

PRACTICAL POINTERS FOR PRIMARY CARE

INDEX

JANUARY – JUNE 2007

PRACTICAL CLINICAL POINTS

MEDICAL SUBJECT HEADINGS

HIGHLIGHTS AND *EDITORIAL COMMENTS*

LINKS TO THE FULL ABSTRACTS

**JAMA, NEJM LANCET, BMJ
ARCHIVES INTERNAL MEDICINE,
ANNALS INTERNAL MEDICINE
www.practicalpointers.org**

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This index is a reference document based on articles abstracted from 6 flagship journals January-June 2007. It provides a means of recalling to memory, in an evening or two, what the editor considered new and important for primary care.

The numbers in the brackets refer to the full abstract. For example, [3-6] refers to the sixth article abstracted in March. .

It consists of 4 parts:

- 1) “Practical Clinical Points”: This provides an instant reminder of points of clinical interest and importance which primary care clinicians should advise patients about, consider, and be aware of. Links are supplied to the “Highlights of Abstracts and *Editorial Comments*” section.
- 2) “Medical Subject Headings” (MeSH): A list of medical subject headings from aortic abdominal aneurysm to venous thromboembolism arranged and linked alphabetically to the “Highlights and *Editorial Comments*” section.
- 3) “Highlights of Abstracts and *Editorial Comments*” section linked alphabetically to each MeSH. (There may be several articles listed under a MeSH.) The highlights contain a condensation of each abstract. The *Editorial Comments* are those of the editor alone, based on his years-long experience as a practicing primary care internist and as editor and publisher of *Practical Pointers for Primary Care*.
- 4) The abstract itself provides more detailed information, and the citation.

Monthly issues for the past 6 years may be found on the website (www.practicalpointers.org).

I hope you find *Practical Pointers for Primary Care* useful and interesting.

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

Practical Clinical Points January – June 2007

These clinical points were abstracted from articles published in 6 flagship journals from January to June 2007. The journal editors considered the articles, after peer review, worthy of publishing.

The editor of *Practical Pointers* selected them because he believed they present applications to every day practice primary care clinicians might seriously consider.

However, fashions in medicine change. As more definitive studies and observations over longer times become available some of these clinical applications undoubtedly will also change.

Meanwhile, I believe they represent the latest information generally available.

Editor

Advise:

Against use of aspirin + warfarin for anticoagulation [1-12]

No more than 81 mg of aspirin daily for long-term prevention of cardiovascular disease [5-5]

A low-glycemic load diet as a prudent approach to prevention of diabetes, heart disease, and obesity. [3-2] [5-2]

Young doctors not to address elderly patients by their first name, especially on the first meeting [6-10]

Virtually all elders to get a “shingles” shot [3-8]

Young women to be immunized against human papilloma virus to prevent cervical cancer [2-9] [5-6]

All patients to adopt a low salt, high potassium diet to reduce risk of hypertension [5-1]

Social isolation at onset of a flu epidemic [6-4]

Morbidly obese patients who are considering bariatric surgery to read this article [5-10]

Treat gonococcal infections according to the new CDC recommendations [6-10]

Consider:

Hormone replacement therapy is safe when used in younger postmenopausal women [4-4]

In women in their 40s, there is no simple recommendation for mammography screening. Fully informing patients about risks and benefits guides their individual choice. [4-7]

Checking patients more frequently for celiac disease by determining antibody to transglutaminase [5-7]

Treating migraine with combined naproxen-sumatriptan [4-8]

If you prescribe a drug for off-label use, you have the responsibility to be well informed about the product, base its use on firm scientific rationale and on sound medical evidence, and maintain records of the product’s usefulness and effects [2-5]

Glucosamine-chondroitin supplements are safe for treatment of osteoarthritis, although not regulated by the FDA. The combination may be effective in the subgroup of patients with moderate to severe knee pain. There is a high placebo response. [1-9]

Under prescribing of opioids remains a major barrier to effective pain control. “Morphine kills the pain, not the patient.” [4-5]

Physicians do not routinely consider patient's costs for the prescribed intervention. Costs are an important part of the benefit / harm-cost ratio [4-9]

The renin-angiotensin system is related to left ventricular hypertrophy, atrial fibrillation, stroke, atherosclerosis, and type-2 diabetes. Blocking the system will reduce organ damage in hypertension, atherosclerosis and diabetes [4-1]

There is no evidence to support the warning that pregnant women should not eat seafood. [2-4]

Thrombolysis in acute stroke should now be considered a part of routine therapy in patients seen within 3 hours of onset. [1-1]

Despite what might be said, people at the end-of-life rarely want everything or nothing [2-3]

Be aware that:

Snus, a Swedish form of smokeless tobacco, is less harmful than our snuff, and never causes lung cancer or COPD. This article argues that we should not delay in allowing snus to compete with cigarettes [6-6]

The "polypill" concept refuses to die. [1-8]

In patients with back and extremity pain, surgery for ruptured disk is more effective than surgery for spinal stenosis [5-8]

Chest compression only (avoiding mouth-to mouth breathing) may be the preferred method for cardiac resuscitation by bystanders [3-3]

Treatment of hypertension (even modest elevations of BP) may improve diastolic function [6-1]

Siesta may lower CHD mortality [2-8]

Estrogen-alone therapy for postmenopausal (hysterectomized) women in their 50s may reduce risk of coronary disease [6-2]

Folic acid supplementation reported to improve cognitive function (Consider the benefit / harm-cost ratio of folic acid) [1-11]

Angiotensin II blockers as supplements to other antihypertension drugs may reduce risk of cardiovascular events [4-2]

Treatment of H pylori infection in patient with dyspepsia benefits few [1-7]

Even modest exercise at 50% of recommended levels leads to a training effect [5-9]

Folic acid supplementation is reported to reduce risk of stroke. Consider the benefit / harm-cost ratio of folic acid [6-8]

Cardiac synchronization may benefit patients with left ventricular systolic dysfunction and prolonged QRS interval [6-9]

A new vaccine for hepatitis E is undergoing testing and looks promising [3-10]

Almost all American men and women have risk factors for cardiovascular disease. Lifestyle changes are basic, especially diet [3-4]

In elderly patients, a BMI of 25 to 29 is related to lower mortality rates, and longer disability-free life expectancy. Being a little overweight as you age may not be so bad [4-6]

MEDICAL SUBJECT HEADINGS (MeSH) JANUARY-JUNE 2007

ABDOMINAL AORTIC ANEURYSM

ACUPUNCTURE

ADIPOSITY

ANTICOAGULANT THERAPY (See ASPIRIN)

“ART” OF MEDICINE

ASPIRIN

ATHEROSCLEROSIS

BACK PAIN

BACK SURGERY

BARIATRIC SURGERY (See OBESITY)

BREAST CANCER

CALORIE RESTRICTION

CARDIAC ARREST

CARDIAC RESYNCHRONIZATION
THERAPY

CARDIOVASCULAR DISEASE

CARDIOVASCULAR RISK FACTORS

CELIAC DISEASE

CHOLESTEROL

COGNITIVE FUNCTION (See FOLIC ACID)

COMBINED ASPIRIN-WARFARIN (See
CARDIOVASCULAR DISEASE)

CONTROVERSIAL CLINICAL PRACTICES

CORONARY HEART DISEASE

DEMENTIA

DIASTOLIC HEART FAILURE

DYSPEPSIA

E-MEDICINE

END-OF-LIFE CARE (See TERMINALLY ILL
PATIENTS)

FITNESS

FOLIC ACID

GLYCEMIC-INDEX - GLYCEMIC LOAD

GONOCOCCAL INFECTIONS

GREETING THE PATIENT

HEADACHE

HEART FAILURE

HELICOBACTER PYLORI (See DYSPEPSIA)

HEPATITIS

HERPES ZOSTER

HORMONE REPLACEMENT THERAPY

HUMAN PAPILLOMAVIRUS (HPV)

HYPERTENSION

INFLUENZA

IRRITABLE BOWEL SYNDROME

MACROLIDE-RESISTANT STREPTOCOCCI

MEDICAL MYTHS

MIGRAINE

MYOCARDIAL INFARCTION

OBESITY

OFF LABEL DRUGS

OPIATES

OSTEOARTHRITIS

OSTEOPENIA

OSTEOPOROSIS

PAIN

PATIENT EXPECTATIONS: Requests for
Prescriptions

PERIODIC HEALTH EVALUATION

PERTUSSIS

PHYSICIANS' CONSIDERATION OF
PATIENT'S COSTS

“POLYPILL”

RENIN-ANGIOTENSIN SYSTEM

SEAFOOD

SIESTA (See CORONARY HEART DISEASE)

SNUS (See TOBACCO)

STROKE AND TIA

TERMINALLY ILL PATIENTS

TOBACCO

URINARY INCONTINENCE

VARICELLA

VENOUS THROMBOEMBOLISM

ABDOMINAL AORTIC ANEURYSM

“Extensive Periaortic Inflammation” “It Is Not Uncommon”

1-13 INFLAMMATORY ABDOMINAL AORTIC ANEURYSM

This article describes an important variant AAA, inflammatory AAA (**I-AAA**), the symptoms of which are so protean that patients may present to a wide range of physicians. Like classical atherosclerotic A-AAA, it most commonly affects the infrarenal portion of the aorta.

I-AAA was not described before 1972. Few physicians are familiar with it.

It differs from classical A-AAA in many ways:

The risk of rupture is less than 5%.

Patients are usually younger, male, and smokers.

The great majority of patients with I-AAA are symptomatic at presentation (in contrast to A-AAA).

Pain in the back and abdomen is common. Abdominal tenderness (with or without a pulsating mass) occurs in about one third of patients. Systemic symptoms (fever, malaise, weight loss) may be associated. Symptoms are so protean that patients may present to a wide range of physicians.

CT and MRI imaging show a characteristic cuff of soft tissue inflammation surrounding the aneurysm. There is an extraordinary expansion of the adventitia due to inflammation.

It may be an autoimmune disorder. Sed rate, C-reactive protein and other inflammatory cytokines may be elevated.

Corticosteroids and corticosteroid-sparing drugs (eg, methotrexate). relieve symptoms and reduce the inflammation.

Smoking cessation is critical.

This was my introduction to inflammatory abdominal aortic aneurysm. (I-AAA)

I spent a lot of time abstracting details about I-AAA. I believe it was worthwhile. I-AAA patients may present with obscure symptoms, especially back and abdominal pain. Abdominal scan may reveal the diagnosis and lead to effective symptomatic treatment.

Although the condition is rare, primary care clinicians should know about it.

Read the full abstract for a description of an individual case.

ACUPUNCTURE

“How Acupuncture Works Is Not Readily Understood”

4-3 ACUPUNCTURE: A Clinical Conference

The limited ability of many commonly used interventions to reduce pain and improve function, combined with significant adverse effects of some drugs. has led many patients to try therapies outside the

mainstream of medicine. A National Health Survey reported that 41% of respondents with arthritis had used some form of complementary-alternative medicine.

“The perception of acupuncture as a legitimate medical intervention expanded when the National Institutes of Health and the FDA held consensus development and technological assessment conferences (1998) that resulted in recommendations on the potential use of acupuncture, in particular for pain-related conditions, as well as post-operative and chemotherapy-induced nausea and vomiting, and when the FDA reclassified acupuncture needles from investigational devices to medical devices.”

Surveys of rheumatologists and pain specialists reported that 56% to 84% considered acupuncture a legitimate medical practice.

From the Western medical viewpoint, how acupuncture works is not readily understood. “High-quality evidence evaluating complimentary-alternative medicine has been scarce.”

The discussant focuses on the role of acupuncture relative to other treatments for the pain of osteoarthritis.

Randomized trials (acupuncture vs sham acupuncture) have reported contradictory efficacies. The benefits of some of the other knee osteoarthritis treatments (eg, intra-articular corticosteroids relative to placebo) are larger than the effects of acupuncture (relative to sham acupuncture). “The definition of appropriate sham acupuncture is still not resolved.”

There are a wide variety of schools of acupuncture, ranging from traditional Chinese methods to Western styles. Japanese and Chinese acupuncture are very different. As a consequence, there are many distinct styles of practice. Points of acupuncture vary. Points chosen for treatment vary from treatment to treatment. Variations include depth of needle penetration, the number of needles used, diameter and length of the needles, and the length of time needles are left in place. Different types of needle stimulation are used—manual, heat, electrical.

Most clinicians use multidisciplinary approaches to the management of osteoarthritis, recognizing that most available treatments have small effects. Different treatments used concurrently may provide incremental improvements. Adding acupuncture may increase costs. Some patients respond; some do not.

Cultural factors, which include expectations and beliefs, are extremely important influences on the outcomes of many treatments, acupuncture included.

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I enjoyed this article. I abstracted it in detail to enhance my understanding. I came away with the following thoughts:

There is no such thing as “acupuncture”. There are acupuncture(s). There is no standard on which to base determination of efficacy.

There is no established biological basis for belief that acupuncture is more than a placebo effect.

There is no good evidence for other than short-term effects (6 to 12 months). Long term benefits are not reported.

I would not deny the power of the placebo. Indeed, all primary care clinicians rely on it to some degree every day. The power of the placebo rests on patient- and physician-beliefs and enthusiasm.

Would I prescribe or advise acupuncture? No. But I would not deter any patient from trying it if the patient requests it and believes it may provide some relief. (Likely based on enthusiastic reports of friends and relatives.)

ADIPOSITY

Does Calorie Restriction Have Benefits Above And Beyond The Effect In Lowering Incidence Of Chronic Diseases?

3-6 AGING, ADIPOSITY AND CALORIE RESTRICTION

Maximum life span, defined as the average life span of the longest-lived decile of a cohort, is often used as a standard for evaluating the aging process.

Life expectancy, defined as the age at which 50% of the population survives after birth, has markedly increased in most developed countries. (From about 45 years in the early 1900s to about 75 years in men and 80 years in women today.) This increase is due primarily to improved sanitation, better hygiene, reduced infant mortality, development of antibiotics and vaccines, and better health care.

Recently, there has been increasing interest in the potential therapeutic use of calorie restriction to obtain optimal health and increase life span in humans. Calorie restriction, defined as a reduction in calorie intake below usual ad libitum intake, (while maintaining adequate nutrition) has been shown to increase maximum life span in many animal species. In laboratory rodents, calorie restriction increases longevity by preventing or delaying onset of chronic diseases (diabetes, atherosclerosis, cardiomyopathy, autoimmune diseases, respiratory diseases, and cancer).

The reduction in chronic diseases does not completely explain the increase in lifespan, and the preservation of function at more youthful levels, which occurs in the calorie-restricted rodents. About 1/3 of such rodents die without evidence of organ pathology. "These data support the notion that the common link between aging and chronic disease is not inevitable, and that it is possible to live longer without experiencing a cumulative increase in serious morbidity and disability."

Data suggest that the effects of calorie restriction on maximum life span are not simply a result of leanness induced by such restriction. Maximum life span does not increase in male rats that maintain a low body fat mass by performing regular exercise. It does increase in sedentary male rats that are food restricted to keep their body weights the same as those of the exercisers.

Conclusion:

- 1) Calorie restriction is an important determinant of health.
- 2) Excessive energy intake is a form of malnutrition that leads to unfavorable body composition, organ dysfunction, and premature mortality.
- 3) The precise caloric intake needed for optimal health and function likely varies for each individual depending on genetic background, age, energy expenditure, and diet composition.
- 4) The optimal calorie intake needed to slow the aging process is not known. The available data

support the notion that calorie restriction in humans leads to many of the same metabolic adaptations and reductions in multiple chronic disease risk factors that occur in calorie-restricted animal models, even when restriction is started in midlife.

- 5) Even if calorie restriction does not prolong maximum life span, it could increase life expectancy and the quality of life by reducing the burden of chronic diseases.

I enjoyed this article. I abstracted it in detail because it presents one of the most important health considerations in a somewhat different way. It suggests that properly restricting quantity while maintaining quality of food intake is essential for maintaining health. And that properly restricting quantity per se has a beneficial effect in addition to its effects in controlling body mass index and incidence of chronic disease.

“Calorie restriction” may be a misnomer. “Optimum calorie intake” may be a better term. It is obvious that Americans eat too much. We have the habit of eating to the point of satiety (where ingestion of more food would cause discomfort). A better approach is to save room for dessert, and then skip the dessert.

Ad libitum caloric intake usually means excessive intake, not only intake of the wrong kinds of food, but also the quantity. “Eat yourself to death, Joe”. “If you keep on overloading your truck, it will break down sooner.” “Eat less than you would like to”. If only it were not so difficult long-term.

Animals on an ad libitum diet also eat too much. “Fat cat.”

“ART” OF MEDICINE

“There Is No One Division Of Medicine By Which We Know And Another By Which We Act. “

1-5 WHAT STAYS CONSTANT AT THE HEART OF MEDICINE

To identify the art of medicine with “artfulness” is to fall into a set of modern confusions. The art of medicine is not about appearance at the expense of substance, but rather the way in which knowledge is related to advice and treatment.

The problem might be reformulated in this way: medicine requires knowledge of universals, and of the application of them to particular instances as embodied in individual patients.

Medical art may be a form of knowledge that is more probabilistic than the demonstrative certainty of science, but it is crucially important knowledge nevertheless. Its exercise requires not only knowledge of content, but something called “judgment”. Judgment requires attending to a patient.

For thousands of years, the question of how best to associate the universal and the particular has been the real doctor’s dilemma. No formulae, however good, can ever obscure the second part of medical knowledge, which comes from clinical judgment.

Few, if any, primary care clinicians completely master melding the “art” with the “science”. But keep on trying.

ASPIRIN

Benefits of Combined Therapy Are Questionable. There Is An Increased Risk Of Major Bleeding.

1-12 COMBINED ASPIRIN-ORAL ANTICOAGULANT THERAPY COMPARED WITH ORAL ANTICOAGULANT THERAPY ALONE AMONG PATIENTS AT RISK FOR CARDIOVASCULAR DISEASE

Combination therapy [CT]—oral anticoagulants [OAC] + low-dose aspirin—is recommended by the American College of Chest Physicians *only* for patients with a mechanical prosthetic heart valve. Despite this recommendation, a considerable number of patients with chronic atrial fibrillation (AF) receive combined therapy.

Despite a lack of evidence for the efficacy of CT, some experts have suggested that adding aspirin to OAC therapy might be useful because patients using OAC frequently have concomitant coronary artery disease, or are at high risk for stroke.

This systematic review and meta-analysis of randomized controlled trials (RCTs) compared OAC-alone with OAC + aspirin to assess benefits and risks.

Risk of arterial thromboembolism was lower in the OAC + aspirin groups, but *only* in studies of mechanical valves. (Odds ratio OAC + aspirin vs OAC alone = 0.27)

There was no difference in outcomes (OAC + aspirin vs OAC-alone) in risk of arterial thromboembolism in patients with atrial fibrillation or coronary disease.

The risk of major bleeding was higher in patients receiving combined therapy:

Combined therapy 3.8%

OAC-alone 2.8%

NNT to harm = 100.

Conclusion: Benefits from combined OAC + aspirin in reducing thromboembolic events are questionable. There is an increased risk of major bleeding.

I believe primary care clinicians should be very wary of prescribing combined therapy.

Should Not Be Greater Than 75 or 81 Mg/Day.

5-5 ASPIRIN DOSE FOR THE PREVENTION OF CARDIOVASCULAR DISEASE

This systematic review analyzed 11 studies of aspirin therapy for CVD.

A. Therapy requiring an immediate effect (eg, acute myocardial infarction, TIA, stroke):

Aspirin taken orally is rapidly absorbed. Peak plasma levels are achieved rapidly (30 minutes).

A wide range of aspirin doses, preparations, and methods of ingestion have been evaluated to achieve maximal antiplatelet activity. Absorption and onset of antiplatelet activity are shortened by chewing the tablet or drinking a solution (eg, *Alka-Seltzer*). Maximum inhibition of thromboxane production is achieved in 20 to 30 minutes compared with swallowing a whole aspirin tablet (60 minutes). To rapidly achieve maximal antiplatelet activity of aspirin at least 163 mg should be chewed or dissolved and then swallowed.

B. Long-term therapy:

Aspirin irreversibly inactivates platelet COX-1. De-novo synthesis of new COX-1 by platelets

is minimal. The long-term effects of aspirin on platelets are cumulative.

Once complete inactivation of platelet COX-1 is achieved, minimal doses of aspirin are required to ensure adequate acetylation of COX-1 and inactivation of thromboxane production. New platelets containing the normal amounts of COX-1 are formed at a rate of 10% daily. As little as 30 mg of aspirin daily is required to completely inhibit thromboxane production in healthy individuals. In patients with chronic stable angina, thromboxane synthesis is chronically elevated and 50 mg of aspirin daily may be needed.

A number of trials and meta-analyses have evaluated the optimal aspirin dose in various clinical settings. “The one nearly constant finding among all of these studies has been the lack of a relationship between increasing aspirin dosage and improved efficacy. In fact, the trend in benefit has almost uniformly favored lower dosages.”

The 11 trials reviewed by this study included nearly 10 000 patients with atherosclerotic disease receiving doses of 30 to 1300 mg per day). A significant benefit of higher doses was not demonstrated in any trial. In most trials, the lowest event rates were realized among patients randomized to the low-dose groups.

The major risk of aspirin (as with other NSAIDs) is bleeding—the majority from the g.i. tract. Although this increase is more commonly attributed to non-aspirin NSAIDs, a recent evaluation of patients hospitalized for ulcer bleeding found that aspirin was responsible for as much ulcer bleeding as all other NSAIDs combined. Low-dose aspirin was one of the most common causal agents.

