUS

“Patients with Barrett's oesophagus are at low risk of oesophageal adenocarcinoma. This risk is almost exclusively in patients with specialized intestinal metaplasia.”

“Up to 8 years after diagnosis we found no increased risk of malignancy with time.”

Surveillance of patients with BE at a risk of malignant transformation of 1% per year may be cost effective, but only in men over age 70. This questions the value of universal endoscopic screening for cancer in patients with BE.

Primary care clinicians in the USA refer patients with BE to gastroenterologists. They will usually advise periodic endoscopic screening .

BENIGN PROSTATIC HYPERPLASIA (BPH)

12-4 THE LONG-TERM EFFECT OF DOXAZOCIN, FINASTERIDE, AND COMBINATION THERAPY ON THE CLINICAL PROGRESSION OF BENIGN PROSTATIC HYPERPLASIA

This study assessed the long-term effects of diazoxide (an alpha blocker) alone, finasteride (a reductase inhibitor) alone, and the combination on clinical progression of BPH. It concluded that long-term therapy with combined drugs reduced the risk of clinical progression significantly more than either drug alone.

The number needed to treat by combined therapy over 5 years was 8, vs 14 to 15 for the drugs used alone.

Risk of acute retention and need for invasive therapy were reduced by finasteride but not by doxazocin.

The risk of overall clinical progression increased with increasing baseline PSA levels and prostate volume in the doxazocin group, but *not* in the finasteride or combination group. No alpha blocker stops the progression of prostate size.

Finasteride reduces circulating dihydro-testosterone levels by about 80%; PSA levels by 50%; and prostate size by 20%. Reductase inhibitors do not act rapidly, and often require 6 months to reduce prostate size.

Current initial therapy in most cases consists of an alpha blocker given alone. It acts rapidly to relieve symptoms. In the current study, clinical progression occurred in only 17% of men in the placebo group. In men with a low PSA and modest prostate size, progression of BPH may be slow and use of a reductase inhibitor may be delayed. The study does support dual use in men whose symptoms progress during monotherapy, or in men at high risk of progression. (PSA over 4 mg/mL or prostate volume more 40 mL on ultrasound).

BEREAVEMENT

11-10 END-OF-LIFE CARE AND THE EFFECTS OF BEREAVEMENT ON FAMILY CAREGIVERS OF PERSONS WITH DEMENTIA

Caregivers in this study showed remarkable resilience in adapting to the death of their relatives. A large majority reported feeling relieved by the death, although persons whose relatives were institutionalized did not show as rapid a recovery from depressive symptoms. This suggests that relief from providing daily care did not alone account for the caregivers' recovery from bereavement.

Investments in resources for intervention and support may have the largest benefit when they are applied to caregivers and patients in the period immediately preceding the patient's death. When caregivers know that their relative is on a trajectory toward death, and when they are aware of the patient's disability and suffering, they grieve for the loss of the patient before the death.

Clinicians should view bereavement not only as a phenomenon that affects caregivers after the death, but also as one that affects many caregivers before the death occurs.

BREAST CANCER

4-4 MAMMOGRAPHIC SCREENING FOR BREAST CANCER.

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

The downside: False positive results necessitate further investigation. Nationally, an average of 11% of screening mammograms are read as abnormal. BC is subsequently found in about 3% of these women (0.3% of all mammograms). Thus, a woman has about a 10% chance of a false positive result with each mammogram. Because women are screened repeatedly, the risk of a false positive increases over time. One study estimated that, after 10 mammograms, about half of

women age 40 to 64 will have had a false positive leading to needle biopsy or open biopsy in about 20%. The malpractice climate in the USA may work to increase the numbers of false positive reports.

8-1 BREAST CANCER AND HORMONE-REPLACEMENT THERAPY IN THE MILLION WOMEN STUDY

This remarkable, country-wide study confirms that current use of HRT is associated with increased risk of incident and fatal BC. Between 1996 and 2001, one half of the million women age 50-64 in this UK cohort were using HRT.

The risk is substantially less for estrogen-alone than for E-P combinations.

Use of HRT by women aged 50-64 in the UK over the past decade is estimated to have resulted in 20 000 extra cases of BC; 15 000 of these associated with E-P use; 5000 with use of estrogen alone. (Ie, *progestins are the major culprit.*)

Women who are presently taking estrogen-progestin may be told there is one additional chance in 150 of an invasive BC over 5 years; and one additional chance in 800 if they are taking estrogen alone.

Risk increases with duration of use. Past users (5 or more years previously) were not at increased risk.

11-5 A RANDOMIZED TRIAL OF LETROZOLE IN POSTMENOPAUSAL WOMEN AFTER FIVE YEARS OF TAMOXIFEN THERAPY FOR EARLY-STAGE BREAST CANCER

Letrozole, an aromatase inhibitor, begun after 5-years of tamoxifen had been completed, significantly improved disease-free survival. Aromatase is the enzyme which converts the androgenic substrates, androstenedione and testosterone, into estradiol. Letrozole (*Femara*) is one of several new aromatase inhibitors (a third generation). This drug binds to the aromatase and almost completely inactivates it, thus providing maximal endocrine control of breast cancer (**BC**).

The aromatase inhibitors are challenging tamoxifen, the previous gold standard for treatment of postmenopausal women with estrogen-receptor-positive BC. In advanced BC, letrozole is clearly superior to tamoxifen as first-line therapy. Aromatase inhibitors are also being considered in chemoprevention, a strategy in which tamoxifen has already been shown to reduce incidence of BC.

Tamoxifen blocks the binding of estradiol to the BC cells. It has dual effects which are complex, both antagonistic and agonistic. After 5 years of treatment its agonistic effects may predominate. Aromatase inhibitors do not have agonistic effects.

There was also a reduction in the frequency of new primary BC in the contralateral breast (relative reduction of 46%).

BULIMIA NERVOSA

8-11 BULIMIA NERVOSA

Has 3 key features: 1) Intense preoccupation with body weight and shape; 2) Repetitive episodes of binge eating-- uncontrollable eating a large quantity of food in a defined period—usually less than 2 hours; 3) Routinely taking extreme measures to prevent weight gain: self induced vomiting, fasting, exercise, and misuse of laxatives and diuretics. Some patients take up to 50 laxative pills per day. Severe constipation with a laxative-dependence syndrome may result.

Anorexia nervosa differs. Patients with BN maintain a normal weight.

The challenge for primary care clinicians is to suspect and recognize BN in select young women who present with vague symptoms, anxiety and depression. The clinical clues cited may help. A metabolic package might very well reveal a metabolic alkalosis.

“Hypokalemia in an otherwise healthy young woman is highly specific for BN.”

CANNABIS

1-8 ESCALATION OF DRUG USE IN EARLY-ONSET CANNABIS USERS VS CO-TWIN CONTROLS.

Associations between early cannabis use and later drug use and abuse/dependence cannot be explained solely by common predisposing genetic or environmental factors. Early initiation of cannabis (before age 17) was associated with significantly increased risk of other drug use and abuse/dependence later in life. This is consistent with early use of marijuana having a causal role as a risk factor.

Regardless of the mechanisms underlying the associations, it is apparent that young people who initiate cannabis at an early age are at heightened risk of progressing to other drug use and drug abuse/dependence.

CARDIOVASCULAR DISEASE

1-3 MULTIFACTORIAL INTERVENTION AND CARDIOVASCULAR DISEASE IN PATIENTS WITH TYPE 2 DIABETES

A targeted long-term intensive intervention aimed at multiple risk factors (hypertension, dyslipidemia, microalbuminuria) in patients with DM-2 and microalbuminuria reduced the risk of cardiovascular and microvascular events by about 50%.

3-1 INFLUENZA VACCINATION AND REDUCTION IN HOSPITALIZATIONS FOR CARDIAC DISEASE AND STROKE AMONG THE ELDERLY

In the elderly, vaccination against influenza was associated with large reductions in numbers of hospitalizations from heart disease, cerebrovascular disease, as well as pneumonia and influenza. Risk of death was reduced by about 50%.

Flu vaccination is one of the most cost-effective health interventions. Primary care clinicians bear responsibility for increasing uptake by the general population.

3-3 CEREAL, FRUIT, AND VEGETABLE FIBER INTAKE AND THE RISK OF CARDIOVASCULAR DISEASE IN ELDERLY INDIVIDUALS.

Cereal fiber consumption (equivalent to 2 slices of whole grain bread) in later life was associated with lower risk of incident CVD.

6-1 A STRATEGY TO REDUCE CARDIOVASCULAR DISEASE BY MORE THAN 80%

A proposed pill, to be taken by everyone, contains low doses of a statin drug, 3 antihypertension drugs, folic acid and aspirin.

The authors calculate that one third of people taking the pill from age 55 would benefit, gaining on average 11 years of life free from an ischemic heart disease event or stroke.

“The preventive strategy is radical.” It is time to discard the view that risk factors need to be measured and treated individually if found to be ‘abnormal’. Instead, it should be recognized that in Western society the risk factors are high in all of us, so everyone is at risk.”

6-11 USE OF ANTIOXIDANT VITAMINS FOR THE PREVENTION OF CARDIOVASCULAR DISEASE

A lack of beneficial effect was seen consistently for various doses of these two vitamins in diverse populations. The routine use of vitamin E is not supported. The use of beta carotene is associated with a small but significant excess of all-cause mortality and cardiovascular death.

8-9 CARDIOVASCULAR RISK FACTORS AND INCREASED CAROTID INTIMA-MEDIA THICKNESS IN HEALTHY YOUNG ADULTS

Atherosclerosis is a slowly progressive process possibly starting at a young age. Preventive measures taken early in life might postpone the development of atherosclerosis and decrease risk of clinical cardiovascular disease (CVD).

Unfavorable cardiovascular risk factors (cigarette smoking, diabetes, dyslipidemia, and hypertension) were related to greater CIMT in young adulthood. Effort to change modifiable risk factors early in life may retard development of atherosclerosis and the onset of clinical cardiovascular disease later in life.

8-10 REGRESSION OF CAROTID AND FEMORAL ARTERY INTIMA-MEDIA THICKNESS IN FAMILIAL HYPERCHOLESTEROLEMIA

High dose simvastatin over 2 years reduced combined carotid/femoral IMT in more than two thirds of patients. The largest effect was on the femoral artery. This degree of reduction of IMT. . . “will likely have a significant clinical impact on the prevention of coronary artery disease”. Primary care clinicians might easily extrapolate these results to other patients with high cholesterol levels. Atherosclerosis is reversible.

8-8 EMERGING RISK FACTORS FOR ATHEROSCLEROTIC VASCULAR DISEASE.

This critical review highlights 4 emerging risk predictors: C-reactive protein, Lipoprotein (a), Fibrinogen, and Homocysteine.

“Their optimal use in routine screening and risk stratification remains to be determined.”

“The explanatory power of the *major established* cardiovascular risk factors has been systematically underestimated.”
(See previous abstract.)

Primary care clinicians and their patients have not even begun to assess, prevent, and treat the established major, modifiable risk factors. Until we do, I believe we need no more risk factors.

We will, with interest, however, follow the basic science investigations aimed at determining the best mix of risk factors on which to base clinical interventions.

9-8 ABILITY OF EXERCISE TESTING TO PREDICT CARDIOVASCULAR AND ALL-CAUSE DEATH IN ASYMPTOMATIC WOMEN: A 20-YEAR FOLLOW-UP OF THE LIPID RESEARCH CLINICS PREVALENCE STUDY

Exercise capacity and heart rate responses were strong, graded, and independent predictors of cardiovascular and all-cause mortality. Not achieving target heart rate and slow return of the rapid heart rate induced by exercise toward normal predicted future mortality in younger women.

ST segment depression, while predictive in men, had no value in women.

The benefit of exercise testing in asymptomatic women is in determining their cardiovascular fitness.

Women need more fitness exercise independent of their weight, blood pressure, or lipid levels.

10-17 THE GREATEST THREAT TO WOMEN’S HEALTH

Heart attacks and stroke kill twice as many women as all cancers combined. Moreover, contrary to conventional wisdom, women are more likely to die from cardiovascular disease than men.

Getting women to stop smoking, eat healthily, drink alcohol only in moderation, lose weight if appropriate, and take regular exercise involves changing behaviors that are often ingrained from childhood.

More than half of all deaths and disability from heart disease and stroke can be prevented.

“Advising women, as well as men, about their risks of cardiovascular disease should, we urge, be mandatory for all primary care practitioners.”

11-2 EFFECTS OF DIFFERENT BLOOD-PRESSURE-LOWERING REGIMENS ON MAJOR CARDIOVASCULAR EVENTS: OVERVIEW OF RANDOMIZED TRIALS

This study estimated the effects of strategies based on different drug classes and on those targeting different BP goals on the risks of major cardiovascular events and death.

Treatment with any commonly-used regimen reduces the risk of total major cardiovascular events.

A larger reduction in BP reduces risk of total cardiovascular events. BP-lowering is a major component of the benefit conferred by the regimens investigated. There was a larger reduction in stroke and total major cardiovascular events from regimens aimed at a lower BP goal.

ACE-inhibitor-based regimens benefit across a wide range of hypertensive and non-hypertensive patients who are at high risk for cardiovascular disease.

ACE inhibitor or diuretic or beta-blocker are much more effective in preventing heart failure than calcium antagonists.

For stroke, there is a greater effect of regimens based on calcium antagonists than those based on diuretics or beta-blockers, but the results were of borderline significance.

Reductions in systolic BP of 2, 4, 6, 8, and 10 mmHg were associated with lower risk of stroke, major cardiovascular disease, coronary heart disease, cardiovascular death, and total mortality.

CAREGIVERS

11-10 END-OF-LIFE CARE AND THE EFFECTS OF BEREAVEMENT ON FAMILY CAREGIVERS OF PERSONS WITH DEMENTIA

Caregivers in this study showed remarkable resilience in adapting to the death of their relatives. A large majority reported feeling relieved by the death, although persons whose relatives were institutionalized did not show as rapid a recovery from depressive symptoms. This suggests that relief from providing daily care did not alone account for the caregivers' recovery from bereavement.

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Clinicians should view bereavement not only as a phenomenon that affects caregivers after the death, but also as one that affects many caregivers before the death occurs.

CERVICAL CANCER

2-6 ADDING A TEST FOR HUMAN PAPILLOMA VIRUS DNA TO CERVICAL-CANCER SCREENING

Virtually all squamous-cell cervical carcinomas contain one of eighteen types of human papilloma virus (HPV). The relative risk of cervical cancer associated with persistent infection with high-risk types of HPV (especially types 16 and 18) is higher than the risk of lung cancer associated with smoking.

The discovery that continued presence of tumor-producing HPV is necessary for development of cervical cancer is revolutionizing our approaches to screening and prevention. An obvious corollary is that the absence of infection means that the risk of cervical cancer is negligible.

10-1 RISK OF CERVICAL CANCER ASSOCIATED WITH EXTENDING THE INTERVAL BETWEEN CERVICAL-CANCER SCREENINGS

Compared with annual screening, screening performed once three years after the last negative test in women who previously had 3 or more consecutive negative PAP tests, is associated with an average excess risk of cervical cancer of approximately 3 in 100 000. If continued, screening annually after 3 negative tests, would result in thousands and thousands of additional PAP tests and colposcopic examinations to detect only one additional case of cervical cancer.

The US Preventive Services Task Force recently recommended screening be performed “at least every 3 years” rather than every year. The American Cancer Society suggests lengthening the intervals between screenings to as long as 3 years among women age 30 and over who previously have had negative results on three or more consecutive cervical cancer tests.

Given that half of all cases of cervical cancer occur in women who have never been screened, screening all women at least once would be expected to contribute more to decreasing mortality than the continued annual testing. The focus should be on screening women who have rarely or never undergone screening.

CHOLESTEROL

3- 17 APOLIPOPROTEINS VERSUS LIPIDS AS INDICES OF CORONARY RISK AND AS TARGETS FOR STATIN TREATMENT.

Apo-lipo-protein B (**APO-B**) is a measure of the total number of atherogenic particles. APO-B is a *risk* factor, as is LDL-cholesterol. The *higher* the ABO-B, the *higher* the risk. In contrast, **APO-A1** is a *protective* factor, as is HDL-c. The *higher* the APO-A1, the *lower* the risk. Many studies show that APO-B is a better marker of risk of vascular disease and a better guide to the adequacy of statin treatment than any cholesterol index.

We are still pursuing the search for the best, most accurate, most reproducible, least costly risk factor for cardiovascular disease. LDL-cholesterol remains the choice at present. Other candidates are forthcoming, including C-reactive protein and APO-B. It will be interesting to follow the search. RTJ

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

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

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

6-3 HEART PROTECTION STUDY OF CHOLESTEROL-LOWERING SIMVASTATIN IN 5963 PEOPLE WITH DIABETES

Cholesterol-lowering therapy is beneficial for people with diabetes even if they do not already have manifest coronary disease or high cholesterol concentrations. Simvastatin reduced the rate of first major vascular events by about a quarter in a wide range of diabetic patients. Treatment over 5-years could prevent about 5 events per 100 persons treated,

8-10 REGRESSION OF CAROTID AND FEMORAL ARTERY INTIMA-MEDIA THICKNESS IN FAMILIAL HYPERCHOLESTEROLEMIA

High dose simvastatin over 2 years reduced combined carotid/femoral IMT in more than two thirds of patients. The largest effect was on the femoral artery. This degree of reduction of IMT. . . “will likely have a significant clinical impact on the prevention of coronary artery disease”.