Aspirin inhibits COX-1 in the gastric mucosa (as well as in platelets) and decreases the production of prostaglandins which protect the gastric mucosa. The influence of aspirin on gastric prostaglandins is dose-dependent. Almost 50% inhibition occurs at 30 mg / day—maximal inhibition at 1300 mg / day. “All conventional doses of aspirin are associated with increased bleeding risk.” But, a relationship between higher aspirin dose and increased risk of bleeding has been demonstrated in clinical trials. A UK trial found almost double the risk among patients randomized to 1200 mg/day compared with 300 mg/day. A Dutch trial found a trend toward less bleeding in the group receiving 30 mg/day compared with 283 mg/day. However, not all pooled study analyses have come to the same conclusion.

Considering that 50 million Americans are taking daily aspirin, if there is a difference in risk of major g.i. bleeding between 30 mg and 325 mg, then the larger dose would lead to an excess of 900 000 major bleeding events per year.

An association between increases in aspirin dose and adverse effects has been confirmed. No such dose relationship has been identified for efficacy.

Conclusion: Currently available clinical data do not support the routine, long term use of aspirin dosages greater than 75 to 81 mg/d in the setting of cardiovascular disease prevention. Higher doses are associated with increased risks of gastrointestinal bleeding.

ATHEROSCLEROSIS

Is Drug Therapy Appropriate For Primary Prevention In Individuals At Low-Risk?

3-5 PRIMARY PREVENTION OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

This article raises a number of fundamental questions for the medical and public health communities. Are medical (drug) strategies appropriate for primary prevention in *low-risk individuals*? If preventive strategies are limited to high-risk individuals, the overall population effect on incidence of clinical disease will be relatively minor. A major, yet highly underappreciated problem with the high-risk strategy is that it has a relatively minor effect on overall population incidence of disease. “Low risk” does not mean “no risk”. Most of the public burden of disease can be attributed to low-risk individuals with relatively “normal” levels of cholesterol and blood pressure.

Epidemiological data have provided overwhelming evidence that low-risk populations are the source of most clinical disease. This is particularly true for complex, multifactorial diseases such as atherosclerosis, for which continuous variables (including BP and lipids) conspire to increase risk across a wide spectrum of the population. Some have proposed that the low-risk population would be best served by population-based strategies outside the realm of traditional medical testing and therapy. This raises the question: might a medical (drug) strategy be routinely applicable to the low-risk population?

The author defines “low risk” based on the Framingham Risk Score. “Low risk” can be defined many different ways. Definition seems to be in the eye of the beholder.

A tremendous public health burden of clinical atherosclerosis arises from the population of low-risk individuals. Should we apply universal drug therapy to the low risk population?

Consider a non-smoking, physically active 21-year-old with no family history of cardiovascular disease or diabetes, and a BMI of 22, a BP of 115/70, a fasting blood glucose of 70, a LDL-cholesterol of 69, a HDL-cholesterol of 62, and abdominal girth of 30 inches.

Risks are continuous. All persons (no exceptions) over age 50 will be at a higher risk for atherosclerotic disease relative to this 21-year-old. Individuals with levels of risk factors below the arbitrarily set “acceptable” levels will benefit when the risk is lowered toward these baseline levels.

Our classical approach to drug therapy for primary cardiovascular risk prevention is to test first, then treat if the test levels are above the arbitrarily set “acceptable” levels, and then follow-up indefinitely. This limits prevention to a relatively few individuals who are motivated, have access to continuing medical care, and can afford it.

If the risk of disease is universal, should not everyone receive treatment to retard progression as much as possible? We do this now by universal applications of lifestyle interventions. The problem is that lifestyle interventions rarely achieve adequate reductions in risk factors.

A new approach to primary prevention of the epidemic of cardiovascular disease is to prescribe drugs to all persons above a certain age without testing and without follow-up—similar to immunization of the entire population against influenza. We do not determine if individuals are at “high risk” or “low risk” for flu. We immunize everyone.

The purpose is to do much more good than harm to society as a whole, with a low cost. This is, of course, contrary to our classical teaching and practice.

As I was abstracting this article, I kept thinking about the “polypill” (statin drug, aspirin, thiazide diuretic, folic acid, and ACE inhibitor all combined at low dose in one pill). It has been proposed that if all persons over age 50 would take the pill, the prevalence of atherosclerotic disease would decrease dramatically. This universal primary prevention would remove from the population the requirement for screening tests and follow-up. It would represent a sea-change in use of preventive therapy.

A commentary in NEJM January 18, 2007; 356: 212 by Srinath Reddy suggested a pill for general use in India. It consists of aspirin, ACE inhibitor, statin, and beta-blocker. The World Heart Federation announced that it would support the development of such a pill.

A commentary in JAMA July 26, 2006; 296: 377-80 by Bridget M Kuehn, quotes Robert A Rizza, president of the American Diabetes Assn. He suggests a daily generic “polypill” for all patients with diabetes: metformin, aspirin, statin, and an ACE inhibitor. (This “polypill” would also be beneficial for preventive therapy for non-diabetic patients with impaired fasting glucose 110 to 125 mg/dL and impaired glucose tolerance 140 to 199 mg/dl 2 hours after an oral glucose load..)

Any such drug combinations must be at very low cost and be associated with very low risk of adverse effects.

I believe it likely that more individuals will be taking primary preventive drug therapy in the future

BACK PAIN

“Overtreatment Is Often The Major Danger For These Patients.”

3-9 LOW BACK PAIN: Clinical Update

This article summarizes the basic principles of management and outcome assessment for back pain on which evidence-based daily practice can be based. I included only the points regarding acute back pain (< 6 weeks duration) because primary care clinicians will deal especially with this. See the original article for comments on sub-acute and chronic back pain.

Eleven clinical points. See the full abstract

BACK SURGERY

Prognosis Is Better With Ruptured Disk Than With Spinal Stenosis.

5-8 BACK SURGERY—WHO NEEDS IT?

Two studies in this issue of NEJM help define the type of patients who may benefit from surgery.

The first study randomized patients with severe sciatica due to herniated disks. None had resolution of pain within 6 to 12 weeks of conservative treatment. Patients were randomized to 1) early discectomy, or 2) continued non-surgical therapy, or delayed surgery.

Reserving surgery for patients whose pain did not sufficiently improve for 6 to 12 weeks of non-surgical treatment is important because, even without surgery, sciatica improves within 3 months in 75% of patients.

Even among patients with persistent sciatica, recovery was likely whether or not surgery was performed. Most herniated disks shrink over time. But surgery accelerates the pace of recovery, and for some patients faster recovery may be worth the risks.

After a year, however, recovery was about the same with non-surgery as with surgery (95% in both groups), although almost 40% of patients initially assigned to the non-surgical group crossed-over to surgery.

The second study addressed degenerative spondylolisthesis with associated spinal stenosis. This condition causes both back and leg pain. The study was randomized, but there were so many unintended crossovers from the non-surgical group to the surgical group that the authors highlighted their analysis according to treatment received rather than intention-to-treat, essentially creating a single large cohort study. (*Indicating that many patients perceived a high degree of pain and disability.*)

About 95% of surgical patients underwent a spinal fusion procedure. Thus, the study was essentially a trial of fusion for spondylolisthesis. Fusion surgery is more invasive than discectomy, with higher complication rates.

The study reported that surgery offered a significant advantage over non-surgical therapy. “The study further solidifies the basis of performing spinal fusion in patients with persistent leg pain, spondylolisthesis, and associated spinal stenosis.”

At 2 years, treatment outcomes were determined in 511 patients. In all outcomes, including improvement in pain and functioning, surgery was superior to non-surgical care.

Patients’ ratings surgery vs no-surgery:

Very or somewhat satisfied with symptoms 69% vs 32%

Self-rated major improvement 74% vs 24%

Although surgery often relieved symptoms, many were not satisfied with the results of their surgery. Prognosis is not as good as with ruptured disks.

BREAST CANCER

“No Simple Recommendation Applies To All Women In Their 40s”

4-7 BREAST CANCER SCREENING FOR WOMEN IN THEIR 40s: Moving from Controversy about Data to Helping Individual Women

Women in the USA now generally expect that screening should begin at age 40.

For every 10 000 women screened regularly starting at age 40, 6 might benefit through decreased risk of death due to BC. This modest benefit requires multiple screening examinations and follow-up for all 10 000 for more than a decade. Thus, 9994 women receive no mortality benefit because most women will not develop BC, and some will have cancer detected too late for a cure.

What are the potential harms of screening? False positive results are more common in younger women.

Among those starting screening at age 40, about half might receive at least one false positive result over a decade of annual screening. Further diagnostic procedures follow, with about 2000 women eventually undergoing a biopsy. Anxiety is increased. Costs are considerable.

“In the field of breast cancer screening, the actual practice of evidence-based medicine becomes deeply entangled with social, political, and economic forces.”

Failure or delay in BC diagnosis has been the most common issue in medical malpractice claims against physicians.

“In the face of continuing controversy about evidence, our priority now should be to help women make informed decisions.” “No simple recommendation applies to all women in their 40s. We must learn to become comfortable with using the art of medicine to translate the existing science. We must listen carefully to our patient and communicate honestly the benefits and limitations of our imperfect tests.”

CALORIE RESTRICTION

Does Calorie Restriction Have Benefits Above And Beyond The Effect In Lowering Incidence Of Chronic Diseases?

3-6 AGING, ADIPOSITY AND CALORIE RESTRICTION

Maximum life span, defined as the average life span of the longest-lived decile of a cohort, is often used as a standard for evaluating the aging process.

Life expectancy, defined as the age at which 50% of the population survives after birth, has markedly increased in most developed countries. (From about 45 years in the early 1900s to about 75 years in men and 80 years in women today.) This increase is due primarily to improved sanitation, better hygiene, reduced infant mortality, development of antibiotics and vaccines, and better health care.

Recently, there has been increasing interest in the potential therapeutic use of calorie restriction to obtain optimal health and increase life span in humans. Calorie restriction, defined as a reduction in calorie intake below usual ad libitum intake, (while maintaining adequate nutrition) has been shown to increase maximum life span in many animal species. In laboratory rodents, calorie restriction increases longevity by preventing or delaying onset of chronic diseases (diabetes, atherosclerosis, cardiomyopathy, autoimmune diseases, respiratory diseases, and cancer).

The reduction in chronic diseases does not completely explain the increase in lifespan, and the preservation of function at more youthful levels, which occurs in the calorie-restricted rodents. About 1/3 of such rodents die without evidence of organ pathology. “These data support the notion that the common link between aging and chronic disease is not inevitable, and that it is possible to live longer without experiencing a cumulative increase in serious morbidity and disability.”

Data suggest that the effects of calorie restriction on maximum life span are not simply a result of leanness induced by such restriction. Maximum life span does not increase in male rats that maintain a low body fat mass by performing regular exercise. It does increase in sedentary male rats that are food restricted to keep their body weights the same as those of the exercisers.

Conclusion:

- 1) Calorie restriction is an important determinant of health.
- 2) Excessive energy intake is a form of malnutrition that leads to unfavorable body composition, organ dysfunction, and premature mortality.
- 3) The precise caloric intake needed for optimal health and function likely varies for each individual depending on genetic background, age, energy expenditure, and diet composition.
- 4) The optimal calorie intake needed to slow the aging process is not known. The available data support the notion that calorie restriction in humans leads to many of the same metabolic adaptations and reductions in multiple chronic disease risk factors that occur in calorie-restricted animal models, even when restriction is started in midlife.
- 5) Even if calorie restriction does not prolong maximum life span, it could increase life expectancy and the quality of life by reducing the burden of chronic diseases.

I enjoyed this article. I abstracted it in detail because it presents one of the most important health considerations in a somewhat different way. It suggests that properly restricting quantity while maintaining quality of food intake is essential for maintaining health. And that properly restricting quantity per se has a beneficial effect in addition to its effects in controlling body mass index and incidence of chronic disease.

“Calorie restriction” may be a misnomer. “Optimum calorie intake” may be a better term. It is obvious that Americans eat too much. We have the habit of eating to the point of satiety (where ingestion of more food would cause discomfort). A better approach is to save room for dessert, and then skip the dessert.

Ad libitum caloric intake usually means excessive intake, not only intake of the wrong kinds of food, but also the quantity. “Eat yourself to death, Joe”. “If you keep on overloading your truck, it will break down sooner.” “Eat less than you would like to”. If only it were not so difficult long-term.

Animals on an ad libitum diet also eat too much. “Fat cat.”

CARDIAC ARREST

Cardiac-Only Resuscitation By Bystanders Is The Preferable Approach

3-3 CARDIAC ARREST—GUIDELINE CHANGES

Cardiopulmonary resuscitation (**CPR**) is traditionally defined as chest compression and ventilation. The need for chest compression is unquestionable. The need or advisability of intermittent ventilation for out-of-hospital, non-respiratory, primary cardiac arrest has become controversial.

Eliminating the need for mouth-to-mouth ventilation (**M-T-M-V**) will dramatically increase the occurrence of bystander-initiated resuscitation efforts and will increase survival.

An article in this issue of Lancet¹ provides evidence that chest compression without ventilation is preferable.

M-T-M-V is detrimental:

- 1) It greatly decreases bystander-initiated resuscitation.

- 2) Survival is better in individuals with cardiac arrest who receive chest compression only, than in those in whom no rescue efforts are started until arrival of emergency personnel.
- 3) M-T-M-V by single bystanders requires inordinately long interruptions of essential chest compression. Time spent on M-T-M-V takes precious time away from chest compressions that support cerebral and coronary perfusion.
- 4) M-T-M-V increases intrathoracic pressures, thereby reducing venous return to the chest. This reduces the already marginal coronary and cerebral blood flow.

A major flaw with the current, and all previous guidelines for cardiac arrest, is that they recommend the same approach of resuscitation for two entirely different clinical conditions: primary cardiac arrest, and respiratory arrest (such as drowning and drug overdose). In the first, arterial blood is well oxygenated; in the latter, the arterial blood is so severely desaturated that it contributes to secondary cardiac arrest. We should continue the old guidelines for assisted ventilations and chest-compressions for respiratory arrest.

The guidelines should promptly be changed to chest compression-alone for witnessed unexpected sudden collapse which is in all probability cardiac arrest.

Conclusion: Cardiac-only resuscitation by bystanders is the preferable approach to resuscitation for adult patients with witnessed out-of-hospital cardiac arrest, especially those with apnea², or short periods of untreated arrest.

1 Lancet March 17, 2007; 369: 920-26 “Cardiopulmonary Resuscitation by Bystanders with Chest Compression Only”
This was an observational study of over 4000 out-of-hospital cardiac arrests witnessed in Japan:

Overall, any resuscitation attempt was associated with a higher proportion having favorable neurological outcomes than no attempted resuscitation (6.2% vs 2.2%)

In the subset of patients with a shockable rhythm, cardiac-only resuscitation resulted in a favorable outcome in 19.4% vs 11.2% in those receiving M-T-M-V plus chest compression.

Resuscitation started within 4 minutes: favorable outcome in 10.1% for cardiac-only resuscitation vs 5.1% receiving M-T-M-V plus chest compression.

There was no evidence of any benefit from the addition of M-T-M-V in any subgroup.

2 90% of subjects were apneic.

CARDIAC RESYNCHRONIZATION THERAPY

Moderate Effectiveness In Clinical Practice

6-9 CARDIAC RESYNCHRONIZATION THERAPY FOR PATIENTS WITH LEFT VENTRICULAR SYSTOLIC DYSFUNCTION: A Systematic Review

Despite many advances, for many patients with heart failure (**HF**), morbidity and mortality remains high, and quality-of-life is poor. “Thus, there is increasing enthusiasm for the therapeutic potential of atrial-synchronized biventricular pacemakers (cardiac resynchronization therapy; **CRT**) in patients with heart failure and left ventricular (**LV**) systolic dysfunction.”

About 1% to 3% of all patients discharged alive after their initial hospitalization for HF meet CRT trial criteria:

LVEF < 35%

QRS > 120 milliseconds

Sinus rhythm

NYHA class 3 or 4 despite optimal medical therapy

This review summarizes the current evidence regarding the efficacy (outcomes in randomized trials) and effectiveness (outcomes in clinical settings), and safety of CRT in patients with LV systolic dysfunction.

In randomized, controlled trials, 59% of CRT recipients improved at least one NYHA class vs 37% of controls.

Compared with controls, left ventricular ejection fraction increased by 3%; 6-minute walk test distance increased by 24 meters; and quality-of-life increased by 8 points on a living with heart failure questionnaire. Hospitalizations for HF were less frequent in the CRT subjects (19% vs 27%). All cause mortality 13% vs 15%.

. Safety: Implantation success = 93%; peri-implantation mechanical complications 4%; peri-implantation deaths 0.3%; 5% malfunctioned within 6 months; 2% hospitalized for infections in the implant site; lead problems in 7%.

Conclusion: CRT is efficacious in clinical practice, and is cost-effective therapy for patients with class 3 or 4 HF (despite optimal medical management), and a LVEF less than 35%, sinus rhythm, ventricular dyssynchrony (currently identified by a prolonged QRS duration).

Primary care clinicians should know about this intervention, and be able to inform suitable patients about its availability. Some patients may be interested. To me, the increase in quality of life would be the most attractive outcome.

But, take care in referral! The track record of the reference cardiology group must be known. I would not rely on this report to judge adverse effects.

CARDIOVASCULAR DISEASE

Benefits of Combined Therapy Are Questionable. There Is An Increased Risk Of Major Bleeding.

1-12 COMBINED ASPIRIN-ORAL ANTICOAGULANT THERAPY COMPARED WITH ORAL ANTICOAGULANT THERAPY ALONE AMONG PATIENTS AT RISK FOR CARDIOVASCULAR DISEASE

Combination therapy [CT]—oral anticoagulants [OAC] + low-dose aspirin—is recommended by the American College of Chest Physicians *only* for patients with a mechanical prosthetic heart valve. Despite this recommendation, a considerable number of patients with chronic atrial fibrillation (AF) receive combined therapy.

Despite a lack of evidence for the efficacy of CT, some experts have suggested that adding aspirin to OAC therapy might be useful because patients using OAC frequently have concomitant coronary artery disease, or are at high risk for stroke.

This systematic review and meta-analysis of randomized controlled trials (RCTs) compared OAC-alone with OAC + aspirin to assess benefits and risks.

Risk of arterial thromboembolism was lower in the OAC + aspirin groups, but *only* in studies of mechanical valves. (Odds ratio OAC + aspirin vs OAC alone = 0.27)

There was no difference in outcomes (OAC + aspirin vs OAC-alone) in risk of arterial thromboembolism

in patients with atrial fibrillation or coronary disease.

The risk of major bleeding was higher in patients receiving combined therapy:

Combined therapy 3.8%

OAC-alone 2.8%

NNT to harm = 100.

Conclusion: Benefits from combined OAC + aspirin in reducing thromboembolic events are questionable. There is an increased risk of major bleeding.

I believe primary care clinicians should be very wary of prescribing combined therapy.

Is Drug Therapy Appropriate For Primary Prevention In Individuals At Low-Risk?

3-5 PRIMARY PREVENTION OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

This article raises a number of fundamental questions for the medical and public health communities. Are medical (drug) strategies appropriate for primary prevention in *low-risk individuals*? If preventive strategies are limited to high-risk individuals, the overall population effect on incidence of clinical disease will be relatively minor. A major, yet highly underappreciated problem with the high-risk strategy is that it has a relatively minor effect on overall population incidence of disease. “Low risk” does not mean “no risk”. Most of the public burden of disease can be attributed to low-risk individuals with relatively “normal” levels of cholesterol and blood pressure.

Epidemiological data have provided overwhelming evidence that low-risk populations are the source of most clinical disease. This is particularly true for complex, multifactorial diseases such as atherosclerosis, for which continuous variables (including BP and lipids) conspire to increase risk across a wide spectrum of the population. Some have proposed that the low-risk population would be best served by population-based strategies outside the realm of traditional medical testing and therapy. This raises the question: might a medical (drug) strategy be routinely applicable to the low-risk population?

The author defines “low risk” based on the Framingham Risk Score. “Low risk” can be defined many different ways. Definition seems to be in the eye of the beholder.

A tremendous public health burden of clinical atherosclerosis arises from the population of low-risk individuals. Should we apply universal drug therapy to the low risk population?

Consider a non-smoking, physically active 21-year-old with no family history of cardiovascular disease or diabetes, and a BMI of 22, a BP of 115/70, a fasting blood glucose of 70, a LDL-cholesterol of 69, a HDL-cholesterol of 62, and abdominal girth of 30 inches.

Risks are continuous. All persons (no exceptions) over age 50 will be at a higher risk for atherosclerotic disease relative to this 21-year-old. Individuals with levels of risk factors below the arbitrarily set “acceptable” levels will benefit when the risk is lowered toward these baseline levels.

Our classical approach to drug therapy for primary cardiovascular risk prevention is to test first, then treat if the test levels are above the arbitrarily set “acceptable” levels, and then follow-up indefinitely. This limits prevention to a relatively few individuals who are motivated, have access to continuing medical care, and can afford it.

If the risk of disease is universal, should not everyone receive treatment to retard progression as much as possible? We do this now by universal applications of lifestyle interventions. The problem is that lifestyle interventions rarely achieve adequate reductions in risk factors.

A new approach to primary prevention of the epidemic of cardiovascular disease is to prescribe drugs to all persons above a certain age without testing and without follow-up—similar to immunization of the entire population against influenza. We do not determine if individuals are at “high risk” or “low risk” for flu. We immunize everyone.

The purpose is to do much more good than harm to society as a whole, with a low cost. This is, of course, contrary to our classical teaching and practice.

As I was abstracting this article, I kept thinking about the “polypill” (statin drug, aspirin, thiazide diuretic, folic acid, and ACE inhibitor all combined at low dose in one pill). It has been proposed that if all persons over age 50 would take the pill, the prevalence of atherosclerotic disease would decrease dramatically. This universal primary prevention would remove from the population the requirement for screening tests and follow-up. It would represent a sea-change in use of preventive therapy.

A commentary in NEJM January 18, 2007; 356: 212 by Srinath Reddy suggested a pill for general use in India. It consists of aspirin, ACE inhibitor, statin, and beta-blocker. The World Heart Federation announced that it would support the development of such a pill.

A commentary in JAMA July 26, 2006; 296: 377-80 by Bridget M Kuehn, quotes Robert A Rizza, president of the American Diabetes Assn. He suggests a daily generic “polypill” for all patients with diabetes: metformin, aspirin, statin, and an ACE inhibitor. (This “polypill” would also be beneficial for preventive therapy for non-diabetic patients with impaired fasting glucose 110 to 125 mg/dL and impaired glucose tolerance 140 to 199 mg/dl 2 hours after an oral glucose load..)

Any such drug combinations must be at very low cost and be associated with very low risk of adverse effects.

I believe it likely that more individuals will be taking primary preventive drug therapy in the future.

Hormones Remain A Reasonable Option For The Short-Term Treatment Of Menopausal Symptoms.

4-4 POSTMENOPAUSAL HORMONE THERAPY AND RISK OF CARDIOVASCULAR DISEASE BY AGE AND YEARS SINCE MENOPAUSE

This study (a secondary analysis) explored whether the effects of hormone therapy on risk of cardiovascular disease (CVD) vary by age or years since menopause.

The WHI trials enrolled over 27 000 predominantly healthy postmenopausal women aged 50 to 79.

Over 10 000 had undergone hysterectomy and received conjugated equine estrogen-alone (0.625 CEE-alone) vs placebo.

Over 16 000 received CEE + medroxyprogesterone (CEE 0.625 mg + MPA 2.5 mg) vs placebo.

CEE-alone

No indication that it is a risk factor for CHD up to 20 years after menopause. Risk increases at age 70

Associated with increased risk of stroke at all ages.

CEE + MPA:

No indication that it is a risk factor for CHD up to 10 years after menopause. Risk increases after 10 years.

Associated with increased risk of stroke at all ages.

Conclusion: Women who initiated HRT closer to menopause tended to have reduced risk of CHD. Risk increased in women more distant from menopause. The risk of stroke was elevated regardless of years since menopause.

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The article did not list baseline risk factors. I would expect that women who developed HRT-associated cardiovascular events would be at higher risk if they had more risk factors at onset of menopause. (Eg, smoking, hypertension, dyslipidemia). Indeed, women without risk factors who take HRT would probably be at lower risk for events than women who do not take HRT, but have a number of risk factors.

I am sure the authors would recommend use of HRT at the lowest dose and for the shortest period.

Progesterone (not estrogen) seems to increase risks of CHD and breast cancer. Both are related to increased risk of stroke.

“Prevented More Cardiovascular Events than Supplementation of Conventional Treatments”

4-2 VALSARTAN IN A JAPANESE POPULATION WITH HYPERTENSION AND OTHER CARDIOVASCULAR DISEASE: The Jikei Heart Study

This study investigated whether addition of the angiotensin-II blocker, valsartan (*Diovan*; Novartis) to conventional cardiovascular treatment is effective in Japanese patients with cardiovascular disease.

The cardiovascular diseases in this study population—heart failure, hypertension, and coronary heart disease—are all disorders in which activation of the renin-angiotensin-aldosterone system is thought to play a major part.

Randomized, controlled trial entered over 3000 Japanese patients (mean age 65). All were undergoing conventional treatment for hypertension, CHD, HF, or a combination of these disorders.

Randomized to: 1) valsartan [40 to 160 mg daily], or 2) controls.

Controls were given either an increased dose of their existing treatment, or an additional conventional treatment, to achieve BP control aimed at 130/80. (Drugs at baseline, and continued during the trial, included calcium blockers, ACE inhibitors, beta-blockers, alpha-blockers, thiazides, statins, and fibrates. ACE inhibitors were given in about 1/3 of patients, and were continued in both groups.)

Primary outcome = composite of cardiovascular morbidity and mortality. Analysis by intention to treat. Follow-up for 3 years.

Mean BP for both groups at 3 years = 132/77

Effects on all endpoints (rate per 1000 patient-years):

	Valsartan	Control	NNT
Composite endpoint	21 (6.0%)	35 (9.7%)	27
Stroke or TIA	8	11	
Angina pectoris	4	12	
New HF or exacerbation	4	8	
Dissecting aneurysm	0.5	2.3	
All cause mortality	6.5	6.3	

Mortality, myocardial infarction, or progression of renal disease did not differ between groups.

Conclusion: The addition of valsartan to conventional treatment prevented more cardiovascular events than supplementation of conventional treatments. These results cannot be explained by a difference in BP control.

I believe that primary care clinicians should give ACE inhibitors and AT-II blockers (preferably the latter) the benefit of the doubt, and prescribe them more frequently. Their overall benefits (see the preceding abstract) exceed the benefits resulting from other BP-lowering drugs.

Should Not Be Greater Than 75 or 81 Mg/Day.

5-5 ASPIRIN DOSE FOR THE PREVENTION OF CARDIOVASCULAR DISEASE

This systematic review analyzed 11 studies of aspirin therapy for CVD.

A. Therapy requiring an immediate effect (eg, acute myocardial infarction, TIA, stroke):

Aspirin taken orally is rapidly absorbed. Peak plasma levels are achieved rapidly (30 minutes).

A wide range of aspirin doses, preparations, and methods of ingestion have been evaluated to achieve maximal antiplatelet activity. Absorption and onset of antiplatelet activity are shortened by chewing the tablet or drinking a solution (eg, *Alka-Seltzer*). Maximum inhibition of thromboxane production is achieved in 20 to 30 minutes compared with

swallowing a whole aspirin tablet (60 minutes). To rapidly achieve maximal antiplatelet activity of aspirin at least 163 mg should be chewed or dissolved and then swallowed.

B. Long-term therapy:

Aspirin irreversibly inactivates platelet COX-1. De-novo synthesis of new COX-1 by platelets is minimal. The long-term effects of aspirin on platelets are cumulative.

Once complete inactivation of platelet COX-1 is achieved, minimal doses of aspirin are required to ensure adequate acetylation of COX-1 and inactivation of thromboxane production. New platelets containing the normal amounts of COX-1 are formed at a rate of 10% daily. As little as 30 mg of aspirin daily is required to completely inhibit thromboxane production in healthy individuals. In patients with chronic stable angina, thromboxane synthesis is chronically elevated and 50 mg of aspirin daily may be needed.

A number of trials and meta-analyses have evaluated the optimal aspirin dose in various clinical settings.

“The one nearly constant finding among all of these studies has been the lack of a relationship between increasing aspirin dosage and improved efficacy. In fact, the trend in benefit has almost uniformly favored lower dosages.”

The 11 trials reviewed by this study included nearly 10 000 patients with atherosclerotic disease receiving doses of 30 to 1300 mg per day). A significant benefit of higher doses was not demonstrated in any trial. In most trials, the lowest event rates were realized among patients randomized to the low-dose groups.

The major risk of aspirin (as with other NSAIDs) is bleeding—the majority from the g.i. tract. Although this increase is more commonly attributed to non-aspirin NSAIDs, a recent evaluation of patients hospitalized for ulcer bleeding found that aspirin was responsible for as much ulcer bleeding as all other NSAIDs combined. Low-dose aspirin was one of the most common causal agents.

Aspirin inhibits COX-1 in the gastric mucosa (as well as in platelets) and decreases the production of prostaglandins which protect the gastric mucosa. The influence of aspirin on gastric prostaglandins is dose-dependent. Almost 50% inhibition occurs at 30 mg / day—maximal inhibition at 1300 mg / day. “All conventional doses of aspirin are associated with increased bleeding risk.” But, a relationship between higher aspirin dose and increased risk of bleeding has been demonstrated in clinical trials. A UK trial found almost double the risk among patients randomized to 1200 mg/day compared with 300 mg/day. A Dutch trial found a trend toward less bleeding in the group receiving 30 mg/day compared with 283 mg/day.

However, not all pooled study analyses have come to the same conclusion.

Considering that 50 million Americans are taking daily aspirin, if there is a difference in risk of major g.i. bleeding between 30 mg and 325 mg, then the larger dose would lead to an excess of 900 000 major bleeding events per year.

An association between increases in aspirin dose and adverse effects has been confirmed. No such dose relationship has been identified for efficacy.

Conclusion: Currently available clinical data do not support the routine, long term use of aspirin dosages greater than 75 to 81 mg/d in the setting of cardiovascular disease prevention. Higher doses are associated with increased risks of gastrointestinal bleeding.

CARDIOVASCULAR RISK FACTORS

“Lifestyles: First And Foremost Eating Patterns From Preconception On.”

3-4 LOW RISK—And the “No More Than 50%” Myth/Dogma

Medical myths/dogmas die hard. New bodies of knowledge for prevention and control of cardiovascular disease have had to disprove and displace myths/dogmas held in the past.

In the 1950s:

Atherosclerosis is part of normal aging. Nothing can be done about it.

Cholesterol levels and blood pressure normally rise with age.

Normal blood pressure is 100 plus your age.

Normal cholesterol is as high as 300 mg/dL.

Most high blood pressure is essential hypertension, and of unknown cause.

Treatment of high blood pressure gets at a symptom and not at the underlying disease, and can do more harm than good by lowering blood flow to the brain and heart. Therapeutic nihilism and judicious neglect are right.

All these are now bygone notions, refuted by massive data. But, other longstanding myths/dogmas about the CVD epidemic persist. One long-standing myth/dogma—still bruited about—is contrary to scientific fact. The dogma persists that the established risk factors for CVD account for no more than 50% of CVD events, and many people who experience CVD events have no risk factors.

In 2005-06, the MrFIT intervention trial expanded the risk factors for atherosclerotic disease to consideration of 5 major factors: total cholesterol, systolic BP; diabetes; smoking; and body mass index.

Based on these factors, low risk was rare. Very few individuals were without all 5 factors:

Only 4% of middle-aged African American women

Only 9% of white American women

Only 3% of African American men

Only 6% of white American men

A key strategic challenge—and opportunity—for medical care and public health is to achieve a progressive increase in the proportion of the population at low risk. “The essence of this advance is progressive steady improvements in lifestyles, first and foremost eating patterns from preconception on.”

“The notion that these risk factors account for no more than 50% of CVD events is myth/dogma and is dead wrong.”

I abstracted this article as a prelude to the following. The definition of “low risk” of cardiovascular events varies, depending on the number and effect of the individual components. As the number of risk

components increases, the number of persons at “low risk” declines. No adults in our society are without some risk. How should we treat them?

“Best Proven Interventions to Reduce Target Organ Damage in Hypertension, Atherosclerosis, and Diabetes.”

4-1 RENIN-ANGIOTENSIN SYSTEM AND CARDIOVASCULAR RISK

The renin-angiotensin system (**RAS**) is a major regulatory system for cardiovascular and renal function. Angiotensin-converting enzyme inhibitors (and by extension, angiotensin-II blockers) have been described as having the broadest effect of any drug in cardiovascular medicine.

This review article begins with a brief description of the biology of the renin-angiotensin system.

It continues with consideration of the relation between RAS and:

- 1) Left ventricular hypertrophy
- 2) Atrial fibrillation
- 3) Stroke
- 4) Atherosclerosis
- 5) Type-2 diabetes.

“ARBs and ACE inhibitors are best proven interventions to reduce target organ damage in hypertension, atherosclerosis, and diabetes.”

Conclusion: Improvement in the patient’s cardiovascular risk by drugs which attenuate activity of the renin-angiotensin system is not related to BP reduction alone. Risk-reduction includes many other non-hemodynamic effects.

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Read the full abstract.

I believe these ACE inhibitors and angiotensin II blockers have become major therapeutic interventions in primary care. Clinicians should become thoroughly familiar with their actions and benefits. And prescribe them more frequently.

There is much to lead primary care clinicians to choose angiotensin-II blockade (over ACE inhibition). ARBs are much better tolerated than ACE inhibitors. They are not associated with the annoying dry cough and angioedema produced by ACE-inhibitors

CELIAC DISEASE

“Most Cases Are Unrecognized”

5-7 COELIAC DISEASE IN PRIMARY CARE

Celiac disease (**CD**) is characterized by a life-long intolerance to certain proteins (known collectively as gluten) contained in wheat, rye, and barley. It is an unusual combination of food intolerance and auto-immunity. The resultant chronic inflammation of the proximal small intestine results in atrophy of villi, and abnormal intestinal permeability with impaired absorption of nutrients and increased secretion of solids.

CD affects about 1% of the general population. Most cases are unrecognized. Diagnosis is often delayed. “This is surprising, given how common the disease is, and how seriously its effects can be.” It may be because most patients with CD do not have typical symptoms of malabsorption. Even if these symptoms are present, their non-specific nature may not trigger diagnostic suspicion of the disease.

The gold standard for the diagnosis of CD is a positive duodenal biopsy.

In primary care, the American Gastroenterology Association recommends the use of antibody to transglutaminase as the single diagnostic serological test. But, positive results are not sufficient to diagnose CD. Biopsy is still essential, especially if the patient is to be placed on a life-long gluten-free diet.

A gluten-free diet corrects anemia, and restores normal nutritional and biochemical status. It substantially improves quality of life, particularly if troublesome gastrointestinal symptoms have been present.

This issue of BMJ reports a validated clinical prediction rule to determine all cases of celiac disease in people referred for gastroscopy.:

All received 1) test for antibody to transglutaminase, and 2) duodenal biopsy.

A. They classified patients as being at

- 1) “High risk” for CD. (N = 739 with diarrhea, weight loss, and/or anemia), or
- 2) “Low risk” (N = 1261. All other patients with indications for gastroscopy: abdominal pain; reflux; dyspepsia; nausea and vomiting, and chest pain. Ie, not suggestive of CD.)

B. Results:

1) High risk patients (n = 739)

Antibody to transglutaminase positive (n = 154; CD diagnosed by biopsy in 64 [40%])

Antibody to transglutaminase negative (n = 585 CD diagnosed by biopsy in 7 [1.2%])

2) Low risk patients (n = 1161)

Antibody to transglutaminase positive (n = 91; CD diagnosed by biopsy in 6 [7%])

Antibody to transglutaminase negative (n = 1170; CD diagnosed by biopsy in none [0%])

. The investigators developed a prediction rule:

All patients with a clinically “high risk” should be biopsied.

All patients with a positive antibody to transglutaminase should be biopsied.

Patients at “low risk” of CD, and a negative antibody test do not require biopsy.

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CD is a mimic. Primary care clinicians should put it on top of their “Am I missing something” list. Diagnosis may prevent years of disability and even death.

Some primary care clinicians may wish to recommend a gluten-free diet for a few weeks as a therapeutic test.

CHOLESTEROL

“Unlikely To Produce Lipid Benefits.”

2-12 EFFECT OF RAW GARLIC VS COMMERCIAL GARLIC SUPPLEMENTS ON PLASMA LIPID CONCENTRATING IN ADULTS WITH MODERATE HYPERCHOLESTEROLEMIA

This study compared the effects of raw garlic, and 2 garlic supplements with distinctly different formulations on the plasma lipid concentrations in adults with moderate hyper-cholesterolemia..

Recruited and randomized 192 adults (age 30-65) from the community who had a fasting LDL-cholesterol concentration of 130 to 190 mg/dL (mean = 151), a triglyceride level under 250 mg/dL, and a body mass index of 19 to 30.

Provided garlic in 3 forms: 1) raw garlic, 2) *Garlicin*, and 3) *Kyloic-100*. *Garlicin* was selected to represent powdered garlic supplements. *Kyloic* was selected because it is one of the most popular brands. It is an aged powdered garlic supplement. 4) A placebo group was added.

The products were consumed 6 days a week for 6 months: raw garlic as a crushed average size clove; *Garlicin* and *Kyloic* given at 1 1/2 to 3 times the recommended dose.

There were no clinically or statistically significant effects of the 3 garlic forms on LDL-c.

Six month changes in LDL-c (means; mg/dL)

Raw garlic	+0.4
<i>Garlicin</i>	+3.2
<i>Kyloic</i>	+0.2
Placebo	-3.9

Conclusion: None of the forms of garlic tested, when given at an approximate dose of a 4-g garlic clove daily for 6 months, had significant effects on LDL-c.

It is difficult to prove a negative. Proponents of natural products can readily cite reasons why a trial does not disprove efficacy.

Garlic is widely advertised to lower cholesterol. I believe this property is now disproved. Such advertisements should not be allowed. As the editorialist states, there remains a possibility that garlic does reduce risk of cardiovascular disease for other reasons. Admittedly, LDL-c is an intermediate endpoint, but a good one.

It would take a large, long, and expensive randomized trial of garlic products, with the endpoint of cardiovascular disease incidence, to prove or disprove this point. I doubt if such a trial will be completed. Meanwhile garlic will likely continue to be widely used.

CONTROVERSIAL CLINICAL PRACTICES

The Doctor-Patient Relationship Should Retain The Moral Agency Of Both The Physician And The Patient

2-11 RELIGION, CONSCIENCE, AND CONTROVERSIAL CLINICAL PRACTICES

Should health professionals refuse to provide treatments to which they object on moral grounds?

Recent controversies regarding physicians and pharmacists who refuse to prescribe or dispense emergency and other contraceptives have sparked a debate about moral objections in providing some types of health care.

Most people believe that health professionals should *not* have to engage in medical practices about which they have moral qualms. On the other hand, most people also believe that patients should have access to legal treatments, even in situations in which their physicians are troubled about moral implications of those treatments.

Is it ethical for physicians to describe their objections to the patient? Should physicians have the right to refuse to discuss, provide, or refer patients for legal medical interventions to which they have religious or moral objections?

Historically, doctors and nurses have not been required to participate in abortions or suicide, even where those interventions are legally sanctioned.

This study aimed at understanding how physicians think about their ethical rights and obligations when conflicts emerge in clinical practice.

Conclusion: On moral grounds, many physicians refuse to provide some services which society considers legal, and do not consider themselves obligated to disclose information about, or to refer patients, for legal but morally controversial, medical procedures.

Read the entire abstract.

The message of this article extends far beyond the limited circumstances described. It extends to placing judgments on others under many circumstances. Many physicians and pharmacists apparently consider providing a service they consider immoral (or refusing to refer to another professional who will provide the service) a form of aiding and abetting immoral behavior. It is a form of imposition of one's belief on another.

When an authoritarian professional refuses to discuss alternatives, or to refer to another professional, patients (and especially teenagers) are placed at an overwhelming disadvantage. What if the clinician does not know, or will not disclose the name of another professional who will provide the service? What if the patient cannot, for economic or practical reasons, consult with a second provider?

The article suggests that patients who want information about, and access to, such procedures may need to inquire proactively to determine whether their physician would accommodate such requests. Is this practical?

I can imagine this scenario between patient and a professional:

Physician or pharmacist: "I can not provide this service to you."

Patient: "Why not, Dr. Jones?"

Physician: "I believe it is immoral".

Patient: "Do you believe it is a sin?"

Dr. Jones: "Yes, I do."

Patient: "Dr. Jones, are you a sinner?"

CORONARY HEART DISEASE

“May Reduce Coronary Mortality”

2-8 SIESTA IN HEALTHY ADULTS AND CORONARY MORTALITY IN THE GENERAL POPULATION

This study evaluated the association between siesta and CHD mortality in adults in Greece over a follow-up mean of 6 years. . No subject had a history of CHD, stroke, or cancer.

At baseline, all individuals were asked whether they took midday naps, the average duration, and the weekly frequency.

Categorized participants into:

Never taking naps

Systematic napping:

Occasional napping:

The association between naps and CHD mortality was stronger in working men

Adjusted CHD mortality ratios in men according to nap-taking and current working status:

Taking midday naps	Currently working (28 deaths)	Currently not working (57 deaths)
No	1.00	1.00
Occasional	0.36	0.86
Systematically	0.36	0.61
Occasional + systematic	0.36	0.64

“We interpret our findings as indicating that among healthy adults, siesta, possibly on account of stress-releasing consequences, may reduce coronary mortality.”

Conclusion: After controlling for potential confounders, siesta of apparently healthy individuals, particularly working men, was associated with lower CHD mortality.

This article gathered considerable interest by the lay press in the US.

The authors mention that the Mediterranean population has two benefits going: diet and siesta.

I was unable to calculate the absolute benefit of siesta in working men from the data presented. As there were only 28 deaths among 7300 subjects, the absolute benefit must have been very small.

“Estrogen Therapy May Have Cardioprotective Effects In Younger Women.”

6-2 ESTROGEN THERAPY AND CORONARY-ARTERY CALCIFICATION: The WHI-CACS Trial

This **WHI-CACS** study determined whether the coronary-artery calcium burden differed (after 7 years of therapy) among women age 50 to 59 at baseline who received estrogen-alone vs those who received placebo.

The study was restricted to women age 50-59 (mean = 55) at randomization. This is the most clinically relevant age group with regard to initiation of CEE for menopausal symptoms.

Between May and September 2005, 1079 women underwent CT examinations of the heart. At that time, subjects' mean age was 65 years. They had taken CEE or placebo for an average of 7 years.

Mean calcium score:	CEE (n = 547)	Placebo (n = 527)
	83	123

“Estrogen therapy may have cardioprotective effects in younger women.” But, estrogen has complex biological effects that may vary according to the underlying state of the vasculature. It is possible that estrogen could reduce coronary artery calcium scores but still increase the risk of clinical CHD events, owing to adverse effects on thrombosis and plaque rupture, which are more likely in older women.