Primary care clinicians might easily extrapolate these results to other patients with high cholesterol levels.

Atherosclerosis is reversible.

9-4 LIFETIME RISK OF CORONARY HEART DISEASE BY CHOLESTEROL LEVELS AT SELECTED AGES.

For persons *of all ages*, lifetime risk of CHD increases as total cholesterol levels rise from under 200 to over 240. This supports the important role of cholesterol screening at all ages.

This article is of considerable clinical importance even though it provided no outcomes from lifestyle or drug interventions. Patients, old and young, now have a reasonable prediction of lifetime risk according to total cholesterol levels.

(And cholesterol subfractions.) Old, and young should be screened periodically. The data may convince some younger persons to intervene to reduce their lifetime risk.

Guidelines suggest lipid screening begin at age 20.

10-8 TAKING SIMVASTATIN IN THE MORNING COMPARED WITH EVENING

The statin drug, simvastatin, taken in the evening produced lower cholesterol levels. Lowering LDL-c by 10 mg/dL is clinically significant. This is achieved with no additional cost or inconvenience

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

2-7 COMBINED SALMETEROL AND FLUTICASONE IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Combined inhaled long-acting beta agonist/corticosteroid produced better control of symptoms and lung function than the use of either component alone, with no greater risk of adverse effects.

“This combination treatment should be considered for patients with COPD.”

9-16 METHYLXANTHINES FOR EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

When given in conjunction with other standard treatments, methylxanthines did not confer statistically significant benefits for lung function, clinical outcomes, and symptoms in patients with exacerbations of COPD. They significantly increase nausea and vomiting.

COLONOSCOPY

12-10 SCREENING VIRTUAL COLONOSCOPY—READY FOR PRIME TIME?

A new virtual colonoscopy (VC) used a multidirectional CT scanner providing a primary 3-dimensional endoluminal display. It permitted faster, higher-resolution imaging than previously obtainable. Residual fluid and stool was tagged by contrast material. The imaging software digitally removed all opacified fluid and stool from the colon by a process called “electronic cleansing”.

The study subjects received the VC followed by conventional colonoscopy for comparison:

Sensitivity of VC for detection of adenomas vs traditional colonoscopy:

10 mm or larger was 92% vs 88%

8 mm or larger was 92% vs 89%

6 mm or larger was 86% vs 90%

The study suggests that VC can detect polyps of 6 mm or larger as accurately as conventional colonoscopy in a population with a low prevalence of colorectal neoplasia.

Decisions regarding the use of VC as a first-line screening test will require more information about cost and insurance coverage. “The performance of VC in this asymptomatic population is impressive, with detection rates similar to those achieved by conventional colonoscopy.” Only if the important questions about the appropriate size threshold and the surveillance of smaller polyps can be resolved will VC be ready for prime time.

The bugaboo is the need for follow-up conventional colonoscopy to remove suspicious polyps.

Patients will be asking about this. Application in the local community is likely to be far-off.

COLORECTAL ADENOMAS

3-11 A RANDOMIZED TRIAL OF ASPIRIN TO PREVENT COLORECTAL ADENOMAS IN PATIENTS WITH PREVIOUS COLORECTAL CANCER

Compared with placebo, a daily dose of 325 mg aspirin reduced risk of adenoma development in patients with a history of surgery for CRC. (High risk patients.)

3-12 A RANDOMIZED TRIAL OF ASPIRIN TO PREVENT COLORECTAL ADENOMAS

Low-dose aspirin had a moderate chemoprotective effect on adenoma formation.

5-10 DIETARY FIBRE AND COLORECTAL ADENOMA IN COLORECTAL CANCER EARLY DETECTION PROGRAMME

Dietary fiber from grains, cereals and fruits was associated with decreased risk of distal colon and sigmoid adenomas.

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3-13 ASPIRIN AND PREVENTION OF COLORECTAL CANCER

Among persons with a history of adenomas or CRC the number of recurrences of adenomas prevented by aspirin (*secondary prevention*) would be higher than the number of episodes of bleeding. However, the cumulative clinical importance of bleeding probably exceeds that of surrogate neoplasm-related outcomes, especially when the effect of colonoscopic surveillance is taken into account.

If aspirin is used for *primary* prevention of CRC, it would have to be given for 10 to 20 years, the time it takes for CRC to develop. The cumulative adverse effects of aspirin over this time outweigh any benefit in prevention of CRC, particularly when prevention by screening for CRC is considered. Long-term use of aspirin for primary prevention of CRC is not cost-effective. It does not obviate the need for screening and surveillance.

Aspirin does reduce risk of recurrent colorectal neoplasia. Whether aspirin has a role in preventing colorectal cancer and whether it can be used to decrease the required frequency of screening or surveillance must await results of clinical trials.

4-2 COLON CANCER SCREENING GUIDELINES

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

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

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

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

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CONTRACEPTION

1-11 PRESCRIBING ORAL CONTRACEPTIVES FOR WOMEN OLDER THAN 35 YEARS OF AGE.

OC can be safely prescribed to many women over age 35.

There are many risks and absolute contraindications. Primary care clinicians should review risks before prescribing.

10-10 COMBINATION ESTROGEN-PROGESTIN ORAL CONTRACEPTIVES.

The substantial benefits of O-Cs include avoidance of the dangers of pregnancy as well as a reduction in risk of ovarian cancer, acne, dysfunctional uterine bleeding, and possibly endometrial cancer.

Risks include venous thromboembolism and arterial vascular disease (myocardial infarction and stroke). The challenge for clinicians is to identify women in whom the risks outweigh the benefits. Both the American College of Obstetricians and Gynecologists and the WHO have published guidelines which differ only slightly. (*See abstract*)

At present, the doses of estrogen contained in O-Cs are 2 to 5 times less and the progestin content is 5 to 10 times less than originally formulated. This reduces the risk of venous thrombosis without any loss of effectiveness.

“Even when the health risks are taken into account, the net health benefit of oral-contraceptive use is great, especially given the effect on risk of ovarian cancer and effectiveness in preventing pregnancy.”

Hypertension and smoking are the most common contraindications to be considered.

CORONARY HEART DISEASE

1-13 ROLE OF DRINKING PATTERN AND TYPE OF ALCOHOL CONSUMED IN CORONARY HEART DISEASE IN MEN

Among men, consumption of alcohol at least 3 to 4 times per week reduced risk of MI. Neither the type of beverage, nor the proportion consumed with meals substantially altered the association.

Men who increased their alcohol consumption by a moderate amount during the follow-up had a decreased risk of MI.

1-15 DRUG ELUTING STENTS IN VASCULAR INTERVENTION

Immunosuppressive agents (which inhibit tumor-cell growth) may also inhibit the benign tissue proliferation characterizing intimal hyperplasia. Several immunosuppressants have been tested for potential to inhibit restenosis. Stents coated with the agents are becoming available. Local drug delivery achieves higher tissue concentrations of drugs, while producing no systemic effects. This is associated with a marked reduction in the risk of re-stenosis.

“The clinical impact of the elimination of restenosis may influence the approach to coronary artery disease, the future of cardiac surgery, and health-care economics.”

2-5 EFFECT OF IBUPROFEN ON CARDIOPROTECTIVE EFFECT OF ASPIRIN

Ibuprofen negates the protective effect of low dose aspirin. Use another NSAID.

3-15 OUTCOME OF ELDERLY PATIENTS WITH CHRONIC SYMPTOMATIC CORONARY ARTERY DISEASE WITH INVASIVE VS OPTIMIZED MEDICAL TREATMENT STRATEGY.

After one year, there was no difference in quality-of-life between optimized medical therapy vs early invasive therapy. However, about half of the medical group needed hospitalization and later revascularization during the year. Death and non-fatal MI occurred at similar rates.

Elderly patients with severe angina have a difficult choice.

3- 17 APOLIPOPROTEINS VERSUS LIPIDS AS INDICES OF CORONARY RISK AND AS TARGETS FOR STATIN TREATMENT.

Apo-lipo-protein B (**APO-B**) is a measure of the total number of atherogenic particles. APO-B is a *risk* factor, as is LDL-cholesterol. The *higher* the ABO-B, the *higher* the risk. In contrast, **APO-A1** is a *protective* factor, as is HDL-c. The *higher* the APO-A1, the *lower* the risk. Many studies show that APO-B is a better marker of risk of vascular disease and a better guide to the adequacy of statin treatment than any cholesterol index.

We are still pursuing the search for the best, most accurate, most reproducible, least costly risk factor for cardiovascular disease. LDL-cholesterol remains the choice at present. Other candidates are forthcoming, including C-reactive protein and APO-B. It will be interesting to follow the search. RTJ

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

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

7-4 MORTALITY RISK REDUCTION ASSOCIATED WITH SMOKING CESSATION IN PATIENTS WITH CORONARY DISEASE.

Smoking cessation has a greater effect on reducing the risk of mortality among patients who smoke than the effect of any other intervention. Risk of death was reduced by 36% in those who quit.

Ask your patients who smoke to read this article.

8-2 ESTROGEN PLUS PROGESTIN AND THE RISK OF CORONARY HEART DISEASE.

E-P, in standard dose, does not confer cardiac protection. It may slightly increase risk of CHD, especially during the first year of use. Primary care clinicians may consider prescribing low-dose aspirin for primary prevention, at least during the first year. Treatment to improve lipid profiles reduces risk.

E-P should not be prescribed for the prevention of cardiovascular disease.

Any possible increase in incidence of CHD (about 6 extra cases per 10 000 patient-years) is minor compared with the risk for breast cancer.

8-7 PREVALENCE OF CONVENTIONAL RISK FACTORS IN PATIENTS WITH CORONARY HEART DISEASE.

At least 80% to 90% of patients with CHD have conventional risk factors (cigarette smoking, diabetes, dyslipidemia, and hypertension). This is probably an underestimate. Clinical medicine, public health policies, and research efforts should place significant emphasis on the 4 factors and lifestyle behaviors. Non-traditional risk factors and genetic causes deserve less emphasis.

“Although widely asserted, the belief that more than 50% of patients with CHD lack conventional risk factors is not supported by primary data.” “In essence, patients without conventional risk factors are unlikely to develop CHD.”

“The true prevalence of conventional risk factors is certainly higher than identified in our study.” Many patients with hypertension and diabetes are not aware of their condition. More stringent cutoffs for BP, lipids, and blood glucose have been increasingly recommended.

“It is increasingly clear that the 4 conventional risk factors and their resulting health risks are largely preventable by a healthy life-style.”

Primary care clinicians have their hands full encouraging patients to deal with these conventional risk factors. We don't need more at this time.

9-3 EFFICACY OF PERINDOPRIL IN REDUCTION OF CARDIOVASCULAR EVENTS AMONG PATIENTS WITH STABLE CORONARY ARTERY DISEASE

Among patients with *stable* CAD without apparent heart failure, the angiotensin converting enzyme inhibitor, perindopril (*Aceon*) improved outcomes. This was in addition to use of other preventive drugs. [NNT(4 years to benefit one) = 50]

ACE inhibitors have been shown to have the broadest impact of any drugs in cardiovascular medicine, reducing the risk of death, myocardial infarction, stroke, diabetes, and renal impairment. They benefit patients with heart failure, post myocardial infarction left ventricular dysfunction, peripheral vascular disease, diabetes, stroke, and transient ischemic attacks.

As long-term therapy, perindopril is expensive. It has not been compared with less expensive ACE inhibitors (eg, enalapril) which may be just as effective.

ACE inhibition is underused in primary care practice.

9-4 LIFETIME RISK OF CORONARY HEART DISEASE BY CHOLESTEROL LEVELS AT SELECTED AGES.

For persons *of all ages*, lifetime risk of CHD increases as total cholesterol levels rise from under 200 to over 240. This supports the important role of cholesterol screening at all ages.

This article is of considerable clinical importance even though it provided no outcomes from lifestyle or drug interventions. Patients, old and young, now have a reasonable prediction of lifetime risk according to total cholesterol levels. (And cholesterol subfractions.) Old, and young should be screened periodically. The data may convince some younger persons to intervene to reduce their lifetime risk

Guidelines suggest lipid screening begin at age 20.

10-11 CURRENT SMOKING, SMOKING CESSATION, AND THE RISK OF SUDDEN CARDIAC DEATH IN PATIENTS WITH CORONARY ARTERY DISEASE.

In smokers with CAD who quit, risk of sudden cardiac death (SCD) is significantly reduced and compares with the risk of those who never smoked. The decline in risk associated with cessation is immediate and not time dependent. This supports the view that the risk is due to direct toxic effects. The risk in smokers is not related to the amount of smoking.

In absolute terms, smoking cessation and never smoking resulted in a 3.5% lower risk of SCD over 8 years compared with those who continued to smoke. [NNT(8 years to prevent one SCD) = 30]. And a 11% reduction in all-cause death. [NNT = 10].

The risk of continuing smoking on SCD is even more pronounced than other risk factors—age, sex, New York Heart Association functional class, BP, and dyslipidemia.

Cessation is certainly one of the most effective preventive measures. Despite being informed of the risks, many patients continue to smoke. Primary care clinicians who succeed in getting recalcitrant smokers to stop achieve a major therapeutic intervention. Would asking them to read a copy of this article help? RTJ

COX-2 INHIBITORS

11-8 EFFECTS OF PERIOPERATIVE ADMINISTRATION OF A SELECTIVE CYCLO-OXYGENASE 2 INHIBITOR ON PAIN MANAGEMENT AND RECOVERY AFTER KNEE REPLACEMENT.

Perioperative (before and after surgery) use of a COX-2 inhibitor was effective component of multimodal analgesia. It reduced opioid consumption, pain, vomiting, and sleep disturbance. It shortened the time physical therapy was needed to achieve effective joint range of motion.

Pain is the 5th monitored vital sign. Efficient management of pain improves postoperative clinical outcomes. After total knee arthroplasty (TKA), inadequate control of postoperative pain is associated with poor functional recovery.

Surgical trauma induces cyclo-oxygenase 2 (COX-2) which then promotes synthesis of prostaglandins that sensitize peripheral nociceptors and mediate central sensitization. NSAIDs as well as opioids decrease this inflammatory response. Pre-operative administration of NSAIDs may be effective by establishing a sufficient tissue NSAID concentration to inhibit early production of prostaglandins before the onset of tissue trauma, thus attenuating the development of hyperalgesia.

I wonder if sports medicine enthusiasts might offer pre-game COX-2 inhibitors to players (eg, football) who might be subject to injury during a game. This might lessen the period of disability if a serious injury should occur.

C-REACTIVE PROTEIN

2-12 PANEL ENDORSES LIMITED ROLE FOR CRP TESTS

C-reactive protein (CRP) has emerged as the leading inflammatory marker for cardiovascular disease.

Does the test add anything to the list of risk markers now available? How should it be used?

A guideline suggests that CRP has its greatest utility in people deemed at intermediate risk of CVD. (intermediate risk = 10% to 20% risk of developing CVD in the next 10 years as calculated from the Framingham risk score.) Physicians should assess traditional risk factors and calculate the absolute Framingham risk score before testing with CRP.

<http://hin.nhlbi.nih.gov/atp/iii/calculator.asp?usertype=prof> .

CRP should not be used routinely, or as an alternative to traditional risk factor assessment. It is not known if an elevated CRP as the sole risk marker needs treatment.

DEATH AND DYING

7-8 NURSES' EXPERIENCES WITH HOSPICE PATIENTS WHO REFUSE FOOD AND FLUIDS TO HASTEN DEATH.

Voluntary refusal of food and fluids has been proposed as an alternative to physician-assisted suicide (PAS) for terminally ill patients who wish to hasten death. Oregon hospice nurses reported the quality of the process of dying for most of these patients was good.

But, "We don't know enough about it." "We have to get this out and talk about it, because this is happening."

DELAYED PRESCRIBING

12-1 DELAYED PRESCRIPTIONS

Best evidence indicates that antibiotics are of minimal or no benefit for sore throat, acute bronchitis, the common cold, and otitis media. Antibiotics continue to be commonly used for these conditions. This is potentially inappropriate prescribing.

This has prompted the use of delayed (or "as needed", or "if") prescriptions. These prescriptions are written with the proviso that they are not to be used immediately—only later if symptoms do not improve in a few days. Use of a delayed prescription should be restricted to patients who request antibiotics or for whom the doctor thinks one is not immediately indicated.

A randomized trial in 1997 gave prescriptions for antibiotics for respiratory infections: 1) to be filled immediately, or 2) to be filled after 3 days, or 3) no antibiotic prescription.

The immediate group filled 99%.

The delayed group filled 31%.

In the no-prescription group, 13% filled an antibiotic prescription after a return visit to the physician.