Conclusion: Among women age 50-59 estrogen at baseline, estrogen-alone given for 7 years was associated with a lower coronary artery calcium burden than those who received placebo.

This should reassure women who have recently undergone menopause and need relief of symptoms. Coronary calcium is, of course, a surrogate outcome for coronary events. The investigators did not mention rate of clinical events. I presume there were few in this age group.

Women who had hysterectomy, and thus can take estrogen-alone for menopausal symptoms, are in the minority. The larger problem concerns those who require combined estrogen-progesterone. I believe combined E + P is associated with more adverse effects (stroke, breast cancer, and CHD events) than E-alone. Nevertheless, E + P is reasonably safe, and safer in younger postmenopausal women than in older women.

E-alone is not entirely safe. It is associated with increased risk of stroke and venous thromboembolism.

I believe that women who have no traditional risk factors and who take hormones at any time postmenopause are less likely to be at risk for adverse effects than women who have a number of traditional risk factors and do not take hormones.

Another study by the WHI “Effects of Conjugated Estrogens on Breast Cancer” JAMA April 12, 2006 (See Practical Pointers April 2006 [4-9] provides some reassurance about the risk of breast cancer in postmenopausal women taking estrogen-alone therapy. Over 10 000 women, the majority over age 60, were randomized to CEE or placebo and followed for 7 years. There was no increase in incidence of breast cancer in the CEE group. .

I believe progesterone is the main hormonal risk factor for breast cancer.

DEMENTIA

“Significantly Improved Domains Of Cognitive Function”

1-11 EFFECT OF 3-YEAR FOLIC ACID SUPPLEMENTATION ON COGNITIVE FUNCTION IN OLDER ADULTS: The FACIT Trial

Poor folate status is a suspected risk factor for age-related cognitive decline.

This trial considered the effect of folic acid supplementation on cognitive function in older adults in the Netherlands who had higher homocysteine levels. (A possible indicator of folic acid deficiency.)

On the assumption that a high concentration of plasma homocysteine is a risk factor for vascular disease, the trial selected subjects expected to benefit from folic acid's homocysteine-lowering effect. It excluded participants with normal plasma homocysteine concentrations (less than 13 umol/L; 73% of those screened)

Changes (mean) in cognitive performance over 3 years: (Z scores)

	Folic acid	Placebo
Global cognitive function	+ 0.067	-0.031
Memory	+0.480	+0.142
Information processing speed	-0.072	-0.159 (All statistically significant)

By the investigators calculation, the 3-year folic acid supplementation (mean age 60 to 63) conferred to an individual the performance of someone 4.7 years younger for memory, 2.1 years younger for information processing speed, and 1.5 years younger for global cognitive functioning.

Memory—specifically delayed memory—is the most clinically relevant test. Supplementation improved performance on the delayed recall sub-test of the 15 word-learning test by 0.47 words, similar to a performance of an individual 6.9 years younger.

“Given the general scarcity of positive findings from other trials . . . our results need to be confirmed by other investigators.”

Conclusion: In patients with raised serum homocysteine levels, 3-year folic acid supplementation improved performance on tests that measure information processing speed and memory domains that are known to decline with age.

The effect of folic acid on atherosclerosis has been controversial and continues to be hotly debated. Although doubt persists, there is provocative evidence that low folic acid levels (and high homocysteine levels) are related to increased risk of atherosclerotic disease—and now, cognitive function.

The benefit/harm-cost ratio of folic acid supplementation may be high in those with higher homocysteine levels. Although the benefit is still not established, the denominator of the ratio (harm and cost) is extremely low. Thus, the ratio may be high.

How should the primary care clinician act on this information about higher doses of folic acid?

I would not advise patients to purchase a separate supplement of 800 ug of folic acid. I would advise them that the folic acid content of the daily multivitamin supplement (usually containing 400 ug) they may be taking may be beneficial.

More effective, however, are the well-established means of retarding the atherosclerotic process, thus preventing the adverse effects of atherosclerosis on the brain (vascular dementia).

I congratulate the investigators on completion of a detailed and difficult study. They are understandably enthusiastic about the benefits of folic acid. However, they caution that confirmation is required. The study does not establish any clinically significant benefit in delaying onset of dementia.

DIASTOLIC HEART FAILURE

Diastolic Function Was Improved In Both Groups

6-1 EFFECT OF ANGIOTENSIN RECEPTOR BLOCKADE AND ANTIHYPERTENSIVE DRUGS ON DIASTOLIC FUNCTION IN PATIENTS WITH HYPERTENSION AND DIASTOLIC DYSFUNCTION:

Diastolic dysfunction is characterized by impaired ventricular relaxation and abnormalities of ventricular filling. It is an important pathophysiological intermediate between hypertension and heart failure (HF), especially HF with normal systolic ejection fraction.

This study aimed to determine whether lowering BP with an angiotensin II receptor blocker would improve diastolic function to a greater extent than would non-renin-angiotensin-aldosterone system (RAAS) pharmacological approaches.

Double-blind, randomized, placebo-controlled trial entered 384 patients mean age 61. All had a history of stage 1 or stage 2 hypertension. All had systolic ejection fractions over 50%.

Patients were randomized to: 1) Valsartan (*Diovan*; Novartis) 160 mg once daily titrated up to 320 mg once daily in addition to standard antihypertension therapy, or 2) Placebo in addition to standard antihypertension therapy (diuretics, beta-blockers, calcium blockers, and alpha blockers). The goal was to achieve a BP < 135/80 in both groups.

Determined the lateral mitral annular relaxation velocity by doppler echocardiography.

Patients were included in the study on the basis of velocities lower than age-specific cutoff values.

Outcomes (means)	Baseline		38 weeks	
	Valsartan	Placebo	Valsartan	Placebo
Systolic BP	144	141	131	135
Diastolic BP	86	87	79	82

Compared with baseline, increases in relaxation velocities were observed at 38 weeks in both groups. (But no significant difference between groups)

There were reductions from baseline to follow-up in isovolumetric relaxation time, ventricular wall thickness, left ventricular mass, left ventricular end-diastolic volume, left ventricular end-systolic volume, and left atrial volume; and an increase in ejection fraction in both groups.

Diastolic dysfunction represents a central abnormality in patients with HF. It is characterized by delayed relaxation, slowed and incomplete filling of the left ventricle, and decreased distensibility of the left ventricle. (An upward shift in the relation between end-diastolic pressure and left ventricular volume. A greater diastolic pressure is required to fill the left ventricle to the same volume.)

Conclusion: Lowering BP improved diastolic function irrespective of the type of anti-hypertension agent used.

It has long been appreciated that diastolic function is impaired in many patients with HF while systolic ejection fractions remain normal (over 50%). Diastolic function has been difficult to measure. Fortunately,

more precise measurements are becoming available. This study is an important addition to the pathophysiology of HF.

Diastolic dysfunction can occur at relatively low stages of hypertension and at a relatively young age. As we age, our ventricles become stiffer, especially if we have increases in BP, even modest increases. Note the baseline mean BP was 144/86. This degree of hypertension may not be treated in primary care practice, particularly in elderly patients. It is becoming evident that treating even this modest degree of hypertension will bring benefits. Treat BP early and vigorously, including stage 1 hypertension. This will reduce the incidence of HF.

These investigators tilt toward use of RAAS inhibition (an angiotensin II blocker in preference to an ACE inhibitor) in addition to other drugs as needed.

Deciding to treat modest elevations of BP in the elderly is more difficult than in younger patients. Adverse effects of anti-hypertension drugs are more frequent as kidney and liver function declines, and elimination of drugs is impaired. Adverse effects are more disturbing in older persons. Treat them gently and gradually. I believe even a modest decrease in BP will improve diastolic function.

DYSPEPSIA

H Pylori Is Likely To Cause About 9% Of Dyspepsia Cases Where No Ulcers Are Detected.

1-7 DYSPEPSIA AND HELICOBACTER PYLORI

Dyspepsia is not a diagnosis. It is a term used to describe a range of symptoms, from upper abdominal pain to heartburn, nausea, bloating, and retrosternal pain. It occurs in up to 40% of adults in the UK. A general practitioner will see on average 210 patients with dyspepsia each year.

Most dyspepsia is “functional”—ie, no abnormalities are found on endoscopy.

The Cochran review of initial management strategies for dyspepsia:

Proton pump inhibitors (**PPIs**) are more effective than histamine receptors and antacids.

Initial endoscopy is associated with a small reduction in risk of recurrent dyspepsia symptoms compared with test and treat. But, it is not cost-effective.

Test and treat for H pylori may be more effective than acid suppression alone.

Infection with H pylori is likely to cause about 9% of dyspepsia cases where no ulcers are detected.

You should urgently refer patients older than age 55 with dyspepsia of recent onset that is persistent (lasting 4 to 6 weeks), or unexplained (not related to NSAIDs) even in the absence of alarm symptoms.

Do not underestimate the risks associated with NSAIDs. About 10% to 20% of people who use these drugs regularly will develop peptic ulcer that is detectable with endoscopy. 1% develop perforation or bleeding. Offer protection with a PPI to those who require NSAIDs regularly.

Screening: “Would screening the general population for H pylori be cost effective?” Probably not.

Diagnosis: The urea breath test is the most accurate way to detect H pylori.

In dyspeptic patients positive for H pylori, eradication treatment has been reported to relieve symptoms in 3% to 14% of patients.

Which eradication treatment?

Seven day full dose PPI + either

- 1) Metronidazole 400 mg + clarithromycin 250 mg, or
- 2) Amoxicillin 1 g + clarithromycin 250 mg

No mention of the possible connection between H pylori and gastric cancer.

Read the full abstract. for details

E-MEDICINE

Communication Into One Manageable Channel.

6-7 COMMUNICATION BETWEEN PHYSICIANS AND PATIENTS IN THE ERA OF E-MEDICINE

Clinics are beginning to invite patients to use a secure Internet link to communicate with physicians and staff members. The field is evolving swiftly. Web messaging is an attempt to direct round-the-clock communication into one manageable channel.

E-medicine could comprise 4 major types of services: 1) online appointment scheduling, 2) electronic prescription refills, 3) general messaging capabilities, and 4) “Web visits” with physicians. General messages permit patients to ask simple questions, obviating many telephone calls. “Web visits” are structured consultations focused on non-urgent chief complaints involving menus of questions tailored to the problem, brief answers by the patient, and a response from the physician within a certain period.

E-medicine may also enable hospitals to improve transitions of care of patients.

The federal government has set out a National Information Technology plan with a goal of establishing electronic health records systems for most Americans by 2014.

What do doctors think? Many appreciate the asynchronous nature of Web messaging. Patients contact doctors at their convenience. Physicians respond when they have a moment. Most physicians find it much easier to respond to queries in this form than to return phone calls.

The emerging model will improve the practice of medicine, but will also bring new challenges.

“The ‘laying on of hands’ will increasingly include the ‘pressing of keys’.

Physician-patient communication has been at times a weak link in the relationship. Patients remain anxious waiting for a report of a biopsy or lab result. E-medicine may facilitate more timely reporting.

I would regret the loss of “laying on of hands”. Our world is becoming less personal. Machines are replacing the human voice. Is it your doctor responding, someone who does not know you, or even a machine?

But, I believe, ready or not, in the name of efficiency, the brave new world is coming. Get ready!

FITNESS

Modest Exercise For Little Over An Hour A Week Had A Training Effect.

5-9 EFFECTS OF DIFFERENT DOSES OF PHYSICAL ACTIVITY ON CARDIORESPIRATORY FITNESS AMONG SEDENTARY, OVERWEIGHT OR OBESE POSTMENOPAUSAL WOMEN WITH ELEVATED BLOOD PRESSURE

Cardiovascular disease is the primary cause of death in postmenopausal women (30% of these women report no physical activity at all). The presence of inactivity increases with age. Fitness declines at 1% to 2% per year during the postmenopausal years. Physiological changes associated with aging may decrease the body's ability to maintain or improve fitness.

This trial examined the effect of 50%, 100%, and 150% of the NIH physical activity recommendations on cardio-respiratory fitness in sedentary, overweight or obese, postmenopausal women with elevated BP.

Randomized, dose-response exercise trial entered 464 volunteer postmenopausal women (age 45 to 75; mean = 57). None had a history of cardiovascular disease or any other serious medical condition. All were sedentary (not exercising over 20 minutes on more than 3 days per week and taking less than 8000 steps/day assessed by pedometer). All were overweight or obese (mean BMI = 32); mean BP = 140/81.

Randomized to:

- 1) Non-exercise group asked to maintain their usual daily activity.
- 2) Exercise groups:
 - 4 kcal/kg/wk. (50% of recommended exercise level)
 - 8 kcal/kg/wk. (100% of recommended exercise level)
 - 12 kcal/kg/wk. (150% of the recommended exercise level)

All exercise groups continued to participate in the laboratory supervised exercise sessions 3 or 4 times a week for 6 months. All participants continued their usual activities (except for the training periods) during the week.

Mean minutes of exercise per week: 4 kcal/kg/week = 72; 8 kcal/kg/week = 139; 12 kcal/kg/week = 192.

At 6 months, the exercise groups increased their absolute VO₂ compared with the no-exercise group: 4 kcal/kg/week +4.2%; 8 kcal/kg/week +6.0%; 12 kcal/kg/week +8.2% (a training effect).

The primary finding of the trial: A controlled exercise program in postmenopausal women resulted in a dose-response increase in fitness. Women who exercised 3 or 4 times a week increased their fitness in proportion to the amount of energy expended during the exercise sessions.

“Perhaps the most striking finding of our study is that even activity at the 4-kcal/kg/week level (approximately 72 minutes pre week) was associated with a significant improvement in fitness compared with women in the non-exercise group.”

Conclusion: Previously sedentary, overweight, or obese postmenopausal women experienced a graded dose-response in fitness across levels of exercise training. Even modest exercise for little over an hour a week had a training effect.

FOLIC ACID

“Significantly Improved Domains Of Cognitive Function”

1-11 EFFECT OF 3-YEAR FOLIC ACID SUPPLEMENTATION ON COGNITIVE FUNCTION IN OLDER ADULTS: The FACIT Trial

Poor folate status is a suspected risk factor for age-related cognitive decline.

This trial considered the effect of folic acid supplementation on cognitive function in older adults in the Netherlands who had higher homocysteine levels. (A possible indicator of folic acid deficiency.)

On the assumption that a high concentration of plasma homocysteine is a risk factor for vascular disease, the trial selected subjects expected to benefit from folic acid’s homocysteine-lowering effect. It excluded participants with normal plasma homocysteine concentrations (less than 13 umol/L; 73% of those screened)

Changes (mean) in cognitive performance over 3 years: (Z scores)

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The benefit/harm-cost ratio of folic acid supplementation may be high in those with higher homocysteine levels. Although the benefit is still not established, the denominator of the ratio (harm and cost) is extremely low. Thus, the ratio may be high.

How should the primary care clinician act on this information about higher doses of folic acid? I would not advise patients to purchase a separate supplement of 800 ug of folic acid. I would advise them that the folic acid content of the daily multivitamin supplement (usually containing 400 ug) they may be taking may be beneficial.

More effective, however, are the well-established means of retarding the atherosclerotic process, thus preventing the adverse effects of atherosclerosis on the brain (vascular dementia).

I congratulate the investigators on completion of a detailed and difficult study. They are understandably enthusiastic about the benefits of folic acid. However, they caution that confirmation is required. The study does not establish any clinically significant benefit in delaying onset of dementia.

“Our Findings Remain To Be Confirmed.”

6-8 EFFICACY OF FOLIC ACID SUPPLEMENTATION IN STROKE PREVENTION: A meta-analysis

Initial epidemiological evidence supported the hypothesis linking elevated homocysteine levels with increased risk of coronary artery disease, stroke, and deep vein thrombosis; and that treatment with folic acid reduced risk.

Randomized trials have reported inconsistent results, and have not supported the hypothesis that lowering homocysteine reduces risks. Most of these trials have been conducted in patients with established cardiovascular disease. It is possible that folic acid supplementation could have a greater protective effect in primary rather than in secondary prevention; and that different cardiovascular endpoints could respond differently to folic acid.

This meta-analysis focused on stroke as the disease endpoint in relation to folic acid supplementation. Collected data from 8 randomized trials (over 16 500 individuals, most over age 60) of folic acid (with or without B6 and B12) supplementation vs placebo. All reported stroke as one of the endpoints. All trials included individuals with pre-existing cardiovascular or renal conditions.

Pooling results of all trials indicated a statistically significant reduced risk of stroke in the folic acid treatment groups. (Relative risk [RR] = 0.82; folic acid vs placebo). Longer-duration trials were associated with greater benefit in reducing stroke. Less than 36 months RR = 1.0; longer than 36 months RR = 0.71. In the one study of subjects with a history of stroke, the RR was 1.04 vs a RR of 0.75 in 7 studies of subjects without a history of stroke (but with other vascular diseases).

“Our meta-analysis provides coherent evidence that folic acid supplementation can significantly reduce the risk of stroke in primary prevention.”

There is continued controversy with regard to whether folic acid can lead to improved outcomes for other cardiovascular endpoints. Several randomized trials of folic acid supplementation have in general yielded negative results. However, different endpoints (eg stroke vs other cardiovascular endpoints) could respond differently.

“Our findings remain to be confirmed.”

Conclusion: “Our findings indicate that folic acid supplementation can effectively reduce the risk of stroke in primary prevention.”

The homocysteine-folic acid controversy seems to have 9-cat-lives.

This meta-analysis was not really an analysis of “primary” prevention. At baseline, all subjects had established atherosclerotic disease. In a truly “primary” prevention trial all subjects at baseline should be free of atherosclerotic disease.

It would take a long time and a large trial of folic acid supplementation vs placebo in subjects without any atherosclerotic vascular disease at baseline to determine any benefit.

This meta-analysis does not convince me. What would be the reason to consider that stroke (a vascular disease) differs from other vascular diseases?

How should primary care clinicians respond to the presently available information?

I believe it reasonable, since doubt remains, to offer supplementation. The benefit / harm-cost ratio of folic acid may be high because the harm-cost is so low.

GLYCEMIC-INDEX GLYCEMIC LOAD

“A Prudent Approach To The Prevention And Treatment Of Diabetes, Heart Disease, And Obesity.”

3-2 THE LOW-GLYCEMIC-INDEX DIET: A Clinical Update

Recently, the glycemic index (**GI**) has attracted considerable interest with the publication of research linking it to important health outcomes

The GI constitutes an empirical system for classifying carbohydrate-containing foods. It is determined by measuring the 2-hour incremental area-under-the-blood-glucose-curve after consuming a test food (containing 50 g available carbohydrate), relative to that of a control of either white bread or glucose.

A related term, the glycemic load (**GL**)—the average GI multiplied by the carbohydrate amount—takes into account differences in carbohydrate content among foods, meals, and diets.

A high-GI diet elicits a sequence of hormonal events that challenge glucose homeostasis:

- 1) Shortly after a high-GL meal, blood insulin rises higher than after a low-GL meal with similar nutrients.
- 2) A high-GL meal inhibits glucagon secretion.
- 3) The striking increase in the insulin/glucagon ratio constitutes a powerful anabolic stimulus, promoting uptake of nutrients into the liver, muscle, and fat tissue, and suppressing hepatic glucose output.
- 4) Within 60 minutes after a high GI meal, blood glucose begins to *fall*, often reaching levels below fasting; release of fatty acids from adipose tissue is suppressed. This stimulates hunger and overeating in the body’s attempt to restore concentrations of metabolic fuels to normal.
- 5) The early postprandial hyperglycemia and hyperinsulinemia and the late postprandial hypoglycemia and counter-regulatory hormone response could adversely affect body composition, and increase risk for diabetes, cardiovascular disease, and cancer.

Most studies report beneficial effects of a low GI-GL diet on health. Virtually no studies have found health benefits with a *high* GI-GL diet.

The low-GI diet, with its focus on carbohydrate *quality* rather than quantity aims to address an underlying physiological cause of diseases arising from excessive swings in post-prandial glycemia. Because this diet does not restrict either fat or carbohydrate, it may be more behaviorally sustainable.

“The clinician should consider a low-GI diet to be a prudent approach to the prevention and treatment of diabetes, heart disease, and obesity.”

Would eating 6 small meals a day provide similar benefits? Certainly, we should advise patients to avoid consuming large quantities of food at any meal.

See Practical Punters November 2006 [11-4] for a study reporting that high glycemic load diets increase risk of coronary heart disease.

I do believe that a low glycemic load diet is an important part of the healthy diet. Along with very low saturated fats, low salt, no trans fats, and balanced calorie consumption.

A Low-Glycemic Load Diet Promotes More Weight Loss In Patients With A High Insulin-Response To Glucose.

5-2 EFFECTS OF LOW-GLYCEMIC LOAD VS LOW-FAT DIET IN OBESE YOUNG ADULTS

Some individuals have a higher insulin response to glucose ingestion. They may be more likely to develop postprandial hypoglycemia.

This randomized trial enrolled 73 obese young adults (mostly female; age range 18-35; mean = 27) for 18 months. All had a BMI of 30 and above. Prior to randomization, a 75-g glucose tolerance test determined serum insulin levels at 30 minutes. The median serum insulin concentration at this time was 58 micro-IU/mL.

Subjects were randomized to: 1) Low-glycemic load diet: 40% of energy from carbohydrate (emphasizing low glycemic index foods); 35% from fat; and 25% from protein, or 2) Low-fat diet: 20% of energy from fat; 55% from carbohydrate; and 25% from protein. The diets were ad lib. No calorie counting or limitation on the quantity of food intake was involved. Intake was determined by the subjects' feeling of satiety.

Results at 18 months:

1) Subjects with baseline insulin concentrations greater than 58 micro-IU/mL:

Individuals on the low glycemic load diet lost 5.8 kg

Individuals on the low fat diet lost 1.2 kg

2) Subjects with baseline insulin concentrations below 58 micro-IU/mL.

Individuals on a low glycemic load diet lost about 2 kg

Individuals on a low fat diet also lost about 2 kg.

(I.e, insulin concentration was an effect moderator for weight loss.)

Conclusion: For obese individuals with high insulin concentrations after a glucose load, a low-glycemic diet may promote more weight loss than a low-fat diet.

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If you are a “high insulin responder” then changing your diet to a low glycemic load diet would lower the resultant post-prandial blood glucose elevation, and lower the insulin response. This would in turn result in the 2-hour post-meal blood glucose being higher than at baseline. Post-prandial hypoglycemia would be less likely to occur; hunger would not be as acute; and caloric intake would likely be less. Weight loss would be more likely to be greater than with a low fat, higher carbohydrate diet.

GONOCOCCAL INFECTIONS

“Gonococcus is an incredible bug because it adapts incredibly quickly.”

6-5 GONOCOCCAL INFECTIONS

Update from the CDC:

Fluoroquinolones no longer recommended

See the full abstract for the current CDC recommendations.

Lancet May 12, 2007; 369: 1592 “World Report”, by Michael McCarthy, Lancet Staff. comments:

“Gonococcus is an incredible bug because it adapts incredibly quickly.”

Cephalosporins now remain the last class of antibiotic for which important resistance has not been detected.

“Emergence of strains resistant to cephalosporins is only a matter of time.”

GREETINGS ON THE FIRST MEDICAL ENCOUNTER

“Can Set A Positive Tone”

6-10 AN EVIDENCE-BASED PERSPECTIVE ON GREETINGS IN MEDICAL ENCOUNTERS

The purpose of this study was to provide some guidance by defining patient-expectations for physician behavior during the greeting stage of the initial medical visit.

Conducted a cross-sectional random telephone survey of adults (ie, patients) in the US. (415 persons responded.) Asked closed-ended questions about their preferences for shaking hands, use of patients’ names, and use of physicians’ names, especially at the first meeting.

The majority of patients preferred the doctor to shake hands. A surprising number wished to be addressed by their first names. Most wanted the doctors to introduce themselves with their first and last names.

“While greetings may seem a rather mundane aspect of physician-patient communication, attention to this task can set a positive tone for the encounter, and increase the chances of developing a therapeutic clinical relationship.”

Conclusion: Physicians should be encouraged to shake hands, and initially use patient’s first and last names, and introduce themselves with their own first and last names.

This would seem a self-evident courtesy to someone as old as I am. The younger generation may differ. I know that some elders bristle when a young doctor calls them by their first name before they develop a closer relationship.

Although this may seem old-fashioned to some, I believe it common courtesy, when encountering another person (or when calling on the telephone) to first say “good morning”, “good afternoon”, or “good evening” before launching into the purpose or question of the encounter. This recognizes the individual first, and only secondarily as a source of information.

HEADACHE

2-2 HEADACHES: Master Classes for GPs

This is a straightforward and practical review.

It includes comments on migraine. medication overuse HA, cluster HA, dangerous HA, and temporal arteritis.

Also practical management tips and common pitfalls.

Some may find it useful to save as reference.

Read the full abstract.

HEART FAILURE

Moderate Effectiveness In Clinical Practice

6-9 CARDIAC RESYNCHRONIZATION THERAPY FOR PATIENTS WITH LEFT VENTRICULAR SYSTOLIC DYSFUNCTION: A Systematic Review

Despite many advances, for many patients with heart failure (**HF**), morbidity and mortality remains high, and quality-of-life is poor. “Thus, there is increasing enthusiasm for the therapeutic potential of atrial-synchronized biventricular pacemakers (cardiac resynchronization therapy; **CRT**) in patients with heart failure and left ventricular (**LV**) systolic dysfunction.”

About 1% to 3% of all patients discharged alive after their initial hospitalization for HF meet CRT trial criteria:

LVEF < 35%

QRS > 120 milliseconds

Sinus rhythm

NYHA class 3 or 4 despite optimal medical therapy

This review summarizes the current evidence regarding the efficacy (outcomes in randomized trials) and effectiveness (outcomes in clinical settings), and safety of CRT in patients with LV systolic dysfunction.

In randomized, controlled trials, 59% of CRT recipients improved at least one NYHA class vs 37% of controls.

Compared with controls, left ventricular ejection fraction increased by 3%; 6-minute walk test distance increased by 24 meters; and quality-of-life increased by 8 points on a living with heart failure questionnaire.

Hospitalizations for HF were less frequent in the CRT subjects (19% vs 27%). All cause mortality 13% vs 15%.

Safety: Implantation success = 93%; peri-implantation mechanical complications 4%; peri-implantation deaths 0.3%; 5% malfunctioned within 6 months; 2% hospitalized for infections in the implant site; lead problems in 7%.

Conclusion: CRT is efficacious in clinical practice, and is cost-effective therapy for patients with class 3 or 4 HF (despite optimal medical management), and a LVEF less than 35%, sinus rhythm, ventricular dyssynchrony (currently identified by a prolonged QRS duration).

Primary care clinicians should know about this intervention, and be able to inform suitable patients about its availability. Some patients may be interested. To me, the increase in quality of life would be the most attractive outcome.

But, take care in referral! The track record of the reference cardiology group must be known. I would not rely on this report to judge adverse effects.

HEPATITIS

“The Burden Of Hepatitis E Is Grossly Underestimated.” A New Vaccine May Be Effective

3-10 SAFETY AND EFFICACY OF A RECOMBINANT HEPATITIS E VACCINE: A Phase II Trial

Large outbreaks of hepatitis E were first recognized in the early 1980s. It is endemic in some areas of the world, transmitted by the fecal-oral route. (The virus has been found in contaminated waste water and sewage.) Person-to-person transmission is uncommon. Hepatitis E is typically a self-limited acute hepatitis, usually lasting 1 to 4 weeks. It does not progress to chronic disease.

Hepatitis E virus (**HEV**) infection is a major public health problem in many developing countries. Hepatitis E occurs sporadically and in epidemics, and causes substantial rates of death and complications, especially in pregnant women. On the basis of data from serological tests, an estimated one third of the world's population has been infected with the HEV. In India, the lifetime prevalence is more than 60%.

Clinically, the infection is indistinguishable from other types of acute viral hepatitis. The severity of the disease increases with age. The overall fatality rate is estimated to be as high as 3%. Pregnant women who develop the infection have the highest risk of acute hepatic failure. Their case fatality rate is high, as are rates of abortion.

A new recombinant protein vaccine (**rpHEV** vaccine) has been developed.

This study entered 2000 healthy Nepalese Army personnel (almost all male; mean age 25). All were considered susceptible to hepatitis E on the basis of low titers of antibody to HEV at baseline.

Randomized to 1) three doses of vaccine at 0, 1 and 6 months, or 2) three doses of placebo.

Identified acute hepatitis by active surveillance (including hospital). The hepatitis was defined clinically and confirmed by presence of HEV RNA by polymerase-chain-reaction, or by a major rise in anti-HEV antibody.

After 3 doses, hepatitis E developed in 69 subjects—66 in the placebo group and 3 in the vaccine group. Vaccine efficacy was 95%.

The virus may infect travelers to endemic regions. The vaccine may be useful for travelers.

Is there a hepatitis F?

HERPES ZOSTER

3-8 VARICELLA-ZOSTER VACCINE FOR THE PREVENTION OF HERPES ZOSTER

Herpes zoster (HZ; “shingles”) develops in about 30% of people over a lifetime. Up to 1 million cases occur in the US annually. Risk increases with age, beginning at age 50, when cell-mediated immunity begins to decline. HZ is 10 times as likely in people over age 60 as in younger people. One or more episodes of HZ will develop in up to half of people over age 85. HZ is more common in immunocompromised people.

Post herpetic neuralgia is challenging and debilitating. It can last for weeks, months, and even years. More than 40% of people over age 60 who have had HZ have PHN.

As immunity wanes in older adults, a higher dose of vaccine (as compared with the varicella vaccine given to children) is required to produce immunity. The new HZ vaccine (*Zostavax*; Merck) contains about 14 times the plaque-forming units per dose as the attenuated live chickenpox vaccine given to children. The HZ vaccine increases cell-mediated immunity to a new set point above the “immunological threshold” below which a person is at risk for HZ.

A large clinical study evaluated efficacy of the HZ vaccine in over 38 000 persons over age 60 followed for 3 years. The incidence of HZ was 51% lower in those receiving the vaccine vs placebo. The incidence of PHN was 67% lower. The median duration of pain was shorter (21 days vs 24 days), and the severity of pain was lower.

About 17 people would need to be vaccinated to prevent one case of HZ, and about 31 would be needed to treat to prevent one case of PHN. (Estimated costs = \$3,300 and \$ 6,400.)

Adverse effects were limited to local reactions at the site of the inoculation.

Virtually all persons now age 60 and above have had clinical or subclinical chickenpox. It is not necessary to determine whether there is a history of chickenpox before giving routine HZ vaccine.

Efficacy of the vaccine for people who have had a previous episode of HZ is unknown. The Advisory Committee on Immunization Practices recommends that this group of patients should receive the vaccine.

Administration is advised for all persons over age 60, “unless there is a contraindication”.

If vaccine is in short supply, I would postpone administration to patients who have had HZ.

I would not hesitate to administer the vaccine for patients age 50-59 should they request it.

HORMONE REPLACEMENT THERAPY

Hormones Remain A Reasonable Option For The Short-Term Treatment Of Menopausal Symptoms.

4-4 POSTMENOPAUSAL HORMONE THERAPY AND RISK OF CARDIOVASCULAR DISEASE BY AGE AND YEARS SINCE MENOPAUSE

This study (a secondary analysis) explored whether the effects of hormone therapy on risk of cardiovascular disease (CVD) vary by age or years since menopause.

The WHI trials enrolled over 27 000 predominantly healthy postmenopausal women aged 50 to 79.

Over 10 000 had undergone hysterectomy and received conjugated equine estrogen-alone (0.625 CEE-alone) vs placebo. Over 16 000 received CEE + medroxyprogesterone (CEE 0.625 mg + MPA 2.5 mg) vs placebo.

A. CEE-alone

No indication that it is a risk factor for CHD up to 20 years after menopause. Risk increases at age 70

Associated with increased risk of stroke at all ages.

B. CEE + MPA:

No indication that it is a risk factor CHD up to 10 years after menopause. Risk increases after 10 years.

Associated with increased risk of stroke at all ages.

Conclusion: Women who initiated HRT closer to menopause tended to have reduced risk of CHD. Risk increased in women more distant from menopause. The risk of stroke was elevated regardless of years since menopause.

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The article did not list baseline risk factors. I would expect that women who developed HRT-associated cardiovascular events would be at higher risk if they had more risk factors at onset of menopause. (Eg, smoking, hypertension, dyslipidemia). Indeed, women without risk factors who take HRT would probably be at lower risk for events than women who do not take HRT, but have a number of risk factors.

I am sure the authors would recommend use of HRT at the lowest dose and for the shortest period.

Progesterone (not estrogen) seems to increase risks of CHD and breast cancer. Both are related to increased risk of stroke.

The Importance Of Timing

6-3 HRT AND THE YOUNG AT HEART

Clarity about hormone-replacement therapy (HRT) is emerging. Its effects differ according to the age of the recipient. This underscores the importance of timing. The WHI-CACS and other WHI studies support the “timing hypothesis” for HRT. HRT is related to more adverse cardiovascular effects in older women. As women age, the underlying biological characteristics of the vessel wall and the vascular response to HRT change.

The WHI-CACS supports recent consensus statements of two large societies of menopause practitioners which strongly endorse the timing hypothesis and recognize the potentially beneficial effects of HRT in younger postmenopausal women.

It is important to continue to emphasize that HRT should not be considered as a strategy to *prevent* CVD in women. There are proven therapies for prevention that remain underused.

The editorialists go on to describe the recent history of recommendations for HRT. (*See the full abstract.*) The perceived safety and recommendations for use of HRT have varied over the past decades, and have led to confusion among patients and physicians alike.

A clearer consensus is now evolving. HRT in younger postmenopausal women is safe.

I enjoyed reviewing the conflicting reports about post-menopausal hormone therapy. The best guidelines of “evidence-based-medicine” can vary over the years. No wonder women and their physicians were confused.

The term “hormone replacement therapy” (HRT) is confusing, and I believe should be abandoned. There is a great clinical difference between estrogen-alone, progesterone-alone, and both combined. Perhaps post-menopausal xxx therapy (xxx specifying the hormone used) would be a better term.

“Estrogen Therapy May Have Cardioprotective Effects In Younger Women.”

6-2 ESTROGEN THERAPY AND CORONARY-ARTERY CALCIFICATION: The WHI-CACS Trial

This **WHI-CACS** study determined whether the coronary-artery calcium burden differed (after 7 years of therapy) among women age 50 to 59 at baseline who received estrogen-alone vs those who received placebo.

The study was restricted to women age 50-59 (mean = 55) at randomization. This is the most clinically relevant age group with regard to initiation of CEE for menopausal symptoms.

Between May and September 2005, 1079 women underwent CT examinations of the heart. At that time, subjects’ mean age was 65 years. They had taken CEE or placebo for an average of 7 years.

Mean calcium score:	CEE (n = 547)	Placebo (n = 527)
	83	123

“Estrogen therapy may have cardioprotective effects in younger women.” But, estrogen has complex biological effects that may vary according to the underlying state of the vasculature. It is possible that estrogen could reduce coronary artery calcium scores but still increase the risk of clinical CHD events, owing to adverse effects on thrombosis and plaque rupture, which are more likely in older women.

Conclusion: Among women age 50-59 estrogen at baseline, estrogen-alone given for 7 years was associated with a lower coronary artery calcium burden than those who received placebo.

This should reassure women who have recently undergone menopause and need relief of symptoms.

Coronary calcium is, of course, a surrogate outcome for coronary events. The investigators did not mention rate of clinical events. I presume there were few in this age group.

Women who had hysterectomy, and thus can take estrogen-alone for menopausal symptoms, are in the minority. The larger problem concerns those who require combined estrogen-progesterone. I believe combined E + P is associated with more adverse effects (stroke, breast cancer, and CHD events) than E-alone. Nevertheless, E + P is reasonably safe, and safer in younger postmenopausal women than in older women.

E-alone is not entirely safe. It is associated with increased risk of stroke and venous thromboembolism.

I believe that women who have no traditional risk factors and who take hormones at any time postmenopause are less likely to be at risk for adverse effects than women who have a number of traditional risk factors and do not take hormones.

Another study by the WHI "Effects of Conjugated Estrogens on Breast Cancer" JAMA April 12, 2006 (See Practical Pointers April 2006 [4-9] provides some reassurance about the risk of breast cancer in postmenopausal women taking estrogen-alone therapy. Over 10 000 women, the majority over age 60, were randomized to CEE or placebo and followed for 7 years. There was no increase in incidence of breast cancer in the CEE group. .

I believe progesterone is the main hormonal risk factor for breast cancer.

HUMAN PAPILOMA VIRUS (HPV)

Overall Prevalence Of HPV Types Included In The Vaccine = 3.4% (3 million women)

2-9 PREVALENCE OF HPV INFECTION AMONG FEMALES IN THE UNITED STATES

Human papilloma virus (HPV) is the most common sexually transmitted infection. Prevalence is highest among young persons, within the first few years after sexual debut.

HPV types are categorized according to their epidemiological association with cervical cancer (types 16 and 18); and genital warts (types 6 and 11). Worldwide, approximately 70% of cervical cancers are due to HPV 16 and 18.

A highly efficacious quadrivalent prophylactic vaccine against types 6, 11, 16, and 18 was licensed in June 2006. It is recommended for routine use in females age 11 to 12 years. It is close to 100% effective in preventing the infection and cervical cancer precursors and genital lesions associated with the types included.

In 2003-04, The National Health and Nutrition Examination Survey (NHANES) used a representative sample of US non-institutionalized women (age 14 to 59; n = 1921) to determine baseline population prevalence of HPV before widespread availability of a vaccine.

Women provided a self-collected vaginal swab specimen for determination of HPV DNA by polymerase chain reaction, followed by determination of the type(s).

Overall prevalence = 27%. (42 types; corresponds to 25 million females in the US.)

Overall, 3.4% of the study participants had infections with types included in the quadrivalent vaccine (HPV 6, 11, 16, 18; 3 million women). Of women age 14 to 19, 6% had at least 1 of the 4 types

Overall prevalence of high risk types 16 and 18 was 2.3%

Conclusion: Overall HPV prevalence in the US is high (27%)—highest in ages 20-24. The prevalence of types included in the HPV vaccine was relatively low.

The health, social, and economic burden of HPV infections are considerable. This includes the expense, bother, and anxiety produced by positive Pap smears.

I was unable to determine the length of immunity from the vaccine or whether a booster will be necessary.

There is controversy about efforts to make vaccination against HPV mandatory for girls age 11 to 12. Why not vaccinate boys? Certainly “herd” immunity would play a large role here.

Effective Prophylaxis. Not Effective Treatment

5-6 QUADRIVALENT VACCINE AGAINST HUMAN PAPILLOMAVIRUS TO PREVENT HIGH-GRADE CERVICAL LESIONS

Multicenter, multicountry randomized, double-blind trial assigned over 12 000 women between ages 15 and 26 (mean = 20) to: 1) Three doses of the vaccine, or 2) Placebo injections. Injections were given at day 1, month 2, and month 6.

Efficacy was almost 100% in the susceptible population (n = 10 565). Only one vaccinated individual without HPV infection at baseline (determined by PCR or serology) developed cervical intraepithelial neoplasia (CIN-3)

This single subject was positive for HPV-52 at baseline.

Vaccination was *not* effective in those who were positive for HPV-16 or 18 at baseline. (n = 782) In this group there were 98 cases of CIN-2 or 3, and 5 cases of adenocarcinoma in situ—most due to HPV-16.

Conclusion: In young women who had *not* previously been infected with HPV-16 or HPV-18, vaccination lowered the occurrence of high-grade cervical intraepithelial neoplasia related to HPV-16 or HPV-18. Widespread immunization of female children and adolescents may result in substantial decrease in HPV-16 or HPV-18 related cervical disease, including cervical cancer.

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Recently there has been some discussion of mandatory immunization of young girls before onset of sexual activity. Enthusiasm for this is waning.

HYPERTENSION

“Prevented More Cardiovascular Events than Supplementation of Conventional Treatments”

4-2 VALSARTAN IN A JAPANESE POPULATION WITH HYPERTENSION AND OTHER CARDIOVASCULAR DISEASE: The Jikei Heart Study

This study investigated whether addition of the angiotensin-II blocker, valsartan (*Diovan*; Novartis) to conventional cardiovascular treatment is effective in Japanese patients with cardiovascular disease.

The cardiovascular diseases in this study population—heart failure, hypertension, and coronary heart

disease—are all disorders in which activation of the renin-angiotensin-aldosterone system is thought to play a major part.

Randomized, controlled trial entered over 3000 Japanese patients (mean age 65). All were undergoing conventional treatment for hypertension, CHD, HF, or a combination of these disorders.

Randomized to: 1) valsartan [40 to 160 mg daily], or 2) controls.

Controls were given either an increased dose of their existing treatment, or an additional conventional treatment, to achieve BP control aimed at 130/80. (Drugs at baseline, and continued during the trial, included calcium blockers, ACE inhibitors, beta-blockers, alpha-blockers, thiazides, statins, and fibrates. ACE inhibitors were given in about 1/3 of patients, and were continued in both groups.)

Primary outcome = composite of cardiovascular morbidity and mortality. Analysis by intention to treat.

Follow-up for 3 years.

Mean BP for both groups at 3 years = 132/77

Effects on all endpoints (rate per 1000 patient-years):

	Valsartan	Control	NNT
Composite endpoint	21 (6.0%)	35 (9.7%)	27
Stroke or TIA	8	11	
Angina pectoris	4	12	
New HF or exacerbation	4	8	
Dissecting aneurysm	0.5	2.3	
All cause mortality	6.5	6.3	

Mortality, myocardial infarction, or progression of renal disease did not differ between groups.

Conclusion: The addition of valsartan to conventional treatment prevented more cardiovascular events than supplementation of conventional treatments. These results cannot be explained by a difference in BP control

I believe that primary care clinicians should give ACE inhibitors and AT-II blockers (preferably the latter) the benefit of the doubt, and prescribe them more frequently. Their overall benefits (see the preceding abstract) exceed the benefits resulting from other BP-lowering drugs.

“Sodium is necessary, but not sufficient”

5-1 SODIUM AND POTASSIUM IN THE PATHOGENESIS OF HYPERTENSION

Primary hypertension results from the interplay of internal derangements (primarily in the kidney), and the external environment. Sodium, the main extracellular cation, has long been considered the pivotal environmental factor. Numerous studies have shown the adverse effect of a surfeit of sodium on arterial pressure.

By contrast, potassium is the main intracellular cation. Abundant evidence indicates that a potassium deficit has a critical role in the pathogenesis of hypertension.

This review examines how the interdependency of sodium and potassium influences blood pressure (BP). Sodium and potassium act together to influence BP. Excess sodium and a deficit of potassium are the dominant environmental factors in the pathogenesis of primary hypertension.

“Primary hypertension and age-related increases in blood pressure are virtually absent in populations in which individual consumption of sodium chloride is less than 50 mmol/day.” (~ 3 grams of NaCl). “It appears, then, that sodium intake that exceeds 50 to 100 mmol per day (3 to 6 grams of NaCl) is necessary, but not sufficient for the development of primary hypertension.”