The reduction in use of antibiotics for upper respiratory infections through using delayed prescriptions is as effective, and in many cases, more effective than educational projects.

DEMENTIA

3-5 SILENT BRAIN INFARCTS AND THE RISK OF DEMENTIA AND COGNITIVE DECLINE

Silent brain infarcts are common in the elderly. Persons with silent brain infarcts had an increased risk of dementia, and a steeper decline in cognitive function than persons without such lesions.

In clinical practice—How can we intervene to benefit the patient? The hope is that treatment directed at vascular disease will reduce the burden of dementia. We should optimize cardiovascular health by established means: control of hypertension; lipid control; weight control; exercise; smoking-avoidance.

Other possible beneficial interventions: low-dose aspirin; one alcoholic drink daily; and folic acid supplementation to reduce homocysteine levels.

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

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

5-11 ESTROGEN PLUS PROGESTIN AND THE INCIDENCE OF DEMENTIA AND MILD COGNITIVE IMPAIRMENT IN POSTMENOPAUSAL WOMEN

Estrogen + progestin did not reduce the risk for probable dementia in postmenopausal women age 65 and older.

6-15 LEISURE ACTIVITIES AND THE RISK OF DEMENTIA IN THE ELDERLY

Participation in leisure-time mental activities was associated with reduced risk of dementia and rate of decline in memory.

Frequent participation in leisure-cognitive activities was associated with a reduced risk of dementia over an ensuing 5 years. The activities include playing board games, reading, playing musical instruments, and doing crossword puzzles. The brain has use-dependent plasticity. Effortful mental activity may not only strengthen existing connection, but stimulate neurogenesis. Persistent engagement by the elderly in effortful mental activities may promote plastic changes in the brain that circumvent the pathology underlying the dementia.

7-9 CLINICAL AND ORGANIZATIONAL FACTORS ASSOCIATED WITH FEEDING TUBE USE AMONG NURSING HOME RESIDENTS WITH ADVANCED COGNITIVE IMPAIRMENT

A growing proportion of the approximately 4 million older US adults with Alzheimer's disease or other dementias are surviving to the advanced stages of their disease. Eating and swallowing problems typically develop during the terminal stages. Whether to initiate feeding tube use or to focus on comfort care is a challenging dilemma facing families, clinicians and institutions.

Growing empirical data and expert opinion indicates that feeding tubes has no demonstrable health benefits in this population, and may be associated with increased risks and discomfort.

The quality of care of cognitively impaired patients in nursing homes is inversely related to the numbers who have feeding tubes in place.

“Comprehensive implementation of advanced care planning is likely to reduce the use of feeding tubes.”

11-10 END-OF-LIFE CARE AND THE EFFECTS OF BEREAVEMENT ON FAMILY CAREGIVERS OF PERSONS WITH DEMENTIA

Caregivers in this study showed remarkable resilience in adapting to the death of their relatives. A large majority reported feeling relieved by the death, although persons whose relatives were institutionalized did not show as rapid a recovery from depressive symptoms. This suggests that relief from providing daily care did not alone account for the caregivers' recovery from bereavement.

Investments in resources for intervention and support may have the largest benefit when they are applied to caregivers and patients in the period immediately preceding the patient's death. When caregivers know that their relative is on a trajectory toward death, and when they are aware of the patient's disability and suffering, they grieve for the loss of the patient before the death.

Clinicians should view bereavement not only as a phenomenon that affects caregivers after the death, but also as one that affects many caregivers before the death occurs.

11-11 DEMENTIA WITH LEWY BODIES

Dementia with Lewy bodies (**DLB**) is one of the 3 most common causes of dementia in older people. Alzheimer's disease and vascular dementia are the other two.

The clinical presentation of DLB typically includes: fluctuating cognitive impairment, visuospatial dysfunction, marked attention deficits, psychiatric symptoms (especially complex visual hallucinations), and mild extrapyramidal features. DLB can usually be differentiated from Parkinson's disease with dementia because in DLB the motor symptoms usually develop *after* the cognitive impairment. Some authorities require, as a diagnostic criterion for Parkinson's disease, a delay of at least 12 months between the onset of motor symptoms and subsequent cognitive impairment.

My dictionary defines Lewy body as an eosinophilic inclusion body found in the cytoplasm of neurons in the cortex and brain stem in Parkinson's disease and some forms of dementia. But, as I understand it, DLB is not a form of Parkinsonism, although when dementia occurs in Parkinsonism, the two may be confused. The pathology differs.

There is a “need to maintain a high degree of awareness of DLB especially when prescribing neuroleptic drugs for people whose dementia is characterized by early psychiatric symptoms.” Neuroleptic drugs (more simply anti-psychotic drugs) include phenothiazines. (eg, chlorpromazine [*Thorazine*], thioridazine, perphenazine, fluphenazine). Severe neuroleptic sensitivity reactions may occur.

DLB may respond to cholinesterase inhibitors.

I abstracted this short article to learn more about Lewy dementia. I had not understood much about it.

Still, making the diagnosis does not help the patients much.

DEPRESSION

6-16 AWARENESS ABOUT DEPRESSION: Important for All Physicians

A nationally representative household survey of the 48 contiguous United States found that the lifetime prevalence of major depression is 16%. Recognition and treatment of depression in primary care practice is woefully inadequate.

Screening is indicated in primary care practice.

A helpful website is cited.

12-7 SCREENING FOR DEPRESSION IN PRIMARY CARE WITH TWO VERBALLY ASKED QUESTIONS

The US Preventive Services Task Force endorsed screening for depression, but did not recommend a specific tool. Many primary care clinicians find screening questionnaires for depression too cumbersome and time consuming for routine use.

This study used a simple screening tool of two questions. If one or two were answered positively, the screen was considered positive, and further questions were asked to determine if major depression was present. (A composite interview--the “Gold Standard”)

The screening questions:

- 1) During the past month have you often been bothered by feeling down, depressed, or hopeless?
- 2) During the past month have you often been bothered by little interest or pleasure in doing things?

In the community setting, the two verbally asked questions have a good sensitivity (97%) and reasonable specificity (67%) for screening for depression. If the screen was negative (both questions answered negatively) major depression is almost surely absent.

About 5 false positives would occur for every true positive when asking the questions alone.

This is common in screening studies which are in essence a diagnostic test performed in a low prevalence setting. Further questions will be required to clarify presence or absence of depression.

DIABETES

1-3 MULTIFACTORIAL INTERVENTION AND CARDIOVASCULAR DISEASE IN PATIENTS WITH TYPE 2 DIABETES

A targeted long-term intensive intervention aimed at multiple risk factors (hypertension, dyslipidemia, microalbuminuria) in patients with DM-2 and microalbuminuria reduced the risk of cardiovascular and microvascular events by about 50%.

1-4 GLYCEMIC EFFECTS OF POSTMENOPAUSAL HORMONE THERAPY

In women with established coronary heart disease, hormone therapy reduced the incidence of type 2 diabetes by 3.3% compared with those taking placebo. NNT (4 years to prevent one case) = 30.

And reduced incidence of diabetes by 12% in those with impaired glucose tolerance at baseline.

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

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

5-3 USING NEW INSULIN STRATEGIES IN THE OUTPATIENT TREATMENT OF DIABETES.

One daily injection of insulin glargine along with mealtime injections of insulin lispro significantly improves glycemic control in patients with poorly controlled type 2 DM. The combination matches each patient's needs, simplifies adjustment of dose, and improves control while causing fewer episodes of hypoglycemia. "They are easier to use than many patients and clinicians realize."

6-3 HEART PROTECTION STUDY OF CHOLESTEROL-LOWERING SIMVASTATIN IN 5963 PEOPLE WITH DIABETES

Cholesterol-lowering therapy is beneficial for people with diabetes even if they do not already have manifest coronary disease or high cholesterol concentrations. Simvastatin reduced the rate of first major vascular events by about a quarter in a wide range of diabetic patients. Treatment over 5-years could prevent about 5 events per 100 persons treated,

6-5 RELATIONSHIP OF WALKING TO MORTALITY AMONG US ADULTS WITH DIABETES

Regular walking is likely to increase longevity across a diverse spectrum of adults with diabetes. Successful efforts to increase physical activity in the diabetic population could have broad public health benefits.

6-6 WALKING, THE BEST MEDICINE FOR DIABETES?

"Walking is probably the 'best medicine' for both prevention and treatment of diabetes mellitus."

6-7 INTENSIVE DIABETES THERAPY AND CAROTID INTIMA-MEDIA THICKNESS IN TYPE 1 DIABETES MELLITUS

Intensive therapy over an extended time resulting in a mean HbA1c of 7.2% decreased progression of intima-media thickness. Evidence that tight control may delay macro-vascular disease.

6-13 REGRESSION OF MICROALBUMINURIA IN TYPE 1 DIABETES.

Urinary albumin excretion does not imply inexorable progression of diabetic nephropathy. Regression frequently occurs, associated with lower HbA1c levels, lower BP, and lower levels of cholesterol and triglycerides.

8-15 POOR GLYCEMIC CONTROL CAUSED BY INSULIN INDUCED LIPOHYPERTROPHY.

Prevalence of lipohypertrophy in patients with type 1 diabetes is estimated to be around 20% to 30%. It is due to a cellular response of adipocytes to the local effects of injected insulin. Immunological factors may be important. Frequent injection into the same site is related to incidence.

Injection repeatedly given into these sites may lead to problems of glycemic control. Insulin absorption can be significantly delayed.

10-6 SUSTAINED EFFECT OF INTENSIVE TREATMENT OF TYPE 1 DIABETES MELLITUS ON DEVELOPMENT OF PROGRESSION OF DIABETIC NEPHROPATHY

The development of decreasing glomerular filtration rate and end-stage renal disease is a long pathological process presumably reflecting the effects of hyperglycemia on renal cells.

The Diabetes Control and Complications Trial (DCCT; 1993) demonstrated the benefits of intensive treatment of diabetes over 6.5 years in reducing glycemic levels and slowing the progression of diabetic nephropathy. The present study followed the DCCT cohort for an additional 8 years to determine if the benefits of intensive vs conventional treatments on kidney function would persist.

Benefits were persistent, reducing incidence of hypertension and albuminuria for 8 years after the end of the original study despite deteriorating glucose control.

In addition, there were clear residual benefits of intensive treatment on future development of hypertension over the ensuing 8 years.

The intensively treated participants had few manifestations of nephropathy during the DCCT due to their relatively low level of HbA1c. The near normal hyperglycemic control for 6.5 years may have simply delayed the development of indicators of diabetic nephropathy during the 8 more years of follow-up.

I believe primary care clinicians will have little difficulty extrapolating these benefits to patients with type 2 diabetes. The greater the number of days with normal glucose levels, the longer the delay in development of microvascular complications.

10-9 INHALED INSULIN PROVIDES IMPROVED GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS INADEQUATELY CONTROLLED WITH ORAL AGENTS.

Recently, a dry powder inhaled insulin (**IN-I**) system has been developed. It provides a new method of treatment. The pulmonary route exploits the large vascular bed and permeability of the alveoli to deliver insulin directly into the blood stream. IN-I has a rapid onset of action, actually faster than injected regular insulin and insulin lispro. Its duration of action is about 6 hours.

Pre-meal inhaled powdered insulin (**IN-I**) added to oral agents produced a significantly greater reduction in HbA1c than oral agents alone (metformin or sulfonylurea, or both)—a mean reduction in HbA1c of 2.3 %. HbA1c remained stable in the control group—about 10%

One third of the IN-I + oral agents group achieved a HbA1c less than 7% vs none in the oral agents alone group. (Mean HbA1c dropped from about 10% to 7.5% in the IN-I group.)

Fasting plasma glucose improved significantly.

This means of administration will eliminate the fear of injections. Patient satisfaction was high--97% opted to continue in a 1-year extension of the therapy.

This is an early proof of concept study. Primary care clinicians will watch for developments with great interest. Cost is to be determined.

DIETARY SUPPLEMENTS

1-2 ADVERSE EVENTS ASSOCIATED WITH DIETARY SUPPLEMENTS

“Dietary supplements” are associated with adverse effects that include all organ systems, age groups, and levels of severity,

Associations between adverse effects and ingredients are difficult to verify. Information systems are incomplete.

Our strong message should be:”. “You do not know what you are taking”. “You do not know if it is safe”.

DIET

4-7 EFFICACY AND SAFETY OF LOW-CARBOHYDRATE DIETS

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

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

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

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

Thus, low-carbohydrate diets reduce caloric intake.

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

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

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

6-4 ADHERENCE TO A MEDITERRANEAN DIET AND SURVIVAL IN A GREEK POPULATION

The traditional Mediterranean diet (**MD**) is characterized by a high intake of vegetables, legumes, fruits, nuts, and cereals (largely unrefined). Also a high intake of olive oil (the principal source of fat), a low intake of saturated fats, and a moderately high intake of fish. Dairy products are mostly in the form of cheese and yogurt. Intake of meat and poultry is low-to-moderate. Wine is often taken with meals.

Greater adherence to the diet was associated with a significant reduction in mortality.

DOCTOR’S WORK

5-2 WHAT DO DOCTORS FIND MEANINGFUL ABOUT THEIR WORK?

Making a difference in someone else’s life was the most common theme in the doctors’ stories. It was not making a brilliant diagnosis or an adroit technical intervention. Most of these stories took place in the context of chronic, incurable conditions, or end-of-life care. The doctors felt awed and deeply rewarded that their mere presence could be healing and comforting to patients.

ECHINACEA

12-9 EFFICACY AND SAFETY OF ECHINACEA IN TREATING UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN

Echinacea is a herbal remedy widely used for prevention and treatment of upper respiratory infections (**URIs**). It is one of the most commonly used herbal remedies in the USA . Three species of echinacea are used. Beneficial effects are thought to be due to its “immunomodulating” activity, most notably macrophage activation and enhanced neutrophil phagocytosis.

This study postulated that treatment with *E purpurea* would result in at least a 1.5- to 2-day reduction in duration of URIs in children, and that symptoms would be less severe than in patients receiving placebo.

The preparation used in this study was *not* effective in treating URIs in children. After the trial was completed, parents could *not* guess correctly whether their child had taken echinacea or placebo. “Our results do *not* support the use of echinacea for treatment of URIs in children.” Its use was associated with an increased risk of rash.

This study was supported by a grant from the National Center for Complementary and Alternative Medicine, Bastyr University (an alternative medicine institution) and National College of Naturopathic Medicine, Portland Oregon.

It continues to amaze me that so many persons take unstandardized and unproven nostrums and give them to their children. I am sure devotees will fault this study. They will remain convinced that echinacea is beneficial.

EMERGENCY CONTRACEPTION

11-3 EMERGENCY CONTRACEPTION

Progestin alone has been approved by the FDA for emergency contraception (**EC**)—a total of 1.5 mg of levonorgestrel—two 0.75 mg tablets to be taken 12 hours apart (*Plan B*). (*Both tablets can be taken at once without loss of efficacy.*)

Pregnancy rates are lowest when EC is used within 12 hours of unprotected intercourse. Most studies report a monotonic decrement in effectiveness as the interval increases. Two studies have indicated that EC given within 5 days is still effective. “Emergency contraception should thus be offered for any act of unprotected intercourse that has occurred in the preceding 5 days.” Because the day of ovulation is generally unknown, even in women who report regular cycles, treatment is indicated regardless of the cycle day on which unprotected intercourse occurred.

There are no absolute contraindications. Even in women who have contraindications to long-term use of birth control pills, the balance of risks and benefits favors the brief exposure of EC over the risks of pregnancy. Ectopic pregnancy has been reported, but there is no good evidence of increased risk.

The FDA is currently evaluating an application for over-the-counter status for the levonorgestrel-only formulation. It is highly suitable for such a switch. The dose is the same for everyone; no contraindications to use; adverse events are rare; no potential for addiction; repeated use is safe and reasonably effective. Use is highly acceptable to patients and is associated with high rates of continuation of oral contraceptives.

END-OF-LIFE CARE

11-10 END-OF-LIFE CARE AND THE EFFECTS OF BEREAVEMENT ON FAMILY CAREGIVERS OF PERSONS WITH DEMENTIA

Caregivers in this study showed remarkable resilience in adapting to the death of their relatives. A large majority reported feeling relieved by the death, although persons whose relatives were institutionalized did not show as rapid a recovery from depressive symptoms. This suggests that relief from providing daily care did not alone account for the caregivers’ recovery from bereavement.

Investments in resources for intervention and support may have the largest benefit when they are applied to caregivers and patients in the period immediately preceding the patient’s death. When caregivers know that their relative is on a trajectory toward death, and when they are aware of the patient’s disability and suffering, they grieve for the loss of the patient before the death.

Clinicians should view bereavement not only as a phenomenon that affects caregivers after the death, but also as one that affects many caregivers before the death occurs.

ETHICS

8-3 IS OPPORTUNISTIC DISEASE PREVENTION IN THE CONSULTATION ETHICALLY JUSTIFIABLE?

Consultations in primary health care have been suggested as an ideal setting for health promotion and disease prevention. Doctors are expected to discuss preventive measures even when they are not among the reasons for the consultation. Opportunistic preventive medicine is considered a part of good medical practice. This article asks. . .Is this ethically justifiable?

The authors argue that doctors should maintain a clear focus on each patient’s reasons for seeking help rather than be distracted by an increasing list of preventive measures. They maintain that, from a moral point of view, initiatives to improve health among people who are currently free of symptoms is fundamentally different from curative medicine—the condition for which the patient consults.

Physicians who offer a screening test carry a considerable responsibility. They must offer enough information about risks and benefits in order to enable the patient to give informed consent. Informed consent presupposes an understanding of the limitations of the screening test. Every test carries a chance of misclassification of disease. A false positive test may result in further interventions that do not benefit the patient, and may cause harm.

“Once medical risk has been passed on to a person, it cannot be retracted. Respect for autonomy should therefore also honor the person’s right *not* to be opportunistically confronted with knowledge about biomedical risks that are unrelated to his or her reasons for seeing the doctor.”

“As the list of accessible preventive tests lengthens and thresholds for intervention are lowered, a doctor who adheres to all recommendations for provision of preventive services may ultimately be able to find something abnormal in everybody.”

Think twice before advising screening tests.

EVIDENCE-BASED MEDICINE

12-8 REVIEW OF SENSITIVITY, SPECIFICITY, PREDICTIVE VALUES AND LIKELIHOOD RATIOS

Calculate sensitivity from the left column; specificity from the right column; positive predictive value from the top row; negative prediction value from the bottom row; the likelihood ratios from both columns.

See text.

EXERCISE TESTING

9-8 ABILITY OF EXERCISE TESTING TO PREDICT CARDIOVASCULAR AND ALL-CAUSE DEATH IN ASYMPTOMATIC WOMEN: A 20-YEAR FOLLOW-UP OF THE LIPID RESEARCH CLINICS PREVALENCE STUDY

Exercise capacity and heart rate responses were strong, graded, and independent predictors of cardiovascular and all-cause mortality. Not achieving target heart rate and slow return of the rapid heart rate induced by exercise toward normal predicted future mortality in younger women.

ST segment depression, while predictive in men, had no value in women.

The benefit of exercise testing in asymptomatic women is in determining their cardiovascular fitness.

Women need more fitness exercise independent of their weight, blood pressure, or lipid levels.

FATTY LIVER DISEASE

6-8 NON-ALCOHOLIC FATTY LIVER DISEASE: An Unrecognized Cause Of Cryptogenic Cirrhosis

Cryptogenic cirrhosis (CC) is a significant contributor to liver related morbidity. Non-alcoholic fatty liver disease (NAFLD) is the most common cause of CC. The diagnosis of cirrhosis in these patients is usually delayed by almost a decade and is often not established until after the patient develops hepatocellular carcinoma or other complications of advanced liver disease. Once cirrhosis is diagnosed, mortality is greater than that of hepatitis C virus related cirrhosis.

Existing evidence, albeit scant, suggests that NAFLD is a spectrum, progressing from hepatic steatosis to non-alcoholic steatohepatitis, and then on to cirrhosis. Over 6 million US adults have NAFLD, and 640 000 may have cirrhosis. This may exceed the numbers infected with hepatitis C. Prognosis is just as bad.

Diagnosis remains one that is established only after other causes of chronic liver disease have been excluded. NAFLD can be more readily suspected if the patient is obese and has diabetes. Primary care clinicians have an opportunity for prevention by controlling obesity, lipids, and diabetes.

FEEDING TUBE

7-9 CLINICAL AND ORGANIZATIONAL FACTORS ASSOCIATED WITH FEEDING TUBE USE AMONG NURSING HOME RESIDENTS WITH ADVANCED COGNITIVE IMPAIRMENT

A growing proportion of the approximately 4 million older US adults with Alzheimer's disease or other dementias are surviving to the advanced stages of their disease. Eating and swallowing problems typically develop during the terminal stages. Whether to initiate feeding tube use or to focus on comfort care is a challenging dilemma facing families, clinicians and institutions.

Growing empirical data and expert opinion indicates that feeding tubes have no demonstrable health benefits in this population, and may be associated with increased risks and discomfort.

The quality of care of cognitively impaired patients in nursing homes is inversely related to the numbers who have feeding tubes in place.

“Comprehensive implementation of advanced care planning is likely to reduce the use of feeding tubes.”

FIBER

3-3 CEREAL, FRUIT, AND VEGETABLE FIBER INTAKE AND THE RISK OF CARDIOVASCULAR DISEASE IN ELDERLY INDIVIDUALS.

Cereal fiber consumption (equivalent to 2 slices of whole grain bread) in later life was associated with lower risk of incident CVD.

5-10 DIETARY FIBRE AND COLORECTAL ADENOMA IN COLORECTAL CANCER EARLY DETECTION PROGRAMME

Dietary fiber from grains, cereals and fruits was associated with decreased risk of distal colon and sigmoid adenomas.

FITNESS

PHYSICAL ACTIVITY (SEE ALSO FITNESS)

5-8 RELATIONSHIP OF CHANGES IN PHYSICAL ACTIVITY AND MORTALITY AMONG OLDER WOMEN

Increasing and maintaining physical activity levels could lengthen life for older women.

6-5 RELATIONSHIP OF WALKING TO MORTALITY AMONG US ADULTS WITH DIABETES

Regular walking is likely to increase longevity across a diverse spectrum of adults with diabetes. Successful efforts to increase physical activity in the diabetic population could have broad public health benefits.

6-6 WALKING, THE BEST MEDICINE FOR DIABETES?

“Walking is probably the ‘best medicine’ for both prevention and treatment of diabetes mellitus.”

9-8 ABILITY OF EXERCISE TESTING TO PREDICT CARDIOVASCULAR AND ALL-CAUSE DEATH IN ASYMPTOMATIC WOMEN: A 20-YEAR FOLLOW-UP OF THE LIPID RESEARCH CLINICS PREVALENCE STUDY

Exercise capacity and heart rate responses were strong, graded, and independent predictors of cardiovascular and all-cause mortality. Not achieving target heart rate and slow return of the rapid heart rate induced by exercise toward normal predicted future mortality in younger women.

ST segment depression, while predictive in men, had no value in women.

The benefit of exercise testing in asymptomatic women is in determining their cardiovascular fitness.

Women need more fitness exercise independent of their weight, blood pressure, or lipid levels.

FONDAPARINUX

10-3 SUBCUTANEOUS FONDAPARINUX VERSUS INTRAVENOUS UNFRACTIONATED HEPARIN IN THE INITIAL TREATMENT OF PULMONARY EMBOLISM.

Once-daily fondaparinux without monitoring is at least as effective and safe as adjusted-dose IV unfractionated heparin in the initial treatment of hemodynamically stable patients with pulmonary embolism.

“Because of its simplicity, once-daily subcutaneous fondaparinux without anticoagulation monitoring could replace intravenous administration of unfractionated heparin in most patients.”

FRACTURE

2-1 ACCURACY OF OTTAWA ANKLE RULES TO EXCLUDE FRACTURES OF THE ANKLE AND MID-FOOT

1) Inability to bear weight and walk 4 steps immediately after the injury, or on presentation to the emergency department.

2) Bony tenderness localized to the posterior edge (and up to 6 cm above) either malleolus (four spots).

Fewer than 2% of patients negative for fracture by the rules actually had fracture.

Application of the rules greatly reduces the number of X-rays taken.

3-4 EFFECT OF FOUR MONTHLY ORAL VITAMIN D₃ (CHOLECALCIFEROL) SUPPLEMENTATION ON FRACTURES AND MORTALITY IN MAN AND WOMEN LIVING IN COMMUNITY.

Vitamin D supplements of 100 000 IU given orally every 4 months for *primary* prevention was associated with a lower risk of fractures (and without adverse effects) in older men and women living in the community.

This is equivalent to our usual dose of 800 IU daily. Calcium supplements would have lowered risk even more.

GENERAL PRACTICE

3-7 MOVING BEYOND SINGLE AND DUAL DIAGNOSIS IN GENERAL PRACTICE.

“The awkward phrase ‘multiple morbidity’ describes the common predicament of the many patients who have more than one health problem.” Poor health is inextricably linked to low income, unemployment, poor housing, and inadequate social support as well as old age.

The trend towards more specialization tends to disadvantage people with multiple morbidity. The effective management of such patients depends heavily on primary care practice.

“As general practitioners it is our job to manage all of a patient’s health problems by drawing on help for specialists where we can.”

GLUCOSAMINE

7-3 STRUCTURAL AND SYMPTOMATIC EFFICACY OF GLUCOSAMINE AND CHONDROITIN IN KNEE OSTEOARTHRITIS

Evidence that glucosamine benefits symptoms and slows joint deterioration.

The purity and dose of these over-the-counter preparations are not regulated by the FDA.

Primary care clinicians may be willing to prescribe it despite regulation by the FDA.

GOUT

10-13 GOUT

Hyperuricemia is central to gout, but does not inevitably cause disease. Indeed, urate levels are frequently normal during attacks. Factors other than serum urate contribute to clinical gout in an additive manner—hypertension, thiazide and loop diuretics, obesity, and high alcohol intake. Gout is also associated with insulin resistance.

Lifestyle changes sometimes return uric acid levels to normal—stop drinking alcohol, switch from thiazides, or, if obese, lose weight. Conventional low purine diets are unpalatable and typically are only moderately effective.

Treatment of acute attacks include NSAIDs, corticosteroids, and colchicine.

Long term prophylactic treatment includes NSAIDs, colchicine, and allopurinol.

Although most patients have substantially reduced renal urate clearance (probenecid may be used for these patients). . . “It is common and acceptable practice to use the xanthine oxidase inhibitor allopurinol (*Generic; Zyloprim*), which inhibits uric acid synthesis whether or not the patient overproduces urate.” “Irrespective of the cause of hyperuricemia, allopurinol is the most frequently used anti-hyperuricemic agent.” Its once-daily administration is convenient and effective regardless of the cause of the hyperuricemic.

GYNECOMASTIA

8-13 ENDOCRINE TREATMENT OF PHYSIOLOGICAL GYNECOMASTIA

“Physiological” gynecomastia is due to an altered ratio between free estradiol (a stimulant) and testosterone (an inhibitor). Anti-estrogens such as tamoxifen (*Nolvadex*) have therefore been suggested as non-surgical treatment. Various published studies have used tamoxifen at a dose of 10 to 40 mg daily for several months. Resolution of the lump and pain has been reported in 80% of cases. Only minor and reversible side effects were reported.

HEART DISEASE

11-4 STARTING EARLIER TO PREVENT HEART DISEASE.

Two studies reported in the November 5 issue of JAMA measured carotid artery intima/media thickness (IMT) in young adults (age 24 to 37). LDL-cholesterol and BMI had been measured in childhood, up to 22 years earlier. Higher childhood levels of both predicted increased adult carotid IMT. In one study, systolic BP and smoking in adolescence also predicted increased IMT. (The higher the carotid IMT, the greater the extent of coronary atherosclerosis.)

It is clear that risk factors begin to matter during adolescence, the age range during which fatty streaks in the coronary arteries begin to be converted to raised lesions, and when high-risk populations begin to diverge from low-risk populations. “It may be possible that risk factors in the early teen-age years are associated with permanent damage to the arterial wall.”

Assessing risk factors in youth is easy and inexpensive. Cholesterol and other risk factors do matter during adolescence. It may now be time to reconsider the age at which measurement of cholesterol and life-style changes should begin. The difficulty of changing life styles in teenagers, however, should not be underestimated. Physicians caring for children and adolescents should be sure their patients and their parents know it is beneficial and safe to promote and maintain a healthy life style.

Changing ingrained life-style habits in teen-agers is almost impossible. Parents must set the example and begin lifetime habits of their children at a pre-teen age.

HEART FAILURE

2-9 EFFECTS OF INITIATING CARVEDILOL IN PATIENTS WITH SEVERE CHRONIC HEART FAILURE

Benefits of beta-blocker therapy with carvedilol were evident within a few weeks in patients with advanced HF who were euvoletic. Benefits were similar to those obtained by long-term therapy.

Initiation of treatment was well tolerated when a go-slow, go-low dose was used.

2-10 ASSOCIATION OF SERUM DIGOXIN CONCENTRATION AND OUTCOMES IN PATIENTS WITH HEART FAILURE

Higher serum concentrations of digoxin were associated with increased mortality in patients with HF who were in normal sinus rhythm. The most effective concentration may be 0.5 to 0.8 ng/mL .

2-11 CARDIAC RESYNCHRONIZATION AND DEATH FROM PROGRESSIVE HEART FAILURE

Recently, cardiac pacemakers have been modified to correct ventricular dyssynchrony (left bundle branch block). The new pacemakers use a left ventricular lead that ensures stimulation of the left ventricle at, or near, the time of right ventricular depolarization. Synchronization enhances cardiac function and reduces myocardial oxygen consumption. It improves exercise capacity, functional class, and quality of life.

Use of the pacemaker was associated with a reduction in mortality from 3.5% to 1.7% over 6 months among patients with advanced HF.

3-14 PLASMA HOMOCYSTEINE AND RISK FOR CONGESTIVE HEART FAILURE IN ADULTS WITHOUT PRIOR MYOCARDIAL INFARCTION

An increased plasma homocysteine level independently predicted risk of development of CHF in adults without prior myocardial infarction. Another indication for supplementation with folate?

3-16 PROGNOSTIC IMPORTANCE OF WEIGHT LOSS IN CHRONIC HEART FAILURE AND THE EFFECT OF TREATMENT WITH ANGIOTENSIN-CONVERTING-ENZYME INHIBITORS

Cardiac cachexia is common in chronic HF. It independently predicts a poor outcome. This may assist decisions for Hospice care. Enalapril delays development of cardiac cachexia in some patients.

4-9 ALDOSTERONE BLOCKADE AND HEART FAILURE

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

5-9 HEART FAILURE

This review article comments on diastolic HF and presents new staging and treatment options for systolic HF.

The diagnosis of diastolic HF is usually made by a clinician who recognizes the typical signs and symptoms of HF and is not deterred by the finding of normal systolic function (ie, a normal ejection fraction) on echocardiography. Echocardiography may also be useful in detecting diastolic filling abnormalities. Diastolic HF is common.

HF is largely preventable, primarily through control of risk factors. A new approach to the classification and progression of systolic HF emphasizes four stages of HF which differ from the classical NYHA functional classification.

7-10 COMPARISON OF CARVEDILOL AND METOPROLOL ON CLINICAL OUTCOMES IN PATIENTS WITH CHRONIC HEART FAILURE

Carvedilol extended survival compared with metoprolol.

However, the challenge in primary care is not so much which beta-blocker to choose, but judicious use of a beta-blocker in select patients with heart failure. They are underused in primary care practice for treatment of heart failure.

9-6 EFFECTS OF CANDESARTAN ON MORTALITY AND MORBIDITY IN PATIENTS WITH CHRONIC HEART FAILURE

ACE inhibitors have been shown to have the broadest impact of any drug in cardiovascular medicine, reducing the risk of death, myocardial infarction, stroke, diabetes, and renal impairment. They benefit patients with heart failure, left ventricular dysfunction, peripheral vascular disease, diabetes, stroke, and transient ischemic attacks.

Candesartan, blocks angiotensin II at the cellular level. Given to patients with heart failure in *addition* to other drugs (including ACE inhibitors) it was associated with reduced cardiovascular deaths and hospital admissions for heart failure.

Reducing angiotensin II levels is a basic therapy in cardiovascular disease. ACE inhibitors have been the standard. Addition of an angiotensin II blocker may benefit slightly. They should be used when the patients cannot tolerate ACE inhibitor.

9-7 POLYPHARMACY AND COMORBIDITY IN HEART FAILURE

Primary care clinicians are responsible for reviewing medication lists with a goal of eliminating medications that are not known to provide clear benefits. Little evidence is available to guide polypharmacy in patients with heart failure and other common conditions

Too many patients, especially the elderly, are taking too many drugs.

Primary care clinicians should insist that their patients bring to the office for review all medications they use, including those prescribed by other physicians, standard drugs bought over the counter, and herbal nostrums used as “alternative” medicines. This seems difficult for patients to do, but is most important.

10-15 PROGNOSTIC IMPORTANCE OF PHYSICAL EXAMINATION FOR HEART FAILURE IN NON-ST-ELEVATION ACUTE CORONARY SYNDROMES: *The Enduring value of Killip Classification*

The Killip classification first proposed in 1967:

Killip I—no evidence of HF

Killip II—mild HF, with rales involving 1/3 or less of the posterior lung fields and a systolic BP 90 mm or higher.

Killip III—pulmonary edema with rales involving more than 1/3 of the posterior lung fields, and systolic BP of 90 or more.

Killip IV—cardiogenic shock with any rales and systolic BP under 90.

Killip classification is a powerful independent predictor of all-cause mortality in patients with *non*-ST –elevation acute coronary syndromes as well as in ST-elevation myocardial infarction.

Age, Killip class, heart rate, systolic BP and ST depression should receive particular attention in the initial assessment of *non*-ST –elevation acute coronary syndromes.