Isolated populations that eat natural foods (in which hypertension affects less than 1% of people) have an individual potassium intake that exceeds about 6 grams a day, and a sodium intake of only 0.5 to 1.0 grams—a ratio greater than 3/1 and closer to 10/1). People in industrialized countries (in which hypertension affects about one third of the population) ingest 1.2 to 2.7 grams of potassium, and as much as 2.3 to 9.2 grams of sodium.

Differences in prevalence of hypertension have been attributed to the sodium intake, but could also reflect differences in potassium intake. Population studies have shown an inverse relation between potassium intake and BP, the prevalence of hypertension, and the risk of stroke.

A modified diet that approaches the high potassium:sodium ratio of the diets of our human ancestors is a critical strategy for the primary prevention and treatment of hypertension.

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The article goes into much more detail. I believe it should be required reading for all primary care clinicians. It may also motivate patients to be more concerned about their diet.

Primary hypertension is no longer “essential” or idiopathic. It is a disease of civilization.

The taste for salt is acquired. People who are reared on a low salt diet, when moving to a population with high salt intakes will complain that the food is too salty.

Unfortunately, fruit and vegetables are often more costly than most other foods.

INFLUENZA

“Successful Control Of Annual Influenza Epidemics Depends On Vaccinating A High Proportion Of Children.”

2-6 LIVE ATTENUATED versus INACTIVATED INFLUENZA VACCINE IN INFANTS AND YOUNG CHILDREN

This study compared the safety and efficacy of live attenuated vaccine administered by nasal spray vs killed vaccine administered by injection.

During the 2004-05 flu season, randomly assigned over 7800 children age 6 months to 5 years to:
1) live attenuated vaccine (*FluMist*), or 2) killed vaccine (*Fluzone*).

Influenza attack rates (confirmed by culture):

	Live vaccine (N = 3916)	Killed vaccine (N = 3936)
A/H1N1	3 (0.1%)	27 (0.7%)

A/H3N2	37 (0.9%)	178 (4.5%)	
B	115 (2.9%)	136 (3.5%)	
Regardless of match	153 (3.9%)	338 (8.6%)	[NNT = 21]

Serious adverse effects were more common in children age 6 months to age 1 year. Live vaccine was related to a higher risk of significant wheezing in infants age 6 months to 1 year.

“Many believe that the successful control of annual influenza epidemics depends on vaccinating high proportion of children.”

In addition to its high acceptability because of the mode of administration, the significantly higher efficacy of this live attenuated vaccine than the licensed inactivated vaccine suggests that it can play an important role in the control of influenza.

Conclusion: Among young children, live attenuated vaccine had better efficacy than the inactivated vaccine. Live vaccine should be a highly effective, safe vaccine for children *age 12 months to 5 years* who do not have a history of asthma or wheezing.

This study did not include a placebo group. It assumed that flu vaccine does provide protection.

Practical Pointers is addressed mainly to adult primary care medicine. Articles of pediatric interest are rarely abstracted. I abstracted this study because it does indeed pertain to adult medicine. Immunization of very young children against flu not only protects them, but extends protection to the family. The “herd” immunity effect benefits not only the recipients of the vaccine, but persons who have not been immunized. The goal remains—to attain universal vaccination against flu.

The antigenic effect of live virus depends on establishment of viral replication in the recipient (a mild infection). It is more effective in persons who do not have antibodies against the virus. (eg, young children). Live virus is less effective in adults who have some degree of immunity, which blocks the replication process. In adults, the immune response to killed vaccine is greater than the response to live vaccine. See Practical Pointers December 2006.

Back To Basics

6-4 SOCIAL MEASURES MAY CONTROL PANDEMIC FLU *A Message from a Recent Conference In Barcelona*

Non-pharmacological interventions may be as important as, or even more important than, drugs and vaccines in fighting pandemic flu.

“Social distancing” will be important to help reduce the numbers of cases and also to slow the spread of the epidemic, buying time for production of a vaccine.

I believe “old-fashioned” prophylaxis and hygienic methods are indeed effective, but oft forgotten. “Ring prophylaxis”—isolating and treating the patient while using prophylaxis for those closely

associated—is also a necessary intervention to control epidemics. Individuals must be responsible for their own “social isolation”.

IRRITABLE BOWEL SYNDROME

5-4 IRRITABLE BOWEL SYNDROME: Clinical Update

A concise review.

Thirteen clinical points from the Rome criteria to drug treatment

Read the full abstract.

MACROLIDE-RESISTANT STREPTOCOCCI

Resistance Developed Within A Few Days

2-7 EFFECT OF AZITHROMYCIN AND CLARITHROMYCIN THERAPY ON PHARYNGEAL CARRIAGE OF MACROLIDE-RESISTANT STREPTOCOCCI IN HEALTHY VOLUNTEERS.

Two macrolides, clarithromycin and azithromycin are among the drugs of choice for treatment of respiratory infections. Respiratory pathogens (*Streptococcus pneumoniae*, *Streptococcus pyogenes*) are commonly resistant to macrolides. Resistance is increasing. This is most likely due to their inappropriate use.

This randomized, double-blind trial followed 204 healthy volunteers (mean age 24) for 42 days. Obtained pharyngeal swabs at baseline, and periodically, to culture and determine macrolide resistance by growth characteristics on erythromycin containing plates.

Randomized subjects to: 1) clarithromycin—500 mg twice daily for 7 days, 2) azithromycin—500 mg once daily for 3 days, and 3) matching placebo groups.

At baseline, macrolide resistance, determined by this method, was present in about 25% to 30% of each of the 3 groups. Immediately after macrolide use, a large increase in the proportion of macrolide resistance was noted in both clarithromycin and azithromycin groups, but not in the placebo groups. Resistance peaked to over 80% at day 4 in the azithromycin group, and at day 8 in the clarithromycin group. Over 42 days, resistance decreased to 60%-70% in the antibiotic groups. Resistance in the placebo groups remained stable.

The study followed a subgroup of subjects for a total of 180 days. Resistance fell slightly from day 42, but continued to remain higher than in the placebo groups.

Conclusion: Antibiotic use was an important driver of the emergence of antibiotic resistance. “Physicians prescribing antibiotics should take into account the striking ecological side-effects of such antibiotics.”

I abstracted this article because several points impressed me:

- 1) The high percentage (25%-30%) of streptococci considered by the study to be resistant at baseline, before any antibiotic had been given.*
- 2) The immediate (within days) development of resistance.*

- 3) *The duration of resistance (months).*
- 4) *The gradual waning of resistance (over 180 days in this study).*
- 5) *The possible extension of resistance of bacteria, other than streptococci, induced by macrolides.*

The study does not link antibiotic exposure (and development of resistance to the antibiotic in an individual) to the clinical outcome of illness in that individual. I believe both antibiotics would be curative in many patients despite presence of resistance. I doubt that the 25% to 30% of patients who carry resistant organisms who develop clinical illness would fail to respond to either antibiotic.

MEDICAL MYTHS

“Lifestyles: First And Foremost Eating Patterns From Preconception On.”

3-4 LOW RISK—And the “No More Than 50%” Myth/Dogma

Medical myths/dogmas die hard. New bodies of knowledge for prevention and control of cardiovascular disease have had to disprove and displace myths/dogmas held in the past.

In the 1950s:

Atherosclerosis is part of normal aging. Nothing can be done about it.

Cholesterol levels and blood pressure normally rise with age.

Normal blood pressure is 100 plus your age.

Normal cholesterol is as high as 300 mg/dL.

Most high blood pressure is essential hypertension, and of unknown cause.

Treatment of high blood pressure gets at a symptom and not at the underlying disease, and can do more harm than good by lowering blood flow to the brain and heart. Therapeutic nihilism and judicious neglect are right.

All these are now bygone notions, refuted by massive data. But, other longstanding myths/dogmas about the CVD epidemic persist. One long-standing myth/dogma—still bruited about—is contrary to scientific fact. The dogma persists that the established risk factors for CVD account for no more than 50% of CVD events, and many people who experience CVD events have no risk factors.

In 2005-06, the MrFIT intervention trial expanded the risk factors for atherosclerotic disease to consideration of 5 major factors: total cholesterol, systolic BP; diabetes; smoking; and body mass index.

Based on these factors, low risk was rare. Very few individuals were without all 5 factors:

Only 4% of middle-aged African American women

Only 9% of white American women

Only 3% of African American men

Only 6% of white American men

A key strategic challenge—and opportunity—for medical care and public health is to achieve a progressive increase in the proportion of the population at low risk. “The essence of this advance is progressive steady improvements in lifestyles, first and foremost eating patterns from preconception on.”

“The notion that these risk factors account for no more than 50% of CVD events is myth/dogma and is dead wrong.”

I abstracted this article as a prelude to the following. The definition of “low risk” of cardiovascular events varies, depending on the number and effect of the individual components. As the number of risk components increases, the number of persons at “low risk” declines. No adults in our society are without some risk. How should we treat them?

MIGRAINE

The Two-Drug Tablet Provided More Favorable Clinical Benefits

4-8 SUMATRIPTAN-NAPROXIN FOR ACUTE TREATMENT OF MIGRAINE

“None of the currently available monotherapeutic agents provides broad coverage of the multiple pathogenic processes in migraine, which is thought to involve multiple neural pathways that appear to be sequentially activated and sensitized as a migraine attack develops.” Multi-mechanism-targeted therapy may confer advantages over monotherapy.

This study compared efficacy and safety of a two-drug, fixed-dose tablet containing a triptan and naproxen vs each as monotherapy, and vs placebo.

Compared with sumatriptan-alone (S), naproxen-alone (N) , and placebo, a pill containing both (S + N):

Provided better relief of headache at 2 hours (NNT = 3; S + N vs placebo)

Provided better sustained relief 2 to 24 hours (NNT = 6; S + N vs placebo)

Reduced incidence of recurrence of headache within 24 hours (NNT = 3; S + N vs placebo)

Reduced use of rescue medication.

Adverse events: dizziness, somnolence, paresthesias, nausea, dry mouth—all from 2% to 5%.

No statistically significant differences in overall adverse events between S + N, N-alone, and S-alone

Development of the tablet was motivated by the rationale that concurrent use of two agents with complementary anti-migraine mechanisms might confer additive benefit relative to either alone.

Conclusion: S +N as a single tablet for acute migraine resulted in more favorable clinical benefit than either monotherapy with S or monotherapy with N.

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I was puzzled. The article reported 2 replicate randomized, double-blind studies, Results were similar. Dr. Brandes (personal communication) reported that, for approval of a drug, the FDA requires two trials supplying data and meeting primary end-points. The trials are usually reported separately. The JAMA accepted the results of both trials and permitted publication in one article.

Study supported by GlaxoSmithKline. Obviously the article was slanted to promote the 2 drugs combined in one tablet. I wonder if results would be similar if 2 separate tablets were co-administered. And if costs would be lower.

MYOCARDIAL INFARCTION

“Outcomes Of RCTs Should Always Be Extrapolated With Caution To Real-Life Patients.”

1-6 EXTERNAL VALIDITY OF CLINICAL TRIALS IN ACUTE MYOCARDIAL INFARCTION

The relevance of randomized controlled trials (RCTs) to clinical practice may be hampered by doubts regarding their external validity. RCTs tend to recruit highly selected populations that may not represent patients encountered in everyday practice.

This study compared: 1) patients with acute myocardial infarction (AMI) enrolled in RCTs of reperfusion therapy with 2) patients with AMI who were eligible for enrollment but who were not enrolled and with 3) patients with AMI who were not eligible for enrollment.

Based on baseline characteristics, patients included in the RCTs differed from those not included (but eligible) and from those considered ineligible. Patients included had the lowest baseline risk of death: lower age; fewer women; and less frequent past history of myocardial infarction, diabetes, hypertension, TIA and stroke, and peripheral arterial disease.

Patients in the group eligible of inclusion in the RCT (but not included) had higher baseline risks of death.

Ineligible patients had still higher risks. Actual hospital mortality showed a similar gradient (3.6%; 7.1%; 11.4%)

It is usually accepted that, while RCTs enroll a highly selected population, the outcomes can be extrapolated to real-life patients who fulfill the main inclusion and exclusion criteria, but are not enrolled.

There are important concerns about the external validity of RCTs

Conclusion: Patients with AMI enrolled in RCTs differed markedly in terms of their baseline characteristics, hospital treatment, and outcomes from patients who would have been eligible for inclusion, but were not included. Caution is necessary when extending the findings obtained in RCTs to the general population.

Although primary care clinicians would not likely care for many patients with AMI in hospitals, I abstracted this article to again point out the pitfalls of too strict application of results of RCTs to individual patients seen in every day primary care practice.

We must always ask “Do the results of this RCT apply to my next patient?” There are many reasons why they may not apply, and may cause more harm than benefit.

Many times social constraints prevent application of the RCT treatment: very old age, lack of insurance, medical illiteracy, and patient non-compliance and preference.

Keen clinical judgment must be applied to all patients. The “art” of medicine is indeed long and difficult.

Read the following abstract.

Benefits Were Mediated By Drug Effects; They Did Not Reflect “Healthy Behavior”.

1-10 RELATIONSHIP BETWEEN ADHERENCE TO EVIDENCE-BASED PHARMACOTHERAPY AND LONG-TERM MORTALITY AFTER ACUTE MYOCARDIAL INFARCTION.

This study asks: Are the benefits of drugs attributable to a drug’s biological responsiveness (drug effect), or to the adoption of healthier lifestyles that often accompany adherence behaviors (healthy user effect)? Are mortality differences after an acute myocardial infarction (AMI) attributable to the “healthy adherer” effect, or due to the pharmacological action of drugs?

The population-based observational study followed over 31 000 elderly survivors of AMI (mean age 75).

All patients had filled at least one of 3 possible drug prescriptions: statins, beta-blockers, or calcium blockers. Statins and beta-blockers are recommended for secondary prevention after an AMI. Calcium blockers were considered a control, given the absence of any clinical trial-proven post AMI survival benefit.

Divided patient adherence into 3 categories:

- 1) High adherence (80% or over of days covered).
- 2) Intermediate (40% to 79% of days covered)
- 3) Low (less the 40% of days covered)

Follow-up = a median of 2.4 years. Main outcome measure = long-term survival.

Results:

Deaths (%)	High adherers	Intermediate adherers	Low adherers
Statins	16	20	24
Beta-blockers	21	23	25
Calcium blockers	30	31	27

(No statistically significant association between calcium blocker use and mortality.)

There was a positive and graded relation between mortality and adherence to drugs known to be effective in secondary prevention in patients with a history of AMI. There was no relationship between mortality and adherence to a drug known to be ineffective in secondary prevention.

Conclusion: The mortality benefits associated with adherence to drugs known to be effective in secondary prevention of mortality after an AMI were mediated by drug effects more so than by generic healthy-adherer behavioral attributes.

This underscores the need to optimize patient behavior patterns which will increase adherence to taking effective drugs prescribed for secondary prevention. This will maximize survival gains of drug therapies in real-world populations.

I believe the “healthy user“ effect could be applied to all drugs, effective as well as ineffective. The healthy user benefit would be due to more favorable lifestyles adopted by persons who are conscientiously concerned about their health.

Lifestyle interventions take a long-time to become evident. The effect would not be evident in high-risk patients in whom adverse outcomes occur over a short time (as following AMI). This may be the reason no benefit was evident in the calcium blocker group—no time to occur.

Part of the reason statins and beta-blockers demonstrate benefit may have been due to the healthy user effect, but it would be more evident long-term in patients not at high risk.

OBESITY

“It Would Seem That Becoming Slightly Overweight May Not Be So Bad.”

4-6 THE EFFECT OF OBESITY ON DISABILITY VS MORTALITY IN OLDER AMERICANS

This study (Established Populations for Epidemiological Studies of the Elderly) examined the association between BMI and subsequent mortality and incident disability during 7 years, and estimated the effect of BMI on life expectancy and disability-free life expectancy in initially non-disabled persons.

Entered over 12 500 persons age 65 and older (mean = 72) between 1982 and 1993. None were disabled. None had limitations in activities of daily living (ADL). Grouped BMI according to NIH obesity standards: < 18.5 underweight; 18.5-24.9 normal weight; 25 to 29.9 overweight; 30 to 34.9 obesity.

Results:

A. Relation between BMIs and mortality: BMIs associated with the minimum hazard of mortality were between 25.1 and 29.9 (overweight). There was a difference between men and women: For men, the total life expectancy was greatest with BMIs between 25 and 29.9. For women it was between 30 and 34.9 (obese).

B. Relation between BMIs and disability: The lowest point-hazard ratio for disability associated with ADL was a BMI of 24. Hazard ratio for disability rose to ~ 1.2 as BMI rose to 27. Hazard ratio for disability rose to ~ 1.2 as BMI fell to 22-23

C. Disability-free life expectancy: Disability-free life expectancy was greatest among both men and women with a BMI of 25 to 29.9 (overweight). The estimated total life expectancy that will be disability-free fell sharply for subjects with BMI 30 and higher (obese).

Loss of independence is one of the most feared outcomes experienced by older individuals, and is a major contributor to poor quality of life.

The association between elevated BMIs and subsequent disability provides evidence that obesity (BMIs > 30) in older populations is associated with substantial increase in risk of poor health outcomes.

The association between elevated BMI and mortality may be attenuated by selective survival. Elevated BMI is clearly associated with increased mortality at younger ages. It is possible that persons susceptible to increased early mortality associated with elevated BMI die at younger ages, weakening the observed relationship at older ages. Only about half of the study cohort survived to age 65. Because of the effect of obesity on mortality tends to decline with age, those available to participate in a study of older persons constitute “healthy survivors”.

“At the individual level, considering the trade-off between total and disability-free life expectancy, it would seem that becoming slightly overweight may not be so bad.”

Conclusion: “Assessment of the effect of obesity on the health of older Americans should account for mortality and incidence of disability.”

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If you avoid the risks of being overweight at younger age, and you make it to age 65-70 it may be better to be a little overweight. This may give some of us elders comfort as we age and our daily energy expenditures decline while our food-intake habits remain fixed.

A Low-Glycemic Load Diet Promotes More Weight Loss In Patients With A High Insulin-Response To Glucose.

5-2 EFFECTS OF LOW-GLYCEMIC LOAD VS LOW-FAT DIET IN OBESE YOUNG ADULTS

Some individuals have a higher insulin response to glucose ingestion. They may be more likely to develop postprandial hypoglycemia.

This randomized trial enrolled 73 obese young adults (mostly female; age range 18-35; mean = 27) for 18 months. All had a BMI of 30 and above. Prior to randomization, a 75-g glucose tolerance test determined serum insulin levels at 30 minutes. The median serum insulin concentration at this time was 58 micro-IU/mL.

Subjects were randomized to: 1) Low-glycemic load diet: 40% of energy from carbohydrate (emphasizing low glycemic index foods); 35% from fat; and 25% from protein, or 2) Low-fat diet: 20% of energy from fat; 55% from carbohydrate; and 25% from protein. The diets were ad lib. No calorie counting or limitation on the quantity of food intake was involved. Intake was determined by the subjects' feeling of satiety.

Results at 18 months:

1) Subjects with baseline insulin concentrations greater than 58 micro-IU/mL:

Individuals on the low glycemic load diet lost 5.8 kg

Individuals on the low fat diet lost 1.2 kg

2) Subjects with baseline insulin concentrations below 58 micro-IU/mL.

Individuals on a low glycemic load diet lost about 2 kg

Individuals on a low fat diet also lost about 2 kg.

(Ie, insulin concentration was an effect moderator for weight loss.)

Conclusion: For obese individuals with high insulin concentrations after a glucose load, a low-glycemic diet may promote more weight loss than a low-fat diet.

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If you are a “high insulin responder” then changing your diet to a low glycemic load diet would lower the resultant post-prandial blood glucose elevation, and lower the insulin response. This would in turn result in the 2-hour post-meal blood glucose being higher than at baseline. Post-prandial hypoglycemia would be less likely to occur; hunger would not be as acute; and caloric intake would likely be less. Weight loss would be more likely to be greater than with a low fat, higher carbohydrate diet.

Surgery Should Not Be Performed If Systematic Follow-Up Is Not Available

5-10 BARIATRIC SURGERY FOR MORBID OBESITY

Bariatric surgery reduces caloric intake by modifying the anatomy of the g.i. tract. Operations are classified as restrictive or malabsorptive. The changing popularity of specific surgical procedures over time suggests that the ideal procedure has not been established. Laparoscopic procedures are available.

Conditions associated with obesity consistently improve after surgery. (Eg, 77% of patients with type 2 diabetes no longer required medications after surgery.)

Thorough medical evaluation is required prior to surgery. The psychological evaluation of candidates for surgery is one of the most important and difficult elements of the clinical assessment. Most patients presenting for surgery have one or more psychiatric disorders.

Patients undergoing surgery often believe they will lose more weight than is consistent with clinical experience. And may think that minimal personal effort or risk is involved.

Perioperative care requires specialized expertise and facilities. Choosing surgeons and hospitals that have great experience is essential.

A comprehensive plan for long-term care is necessary. Surgery should not be performed if systematic follow-up is not available, and should not be planned until the patient has made a commitment to participate in such care.

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Surgical treatment is complex—not to be undertaken lightly. Reading the original article may be helpful to patients with morbid obesity who are considering surgery.

Bariatric surgery is the only effective treatment for morbid obesity.

OFF-LABEL DRUGS

Be Well Informed; Base Use On Firm Rationale; Keep Good Records

2-5 OFF-LABEL DRUGS: *Experts Weigh In On Promotion and Prescription*

“Off-label drug use has been around for decades. It is perfectly legal for practitioners to prescribe them for a condition not described in the approved labeling if it seems reasonable or appropriate.”