Cardiogenic shock tends to develop during hospitalization, often secondary to recurrent ischemia or infarction. Once it develops, it is associated with an extremely high mortality rate. This delay in presentation of shock in *non*-ST-elevation acute coronary syndromes creates a fortuitous window, during which early revascularization may prevent shock.

11-9 DIASTOLIC HEART FAILURE

Diastolic heart failure (**DHF**) refers to the clinical syndrome of heart failure (**HF**) with a preserved left ventricular ejection fraction (0.50 and above) in the absence of major valvular disease. About a third of patients with HF seen by clinicians have DHF as so defined.

The pathophysiology of DHF is characterized by a *low cardiac output* resulting from impeded flow into the left ventricle caused by thick ventricular walls and a small ventricular cavity.

Clinically, patients with DHF are elderly, more likely female, and often have a raised BP and associated left ventricular hypertrophy. However, clinical characteristics by themselves cannot reliably distinguish systolic from diastolic HF. To make

the distinction, it is therefore important to obtain an imaging study, typically echocardiography, to estimate left ventricular ejection fraction.

Mechanisms contributing to abnormal left ventricular diastolic properties include: stiff large arteries, hypertension, myocardial ischemia, and diabetes.

Acute treatment includes: BP control, relief of ischemia, control of ventricular rate in patients with atrial fibrillation. Chronic treatment includes restriction of dietary sodium, and control of hypertension. Treatment is largely empirical.

HEEL PAIN

9-15 EFFECT OF MAGNETIC VS SHAM-MAGNETIC INSOLES ON PLANTAR HEEL PAIN: A RANDOMIZED CONTROLLED TRIAL

Magnetic insoles did not benefit any more than sham insoles. Many patients who use them will not be convinced despite this well-controlled study.

HISTORY TAKING

5-1 “BUILDING” A HISTORY RATHER THAN “TAKING” ONE

Adopting a “narrative-based medicine”(NBM) approach enables the sharing of information between patient and doctor. It incorporates the patient’s narrative into the sharing process. This article suggests a framework of skills and attitudes that can act as a foundation to improve the medical interview.

The essence of a narrative-based approach involves the physician simultaneously attending to two narratives—one from the biomedical perspective, and one from the patient’s perspective. Listen to the patient!

HOMOCYSTEINE

3-14 PLASMA HOMOCYSTEINE AND RISK FOR CONGESTIVE HEART FAILURE IN ADULTS WITHOUT PRIOR MYOCARDIAL INFARCTION

An increased plasma homocysteine level independently predicted risk of development of CHF in adults without prior myocardial infarction. Another indication for supplementation with folate?

HORMONE REPLACEMENT THERAPY

1-4 GLYCEMIC EFFECTS OF POSTMENOPAUSAL HORMONE THERAPY:

In women with established coronary heart disease, hormone therapy reduced the incidence of type 2 diabetes by 3.3% compared with those taking placebo. NNT (4 years to prevent one case) = 30.

And reduced incidence of diabetes by 12% in those with impaired glucose tolerance at baseline.

5-4 COMBINATION THERAPY WITH HORMONE REPLACEMENT AND ALENDRONATE FOR PREVENTION OF BONE LOSS IN ELDERLY WOMEN

Combination therapy with HRT + alendronate was superior to either drug alone in increasing BMD.

5-11 ESTROGEN PLUS PROGESTIN AND THE INCIDENCE OF DEMENTIA AND MILD COGNITIVE IMPAIRMENT IN POSTMENOPAUSAL WOMEN

Estrogen + progestin did not reduce the risk for probable dementia in postmenopausal women age 65 and older.

8-1 BREAST CANCER AND HORMONE-REPLACEMENT THERAPY IN THE MILLION WOMEN STUDY

This remarkable, country-wide study confirms that current use of HRT is associated with increased risk of incident and fatal BC. Between 1996 and 2001, one half of the million women age 50-64 in this UK cohort were using HRT.

The risk is substantially less for estrogen-alone than for E-P combinations.

Use of HRT by women aged 50-64 in the UK over the past decade is estimated to have resulted in 20 000 extra cases of BC; 15 000 of these associated with E-P use; 5000 with use of estrogen alone. (Ie, *progestins are the major culprit.*)

Women who are presently taking estrogen-progestin may be told there is one additional chance in 150 of an invasive BC over 5 years; and one additional chance in 800 if they are taking estrogen alone.

Risk increases with duration of use. Past users (5 or more years previously) were not at increased risk.

8-2 ESTROGEN PLUS PROGESTIN AND THE RISK OF CORONARY HEART DISEASE.

E-P, in standard dose, does not confer cardiac protection. It may slightly increase risk of CHD, especially during the first year of use. Primary care clinicians may consider prescribing low-dose aspirin for primary prevention, at least during the first year. Treatment to improve lipid profiles reduces risk.

E-P should not be prescribed for the prevention of cardiovascular disease.

Any possible increase in incidence of CHD (about 6 extra cases per 10 000 patient-years) is minor compared with the risk for breast cancer.

8-12 DIFFERENTIAL ASSOCIATION OF ORAL AND TRANSDERMAL OESTROGEN-REPLACEMENT THERAPY WITH VENOUS THROMBOSIS RISK.

Oral, but not transdermal ERT, was associated with risk of VTE in postmenopausal women. Transdermal administration avoids the first pass through the liver and blunts production of thrombogenic proteins by the liver.

A good example of the advantages of transdermal application of drugs.

HUMAN PAPILLOMA VIRUS

2-6 ADDING A TEST FOR HUMAN PAPILLOMA VIRUS DNA TO CERVICAL-CANCER SCREENING

Virtually all squamous-cell cervical carcinomas contain one of eighteen types of human papilloma virus (HPV). The relative risk of cervical cancer associated with persistent infection with high-risk types of HPV (especially types 16 and 18) is higher than the risk of lung cancer associated with smoking.

The discovery that continued presence of tumor-producing HPV is necessary for development of cervical cancer is revolutionizing our approaches to screening and prevention. An obvious correlary is that the absence of infection means that the risk of cervical cancer is negligible.

HYALURONIC ACID

12-6 INTRA-ARTICULAR HYALURONIC ACID IN TREATMENT OF KNEE ARTHRITIS

“Based on the findings of this meta-analysis, intra-articular hyaluronic acid has, at best, modest efficacy in the treatment of knee osteoarthritis. This effect . . . “is equivalent to the effect of NSAIDs over that of acetaminophen, an effect that itself remains controversial.” .” “Our findings suggest the controversy surrounding the efficacy of intra-articular hyaluronic acid is justified and the best evidence does not support its efficacy.”

At least 17 of the 22 trials were industry sponsored. Others have suggested that findings from industry-sponsored trials compared with those that were otherwise funded showed that research funded by pharmaceutical companies was more likely to have outcomes favoring the sponsor.

All 22 studies reported improvement of pain in the intra-articular placebo groups. Placebo injections may have efficacy for treating knee OA. The investigators calculated that intra-articular placebo accounted for 79% of the efficacy of intra-articular hyaluronic acid.

“This supports our hypothesis that the majority of the effect of intra-articular hyaluronic acid is an intra-articular placebo effect.”

Publication bias may overestimate the effect. Compared with lower-molecular-weight hyaluronic acid, the higher-molecular weight hyaluronic acid may be more efficacious, but heterogeneity of studies limits definitive conclusions.

I doubt this study will deter enthusiasts from using HA. Individual patients who have apparently obtained relief may insist on continuing.

The only way an individual’s response can be accurately determined is by an N-of-one trial. I doubt this would be feasible considering the ethical issues involved.

HYPERTENSION

2-2 A COMPARISON OF OUTCOMES WITH ANGIOTENSIN-CONVERTING-ENZYME INHIBITORS AND DIURETICS FOR HYPERTENSION IN THE ELDERLY. .

Initiation of antihypertension treatment with ACE inhibitor in older men appeared to lead to better outcomes than diuretics despite similar reductions of BP. Patients often required 2 or more drugs.

NNT to benefit one male patient over 1 year = 270. No benefit in females.

2-3 INITIAL TREATMENT OF HYPERTENSION

On the basis of available data, diuretics or beta-blockers remain appropriate for the initial treatment of uncomplicated hypertension.

“In patients over age 65, morbidity and mortality from cardiovascular disease are reduced when systolic blood pressure is lowered to a level below 160 mm Hg. Whether levels below 140 mm Hg provide additional protection is unclear.” “Optimal blood pressure targets remain to be determined, particularly for elderly patients.”

Primary care clinicians should develop a set initial drug protocol for treating long standing (ie, lifetime) illnesses which require long-term costly medication. We should aim to provide the least expensive, least toxic drugs and drug doses, which are easiest to take, and more likely to lead to compliance. The editor of Practical Pointers suggests a protocol.

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

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

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

5-5 THE SEVENTH REPORT OF THE JOINT NATIONAL COMMITTEE ON PREVENTION, DETECTION, EVALUATION, AND TREATMENT OF HIGH BLOOD PRESSURE. The JNC-VII

Provides new guidelines and key messages: Individuals with a systolic 120-139 or a diastolic 80–90 should be considered as *pre-hypertensive*. They require health-promoting lifestyle modifications to prevent CVD.

The committee recognizes that the responsible physician’s judgment remains paramount.

5-6 HEALTH OUTCOMES ASSOCIATED WITH VARIOUS ANTIHYPERTENSIVE THERAPIES USED AS FIRST-LINE AGENTS

Low-dose diuretics are the treatment of first choice for patients with uncomplicated hypertension who require drug treatment. They are the most effective drugs for preventing cardiovascular disease morbidity and mortality.

6-9 PROGNOSTIC VALUE OF AMBULATORY BLOOD PRESSURE RECORDINGS IN PATIENTS WITH TREATED HYPERTENSION

In patients with *treated* hypertension, a higher ABP, systolic or diastolic, predicted cardiovascular events even after adjustment for classic risk factors including office BP. As judged by ABP, office BP may be misleading.

6-10 AMBULATORY BLOOD-PRESSURE MONITORING IN CLINICAL PRACTICE

24-hour ABP monitoring yields readings during all the patient's activities, and gives a far better representation of the "blood pressure burden" than that obtained during office visits.

ABP should be used more often in clinical practice.

"For those whose ambulatory blood pressure is truly normal (< 130/80) despite an elevated office blood pressure, and in whom there is no evidence of other cardiovascular risk factors or target-organ disease, avoidance of unnecessary drug therapy would be a clear benefit of the monitoring procedure."

6-2 VALUE OF LOW DOSE COMBINATION TREATMENT WITH BLOOD PRESSURE LOWERING DRUGS

Combining low dose drug treatment for hypertension increases efficacy and reduces adverse effects. Three drugs at half dose are estimated to lower risk of stroke by 63% and ischemic heart disease by 46% at age 60-69.

11-2 EFFECTS OF DIFFERENT BLOOD-PRESSURE-LOWERING REGIMENS ON MAJOR CARDIOVASCULAR EVENTS: OVERVIEW OF RANDOMIZED TRIALS

This study estimated the effects of strategies based on different drug classes and on those targeting different BP goals on the risks of major cardiovascular events and death.

Treatment with any commonly-used regimen reduces the risk of total major cardiovascular events.

A larger reduction in BP reduces risk of total cardiovascular events. BP-lowering is a major component of the benefit conferred by the regimens investigated. There was a larger reduction in stroke and total major cardiovascular events from regimens aimed at a lower BP goal.

ACE-inhibitor-based regimens benefit across a wide range of hypertensive and non-hypertensive patients who are at high risk for cardiovascular disease.

ACE inhibitor or diuretic or beta-blocker are much more effective in preventing heart failure than calcium antagonists.

For stroke, there is a greater effect of regimens based on calcium antagonists than those based on diuretics or beta-blockers, but the results were of borderline significance.

Reductions in systolic BP of 2, 4, 6, 8, and 10 mmHg were associated with lower risk of stroke, major cardiovascular disease, coronary heart disease, cardiovascular death, and total mortality.

12-2 EXTENT OF CARDIOVASCULAR RISK REDUCTION ASSOCIATED WITH TREATMENT OF ISOLATED SYSTOLIC HYPERTENSION

A great many older adults remain at high risk of heart disease and stroke from untreated isolated systolic hypertension (**ISH**; systolic > 140, diastolic < 90). Treatment of ISH is associated with clear benefits. The Systolic Hypertension in the Elderly Program (*JAMA 1991*) demonstrated a 36% reduction in stroke among participants assigned to active BP treatment. The Systolic Hypertension in Europe trial (*Lancet 1998*) reported that active treatment of ISH significantly reduced the incidence of dementia. And also exerted a strong effect in preventing heart failure.

This subset of the SHEP study was begun after closure of the original study. It compared risk of death and cardiovascular event rates in actively treated patients with ISH, vs placebo controls, and normotensive controls. Follow up was up to 14 years. Event rates were decreased by 21% in the actively treated group.

Early treatment, before advanced atherosclerosis develops, results in the best long-term outcomes. The prevalence of subclinical atherosclerosis in individuals with ISH is high compared with normotensive controls. Active treatment of ISH is

associated with slower progression of subclinical atherosclerosis. The development of atherosclerosis with ISH likely adds to the acceleration of vascular stiffening, which is the underlying cause of ISH. Thus, early treatment may slow not only the progression of atherosclerosis, but progression of ISH as well.

Severe ISH may be difficult to control, requiring multiple drugs.

12-3 OVERCOME CLINICAL INERTIA TO CONTROL SYSTOLIC BP

It is clear that in individuals younger than age 50, diastolic BP (**DBP**) is a better predictor of future complications of hypertension than in older individuals. For those older than 50, systolic BP (**SBP**) is a better predictor. Most persons with hypertension are older than 50. For these patients control of SBP is a high priority, even in the face of a normal DBP.

“Systolic blood pressure alone correctly classifies hypertensive status in about 98% of adults.”

Most patients with elevated SBP need aggressive treatment to reach the evidence-based goal of less than 140. We are beginning to see that 130 and even 120 is some groups such as those with diabetes, congestive heart failure, and chronic kidney disease is a beneficial goal. SBP in these mostly older patients is the variable that indicates the need for more intensive therapy.

INFECTION

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

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

INFLUENZA

3-1 INFLUENZA VACCINATION AND REDUCTION IN HOSPITALIZATIONS FOR CARDIAC DISEASE AND STROKE AMONG THE ELDERLY

In the elderly, vaccination against influenza was associated with large reductions in numbers of hospitalizations from heart disease, cerebrovascular disease, as well as pneumonia and influenza. Risk of death was reduced by about 50%.

Flu vaccination is one of the most cost-effective health interventions. Primary care clinicians bear responsibility for increasing uptake by the general population.

6-12 EFFECTIVENESS OF NEURAMINIDASE INHIBITORS IN TREATMENT AND PREVENTION OF INFLUENZA A AND B

Evidence consistently supports the view that zanamivir (*Relenza*) and oseltamivir (*Tamiflu*) are clinically effective in treating and preventing flu. Evidence is limited for treatment of certain populations as well as for prevention strategies. The numbers needed to treat to prevent one person from developing flu may be high.

Choosing individuals for whom the drugs are indicated would be a clinical-judgment call, depending largely on cost, personal preference, and likelihood of severe complications from flu.

The drugs are no substitute for vaccination. They may be adjunctive therapy on occasion.

INSULIN

10-9 INHALED INSULIN PROVIDES IMPROVED GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS INADEQUATELY CONTROLLED WITH ORAL AGENTS.

Recently, a dry powder inhaled insulin (**IN-1**) system has been developed. It provides a new method of treatment. The pulmonary route exploits the large vascular bed and permeability of the alveoli to deliver insulin directly into the blood

stream. IN-I has a rapid onset of action, actually faster than injected regular insulin and insulin lispro. Its duration of action is about 6 hours.

Pre-meal inhaled powdered insulin (**IN-I**) added to oral agents produced a significantly greater reduction in HbA1c than oral agents alone (metformin or sulfonylurea, or both)—a mean reduction in HbA1c of 2.3 %. HbA1c remained stable in the control group—about 10%

One third of the IN-I + oral agents group achieved a HbA1c less than 7% vs none in the oral agents alone group. (Mean HbA1c dropped from about 10% to 7.5% in the IN-I group.)

Fasting plasma glucose improved significantly.

This means of administration will eliminate the fear of injections. Patient satisfaction was high--97% opted to continue in a 1-year extension of the therapy.

This is an early proof of concept study. Primary care clinicians will watch for developments with great interest. Cost is to be determined.

INTIMA-MEDIA THICKNESS

6-7 INTENSIVE DIABETES THERAPY AND CAROTID INTIMA-MEDIA THICKNESS IN TYPE 1 DIABETES MELLITUS

Intensive therapy over an extended time resulting in a mean HbA1c of 7.2% decreased progression of intima-media thickness. Evidence that tight control may delay macro-vascular disease.

8-9 CARDIOVASCULAR RISK FACTORS AND INCREASED CAROTID INTIMA-MEDIA THICKNESS IN HEALTHY YOUNG ADULTS

Atherosclerosis is a slowly progressive process possibly starting at a young age. Preventive measures taken early in life might postpone the development of atherosclerosis and decrease risk of clinical cardiovascular disease (**CVD**).

Unfavorable cardiovascular risk factors (cigarette smoking, diabetes, dyslipidemia, and hypertension) were related to greater CIMT in young adulthood. Effort to change modifiable risk factors early in life may retard development of atherosclerosis and the onset of clinical cardiovascular disease later in life.

8-10 REGRESSION OF CAROTID AND FEMORAL ARTERY INTIMA-MEDIA THICKNESS IN FAMILIAL HYPERCHOLESTEROLEMIA

High dose simvastatin over 2 years reduced combined carotid/femoral IMT in more than two thirds of patients. The largest effect was on the femoral artery. This degree of reduction of IMT. . . “will likely have a significant clinical impact on the prevention of coronary artery disease”.

Primary care clinicians might easily extrapolate these results to other patients with high cholesterol levels. Atherosclerosis is reversible.

ISOLATED SYSTOLIC HYPERTENSION

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JET LAG

2-4 THE PREVENTION AND TREATMENT OF JET LAG.

The Cochrane Review concludes that 2 to 5 mg melatonin taken at bedtime at the new destination is effective, and may be worth repeating for the next two to four days.

The article gives other suggestions for minimizing both travel fatigue and jet lag.

LITERACY AND HEALTH.

11-1 THE CRUCIAL LINK BETWEEN LITERACY AND HEALTH.

In 1993, the National Adult Literacy Survey reported that half of adult Americans have limited literacy skills. They struggle to reliably complete many simple daily tasks such as completing forms, reading signs, or using transportation schedules. At least as many patients, then, must struggle with health care’s many forms, educational materials, and directions.

“The physician should never presume that a patient is literate.” Even the most poised and articulate persons may have trouble reading. People with reading problems are unlikely to step forward and ask for help.

One method to improve communication is called “closing the loop”. The physician asks the patients to restate the message in their own words. This teach-back method assures the physician that the patient understands.

This is a good example of the large gap between “evidence based medicine” (**EBM**) and the real world of primary care. I do not recall reading in the entrance criteria of trials that all subjects were medically literate--nor in the exclusion criteria that those with poor literacy were excluded. I believe exclusion is automatic.

Randomized trials, the basis of EBM, deal with a well-defined group of subjects. Patients seen in primary care often do not fit into the group. This will require the clinician to use her best clinical judgment to fit the circumstances. As important as EBM is, I believe it does not apply to a large majority of clinic patients. RTJ

LOW BACK PAIN

11-6 EFFECT OF FIRMNESS OF MATTRESS ON CHRONIC NON-SPECIFIC LOW-BACK PAIN

Randomized, double-blind, controlled, multicenter trial assessed 313 adults (median age 44) who had chronic low-back pain. None had referred pain. All complained of backache while lying in bed and on arising.

At 90 days, patients using the medium-firm mattress were about twice as likely to improve as were patients using firm mattresses.

Outcomes for less pain in bed (Odds Ratio = 2.4), less pain on arising (OR = 1.93) and less disability (OR = 2.1) as compared with the firm mattress.

Throughout the study, the medium-firm group had less daytime low-back pain.

“The results of this study suggest that, although psychosocial factors have an effect on disability, some biomechanical factors also have an effect and should be taken into consideration.”

How can the primary care clinician apply these results? I believe it comes down to a N of 1 study. If possible, patients may try a variety of mattresses. This may not be practical. If the patient considers his mattress to be firm, a less firm one may be tried. If he considers it to be soft, a firmer one may be tried.

MAGNETIC INSOLES

9-15 EFFECT OF MAGNETIC VS SHAM-MAGNETIC INSOLES ON PLANTAR HEEL PAIN: A RANDOMIZED CONTROLLED TRIAL

Magnetic insoles did not benefit any more than sham insoles. Many patients who use them will not be convinced despite this well-controlled study.

MAMMOGRAPHY

4-4 MAMMOGRAPHIC SCREENING FOR BREAST CANCER.

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

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

7-7 WOMEN NEED BETTER INFORMATION ABOUT ROUTINE MAMMOGRAPHY

The public should be told about all the outcomes of screening in terms it can understand. Surgical and psychological morbidities are important outcomes. Unnecessary treatments arise from overdiagnosis. This includes biopsies, segmental excisions, mastectomies, and even radiotherapy. “Until tools are developed that are capable of measuring a wide variety of outcomes, we cannot weigh the evidence satisfactorily.”

“The age at which the trade-off between benefit and harm becomes acceptable is a subjective judgment that cannot be answered on scientific grounds.” Most women who are screened have not been educated about the uncertainties.

METABOLIC SYNDROME

7-6 THE METABOLIC SYNDROME

The close association of type 2 diabetes with cardiovascular disease (**CVD**) led to the hypothesis that the two arise from a common antecedent. This concept has been codified by the WHO and others as “the metabolic syndrome”. This diagnosis might hold the promise for enhanced prevention of diabetes and CVD.

The metabolic syndrome: Obesity (especially central obesity); Dyslipidemia (especially high triglycerides and low HDL-cholesterol); Hyperglycemia; Hypertension

Is the risk associated with a cluster of all 4 traits likely to exceed the sum of the four traits? I believe. . . “The whole is greater than the sum of the parts”?

MIGRAINE

1-9 PROPHYLACTIC TREATMENT OF MIGRAINE WITH AN ANGIOTENSIN-II RECEPTOR BLOCKER

In this study, the angiotensin II blocker, candesartan, provided effective migraine prophylaxis with tolerability comparable to that of placebo.

MYELOPEROXIDASE

10-16 PROGNOSTIC VALUE OF MYELOPEROXIDASE IN PATIENTS WITH CHEST PAIN

Clinical criteria, ECG criteria, and conventional laboratory tests, including troponin T, often do not adequately predict the risk of cardiovascular events in patients presenting with acute coronary syndromes.

C-reactive protein and other markers have been advocated as a more accurate means of gauging risk, but additional tools are needed to predict vulnerability of coronary arteries to major events in the near term. Myeloperoxidase is an excellent candidate. It predicts cardiovascular risks independently of C-reactive protein and other markers of inflammation.

“Our findings suggest that myeloperoxidase serves as a marker of the vulnerable plaque and one that can be used to identify patients at *imminent* risk for major adverse cardiac events, independently of evidence of myocardial necrosis.”

A single measurement of myeloperoxidase independently predicted early risk of myocardial infarction, as well as the risk of major adverse cardiac events in the ensuing 30 days and 6 months. It identified patients at risk in the absence of myocardial necrosis.

This is a preliminary report. Watch for developments.

MYOCARDIAL INFARCTION

1-6 IMPACT OF CHANGING DIAGNOSTIC CRITERIA ON INCIDENCE, MANAGEMENT, AND OUTCOME OF ACUTE MYOCARDIAL INFARCTION

Adding troponin levels as criterion for the diagnosis identified many more patients as having an acute myocardial infarction.

1-12 PRIMARY ANGIOPLASTY VERSUS INTRAVENOUS THROMBOLYTIC THERAPY FOR ACUTE MYOCARDIAL INFARCTION.

Primary PTCA is more effective than thrombolytic therapy for treatment of ST-elevation AMI.

9-2 ORAL XIMELAGATRAN FOR SECONDARY PROPHYLAXIS AFTER MYOCARDIAL INFARCTION

In patients with a recent MI, long term treatment with ximelagatran, combined with aspirin, was more effective than aspirin alone in reducing frequency of major cardiovascular events. [NNT (for 6 months to benefit one) = 33]

Ximelagatran is the first of a new class of *oral direct-thrombin inhibitors* under investigation. It is rapidly metabolized to its active form, melagatran. It is stable over time. Its metabolism is unaffected by age, sex, body weight, or ethnic origin. It is not affected by the hepatic cytochrome P450 enzyme system, thus providing a low potential for drug-drug interactions. There are no relevant food or alcohol interactions. “Melagatran’s pharmacokinetics are unchanged and the pharmacodynamic properties show only minor additive effects when oral ximelagatran and acetylsalicylic acid are given concomitantly.”

Ximelagatran has undergone extensive assessment in patients with venous thromboembolism and atrial fibrillation. It has a rapid onset of action, achieves a peak level within 2 hours, and has a half-life of 4 hours. It is administered twice daily. There is no need of monitoring and dose adjustments. (*Monitoring of liver and kidney function is required. RTJ*) Ximelagatran is primarily excreted by the kidney. Data on patients with kidney dysfunction are limited.

With the 24 mg BID dose, the bleeding rate was low, and high concentrations of alanine amino transferase occurred less frequently (7%).

“It is good news that the more than half century wait of new and improved oral antithrombotics finally appears to be ending.”

10-16 PROGNOSTIC VALUE OF MYELOPEROXIDASE IN PATIENTS WITH CHEST PAIN

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C-reactive protein and other markers have been advocated as a more accurate means of gauging risk, but additional tools are needed to predict vulnerability of coronary arteries to major events in the near term. Myeloperoxidase is an excellent candidate. It predicts cardiovascular risks independently of C-reactive protein and other markers of inflammation.

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A single measurement of myeloperoxidase independently predicted early risk of myocardial infarction, as well as the risk of major adverse cardiac events in the ensuing 30 days and 6 months. It identified patients at risk in the absence of myocardial necrosis.

This is a preliminary report. Watch for developments.

11-12 VALSARTAN, CAPTOPRIL, OR BOTH IN MYOCARDIAL INFARCTION COMPLICATED BY HEART FAILURE, LEFT VENTRICULAR DYSFUNCTION, OR BOTH

Angiotensin-converting-enzyme inhibitors (**ACE-I**) do not completely block production and effects of angiotensin II. Likewise, angiotensin-receptor blockers (**ARB**) do not completely block angiotensin II. But, they do act differently. Investigators have speculated that adding the two would produce greater benefits than either one used alone.

In this study, however, use of the two drugs together did not benefit any more than either used alone. Valsartan is as effective as captopril (but not more effective) as measured by risk of death in patients who are at high risk for cardiovascular events after a myocardial infarction. The combination increased adverse effects without improving survival.

I abstracted this study because it contrasts with other studies reported in *Practical Pointers*. Doubt remains about the efficacy of combined ACE inhibitors and ARBs. See “Effects of Candesartan on Mortality and Morbidity in Patients with

Chronic Heart Failure” *Practical Pointers* September 2003. The study reported a slight benefit when candesartan was added to ACE inhibitors. (NNT = 25 to 50) Hyperkalemia, hypotension, and increased creatinine levels occurred more commonly in the combined group.

I believe primary care clinicians should avoid the combination until clarification is available. ARB may be used when ACE inhibitors are not tolerated. RTJ

NON-ALCOHOLIC FATTY LIVER DISEASE

6-8 NON-ALCOHOLIC FATTY LIVER DISEASE: An Unrecognized Cause Of Cryptogenic Cirrhosis

Cryptogenic cirrhosis (CC) is a significant contributor to liver related morbidity. Non-alcoholic fatty liver disease (NAFLD) is the most common cause of CC. The diagnosis of cirrhosis in these patients is usually delayed by almost a decade and is often not established until after the patient develops hepatocellular carcinoma or other complications of advanced liver disease. Once cirrhosis is diagnosed, mortality is greater than that of hepatitis C virus related cirrhosis.

Existing evidence, albeit scant, suggests that NAFLD is a spectrum, progressing from hepatic steatosis to non-alcoholic steatohepatitis, and then on to cirrhosis. Over 6 million US adults have NAFLD, and 640 000 may have cirrhosis. This may exceed the numbers infected with hepatitis C. Prognosis is just as bad.

Diagnosis remains one that is established only after other causes of chronic liver disease have been excluded. NAFLD can be more readily suspected if the patient is obese and has diabetes. Primary care clinicians have an opportunity for prevention by controlling obesity, lipids, and diabetes.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

8-14 EXPOSURE TO NON-STEROIDAL ANTI-INFLAMMATORY DRUGS DURING PREGNANCY AND RISK OF MISCARRIAGE

NSAIDs and aspirin were associated with an increased risk of miscarriage. Acetaminophen was not.

OBESITY

1-10 OBESITY AND ADULTHOOD AND ITS CONSEQUENCES FOR LIFE EXPECTANCY

Obesity in adulthood is associated with decreases in life expectancy among men, women, smokers and non-smokers. (Up to 7 years of life lost.) Combined smoking/obesity doubles risk.

4-6 WEIGHT LOSS COUNSELING REVISITED.

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

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

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

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

Ultimately, prevention is the goal.

4-7 EFFICACY AND SAFETY OF LOW-CARBOHYDRATE DIETS

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

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

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

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

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

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

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

OSTEOARTHRITIS

7-3 STRUCTURAL AND SYMPTOMATIC EFFICACY OF GLUCOSAMINE AND CHONDROITIN IN KNEE OSTEOARTHRITIS

Evidence that glucosamine benefits symptoms and slows joint deterioration.

The purity and dose of these over-the-counter preparations are not regulated by the FDA.

Primary care clinicians may be willing to prescribe it despite regulation by the FDA.

12-6 INTRA-ARTICULAR HYALURONIC ACID IN TREATMENT OF KNEE ARTHRITIS

“Based on the findings of this meta-analysis, intra-articular hyaluronic acid has, at best, modest efficacy in the treatment of knee osteoarthritis. This effect . . . “is equivalent to the effect of NSAIDs over that of acetaminophen, an effect that itself remains controversial.” .” “Our findings suggest the controversy surrounding the efficacy of intra-articular hyaluronic acid is justified and the best evidence does not support its efficacy.”

At least 17 of the 22 trials were industry sponsored. Others have suggested that findings from industry-sponsored trials compared with those that were otherwise funded showed that research funded by pharmaceutical companies was more likely to have outcomes favoring the sponsor.

All 22 studies reported improvement of pain in the intra-articular placebo groups. Placebo injections may have efficacy for treating knee OA. The investigators calculated that intra-articular placebo accounted for 79% of the efficacy of intra-articular hyaluronic acid.

“This supports our hypothesis that the majority of the effect of intra-articular hyaluronic acid is an intra-articular placebo effect.”

Publication bias may overestimate the effect. Compared with lower-molecular-weight hyaluronic acid, the higher-molecular weight hyaluronic acid may be more efficacious, but heterogeneity of studies limits definitive conclusions.

I doubt this study will deter enthusiasts from using HA. Individual patients who have apparently obtained relief may insist on continuing.

The only way an individual's response can be accurately determined is by an N-of-one trial.

I doubt this would be feasible considering the ethical issues involved.

OSTEOPOROSIS

5-4 COMBINATION THERAPY WITH HORMONE REPLACEMENT AND ALENDRONATE FOR PREVENTION OF BONE LOSS IN ELDERLY WOMEN

Combination therapy with HRT + alendronate was superior to either drug alone in increasing BMD.

9-17 PARATHYROID HORMONE PLUS ALENDRONATE—A Combination That Does Not Add Up

It would be plausible to assume that the effect of a bisphosphonate + parathyroid hormone would be additive, since their mechanisms of action differ. Unfortunately, this is not the case. Disappointing !

Apparently, alendronate impairs the anabolic activity of parathyroid hormone.

OUTDATED DRUGS

1-14 OUTDATED DRUGS MAY BE USEFUL

This letter to the editor brings up an important practical point. Should we discard all drugs when they become outdated?

The correspondent believes that many drugs maintain potency long after expiration date. In developing countries and “free” clinics in the USA, the choice may be “outdated” or “none at all”.

PAIN CONTROL

11-8 EFFECTS OF PERIOPERATIVE ADMINISTRATION OF A SELECTIVE CYCLO-OXYGENASE 2 INHIBITOR ON PAIN MANAGEMENT AND RECOVERY AFTER KNEE REPLACEMENT.

Perioperative (before and after surgery) use of a COX-2 inhibitor was effective component of multimodal analgesia. It reduced opioid consumption, pain, vomiting, and sleep disturbance. It shortened the time physical therapy was needed to achieve effective joint range of motion.

Pain is the 5th monitored vital sign. Efficient management of pain improves postoperative clinical outcomes. After total knee arthroplasty (TKA), inadequate control of postoperative pain is associated with poor functional recovery.

Surgical trauma induces cyclo-oxygenase 2 (COX-2) which then promotes synthesis of prostaglandins that sensitize peripheral nociceptors and mediate central sensitization. NSAIDs as well as opioids decrease this inflammatory response. *Pre-operative* administration of NSAIDs may be effective by establishing a sufficient tissue NSAID concentration to inhibit early production of prostaglandins before the onset of tissue trauma, thus attenuating the development of hyperalgesia.

I wonder if sports medicine enthusiasts might offer pre-game COX-2 inhibitors to players (eg, football) who might be subject to injury during a game. This might lessen the period of disability if a serious injury should occur.

PARATHYROID HORMONE

9-17 PARATHYROID HORMONE PLUS ALENDRONATE—A Combination That Does Not Add Up

It would be plausible to assume that the effect of a bisphosphonate + parathyroid hormone would be additive, since their mechanisms of action differ. Unfortunately, this is not the case. Disappointing !