According to the FDA, when prescribing a product for an indication not in the approved labeling, physicians “have the responsibility to be well informed about the product, to base its use on firm scientific rationale, and on sound medical evidence, and to maintain records of the product’s usefulness and effects”.

“Inappropriate off-label prescribing could have an effect on many patients because 21% of the 725 million total drug prescriptions reported in the study lacked FDA approval for the condition they were used to treat.”

The FDA Modernization Act of 1997 permitted drug companies to disseminate valid information—such as peer-reviewed studies published in scientific journals—about the safety and effectiveness of off-label uses that have been or will be studied and submitted for FDA approval. The FDA deemed other forms of off-label promotion illegal. However, a number of companies have falsely marketed their drugs for treatment of a variety of other conditions.

OPIATES

“Physicians Have Become More Comfortable About Using These Drugs”

1-3 OPIOID PRESCRIPTIONS SOAR: Increase in Legitimate Use as Well as Abuse

According to a recent survey—“Pain is a serious, undertreated health problem in the United States—19% of US adults reported chronic pain; 34% reported recurrent pain. Some 63% of patients with pain had spoken to their physician about their pain, but only 31% reported complete relief, and 21% reported little or no relief.”

Campaigns to make pain control a priority have succeeded in raising patient and physician awareness of the need for analgesics. Opioids are now among the most prescribed drugs.

By far, the most commonly used prescription analgesic in the US is hydrocodone/acetaminophen (eg. *Vicodin*), with over 100 million prescriptions in 2005.

“Physicians have become more comfortable about using these drugs as they have learned more about them.” Physical dependence on a drug, which develops in most patients who use opioids for prolonged periods, can be treated by tapered withdrawal. This differs from addiction and its associated damaging behaviors.

State and national organizations are emphasizing the importance of managing pain. “These policies provide reassurance to physicians that appropriate prescribing will not lead to punitive action.”

The positive trend in legitimate use in improving pain control in patients has been shadowed by growing abuse of opioids. There is a growing trend of abuse of prescription pain medications.

In the US, the abuse of prescription pain medications is widespread and is not concentrated in urban areas. In addition to pharmacy theft and stealing or sharing the prescriptions of friends and relatives, “doctor shopping” is another possible source of abuse.

The article presents a guideline from the Federation Of State Medical Boards outlining physicians’ responsibilities regarding their oversight of prescription narcotics.

Pain-control is one of the most important functions of primary care.

I believe most primary care clinicians know their patients well, and can and do monitor prescription drug use carefully to avoid misuse.

OSTEOARTHRITIS

Are Popular, Are Safe, But Are They Effective?

1-9 EFFICACY OF GLUCOSAMINE AND CHONDROITIN AS SUPPLEMENTS TO TREAT OSTEOARTHRITIS

Glucosamine and chondroitin sulfate are popular over-the-counter drugs. Glucosamine is an amino sugar that may play a role in cartilage formation. Chondroitin is one of the proteoglycans that give cartilage elasticity. They are considered to be “supplements” and are not regulated by the FDA. An estimated 1 million people in the US take them. Their effectiveness in easing joint pain and preventing disease progression is unproven.

Results from clinical trials are interpreted differently.

The largest study to date, funded by the National Institutes of Health, compared: glucosamine-alone; chondroitin-alone; both combined; celecoxib; and placebo. The study concluded that glucosamine-chondroitin in combination may be effective in the subgroup of patients with moderate or severe knee pain.

But, “The outcome of GAIT was not straight forward, so it was difficult to give a distinct and clear message.” There was an unusually high response rate (60%) in the placebo group. “This and other trials with glucosamine and chondroitin have faced challenges in design, implementation, and analysis.”

Stakeholders are remarkably polarized on these issues.

Since supplements are not regulated by the FDA, a lack of standardization and quality control can make it difficult to accurately interpret and compare studies.

While disagreement persists about efficacy, almost all agree that these supplements are safe.

It is remarkable and somewhat discouraging that, after all these years, the benefit/harm-cost ratio of these supplements is not clarified. The numerator is in doubt. The denominator is clearer. Harm is nil. Cost is lower than other drugs.

How should the primary care clinician act on this information? There must be a large placebo effect in reducing discomfort from osteoarthritis. If my patient finds the drug(s) helpful, I would not dissuade her from taking them. Alternative drugs, including acetaminophen and NSAIDs may or may not be more helpful. But they may be more harmful, and may not cost less.

I could suggest a N = 1 trial for an individual. I doubt if many would implement and conclude it.

I do believe the supplements do have some beneficial effect (beyond the placebo effect), based mainly on the fact that they continue to be used by so many persons over so many years.

OSTEOPENIA

5-3 OSTEOPENIA

Bone mineral density (**BMD**; expressed as grams per square centimeter) is a better predictor of fracture than BP is of stroke. The relative risk of hip fracture is 2.6 for each 1 standard deviation (**SD**) decrease in BMD at the hip. The risk of fracture is continuous, with no absolute cutoff value to define a pathological state.

The WHO has defined osteopenia and osteoporosis based on “T-scores”. (*Standard deviations of bone mineral density from the mean of young persons. See the full abstract.*)

An estimated 33 million Americans (the great majority, women) have osteopenia. Osteopenia is analogous to pre-hypertension, impaired fasting glucose, and borderline high cholesterol in defining an intermediate-risk group with somewhat uncertain boundaries.

Although the risk of fragility (low trauma) fracture is greater among individuals with osteoporosis than among those with osteopenia, the numbers of individuals in the population who have osteopenia is far greater than those with osteoporosis. (39% vs 6% in primary care practice.) The frequency of fragility fractures overall is greater in persons with osteopenia than with osteoporosis. The lifetime risk of fragility

fracture is 40% in women and 13% in men. Because osteopenia is much more common than osteoporosis, the majority of fractures occur in patients with osteopenia.

Measurements of bone mineral density alone cannot effectively discriminate between patients with osteopenia who will have fractures, and those who will not have a fracture.

A clinical dilemma posed by osteopenia arises when BMD in the osteopenic range is identified in patients without an obvious indication for drug treatment (such as a fragility fracture). There are risk factors other than BMD which identify patients with osteopenia who are at increased risk for fracture as compared with others with similar values for BMD. (*See the full abstract.*)

“Clinical risk factors should be considered in combination with measurement of bone mineral density to estimate fracture risk and guide investigation.” The patient’s own valuation of risks and benefits should influence the choice between lifestyle treatment alone or lifestyle + drug therapy.

“Unless the patient strongly prefers to take anti-resorptive medication, or has a T-score near the osteoporotic range with several risk factors for fracture, encouragement of lifestyle modifications with reassessment in 2 to 3 years is a reasonable strategy, and is our recommendation for the majority of patients with osteopenia.”

Prevention of osteoporosis with drug therapy implies a beginning of therapy before osteoporosis develops. That is, either when the patient has a normal bone mineral density, or is osteopenic. Drug treatment is recommended for patients with osteoporosis. Recommendations about treatment for patients with osteopenia vary. I would err on the side of beginning drug treatment at an earlier stage and at an earlier age.

At present, drugs are considered for prevention of further bone loss (secondary treatment), not for primary prevention of osteopenia and osteoporosis.

I believe that any disabling disease with a lifetime risk of 40% should be prevented. We should not wait until it is established to treat. We do not wait for stroke to treat hypertension. We do not wait for a myocardial infarction before treatment of dyslipidemia. Anyone living in a retirement complex as I do will see their friends (both male and female) develop disabling kyphosis and hip fractures. I believe many of these could be prevented by interventions started at an earlier stage and at an earlier age than now is recommended. Why not a “polypill” (combined vitamin D + calcium + low dose bisphosphonate) to be taken regularly, beginning at age 50, to prevent bone loss much as a “polypill” is recommended by some authorities for universal prevention of cardiovascular disease.

I certainly would welcome such a long-range study.

Optimum intake of Vitamin D and calcium should be established at all ages, including the young. This may require lifelong supplements.

OSTEOPOROSIS

5-11 ONCE-YEARLY ZOLEDRONIC ACID FOR TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

A single *intravenous* infusion of zoledronic acid (ZA; a bisphosphonate) decreases bone turnover and improves bone density at 12 months in postmenopausal women with osteoporosis.

This study assessed the effects of annual infusions of ZA on fracture risk over a 3-year period.

Randomized, double-blind, placebo-controlled trial entered over 3800 postmenopausal patients (mean age = 73). All had a bone mineral density T-score of -2.5 or less (*osteoporosis*) at the femoral neck, with or without existing vertebral fracture, or a T-score of -1.5 or less (*osteopenia*) with evidence of at least 2 mild vertebral fractures or one moderate vertebral fracture.

Randomized to: 1) ZA (5 mg) given i.v. as a single dose over 15 min, or 2) Placebo i.v. Both were given at baseline, at 1, and at 2 years. In addition, all patients received oral daily calcium (1000 to 1500 mg), and vitamin D (400 to 1200 IU).

Treatment with ZA reduced the risk of fracture during 3 years

	ZA	Placebo	Absolute difference	NNT*
Vertebral fracture	3.3%	10.9%	7.6%	14
Hip fracture	1.4%	2.5%	1.1%	91

Adverse effects: Post-dose symptoms occurred more commonly in the ZA group than in the placebo group: transient slight increase in serum creatinine, chills, fever, myalgia, flu-like symptoms, headache, arthralgia, nausea, bone pain, back pain. (6% for placebo vs 16% for ZA.) Atrial fibrillation (0.5% for placebo vs 1.3% for ZA.)

Conclusion: A once-yearly infusion of ZA during a 3-year period was associated with a sustained reduction in risk of fractures. “In addition, the treatment had a favorable safety profile and was generally well tolerated.”

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The study was not a valid comparison. The proper protocol to determine efficacy and safety of a new drug is to compare it with an effective, established drug if one is available, and not with a placebo.

I would not prescribe or advise ZA for my patients should it become generally available. Much longer observations must be in place to assess safety to convince me that it is preferable.

PAIN

“Physicians Have Become More Comfortable About Using These Drugs”

1-3 OPIOID PRESCRIPTIONS SOAR: Increase in Legitimate Use as Well as Abuse

According to a recent survey—“Pain is a serious, undertreated health problem in the United States—19% of US adults reported chronic pain; 34% reported recurrent pain. Some 63% of patients with pain had spoken to their physician about their pain, but only 31% reported complete relief, and 21% reported little or no relief.”

Campaigns to make pain control a priority have succeeded in raising patient and physician awareness of the need for analgesics. Opioids are now among the most prescribed drugs.

By far, the most commonly used prescription analgesic in the US is hydrocodone/acetaminophen (eg. *Vicodin*), with over 100 million prescriptions in 2005.

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Pain-control is one of the most important functions of primary care.

I believe most primary care clinicians know their patients well, and can and do monitor prescription drug use carefully to avoid misuse.

“Under-Prescribing Of Opioids Remains A Major Barrier To Effective Pain Control”

4-5 MORPHINE KILLS THE PAIN, NOT THE PATIENT

Public and professional anxieties about the effects of morphine continue to hinder adequate access to analgesia. The best known fact about morphine among the public is that it can be addictive. (In fact, the risk of iatrogenic addiction is under 0.1%.) For physicians, the second best known fact is that morphine can precipitate respiratory depression.

A recent study from the US National Hospice Outcomes Project compared opioid use and survival at the end of life. Hospice inpatients (n = 725) with end-stage cancer, lung disease, or heart disease were followed up to death. The length of stay was *positively* correlated with the maximum daily opioid dose received, even when that dose exceeded 15 times the average for patients in the UK. Neither absolute dose nor change in dose was linked to shortened survival.

Patients who are given the incremental dose-titration practiced in palliative care centers are not at risk of respiratory depression.

Under-prescribing of opioids remains a major barrier to effective pain control. “Physicians should be encouraged to use opioids effectively to relieve suffering at the end of life.”

“Patients Generally Received What They Asked For”

PATIENT EXPECTATIONS

3-1 MANAGEMENT OF PATIENT EXPECTATIONS IN PRIMARY CARE PRACTICES

“Patients may approach medical encounters concerned that their expectations will not be met owing to constraints on medical spending, and the intercalation of managed care systems directly in their relationship with the physician.” This may be particularly true about expectations for new medications, diagnostic tests, and specialist referrals. Direct-to-consumer marketing and media hype have inflated such expectations.

This study characterized negotiations between patients who had expectations of new medications, tests, or referrals, and their primary care physicians.

Overall, 67% of the expectations were met.

For 73% of unmet expectations, patients stated that the physician gave them a reason for not meeting the expectation. For almost all of these, medical necessity was cited as the reason for providing an alternative choice, or for not granting the request. The great majority of patients reported that the explanation was satisfactory.

Physician post-visit survey:

Physicians reported not meeting 19% of patients’ requests.

The most common rationale was that the request was not medically indicated (61%).

The physician would *not* have fulfilled 62 of 138 requests had the patient not asked.

When physicians met the expectations, they sometimes felt “uncomfortable” about doing so.
(13% of the time)

Patient satisfaction, trust in physician, and patient empowerment:

90% rated the physician’s performance as “excellent” or “very good”.

Trust in the physician was generally high.

Over 90% felt involved in the decision-making process. Over 90% reported that their physician “definitely” or “probably” would ask them for help in making the decision between choice of treatments; 81% were often given some control over treatment; 69% were asked to take some responsibility for treatment.

“Unmet expectations did not seem to negatively impact patient’s satisfaction with, or trust in, the physician.” Alternatives were almost always acceptable to the patient.

“For physicians, learning how to effectively negotiate and respond to patient requests might assist in developing effective paradigms for cost-effective practice that do not negatively affect patient satisfaction.”

Conclusion: Patients generally received what they asked for. Physicians often altered their behavior to honor patients’ requests.

I enjoyed this article. It portrays the present state of primary care practice.

It is a commentary on the power of the marketing departments of drug companies.

It illustrates the sea change which has led the doctor-patient relationship away from the authoritarian-paternalistic style of previous years, to the now accepted relationship in which patients express their autonomy.

Patients now participate in choosing the type of care they wish to receive, and negotiate with the physician in obtaining it. Patients are taking an active part in their care.

The new paradigm places a requirement for doctors to develop more sensitivity and skill in guiding patients. This will take more time.

It has an upside and a downside:

Upside: Including patients in decisions will likely lead to increased responsibility for their own care, to greater compliance, and to increased satisfaction.

Downside: Complying with requests for a different drug (perhaps one recently approved by The FDA and highly advertised), or a more detailed test or examination (perhaps for an expensive laboratory or imaging study), will increase medical costs and dependence on insurance coverage. It may lead patients to unnecessary involvement in the “system” of follow-ups, repeated testing (with the likelihood of more false positive tests), and continuing anxiety. Patients who receive a newly approved drug within several years of approval, run the risk of developing adverse effects which are not uncovered during phase III trials.

I believe physicians should never have to feel “uncomfortable” about filling a patient-request. Such feelings indicate doubts about the appropriateness of the request. If physicians feel the request is not appropriate and will lead to more harm than good, they should deny the request with clear reasons for the denial.

*While abstracting this article I thought of a study concerning the doctor-patient relationship. “Effect of Patient Completed Agenda on the Outcome of Consultation” *BMJ* May 27, 2006; 332: 1238-41 *Practical Pointers* May 2006 [5-1]. It described a method by which patients record their thoughts and questions about a forthcoming consultation, and express expectations about what they would like the doctor to do. It presents 5 points to help the doctor understand the patient’s viewpoint and desires about the consultation. It uncovered a pool of unrecognized patient-needs.*

PERIODIC HEALTH EVALUATION

Schedule for a “Complete Physical”, or Deliver Preventive Services in The Context of Ongoing Clinical Care?

2-10 THE VALUE OF THE PERIODIC HEALTH EVALUATION: Systematic Review

The PHE consists of one or more visits to a health care provider to assess patients’ overall health and risk factors. It results in delivery of clinical preventive services that are tailored to a patient’s age, sex, and clinical risk factors and laboratory testing. The PHE may improve patient outcomes and the public’s health.

It could, however, induce unnecessary costs and patient harms. Early studies of the PHE, performed before the adoption of current preventive services guidelines, were costly and demonstrated minimal

improvements in clinical outcomes. Because of concern over the value of the PHE, some experts have advocated episodic targeted delivery of preventive services in the context of ongoing clinical care.

In light of conflicting opinions regarding the PHE's impact on health, costs, and non-uniformity of its implementation, these investigators performed a systematic review of the evidence to ascertain benefits and harms.

This systematic review selected 21 studies assessing the delivery of preventive services, clinical outcomes, and costs among patients receiving the PHE versus those receiving usual care. Defined "usual care" as the delivery of clinical preventive services in the absence of a health care provider visit designated for the primary purpose of assessing the patient's health and risk factors for disease.

Compared with usual care, the PHE had consistently beneficial association with patients' receipt of gynecological examination and Pap smears, cholesterol screening, and fecal occult blood testing.

The PHE had a beneficial effect on patient "worry" in one randomized trial, but had mixed effects on other outcomes and costs.

Conclusion: The PHE has a beneficial effect on the delivery of some preventive services, and may have a beneficial effect on patients' worry.

This is not a strong study. There is too much heterogeneity. I believe it does concur with the experience of most primary care clinicians. I believe also that, since primary care clinicians care for many patients with chronic diseases over a long-term, there will be ample opportunity to apply the goals of the PHE episodically. This approach may be time- and expense-saving.

We should focus on long-term control of the "big 5" risk factors (in addition to any acute and continuing health problems the patient may present).

Smoking and alcohol

Diet and lipid control

Exercise

Body mass index

Blood pressure.

Some patients may wish to schedule an appointment for a periodic "check up" focused on their general health. This may provide them reassurance and possibly uncover previously undiagnosed risk factors. I would not deny this service. Indeed, patients who schedule PHEs may be more compliant and interested in continuing to focus on reduction of risk factors.

Some risk factors should not be routinely investigated without full informed consent of the patient. (g, PSA testing)

There comes a time when we should limit investigations usually considered part of the PHE. Elderly patients may not live long enough to gain any benefit from continuing risk reduction, and may not wish to be bothered or worried any longer, but to enjoy to the fullest possible each day granted them.

PERTUSSIS

The Epidemiology Is Changing. Adolescents And Adults Need Immunization

1-4 THE CONTROL OF PERTUSSIS—2007 AND BEYOND

During the past 2 decades, there has been a slow, steady resurgence of pertussis, although rates have not approached the levels of the pre-vaccine era. The shift from the whole-cell vaccine in the 1990s to the acellular vaccine was associated with reduced rates of adverse effects. But the incidence of pertussis continued to increase.

The epidemiological shift is probably multifactorial:

Limited duration of immunity from both the natural infecting and vaccination.

Increasing incidence of infection in adolescents and adults who previously received a less-effective whole-cell vaccine.

Improved laboratory methods for diagnosis..

The changing picture probably represents both a real epidemic and a pseudo-epidemic. The “marching cohort” of infected preadolescents and adolescents indicates that the shift in epidemiology is not just a consequence of changing patterns of laboratory testing.

Pertussis remains underdiagnosed and underreported. Practitioners will need to carefully evaluate patients in whom they suspect pertussis.

The Advisory Committee on Immunization Practices recommends that all adolescents and adults receive acellular vaccine combined with diphtheria and tetanus toxoid (Tdap).

The Johns Hopkins web site to guide therapy for infectious disease (<http://hopkins-abxguide.org/>):

Advises clarithromycin or erythromycin as first choice therapy for pertussis

Second choice—trimethoprim-sulfamethoxazole

PHYSICIAN CONSIDERATION OF PATIENTS' COSTS

Physicians Do Not Often Consider Patients' Costs

4-9 PHYSICIAN CONSIDERATION OF PATIENTS' OUT-OF-POCKET COSTS IN MAKING COMMON CLINICAL DECISIONS

Patients face growing cost pressures. Physicians do not often consider issues about costs.

This study analyzed data on how frequently physicians considered their patients' O-O-P costs. Does consideration of O-O-P costs affect clinical decision making?

Asked: How often do you consider an insured patient's O-O-P costs when:

- 1) Prescribing a generic over a brand-name drug?
- 2) Deciding the types of tests to recommend ?
- 3) Choosing between inpatient and outpatient care settings?

Seventy eight % of physicians reported regularly (always or usually) taking patients' O-O-P costs into account when prescribing generic over brand-name drugs; 51% reported considering the costs in choosing out-patient vs in-patient care settings; 40% did so in selecting diagnostic tests.

Physicians treating patients of lower socio-economic status tended to be more likely to consider costs, as were physicians who had more patients receiving Medicaid.

Conclusion: Physicians do not routinely consider patient's costs.

This is a clinically valid and important consideration. Primary care clinicians should routinely consider costs of drugs and treatments to individual patients. It benefits little to make an evidence-based diagnosis and prescribe an evidence-based drug if the patient cannot afford to have the prescription filled.

O-O-P costs are only half of the economic burden. Costs to the government and insurance companies are the other half. Patients eventually pay for both. There is only so much money available for health care. When lower cost services are applied, more funds will be available for additional care.

Pharmacists in the community may help a great deal in determining costs. Costs are also readily available on the drug store web pages.

Considerable savings can be achieved by use of a pill cutter. Many drugs have a high therapeutic index (eg, statin drugs; antihypertension drugs). A higher dose pill may be cut in half or in quarters for the daily dose. It often makes little difference clinically if the cut-dose varies somewhat from one day to the next.

Many scored pills are available. Patients can easily manage their daily dose by breaking the pill in half. Drug stores do not charge double for a pill which is twice as strong. Indeed, some pills at twice the dose cost very little more.