Apparently, alendronate impairs the anabolic activity of parathyroid hormone.

PATIENTS RELATIONSHIP WITH THEIR DOCTORS

9-13 PATIENTS PUT THEIR RELATIONSHIP WITH THEIR DOCTORS AS SECOND ONLY TO THAT OF THEIR FAMILIES

A new international study given at the World Medical Association annual assembly reported that, although the doctor-patient relationship has become less paternalistic, it still holds a central and trusted place in society. The authors warn that, to keep this status, doctors will need to measure up to patients' higher expectations of care.

“The patient-physician relationship is part of the critical underpinnings of stable societies.”

It is still a privilege to be a physician.

PREGNANCY

8-14 EXPOSURE TO NON-STEROIDAL ANTI-INFLAMMATORY DRUGS DURING PREGNANCY AND RISK OF MISCARRIAGE

NSAIDs and aspirin were associated with an increased risk of miscarriage. Acetaminophen was not.

PREMENSTRUAL DYSPHORIC DISORDER

1-5 PREMENSTRUAL DYSPHORIC DISORDER

Selective serotonin reuptake inhibitors (SSRI) are first-line agents for PDD. Several trials have demonstrated they are superior to placebo for treatment of the emotional and physical symptoms.

Fluoxetine (Prozac) and Sertraline (Zoloft) are the most studied. A 20 mg dose of fluoxetine is as effective as the 60 mg and has fewer adverse effects and fewer dropouts. SSRIs may be given continuously or for two weeks before the expected period. Luteal phase administration has been effective.

PREVENTION

8-3 IS OPPORTUNISTIC DISEASE PREVENTION IN THE CONSULTATION ETHICALLY JUSTIFIABLE?

Consultations in primary health care have been suggested as an ideal setting for health promotion and disease prevention. Doctors are expected to discuss preventive measures even when they are not among the reasons for the consultation. Opportunistic preventive medicine is considered a part of good medical practice. This article asks. . .Is this ethically justifiable?

The authors argue that doctors should maintain a clear focus on each patient's reasons for seeking help rather than be distracted by an increasing list of preventive measures. They maintain that, from a moral point of view, initiatives to improve health among people who are currently free of symptoms is fundamentally different from curative medicine—the condition for which the patient consults.

Physicians who offer a screening test carry a considerable responsibility. They must offer enough information about risks and benefits in order to enable the patient to give informed consent. Informed consent presupposes an understanding of the limitations of the screening test. Every test carries a chance of misclassification of disease. A false positive test may result in further interventions that do not benefit the patient, and may cause harm.

“Once medical risk has been passed on to a person, it cannot be retracted. Respect for autonomy should therefore also honor the person's right *not* to be opportunistically confronted with knowledge about biomedical risks that are unrelated to his or her reasons for seeing the doctor.”

“As the list of accessible preventive tests lengthens and thresholds for intervention are lowered, a doctor who adheres to all recommendations for provision of preventive services may ultimately be able to find something abnormal in everybody.”

Think twice before advising screening tests.

PROSTATE CANCER

4-1 SCREENING FOR PROSTATE CANCER

“Few issues are as controversial.” Adequate evidence is absent.

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

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

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

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

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

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

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

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

5-7 VARIATION OF SERUM PROSTATE-SPECIFIC ANTIGEN

PSA may fluctuate over short periods of time. A single elevated PSA should be viewed with caution.

An isolated elevation of PSA should be confirmed several weeks later before proceeding with further testing, including biopsy.

6-14 NONINVASIVE DETECTION OF CLINICALLY OCCULT LYMPH-NODE METASTASES IN PROSTATE CANCER.

High resolution MRI with magnetic iron-containing nanoparticles allowed detection of small and otherwise undetectable lymph-node in patients with metastatic PC.

7-12 THE INFLUENCE OF FINASTERIDE ON DEVELOPMENT OF PROSTATE CANCER

Finasteride prevents or delays the appearance of PC at a risk of increasing incidence of high grade cancers.

Not yet ready for general use, but provocative. Preventive or delaying measures may be in the offing.

PULMONARY EMBOLISM

10-3 SUBCUTANEOUS FONDAPARINUX VERSUS INTRAVENOUS UNFRACTIONATED HEPARIN IN THE INITIAL TREATMENT OF PULMONARY EMBOLISM.

Once-daily fondaparinux without monitoring is at least as effective and safe as adjusted-dose IV unfractionated heparin in the initial treatment of hemodynamically stable patients with pulmonary embolism.

“Because of its simplicity, once-daily subcutaneous fondaparinux without anticoagulation monitoring could replace intravenous administration of unfractionated heparin in most patients.”

RENAL DISEASE

1-16 COMBINATION TREATMENT OF ANGIOTENSIN-II RECEPTOR BLOCKER AND ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR IN NON-DIABETIC RENAL DISEASE (COOPERATE)

Combined ACE-I and A II-I therapy safely retarded progression of non-diabetic renal disease more effectively than either drug alone.

REQUESTS FOR CLINICAL SERVICES

7-5 DIRECT OBSERVATION OF REQUESTS FOR CLINICAL SERVICES IN OFFICE PRACTICE.

Patient-requests for prescriptions are becoming more frequent as direct-to-the-public advertising by drug companies becomes more common. Patient-requests for consultations, and tests are also becoming more frequent as the public becomes more sophisticated.

Primary care clinicians will find it necessary to negotiate with patients about these requests. Physicians' role in educating patients about risks, benefits, and costs of new “miracle” drugs is becoming more important.

Primary care clinicians must increasingly understand patients' anxieties and what they really want to receive from the consultation. The patient negotiates from fear and uncertainty. The physician negotiates from a specialized knowledge. Meeting a common ground satisfactory to both requires patience and give-and-take.

RESTLESS LEG SYNDROME

10-12 RESTLESS LEG SYNDROME SYMPTOMS IN PRIMARY CARE.

Restless leg syndrome (**RLS**) is a sleep disorder that accounts for a significant proportion of patients with sleep complaints.

Currently, to be considered positive for RLS, four criteria must be met:

1. Urge to move the legs, usually accompanied by an unpleasant sensation in the legs.
2. Symptoms must be aggravated by rest.
3. Symptoms must be alleviated by movement, in particular, walking.
4. Must be worse in the evening or at night either currently or in the past when the condition first started.

In this study, twenty four percent of patients were positive for all 4 of the essential symptoms.; 15% reported the symptoms at least weekly. A large number of RLS patients may be seen by primary care clinicians.

A variety of drugs has been recommended for treatment: dopamine precursors (eg, levodopa; *Laradopa*), dopamine agonists (eg bromocriptine; *Parlodel*), anticonvulsants, benzodiazepines, and even opioids.

The variety of drugs recommended for treatment speaks for the lack of studies to determine preference. Drug therapy in practice would likely be based on trial and error. The FDA has not reviewed them for specific use in RLS.

SCREENING

2-6 ADDING A TEST FOR HUMAN PAPILLOMA VIRUS DNA TO CERVICAL-CANCER SCREENING

Virtually all squamous-cell cervical carcinomas contain one of eighteen types of human papilloma virus (HPV). The relative risk of cervical cancer associated with persistent infection with high-risk types of HPV (especially types 16 and 18) is higher than the risk of lung cancer associated with smoking.

The discovery that continued presence of tumor-producing HPV is necessary for development of cervical cancer is revolutionizing our approaches to screening and prevention. An obvious correlary is that the absence of infection means that the risk of cervical cancer is negligible.

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4-4 MAMMOGRAPHIC SCREENING FOR BREAST CANCER.

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

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

10-1 RISK OF CERVICAL CANCER ASSOCIATED WITH EXTENDING THE INTERVAL BETWEEN CERVICAL-CANCER SCREENINGS

Compared with annual screening, screening performed once three years after the last negative test in women who previously had 3 or more consecutive negative PAP tests, is associated with an average excess risk of cervical cancer of approximately 3 in 100 000. If continued, screening annually after 3 negative tests, would result in thousands and thousands of additional PAP tests and colposcopic examinations to detect only one additional case of cervical cancer.

The US Preventive Services Task Force recently recommended screening be performed “at least every 3 years” rather than every year. The American Cancer Society suggests lengthening the intervals between screenings to as long as 3 years among women age 30 and over who previously have had negative results on three or more consecutive cervical cancer tests.

Given that half of all cases of cervical cancer occur in women who have never been screened, screening all women at least once would be expected to contribute more to decreasing mortality than the continued annual testing. The focus should be on screening women who have rarely or never undergone screening.

12-7 SCREENING FOR DEPRESSION IN PRIMARY CARE WITH TWO VERBALLY ASKED QUESTIONS

The US Preventive Services Task Force endorsed screening for depression, but did not recommend a specific tool. Many primary care clinicians find screening questionnaires for depression too cumbersome and time consuming for routine use.

This study used a simple screening tool of two questions. If one or two were answered positively, the screen was considered positive, and further questions were asked to determine if major depression was present. (A composite interview--the “Gold Standard”)

The screening questions:

- 1) During the past month have you often been bothered by feeling down, depressed, or hopeless?
- 2) During the past month have you often been bothered by little interest or pleasure in doing things?

In the community setting, the two verbally asked questions have a good sensitivity (97%) and reasonable specificity (67%) for screening for depression. If the screen was negative (both questions answered negatively) major depression is almost surely absent.

About 5 false positives would occur for every true positive when asking the questions alone.

This is common in screening studies which are in essence a diagnostic test performed in a low prevalence setting. Further questions will be required to clarify presence or absence of depression.

12-10 SCREENING VIRTUAL COLONOSCOPY—READY FOR PRIME TIME?

A new virtual colonoscopy (VC) used a multidirectional CT scanner providing a primary 3-dimensional endoluminal display. It permitted faster, higher-resolution imaging than previously obtainable. Residual fluid and stool was tagged by contrast material. The imaging software digitally removed all opacified fluid and stool from the colon by a process called “electronic cleansing”.

The study subjects received the VC followed by conventional colonoscopy for comparison:

Sensitivity of VC for detection of adenomas vs traditional colonoscopy:

- 10 mm or larger was 92% vs 88%
- 8 mm or larger was 92% vs 89%
- 6 mm or larger was 86% vs 90%

The study suggests that VC can detect polyps of 6 mm or larger as accurately as conventional colonoscopy in a population with a low prevalence of colorectal neoplasia.

Decisions regarding the use of VC as a first-line screening test will require more information about cost and insurance coverage. “The performance of VC in this asymptomatic population is impressive, with detection rates similar to those

achieved by conventional colonoscopy.” Only if the important questions about the appropriate size threshold and the surveillance of smaller polyps can be resolved will VC be ready for prime time.

The bugaboo is the need for follow-up conventional colonoscopy to remove suspicious polyps.

Patients will be asking about this. Application in the local community is likely to be far-off.

SELF ESTEEM

9-10 SELF ESTEEM AND HEALTH

There are two basic human needs—health and autonomy. Autonomy is closely linked with self esteem and the earning of respect. “Low levels of autonomy and low self esteem are likely to be related to worse health.” Increasing pride in one’s identity may have a more favorable effect on health behaviors and risks than focusing on how to change the risks themselves. There is a link between low self esteem and ill health. “All people have a basic need for autonomy and self esteem.”

Primary care clinicians can enhance the self-esteem of patients with low esteem by listening carefully to their problems and showing respect and concern.

SENSITIVITY, SPECIFICITY, PREDICTIVE VALUES, AND LIKELIHOOD RATIOS

12-8 REVIEW OF SENSITIVITY, SPECIFICITY, PREDICTIVE VALUES AND LIKELIHOOD RATIOS

Calculate sensitivity from the left column; specificity from the right column; positive predictive value from the top row; negative prediction value from the bottom row; the likelihood ratios from both columns.

See text.

SMOKING

7-4 MORTALITY RISK REDUCTION ASSOCIATED WITH SMOKING CESSATION IN PATIENTS WITH CORONARY DISEASE.

Smoking cessation has a greater effect on reducing the risk of mortality among patients who smoke than the effect of any other intervention. Risk of death was reduced by 36% in those who quit.

Ask your patients who smoke to read this article.

10-11 CURRENT SMOKING, SMOKING CESSATION, AND THE RISK OF SUDDEN CARDIAC DEATH IN PATIENTS WITH CORONARY ARTERY DISEASE.

In smokers with CAD who quit, risk of sudden cardiac death (**SCD**) is significantly reduced and compares with the risk of those who never smoked. The decline in risk associated with cessation is immediate and not time dependent. This supports the view that the risk is due to direct toxic effects. The risk in smokers is not related to the amount of smoking.

In absolute terms, smoking cessation and never smoking resulted in a 3.5% lower risk of SCD over 8 years compared with those who continued to smoke. [NNT(8 years to prevent one SCD) = 30]. And a 11% reduction in all-cause death. [NNT = 10].

The risk of continuing smoking on SCD is even more pronounced than other risk factors—age, sex, New York Heart Association functional class, BP, and dyslipidemia.

Cessation is certainly one of the most effective preventive measures. Despite being informed of the risks, many patients continue to smoke. Primary care clinicians who succeed in getting recalcitrant smokers to stop achieve a major therapeutic intervention. Would asking them to read a copy of this article help? RTJ

SOCIAL ANXIETY DISORDER

9-5 SOCIAL ANXIETY DISORDER

The hallmark of social anxiety disorder (SAD) is extreme and persistent fear of embarrassment and humiliation. People with SAD (also known as social phobia) avoid participating in social and public activities such as public speaking, social gatherings, and meetings. The intense symptoms of SAD interfere with functioning and cause marked distress.

It is the third most prevalent psychiatric disorder in the USA. Paroxetine and sertraline are effective drug therapy.

SAD can be differentiated from panic disorder by its consistent relation to social issues.

Less severe, and more common symptoms can benefit from beta-blockers.

SORE THROAT

1-1 WHY DO GENERAL PRACTITIONERS PRESCRIBE ANTIBIOTICS FOR SORE THROAT?

Describing the difference between “Evidence Based Medicine” and the “Real World” of practice. Despite the power of EBM, there are many instances and reasons for deviation.

SPIRINOLACTONE

7-13 INTERACTION OF SPIRINOLACTONE WITH ACE INHIBITORS OR ANGIOTENSIN-RECEPTOR BLOCKERS

Spirinolactone and ACE inhibitors act synergistically or additively to increase plasma potassium levels. Toxic and even lethal concentrations may result. Spironolactone is established as an important additive in therapy for patients with severe heart failure. The dose should not exceed 25 mg daily, and in some patients should be less.

STENTS

1-15 DRUG ELUTING STENTS IN VASCULAR INTERVENTION

Immunosuppressive agents (which inhibit tumor-cell growth) may also inhibit the benign tissue proliferation characterizing intimal hyperplasia. Several immunosuppressants have been tested for potential to inhibit restenosis. Stents coated with the agents are becoming available. Local drug delivery achieves higher tissue concentrations of drugs, while producing no systemic effects. This is associated with a marked reduction in the risk of re-stenosis.

“The clinical impact of the elimination of restenosis may influence the approach to coronary artery disease, the future of cardiac surgery, and health-care economics.”

ST JOHNS WORT

9-14 EFFECT OF ST JOHN’S WORT ON DRUG METABOLISM BY INDUCTION OF CYTOCHROME P450 3A4 ENZYME

Long-term dosing of St John’s wort results in *induction* of the liver enzyme cytochrome P450 3A4. This hastens metabolism of many drugs and diminishes their plasma levels and clinical effectiveness. This leads to increased dosage requirements of the 50% of drugs metabolized by this liver enzyme.

St. John’s wort can significantly alter the effectiveness and dosing of a wide range of medications.

Patients’ use of herbal nostrums continues undiminished. “Natural” is considered harmless even by the most sophisticated patients. This is another good reason for primary care clinicians to insist that patients “brown bag” all medications they take at each office visit.

STREP THROAT

7-1 DIAGNOSING STREP THROAT IN THE ADULT PATIENT: DO CLINICAL CRITERIA REALLY SUFFICE?

Recently the American College of Physicians recommended an algorithm which may be used to diagnose group A strep pharyngitis on clinical grounds alone, eschewing microbiological testing.

Tonsillar exudates

Tender anterior cervical adenopathy

Fever

Absence of cough.

The ACP guidelines allow empirical antibiotic treatment for patients who meet 3 or 4 of the criteria, and non-treatment for all others.

Other prestigious organizations recommend rapid antigen testing or culture before treatment is begun.

Most primary care clinicians would likely chose to treat with penicillin on clinical grounds.

STROKE

2-8 ALCOHOL CONSUMPTION AND RISK OF STROKE: A Meta-analysis

Heavy alcohol consumption increases risk of stroke. Light-to-moderate consumption protects against ischemic stroke, but not against hemorrhagic stroke.

3-1 INFLUENZA VACCINATION AND REDUCTION IN HOSPITALIZATIONS FOR CARDIAC DISEASE AND STROKE AMONG THE ELDERLY

In the elderly, vaccination against influenza was associated with large reductions in numbers of hospitalizations from heart disease, cerebrovascular disease, as well as pneumonia and influenza. Risk of death was reduced by about 50%.

Flu vaccination is one of the most cost-effective health interventions. Primary care clinicians bear responsibility for increasing uptake by the general population.

3-5 SILENT BRAIN INFARCTS AND THE RISK OF DEMENTIA AND COGNITIVE DECLINE

Silent brain infarcts are common in the elderly. Persons with silent brain infarcts had an increased risk of dementia, and a steeper decline in cognitive function than persons without such lesions.

In clinical practice—How can we intervene to benefit the patient? The hope is that treatment directed at vascular disease will reduce the burden of dementia. We should optimize cardiovascular health by established means: control of hypertension; lipid control; weight control; exercise; smoking-avoidance.

Other possible beneficial interventions: low-dose aspirin; one alcoholic drink daily; and folic acid supplementation to reduce homocysteine levels.

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

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

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

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

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

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

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

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6-17 ASPIRIN AND TICLOPIDINE FOR PREVENTION OF RECURRENT STROKE IN BLACK PATIENTS: A Randomized Trial

Ticlopidine was *not* more effective than aspirin in preventing recurrent stroke in Afro-Americans. Aspirin is a better treatment than ticlopidine for aspirin-tolerant Afro-Americans with noncardioembolic ischemic stroke.

8-4 A RISK SCORE FOR PREDICTION OF STROKE OR DEATH IN INDIVIDUALS WITH NEW-ONSET ATRIAL FIBRILLATION IN THE COMMUNITY: *The Framingham Heart Study*

This risk score for embolic stroke was derived from 5 risk predictors: advancing age, female sex, increasing systolic BP, prior stroke or TIA, and diabetes. The score can be used to estimate *absolute* risk of stroke (5% to 75% over 5 years) and help to negotiate treatment decisions with patients with AF at the time they are first diagnosed. . Risk may be stratified into mild, moderate or severe.

Although some physicians and patients may more readily accept and act on a numerical risk prediction, I believe primary care clinicians can just as accurately judge risk without creating a numerical 5-year “risk”. Most patients will eventually end up receiving anticoagulation. It is nevertheless important to spare those at low risk from the potential adverse effects of warfarin therapy and use aspirin instead. Patients with AF, but without structural heart disease, (including no hypertension) are at relatively low risk, especially if they are under age 65.

To anticoagulate or not anticoagulate is a difficult and important decision. It remains a clinical-judgment call. For each patient, clinicians must strike an acceptable balance between risk of ischemic stroke and bleeding. In the absence of an absolute or important relative contraindication, the data seem compelling that warfarin therapy should be offered to most patients with AF. The difficulty is to know what threshold of stroke risk is low enough so that the potential risk of warfarin therapy outweighs its potential benefits. For most patients the potential benefits of stroke prevention will outweigh the potential risks of bleeding secondary to warfarin.

An article (*Annals Internal Medicine April 28 , 2003; 163: 936-43; Practical Pointers April 2003*) differs somewhat in suggesting that up to 1/3 of patients with AF can be classified as low-risk and treated with aspirin.

9-1 EFFECT OF INTENSITY OF ORAL ANTICOAGULATION ON STROKE SEVERITY AND MORTALITY IN ATRIAL FIBRILLATION

Emboli of atrial origin are larger than average. The brain infarcts they produce are more disabling and lethal.

Among patients with non-valvular AF, the degree of anticoagulation at admission for stroke was associated with risk of disability and death. Anticoagulation that resulted in an INR of 2.0 or greater reduced frequency and severity of ischemic stroke and risk of death. This is evidence against INR targets below 2.0

Risk of hemorrhagic stroke did not increase until INR was 4.0 or above.

INR below 2.0 and aspirin protect against stroke less effectively than INR 2.0 to 3.0, but are superior to use of no anticoagulant. Aspirin is adequate prophylaxis in patients considered at low risk for thromboembolic stroke. Eventually almost all patients with AF will become high risk due to age and co-morbidity. As age progresses, risk of bleeding from warfarin increases. This dilemma must be solved on an individual basis. Patients accepting warfarin must be carefully controlled at a stable INR around 2.5.

“Our results provide further support for anticoagulation to achieve an INR of 2.0 or greater (eg, 2.5) in patients with non-valvular atrial fibrillation.”

11-7 STROKE PREVENTION WITH ORAL DIRECT THROMBIN INHIBITOR XIMELAGATRAN COMPARED WITH WARFARIN IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION.

Ximelagatran is a direct thrombin inhibitor which is given orally.. Its pharmacokinetic profile is predictable and stable overtime. It has low potential for drug-drug interactions and does not require monitoring or dose adjustment.

Fixed dose ximelagatran was at least as effective as well-controlled warfarin for prevention of stroke and systemic embolism. It is much easier to use.

Practical Pointers has abstracted several articles on the new oral anticoagulant ximelagatran. (See October 2003 issue.)

Ximelagatran looks very promising.

SUDDEN ACUTE RESPIRATORY SYNDROME (SARS)

3-6 SUDDEN ACUTE RESPIRATORY SYNDROME (SARS)

“Plagues are as certain as death and taxes. The optimism of the 1960s and 1970s has given way to a mature realism that relationship between human beings and microbes is neither completely predictable nor biased in favor of humans.” Is SARS a rehearsal for the next pandemic of influenza.?

The disease represents a sudden jump from animal species to humans. The virus probably evolved in animals for eons and for some reason suddenly became able to infect humans.

The SARS story has been astounding! In a short period of 2 months, the world-wide epidemiology has been described, the virus identified, its genetic code determined, and control measures instituted and found effective. As of the end of April 2003, the epidemic has been declared to be controlled in Vietnam and in Toronto Canada because no new cases were reported over a 3 week period. How would the history of the 20th century have changed if we had the technology, control measures, and world-wide instantaneous communication available during the 1918 influenza epidemic?

The ability of the virus to spread and cause serious illness and death in healthy persons increases the alarm. Is SARS a rehearsal for the next pandemic of influenza.?

URINARY TRACT INFECTION

7-2 ACUTE UNCOMPLICATED URINARY TRACT INFECTION IN WOMEN.

Trimethoprim-sulfamethoxazole (TM-S) for 3 days remains the therapy of choice. Telephone consultation and treatment is safe.

For recurrent episodes of infection and for prophylaxis, self treatment is a reasonable clinical approach.

VASOVAGAL SYNCOPE

5-12 PACEMAKER THERAPY FOR PREVENTION OF SYNCOPE IN PATIENTS WITH RECURRENT SEVERE VASOVAGAL SYNCOPE

Pacing therapy did not significantly reduce the risk of recurrent syncope in patients with vasovagal syncope.

VENOUS THROMBOEMBOLISM

3-2 LONG-TERM, LOW-INTENSITY WARFARIN THERAPY FOR THE PREVENTION OF RECURRENT VENOUS THROMBOEMBOLISM.

Long-term, low-intensity warfarin therapy with a target INR of 1.5 to 2.0 was highly effective in preventing recurrent VTE in patients with a history of *idiopathic* VTE, including patients with thrombophilia due to factor V Leiden and prothrombin mutations.

For patients with acute VTE, low-dose warfarin is appropriate after a 3-month course of conventional-dose warfarin. How long should therapy be continued? No definite answer, but probably long-term.

8-12 DIFFERENTIAL ASSOCIATION OF ORAL AND TRANSDERMAL OESTROGEN-REPLACEMENT THERAPY WITH VENOUS THROMBOSIS RISK.

Oral, but not transdermal ERT, was associated with risk of VTE in postmenopausal women. Transdermal administration avoids the first pass through the liver and blunts production of thrombogenic proteins by the liver.

A good example of the advantages of transdermal application of drugs.

8-6 D-DIMER LEVELS AND RISK OF RECURRENT VENOUS THROMBOEMBOLISM 8-5 COMPARISON OF LOW-INTENSITY WARFARIN THERAPY WITH CONVENTIONAL-INTENSITY WARFARIN THERAPY FOR LONG-TERM PREVENTION OF RECURRENT VENOUS THROMBOEMBOLISM

“The intensity of anticoagulation for patients who have had unprovoked venous thromboembolism should not be reduced after the first three months of treatment.” Such a reduction increases risk of recurrence. INR should remain at 2.0 to 3.0.

Risk of recurrent VTE was 0.7 per 100 patient-years in the INR 2.0 to 3.0 group vs 2.8 per 100 patient years in the INR 1.5 to 1.9 group.

In this study, there was no evidence that aiming for an INR of 1.5 to 1.9 (vs 2.0 to 3.0) reduced risk of bleeding.

I believe that in the “real world” of primary care, aiming for a higher INR will be related to an increased risk of bleeding. Indeed, bleeding risk is increased in patients who aim for the lower INR as compared with placebo.

An article in *NEJM April 10, 2003; 348; 1425-34* reported that a low-level INR (target 1.5 to 2.0; compared with placebo) in patients with unprovoked VTE was highly effective in preventing recurrence. It is likely that a higher target will be slightly more effective in prevention, but will lead to greater risk of bleeding. Again a clinical judgment call based on individual-patient characteristics and preferences.

After 3-months of anticoagulation for a first episode of unprovoked VTE, measuring D-dimer levels allowed identification of a subset of patients with very low risk of recurrence. Patients with a level of less than 250 ng/mL 3 weeks after discontinuation of oral anticoagulation were at low risk.

The cumulative probability of recurrent VTE at 2 years among those with levels < 250 was 3.7%. Among those with higher levels was 11.5%

A higher D-dimer is likely to be related to ongoing thrombosis-thrombolysis due to a thrombogenic potential.

10-2 TREATING THROMBOSIS IN THE 21ST CENTURY

Now, a minimal anti-thrombin-binding unit of heparin, a pentasaccharide called fondaparinux, has been synthesized and is undergoing clinical trials. Fondaparinux enhances anti-thrombin activity. It is a specific inhibitor of activated factor X (Xa). It requires subcutaneous administration. It can be given once a day on a weight basis. It does not require laboratory monitoring.

A second new anticoagulant (melagatran) took its cue from the leech which produces a direct thrombin inhibitor (hirudin). Hirudin acts independently of anti-thrombin and other plasma proteins. The discovery of hirudin led to other direct thrombin inhibitors, one of which is melagatran. Melagatran can also neutralize clot-bound thrombin. Chemical modification (to “ximelagatran”) allows better oral absorption. It is the first new oral anticoagulant since warfarin. Like fondaparinux, it does not require laboratory monitoring.

10-4 COMPARISON OF XIMELAGATRAN WITH WARFARIN FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM AFTER TOTAL KNEE REPLACEMENT

Fixed dose ximelagatran 36 mg bid, administered without coagulation monitoring, was significantly more effective than warfarin in prevention of thromboembolism after knee replacement. Safety was similar “It could therefore be considered an alternative to other thromboprophylactic agents.”

10-5 SECONDARY PREVENTION OF VENOUS THROMBOEMBOLISM WITH ORAL DIRECT THROMBIN INHIBITOR XIMELAGATRAN

Ximelagatran is a direct thrombin inhibitor undergoing active investigation as an anticoagulant. It is given in a fixed dose daily, and needs no monitoring.

Beginning and continuing extended secondary prevention of VTE with ximelagatran 24 mg bid for an additional 18 months after 6 months of standard anticoagulation effectively prevented recurrences. [NNT = 10]

The incidence of major hemorrhage was low and similar to placebo. Ximelagatran was equally effective in subgroups that had risk factors for recurrence—previous VTE, proximal deep VTE, and pulmonary embolism.

The fixed-dose ximelagatran was well tolerated without monitoring measures of coagulation.

12-5 CLINICAL IMPACT OF BLEEDING IN PATIENTS TAKING ORAL ANTICOAGULANT THERAPY FOR VENOUS THROMBOEMBOLISM

In patients with venous thromboembolism (VTE), there is a perception that the clinical impact of preventing recurrent VTE and possible fatal pulmonary embolism outweighs the risk of bleeding associated with long-term anticoagulation.

The subgroup of patients with idiopathic (unprovoked) VTE, and VTE associated with factor V Leiden, prothrombin mutations, and deficiencies of protein C and protein S make up about half of the thousands of patients in whom symptomatic VTE is diagnosed each year in the USA.

The optimal duration of anticoagulation is still unclear.

This systematic review of randomized, controlled trials and prospective cohort studies (10 757 patients; 4373 patient-years) investigated patients with confirmed idiopathic VTE. All received oral anticoagulant therapy (target INR--2.0 to 3.0) for at least 3 months. Nine of 33 studies reported use for over 3 months (6 to 24 months).

The chances of a major bleed *per year of anticoagulation* were 7 in 100 patients with 1 in 1000 chance of fatality, and about 1 chance in 100 of an intracranial bleed.

The primary care clinician must make some attempt to balance the risk of bleeding vs the benefits of anticoagulation in each individual patient. (*I know of no means of doing this beyond "clinical judgment". RTJ*)

VITAMINS

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

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

6-11 USE OF ANTIOXIDANT VITAMINS FOR THE PREVENTION OF CARDIOVASCULAR DISEASE

A lack of beneficial effect was seen consistently for various doses of these two vitamins in diverse populations. The routine use of vitamin E is not supported. The use of beta carotene is associated with a small but significant excess of all-cause mortality and cardiovascular death.

VITAMIN D

3-4 EFFECT OF FOUR MONTHLY ORAL VITAMIN D₃ (CHOLECALCIFEROL) SUPPLEMENTATION ON FRACTURES AND MORTALITY IN MEN AND WOMEN LIVING IN COMMUNITY.

Vitamin D supplements of 100 000 IU given orally every 4 months for *primary* prevention was associated with a lower risk of fractures (and without adverse effects) in older men and women living in the community.

This is equivalent to our usual dose of 800 IU daily. Calcium supplements would have lowered risk even more.

WARFARIN

3-2 LONG-TERM, LOW-INTENSITY WARFARIN THERAPY FOR THE PREVENTION OF RECURRENT VENOUS THROMBOEMBOLISM.

Long-term, low-intensity warfarin therapy with a target INR of 1.5 to 2.0 was highly effective in preventing recurrent VTE in patients with a history of *idiopathic* VTE, including patients with thrombophilia due to factor V Leiden and prothrombin mutations.

For patients with acute VTE, low-dose warfarin is appropriate after a 3-month course of conventional-dose warfarin. How long should therapy be continued? No definite answer, but probably long-term.

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11-7 STROKE PREVENTION WITH ORAL DIRECT THROMBIN INHIBITOR XIMELAGATRAN COMPARED WITH WARFARIN IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION.

Ximelagatran is a direct thrombin inhibitor which is given orally.. Its pharmacokinetic profile is predictable and stable overtime. It has low potential for drug-drug interactions and does not require monitoring or dose adjustment.

Fixed dose ximelagatran was at least as effective as well-controlled warfarin for prevention of stroke and systemic embolism. It is much easier to use.

Practical Pointers has abstracted several articles on the new oral anticoagulant ximelagatran. (See October 2003 issue.) Ximelagatran looks very promising.

WOMEN’S HEALTH

10-17 THE GREATEST THREAT TO WOMEN’S HEALTH

Heart attacks and stroke kill twice as many women as all cancers combined. Moreover, contrary to conventional wisdom, women are more likely to die from cardiovascular disease than men.

Getting women to stop smoking, eat healthily, drink alcohol only in moderation, lose weight if appropriate, and take regular exercise involves changing behaviors that are often ingrained from childhood.

More than half of all deaths and disability from heart disease and stroke can be prevented.

“Advising women, as well as men, about their risks of cardiovascular disease should, we urge, be mandatory for all primary care practitioners.”

XIMELAGATRAN

9-2 ORAL XIMELAGATRAN FOR SECONDARY PROPHYLAXIS AFTER MYOCARDIAL INFARCTION

In patients with a recent MI, long term treatment with ximelagatran, combined with aspirin, was more effective than aspirin alone in reducing frequency of major cardiovascular events. [NNT (for 6 months to benefit one) = 33]

Ximelagatran is the first of a new class of *oral direct-thrombin inhibitors* under investigation. It is rapidly metabolized to its active form, melagatran. It is stable over time. Its metabolism is unaffected by age, sex, body weight, or ethnic origin. It is not affected by the hepatic cytochrome P450 enzyme system, thus providing a low potential for drug-drug interactions. There are no relevant food or alcohol interactions. “Melagatran’s pharmacokinetics are unchanged and the pharmacodynamic properties show only minor additive effects when oral ximelagatran and acetylsalicylic acid are given concomitantly.”

Ximelagatran has undergone extensive assessment in patients with venous thromboembolism and atrial fibrillation. It has a rapid onset of action, achieves a peak level within 2 hours, and has a half-life of 4 hours. It is administered twice daily. There is no need of monitoring and dose adjustments. (*Monitoring of liver and kidney function is required. RTJ*) Ximelagatran is primarily excreted by the kidney. Data on patients with kidney dysfunction are limited.

With the 24 mg BID dose, the bleeding rate was low, and high concentrations of alanine amino transferase occurred less frequently (7%).

“It is good news that the more than half century wait of new and improved oral antithrombotics finally appears to be ending.”

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