Free clinics frequently dispense generic drugs only. Anecdotally, patients seem to fare just as well.

“POLYPILL”

“A Mere Leap Of Faith.” ?

1-8 THE PREVENTIVE POLYPILL—Much Promise, Insufficient Evidence

Dr. K S Reddy of the All India Institute of Medical Sciences discusses the pros and cons of the “Polypill”.

The pill, was proposed in 2003 by Wald and Law for *universal* use by persons over age 55 to reduce the risk of acute coronary events and stroke. It contained a statin drug, a thiazide, an ACE-inhibitor, a beta-blocker, low-dose aspirin, and folic acid, aimed at reducing LDL-cholesterol, blood pressure, platelet adhesiveness, and homocysteine.

Wald and Law suggested the pill could reduce cardiovascular disease in the population by more than 80%.

The pill would be more readily accepted for *secondary* prevention of cardiovascular disease. For *primary* prevention, the benefit/harm-cost ratio is uncertain.

Read the full abstract.

When I first read the article I thought the authors were presenting the “pill” tongue in cheek. Not so. The staying power of this suggestion has been remarkable.

Many people in the USA are already taking one, two, three, or four of the components. Aspirin, folic acid (in a daily vitamin supplement) and simvastatin (in the UK) are now available over-the-counter.

This goes against the traditional approach to risk reduction by drugs. But, I suspect that many people would take the pill if offered.

At present, outrageous and toxic nostrums and “herbal” medications (for which there is certainly “insufficient evidence”) are widely advertised and freely available over-the-counter.

RENIN-ANGIOTENSIN SYSTEM

“Best Proven Interventions to Reduce Target Organ Damage in Hypertension, Atherosclerosis, and Diabetes.”

4-1 RENIN-ANGIOTENSIN SYSTEM AND CARDIOVASCULAR RISK

The renin-angiotensin system (**RAS**) is a major regulatory system for cardiovascular and renal function.

Angiotensin-converting enzyme inhibitors (and by extension, angiotensin-II blockers) have been described as having the broadest effect of any drug in cardiovascular medicine.

This review article begins with a brief description of the biology of the renin-angiotensin system.

It continues with consideration of the relation between RAS and:

- 1) Left ventricular hypertrophy
- 2) Atrial fibrillation
- 3) Stroke
- 4) Atherosclerosis
- 5) Type-2 diabetes.

“ARBs and ACE inhibitors are best proven interventions to reduce target organ damage in hypertension, atherosclerosis, and diabetes.”

Conclusion: Improvement in the patient’s cardiovascular risk by drugs which attenuate activity of the renin-angiotensin system is not related to BP reduction alone. Risk-reduction includes many other non-hemodynamic effects.

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Read the full abstract.

I believe these ACE inhibitors and angiotensin II blockers have become major therapeutic interventions in primary care. Clinicians should become thoroughly familiar with their actions and benefits. And prescribe them more frequently.

There is much to lead primary care clinicians to choose angiotensin-II blockade (over ACE inhibition). ARBs are much better tolerated than ACE inhibitors. They are not associated with the annoying dry cough and angioedema produced by ACE-inhibitors

SEAFOOD

No Evidence To Support The Warning Of The US Advisory That Pregnant Women Should Limit Their Seafood Consumption

2-4 MATERNAL SEAFOOD CONSUMPTION IN PREGNANCY AND NEURODEVELOPMENT OUTCOMES IN CHILDHOOD

Optimum fetal development is dependent on specific nutrients derived solely from dietary sources. These include essential fatty acids, of which seafood is a major source. In the USA, women are advised to limit their seafood intake during pregnancy to 340 grams per week to avoid fetal exposure to trace amounts of neurotoxins (especially mercury).

Such limitation of seafood consumption could cause intake of long-chain essential fatty acids to fall below quantities adequate for optimum fetal neurodevelopment.

This observational cohort study (over 11 500 women) assessed the possible benefits and hazards to a child's development related to levels of maternal seafood intake during pregnancy.

Postal questionnaires were sent during pregnancy, and then at specific time points after birth of the child to obtain information about diet, education, social circumstances, behavior, and developmental outcomes. Detailed questions about seafood consumption were included.

Compared developmental, behavioral, and cognitive outcomes of children from ages 6 months to 8 years of women consuming 1) no seafood, 2) some seafood (1 -340 g per week) and 3) over 340 g per week

After adjustment, maternal seafood intake during pregnancy of less than 340 g per week was associated with increased risk of their children being in the lowest quartile for verbal IQ compared with mothers who consumed more than 340 g per week. Low maternal seafood intake was also associated with increased risk of suboptimum outcomes for prosocial behavioral, fine motor, communication, and social development scores.

There was no evidence that consumption of more than 3 portions of seafood a week during pregnancy has an adverse effect on the behavior or development of the child. (No evidence of harm.)

By contrast, maternal consumption of more than 340 g of seafood a week was beneficial to the child's neurodevelopment.

Advice that limits seafood consumption might reduce the intake of nutrients necessary for optimum neurological development.

Although methyl mercury undoubtedly has harmful effects on the developing brain, the harm is unlikely to be greater than the overall benefits of nutrients at the concentrations usually present in seafood.

Conclusion: Children of mothers who ate larger amounts of seafood were likely to have more optimum neurodevelopment. This study found no evidence to support the warning of the US advisory that pregnant women should limit their seafood consumption.

STROKE

“Should Now Be Considered A Part Of Routine Care Of Suitable Stroke Patients.”

1-1 THROMBOLYSIS WITH ALTEPLASE FOR ACUTE ISCHAEMIC STROKE

Alteplase (recombinant tissue plasminogen activator) is currently the only approved therapy for patients with acute ischemic stroke. Most stroke associations recommend it as first-line treatment.

Randomized, controlled trials (**RCTs**) have shown that administration within 3 hours of onset of ischemic stroke symptoms is safe and effective.

This study assessed the benefits and harms of alteplase when incorporated into clinical practice across a wide range of centers. (I.e, a pragmatic study.) When it is applied to the community, is it as safe and effective as in RCTs?

Prospective, open, observational study recruited over 6400 patients (age 18 to 80; mean = 68) with stroke from 285 different centers in 14 countries. All received intravenous alteplase (0.9 mg/kg) within 3 hours of stroke onset. The patients had considerable co-morbidity.

Primary outcomes:

A. Symptomatic intracerebral hemorrhage:

At 24 hours 1.7% (Symptomatic intracerebral hemorrhage was defined as a parenchymal hematoma on CT scan combined with 4 or more points worsening on the NIHSS.

At 7 days 7.3% (Any degree of hemorrhage on CT combined with any neurological worsening. This compared with 8.6% in pooled RCTs)

B. Mortality within 3 months = 11%. (Compared with 17% in pooled RCTs.)

Deaths considered to be related to alteplase = 1.5% (96 patients)

C. Complete recovery at 3 months (Rankin score of 0 to 1 = 39% compared with 42% in RCTs).

Outcomes at centers with little experience in administering alteplase within 3 hours compared favorably with outcomes in centers with more experience.

Conclusion: Intravenous alteplase is safe and effective in routine clinical use in the community when used within 3 hours of stroke onset, even in centers with little experience.

RCTs ask the question: Can it work? (Efficacy)

Observational studies ask: Does it work for routine use in the community? (Effectiveness)

Cost-effective studies ask: How much does it cost? Is it worth it? (Efficiency)

This pragmatic study extends an important application to primary care (Effectiveness). I believe it will lead to greater interest in application of alteplase therapy in the community.

Substantial logistic problems connect with this application in the community:

- 1) Making community dwellers aware of the symptoms of stroke and encouraging them to request immediate assistance.*
- 2) A coordinated and prompt emergency transportation system.*
- 3) Provision of trained personnel in emergency departments.*
- 4) Making prompt scanning facilities available 24-hours a day.*

I congratulate the communities, the institutions, and the investigators on completion of a difficult and important study.

Thrombolytic therapy for stroke poses a dilemma—sort of a “Catch 22”. There is no way one can determine if an individual patient will be harmed or benefited.

A. If the patient has little or no residual effects from the stroke, it is not possible to determine if the benefit was due to the thrombolysis. The stroke symptoms may have regressed spontaneously. Although the clinician and the patient may attribute improvement to the therapy, it actually may not have been due to the therapy.

B. If, on the other hand, the patient develops severe disability or dies from a hemorrhage, the clinician and the patient (and the family) will likely blame the thrombolysis for the disaster even if the outcome was due to the natural progression of the stroke.

I believe there are also ethical considerations. Is it ethical to administer a possibly lethal treatment to a patient without first fully informing the patient about risks and benefits, allowing him to make an informed choice? Will taking the time to discuss pros and cons with the patient extend the time to treatment beyond 3 hours?

Age; Blood pressure; Clinical Attributes; Duration

1-2 VALIDATION AND REFINEMENT OF SCORES TO PREDICT VERY EARLY STROKE RISK AFTER TRANSIENT ISCHEMIC ATTACK

This study aimed to validate two existing scores for early risk of stroke after a TIA, and to derive and validate a unified score for prediction of 2-day stroke risk. Patients at high risk need immediate evaluation to optimize stroke prevention. The 2-day risk of stroke after a TIA is most relevant for decisions about urgent evaluation and observation.

The study evaluated over 4800 individuals with TIA. Most patients presented within 24 hours. (Patients who present after 2 days may have an entirely different prognosis.)

Overall, stroke occurred in 442 patients: 4% within 2 days; 5.5% within 7 days; 7.5% within 30 days; 9% within 90 days

The new score (ABCD2) consisted of 5 factors:	Points
Age 60 or over	1
BP > 140/90	1
Unilateral weakness	2
Speech impairment without weakness	1
Duration > 60 minutes	2
Duration 10-59 minutes	1 (A total of 7 to 8 points possible)

(No mention of visual defects. RTJ)

			Risk of stroke (%)		
Outcomes according to score:	Points	% of patients	2-day	7-day	90 day risk
High risk	6-7	21	8	12	18

Moderate risk	4-5	45	4	6	10
Low risk	0-3	34	1	1.2	3.1

Risks of stroke after a TIA are similar to risk of a myocardial infarction after presentation with chest pain. The investigators suggest that stroke has as devastating consequences as myocardial infarction. Patients presenting with chest pain are often treated urgently and observed for 24 hours in the hospital. Patients with TIA should receive the same consideration.

The ABC2 score might be useful in determining which patients are admitted and which need assessment within 24 hours. Based on a previous cost-utility analysis, and ABCD2 score of 4 or greater might justify a 24-hour admission solely on the basis of a greater opportunity to administer thrombolysis early if a subsequent stroke occurs in the hospital as opposed to at home.

The presence of new ischemic lesions on MRI or CT in patients with transient symptoms can portend an increased short-term risk of stroke. Clinical risk scores and imaging studies can be combined to predict risk.

“Brain and vascular imaging is recommended for all patients with TIA to identify causes and target efforts to prevent stroke.”

Conclusion: The ABCD2 score is likely to be more predictive of stroke, especially within 2 days. Patients at high risk need immediate evaluation to optimize stroke prevention.

With the advent of thrombolytic therapy, close observation is required for patients with TIA to determine if stroke will occur, and to make preparations for prompt thrombolytic therapy if it does occur. This would be much easier in hospitalized patients.

I believe this guide would help primary care clinicians to quickly triage patients.

“Our Findings Remain To Be Confirmed.”

6-8 EFFICACY OF FOLIC ACID SUPPLEMENTATION IN STROKE PREVENTION: A meta-analysis

Initial epidemiological evidence supported the hypothesis linking elevated homocysteine levels with increased risk of coronary artery disease, stroke, and deep vein thrombosis; and that treatment with folic acid reduced risk.

Randomized trials have reported inconsistent results, and have not supported the hypothesis that lowering homocysteine reduces risks. Most of these trials have been conducted in patients with established cardiovascular disease. It is possible that folic acid supplementation could have a greater protective effect in primary rather than in secondary prevention; and that different cardiovascular endpoints could respond differently to folic acid.

This meta-analysis focused on stroke as the disease endpoint in relation to folic acid supplementation.

Collected data from 8 randomized trials (over 16 500 individuals, most over age 60) of folic acid (with or without B6 and B12) supplementation vs placebo. All reported stroke as one of the endpoints. All trials included individuals with pre-existing cardiovascular or renal conditions.

Pooling results of all trials indicated a statistically significant reduced risk of stroke in the folic acid treatment groups. (Relative risk [RR] = 0.82; folic acid vs placebo). Longer-duration trials were associated with greater benefit in reducing stroke. Less than 36 months RR = 1.0; longer than 36 months RR = 0.71. In the one study of subjects with a history of stroke, the RR was 1.04 vs a RR of 0.75 in 7 studies of subjects without a history of stroke (but with other vascular diseases).

“Our meta-analysis provides coherent evidence that folic acid supplementation can significantly reduce the risk of stroke in primary prevention.”.

There is continued controversy with regard to whether folic acid can lead to improved outcomes for other cardiovascular endpoints. Several randomized trials of folic acid supplementation have in general yielded negative results. However, different endpoints (eg stroke vs other cardiovascular endpoints) could respond differently.

“Our findings remain to be confirmed.”

Conclusion: “Our findings indicate that folic acid supplementation can effectively reduce the risk of stroke in primary prevention.”

The homocysteine-folic acid controversy seems to have 9-cat-lives.

This meta-analysis was not really an analysis of “primary” prevention. At baseline, all subjects had established atherosclerotic disease. In a truly “primary” prevention trial all subjects at baseline should be free of atherosclerotic disease.

It would take a long time and a large trial of folic acid supplementation vs placebo in subjects without any atherosclerotic vascular disease at baseline to determine any benefit.

This meta-analysis does not convince me. What would be the reason to consider that stroke (a vascular disease) differs from other vascular diseases?

How should primary care clinicians respond to the presently available information?

I believe it reasonable, since doubt remains, to offer supplementation. The benefit / harm-cost ratio of folic acid may be high because the harm-cost is so low.

TERMINALLY ILL PATIENTS

“Despite What They Might Say, People At The End Of Life Rarely Want Everything Or Nothing.”

2-3 DEFINING LIMITS IN CARE OF TERMINALLY ILL PATIENTS

Invasive procedures in terminally ill patients often fail to change the course of the disease. Interventions can become inappropriate overtreatment. Untimely referral to hospice, poor technical performance, overuse of interventions inconsistent with preferences and prognosis, and poor communication, increase the likelihood of inappropriate clinical intervention.

Surrogates usually do not realize that “doing everything” may lead to overtreatment. Doctors often do not take the time to clarify the nature of such requests. Surrogates may not have any idea about the wishes of the patient. Doctors should provide an accurate, sensitively presented account of the predictable

consequences of “doing everything”, and follow up by exploring how these consequences may not serve the goal of providing the best care.

It is imperative for good end-of-life decision-making to identify, explain, and negotiate consensus goals to ensure that appropriate treatment occurs. This requires effective communication skills and cultural sensitivity. The first step in preventing overtreatment of terminally ill patients is for both sides to collect and share information. Doctors must listen to, and focus on, what the patient and family understands about the patient’s condition:

What are you hoping we can achieve?

What do you think the patient would want?

Read the full abstract.

If you practice primary care medicine long enough, you will encounter surrogates who demand that “everything” be done for their relative. I believe, however, that this situation occurs less frequently now than in the past. Suggestions about how to deal with it are welcome.

TOBACCO

“We Should Not Delay In Allowing Snus To Compete With Cigarettes.”

6-6 SNUS—What should the public health response be?

In most developed countries, about a fifth of annual deaths are caused by smoking. Many people have a serious smoking-caused illness each year, the most being respiratory diseases.

Snus, a form of smokeless tobacco, has lower levels of toxins than most other smokeless tobaccos. Snus has been estimated to be 90% less harmful than cigarettes. It has become the dominant form of tobacco used by Swedish men, who now have an unusually low smoking rate.

It is banned in countries in the European Union other than Sweden.

A study from Sweden now reports that oral cancer and lung cancer are *not* increased in snus users compared with never-users. A study from Australia, where snus is also banned, estimates that snus could produce a net health benefit, dependent on how many inveterate smokers would switch to snus.

Snus is not harmless. It can cause gingival recession and adverse outcomes in pregnancy. There is conflicting evidence about cardiovascular risks. However, for all the major smoking-related diseases, the risks are lower with snus than with smoking. Importantly, snus poses *no risk* for lung cancer and chronic obstructive pulmonary disease.

“We believe it is preferable that, if people become addicted to cigarettes or decide to try tobacco, they can use a product that is markedly less harmful than cigarettes.” In Sweden, primary use of snus is associated with reduced risk of cigarette smoking. “We should not delay in allowing snus to compete with cigarettes.” “We should be prepared to accurately inform smokers about the relative risks of cigarettes, snus, and approved smoking-cessation medications.”

I repeatedly said to myself “Amen” while abstracting this article.

All drugs are harmful (no exceptions). This includes the now available drugs marketed for smoking cessation. We accept the possible harm of all drugs to gain a much greater perceived benefit.

I would welcome a head-to-head comparison of snus with the now available nicotine replacement therapies in smokers who wish to quit. How would the benefit / harm-cost ratios compare? Which one would be more acceptable to patients and be more likely to lead to persistent cessation of smoking? If snus were a drug manufactured by “Big Pharma”, I believe it would be FDA approved, widely advertised, and made universally available as a nicotine-based aid to cessation.

If snus were available in the US, I would not hesitate to advise it as an aid to smoking cessation after advising the patient about its possible harms, and offering information about comparable risks and benefits of snus vs other available aids to cessation. Indeed, if a smoker has tried a number of times to quit, I would advise use of snus as another attempt. Snus might be a bridge for smokers to use to gradually taper nicotine dependence.

Snus is not the same as snuff available in the US market. It is less toxic.

URINARY INCONTINENCE

A Remarkable Pioneering Technique Which May Provide Comfort To Many Women

6-11 AUTOLOGOUS MYOBLASTS AND FIBROBLASTS VERSUS COLLAGEN FOR TREATMENT OF STRESS URINARY INCONTINENCE IN WOMEN

A new technique for treatment of stress incontinence involved taking a muscle biopsy, processing the tissue, and placing it in tissue culture flasks to grow myocytes and fibrocytes. The autologous cells were injected into the urethra by guidance with a special ultrasound.

Of 42 women, 38 obtained complete continence. There were no adverse effects.

Read the full abstract.

This is a pioneering application. Although not applicable to primary care, I could not resist abstracting the article. More observation is obviously needed before the technique can be applied generally. If it is perfected and becomes generally available, it has the potential to provide comfort to millions of women.

VARICELLA

Immunity Wanes With Time. A Second (Booster) Shot Is Recommended.

3-7 LOSS OF VACCINE-INDUCED IMMUNITY TO VARICELLA OVER TIME

This study assessed whether vaccine-induced immunity wanes over time. It examined 10 years (1995-2004) of active surveillance data in a population of 350 000 subjects in a well-defined area in California to determine the incidence and severity of breakthrough varicella. (Onset of rash 43 days or more after vaccination.)

Over 11 000 subjects were reported to have varicella during the surveillance period. Of these, 10% had breakthrough disease. (Ie, had received the vaccine, but had nevertheless experienced clinical

chicken pox.)

The annual rate of breakthrough increased from the time since vaccination:

1.6 cases per 1000 person-years within 1 year after vaccination.

9.0 cases per 1000 person-years at 5 years.

58 cases per 1000 person-years at 9 years.

Severity of disease increased with age and as time from vaccination lengthened: children between ages 8 and 12 who had been vaccinated at least 5 years previously were significantly more likely to have moderate or severe disease than those who had been vaccinated less than 5 years previously.

Vaccinated children with moderate-to-severe disease were twice as likely to have complications such as pneumonia, ataxia, and skin superinfection as those with mild disease.

“These data suggest a steady decline over a period of years in disease protection afforded by a single dose of vaccine in the context of diminished circulation of wild-type virus.”

In June 2006, the Advisory Committee on Immunization Practices recommended that children between ages 4 to 6 receive a second dose of vaccine. The committee also recommended that a second catch-up dose be given to children, adolescents, *and adults* who previously had received one dose.

Conclusion: A second dose of varicella vaccine is now recommended for all children. This could improve protection from both primary vaccine failure and waning of vaccine-induced immunity.

Practical Pointers does not usually abstract articles of interest to the pediatric population.

This article applies to adults for several reasons:

1) Young adults who have not had clinical vaccinia in childhood or adolescence may be subject to the infection regardless of past immunization against varicella. I believe it will take time for this concept to be applied to adults who have received the vaccine. If you were age 20, had received the vaccine as a child, and never had clinical disease, would you be anxious to receive a booster?

2) As the population ages, younger adults who have received the vaccine in childhood may consider themselves to have been protected and never to have had chicken pox, and thus believe they are not a candidate for the herpes zoster vaccine. Past subclinical disease, or forgotten disease may indeed make them subject to shingles as they age.

VENOUS THROMBOEMBOLISM

LMWH Carries the Day.

2-1 VENOUS THROMBOEMBOLISM: a Clinical Practice Guideline

This concise review considers;

Initial inpatient treatment of deep venous thrombosis.

Outpatient treatment of deep venous thrombosis.

Initial treatment of pulmonary embolism.

Duration of anti-coagulation.

Anti-coagulation for management of venous thromboembolism pregnancy.

Compression stockings to prevent post-thrombotic syndrome.

Read the full abstract

I enjoy articles such as this which present recommendations in concise, simple, and clear fashion.

The guideline considers deep venous thrombosis (DVT) and pulmonary embolism (PE) separately.

I believe venous thromboembolism (VTE) is a more accurate and inclusive term because risk of PE (asymptomatic as well as symptomatic) is very high (almost universal) in patients with DVT of the lower extremities.